Published in final edited form as:
Ann Rheum Dis. 2014 November ; 73(11): 1942–1948. doi:10.1136/annrheumdis-2013-203407.

Non-viral Opportunistic Infections in New Users of TNF Inhibitor Therapy: Results of the SAfety Assessment of Biologic ThERapy (SABER) Study

John W. Baddley, MD, MSPH[1,2,*], **Kevin L. Winthrop, MD, MPH**[3,*], **Lang Chen, PhD**[1], **Liyan Liu, MD, MsC**[4], **Carlos G Grijalva, MD, MPH**[5], **Elizabeth Delzell, ScD**[1], **Timothy Beukelman, MD, MSCE**[1], **Nivedita M. Patkar, MD, MSPH**[1], **Fenglong Xie, MS**[1], **Kenneth G. Saag, MD, MSc**[1], **Lisa J. Herrinton, PhD**[4], **Daniel H. Solomon, MD, MPH**[6], **James D. Lewis, MD, MSCE**[7], and **Jeffrey R. Curtis, MD, MS, MPH**[1]

[1]University of Alabama at Birmingham, Department of Medicine, Birmingham, Alabama, USA

[2]Birmingham VA Medical Center, Medical Service, Birmingham, Alabama, USA

[3]Oregon Health and Science University, Department of Medicine, Portland, Oregon;, USA

[4]Kaiser Permanente Northern California, Division of Research, Oakland, California, USA

[5]Vanderbilt University, Department of Medicine, Nashville, Tennessee, USA

[6]Brigham and Women's Hospital-Harvard University, Department of MedicineBoston, United States

[7]Center for Clinical Epidemiology and Biostatistics, Perlman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA

Abstract

Objectives—To determine among patients with autoimmune diseases in the United States whether the risk of non-viral opportunistic infections (OIs) was increased among new users of tumor necrosis factor-alpha inhibitors (TNFI), when compared to users of non-biologic agents used for active disease.

Corresponding author:John W. Baddley, MD, MSPH, University of Alabama at Birmingham, Department of Medicine, Division of Infectious Diseases, 1900 University Boulevard, 229 Tinsley Harrison Tower, Birmingham, AL 35294-0006. Phone: 1-(205) 934-5191 ; Fax: 1-(205) 934-5155 ; jbaddley@uab.edu.
*Designates co-primary first authors

Competing Interest
Other authors: competing interests- none declared.

Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Food and Drug Administration or the Agency for Healthcare Research and Quality.

Previous Presentation: This work was presented in part at the 49th Infectious Diseases Society of America Annual Meeting, October 2011, Boston, Massachusetts

Methods—We identified new users of TNFI among cohorts of rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and psoriasis-psoriatic arthritis-ankylosing spondylitis (PsO-PsA-AS) patients during 1998–2007 using combined data from Kaiser Permanente Northern California, two pharmaceutical assistance programs for the elderly, Tennessee Medicaid, and US Medicaid/Medicare programs. We compared incidence of non-viral OIs among new TNFI users and patients initiating non-biologic disease modifying drugs (DMARDs) overall and within each disease cohort. Cox regression models were used to compare propensity-score and steroid-adjusted OI incidence between new TNFI and non-biologic DMARD users.

Results—Within a cohort of 33,324 new TNFI users we identified 80 non-viral OIs, the most common of which was pneumocystosis (n=16). In the combined cohort, crude rates of non-viral OIs among new users of TNFI as compared to those initiating non-biologic DMARDs was 2.7 verus 1.7 per 1000-person years[adjusted hazard ratio (aHR): 1.6, 95% CI: 1.0, 2.6)]. Baseline corticosteroid use was associated with non-viral OIs (aHR 2.5, 95% CI: 1.5, 4.0). In the RA cohort, rates of non-viral OIs among new users of infliximab were higher when compared to patients newly starting non-biologic DMARDs (aHR 2.6, 95% CI 1.2, 5.6) or new etanercept users (aHR 2.9, 95% CI: 1.5, 5.4).

Conclusions—In the US, the rate of non-viral OIs was higher among new users of TNFI with autoimmune diseases as compared to non-biologic DMARD users.

Keywords

opportunistic infection; tumor necrosis factor-alpha; *Pneumocystis*; tuberculosis; rheumatoid arthritis

Introduction

Biologic immunosuppressive therapies such as tumor necrosis factor-alpha (TNF-α) inhibitors (TNFI) represent important treatment advances for patients with rheumatoid arthritis (RA) and a number of other inflammatory conditions. Although these drugs have revolutionized the treatment of inflammatory and rheumatologic disorders, there is an important safety issue: a potential increased risk of infection caused by a broad spectrum of organisms. [1–5]

Infectious complications of biologic medical therapies are often sub-grouped into severe or opportunistic. We and others have demonstrated that at least some TNFI are associated with an increased risk of serious infections compared to non-biologic therapies. [1,2,4,6] Additional reports suggest a possible increased risk of opportunistic infections (OIs), including diseases such as tuberculosis and systemic mycoses, legionellosis and progressive multifocal encephalopathy, among patients treated with TNFI.[7–12] It remains difficult to ascertain the magnitude and significance of the risk because of the rarity of infections and variability in groups under study. For example, a recent report from the French registry estimated the annual sex and age-adjusted incidence rates of all non-mycobacterial opportunistic infections to be 1.52 per 1000 person years.[5] In contrast, a rate of opportunistic infections (herpes zoster and tuberculosis included) of 30 per 1000 person-years among patients using TNFI was estimated with data from the CORRONA registry.

