Risk of serious skin & soft tissue infections in rheumatoid arthritis patients taking anti-TNF drugs

By

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CERTIFICATE OF APPROVAL

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ABSTRACT

Background. Nearly half of the two million people in the U.S. suffering from rheumatoid arthritis (RA) have been treated with anti-TNF drugs that suppress immune functions. Although anti-TNF drug treatment is a highly successful therapy, recent studies indicate that the risk of developing a serious infection is more than 2 times higher among patients taking these drugs. Infections in rheumatoid arthritis patients are often severe and clinically challenging to treat. The objective of this study is to determine if rheumatoid arthritis patients treated with anti-TNF drugs have a higher risk of developing serious skin and soft tissue infections (SSSTIs) that require hospitalization than rheumatoid arthritis patients who do not take anti-TNF drugs.

Methods. We conducted a nested case-control study using data from the Veterans Integrated Service Network 20 (VISN 20) undergoing treatment for RA. We used validated electronic algorithms to identify a cohort of actively treated RA patients. Within this cohort cases of serious skin and soft tissue infection were identified and three sets of controls were randomly selected from the same cohort of RA patients and matched by the cases' index date and VA hospital site number. Multivariate conditional logistic regression was used to test the hypothesis that the risk of serious skin infections among patients taking anti-TNF drugs differs between the two groups, adjusting known confounders and clinically important covariates such as age, sex, ethnicity, other immunosuppressant drug use, co-morbidities, and other autoimmune diseases.

Results. Based on conditional logistic regression, anti-TNF use was not significantly associated with SSSTI (OR: 1.4 (95% CI: 0.604-2.30, p = .74) but patients with diabetes (OR 2.4, 95% CI: 4.064, 11.229, p = .001) or a history of skin infection (OR 5.5, 95% CI: 2.713, 11.229, p < .0001) were more likely to have SSSTI. Prednisone use was significant in univariate analysis (OR 1.9, 95% CI: 1.20-3.05, p = .01) but not in the final model (OR 1.5, 95% CI: 0.90-2.52, p = .12).

Significance. Serious skin and soft tissue infections are a leading cause of hospitalization and represent a substantial public health burden. Current research into the increase of reported serious infections in RA patients since the introduction of these drugs in the U.S. is limited, establishing a need to evaluate infections that result in hospitalizations.

Conclusion. Studies in more generalized RA patient populations have reported a significant increase in infections among patients receiving anti-TNF drugs; however, we did not observe a statistically significant association in the VA patient cohort studied. SSSTIs were not associated with anti-TNF use, but were significantly associated with diabetes, history of skin infection, and high mortality in the VISN 20 RA patient cohort. Further research following these patients prospectively is recommended to provide insight into improving clinical care and preventing future complications and morbidity in this vulnerable patient population.

BACKGROUND AND SIGNIFICANCE

Among the more than two million people in the U.S. suffering from rheumatoid arthritis (Gabriel, 2001), at least 40% have been treated with anti-TNF drugs (Wolfe, 2005). Preliminary studies suggest that the overall rate of serious infections in rheumatoid arthritis (RA) patients taking anti-TNF drugs is 2 times higher than the rate seen in unexposed patients (Curtis, 2006). Current research into the increase of all reported serious infections in rheumatoid arthritis patients since the introduction of these drugs in the U.S. is still emerging. An important subset of these infections is serious skin and soft tissue infections (SSSTIs) that require hospitalization or antibiotic drug use (Dixon, 2006). Infections of the skin and soft tissue occur in numerous body areas but not in bone, ligaments and connective tissue, and serious skin and soft tissue infections are one of the most common causes of hospitalization among all patients in the United States. Possible complications of SSSTIs include abscesses, gangrene (tissue destruction), and thrombophlebitis (inflammation of superficial veins). Some people are prone to recurrence of cellulitis. Although relatively rare, complications can lead to sepsis, amputation, and death. Yet research on the association of serious skin and soft tissue infections with anti-TNF drug use in RA patients remains limited to a small group of studies predominately conducted by European researchers. To date, few studies have been completed in the U.S. investigating this association (Winthrop, 2009), and none have been conducted within the sizeable patient population of the U.S. Veterans Administration Hospital Network. This represents an opportunity to evaluate the association

between anti-TNF drug use and serious skin and soft tissue infections within this well-defined cohort.

Tumor necrosis factor-α (TNF) is a cytokine that plays an important role in immune system regulation. Levels of TNF in RA patients are significantly higher than the general population and these high levels cause joint inflammation, swelling, and pain. Anti-TNF drugs inhibit tumor necrosis factor-α and suppress the inflammation. This class of drugs includes: Infliximab, Adalimumab, and Etanercept (often referred to as “biologics”). Although the use of biologics has been highly successful in treating RA, recent studies including a Canadian prospective cohort study (Khraishi, 2009) and research by Dixon et al. (2006) indicate that the risk of infections, and specifically serious skin and soft tissue infections, may be higher among patients taking this class of drugs due to the resultant immunosuppression.

Several new studies have identified higher rates of persistent viral and bacterial infections among RA patients undergoing treatment with anti-TNF drugs (Winthrop and Chiller, 2009); having compromised immune systems puts this cohort at substantial risk for severe complications. As a result, serious skin and soft tissue infections in immuno-compromised patients can be difficult to treat and often become life threatening (Dryden, 2009). Serious skin and soft tissue infections (44.6% of which are caused by *Staphylococcus aureus)* are one of the most common causes of hospitalization in the U.S., and among patients seeking care at emergency departments, methicillin-resistant *S. aureus* (MRSA) accounts for as many as 59% of the cases (Edelsberg, 2009). Typically, serious skin and

soft tissue infections are associated with high patient morbidity and represent significant challenges to clinical care (Dryden, 2008). The high prevalence of these infections and the significant treatment challenges caused by them create a substantial public health burden (Liu, 2008).

Early analysis of the risk of serious infections among these patients provides evidence that the overall rate of serious infection is higher for RA patients taking anti-TNF drugs, but research on serious skin and soft tissue infections is limited (Bongartz, 2006). Infections in immunosuppressed rheumatoid arthritis patients receiving therapy with biologics may also be more severe than the general population (Furst, 2009). A recent European study estimating the incidence rate of all serious infections in RA patients taking anti-TNF drugs found that 20.5% of these were serious skin and soft tissue infections (Favalli, 2009). Findings from a nationwide survey of infectious disease consultants in the Emerging Infections Network indicate that the reported prevalence of serious skin and soft tissue infections, specifically *Staphylococcus aureus* infection, were the most frequently seen types of infection in RA patients (Winthrop, 2008). Because skin and soft tissue are among the most common sites of infection in RA patients, it is important to study this association further (Furst, 2009).

The known increased risk of all infections in RA patients undergoing anti-TNF therapy underscores the need to determine if the risk is also high among the vast and growing number of patients served by the Veterans Administration hospital plan, given the elevated burden of disease and co-morbidities among

these patients. Moreover, it is vital to evaluate the role of biologics, specifically in increasing the risk of serious skin and soft tissue infections. Serious skin and soft tissue infections frequently require protracted hospitalization, exposing vulnerable patients to the further hazard of contracting antibiotic resistant strains of infection. The high costs of hospitalization and morbidity due to serious skin and soft tissue infections can be prevented in RA patients with careful early monitoring and prompt treatment. Thus the findings of this research will provide valuable insight into improving clinical care to prevent serious infections in rheumatoid arthritis patients receiving therapy with biologics (Dryden, 2009; Winthrop, 2009).

Study Rationale

We conducted this study to determine if the use of drugs inhibiting tumor necrosis factor-α (anti-TNF drugs) is associated with increased occurrence of serious skin and soft tissue infections requiring hospitalization in patients with rheumatoid arthritis compared to rheumatoid arthritis patients not using anti-TNF drugs. We hypothesized that the risk of serious skin and soft tissue infections among patients taking anti-TNF drugs differs from the risk among patients not receiving treatment anti-TNF drugs. Furthermore, we sought to identify potential risk factors for serious skin and soft infections.

Specific Aims

The goal of this study is to determine if rheumatoid arthritis patients treated with anti-TNF drugs have a higher risk of developing serious soft tissue infections than RA patients who do not take anti-TNF drugs. Our two specific aims are:

Aim #1: Describe the burden of disease from serious skin and soft tissue infections (defined as infections requiring hospitalization or antibiotic use and/or antibiotic therapy) among RA patients.

Aim #2: Evaluate whether serious skin and soft tissue infections among RA patients are associated with anti-TNF drug use or other drug therapies.

METHODS

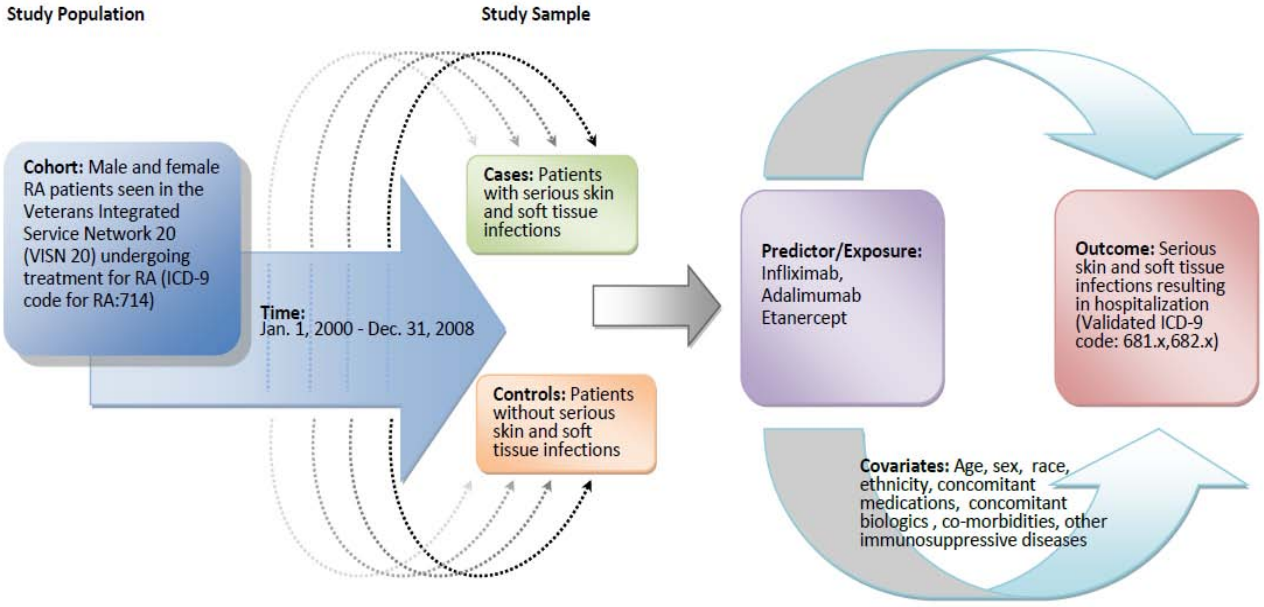
Overview of Design

This is a nested case-control study using de-identified secondary data pulled from a database originally created for a retrospective cohort study of all serious infections in rheumatoid arthritis (RA) patients in the Veterans Integrated Service Network 20 (VISN 20). The subjects for this study were selected from patients enrolled in the Veterans Administration hospital health plan from the time-period of January 1, 2000 to December 31, 2008. To be included in the study, subjects needed a medical record that includes the international classification of disease (ICD-9) code for RA (714) and to have seen a rheumatologist at least two times during the study period; they also needed to have been actively treated for RA as verified by pharmacy codes indicating at least one prescription fill for at least one drug used to treat RA during the study period. Patients not meeting these criteria were excluded from the study database.

To examine the relationship between RA patients treated with anti-TNF drugs and the risk of developing serious skin and soft tissue infections that require hospitalization, exposure to anti-TNF agents was defined as using one of the following drugs within 90 days before the date of diagnosis with a serious skin and soft tissue infection: Infliximab, Adalimumab, or Etanercept. VA hospital RA patients not receiving anti-TNF drugs constituted the unexposed cohort. The outcome of serious skin and soft tissue infections was defined using the FDA classification of “serious infection” being an infection that results in hospitalization

or the use of antibiotic therapy and identified in the patients' medical records using validated ICD-9 CM codes. Validated VA hospital discharge codes were used to identify cases of serious skin and soft tissue infection. A data analyst at the Portland, Oregon VA hospital conducted searches of pharmacy records and clinical databases to obtain descriptive variables, clinically important covariates, and data to aid in the determination of RA severity among cases and controls.

