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COMPARISON OF POST-MARKETING SURVEILLANCE APPROACHES REGARDING INFECTIONS RELATED TO TUMOR NECROSIS FACTOR (TNF) INHIBITORS

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by

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DEDICATION

This effort and all of my academic achievements are dedicated to my beloved parents, Xuequn Chen and Liping Wu, whose unconditional love and support always motivate me to set higher goals and keep moving forward.

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ABSTRACT

Objective: Both spontaneous (voluntary) reporting systems and observational approaches serve as important tools in post-marketing surveillance for adverse drug events, however, each has its own advantages. The primary purpose of this project was to compare and contrast the FDA Adverse Event Reporting System (FAERS) data and findings from observational studies in post-marketing surveillance through examining TNF inhibitors (etanercept, adalimumab, infliximab, certolizumab and golimumab) related infections, and secondarily, to examine the applicability of additional analyses in FAERS, such as multiple logistic regressions and time to onset of event analysis.

Methods: Using MedDRA® preferred terms (PTs), infection and infestation cases in FAERS with each TNF inhibitor as the primary suspect drug were extracted

through Evidex™. PubMed was searched for post-marketing observational studies that reported data on infections related to any of the studied TNF inhibitors. Completed observational studies with results reported on *ClinicalTrials.gov* (OS-CTs) were also extracted. Exclusion criteria for observational studies were: 1) did not assess safety, 2) contained duplicate data from another observational study and 3) reported only pre-specified adverse events. For each infection PT, the percentage of the total number of infections from each source was determined. We contrasted FAERS and observational studies in post-marketing surveillance for TNF inhibitor related infections on duplicates and timeliness, and examined the level of incompleteness and inaccuracy in FAERS data. We then compared the number and level of specificity of identified infections between 3 data sources. We also assessed the consistency in most commonly reported infections through generated rankings from each data source for each TNF inhibitor. Multiple logistic regressions were performed to determine significant predictors of having a more severe event outcome. Kaplan-Meier curves were generated to examine the difference in time to onset of event among different TNF inhibitors.

Results: In FAERS, 163,789 cases were found for all 5 TNF inhibitors with etanercept having the greatest number of cases (n=68,807, 42.0%) and adalimumab having the greatest number of reported PTs (n=824). A total of 53 observational studies from our PubMed search and 52 observational studies from ClinicalTrials.gov were included in our final data synthesis. FAERS rendered the

greatest number and level of specificity of reported TNF inhibitor related infections, followed by ClinicalTrials.gov.

For adalimumab, 4 of 10 infection terms matched between all three data sources (sinusitis, pneumonia, upper respiratory tract infection, and herpes zoster), among which none was reported at rates within 1% of each other. Seven of the top 10 infection terms matched between evidence from FAERS and ClinicalTrials.gov. For etanercept, 4 of 10 infection terms matched between all three data sources (nasopharyngitis, pneumonia, upper respiratory tract infection, and herpes zoster), among which herpes zoster was reported at rates within 1% of each other. Seven of the top 10 infection terms matched between evidence from FAERS and ClinicalTrials.gov. For infliximab, 2 of 10 infection terms matched between all three data sources (pneumonia and urinary tract infection), among which none was reported at rates within 1% of each other. Six of the top 10 infection terms matched between evidence from FAERS and ClinicalTrials.gov. For, certolizumab pegol, 1 of the top 5 infection terms matched all three data sources (urinary tract infection). Three of the top 5 infection terms matched between evidence from FAERS and ClinicalTrials.gov. For golimumab, two of the top 5 infection terms matched between evidence from FAERS and ClinicalTrials.gov

Our results from multiple logistic regressions showed that certolizumab pegol, golimumab, younger ager, being female and less weight were associated with less severe event outcomes (p-values <0.01). A statistically significant difference in the survival rates was observed between different TNF inhibitors

($p<0.001$) in our time to onset of event analysis. Etanercept and infliximab had better survival rates among all TNF inhibitors.

Conclusion: Our analyses demonstrated the beneficial attribute of FAERS to provide specific infection terms regarding the amount and specific level of terms. Our analyses also showed the usefulness of ClinicalTrials.gov, as one of the data source of observational studies, of offering more detailed information on adverse events compared to studies identified in the literature. Results indicate that passive (FAERS) and active (observational studies) pharmacovigilance provide similar results for common infections associated with TNF inhibitors. This finding supports the usefulness of FAERS in post-marketing drug safety assessment.