[13] These studies differed in methodologies, grouping of infectious outcomes, comparator groups and patient populations (RA versus all TNF indications). In addition, most analyses have focused on prevalent, not new users. Therefore, questions remain about the impact of specific TNF agents versus non-biologic therapy and risk of infection associated with TNFI for patients with autoimmune diseases other than RA.

As part of a multi-institutional U.S. initiative, the Safety Assessment of Biologic Therapy (SABER) project, we investigated among patients with RA and other autoimmune or inflammatory diseases whether the risk of non-viral opportunistic infections was increased among new users of TNFI, when compared to new users of non-biologic agents.

METHODS

This retrospective cohort study combined data from 1998 through 2007 from four large US data systems. [14] Exposure to TNFI and other disease-modifying antirheumatic drugs (DMARDs) was determined using pharmacy files and procedure codes (for infusions). Opportunistic infections (OIs) were identified using hospital and outpatient diagnoses. The incidence of OIs between exposure groups was compared using Cox proportional hazard regression models.

Cohort Assembly

Data from four data systems [National Medicaid (MAX) and dual Medicaid-Medicare databases; TennCare; The New Jersey's Pharmaceutical Assistance to the Aged and Disabled (PAAD) and the Pennsylvania's Pharmaceutical Assistance Contract for the Elderly (PACE) programs linked to Medicare data; and Kaiser Permanente Northern California (KPNC)] and a common data model were used to assemble the cohort of patients with who were new users of selected biologic and non-biologic DMARDs. [14] Within each data system, patients with autoimmune diseases were identified as those with an International Classification of Diseases, 9th edition, clinical modification (ICD9-CM)-coded healthcare encounter for an autoimmune disease followed by a prescription filled for, or infusion of, a study DMARD. We required availability of a baseline period of 365 days with continuous enrollment in the respective data system preceding the first qualifying new drug prescription fill or infusion (described below), for ascertainment of study covariates.

Patients were categorized in three mutually exclusive autoimmune disease groups: rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and psoriasis (PsO), psoriatic arthritis (PsA) and ankylosing spondylitis (AS), PsO-PsA-AS. Within the pool of potential cohort members, we identified new users of study medications, defined as having filled one prescription or infusion for a study DMARD after 365 baseline days without prescriptions filled for the specific study medication(s). This "first" filling or infusion date was termed the time zero and marked the beginning of follow-up. Potential RA cohort members were further required to be aged ≥16 years.

Within each cohort, an episode of new medication use began on t0 and follow-up continued through the earliest of the following: death, loss of enrollment, study outcome, switch to a new DMARD regimen, or discontinuation of current regimen (defined as 30 days without

medication). Patients could contribute additional episodes of new medication use for a different medication (in the same or alternate exposure group) if they fulfilled the eligibility criteria again.

Medication Exposures

Claims data on pharmacy prescription fills and infusions were used to determine medication exposure following a new user design. Study DMARDs were classified in two groups: TNFI (including infliximab, adalimumab and etanercept [not included for IBD]); and, alternate non-biologic DMARD regimens. For RA, alternative regimens were initiation of leflunomide, sulfasalazine or hydroxychloroquine after use of methotrexate in the previous year (i.e. methotrexate failures); whereas for IBD, the comparison group was initiation of azathioprine or 6-mercaptopurine (AZA/6-MP). For PsO-PsA-AS the comparison was initiation of non biologic DMARDs (methotrexate, hydroxychloroquine, sulfasalazine and leflunomide).

For all groups, exposed person-time encompassed all follow-up person-time covered by prescription fills (and using 56 days for infliximab) and an additional 30 person-days without subsequent medication available. This 30-day grace period was allowed because some residual effects of study medications could extend beyond the last day of use and to account for imperfect adherence. Thus, this approach allowed a short gap in which outcomes identified after drug supply exhaustion could be related to the most recent exposure. Both TNFI and the non biologic DMARD regimens allowed the concurrent use (continuation or addition) of methotrexate. Analyses of IBD allowed for continuation of or simultaneous initiation of AZA/6-MP in the TNFI group.

Outcomes

The primary outcome was non-viral OIs. Additional analyses were performed for the sub-groups of tuberculosis (TB) and non-tuberculous mycobacterial (NTM) disease patients. For fungal infections, we used primary or non-primary discharge diagnoses or an outpatient diagnosis for histoplasmosis, coccidioidomycosis, cryptococcosis, blastomycosis, or aspergillosis plus an outpatient prescription for at least 30 days of any active systemic antifungal drug (itraconazole, fluconazole, voriconazole).[15] Tuberculosis required an inpatient or outpatient ICD-9 diagnosis code (018.x) plus pharmacy records indicating prescription for pyrazinamide prescribed with 90 days of the diagnosis code. Diagnosis of other non-viral OIs (pneumocystosis, nocardiosis/actinomycosis, non-tuberculous mycobacteria, salmonellosis, listeriosis, legionellosis) required an inpatient or outpatient physician ICD-9 diagnosis code without concomitant anti-infective medication.