Figure 1. Overview of the Nested Case-control Study



Case Identification

97 patients were identified as having had a serious skin and soft tissue infection during the study period of January 1, 2000 to December 31, 2008 and were given an index date based on the date of the hospital discharge for a diagnosis of serious skin and soft tissue infection. Using validated hospital

discharge codes CD-9CM 681.x and 682.x (Schneeweiss, 2007) cases were identified as patients with serious skin and soft tissue infections, provided that the infection occurred during the study period but after their diagnosis with RA. Individuals with medical records indicating SSSTI during the study period but prior to diagnosis with RA did not meet the case finding criteria and were excluded from the study.

Control Selection

RA patients without serious skin and soft tissue infections (no history of serious skin and soft tissue infection in their medical record indicated by the absence of a validated ICD-9 code for SSSTI) from the same VA hospital population as the indentified cases (VISN 20) were designated as potential controls. From this pool we randomly selected three controls for each case with a rheumatoid arthritis office visit within 30 days from the case's serious skin and soft tissue infection diagnosis (index) date at the same VA site as the case. The statistical software SAS version 9.2 (SAS Institute Inc., Cary, NC. 2008) was used to generate the random numbers and to match the cases to three sets of controls.

Data Collection

A data set of VA hospital RA patients was generated by an analyst at the Portland, Oregon VA hospital. Programming was developed to identify cohorts and multiple variables of interest were collected (See Appendix D for

programming instructions and Appendix A for a complete list of variables collected). Patients were identified by ICD-9 codes among RA patients seen in VISN 20 and undergoing treatment for RA (ICD-9 code for RA: 714). Patients who met the programming criteria for cases or controls were selected by an analyst at the Portland VA hospital and a raw data file was generated in Excel.

Predictor Variables

The main predictor variable evaluated was the use of the anti-TNF drugs. Other clinically and epidemiologically important independent variables included co-morbidities, other serious bacterial infections, and concomitant medication use. Co-morbidities evaluated included the following conditions diagnosed anytime during the study time period; diabetes, chronic kidney disease, neoplasm, chronic bronchitis, gastro esophageal reflux disease, HIV infection, chronic liver disease and a prior history of skin infection any time before the index date. Other serious bacterial infections and other inflammatory diseases included meningitis, encephalitis, endocarditis, pneumonia, pyelonerphritis, septic arthritis, osteomyelitis and bacteremia, psoriasis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, uveitis, and psoriatic arthritis. Concomitant medications assessed included use of methotrexate, prednisone, azathioprine, leflunomide, hydroxychlorquine and sulfasalazine within 30 days of the index date as well as prednisone use in the six months prior to the index date and antibiotic 90 use days prior to the index date.

Statistical Analysis

Patient characteristics and demographics were assessed using frequency and means procedures. Cases and controls were compared using chi-square tests or Fisher's exact tests for categorical variables, and two-sample t-tests for continuous variables. Cell counts for each covariate were assessed and variables with fewer than five counts in a cell were evaluated using the exact analysis method.

The continuous variables age, race, ethnicity, number of RA clinic visits, and erythrocyte sedimentation rate (ESR) were categorized and used in the logistic regression. The same variables were also analyzed as continuous variables using t-tests to ensure that categorizing did not alter the significance of these variables. Additionally, data from laboratory tests for anti-CCP antibodies and rheumatoid factors were requested in order to evaluate the severity of disease, but the data contained too few entries to be included in the analysis.

Univariate logistic regression analysis was performed to examine the crude association between serious skin and soft tissue infections and covariates. For this analysis variables with univariate p-values ≤ 0.25 or known clinical importance were considered for inclusion in the multivariate model. (Hosmer & Lemeshow, 2000). Multivariate conditional logistic regression was employed to assess the association between serious skin and soft tissue infections and anti-TNF drug use while adjusting for confounding variables and other covariates.

The primary independent variable, independent variables meeting the univariate inclusion criteria of $\alpha \leq 0.25$ and potential confounding variables were

included in the main effects logistic regression model and variables were selected using a stepwise selection, backward elimination method. Only the primary independent variable and variables having a statistically significant p-value ≤ 0.05 were retained in the final model.

Confounding variables were evaluated by comparing crude and adjusted odds ratios, and variables that altered the crude odds ratio by at least 10% were deemed to be potential confounders. To control for confounding, special attention was paid to potential confounding variables that may be indicators of severity of disease and increased risk of infection such as erythrocyte sedimentation rate, the number of RA office visits in the year prior to infection, and the need for prednisone use, all of which may contribute to confounding by indication. Other potential confounders evaluated include age, sex, race, ethnicity, concomitant medications, biologics, co-morbidities, and other immunosuppressive diseases (see appendix A for a complete list of covariates assessed). Propensity scores for severity of RA, using the "RA medical records-based index of severity [RARBIS]", were not available to use to control for confounding by indication in this patient population because the VA hospital network does not systematically collect this data. However, the erythrocyte sedimentation rate, the number of RA clinic visits, and the need for prednisone use were analyzed as indicators of disease severity. Numerous other variables were also evaluated for possible interactions. (Appendix C). All analyses were performed using SAS V 9.2 (SAS Institute Inc., Cary, NC. 2008).

Power Considerations

Initial sample size calculations using the statistical software PASS indicated the study would need to consist of at least 58 cases and 116 controls in order to detect an effect of 0.05 at the alpha = 0.05 level with 80% power. We were able to identify 97 cases and 292 matched controls.

Quality Control and Data Management

Data for the proposed study has already been collected in accordance with the protocol 1908_#122607: *Serious infections in patients treated with biologic drugs; the creation of a population-based adverse event surveillance system.* The VSD distributive database model was followed in the creation of the primary database. Standardized database files of patient information were created, de-identified and pooled for analysis. The CDC guidelines to evaluate the quality and validity of automated search methodologies were used to ensure quality control of the primary database. Data management was conducted by statisticians at the Oregon VA hospital, and the data that was used for this analysis has been cleaned and checked for errors. A secondary evaluation of the data was completed by randomly selecting cases and controls and conducting chart review of the medical records for those patients to ensure data quality.

Protection of Human Subjects

The dataset was completely de-identified prior to receipt by the investigators and there was no exchange of identifiable data. Names and other identifying information on study subjects obtained for record keeping during the prospective cohort study were not shared with the investigators and no individuals were identified in any reports from this study. The data-pull program automatically removed identifying information and substituted study-specific unique linking identifiers for the analysis dataset. No consent forms were used, as this was a data-only study. This secondary analysis has been granted exemption by the OHSU IRB. HIPPA guidelines were stringently adhered to in the creation of the primary database and approval for this research is currently covered by the Human Subjects Review board protocol #122607.

Secondary Analysis

Anti-TNF drugs did not become widespread until 2004 and in order to assess how the higher rates of biologic use impacted the results of the study, a subset of the data was created to better reflect recent changes in medication prescribing patterns. The subset of the data was analyzed by building additional multivariate conditional logistic regression models that were identical in procedure and design to the original model. Patient data regarding disease outcome and covariates was parsed using SAS to create new data sets based on years, one set from 2000 to 2003 and the other spanning 2004-2008. The same covariates that were evaluated in the initial analysis were analyzed using the

bifurcated data sets. Univariate analysis was conducted to identify independent variables for inclusion in the multivariate model. Only variables meeting the univariate inclusion level of $\alpha \leq 0.25$ were included in the model. Cell counts for covariates with fewer than five counts in a cell were evaluated using the exact analysis method. Using the same inclusion criteria as was used for the initial model, a multivariate regression model was built using variables that were deemed significant in the univariate analysis.

The data was compared to the results of the primary analysis to determine whether risk factors associated with anti-TNF drug use and important covariates and demographics differed among patients prior to the widespread use of anti-TNF drugs. The statistical software SAS version 9.2 was also used for these analyses.

RESULTS

Demographics

Cases and controls did not differ significantly with regard to age, race, and gender. The cohort of patients from the VA hospital network (VISN 20) was predominantly male (92% cases and 89% controls) and white (77% cases and 67% controls) although, for a large percentage of the study population, complete data on race and ethnicity was not available due to missing data entries or patient refusal to respond. Data on ethnicity was obtained but there were too few entries for this variable to be included in the analysis. The proportions of key demographic variables for cases and controls are detailed in Table 1.

The average age of the cases was 63 years old and the average age of controls was 61 years old with ages ranging from 31-88 years old for cases and 25-86 years old for controls. Among cases, 95% of the patients were 50 years old or older while 87% of controls were 50 years old or older. While the majority of the cohort studied was over 50 years old there were slightly more controls in the younger age group of 24 years old to 49 years old (13% controls and 5% of cases).

Patients lived predominantly in Washington, Oregon, and Idaho. 42% of cases and 44% of controls lived in Washington, while 37% of cases and 31% resided in Oregon. Patients living in Idaho consisted of 16% of the cases and 17% of the controls. One percent or fewer of the patients lived in the remaining states, as represented in Table 1. Cases and controls did not differ significantly

with regard to state of residence, which was an expected artifact of matching by VA hospital site.

A total of 83 patients died during the nine year study period. Among those who died during the study time period, 38 were cases and 45 were controls (39% cases and 15% controls). The proportion of cases who died was more than double the proportion of controls who died during the study period, however, death during the study period was not statistically significant at the $\alpha = .05$ level ($p = .19$).

The average number of rheumatology clinical visits needed by patients in the year prior to the index date did not differ greatly between cases and controls, indicating that patients were well matched for severity of rheumatoid arthritis. 35% of cases had greater than 15 rheumatology clinical visits in the 12 months prior to the index date and 41% of controls had greater than 15 rheumatology clinical visits in the 12 months prior to the index date.

Table 1. Demographics

Variable	Case N=97 Frequency (Percent)	Control N=292 Frequency (Percent)
Male	89 (91.75)	261 (89.38)
Age on Index date (mean)	63	61
Age on Index Date - By age groups:		
'24 to 49 year olds'	5 (5.15)	39 (13.36)
'50 year olds and older'	92 (94.85)	253 (86.64)
Race		
WHITE	75 (77.31)	167 (66.80)
BLACK OR AFRICAN AMERICAN	1 (1.03)	14 (5.60)
UNKNOWN OR OTHER RACE	17 (17.52)	66 (22.60)
Death During Study Period	38 (39.18)	45 (15.41)
More than 15 Rheumatology Visits (12 months prior to index date)	34 (35.05)	121 (41.44)
State of Residence		
ALASKA	0 (0.00)	1 (0.34)
ARIZONA	1 (1.03)	4 (1.37)
CALIFORNIA	0 (0.00)	2 (.68)
GEORGIA	0 (0.00)	1 (.34)
IDAHO	16 (16.49)	50 (17.12)
ILLINOIS	0 (0.00)	0 (0.00)
MAINE	1 (1.03)	0 (0.00)
MICHIGAN	0 (0.00)	1 (0.34)
MINNESOTA	0 (0.00)	1 (0.34)
MISSOURI	1 (1.03)	1 (0.34)
MONTANA	0 (0.00)	1 (0.34)
NEVADA	0 (0.00)	1 (0.34)
NEW MEXICO	0 (0.00)	1 (0.34)
NORTH CAROLINA	0 (0.00)	1 (0.34)
OHIO	0 (0.00)	1 (0.34)
OKLAHOMA	0 (0.00)	1 (0.34)
OREGON	36 (37.11)	93 (31.85)
PENNSYLVANIA	0 (0.00)	1 (0.34)
SOUTH CAROLINA	0 (0.00)	1 (0.34)
TEXAS	1 (1.03)	0 (0.00)
UTAH	0 (0.00)	1 (0.34)
WASHINGTON	41 (42.27)	129 (44.18)
WYOMING	0 (0.00)	0 (0.00)

Serious Skin and Soft Tissue Infections

There were a total of 97 cases of serious skin and soft tissue infections indentified by discharge encounter code in the VA patient cohort during the study time period from 2000-2008. The proportion of patients diagnosed with serious skin and soft tissue infections during each year of the study is indicated in Table 2. The average percentage of infections per year over the entire study period was 11% (minimum: 7.22%, maximum: 18.56%). The smallest percentage of cases of serious skin and soft tissue infections occurred in 2000 and 2004 (7.22% each year) and the largest percentage of cases was seen in 2005 (18.56%).

Table 2. Discharge Encounter Year

Discharge Encounter Year	Frequency	Percent	Cumulative Frequency	Cumulative Percent
2000	7	7.22	7	7.22
2001	8	8.25	15	15.46
2002	14	14.43	29	29.90
2003	11	11.34	40	41.24
2004	7	7.22	47	48.45
2005	18	18.56	65	67.01
2006	9	9.28	74	76.29
2007	13	13.40	87	89.69
2008	10	10.31	97	100.00

The distribution of patients diagnosed with serious skin and soft tissue infections during each year of the study is shown in Figure 2. The average number of infections per year over the entire study period from 2000 to 2008 was 11 and ranged from a minimum of 7 cases of serious skin and soft tissue infections in 2000 and again in 2004 to a maximum of 21 cases in 2005. The aggregate frequency of serious skin and soft tissue infection remained fairly constant during the study period, with the exception of 2005, when there were 7 cases above the average number per year.