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CHAPTER ONE: INTRODUCTION

Background and Problem Statement

Post-marketing surveillance refers to the practice of collecting information and monitoring the safety of a product after it has been marketed.[1,2] It is an essential part of pharmacovigilance, which is the science of detecting, assessing, understanding and preventing adverse drug events.[3] . An adverse event (AE) is defined as “any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.”[4] A serious adverse event is defined based on the patient outcome. Any adverse event is by regulatory definitions described as serious if the patient outcome results in “(1) death (2) life-threatening (3) hospitalization (initial or prolonged) (4) disability or permanent damage (5) congenital anomaly/birth defect and (6) required intervention to prevent permanent impairment or damage.”[5]

AEs pose a significant burden on society. Approximately 5% of hospital admissions are caused by adverse events.[6] The incidence of AE-related death ranges from 0.009% to 6.3%, depending on the data source, drug, and other factors.[7–9] A systematic review by Taché et al. reported a median prevalence of AEs of 12.8% for ambulatory care-based studies and a median prevalence of AEs of 5.1% for hospital-based studies.[10] The cost of all AE-related morbidity and mortality as well as the management of AEs in the United States (U.S.) is estimated to be up to 30 billion dollars annually.[11]

In order to fully assess the safety of drugs, FDA regulations require both pre-marketing studies and post-marketing surveillance. Pre-marketing studies consist of preclinical testing (*in vivo* and *in vitro* studies) and clinical testing (Phase 1-2 trials if a drug receives accelerated approval (although some accelerated approval drugs undergo Phase 3 testing as well), and Phase 1-3 if a drug receives regular approval by FDA). Although phase 3 trials require a larger group of participants (1,000-3,000), it is still difficult to identify rare but important adverse events due to more homogeneous population, shorter duration of study follow up period and inability to include data on concomitant medications.[12] Pre-marketing studies may not reflect the real-world situation where a drug may be widely used among patients with varied characteristics for long periods. Post-marketing surveillance, as a continued step to monitor drug safety, takes up an important part of pharmacovigilance.[2] Common types of post-marketing surveillance include spontaneous (voluntary) reporting systems and epidemiological approaches.[13,14]

Spontaneous reporting systems are designed and employed to collect and analyze suspected adverse events observed after drugs have been approved for the market. Healthcare professionals, consumers, the general public and manufacturers usually submit spontaneous reports. Although the word “spontaneous” is used for such systems, manufacturers are mandated to notify the monitoring agencies (such as the U.S. FDA) of any adverse events that the companies have been aware of.[13] For healthcare professionals and consumers, the reporting is spontaneous as it is completely voluntary to contact the

manufacturer and/or relevant agencies about their experience of adverse events.[12–15]

Analyses of spontaneous reports data often involve detecting potential safety signals for suspected drugs and adverse events. A signal indicates how frequently an adverse event is reported in association with the suspect drug compared to other drugs. Common methods used for signal detection include Bayesian statistical methods (e.g. empirical Bayes geometric mean (EBGM)) and frequentist-based methods (e.g. the proportional reporting ratio (PRR)). The signal detection allows one to determine if any disproportionality exists in the reporting of a particular adverse event and a given drug when comparing with other drugs and adverse events.[16,17]

Epidemiological (observational) approaches (here defined as studies using epidemiological study designs, such as case-control studies, cohort studies or electronic database researches, excluding case reports and case series) are also important ways of conducting post-marketing surveillance as these can provide information on prevalence and incidence of adverse events and examine associations between adverse events and suspected treatments.

Rarely, randomized clinical trials are used in the post-marketing surveillance phase, but only when additional evidence is needed for policy decisions as existing evidence from previous randomized clinical trials is insufficient or evidence from new observational studies are not enough for policy decisions or if the purpose is to study a non-approved indication.[18] Sometimes

such trials are also conducted to provide needed evidence that cannot be obtained from prospective observational studies.[18] For example, if an adverse event can be pre-specified and have immediate impact on patients, a randomized clinical trial would be more appropriate. However, such trials are not common and tend to have homogeneous study population in a controlled study environment and conditions, which are not aligned with our study purposes. Thus randomized clinical trials were not included in our study.

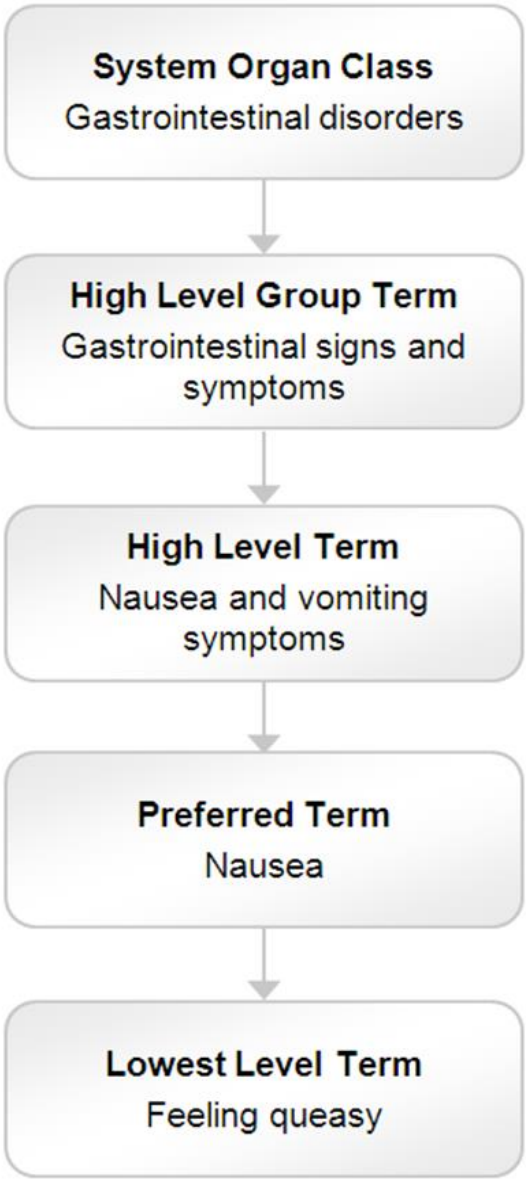
The FDA's Adverse Event Reporting System (FAERS)