Study Covariates

Baseline covariates were measured, including demographics: age, gender, race, residence (urban and rural), nursing home/community dwelling, median area income, calendar year; generic markers of co-morbidity: number of hospitalizations, outpatient and emergency room visits, medication classes filled during baseline; markers of disease severity (extra-articular manifestations of disease, number of intra-articular and orthopedic procedures), number of laboratory tests ordered for inflammatory markers, baseline use of DMARDs;

previous hospitalization due to infection, chronic obstructive pulmonary disease (COPD), diabetes and previous use of antibiotics.

Baseline use of oral glucocorticoids was categorized according to the estimated average daily dose of prednisone equivalents [none, >0-<5 (low dose), 5–10 (medium dose) and >10 mg (high dose] averaged in the 6 months prior to time zero. This covariate was not included in the propensity score so as to be able to estimate its association with infection in outcome models.

Statistical analysis

The effects of potential confounders were controlled for using propensity score (PS) quintiles and baseline corticosteroid use within the past year prior to drug exposure. Covariates included in the PS derivation can be found in online supplemental Table S1. Within each of the four data systems, logistic regression models estimated the site-specific PS for each episode of use within each study disease. A single value summarized covariate information for each medication episode. [14] Visual inspection of the distribution of predicted probabilities across exposure groups showed substantial overlap of PS distributions, indicating that identification of patients with similar covariate distributions for each comparison was feasible. Non-overlapping regions (approximately 1%, 4% and 8% of RA, IBD and Ps-PSO-AS patients, respectively) of the PS were trimmed within each data system.

Cox-proportional hazard regression models assessed the association between exposure groups and study outcomes, with stratification by study site to allow the baseline hazard to vary. Within the RA cohort we evaluated the risk of OIs associated with individual biologic therapies, specifically infliximab and adalimumab (using etanercept as referent). Because patients could contribute more than one treatment episode, standard errors were adjusted using the Huber-White sandwich estimator. The final disease-specific outcome models for the overall cohort and the RA cohort evaluating specific TNFIs included exposure groups, adjustment for PS quintile and baseline glucocorticoid use one year prior to time zero. All analyses were performed in SAS 9.13. This study was approved by the Institutional Review Board of Vanderbilt University, Kaiser Permanente, Brigham and Women hospital, the University of Pennsylvania, and the University of Alabama at Birmingham.

RESULTS

Cohort assembly and baseline characteristics

We identified 407,319 potentially eligible patients with autoimmune diseases in the respective study databases, of which 170,788 (42%) patients were excluded due to having more than one autoimmune disease or autoimmune diseases other than RA, IBD, PsO, PsA or AS. We identified 36,212 (RA), 10,717 (IBD), and 12,137 (PsO-PsA-AS) patients who were either new-users of TNFI therapy or a comparator non-biologic DMARD. Within each disease group, baseline demographic and covariates were relatively similar between TNFI and non-biologic DMARD users (Table 1). The median (IQR) follow-up time in the TNFI and non-biologic groups was 170 (299) and 104 (166) days, respectively.

Opportunistic infections

Across all disease indications, we identified 107 OIs (80 in new TNFI users; Table 2). The most common were pneumocystosis (n=18) nocardiosis/actinomycosis (n=12) and tuberculosis (n=10; Table 2). Of these cases, 74 (69.1%) patients used corticosteroids at the time of the OI event, and 27 (25.2%) patients were receiving methotrexate. Among TNFI users, median time to infection post-initiation of TNFI was 131.5 days (range, 9-1503 days); fifty-six percent of patients who developed an OI did so within 6 months of TNFI initiation. In the combined disease cohort (including RA, IBD and PsO-PsA-AS) and for each specific disease cohort, crude OI incidence rates were higher among those starting TNFI therapy versus the comparator group. For the combined disease cohort, rates among TNFI versus comparator patients were 2.7 vs. 1.7 per 1,000 person years (aHR 1.6; 95% CI 1.0, 2.6; Table 3). Baseline glucocorticoid use was also associated with non-viral OIs (aHR 2.5, 95% CI: 1.5, 4.0).

Rheumatoid arthritis

Compared with non-biologic DMARD patients, the adjusted risk of non-viral OIs in RA patients was not increased significantly among new users of any TNFI (aHR: 1.6, 95% CI: 0.9–3.1; Table 3). Glucocorticoids had a borderline significant association with non-viral OIs (aHR 1.8; 95% CI: 1.0, 2.8). There were differences among specific TNFIs: infliximab, (aHR 2.6, 95% CI 1.2, 5.6) when compared with non-biologic DMARDs, was associated with an increased risk of non-viral OIs (Table 4). In comparisons between specific TNFI, infliximab initiation was associated with an increased risk of non-viral OIs when compared to etanercept (aHR 2.9, 95% CI: 1.5, 5.4).

In the mycobacterial analysis (Table 5) most cases occurred in TNFI users with a crude rate four times greater for tuberculosis in this stratum, although the difference did not reach statistical significance (aHR 4.2; 95% CI: 0.5, 33.5). Rates of NTM were similar between exposure groups (Table 5).