Figure 2. Serious Skin and Soft Tissue Infections by Year

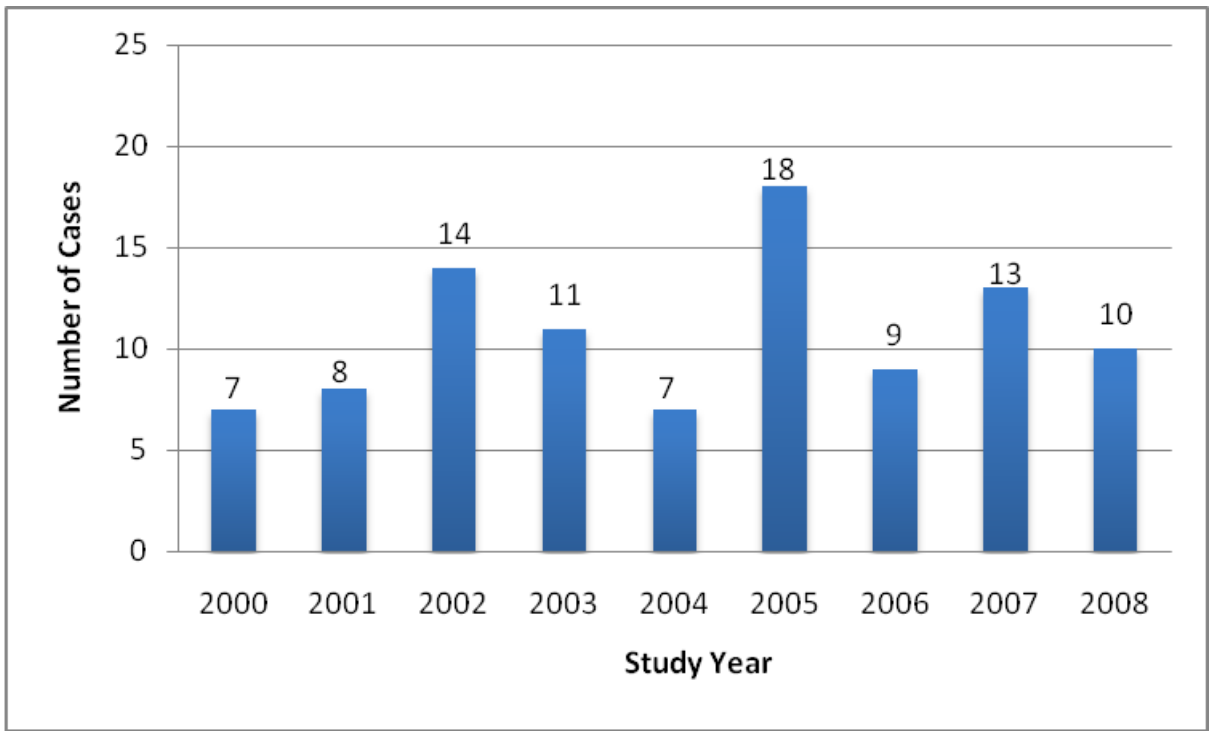
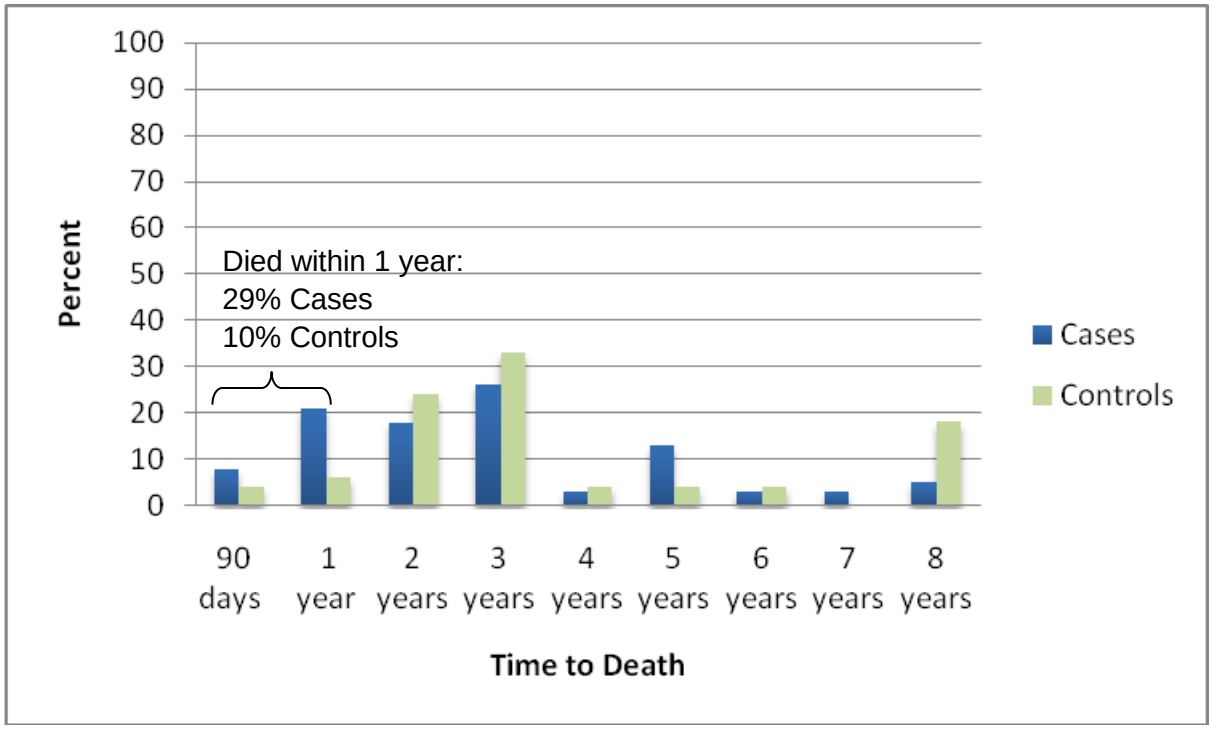


Figure 3 indicates that in addition to a larger proportion of cases dying during the study period than controls, cases on average died sooner than controls. 29% of cases died within one year of the index date (diagnosis with SSSTI) while only 10% of the matched controls died during the same time period.

Figure 3. Time Between Index Date and Death



In this patient population, only 19.59% of cases and 18.15% of controls received anti-TNF drug therapy 90 days before the index date.

Over the entire study time period from 2000-2008 on average 29.90% of cases and 23.97% of controls were prescribed anti-TNF drugs at least one time prior to the index date (Figure 4).

During the years from 2004-2008, the period when anti-TNF drugs became more widely utilized, 25.60% of cases and 31.10% of controls received anti-TNF therapy.

Figure 4. Anti-TNF Drug Use by Year

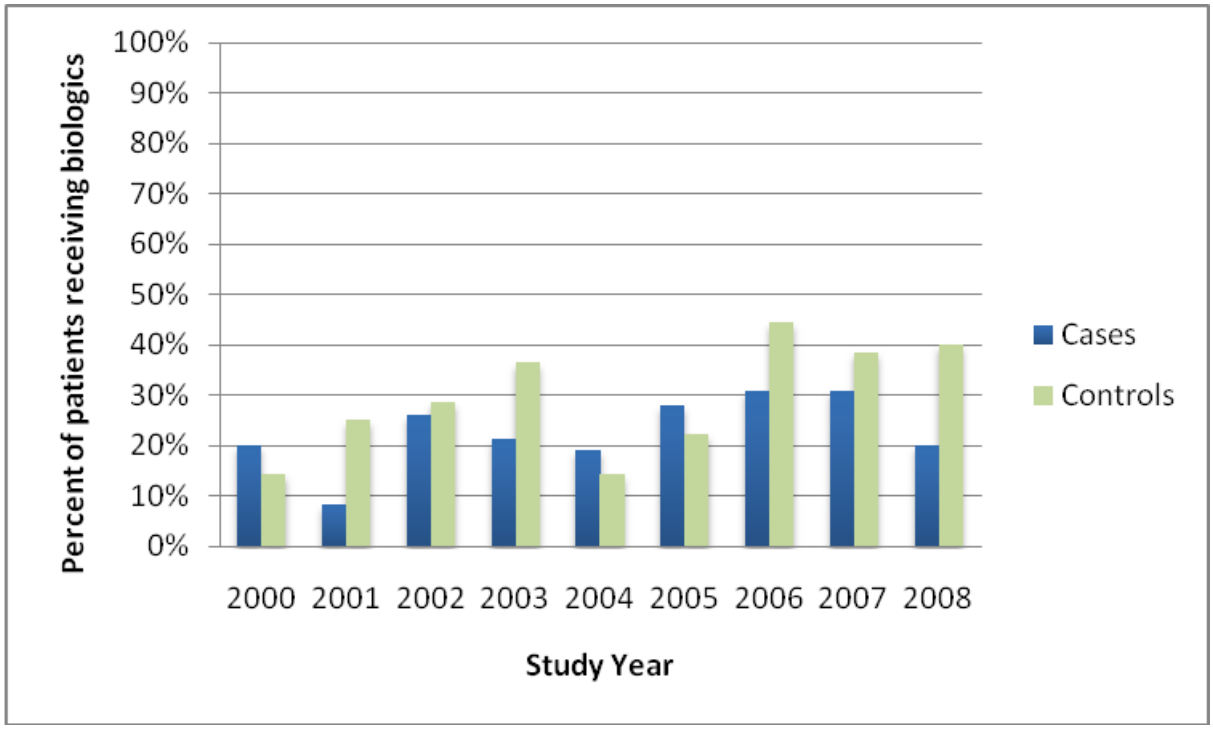


Table 3 shows the distribution of significant categorical covariates for cases only. Of the 97 cases, 39% died during the study period. Numerous co-morbidities were evaluated but only diabetes was significantly associated with infections; 63% of the cases had diabetes. Of the serious infections evaluated, only pneumonia was statistically significant and 4% of the cases had pneumonia during the study period. 27% of cases had a history of having a skin infection in the past. Among cases, 29% received anti-TNF drugs at least once during the study period while 19% were prescribed anti-TNF drugs within 90 days prior to developing a serious skin and soft tissue infection.

A large percentage of cases (89%) received antibiotic treatment 90 days prior to their diagnosis with a serious skin and soft tissue infection. Within thirty days of the index date, 52% of cases and 36% of controls were prescribed prednisone. The higher mortality among cases and larger percentage with diabetes and a history of skin infection, as well as the greater need for prednisone use, may be reflective of overall higher morbidity among cases.

Cases were also evaluated for differences among those who died during the study period and those who did not die, the results are summarized in table 4. There were no statistically significant differences between individuals who died and those who did not die with the exception of the variable prior history of skin infection. Cases who died during the study period were 2.8 times more likely to have a prior history of skin infection compared to cases who did not die during the study (95% Confidence Interval: 1.13-7.64, p = .02), though no adjustment was made for multiple comparison.