In the U.S., the FDA is responsible for monitoring post-marketing drug safety. Post-marketing surveillance work conducted by the FDA is primarily done through maintaining and monitoring reports to its adverse event reporting system. In 1993, the FDA launched a Safety Information and Adverse Event Reporting Program – MedWatch – as its primary tool of post-marketing surveillance.[19] This program aims to increase the reporting of adverse events and to provide a convenient and confidential way to report and share information on adverse events. All spontaneous reports submitted through MedWatch are entered in a standardized way into a computerized information database – the FDA's Adverse Event Reporting System (FAERS). Adverse events in FAERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA®), which is an internationally accepted medical terminology for drug regulations and consists of 5 levels of terms depending on specificity (an example is provided in Figure 1; detailed explanations on MedDRA® terminology can be found through the link:

http://www.who.int/medical_devices/innovation/MedDRAintroguide_version14_0_March2011.pdf). A drug may be reported as a primary suspect drug, a secondary suspect drug, an interacting drug or a concomitant drug, depending on the degree of judgement of the person reporting the AE. FAERS has received over 9 million reports, and the number of reports has been largely increasing.[20] The total number of reports in 2014 was around 1.2 million, a 3.5-fold increase from 2006.[21] Since the FAERS database contains information on individual cases, it allows for further quantitative analyses such as logistic regression and time-to-onset of event analysis.[22–24]

Among all reports in FAERS, etanercept (ENBREL®), a TNF-α inhibitor, has the greatest number of primary suspect cases (n=243,937) as of August 2016. Other marketed TNF inhibitors are also associated with a large number of adverse events cases as the primary suspect drug, such as adalimumab (HUMIRA®, n=185,511) and infliximab (REMICADE®, n=72,641). These large numbers indicate that adverse events related to TNF inhibitors have become major safety concerns.

Figure 1 Example of MedDRA Terminology (Source: www.meddra.org/how-to-use/basics/hierarchy)



Tumor Necrosis Factor (TNF) Inhibitors

TNF inhibitors are an important class of biologics for the treatment of inflammatory conditions, such as Crohn's disease, ankylosing spondylitis, and rheumatoid arthritis. TNF inhibitors work by suppressing the physiologic response to tumor necrosis factor produced by the immune system.[25] Since the first TNF inhibitor was approved in the 1990s, there are five TNF inhibitors currently available on the market: etanercept, infliximab, adalimumab, certolizumab pegol, and golimumab. TNF inhibitors have revolutionized the treatment for immune-mediated inflammatory diseases, but TNF inhibitors are still subject to features of biologics, such as complex substances and structures, and their interference with the immune system, which may increase the risk for opportunistic and viral infections, etc. Thus, TNF inhibitors require more extensive scrutiny.

Inflammatory Arthritis and Inflammatory Bowel Diseases

Inflammatory arthritis (IA) and inflammatory bowel diseases (IBD) are labeled indications for all of the FDA-approved TNF inhibitors. IA includes diseases involving inflammation of the joints and often other tissues, such as rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis and can result in activity limitations due to clinical features such as joint swelling, pain, stiffness and deformity. RA represents the most common type of IA.[26] IBD is characterized by chronic inflammation of all or part of the digestive tract, and is accompanied

by symptoms such as diarrhea, fever, abdominal pain and weight loss. Crohn's disease and ulcerative colitis are the two primary types of IBD. Although the causes of IA and IBD remain unknown, the discovery of the role played by TNF in inflammation has advanced our understanding and has led to the production of TNF inhibitors, which have revolutionized the treatment of IA and IBD. Clinical trials showed that TNF inhibitors were overall well tolerated by rheumatoid arthritis patients and effectively reduce disease activity.[27,28] A meta-analysis by Lee et al. showed that TNF inhibitors combined with methotrexate were significantly better than methotrexate monotherapy in the disease improvement among patients with active rheumatoid arthritis.[29] Another meta-analysis by Gartlehner et al. compared the efficacy of biologics for rheumatoid arthritis treatment and found that TNF inhibitors overall were more efficacious than anakinra (a non-TNF biologic).[27] Superior effect of TNF inhibitors to conventional therapies in IBD was also demonstrated from a systematic review.[30] The authors concluded that TNF inhibitors were associated with effective remission maintenance and reduced risk of disease relapse after withdrawal of TNF inhibitors.