DISCUSSION

Within SABER, a United States multi-institutional research initiative, we studied rates and frequency of non-viral OIs among a large cohort of patients with selected autoimmune diseases. *Pneumocystis* and mycobacterial infections accounted for almost half of the OIs occurring among new users of TNFI therapy and the majority of OIs occurred within six months of TNFI initiation. Across disease indications, non-viral OIs occurred more frequently among patients initiating TNFI agents when compared to those starting non-biologic DMARDS. Glucocorticoid use in the baseline period was associated with increased risk of non-viral OIs.

Although the topic of biologic therapy and OI risk is an important safety issue, little epidemiologic work to document frequency and relative risk, particularly with regard to specific organisms other than tuberculosis, has been completed. [5,13,16,17] Our study identified rates of non-viral opportunistic infections similar to those described in European studies, but our estimates are lower than another North American study which has evaluated

this question, perhaps explained by the definition of OI used.[13] The British registry identified rates of “intracellular infection” of 2.2 per 1000 person-years.[6] The French registry recently published rates of “non-TB opportunistic infection” of 1.56 per 1000 person-years, and previously identified a rate for TB of 1.2 per 1000 person-years among users of anti-TNF agents. [5,18] Our overall rate of 2.7 per 1000 person-years is comparable for new users of TNFI therapy, although the choice of OIs included within the analyses and methods differed slightly. While the French study included herpes zoster but excluded tuberculosis among its outcomes, the British registry included all such infections. We, however, excluded zoster but included mycobacterial infections. Data from the CORRONA collaboration in North America, which included zoster and mycobacterial infections, revealed 10-fold higher rates of OIs than our study, which likely is accounted for by inclusion of zoster.[13]

Although TB has been reported previously as the most frequent OI in this setting, our data suggest that pneumocystosis occurs more frequently than other OIs in the US among TNFI users. Relatively high rates of pneumocystosis have been reported previously from Japan among TNFI users, and sometimes more commonly than TB among infliximab-treated patients.[19–21] However, it is possible that differences in case definition and more sensitive diagnostic procedures typically used in clinical practice (e.g. PCR) may influence higher observed rates in that region when compared to our findings. In addition, we may have underestimated the number of TB cases due to suboptimal sensitivity of diagnostic codes. Moreover, screening practices for latent TB in the US may have led to a smaller number of cases. In our overall population, rates for *Pneumocystis* infection among TNFI users (0.56 per 1000 person-years) and non-biologic DMARD users (0.51 per 1000 person-years) were similar, and probably influenced by concomitant use of glucocorticoids. On the basis of the low rates of pneumocystosis identified in our study, it is doubtful that *Pneumocystis* prophylaxis in US TNFI users would be cost-effective.

Prior to our study, Winthrop and colleagues surveyed infectious disease specialists across the United States, the results of which suggested histoplasmosis to be more common than mycobacterial disease in the setting of biologic therapy.[22] Our study identified histoplasmosis as the fourth most frequent OI. Several of the cohorts we evaluated included patients who did not live within traditional histoplasmosis-endemic areas, which may explain a lower than expected rate within our study.[23] Further, for histoplasmosis and other fungal infections, we required both a diagnostic code and antifungal use to define a case. It is likely that the expected improvement in specificity diminished the sensitivity of our case-finding algorithms; there were patients with diagnostic codes that lacked anti-fungal usage.

While French and British studies have reported rates of OIs to be higher in patients using TNFI therapy, it is likely that only a subset of OIs are influenced by TNF blockade. Those infections by which the host relies upon granulomatous response occur more commonly in those using TNFIs, and biologic mechanisms from animal models and in-vitro studies support this association.[24,25] It is not clear that other OIs, for which the host immune response might be different, are similarly affected. Further, even within *Mycobacterium* species, where tuberculosis and NTM both trigger granulomatous responses, there might be

a differential risk associated with TNF blockade, as observed in our study. Patients can be effectively screened for TB and disease prevented, while no such screening exists for NTM. We suspect there exists a potentially strong confounding by indication bias in our evaluation of NTM risk with TNF blockade, in that most patients with pulmonary NTM are those who have pre-existing lung disease.[26,27] It is possible that rheumatologists and other specialists are more likely to avoid biologic therapies in those patients with baseline severe underlying lung disease.

Use of the monoclonal antibodies infliximab or adalimumab, when compared to etanercept, have been associated with an increased risk of bacterial infections, tuberculosis and other granulomatous diseases in some but not all studies. [4,10,25,28–31] In addition, a variety of biologic mechanisms have been identified that potentially explain this risk differential. [24,28] When evaluating our RA population, we found a similar increased risk for non-viral OIs, strongest among new infliximab users. Of note, we adjusted for baseline glucocorticoid use but did not control for time-varying risks such as differences in prednisone use or methotrexate after drug initiation. This avoided inappropriate adjustment for downstream factors that could be causally related to TNFI initiation.

Our findings must be interpreted in the light of several limitations. We relied on administrative data to identify diseases and outcomes, potentially resulting in misclassification of events. Some measures of disease activity (i.e. DAS28) were not available in the data set. We did not include *Candida* infections due to the poor specificity of diagnostic codes,[15] and we did not include viral infections such as herpes zoster, as it was the topic of another report. [32]

With use of these administrative diagnostic codes, it is also likely we underestimated incidence of several OIs. From a related project conducted within Kaiser Permanente that utilized microbiology data to find cases of TB and NTM, we found NTM diagnostic codes to be only 50% sensitive in detecting cases of disease.[33] For TB diagnosis in this study we required pyrazinamide along with a code for tuberculosis; however, analyses conducted using the Kaiser Permanente and TennCare data suggested that such approaches have suboptimal sensitivity and specificity for tuberculosis. [33,34] The ICD-9 code for TB is used frequently when patients are diagnosed with latent TB infection, making identification of active TB difficult. Despite the potential for outcome misclassification, it is unlikely that this would be differential by drug exposure and the incidence rates would likely be unbiased.