Table 3. Skin and Soft Tissue Infection Cases, (Categorical)

Variables, Cases Only	Frequency	Percent
Total	97	100.00
Death During Study Period	38	39
Significant Co-morbidities		
Diabetes	61	62.89
Discharge 3 months Prior Index Date	14	14.43
Prior History of Skin Infection	26	26.80
ESR > than 30	20	20.61
Other Significant Bacterial Infections		
Pneumonia	4	4.12
Medications		
Biologics 90 Days Before Index Date	19	19.59
Biologics Anytime Before Index	29	29.90
ETANERCEPT	16	16.49
INFLIXIMABIV	2	2.06
ADALIMUMAB	1	1.03
Monoclonals Only (Infliximab & Adalimumab)	3	3.09
Antibiotic use 90 days prior to index date	86	88.66
Concomitant Medications		
Methotrexate within 30 days of index date	20	20.66
Prednisone within 30 days of index date	51	52.58
Prednisone 6 mo. prior to index date	56	57.73
Azathioprine within 30 days of index date	3	3.09
Leflunomide within 30 days of index date	7	7.22
Hydroxychlorquine within 30 days of index date	23	23.73
Sulfasalazine within 30 days of index date	6	6.19

Table 4. Cases who died compared to cases who did not die during the study

Variables, Cases Only	Cases who died (n=38) Frequency (Percent)	Cases who did not die (n=59) Frequency (Percent)	P-Value
Age Group:			
'24 to 49 year olds'	0 (0.00)	5 (8.47)	0.06
'50 year olds and older'	38 (100.00)	54 (91.53)	
Race			
White	31 (86.11)	44 (77.19)	0.91
Black	0 (0.00)	1 (1.75)	
Unknown, Other or Declined	5 (13.89)	12 (21.05)	
Greater than 15 RA Clinic Visits	7 (18.42)	27 (45.76)	0.07
Inflammatory Diseases			
Psoriasis	1 (2.63)	9 (15.25)	0.08
Crohns	1 (2.63)	2 (3.39)	0.83
Ulcerative Colitis	1 (2.63)	2 (3.39)	0.83
Ankylosing Spondylitis	2 (5.26)	2 (3.39)	0.64
Uveitis	1 (2.63)	1 (1.75)	0.75
Psoriatic Arthritis	0 (0.00)	3 (5.08)	0.16
Co-morbidities			
Diabetes	14 (36.84)	22 (37.29)	0.96
Chronic Kidney Disease	9 (23.68)	6 (10.17)	0.07
Neoplasm	6 (15.79)	3 (5.08)	0.08
Chronic Bronchitis	16 (42.11)	28 (47.46)	0.60
Gastroesophageal Reflux	11 (28.95)	25 (42.37)	0.18
HIV	0 (0.00)	0 (0.00)	…
Prior History of Skin Infection	15 (39.47)	11 (18.64)	0.02
Discharge 3 Months Prior	6 (15.79)	8 (13.56)	0.76
Chronic Liver Disease	2 (5.26)	0 (0.00)	0.08
Meningitis	0 (0.00)	0 (0.00)	…
Encephalitis	0 (0.00)	0 (0.00)	…
Endocarditis	0 (0.00)	1 (1.69)	0.42
Pneumonia	2 (5.26)	2 (3.39)	0.65
Pyelonephritis	0 (0.00)	0 (0.00)	…
Septic Arthritis	0 (0.00)	1 (1.69)	0.42
Osteomyelitis	2 (5.26)	3 (5.08)	0.96
Bacteremia	4 (10.53)	8 (13.56)	0.65
Anti-TNF Drugs			
Biologics 90 days Before Index	5 (13.16)	14 (23.73)	0.20
Biologics Anytime Before Index	7 (18.42)	22 (37.29)	0.07
Concomitant Medication*			
Methotrexate within 30 days			
Prednisone within 30 days	7 (18.42)	13 (22.03)	0.66
Prednisone 6 mo. prior	22 (57.89)	29 (49.15)	0.40
Azathioprine within 30 days	23 (60.53)	33 (55.93)	0.65
Leflunomide within 30 days	1 (2.63)	2 (3.39)	0.83
Hydroxychlorquine within 30 days	2 (5.26)	5 (8.47)	0.55
Sulfasalazine within 30 days	10 (26.32)	13 (22.03)	0.63
	2 (5.26)	4 (6.78)	0.76
Antibiotic use 90 days prior	36 (94.74)	50 (84.95)	0.13

Covariate analysis:

Univariate analysis of important covariates was conducted to determine which variables met the criteria for inclusion in the multivariate model. Variables with a univariate p-value $\leq$ 0.25 or known clinical importance were selected for the multivariate model. The results of the univariate analysis of demographic covariates are presented in Table 5.

Age was evaluated as a categorical variable, and to ensure that categorization did not change the significance of this clinically important covariate, age was also evaluated as a continuous variable. Among the demographic variables considered for inclusion in the model, death during the study period was not significantly associated with serious skin and soft tissue infection. Although the variable death during the study period met the univariate inclusion criteria for consideration in the model by having a p-value < 0.25, the odds of having developed a serious skin and soft tissue infection during the study period for patients who subsequently died during the study period compared to patients who did not die during the study period was not statistically significant at the $\alpha \leq 0.05$ statistical significance level. Additionally, because the cause of death was unobtainable this variable was of uncertain clinical meaningfulness and therefore was not included in the multivariate model (OR 1.051, 95% Confidence Interval: .808, 1.693, p = .19).

Co-morbidities were also analyzed at the univariate level to determine if they met the inclusion criteria of having a p-value $\leq$ 0.25 (Table 6). Among the co-morbidities evaluated, only diabetes, chronic kidney disease, chronic

bronchitis and prior history of skin infection met the univariate level for inclusion in the multivariate model. In the univariate analysis the odds of cases with a serious skin infection having diabetes were 2.5 times the odds of controls having diabetes (95% CI: 1.528, 4.134, $p \leq .0001$). The univariate odds ratio for chronic kidney disease was 4.5 (95% CI: 1.981, 10.487, $p < .0001$) and the odds ratio for chronic bronchitis was 2.1 (95% CI: 1.327, 3.429, $p = .10$). Having a prior history of skin infection was also significantly associated with development serious skin and soft tissue infections. (OR: 5.729, 95% CI: 2.870, 11.434, $p < .0001$).

The presence of additional inflammatory diseases including psoriasis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, uveitis, and psoriatic arthritis was assessed for univariate significance, but none met the inclusion criteria for univariate significance (Table 6). Serious bacterial infections were also evaluated for significance at the univariate level; there were no observed incidences of meningitis, encephalitis, and pyelonephritis in either the case or control groups and only one incidence of HIV (in a control) and one patient with endocarditis. As a proxy for severity of disease, the significance of having had more than 15 rheumatology clinic visits in the year prior to the index date was assessed and met the $\alpha \leq 0.25$ univariate inclusion criteria, however, the accuracy of this variable was suspect due to the excessive numbers of visits reported and it was ultimately not considered to be valid for inclusion in the model. (OR: 0.741, 95% CI: .450-1.223, $p = 0.24$).

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Table 5. Univariate Analysis: Demographic Variables

Variable	Case Frequency (Percent)	Control Frequency (Percent)	Odds Ratio	95% Confidence Interval	P-Value
Total	97	292			
Male	89 (91.75)	261 (89.38)	.757	0.330, 1.737	0.51
Age Group:					0.13
'24 to 49 year olds'	5 (5.15)	39 (13.36)	Referent	…	
'50 year olds and older'	92 (94.85)	253 (86.64)	2.707	0.999, 7.331	
Race					
WHITE	75 (80.65)	167 (66.80)	Referent	...	...
BLACK OR AFRICAN AMERICAN	1 (1.08)	14 (5.60)	.195	0.025, 1.534	0.12
OTHER/UNKNOWN, DECLINED	17 (17.52)	66 (22.60)	.67	0.365, 1.220	0.99
Death During Study Period	38 (39)	45 (15.41)	1.051	0.808, 1.693	0.19
Greater than 15 RA Clinic Visits	34	121	0.741	0.450, 1.223	0.24

Table 6. Univariate Analysis: Important Epidemiologic and Clinical Covariates

Variable	Case Frequency (Percent)	Control Frequency (Percent)	Odds Ratio	95% Confidence Interval	P-Value
Total	97	292			
Inflammatory Diseases					
Psoriasis	10 (10.31)	33 (11.30)	0.892	0.411, 1.934	0.77
Crohns †	3 (3.09)	3 (3.09)	2.805	0. 564, 13.962	0.21
Ulcerative Colitis †	3 (3.09)	4 (1.37)	2.121	0.473, 9.514	0.33
Ankylosing Spondylitis †	4 (4.12)	7 (2.40)	1.714	0.502, 5.86	0.39
Uveitis †	2 (2.06)	0 (0.00)	0.138	- ∞, 0.573	0.125
Psoriatic Arthritis †	3 (3.09)	15 (5.14)	0.590	0.168, 2.074	0.41
Co-morbidities					
Diabetes	36 (37.11)	53 (18.15)	2.514	1.528, 4.134	<.0001
Chronic Kidney Disease	15 (15.46)	11 (3.77)	4.558	1.981, 10.487	<.0001
Neoplasm	9 (9.28)	12 (4.11)	2.464	0.993, 6.116	0.5
Chronic Bronchitis	44 (45.36)	81 (27.74)	2.133	1.327, 3.429	0.010
Gastroesophageal Reflux	36 (37.11)	94 (32.19)	1.282	0.777, 2.114	0.33
HIV †	0 (0.00)	1 (0.34)	0.333	0.009, ∞	1.000
Prior History of Skin Infection	26 (26.80)	17 (5.82)	5.729	2.870, 11.434	<.0001
Discharge 3 Months Prior	14 (14.43)	20 (6.85)	2.245	1.098, 4.590	0.0267
Chronic Liver Disease †	2 (2.06)	0 (0.00)	0.167	-∞, 0.7732	0.1667
Other Bacterial Infections*					
Pneumonia †	4 (4.12)	1 (0.34)	12	1.341, 107.63	.03
Septic Arthritis †	1 (1.03)	1 (1.03)	.333	0.004, 26.166	.875

† Cell count less than 5, Exact analysis used

*No cases of meningitis, encephalitis & pyelonephritis; zero cell counts for endocarditis, osteomyelitis & bacteremia

Concomitant medications used by cases and controls were also evaluated for univariate significance and inclusion in the multivariate model. Reported in Table 7 are the results of the univariate analyses. Concomitant medication use was determined based on the presence in the records of an active and filled prescription for other drugs used to treat rheumatoid arthritis and included methotrexate, prednisone, azathioprine, leflunomide, hydroxychlorquine, and sulfasalazine prescribed for use within 30 days of the index date, as well as prednisone prescribed 6 months prior to the index date.

Antibiotic use 90 days prior to the index date was also examined at the univariate level for the inclusion criteria. Among the concomitant medications evaluated for an association with serious skin and soft tissue infections, only the use of prednisone within 30 days of the index date was significant for inclusion in the model at the $\alpha \leq 0.25$ univariate criteria level. The odds ratio for prednisone was 1.921 (95% CI: 1.206, 3.058, $p < .0001$). Among patients in the study, a higher proportion of cases were prescribed prednisone than controls, which may have contributed to the association seen (53% of cases and 37% of controls received prednisone).

The only other class of medication that was significantly associated with the development of serious skin and soft tissue infection was the use of antibiotics 90 days prior to the index date. The largest effect was seen for this covariate and the odds of having developed a SSSTI among patients exposed to antibiotics 90 days prior to the index date was 44.98 times the odds of developing SSSTI among patients who did not receive antibiotics 90 days prior

to the index date (95% CI: 16.41, 123.28, $p < .0001$). The interpretation of this large effect is hindered by the likelihood that prescriptions for antibiotics among cases may be more of an indicator of early treatment for serious skin and soft tissue infection than a true predictor for the odds of developing a serious skin and soft tissue infection. However, because the effect was so significant, multivariate models that included antibiotic use were built, in addition to those not including this covariate in order to compare the impact this variable had on the final model. In the end, because antibiotic use 90 days before the index date may have been related specifically to treatment for a serious skin and soft tissue infection, it was deemed not to be a viable or clinically relevant predictor of serious skin and soft tissue infections in this study and ultimately was not included in the model.

For our primary predictor of interest, a variety of types of anti-TNF drug use was evaluated, including the receipt of any biologic anytime during the study period and biologic use 90 days before the index date. Each biologic was also evaluated individually (Entercept, Infilixmab, and Adalimumab) and a combination of monoclonals only (Infilixmab and Adalimumab) were tested for statistical significance. Reported in Table 7 are the results of the univariate analysis of biologics. None of these covariates were found to be significantly associated with serious skin and soft tissue infection. (Biologics 90 days before index date $p = .74$, Biologics anytime before index date, $p = .23$, Entanercept, $p = .60$, Infliximab, $p = .85$, Adalimumab, $p = .41$, Monoclonals only, $p = .48$).

Table 7. Univariate Analysis: Medications

Variable	Case Frequency (Percent)	Control Frequency (Percent)	Odds Ratio	95% Confidence Interval	P-Value
Total	97	292			
Anti-TNF Drugs					
Biologics 90 days before index date	19 (19.59)	53 (18.15)	1.107	0.604, 2.028	.74
Biologics Anytime Before Index	29 (29.90)	70 (23.97)	1.388	0.815, 2.363	.23
ETANERCEPT Anytime Before Index	16 (16.49)	42 (14.38)	1.184	0.631, 2.22	.5981
INFLIXIMAB IV Anytime Before Index	3 (3.09)	13 (4.45)	0.857	0.178, 4.126	.8475
ADALIMUMAB Anytime Before Index	1 (1.03)	7 (2.40)	0.404	0.47, 3.462	.4083
Monoclonals Only: INFLIXIMAB/ ADALIMUMAB	7 (7.22)	14 (4.79)	0.633	0.178, 2.245	.4781
Concomitant Medications					
Methotrexate within 30 days of index date	20 (20.62)	89 (30.48)	0.578	0.325, 1.029	0.06
Prednisone within 30 days of index date	51 (52.58)	107 (36.64)	1.921	1.206, 3.058	<.0001
Prednisone 6 mo. prior to index date	56 (57.73)	144 (49.32)	1.447	0.898, 2.334	0.13
Azathioprine within 30 days of index date	3 (3.09)	4 (1.37)	2.250	0.504, 10.053	0.29
Leflunomide within 30 days of index date	7 (7.22)	25 (8.56)	0.819	0.345, 1.940	0.65
Hydroxychlorquine within 30 days of index date	23 (23.71)	84 (28.77)	0.784	0.462, 1.330	0.36
Sulfasalazine within 30 days of index date	6 (6.19)	38 (13.01)	0.454	0.187, 1.104	0.08
Antibiotic use 90 days prior to index date	86 (88.66)	51 (17.47)	44.984	16.41, 123.28	<.0001

† Cell count less than 5, Exact Analysis Used

Interaction Terms

Because our predictor (the use of anti-TNF drugs) was not statistically significant, a number of potential interactions were assessed to determine if other covariates moderate the significance of anti-TNF drug use and concomitant medication use in the development of serious skin and soft tissue infections. These included interactions between biologic use and prednisone, antibiotics, age, and methotrexate, as well as interactions between monoclonals and prednisone, antibiotic, age, and methotrexate plus interactions with prednisone and age and prednisone use 6 months prior to the index date. (See Appendix C for a complete table of interactions). Of the interaction terms evaluated, only the use of biologics anytime before the index date*prednisone and the interaction of prednisone*age were statistically significant (*p*-values < 0.0001). Advanced age and prednisone use have been associated with increased risk for infection and may contribute to an interaction effect. These significant interaction terms were included in initial multivariate models but excluded from the final model because they did not meet the statistical significance level of $p \leq 0.05$ and did not improve the fit of the final model.