TNF Inhibitors and Infections

The association between TNF inhibitors and infections has been extensively studied. Infections and serious infections (which can lead to permanent damage or death if untreated) have been observed in patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease and ulcerative colitis, who were on TNF inhibitors.[31–38] Common infections that

have been reported include tuberculosis and fungal infections.[39–41] Serious infections are displayed as boxed warning information in package inserts for all five TNF inhibitors as: “Increased risk of serious infections leading to hospitalization or death, including tuberculosis, bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens.”[25] One explanation of the association between increased risks for infections and TNF inhibitors could be the important role that TNF-α plays in the host immune responses to pathogens.[42] TNF inhibitors work by reducing the TNF- α levels and potentially make patients more vulnerable to opportunistic infections such as tuberculosis.[43]

The risk of opportunistic, viral, fungal, and mycobacterial infections may vary due to multiple factors. Older age, disease severity and use of glucocorticoid drugs are associated with higher risk of infections.[44,45] Previous experience with infections is also significantly associated with increased risk of infections, especially tuberculosis, which is primarily linked to increased risk of progression or reactivation of latent tuberculosis infection as TNF-α plays an essential role in protection against human tuberculosis.[46]

Significance

According to a weekly report from the Centers for Disease Control and Prevention (CDC) in 2013, around 52.5 million (23%) of U.S. adults have been diagnosed with any type of arthritis, and 3% of the total population were affected by IA.[47–49] The prevalence of IBD is estimated to be 1 to 1.3 million in the US.[50]

Adalimumab, etanercept and infliximab are among top 10 selling drugs in the U.S. in 2013 with annual sales ranging from $5.4 billion to $3.9 billion.[51] A study in 2008 estimated that the mean total direct medical expenditure for an rheumatoid arthritis patient would be approximately $13,000 per year.[52] Although TNF inhibitors have revolutionized IA and IBD treatment, they pose a huge financial burden on patients.

As mentioned previously, spontaneous reporting systems and observational studies can serve as useful tools in post-marketing surveillance for TNF inhibitors. Both approaches provide advantages of including a broad spectrum of patients, longer study duration, and allowing assessment on more factors than solely medications of interest, thus, they have a higher probability to identify rare and serious adverse events. However, each approach has its disadvantages.

FAERS data often raise a controversy over the underreporting of adverse events and missing data due to the unique method of data collection. The extent to which the data is underreported is hard to quantify.[12] FAERS data cannot provide information on prevalence or incidence rates because there is no information about the overall population exposed to the medication and thus denominators for the rates cannot be estimated. Case reporting does not require clinical validation and highly depends on the reporter's judgment.

Observational studies, as an active drug surveillance approach, have the advantage of being able to provide both a numerator and a denominator, so one

can calculate event rates from the data and obtain higher quality data (less incomplete information).[53] However, observational studies may generate different findings depending on study design, for instance, case-control versus cohort studies. Methods used to adjust for confounders and bias also may determine the results of observational studies.[13] Unlike spontaneous reporting systems, observational studies, in which researchers collect primary data, are often much more expensive and may include much smaller population. Observational studies also employ secondary data to conduct a retrospective examination, however, it is usually hard to guarantee that all information is accurate and not subject to issues like recall bias or measurement error. Besides, the number of sufficiently large databases is limited and, for very rare events, the study sample needed may be larger than what is available after data cleaning.[12,13]

Since both spontaneous reporting systems and observational studies have their own advantages and disadvantages, each one could be potentially complementary or provide insights that might be contradictory. However, the quality and consistency of data that each approach provides and the ability to identify rare adverse events of these post-marketing monitoring approaches have not been sufficiently studied or compared. Without a comprehensive assessment on each approach, researchers may not be able to develop an optimal procedure for the most efficient and responsive AE surveillance.

Purpose

FAERS data are subject to issues inherent to spontaneous reporting systems, such as underreporting, missing data, and inability to provide prevalence and incidence, while observational studies have relatively smaller population and may generate different findings that are influenced by study design and confounders selected for evaluation. Although both approaches play major roles in post-marketing surveillance, these two are very different approaches. Questions often raised but not yet adequately addressed include: Is evidence from both approaches comparable or consistent? What is needed to consider when interpreting findings from both approaches? Can these two approaches be complementary to each other? Therefore, we conducted this study to answer these questions using TNF inhibitor related infections as the reported AE.

The primary purpose of this project was to compare and contrast FAERS data and findings from observational studies in post-marketing surveillance of TNF inhibitor related infections, and secondarily, to examine the applicability of additional analyses in FAERS, such as multiple logistic regression and time to onset of event analysis. The study goal is to provide researchers with a better understanding of different post-marketing surveillance approaches and to get the most use out of FAERS. The study attempted to provide an understanding of how FAERS data can be utilized and instructions on the interpretation of FAERS data within its inherent limitations.

Specific Aims

Specific Aim 1: To describe and contrast features of FAERS and observational studies in post-marketing surveillance for TNF inhibitor related infections

Research Hypothesis 1: We would observe differences between FAERS data and observational studies data regarding infections related to TNF inhibitors in terms of duplication of cases, completeness and timeliness.

Rationale: As one of the most representative spontaneous reporting systems, FAERS is also subject to weaknesses that are inherent to spontaneous reporting systems, such as underreporting and incompleteness. As observational studies usually take a longer time to follow patients to identify associations between a drug and adverse events, FAERS may provide more timely evidence.