In conclusion, using a US multi-institutional cohort, non-viral OIs among new TNFI users were increased compared with initiators of alternate non-biologic DMARDS in patients with autoimmune diseases. Baseline corticosteroid use was associated with risk of non-viral OIs. Among patients with RA, infliximab was associated with an increased risk of OIs compared with etanercept. *Pneumocystis* and mycobacterial infections remain important OIs among patients with autoimmune diseases receiving TNFIs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

JWB reported consulting for Pfizer, Merck, Astellas and Mayne Pharma and received research support from Bristol-Myers Squibb.

KLW reported grant/research support from Pfizer and consulting for UCB, Pfizer and Genentech.

ED received grant/research support from Amgen.

TB received grant/research support from Pfizer and consulting for Novartis, Roche and Genentech.

LJH had research support from Genentech, Centocor, and Procter and Gamble.

DHS received research support from Abbott, Amgen and Bristol-Myers Squibb.

KGS received grant support from ACAR, Ardea, Savient, Takeda, Regeneron and was a consultant for Ardea, Regeneron, Takea, Savient.

JRC received grant/research support from Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie and was a consultant for Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie.

Funding/Support: This work was supported by the Food and Drug Administration (FDA) US Department of Health and Human Services (DHHS) and the Agency for Healthcare Research and Quality grant U18 HS17919. KL Winthrop's work on this manuscript was funded by an Agency for Healthcare Research and Quality (AHRQ) grant (1K08HS017552-01). Dr. Curtis receives support from the National Institutes of Health (AR053351) and AHRQ (R01HS018517). Dr. Beukelman was supported by NIH grant 5KL2 RR025776-03 via the University of Alabama at Birmingham Center for Clinical and Translational Science. Drs. Grijalva received support from the National Institute of Arthritis and Musculoskeletal and Skin Diseases, grant 5P60AR56116. We are indebted to the Tennessee Bureau of TennCare of the Department of Finance and Administration, which provided the Tennessee Medicare data.

References

1. Grijalva CG, Chen L, Delzell E, et al. Initiation of Tumor Necrosis Factor-alpha Antagonists and the Risk of Hospitalization for Infection in Patients With Autoimmune Diseases. JAMA. 2011; 306:2331–2339. [PubMed: 22056398]
2. Bongartz T, Sutton AJ, Sweeting MJ, et al. 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. 2006; 295:2275–2285. [PubMed: 16705109]
3. Wallis RS. Infectious complications of tumor necrosis factor blockade. Curr Opin Infect Dis. 2009; 22:403–409. [PubMed: 19491672]
4. Curtis JR, Patkar N, Xie A, et al. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. Arthritis Rheum. 2007; 56:1125–1133. [PubMed: 17393394]
5. Salmon-Ceron D, Tubach F, Lortholary O, et al. Drug-specific risk of non-tuberculosis opportunistic infections in patients receiving anti-TNF therapy reported to the 3-year prospective French RATIO registry. Ann Rheum Dis. 2011; 70:616–623. [PubMed: 21177290]
6. Dixon WG, Watson K, Lunt M, et al. 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. 2006; 54:2368–2376. [PubMed: 16868999]
7. Hage CA, Bowyer S, Tarvin SE, et al. Recognition, diagnosis, and treatment of histoplasmosis complicating tumor necrosis factor blocker therapy. Clin Infect Dis. 2010; 50:85–92. [PubMed: 19951231]
8. Brassard P, Kezouh A, Suissa S. Antirheumatic drugs and the risk of tuberculosis. Clin Infect Dis. 2006; 43:717–722. [PubMed: 16912945]