Table 8. Significant Interaction Terms

Variables	Ratio of Odds	95% Confidence Interval	P-Value
Biologics Anytime Before Index*Prednisone Prednisone*Age	0.6523 0.0091	-0.1037,1.4083 1.0021, 0161	<.0001 <.0001

Logistic Regression Modeling

Multivariate models were built to examine the association between anti-TNF drug use and serious skin and soft tissue infections. Only variables evaluated in the multivariate model that met the multivariate significance level of $\alpha \leq 0.05$ were deemed statistically significant.

Based on univariate comparison of cases and controls, diabetes, chronic kidney disease, chronic bronchitis, prior history of skin infection, pneumonia, discharge 3 months prior, prednisone use within 30 days of the index date and antibiotic use 90 days prior to the index date met the univariate inclusion criteria having a p- value ≤ 0.25 and were included in the initial multivariate model with the exception of the variable antibiotic use 90 days prior to the index date. Age and race were also included in the initial multivariate model to assess potential confounding given their clinical importance

Despite the large odds ratio and statistical significance, it was not possible to determine if the association between antibiotic use shortly before the diagnosis with serious skin and soft tissue was a clinically significant predictor of serious skin and soft tissue infections or merely indicative of active treatment for the infection, since the onset dates and the duration of the infection were not available in the patient records. As a result, this covariate was not used in the multivariate analysis. Similarly, the variable death during the study period met the univariate criteria for consideration in the model with a p-value less than 0.25 but the clinical meaningfulness of this variable was questionable without the

cause of death given the possibility that death could have been the result of the serious skin infection.

In the initial multivariate model, chronic kidney disease, chronic bronchitis, pneumonia, discharge 3 months prior, and prednisone use within 30 days of the index date were not significantly associated with serious skin and soft tissue infections ($p > .05$); these were excluded from the final model. Age and race were not statistically significant and also dropped in the final multivariate analysis. The remaining significant variables included diabetes (Odds ratio: 1.876, 95% CI: 1.045, 3.369, $p = .04$) and prior history of skin infection (Odds ratio: 3.980, 95% CI: 1.926, 8.225, $p = .02$) (Table 9).

The final multivariate model consisted of biologic use before the index date, diabetes, and prior history of skin infection (Table 10). Based on conditional logistic regression, anti-TNF drug use was not significantly associated with serious skin and soft tissue infection at the $\alpha = 0.05$ multivariate significance level ($p = .93$). Patients with diabetes were more likely to have serious skin and soft tissue infections, and the odds of having a serious skin and soft tissue infection among patients with diabetes were 2.4 times the odds of having an infection in patients who did not have diabetes (95% CI: 1.411, 4.064, $p = .001$). Having a prior history of skin infection was also highly associated with SSSTI. Patients with a prior history of skin infection had a 5.5 times the odds of having an SSSTI as patients without a prior history of skin infection (95% CI: 2.713, 11.229, $p < .0001$).

Table 9. Multivariate Analysis: Initial Model

Variable	Case N=97 Frequency (Percent)	Control N=292 Frequency (Percent)	CRUDE Odds Ratio (95% CI)	CRUDE P-value	ADJUSTED Odds Ratio (95% CI)	ADJUSTED P-value
Anti-TNF Drugs						
Biologics 90 days before index date	19 (19.59)	53 (18.15)	1.107 (0.604, 2.028)	0.74	1.35 (0.55, 2.300)	0.7127
Age Group:						0.3250
'24 to 49 year olds'	5 (5.15)	39 (13.36)	Referent	…	…	
'50 year olds and older'	92 (94.85)	253 (86.64)	2.707 (0.999, 7.331)	0.0502	.592 (0.208, 1.682)	
Race						
White	75 (80.65)	167 (66.80)	Referent	…	…	...
Black	1 (1.08)	14 (5.60)	0.195 (0.025, 1.534)	0.12	0.354 (0.030, 7.757)	0.4074
Other	17 (17.52)	66 (22.60)	0.670 (0.365, 1.220)	0.99	1.852 (0.561, 6.109)	0.3117
Co-morbidities						
Diabetes	36 (37.11)	53 (18.15)	2.514 (1.528,4.134)	0.77	1.876 (1.045, 3.369)	0.0352*
Chronic Kidney Disease	15 (15.46)	11 (3.77)	4.558 (1.981, 10.487)	<.0001	2.144 (0.823, 5.585)	0.1184
Chronic Bronchitis	44 (45.36)	81 (27.74)	2.133 (1.327,3.429)	0.010	1.589 (0.934, 2.702)	0.0875
Prior History of Skin Infection	26 (26.80)	17 (5.82)	5.729 (2.870, 11.434)	<.0001	3.980 1.926, 8.225	0.0002*
Other Serious Bacterial Infections						
Pneumonia	4 (4.12)	1 (0.34)	0.333 (0.00,13.00)	0.50	5.194 0.484, 55.772	0.1738
Discharge 3 months prior	14 (14.43)	20 (6.85)	2.245	0.027	1.663 0.730,3.787	0.2261
Concomitant Medications						
Prednisone	51 (52.58)	107 (36.64)	1.921	<.0001	1.510 (0.904,2.523)	0.1153

Statistically sign at alpha = 0. 05, Multivariate r-square= 0.1643 , AIC=297.066

Table 10. Multivariate Analysis: Final Model

Variable	Case N=97 Frequency (Percent)	Control N=292 Frequency (Percent)	CRUDE (Univariate) Odds Ratio (95% CI)	CRUDE (Univariate) P-value	ADJUSTED (Multivariate) Odds Ratio (95% CI)	ADJUSTED (Multivariate) P-value
Anti-TNF Drugs Biologics 90 days before index date	19 (19.59)	53 (18.15)	1.107 (0.604, 2.028)	0.74	1.030 (0.532, 1.996)	0.9292
Co-morbidities Diabetes	36 (37.11)	53 (18.15)	2.514 (1.528, 4.134)	<.0001	2.394 (1.411, 4.064)	0.0012*
Prior History of Skin Infection	26 (26.80)	17 (5.82)	5.729 (2.870, 11.434)	<.0001	5.520 (2.713,11.229)	<0.0001*

(*) Statistically significant at alpha = 0.05

Secondary analysis

After building the first model, an additional conditional multivariate logistic regression model was built using the original data but restricted to the period after 2004. The same procedures employed to build the first model were used determine if temporality in prescribing patterns changed the model, given that anti-TNF use did not become widespread until after 2004.

Univariate analysis indicated that only the covariates diabetes, chronic kidney disease, history of prior skin infection, antibiotic use 90 days prior to the index date, and death during the study period were significant at the alpha $\leq$ 0.25 level. Coefficients were evaluated and the data was compared to the results of the primary analysis and no risk factors associated with anti-TNF drug use or important covariates and demographics differed significantly among patients prior to the widespread prescription of anti-TNF drugs in 2004, with the exception of the slightly increased proportion of patients receiving anti-TNF drugs. Interactions were evaluated in the sub-analysis but no significant interactions were seen.

Anti-TNF drug use, concomitant medications and other co-morbidities did not meet the univariate inclusion criteria level of $\alpha \leq 0.25$. Using the same inclusion criteria as was used for the initial model, multivariate analysis was conducted and a multivariate regression model was built using variables that were significant in the univariate analysis. In this final model, only diabetes was significantly associated with SSSTI at the $\alpha = 0.05$ level (OR: 2.5, 95% CI: 2.129, 8.872, $p = .0004$).

Table 11. Multivariate Analysis: 2004-2008 Secondary Analysis Final Model

Variable	Case N=58 Frequency (Percent)	Control N=173 Frequency (Percent)	CRUDE (Univariate) Odds Ratio (95% CI)	CRUDE (Univariate) P-value	ADJUSTED (Multivariate) Odds Ratio (95% CI)	ADJUSTED (Multivariate) P-value
Anti-TNF Drugs Biologics 90 days before index date	13 (22.41)	37 (21.39)	1.081 (0.518, 2.256)	0.8350	1.019	.9529
Diabetes	24 (41.38)	25 (14.45)	4.347 (2.129, 8.872)	<0.0001	2.502	.0004*

(*) Statistically significant at alpha = 05, Multivariate r-square= .0872, AIC=257.382

DISCUSSION

The increasing trend in anti-TNF drug use to treat rheumatoid arthritis makes the investigation of the association of biologics with serious skin and soft tissue infections a clinically and epidemiologically important endeavor. Given the high rate of mortality and co-morbidities among patients in the Veterans Integrated Service Network, understanding risk factors for serious infections is of particular significance for this vulnerable patient cohort.

We evaluated data that spanned both a nine year period that included the years prior to wide-spread anti-TNF drugs as well as a sub-set of data that only included the years after biologics became commonly prescribed. We saw no significant association in our study between the use of anti-TNF drugs and serious skin and soft tissue infections. This finding may be due to the fact that an association is not present in this patient population because of unique characteristics in this cohort or that an association exists but is too small to detect.

In assessing the burden of disease in this cohort the prevalence of serious skin and soft tissue infections identified by our study was lower than reported by other studies of anti-TNF drug use and serious infections in rheumatoid arthritis patients. In our VA patient cohort approximately 2% of the RA patients were identified as having had a serious skin and soft tissue infection while other studies typically reported 6-7% of patients as having an infection. (Dixon, 2006; Favalli, 2009). Because the VA is an open system the possibility exists that

cases of serious skin and soft tissue infection could have been missed if patients sought care outside of the VA hospital network.

It is also important to note that in the VA patient population studied, anti-TNF drugs were prescribed less than 20% of the time, while in the general population as many as 40% of rheumatoid arthritis patients receive anti-TNF drug treatment. The prescribing patterns for anti-TNF treatment may be influenced by the high rates of co-morbidities present among these patients and by VA prescribing guidelines.

Additionally, other studies have reported a significant association with prednisone use as a risk factor for hospitalization for infection (Lane et al. 2010). In this multivariate analysis prednisone use was not statistically significant; however our study only evaluated the risk for serious skin and soft tissue infections resulting in hospitalization as opposed to evaluating all major types of infection which may have limited our power to detect an effect in this patient population.

In this patient cohort, significant predictors of serious skin and soft tissue infections included diabetes and having a prior history of skin infection. In the sub-analysis of data from 2004-2008, the only significant predictor was diabetes. The impact of these findings suggests that patients in the VA cohort with a history of prior skin infection or diabetes are at elevated risk for serious skin and soft tissue infections and hospitalization. The increased morbidity among cases indicates that intervention and careful monitoring of these patients may be important.

Strengths and Limitations

This case-control study is subject to limitations of bias and confounding consistent with this type of study design; the study design will not detect rare events and cannot directly measure risk, although the odds ratio does provide an estimate of the relative risk when the frequency of the outcome is small. Despite these limitations, our study has significant advantages beyond the usual benefits of low cost and time efficiency associated with hypothesis generating research using a case-control study. Because the VA hospital network (VISN 20) encompasses a patient database of thousands of subjects, we had a large study population to draw from and identified 97 cases of serious skin and soft tissue infections, giving our study adequate power to detect even a small effect. Preliminary power calculations based on having only two sets of controls indicated that in order to obtain 80% power to detect a 10% change at the $\alpha = 0.05$ level, the study would only need to consist of 58 cases and 116 controls while we were able to indentify 97 cases for our study who were matched to three sets of controls. Recent studies among non-VA patient demographic groups (mostly European and Canadian studies) found a two-fold or greater difference in risk of serious infections in RA patients taking anti-TNF drugs, we anticipated being able to detect a similarly large effect in the VA hospital patient population, although this association was not seen. However, it is important to note that we did not evaluate the risk for all types of serious infections in this study but focused solely on serious skin and soft tissue infections.