Specific Aim 2: To examine and compare the number of TNF inhibitor related infections identified and the level of specificity of identified TNF inhibitor related infections using FAERS and an observational approach

Research hypothesis 2: We would observe differences in the number of TNF inhibitor related infections identified and the level of specificity of identified TNF inhibitor related infections using FAERS and an observational approach.

Rationale: FAERS database uses MedDRA® hierarchical terminology for infections, from the most general level – System Organ Classes (SOCs) to the most detailed one – MedDRA® Preferred terms, while observational studies often

reported more general terms for infections. It is important to examine whether through the use of FAERS, researchers can identify more unexpected infections related to TNF inhibitors. More specific terms for infections are also important, as they are more useful to clinical practice.

Specific Aim 3: To examine the consistency between FAERS and an observational approach in the type and reporting rates of common infections associated with TNF inhibitors

Research Hypothesis 3: We would observe a difference in the type of infections most commonly reported in FAERS and observational studies. The reporting rates of cases (patients) for the same TNF inhibitor-infection combination would differ as well.

Rationale: FAERS and observational studies are inherently different approaches and both provide their own evidence on association between TNF inhibitors and infections. However, the differences in their evidence have not been examined or described.

Specific Aim 4: To examine the applicability of additional analyses (i.e. multiple logistic regressions and time to onset of adverse events analyses) using FAERS data on TNF inhibitor related infections

Research Hypothesis 4: Additional analyses would be successfully applied to render more evidence on the association between TNF inhibitors and infections and information on predictors of death cases.

Rationale: Commonly used data mining algorithms in FAERS often solely focus on disproportionality and ignore case-level evidence. Novel methods have been developed to address such issues in data mining in spontaneous reporting systems and to help draw an association with the underlying effect between suspect drugs and adverse events.

CHAPTER TWO: REVIEW OF LITERATURE

In this chapter, we present the effectiveness and common adverse events of TNF inhibitors, discuss general issues with spontaneous reporting systems and provide results from our literature review regarding studies that compared FAERS and other post-marketing surveillance approaches, and additional analyses that could be applied to FAERS data.

Overview of TNF Inhibitors

TNF inhibitors are biologics that work through lowering the concentration of TNF at targeted sites of inflammation. TNF inhibitors are widely used for the treatment of rheumatoid arthritis, psoriasis, psoriatic arthritis, Crohn's disease and ankylosing spondylitis.[25] There are five TNF inhibitors approved for marketing by the US FDA: etanercept, infliximab, adalimumab, certolizumab pegol and golimumab. Infliximab, adalimumab and golimumab are anti-TNF α monoclonal antibodies; etanercept is an Fc-fusion protein; and certolizumab pegol currently the only PEGylated anti-TNFα biologic. Although TNF inhibitors all work by binding TNF, patients may respond variably to different TNF inhibitors.

Each TNF inhibitor can be used for several inflammatory diseases. Indications for each TNF inhibitor are summarized in Table 1. TNF inhibitors can be used as monotherapy or in combination with immunosuppressant drugs, such

as methotrexate or corticosteroids, depending on patient disease indication and disease severity. For instance, for patients with established rheumatoid arthritis, TNF inhibitors are often used as the second-line treatment, especially if the patient has moderate to high disease activity.[26] Patients are sometimes recommended to switch to another TNF inhibitor if they failed to respond or inadequately responded to the initial TNF inhibitor. For the treatment of Crohn's disease, adalimumab, infliximab, and certolizumab pegol, are used among patients with moderate to severe disease activity who failed to respond to a corticosteroid therapy or an immunosuppressive agent (such as azathioprine). TNF inhibitors may also be used when corticosteroids are not desired or contraindicated.[54]

Table 1 Labeled Indications for Each TNF Inhibitor*

	Etanercept (ENBREL®)	Adalimumab (HUMIRA®)	Infliximab (REMICADE®)	Certolizumab Pegol (CIMZIA®)	Golimumab (SIMPONI®)
Approval Date	11/02/1998	12/31/2002	08/24/1998	04/22/2008	04/24/2009
Rheumatoid Arthritis	√	√	√	√	√
Juvenile Idiopathic Arthritis	√	√			
Psoriatic Arthritis	√	√	√	√	√
Crohn's Disease		√	√	√	
Ulcerative Colitis		√	√		√
Plaque Psoriasis	√	√	√		
Hidradenitis Suppurativa		√			
Uveitis		√			
Ankylosing Spondylitis	√	√	√	√	√

*Information was extracted from FDA Drug databases (http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm); Approval date is the earliest FDA approval date for any indication.

Effectiveness of TNF Inhibitors

TNF inhibitors are overall well tolerated and have showed superior effectiveness compared to traditional treatment as discussed in the following paragraphs.