9. Alderson JW, Van Dinter TG Jr, Opatowsky MJ. l. Disseminated aspergillosis following infliximab therapy in an immunosuppressed patient with Crohn's disease and chronic hepatitis C: a case study and review of the literature. Gen Med. 2005; 7:7.
10. Wallis RS, Broder M, Wong J, et al. Reactivation of latent granulomatous infections by infliximab. Clin Infect Dis. 2005; 41:S194–S198. [PubMed: 15983899]
11. Major EO. Progressive multifocal leukoencephalopathy in patients on immunomodulatory therapies. Annu Rev Med. 2010; 61:35–47. [PubMed: 19719397]
12. Tubach F, Ravaud P, Salmon-Ceron D, et al. Emergence of Legionella pneumophila pneumonia in patients receiving tumor necrosis factor-alpha antagonists. Clin Infect Dis. 2006; 43:e95–e100. [PubMed: 17051484]
13. Greenberg JD, Reed G, Kremer JM, et al. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. Ann Rheum Dis. 2010; 69:380–386. [PubMed: 19359261]
14. Herrinton LJ, Curtis JR, Chen L, et al. Study design for a comprehensive assessment of biologic safety using multiple healthcare data systems. Pharmacoepidemiol Drug Saf. 2011; 20:1199–1209. [PubMed: 21919113]
15. Schneeweiss S, Robicsek A, Scranton R, et al. Veteran's affairs hospital discharge databases coded serious bacterial infections accurately. J Clin Epidemiol. 2007; 60:397–409. [PubMed: 17346615]
16. Garcia-Vidal C, Rodriguez-Fernandez S, Teijon S, et al. Risk factors for opportunistic infections in infliximab-treated patients: the importance of screening in prevention. Eur J Clin Microbiol Infect Dis. 2009; 28:331–337. [PubMed: 18797940]
17. Dixon WG, Hyrich KL, Watson KD, et al. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis. 2010; 69:522–528. [PubMed: 19854715]
18. Tubach F, Salmon D, Ravaud P, et al. Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: The three-year prospective French research axed on tolerance of biotherapies registry. Arthritis Rheum. 2009; 60:1884–1894. [PubMed: 19565495]
19. Harigai M, Koike R, Miyasaka N. Pneumocystis pneumonia associated with infliximab in Japan. N Engl J Med. 2007; 357:1874–1876. [PubMed: 17978303]
20. Kameda H, Tokuda H, Sakai F. l. Clinical and radiological features of acute-onset diffuse interstitial lung diseases in patients with rheumatoid arthritis receiving treatment with biological agents: importance of Pneumocystis pneumonia in Japan revealed by a multicenter study. Intern Med. 2011; 50:305–313. [PubMed: 21325762]
21. Takeuchi T, Tatsuki Y, Nogami Y, et al. Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. Ann Rheum Dis. 2008; 67:189–194. [PubMed: 17644554]
22. Winthrop KL, Yamashita S, Beekmann SE, et al. 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. 2008; 46:1738–1740. [PubMed: 18419421]
23. Baddley JW, Winthrop KL, Patkar NM, et al. Geographic distribution of endemic fungal infections among older persons, United States. Emerg Infect Dis. 2011; 17:1664–1669. [PubMed: 21888792]
24. Winthrop KL, Chiller T. Preventing and treating biologic-associated opportunistic infections. Nat Rev Rheumatol. 2009; 5:405–410. [PubMed: 19568254]
25. Wallis RS, Broder MS, Wong JY, et al. Beenhouwer DO. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clin Infect Dis. 2004; 38:1261–1265. [PubMed: 15127338]
26. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007; 175:367–416. [PubMed: 17277290]

27. Dirac MA, Horan KL, Doody DR, et al. Environment or Host?: A Case-control Study of Risk Factors for Mycobacterium Avium Complex Lung Disease. Am J Respir Crit Care Med. 2012; 186:684–691. [PubMed: 22859521]

28. Ehlers S. Tumor necrosis factor and its blockade in granulomatous infections: differential modes of action of infliximab and etanercept? Clin Infect Dis. 2005; 41:S199–S203. [PubMed: 15983900]

29. Toh S, Li L, Harrold LR, Bayliss EA, et al. Comparative safety of infliximab and etanercept on the risk of serious infections: does the association vary by patient characteristics? Pharmacoepidemiol Drug Saf. 2012; 21:524–534. [PubMed: 22411435]

30. van Dartel SA, Fransen J, Kievit W, et al. Difference in the risk of serious infections in patients with rheumatoid arthritis treated with adalimumab, infliximab and etanercept: results from the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry. Ann Rheum Dis. 2013; 72:895–900. [PubMed: 22887849]

31. Curtis JR, Xie F, Chen L, et al. The comparative risk of serious infections among rheumatoid arthritis patients starting or switching biological agents. Ann Rheum Dis. 2011; 70:1401–1406. [PubMed: 21586439]

32. Winthrop KL, Baddley JW, Chen L, et al. Association between the initiation of anti-tumor necrosis factor therapy and the risk of herpes zoster. JAMA. 2013; 309:887–895. [PubMed: 23462785]

33. Winthrop K, Baxter R, Liu L, et al. Mycobacterial diseases and antitumour necrosis factor therapy in USA. Ann Rheum Dis. 2013; 72:37–42. [PubMed: 22523429]

34. Grijalva CG, Chung CP, Stein CM, et al. Computerized definitions showed high positive predictive values for identifying hospitalizations for congestive heart failure and selected infections in Medicaid enrollees with rheumatoid arthritis. Pharmacoepidemiol Drug Saf. 2008; 17:890–895. [PubMed: 18543352]