A sub-analysis of data including only the years from 2004 to 2008 was also conducted and mirrors the results of our initial analysis; however, lower rates of anti-TNF drug use in the VA patient population and a smaller sample size may have limited our ability to detect an effect even during the more recent time period.

A common concern when conducting a case-control study is the potential for sampling bias; however, this was minimized by sampling cases and controls in an identical manner and matching three control groups to one group of cases by index date and VA hospital site. All cases and controls in our study were generated and evaluated using identical criteria. A particular strength of our study is that the database is sufficiently large allowing for matching of more than one control to each case. To eliminate the potential for overmatching in the selection process, cases and controls were only matched on the month of the case's index date and site and all other important covariates were adjusted for statistically.

Another limitation of this research is the potential for confounding by indication. Historically, RA patients with a greater severity of symptoms are more likely to be prescribed biologics, but also may be prone to having more serious infections. Because this relationship could potentially obscure our findings, the concern of confounding by indication was addressed by matching three sets of controls to each case by date and location and evaluating numerous factors related to the severity of a patient's RA. Analysis of indicators of RA severity such as the number of RA clinic visits, medication use, ESR and rheumatoid factors enabled us to mitigate the potential for confounding by indication by allowing for

a comparison of disease severity among subjects. The severity of rheumatoid arthritis was comparable between cases and controls indicating that they were sufficiently matched to minimize confounding by indication. Cases, however, had a higher incidence of co-morbidities as well as mortality, suggesting that overall they were in poorer health than controls.

Clinical practice patterns for medication use appear different within the VA network compared to other hospitals, and we saw less anti-TNF drug use than expected. This may be related to clinical considerations based on the high number of co-morbidities in this patient population. As a result, an effect may have been present but was too small to detect by this study. Additionally, it must be noted that not all serious skin and soft tissue infections experienced by this cohort may have been captured in the VA data if patients sought care outside of the VA hospital network.

We anticipated a predominantly male cohort due to the skewed gender distribution of the VA hospital network patient demographic, and gender was not statistically significant when evaluated at the univariate level of alpha ≤ 0.25.

Despite these limitations, findings from this study should yield meaningful results, particularly among immunosuppressed rheumatoid arthritis patient groups within the immense VA hospital network, as well as other hospital networks, and may provide valuable clinical guidance in the ongoing treatment of RA patients.

Future Research

Based on previous studies in other patient populations, we estimated that our study would reveal at least a two-fold greater risk of serious skin and soft tissue infections among VA hospital rheumatoid arthritis patients receiving anti-TNF drug therapy, yet we saw no significant association. The lower percentage of VA patients who received anti-TNF drug treatment and other factors such as severity of disease and demographic issues unique to the VA hospital population may contribute to this result.

The findings of our initial research on the risk of serious skin and soft tissue infection in this patient group suggest the need for further study. Expanding the study to include all VA hospital networks nationally may enhance the power of the study to detect even a small effect, if one is present, and would augment understanding of anti-TNF drug use and the potential risks for infections among VA patients.

Conducting future studies following this cohort prospectively would be beneficial to determine the prevalence and incidence rate of serious skin and soft tissue infections in this patient population. Lastly, further exploration of co-morbidities and the high mortality seen among patients with serious skin and soft tissue infections is warranted.

REFERENCES

1. Becker, J., and K.L. Winthrop. 2009. Update on rheumatic manifestations of infectious diseases. Curr Opin Rheumatol. Jan; 22(1):72-7.

2. Bland, J.M., and D.G. Altman. 1994. Matching. Bmj. 309:1128.

3. Bongartz, T., A.J. Sutton, M.J. Sweeting, I. Buchan, E.L. Matteson, and V. Montori. 2006. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. Jama. 295:2275-2285.

4. Bongartz, T., A.J. Sutton, M.J. Sweeting, I. Buchan, E.L. Matteson, and V. Montori. 2006. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. Jama. 295:2275-2285.

5. Chambers, H.F., R.C. Moellering, Jr., and P. Kamitsuka. 2008. Clinical decisions. Management of skin and soft-tissue infection. N Engl J Med. 359:1063-1067.

6. Curtis, J.R., N. Patkar, A. Xie, C. Martin, J.J. Allison, M. Saag, D. Shatin, and K.G. Saag. 2007. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. Arthritis Rheum. 56:1125-1133.

7. Dixon, W.G., K. Watson, M. Lunt, K.L. Hyrich, A.J. Silman, and D.P. Symmons. 2006. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving

anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 54:2368-2376.

8. Dryden, M. 2008. Complicated skin and soft tissue infections caused by methicillin-resistant Staphylococcus aureus: epidemiology, risk factors, and presentation. Surg Infect (Larchmt). 9 Suppl 1:s3-10.

9. Dryden, M.S. 2009. Skin and soft tissue infection: microbiology and epidemiology. Int J Antimicrob Agents. 34 Suppl 1:S2-7.

10. Edelsberg, J., C. Taneja, M. Zervos, N. Haque, C. Moore, K. Reyes, J. Spalding, J. Jiang, and G. Oster. 2009. Trends in US hospital admissions for skin and soft tissue infections. Emerg Infect Dis. 15:1516-1518.

11. Favalli, E.G., F. Desiati, F. Atzeni, P. Sarzi-Puttini, R. Caporali, F.B. Pallavicini, R. Gorla, M. Filippini, and A. Marchesoni. 2009. Serious infections during anti-TNFalpha treatment in rheumatoid arthritis patients. Autoimmun Rev. 8:266-273.

12. Furst, D.E., E.C. Keystone, B. Kirkham, A. Kavanaugh, R. Fleischmann, P. Mease, F.C. Breedveld, J.S. Smolen, J.R. Kalden, G.R. Burmester, J. Braun, P. Emery, K. Winthrop, B. Bresnihan, F. De Benedetti, T. Dorner, A. Gibofsky, M.H. Schiff, J. Sieper, N. Singer, P.L. Van Riel, M.E. Weinblatt, and M.H. Weisman. 2008. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2008. Ann Rheum Dis. 67 Suppl 3:iii2-25.

13. Furst, D.E. 2008. The Risk of Infections with Biologic Therapies for Rheumatoid Arthritis. Semin Arthritis Rheum. 2010 Apr;39(5):327-46. Epub 2008 Dec 31.

14. Hosmer, D.W. & Lemeshow, S. 2000. Applied logistic regression, 2nd edition. Wiley Interscience, New York.

15. Lane, M.A., McDonald, J, Zeringue, A. Caplan, L. 2010. TNF-α antagonist use and risk of hospitalization for infection in a national cohort of veterans with rheumatoid arthritis. Medicine. *In press.*

16. Liu, C., C.J. Graber, M. Karr, B.A. Diep, L. Basuino, B.S. Schwartz, M.C. Enright, S.J. O'Hanlon, J.C. Thomas, F. Perdreau-Remington, S. Gordon, H. Gunthorpe, R. Jacobs, P. Jensen, G. Leoung, J.S. Rumack, and H.F. Chambers. 2008. A population-based study of the incidence and molecular epidemiology of methicillin-resistant Staphylococcus aureus disease in San Francisco, 2004-2005. Clin Infect Dis. 46:1637-1646.

17. Marsh, J.L., J.L. Hutton, and K. Binks. 2002. Removal of radiation dose response effects: an example of over-matching. Bmj. 325:327-330.

18. NCSS. 2002. Power Analysis and Sample Size Statistical Software: PASS 2002. Kaysville, UT: NCSS, LLC.

19. SAS 9.2, Cary, NC: SAS Institute Inc., 2008.

20. Schneeweiss S, Robicsek A, Scranton R, Zuckerman D, Solomon DH. 2007. Veteran's affairs hospital discharge databases coded serious bacterial infections accurately. J Clin Epidemiol, 60:397-409.

21. Singh, J.A., Holmgren, A.R., Noorbaloochi, S. 2004. Accuracy of Veterans Administration data bases for a diagnosis of rheumatoid arthritis. Arthritis Rheum. Dec. 15; 51 (6); 952-7.

22. Winthrop, K.L. 2006. Serious infections with antirheumatic therapy: are biologicals worse? Ann Rheum Dis. 65 Suppl 3:iii54-57.

23. Winthrop, K.L., S. Yamashita, S.E. Beckmann, and P.M. Polgreen. 2008. Mycobacterial and other serious infections in patients receiving anti-tumor necrosis factor and other newly approved biologic therapies: case finding through the Emerging Infections Network. Clin Infect Dis. 46:1738-1740.

24. Winthrop, K.L., and T. Chiller. 2009. Preventing and treating biologic-associated opportunistic infections. Nat Rev Rheumatol. 5:405-410.

25. Winthrop, K.L., E. Chang, S. Yamashita, M.F. Iademarco, and P.A. LoBue. 2009. Nontuberculous mycobacteria infections and anti-tumor necrosis factor-alpha therapy. Emerg Infect Dis. 15:1556-1561.

APPENDIX A

Table 12. Variables Evaluated for Serious Skin and Soft Tissue Infection

Number	Variable	Variable Type	Response type	Data Label & additional information
1	Serious skin and soft tissue infection	Primary Outcome	Date Month of infection Year of infection Status Control =0 Case=1	Case_ControlID Validated VA Hospital discharge ICD-9 cm codes for hospitalized skin and soft tissue infection: Cellulitis, ICD-9 : 680.x, 681.x, 682.x (first infection during the study period)
2	Group D	Matched group identifier	Numeric	Group_ID_ Class variable for match cases and control, 1 to 3 match per group.
3	Research ID	De-indentified unique patient identifier	Numeric	ResearchID_
4	Site	Matching variable	531,648,648,653, 663,668	_Site_ VA facility number: Site ID number within the Veterans Integrated Service Network 20 locations
5	Discharge encounter Month	Covariate Descriptive variable, cases	Month	Discharge_encounterMonth
6	Discharge encounter Year	Covariate Descriptive variable, cases	Year	Discharge_encounterYear
Demographics & Descriptive Variables				
7	Index Date	Matching variable	Month, day, year	IndexDate Cases: Date of case first SSSTI Controls: Date of matched case SSSTI
8	Age on Index Date - Age groups	Covariate Demographic	Categorical 1='24 to 49 year olds' 2='50 and older'	Age__on_Index_Date_ Categorical design variable Cases: Age at date of case first SSSTI Controls: Age at date of matched case SSSTI
9	Age on Index date continuous	Covariate Demographic	Continuous	Age__continous_

Number	Variable	Variable Type	Response type	Data Label & additional information
10	Ethnicity	Covariate Demographic	Categorical 1='NOT HISPANIC' 2='HISPANIC' 3='UNKNOWN' 4='DECLINED TO ANSWER	Ethnicity
11	Race	Covariate Demographic	Categorical 1='WHITE' 2='BLACK OR AFRICAN AMERICAN' 3='OTHER' (HISPANIC , ASIAN, NATIVE HAWAIIAN OR PACIFIC ISLANDER' AMERICAN INDIAN ALASKA NATIVE' UNKNOWN, DECLINED TO ANSWER)	Race
12	Death During Study Period	Covariate Demographic	No=0 Yes=1	Death_During_Study_Period Death any time between
13	Gender	Covariate Demographic	Male=0 Female=1	Sex
14	More than 15 Rheumatology	Covariate Descriptive	No=0 Yes=1	More_than_15_ Rheumatology office visits 12 months prior to the case index date > 15
15	Number of Rheumatology Visits	Covariate Descriptive	Continuous	NumRheumVisits_continuous_ Number of Rheumatology office visits 12 months prior to the case index date

Number	Variable	Variable Type	Response type	Data Label & additional information
16	State	Covariate Demographic	Categorical 1='ALASKA' 2 ='ARIZONA' 3 ='CALIFORNIA' 4 ='GEORGIA' 5 ='IDAHO ' 6= 'ILLINOIS' 7= 'MAINE' 8= 'MICHIGAN' 9 ='MINNESOTA' 10= 'MISSOURI' 11= 'MONTANA' 12 = 'NEVADA' 13 ='NEW MEXICO' 14= 'NORTH CAROLINA' 15 ='OHIO' 16 ='OKLAHOMA' 17= 'OREGON' 18 ='PENNSYLVANIA' 19 ='SOUTH CAROLINA' 20='TEXAS' 21 ='UTAH' 22='WASHINGTON' 23 ='WYOMING';	State State of residence
Inflammatory Diseases				
17	Psoriasis	Covariate Co-morbidity	No=0 Yes=1	Psoriasis Evidence of additional inflammatory diseases
18	Crohns	Covariate Co-morbidity	No=0 Yes=1	Crohns Evidence of additional inflammatory diseases
19	Ulcerative Colitis	Covariate Co-morbidity	No=0 Yes=1	UlcerativeColitis Evidence of additional inflammatory diseases
20	Ankylosing Spondylitis	Covariate Co-morbidity	No=0 Yes=1	AnkylSpondylitis Evidence of additional inflammatory diseases