Rheumatoid Arthritis: A long-term prospective observational study compared the survival rate of rheumatoid arthritis patients treated with TNF inhibitors and that of patients on traditional disease-modifying anti-rheumatic drugs (DMARDs).[55] The study used data from the British Society of Rheumatology Biologics Register (BSRBR) and all patients included were followed for up to 10 years. The study concluded that patients on etanercept had a better survival than patients on conventional DMARDs with an adjusted hazard ration of 0.72 (95%CI 0.54-0.96). A retrospective observational study examined the effectiveness of etanercept in reducing disease activity and health-related quality of life (HRQoL).[56] The authors found that compared to traditional DMARDs, etanercept is associated with a significant greater decrease in disease activity and better HRQoL among patients with rheumatoid arthritis at 6 months after initiating the treatment. Infliximab was also found to substantially help to reduce disease activity with an average decrease of 8.4 in SJC28 (swollen joint count in 28 joints) and 2.5 in DAS28 (Disease Activity Score in 28 joints) at 36 months.[57]

Crohn's Disease: Superior treatment effects were seen among children and adults with Crohn's disease treated with TNF inhibitors. Walters and

colleagues compared the effectiveness of early treatment with a TNF inhibitor (adalimumab or infliximab) versus an immunomodulator (standard therapy) among children who were newly diagnosed with Crohn's disease.[58] They found that early treatment with a TNF inhibitor was associated with higher rate of remission compared to an immunomodulator at 1 year (relative risk: 1.41 95%CI (1.14-1.75)). Echarri and colleagues examined clinical effectiveness of adalimumab at 2 years of treatment among adult patients with Crohn's disease.[59] They concluded that adalimumab was able to provide sustained clinical remission with a remission rate of 87.5% among included patients at the 2-year endpoint. Lindsay et al. conducted a retrospective study using medical records to assess health resource utilization pre- and post-infliximab treatment. The results demonstrated that infliximab significantly reduced the number of hospitalizations and surgical procedures.[60]

Other Disease Conditions: de Vlam et al. examined the effectiveness of etanercept among patients with psoriatic arthritis.[61] They followed patients for 66 months and found a significant decrease in the mean total Health Assessment Questionnaire score from 27 at baseline to 7.7 at endpoint (lower score means less difficulty in daily movement and activities). Escudero-Vilaplana and colleagues investigated the effectiveness of adalimumab, etanercept and infliximab among patients with ankylosing spondylitis and identified significant improvement in disease activity as well.[62]

Common Adverse Events Related to TNF Inhibitors

There are numerous studies that have examined adverse events related to TNF inhibitors. Major safety concerns that are related to TNF inhibitors include infections and malignancies. Serious infections and malignancies are also listed as boxed warnings for all TNF inhibitors. Bongartz and colleagues performed a systematic review and meta-analysis on the risk for infections and malignancies among patients with rheumatoid arthritis who were treated with TNF inhibitors.[33] They extracted evidence from randomized, placebo-controlled trials of adalimumab or infliximab. The pooled odds ratio for serious infections among patients on TNF inhibitors was 2.0 (95%CI 1.3-3.1) compared with patients on placebo. The pooled odds ratio for malignancies among TNF inhibitor-treated patients was 3.3 (95%CI 1.2-9.1). Several observational studies reported increased risk for infections among TNF inhibitor users with rheumatoid arthritis.[63,64] Increased risk for infections was also identified among patients with other disease conditions. Ford and Peyrin-Biroulet conducted a meta-analysis using data from randomized controlled trials to assess the risk of opportunistic infections among patients with Crohn's disease and ulcerative colitis who were treated with TNF inhibitors.[65] They obtained a relative risk of 2.05 (95% CI 1.10–3.85) when compared TNF inhibitors and placebo. However, some studies did not find significantly increased risk for infections or malignancy associated with TNF inhibitors.[36,66–68]

Issues with Spontaneous Adverse Event Reporting Systems

During the past decades, spontaneous reporting systems have been utilized as the major tool to monitor post-marketing drug safety and to provide sources for drug safety alerts in many countries and areas. Systems such as U.S. FAERS, U.S. Vaccine Adverse Event Reporting System (VAERS), the World Health Organization (WHO) Programme for International Drug Monitoring, and EudraVigilance have served as primary sources for information on new, unusual or rare adverse drug events.

Spontaneous report data have two main advantages: they are relatively inexpensive compared to other post-marketing surveillance approaches and have the potential to capture ongoing and timely safety data of all populations.[13,69,70] Unlike prospective observational studies, which require a large sample size, long follow-up period and researchers' continuous involvement in interviews and assessment, spontaneous reporting systems work in a less costly manner.[71] The maintenance cost of spontaneous reporting systems was found to be the lowest among all the sources of data for pharmacovigilance, yet provide the largest amount of information for drug safety monitoring.[72] Although it is mandated by U.S. law that phase IV post-marketing studies should include either clinical trials that are similar to those conducted before approval or epidemiological studies which use clinical or claims data, less than 50% of the "expected" post-marketing studies were begun on time, or even started at all.[70,73] Spontaneous reports data, received from healthcare professionals, patients or

manufacturers, are able to reflect the real word situation in a much timelier endeavor.

Despite the advantages stated above, spontaneous reporting systems, as passive surveillance systems, have been questioned for years for several issues, including underreporting, stimulated reporting, the Weber effect (explained in a following section), duplication of reports, inability to provide incidence rates and incompleteness.