Table 1

Baseline characteristics of immune mediate inflammatory disease cohorts

Variables	Rheumatoid Arthritis		Inflammatory Bowel Disease		Psoriasis, Psoriatic Arthritis, Ankylosing Spondylitis	
	TNFI (n=24,384)	Non-biologic DMARD (n=11,828)	TNFI (n=3850)	Non-biologic DMARD (n=6867)	TNFI (n=5090)	Non-biologic DMARD (n=7047)
Age, mean (SD), y	57.73 (14.53)	58.47 (14.27)	40.39 (16.13)	40.38 (17.80)	48.82 (15.33)	52.19 (16.82)
Female	20955 (85.9)	10205 (86.3)	2559 (66.5)	4330 (63.1)	2854 (56.1)	4331(61.4)
Race						
White	15244 (62.5)	7340 (62.0)	3010 (78.2)	5075 (73.9)	3716 (73.0)	4986 (70.7)
Black	3927 (16.1)	1831 (15.5)	586 (15.2)	993 (14.5)	357 (7.0)	576 (8.2)
Other	5212 (21.4)	2659 (22.5)	254 (6.6)	799 (11.6)	1017 (20.0)	1489 (21.1)
Nursing Home Resident	992 (4.1)	493 (4.2)	99 (2.6)	167 (2.4)	146 (2.9)	334 (4.7)
≥1 Hospitalization during baseline[1]	6995 (28.7)	3305 (27.9)	2133 (55.4)	3387 (49.3)	1042 (20.5)	1613 (22.9)
Charlson-Deyo Comorbidity score[2], mean (SD)	1.72 (1.13)	1.73 (1.17)	0.51 (.95)	0.47 (0.90)	0.74 (1.13)	0.79 (1.18)
≥1 Inflammatory Marker tested	8955 (36.7)	4380 (37.0)	1094 (28.4)	2058 (30.0)	1045 (20.5)	1370 (19.4)
Mean glucocorticoid use, daily prednisone equivalent doses						
None	9732 (39.9)	5079 (42.9)	1714 (44.5)	2773 (40.4)	4038 (79.3)	5461 (77.5)
(0<5 mg)	7552 (31.0)	3650 (30.9)	609 (15.8)	973 (14.2)	700 (13.8)	1162 (16.5)
(5–10 mg)	4604 (18.9)	2045 (17.3)	594 (15.4)	1167 (17.0)	196 (3.9)	153 (2.2)
(>10 mg)	2495 (10.2)	1056 (8.9)	933 (24.2)	1954 (28.5)	156 (3.1)	275 (3.9)
Any orthopedic surgery	1752 (7.2)	633 (5.4)	66 (1.7)	85 (1.2)	189 (3.7)	177 (2.5)

Variables	Rheumatoid Arthritis		Inflammatory Bowel Disease		Psoriasis, Psoriatic Arthritis, Ankylosing Spondylitis	
	TNFI (n=24,384)	**Non-biologic DMARD (n=11,828)**	**TNFI (n=3850)**	**Non-biologic DMARD (n=6867)**	**TNFI (n=5090)**	**Non-biologic DMARD (n=7047)**
Any intra-articular injection	8607 (35.3)	3596 (30.4)	198 (5.1)	259 (3.8)	695 (13.7)	817 (11.6)
Comorbidites						
COPD	3241 (13.3)	1584 (13.4)	311 (8.1)	484 (7.0)	502 (9.9)	870 (12.3)
Cerebrovascular disease	947 (3.9)	419 (3.5)	82 (2.1)	118 (1.7)	116 (2.3)	248 (3.5)
Diabetes	4618 (18.9)	2266 (19.2)	336 (8.7)	541 (7.9)	1021 (20.1)	1337 (19.0)
Obesity	2153 (8.8)	1227 (10.4)	276 (7.2)	676 (9.8)	697 (13.7)	953 (13.5)
History of Cancer	1795(7.3)	956(7.9)	174(4.4)	352(4.8)	277(5.3)	595(7.4)
≥1 antibiotic dispensed[3]	16627 (68.2)	7234 (61.1)	2775 (72.1)	4419 (64.4)	3178 (62.4)	4075 (57.8)
Medication initiated						
Adalimumab	5888 (24.1)	-	118 (3.1)	-	294 (5.8)	
Etanercept	10283 (42.2)	-	-	-	4270 (83.9)	-
Infliximab	8212 (33.7)	-	3732 (96.9)	-	526 (10.3)	-
Hydroxychloroquine	-	5730 (48.4)	-	-	-	569 (8.1)
Leflunomide		4569 (38.6)				133 (1.9)
Sulfasalazine	-	1531 (12.9)	-	-	-	858 (12.2)
Mercaptopurine	-			3475 (50.6)	-	
Methotrexate	-	-	-		-	5491 (77.9)-
Azathioprine	-	-	-	3392 (49.4)		

[1] Hospitalization for any reason

[2]The Charlson-Deyo co-morbidity index provides an estimate of disease severity and co-morbidities for a given patient.

[3]Any antibiotic prescription

SABER= Safety Assessment of Biologic Therapy; SD=standard deviation; COPD=chronic obstructive pulmonary disease; TNFI=tumor necrosis factor-alpha inhibitor; DMARD=disease-modifying anti rheumatic drug

Table 2

Distribution of non-viral opportunistic infections (n=80) among new TNFI users for all disease indications[1]

Infection	Frequency (%)
Pneumocystosis	16 (20)
Nocardiosis/Actinomycosis	12 (15)
Tuberculosis	10 (12.5)
Histoplasmosis	9 (11.3)
Nontuberculous Mycobacteria	9 (11.3)
Salmonellosis	8 (10)
Listeriosis	4 (5)
Legionellosis	4 (5)
Cryptococcosis	3 (3.8)
Endemic Fungal Infection[1]	1 (1.3)
Toxoplasmosis	1 (1.3)
Coccidioidomycosis	1 (1.3)
Blastomycosis	1 (1.3)
Aspergillosis	1 (1.3)

[1]Only the first OI per patient is listed. One patient with TB was diagnosed with NTM several years later. That NTM case is not listed above but was used in analysis in Table 5.