Number	Variable	Variable Type	Response type	Data Label & additional information
Inflammatory Diseases				
42	Uveitis	Covariate Co-morbidity	No=0 Yes=1	Uveitis Presence of important epidemiologic and clinical covariates prior to index date
43	PsoriaticArthritis	Covariate Co-morbidity	No=0 Yes=1	PsoriaticArthritis Presence of important epidemiologic and clinical covariates prior to index date
Concomitant Medications				
21	Methotrexate	Covariate Concomitant medication	No=0 Yes=1	Methotrexate Evidence of receipt of oral drugs in the outpatient or inpatient pharmacy database within 30 days before or after index date
22	Prednisone	Covariate Concomitant medication	No=0 Yes=1	Prednisone Evidence of receipt of oral drugs in the outpatient or inpatient pharmacy database within 30 days before or after index date
23	Azathioprine	Covariate Concomitant medication	No=0 Yes=1	Azathioprine Evidence of receipt o f oral drugs in the outpatient or inpatient pharmacy database within 30 days before or after index date
24	Leflunamide	Covariate Concomitant medication	No=0 Yes=1	Leflunamide Evidence of receipt o f oral drugs in the outpatient or inpatient pharmacy database within 30 days before or after index date
57	Hydroxychlorquine	Covariate Concomitant medication	No=0 Yes=1	Evidence of receipt o f oral drugs in the outpatient or inpatient pharmacy database within 30 days before or after index date
58	Sulfasalazine	Covariate Concomitant medication	No=0 Yes=1	Evidence of receipt o f oral drugs in the outpatient or inpatient pharmacy database within 30 days before or after index date

Number	Variable	Variable Type	Response type	Data Label & additional information
Co-morbidities				
25	Diabetes	Covariate Co-morbidity	No=0 Yes=1	Diabetes Presence of important epidemiologic and clinical covariates prior to index date
26	Chronic Kidney Disease	Covariate Co-morbidity	No=0 Yes=1	ChronicKidneyDisease Presence of important epidemiologic and clinical covariates prior to index date
27	Neoplasm	Covariate Co-morbidity	No=0 Yes=1	Neoplasm Presence of important epidemiologic and clinical covariates prior to index date
28	Chronic Bronchitis	Covariate Co-morbidity	No=0 Yes=1	ChronicBronchitis Presence of important epidemiologic and clinical covariates prior to index date
29	Gastroesophageal reflux disease	Covariate Co-morbidity	No=0 Yes=1	GRD Presence of important epidemiologic and clinical covariates prior to index date
30	HIV	Covariate Co-morbidity	No=0 Yes=1	HIV Presence of important epidemiologic and clinical covariates prior to index date
31	Prior History of Skin Infection	Covariate Co-morbidity	No=0 Yes=1	HxSkinInfection Skin or soft tissue infection diagnosis before January 1, 2000
32	Discharge 3 months Prior Index Date	Covariate	No=0 Yes=1	Discharge3moPrior Any hospital discharge 3 months prior to the index date
41	Chronic Liver Disease	Covariate Co-morbidity	No=0 Yes=1	ChronicLiverDisease Presence of important epidemiologic and clinical covariates prior to index date

Number	Variable	Variable Type	Response type	Data Label & additional information
Bacterial Infections				
33	Meningitis	Covariate Co-morbidity	No=0 Yes=1	Meningitis Other serious bacterial infections
34	Encephalitis	Covariate Co-morbidity	No=0 Yes=1	Encephalitis Other serious bacterial infections
35	Endocarditis	Covariate Co-morbidity	No=0 Yes=1	Endocarditis Other serious bacterial infections
36	Pneumonia	Covariate Co-morbidity	No=0 Yes=1	Pneumonia Other serious bacterial infections
37	Pyelonerphritis	Covariate Co-morbidity	No=0 Yes=1	Pyelonerphritis Other serious bacterial infections
38	Septic Arthritis	Covariate Co-morbidity	No=0 Yes=1	Septic_Arthritis Other serious bacterial infections
39	Osteomyelitis	Covariate Co-morbidity	No=0 Yes=1	Osteomyelitis Other serious bacterial infections
40	Bacteremia	Covariate Co-morbidity	No=0 Yes=1	Bacteremia Other serious bacterial infections
Medications				
47	Biologics 90 days before index date	Covariate Medication	No=0 Yes=1	ConcomitantBiologics90daysbeforeIndex Evidence of active receipt of 90 days before index date of: a. Infusion drugs (infusion database). Rituximab, Infliximab, Abatacept b. Injection drugs (outpatient pharmacy database). Adalimumab, Etanercept
48	Biologics Anytime Before Index	Covariate Medication	No=0 Yes=1	ConcomitantBioANYTIMEBeforeIndex Evidence of active receipt of biologics anytime from Jan. 1, 2000 to Dec. 31, 2008
49	Biologics Anytime Before Index Drug name	Covariate Medication	1='ENTANERCEPT' 2='INFLIXIMAB' 3='ADALIMUMAB'	Con_Bio_BEFORE_Index_Drug__des_ (des# Var) Evidence of use of infusion and injection drugs - all three biologics combined

Number	Variable	Variable Type	Response type	Data Label & additional information
50	ETANERCEPT	Covariate Medication	No=0 Yes=1	Con_Bio_BEFORE_Index_ETANERCEPT Individual drug
51	INFLIXIMAB	Covariate Medication	No=0 Yes=1	Con_Bio_BEFORE_Index_INFLIXIMAB_ Individual drug
52	ADALIMUMAB	Covariate Medication	No=0 Yes=1	Con_Bio_BEFORE_Index_ADALIMUMAB Individual drug
53	Monoclonals Only (Infliximab & Adalimumab)	Covariate Medication	No=0 Yes=1	monoclonals__infliximab_&_adal Infliximab & Adalimumab combined
54	Antibiotic use 90 days prior to index date	Covariate Medication	No=0 Yes=1	Antibiotic_use_90_days_prior_to_ Any evidence of antibiotic use 3 months prior to the index date
Disease Severity				
44	Erythrocyte sedimentation Rate	Covariate Laboratory value Disease severity	Continuous	ESR Erythrocyte sedimentation rate (rate obtained closest to the index date)
45	Rheumatoid Factor (RF)	Covariate Laboratory value Disease severity	Continuous	RheumFactor_Lab_Value_ Rheumatoid factor seropositivity (within the 12 months prior to case's index date)
46	Anti CCP antibodies	Covariate Laboratory value Disease severity	Continuous	Anti_CCP_antibodies_Lab_Value_
55	Number of Rheumatology visits 12 months prior to index date	Covariate Disease severity	Continuous	__of_Rheum_visits_12_mo_prior_in
56	Prednisone_6_month_prior_to_Inde	Covariate Medication Disease severity	No=0 Yes=1	Prednisone_6_month_prior_to_Inde Need for prednisone use- any prescriptions for prednisone filled 6 months prior to the index date

APPENDIX B

Table 13. Continuous Terms Evaluated

Variable	N=	Mean	Min	Max	Standard Deviation	95% Confidence Interval	P-Value
Age							
Case:	97	63.86	39.00	86.00	9.837	61.88, 65.84	0.13
Control:	292	61.81	25.00	88.00	12.19	60.88, 65.85	
Erythrocyte sedimentation Rate							
Case:	59	50.16	2	141	34.00	41.30, 59.03	<0.01
Control:	137	27.42	1	94	24.59	23.26, 31.57	
Rheumatoid Factor (RF)							
Case:	33	427.8	3.3	5141.0	996.9	74.37, 781.3	.54
Control:	97	302.9	3.6	9547.2	1019.5	97.40,508.3	
Anti CCP antibodies							
Case:	2	...	...	...	...		...
Control:	6	...	...	...	...		...
Number of Rheumatology visits 12 Months Prior To Index Date							
Case:	292	17.61	2.000	389.0	39.43	9.67, 25.56	.65
Control:	97	16.41	2.000	118.0	13.16	14.90, 17.93	

APPENDIX C

Table 14. Interaction Terms Evaluated

	Concomitant Biologics Any time Before Index	**Concomitant Biologics 90 days before**	**Monoclonals**	**Methotrexate**	**Prednisone**	**Prednisone 6 months prior**	**Age**
Concomitant Biologics anytime before Index				Biologics anytime *Methotrexate	Biologics anytime* Prednisone	Biologics anytime* Prednisone 6 months prior	Biologics anytime* Age
Concomitant Biologics 90 days before				Biologics 90 days before* Methotrexate	Biologics 90 days before* Prednisone	Biologics 90 days before* Prednisone 6 months prior	Biologics 90 days before *Age
Monoclonals				Monoclonals *Methotrexate	Monoclonals *Prednisone	Monoclonals* Prednisone 6 months prior	Monoclonals* Age
Methotrexate	Biologics anytime* Methotrexate	Methotrexate* Antibiotic use 90 days prior	Monoclonals *Methotrexate		Methotrexate * Prednisone	Methotrexate * Prednisone 6 months prior	Mexthotrexate* Age
Prednisone	Biologics anytime* Prednisone	Prednisone* Antibiotic use 90 days prior	Monoclonals *Prednisone	Methotrexate* Prednisone			Predisone* Age
Prednisone 6 month prior	Biologics anytime* Prednisone 6 month prior	Prednisone 6 month prior* Antibiotic use 90 days prior	Monoclonals *Prednisone 6 month prior	Prednisone 6 month prior* methotrexate			Prednisone 6 months prior*Age
Antibiotic use 90 days prior	Biologics anytime* Antibiotic use 90 days prior	Concomitant Biologics 90 days before* Antibiotic use 90 days prior	Antibiotic use 90 days prior	Methotrexate* Antibiotic use 90 days prior	Antibiotic use 90 days prior* Prednisone	Antibiotic use 90 days prior* Prednisone 6 months prior	Antibiotic use 90 days prior *Age
Age	Biologics anytime*Age	Concomitant Biologics 90 days before* Age	Monoclonals* Age	Methotrexate* Age	Prednisone *Age	Prednisone 6 months prior*age	

APPENDIX D

PROGRAMMER INSTRUCTIONS:

I. DEFINE RA COHORT:

Descriptive epidemiology of Serious Skin and Soft Tissue Infections (SSSTI's) occurring in patients using anti-TNF agents (etanercept, adalimumab, infliximab)

Please find all patients in the health plan with the following criteria:

(1) ICD-9 code for Rheumatoid arthritis (714) AND
(2) At least two RA/rheumatology clinical visit from the time-period of Jan. 1, 2000 to Dec. 31, 2008 AND
(3) At least one prescription for DMARDs (disease-modifying antirheumatic drugs) OR biologics during the study time period:
   i. Methotrexate (Rheumatrex® and Trexall®) [i]
   ii. Leflunomide (Arava®),
   iii. Sulfasalazine (Azulfidine®)
   iv. Hydroxychloroquine (Plaquenil®)
   v. Rituximab
   vi. Infliximab
   vii. Abatacept
   viii. Adalimumab
   ix. Etanercept
   x. Prednisone

II. DEFINE CASE COHORT:

1. Serious Skin and Soft Tissue Infection CASE (within the RA cohort):
Case finding criteria for Skin and Soft Tissue Infections (SSTI's).
The index date for a case is the first date of diagnosis with infection in the study time period.

Criteria for identifying Serious Skin and Soft Tissue Infection cases:

(1) Hospital discharge ICD-9 cm codes for hospitalized skin and soft tissue infection:
   - Cellulitis, ICD-9
      i. 680.x
      ii. 681.x [1]
      iii. 682.x
      iv. 686.x
      v. 040.0
      vi. 569.61
      vii. 681.xx
      viii. 785.4

[1] Blue denotes validated VA hospital discharge ICD-9cm codes/Schneeweiss; green denotes ICD-9cm codes/Curtis

ix. 728.86
x. 035

(if multiple, use first infection during the study period)

a) Construct Yes/No variable
b) First code date

2. Other Serious Bacterial Infection CASE (within the RA cohort):

Case finding criteria for other serious bacterial infections.
The index date for a case is the first date of diagnosis with infection in the study time period.