Underreporting

Underreporting is the top issue with spontaneous reporting systems. Because the reporting of adverse events for physicians and patients is voluntary by law in many countries (e.g. U.S. and U.K.), the underreporting issue is not unexpected.[70] A systematic review published in 2006 by Hazell and Shakir examined to what extent underreporting existed in spontaneous reporting systems and if reporting rates varied by types of adverse events.[74] The review found a median underreporting rate of 94% for all adverse events based on numerical estimates from 37 included studies and a median underreporting rate of 85% across specific serious adverse events from 19 studies.[74] A study by Aagaard et al. found that reporting rates also varied by countries. High-income countries had higher AE reporting rates while low-income countries had lower rates. However, the number still significantly varied across countries in each group: for high-income countries, the range of annual reports is from 3 to 613 per

million inhabitants; for low-income countries, this range is between 0 and 21 reports per million inhabitants.[75]

Researchers have looked into reasons for underreporting and potential strategies to improve reporting rates. In developing countries, lack of knowledge/awareness of spontaneous reporting system seems to be the major reason for underreporting.[76–78] Having received relevant training and working in a clinical setting are positively associated with adverse events reporting.[79] Continuous training and incentives may be helpful in increasing the reporting rate.[79] Combined strategies that can improve professionals' attitudes and knowledge, as well as their relationship with patients and the medical environment will also help with their participation in spontaneous reporting.[80]

Stimulated Reporting

Stimulated reporting is another major limitation of spontaneous reporting systems. It refers to the concept that the number of adverse events reported might increase due to elevated public disclosure or media attention. For example, the reporting of a certain pair of drug and adverse event may increase after FDA issued a safety alert. An article published in 2013 by Southworth et al. questioned an unusually higher reports rate of bleeding for dabigatran than that for warfarin in FAERS. They later compared the rates of bleeding incidents with warfarin and dabigatran using claims data and evidence from clinical trials and found contrary results. They argued that stimulated reporting could be one of the explanations for this unusual reporting rate in FAERS since this drug was new to

the market and had more media disclosure.[81] However, a study by Hoffman et al., which examined 100 drugs using FAERS data, did not find evidence of FDA alerts' influence on stimulated reporting.[82] More studies are needed to determine whether or not and to what extent the length of time since approval and media exposure increase reporting rates. Besides, other types of exposure may also contribute to the increase in reporting, such as publications of peer reviewed journal articles or media exposure.[82] It is difficult to delineate the effect of a specific factor.

The Weber Effect

The Weber effect was named after Dr. JCP Weber for his discovery of a reporting trend of adverse events. In 1984, Dr. Weber published his study on reported adverse events regarding nine oral non-steroidal anti-inflammatory drugs (NSAIDs) marketed in the United Kingdom (UK). He found that the number of reported adverse events increased during the first two years, reached the highest point near the end of the second year, and then the number dropped.[83] Weber stated, "This decline is due to a reduction in the reporting of clinically mild or trivial reactions. The more serious ADR, such as hematemesis, perforation of peptic ulcers, blood dycrasias, etc. are reported from year to year in a quite constant manner".[83] Based on his study, the Weber effect is understood as a certain reporting pattern of adverse events for a drug during the first several years after the drug has been approved. Another important point that needs to be considered when generalizing Weber's finding is that Weber's studied period was during the implementation of the U.K.'s 'Black Triangle' reporting guidelines,

which encourage healthcare professionals to intensively monitor the black triangle symbol assigned drug and to report suspected adverse events.[84] Any drug that contains a new active substance or has a new route of administration, or medication that has a new combination of ingredients or a new delivery system would be assigned with a black triangle symbol.[85]

Several publications have replicated the Weber effect or examined the existence of such effect in other reporting systems. Hartnell et al. replicated Weber's original study using FAERS data.[86] They examined whether the reporting trend characterized by Weber existed. Five NSAIDs that studied in Weber's original study and marketed in the U.S. were included. For each drug, the Weber effect was observed. Hartnell's study indicates that the Weber effect may affect both UK and US adverse events reports, even though there exist some differences between the reporting systems in these two countries (e.g. FAERS is a centralized reporting system while UK's reporting system consists of 4 regional ones). However, Hartnell et al.'s study did not examine the Weber effect on adverse event reports of other classes of drugs.

In 2014, Hoffman and his colleagues published the results of their study using more current FAERS data (2006-2012) for 62 FDA-approved drugs.[84] They concluded that most of the reporting in FAERs did not demonstrate a Weber effect and suggested that the Weber effect may not exist in modern-day FAERS as now adverse event reports come from multiple sources and FDA has taken additional action to improve the reporting of AEs. Hoffman et al.'s finding is

consistent with other two previous studies, and suggest that the Weber effect should not be assumed during analysis of AE reports.[87,88]

Duplication of Reports

Duplicates are often found in spontaneous reports for two major reasons. The first reason is that reports come from different sources (health professionals, patients and manufacturers), and the same incident may be reported from a different source as a separate case. The second reason is that sometimes multiple reports may be submitted as follow-up updates to an initial case. However, not all follow-ups are successfully identified and linked up to the original report.[89,90] Duplication of reports has a potential to cause misleading interpretations of data and inaccurate conclusions, especially in disproportionality analysis. False positive signals may occur and influence physicians' and pharmacists' prescribing patterns, which could prevent patients from receiving effective and safe treatment.