[2]Defined using ICD-9 484.7 (pneumonia in systemic mycoses).

TNFI=tumor necrosis factor-alpha inhibitor

Table 3

Crude incidence and risk of non-viral opportunistic infections among patients who were new users of TNFI or non-biologic DMARDs.

Exposures	Events[1]	Person-years	Crude rate (per 1000 pyrs), 95% CI	Adjusted Hazard ratios[2]
Rheumatoid Arthritis				
Non biologic DMARD	13	7188	1.8 (1.1, 3.1)	1.00 (Reference)
New users of TNF inhibitors	67	22213	3.0 (2.4, 3.8)	1.6 (0.9, 3.1)
Any baseline glucocorticoid use				1.7 (1.0, 2.8)
Inflammatory Bowel Disease[3]				
AZA/6MP	9	4595	2.0 (1.0, 3.8)	1.00 (Reference)
New users of TNF inhibitors (infliximab or adalimumab)	5	2315	2.2 (0.9. 5.2)	0.97 (0.3, 2.8)
Psoriasis, Psoriatic Arthritis, Ankylosing Spondylitis				
Non biologic DMARD	5	3951	1.3 (0.5, 3.0)	1.00 (Reference)
New users of TNF inhibitors	6	4116	1.5 (0.7, 3.2)	1.4 (0.3, 6.4)
Any baseline glucocorticoid use				4.7 (1.2, 19.6)
All Diseases				
Comparator	27	15734	1.7 (1.2, 2.5)	1.00 (Reference)
New users of TNF inhibitors	78	28493	2.7 (2.2, 3.4)	1.6 (1.0, 2.6)
Any baseline glucocorticoid use				2.5 (1.5, 4.0)

[1] Two patients had 2 OIs each documented. In analysis, only the first OI was counted as an event, totaling 78 in table above.

[2] Adjusted by propensity score quintile and baseline glucocorticoid use one year prior to time zero (reference = no use), except for Inflammatory bowel disease model, where inclusion of steroids produced unstable estimates.

[3] The model including baseline glucocorticoid use for IBD patients resulted in unstable HR estimates.

Estimates were stratified by site and all 95% CIs were based on robust Ses. TNFI=tumor necrosis factor-alpha inhibitor; DMARD=disease-modifying anti rheumatic drug; AZA=azathioprine; 6MP=6 mercaptopurine; CI=confidence interval

Table 4

Specific TNFI and Risk of Non-viral Opportunistic Infections in RA Patients

Exposures	Events	Person-years	Crude rate (per 1000 pyrs), 95% CI	Adjusted Hazard ratios[1]
Comparison of Specific TNFI to Non biologic DMARD				
Non biologic DMARD	13	7443	1.7 (1.0, 3.0)	1.00 (Reference)
Etanercept	13	8641	1.5 (0.9, 2.6)	0.8 (0.4, 1.8)
Any baseline glucocorticoid use				1.7 (0.7, 4.1)
Non biologic DMARD	13	7443	1.7 (1.0, 3.0)	1.00 (Reference)
Adalimumab	15	4282	3.5 (2.1, 5.8)	1.8 (0.6, 5.3)
Any baseline glucocorticoid use				2.8 (0.8, 9.9)
Non biologic DMARD	13	7443	1.7 (1.0, 3.0)	1.00 (Reference)
Infliximab	55	13,519	4.1 (3.1, 5.3)	2.6 (1.2, 5.6)
Any baseline glucocorticoid use				1.7 (0.9, 3.4)
Comparison of Specific TNFIs to Etanercept				
Etanercept	13	8641	1.5 (0.9, 2.6)	Reference
Adalimumab	15	4282	3.5 (2.1, 5.8)	1.8 (0.8, 4.0)
Any baseline glucocorticoid use				2.5 (0.9, 7.3)
Etanercept	13	8641	1.5 (0.9, 2.6)	Reference
Infliximab	40	9263	4.3 (3.2, 5.9)	2.9 (1.5, 5.4)
Any baseline glucocorticoid use				1.6 (0.8, 3.1)

[1] Adjusted by propensity score quintile and baseline glucocorticoid use one year prior to time zero (reference = no use). Estimates were stratified by site and all 95% CIs were based on robust Ses. TNFI=tumor necrosis factor-alpha inhibitor; DMARD=disease-modifying anti rheumatic drug; CI=confidence interval

Table 5

Crude incidence and risk of mycobacterial infection among rheumatoid arthritis patients who were new users of TNFI or non-biologic DMARDs.

Exposures	Events	Person-years	Crude rate (per 1000 pyrs)	Adjusted Hazard ratios[1]
Tuberculosis				
Non biologic DMARD	1	6980	0.1 (0.0, 1.0)	1.00 (Reference)
New users of TNF inhibitors	8	22275	0.4 (0.2, 0.7)	4.2 (0.5, 33.5)
Nontuberculous Mycobacteria				
Non biologic DMARD	4	6981	0.6 (0.2, 1.5)	1.00 (Reference)
New users of TNF inhibitors	10	22272	0.4 (0.2, 0.8)	0.9 (0.3. 3.3)

[1] Adjusted by propensity score quintile. Estimates were stratified by site and all 95% CIs were based on robust Ses. TNFI=tumor necrosis factor-alpha inhibitors; DMARD=disease-modifying anti rheumatic drug.