Criteria for identifying other serious bacterial infection cases:

(1) Hospital discharge ICD-9 cm codes for serious bacterial infections leading to hospitalization:

- Meningitis, ICD-9
  i. 320.x
  ii. 049.x
  iii. 003.21
  iv. 036.0
  v. 049.0
  vi. 091.81
  vii. 098.82
  viii. 320.xx

(if multiple, use first infection during the study period)

a) Construct Yes/No variable
b) First code date

- Encephalitis, ICD-9
  i. 323.x
  ii. 054.3
  iii. 036.1
  iv. 323.x
  v. 094.81
  vi. 054.3
  vii. 062
  viii. 064
  ix. 066.4

(if multiple, use first infection during the study period)

a) Construct Yes/No variable
b) First code date

- Endocarditis, ICD-9
  i. 421.x
  ii. 36.42
  iii. 093.2x
  iv. 98.84
  v. 391.1
  vi. 397.9
  vii. 421.x
  viii. 421.9

ix. 422.92

(if multiple, use first infection during the study period)

a) Construct Yes/No variable
b) First code date

- Pneumonia, ICD-9
  i. 481.x
  ii. 482.x
  iii. 003.22
  iv. 481.0
  v. 482.xx
  vi. 483.x
  vii. 485.x
  viii. 486.x
  ix. 513.0
  x. 480.x

(if multiple, use first infection during the study period)

a) Construct Yes/No variable
b) First code date

- Pyelonerphritis, ICD-9
  i. 590.x. (same code as Curtis)

(if multiple, use first infection during the study period)

a) Construct Yes/No variable
b) First code date

- Septic arthritis, ICD-9
  i. 711.0x
  ii. 049.x
  iii. 003.23
  iv. 056.71
  v. 711.9x
  vi. 098.5x

(if multiple, use first infection during the study period)

a) Construct Yes/No variable
b) First code date

- Osteomyelitis, ICD-9
  i. 730.0x
  ii. 730.1x
  iii. 730.2x (same codes as Curtis)
  iv. 003.24
  v. 526.4
  vi. 376.03

(if multiple, use first infection during the study period)

a) Construct Yes/No variable
b) First code date

- Bacteremia, ICD-9

i. 038.x
ii. 790.7. (same codes as Curtis)

(if multiple, use first infection during the study period)

a) Construct Yes/No variable
b) First code date

III. DESCRIPTIVE VARIABLES: (CASES ONLY)

(1) Age (at index date; the date of discharge ICD-9)
(2) Race
(3) Ethnicity
(4) Sex
(5) Number of rheumatology visits over study time period (Jan. 1, 2000 to Dec. 31, 2008)
(6) State of Residence
(7) VA facility number
(8) Any evidence of additional inflammatory diseases prior to the index date (Construct yes/no variable for the conditions and associated ICD-9 codes:)
   i. Psoriasis (696.0, 696.1),
   ii. Crohn's disease (555),
   iii. Ulcerative Colitis (556),
   iv. Ankylosing spondylitis (720.0).

(9) Presence of important epidemiologic and clinical covariates prior to index date: (Construct yes/no variable for the additional conditions and associated ICD-codes:)
   i. Diabetes Mellitus (250)
   ii. Chronic Kidney Disease (585)
   iii. Neoplasm (200-208, 195, 196, 162)
   iv. Chronic bronchitis, asthma, bronchiectasis, silicosis (491, 492, 493, 494, 495, 496, 502)
   v. Gastroesophageal reflux disease (530.81, 530.11)
   vi. HIV (042-044)

(10) History of skin or soft tissue infection diagnosis before January 1, 2000: ICD-9 code 680-686 and date code given
(11) All English Speaking
(12) Living conditions: Institutionalized or nursing home six months prior to diagnosis of infection
(13) Any evidence of antibiotic use 3 months prior to the index date (Construct yes/no variable)
(14) Any hospital discharge 3 months prior to the index date s (Construct yes/no variable and include discharge date)
(15) Any of the following ICD9 codes 3 months prior to the index date
   a. Meningitis, ICD-9
      i. 320.x
      ii. 049.x

iii. 003.21
iv. 036.0
v. 049.0
vi. 091.81
vii. 098.82
viii. 320.xx
a) Construct Yes/No variable
b) First code date

b. Encephalitis, ICD-9
i. 323.x
ii. 054.3
iii. 036.1
iv. 323.x
v. 094.81
vi. 054.3
vii. 062
viii. 064
ix. 066.4
a) Construct Yes/No variable
b) First code date

c. Endocarditis, ICD-9
i. 421.x
ii. 36.42
iii. 093.2x
iv. 98.84
v. 391.1
vi. 397.9
vii. 421.x
viii. 421.9
ix. 422.92
1. Construct Yes/No variable
2. First code date

d. Pneumonia, ICD-9
i. 481.x
ii. 482.x
iii. 003.22
iv. 481.0
v. 482.xx
vi. 483.x
vii. 485.x
viii. 486.x
ix. 513.0
x. 480.x
1. Construct Yes/No variable
2. First code date

e. Pyelonerphritis, ICD-9
i. 590.x.
1. Construct Yes/No variable

2. First code date

f. Septic arthritis, ICD-9
   i. 711.0x
   ii. 049.x
   iii. 003.23
   iv. 056.71
   v. 711.9x
   vi. 098.5x
      1. Construct Yes/No variable
      2. First code date

g. Osteomyelitis, ICD-9
   i. 730.0x
   ii. 730.1x
   iii. 730.2x
   iv. 003.24
   v. 526.4
   vi. 376.03
      1. Construct Yes/No variable
      2. First code date

h. Bacteremia, ICD-9
   i. 038.x
   ii. 790.7.
      1. Construct Yes/No variable
      2. First code date

IV. DETERMINATION OF DISEASE SEVERITY:

(1) Number of Rheumatology office visits 12 months prior to the case index date

(2) Please collect the following labs to monitor disease severity (within the 12 months prior to index date):

a. Erythrocyte sedimentation rate (rate obtained closest to the index date)
b. Anti-CCP antibodies (Construct yes/no variable)
c. Rheumatoid factor seropositivity (Construct yes/no variable)
d. Presence of erosions on radiographs (Construct yes/no variable)
e. Presence of nodules in subcutaneous tissue under the skin (Construct yes/no variable)
f. Presence of extra-articular RA manifestations ICD-9 code: 714.2 (such as ILD)
   (Construct yes/no variable)
g. Need for prednisone use- any prescriptions for prednisone filled 6 months prior to the index date:
   a. Construct yes/no variable
   b. date of each prescription
   c. total mg. dispensed

V. ADDITIONAL DESCRIPTIVE DATA:

(to be collected for Skin and Soft Tissue Infection CASES ONLY)

(1) Death during study time-period (yes/no). Calculate days between index date and death if applicable.

(2) Concomitant medications: look for evidence of active receipt of the following oral drugs in the outpatient or inpatient pharmacy database within 30 days before or after index date (create yes/no variable)

a. Methotrexate
b. Prednisone (also record dosage at prescription closest in time prior to the index date)
c. Azathioprine
d. Leflunomide

(4) Number of doses during the study period of each drug. Start time would be date of first prescription (or infusion for infliximab).

(5) Concomitant biologics. Look for evidence of active receipt of the following within 90 days before index date (create yes/no variable). If receipt is anytime after diagnosis date, please collect date of first Rx after index date, drug name, and supply.

a. Infusion drugs (infusion database).
Rituximab, Infliximab, Abatacept
b. Injection drugs (outpatient pharmacy database).
Adalimumab, Etanercept

(6) For Skin and Soft Tissue Infection cases, calculate number of anti-TNF drug doses during the study time-period given prior to diagnosis date.

(7) Culture

Any positive bacterial or fungal or mycobacterial culture (s) ± 90 of diagnosis date:

Other data to include:

1. Culture site
2. Species isolated
3. culture dates

I. CONTROL SELECTION AND MATCHING:

Using the same RA cohort as the cases, please randomly select three controls- all members of the RA cohort not identified as a case. Index date for the controls is the nearest RA visit in the same month (and year) as the case's index date. Controls should be matched to each case by month of rheumatology visit and VA facility number.

II. DESCRIPTIVE VARIABLES: (CONTROLS)

(1) Age (at the time the most recent RA clinic visit)
(2) Race
(3) Ethnicity
(4) Sex
(5) Number of rheumatology visits over study time period (Jan. 1, 2000 to Dec. 31, 2008)
(6) State of Residence
(7) VA facility number
(8) Any evidence of inflammatory disease during before index date:
(Construct yes/no variable for the conditions and associated ICD-codes:)
   i. Psoriasis (696.0, 696.1),
   ii. Crohn's disease (555),
   iii. Ulcerative Colitis (556),
   iv. Ankylosing spondylitis (720.0).

(9) Concomitant medications: look for evidence of active receipt of the following oral drugs in the outpatient or inpatient pharmacy database within 30 days before or after the case's index date (create yes/no variable)

   a. Methotrexate
   b. Prednisone (also record dosage at prescription closest in time to the case's index date)
   c. Azathioprine
   d. Leflunomide

(10) Concomitant biologics. Look for evidence of active receipt of the following within 90 days before case's diagnosis date (create yes/no variable). If receipt is anytime before the case's index date, please collect date of first Rx after index date, drug name, and supply.

Infusion drugs (infusion database).
   a. Rituximab, Infliximab, Abatacept

Injection drugs (outpatient pharmacy database).
   b. Adalimumab, Etanercept

(11) Number of doses during the study period of each drug. Start time would be date of first prescription (or infusion for infliximab).

(12) Presence of important epidemiologic and clinical covariates prior to index date:
   i. (Construct yes/no variable for the additional conditions and associated ICD-9 codes:)
   ii. Diabetes Mellitus (250)
   iii. Chronic Kidney Disease (585)
   iv. Neoplasm (200-208, 195, 196, 162)

v. Chronic bronchitis, asthma, bronchiectasis, silicosis (491, 492, 493, 494, 495, 496, 502)
vi. Gastroesophageal reflux disease (530.81, 530.11)
vii. HIV (042-044)

(13) History of latent skin or soft tissue infection diagnosis before January, 2000:
ICD-9 code 680-686 and date code given

(14) Primary language preference (or place of birth if available)

(15) Living conditions: Institutionalized or nursing home six months prior case's index
(Construct yes/no variable)

(16) Death during study time-period (Construct yes/no variable).

(17) Any evidence of antibiotic use 3 months prior to the index date (Construct yes/no variable)

(18) Any hospital discharge 3 months prior to the index date s (Construct yes/no variable and include discharge date)

(19) Any of the following ICD9 codes 3 months prior to the index date

i. Meningitis, ICD-9
   i. 320.x
   ii. 049.x
   iii. 003.21
   iv. 036.0
   v. 049.0
   vi. 091.81
   vii. 098.82
   viii. 320.xx
      a) Construct Yes/No variable
      b) First code date

j. Encephalitis, ICD-9
   i. 323.x
   ii. 054.3
   iii. 036.1
   iv. 323.x
   v. 094.81
   vi. 054.3
   vii. 062
   viii. 064
   ix. 066.4
      a) Construct Yes/No variable
      b) First code date

k. Endocarditis, ICD-9
   i. 421.x
   ii. 36.42
   iii. 093.2x
   iv. 98.84
   v. 391.1
   vi. 397.9
   vii. 421.x
   viii. 421.9

ix. 422.92
    1. Construct Yes/No variable
    2. First code date

l. Pneumonia, ICD-9
    i. 481.x
    ii. 482.x
    iii. 003.22
    iv. 481.0
    v. 482.xx
    vi. 483.x
    vii. 485.x
    viii. 486.x
    ix. 513.0
    x. 480.x
        1. Construct Yes/No variable
        2. First code date

m. Pyelonerphritis, ICD-9
    i. 590.x.
        1. Construct Yes/No variable
        2. First code date

n. Septic arthritis, ICD-9
    i. 711.0x
    ii. 049.x
    iii. 003.23
    iv. 056.71
    v. 711.9x
    vi. 098.5x
        1. Construct Yes/No variable
        2. First code date

o. Osteomyelitis, ICD-9
    i. 730.0x
    ii. 730.1x
    iii. 730.2x
    iv. 003.24
    v. 526.4
    vi. 376.03
        1. Construct Yes/No variable
        2. First code date

p. Bacteremia, ICD-9
    i. 038.x
    ii. 790.7.
        1. Construct Yes/No variable
        2. First code date

III. DETERMINATION OF DISEASE SEVERITY:

(1) Number of Rheumatology office visits 12 months prior to the case index date

(2) Please collect the following labs and test results to monitor disease severity (within the 12 months prior to case's index date):

i. Erythrocyte sedimentation rate (rate obtained closest to the index date)
ii. Anti-CCP antibodies (Construct yes/no variable)
iii. Rheumatoid factor seropositivity (Construct yes/no variable)
iv. Presence of erosions on radiographs (Construct yes/no variable)
v. Presence of nodules in subcutaneous tissue under the skin (Construct yes/no variable)
vi. Presence of extra-articular RA manifestations ICD-9 code: 714.2 (such as ILD)
vii. (Construct yes/no variable)
viii. Need for prednisone use- any prescriptions for prednisone filled 6 months prior to the index date.:
   a. Construct yes/no variable
   b. date of each prescription
   c. total mg. dispensed

[i] http://www.ddw-online.com/therapeutics/205490/treating_rheumatoid_arthritis_with_dmards_and_biologics.html