Hauben and colleagues published an article in 2007 on their experience of encountering an "extreme duplication" in the FAERS database.[91] They ran signal detections for all adverse events for a randomly selected drug, and found a very strong signal of disproportionate reporting for "aortic dissection" as 20 out of a total of 66 cases were related to the drug of interest. However, they found that all of the 20 cases had the same event date and co-suspect medications, and none of which had age reported. Although the FAERS data they used were downloaded through software vendors, this work demonstrated a good example

of how duplication could have huge influence on signal detection analysis and such limitation should always be taken into account during data mining analyses.[91]

Inability to Provide Incidence Rates

The issues stated above help to explain why spontaneous reports do not provide valid estimates of incidence rates for patients who experienced a certain adverse event. The denominator – the total number of patients who are taking the drug of interest – is unknown.[13,89] Without such quantitative measures, it is difficult to directly compare the relative risk between drugs. Additionally, type and severity of reactions also affect reporting rates. Acute adverse events are more likely to be recognized and reported than adverse events showing latent effects of drugs.[13]. Reporting rates may also vary by the length of time that a drug has been approved. Newly approved drugs tend to attract more attention and usually have higher reporting rates in the first three years.[13] All of these factors limit the comparability of risk data for different drugs.

Incompleteness and Inaccuracy

Although in spontaneous reports, information such as basic demographic characteristics of patients (age, gender), suspect and concomitant drugs, indications, and length of treatment are supposed to be listed, missing data may still exist for these items. In 2011, Getz et al. examined the completeness and accuracy of over 10 million adverse event reports in FAERS and found that information regarding patient age, gender, and adverse event starting date and

outcome were generally complete (completion rate ranged between 75%-96%).[92] Information on suspect drugs had much lower rates of completion. For example, primary suspect therapy start and end dates had a completion rate of only 37% and 23%, respectively. The dosage of suspect drugs was also missing for almost 70% of reports. Product name, manufacturer name, and product lot number are also supposed to be filled out in spontaneous reports to FAERS, however, the completion rate of the product lot numbers was only 9%. The study also found that more than one-fourth of reports had inaccurate suspect drug names, and about one-third of suspect drug start dates were inaccurate based on examination of reasonableness. Low rates of completion and inaccuracy of information pose concerns when utilizing spontaneous reports data, especially in the post-marketing context where other potential important confounding variables such as patients' multiple health issues and behavioral risk factors are usually not captured.[92]

Signal Detection Algorithms

Signal detection algorithms have been developed and utilized to identify potential associations between suspected medications and adverse events with large spontaneous report data. Commonly used algorithms include the proportional reporting ratio (PRR), the reporting odds ratio (ROR), and the empirical Bayes geometric mean (EBGM).[16] The PRR and ROR are based on frequentist methods, while EBGM is a Bayesian method. The numerators and denominators for calculating the PRR and the ROR can be explained by a 2x2 contingency table.

Table 2 2x2 Contingency Table for PRR and ROR Calculations

	With an adverse event of interest	Without an adverse event of interest	Total
With a drug of interest	n11	n10	n11+n10
Without a drug of interest	n01	n00	n01+n00
Total	n11+n01	n10+n00	n11+n10+n01+n00

n11: the number of co-occurrences of interest. n11+n10: the total number of co-occurrences with a drug of interest. n11+n01: the total number of co-occurrences with an adverse event of interest. n11+n10+n01+n00: the total number of co-occurrences in the database.[93]

The PRR and ROR are computed as:[93,94]

$$PRR = [n11 \times (n01 + n00)] / [n01 \times (n11 + n10)]$$

$$ROR = (n11 \times n00) / (n10 \times n01)$$

The expected number of co-occurrences of interest, n11(expected), is defined as:[93]

$$n11(expected) = [(n11 + n10) \times (n11 + n01)] / (n11 + n10 + n01 + n00)$$

The EBGM is computed as the observed-to-expected ratio:[93]

$$EBGM = n11/n11(expected)$$

There are certain scoring thresholds to determine a significant signal when using each algorithm. A significant signal suggests a drug with potential increased risk for an adverse event. For analysis using the PRR, a signal is observed for a drug-adverse event pair if: (1) the number of cases is 3 or more, (2) the PRR is greater than 2, (3) the chi-square value for the statistical association is greater than 4.0.[93,94] When using ROR, if the lower bound of the

95% confidence interval (CI, two-sided) is greater than 1.0, a signal was considered.[93]. For the EBGM, a signal is detected if the value for EBGM is equal to or greater than 2.0 and the lower bound of the two-sided 95% CI is also ≥2.0.[93,95]

These different methods for signal detection are reported to be broadly comparable and widely accepted.[96,97] Empirical Bayesian methods may be a better choice if there is variability introduced by small number of reports, while the PRR has the advantages of being straightforward to calculate and interpret.[16,94]

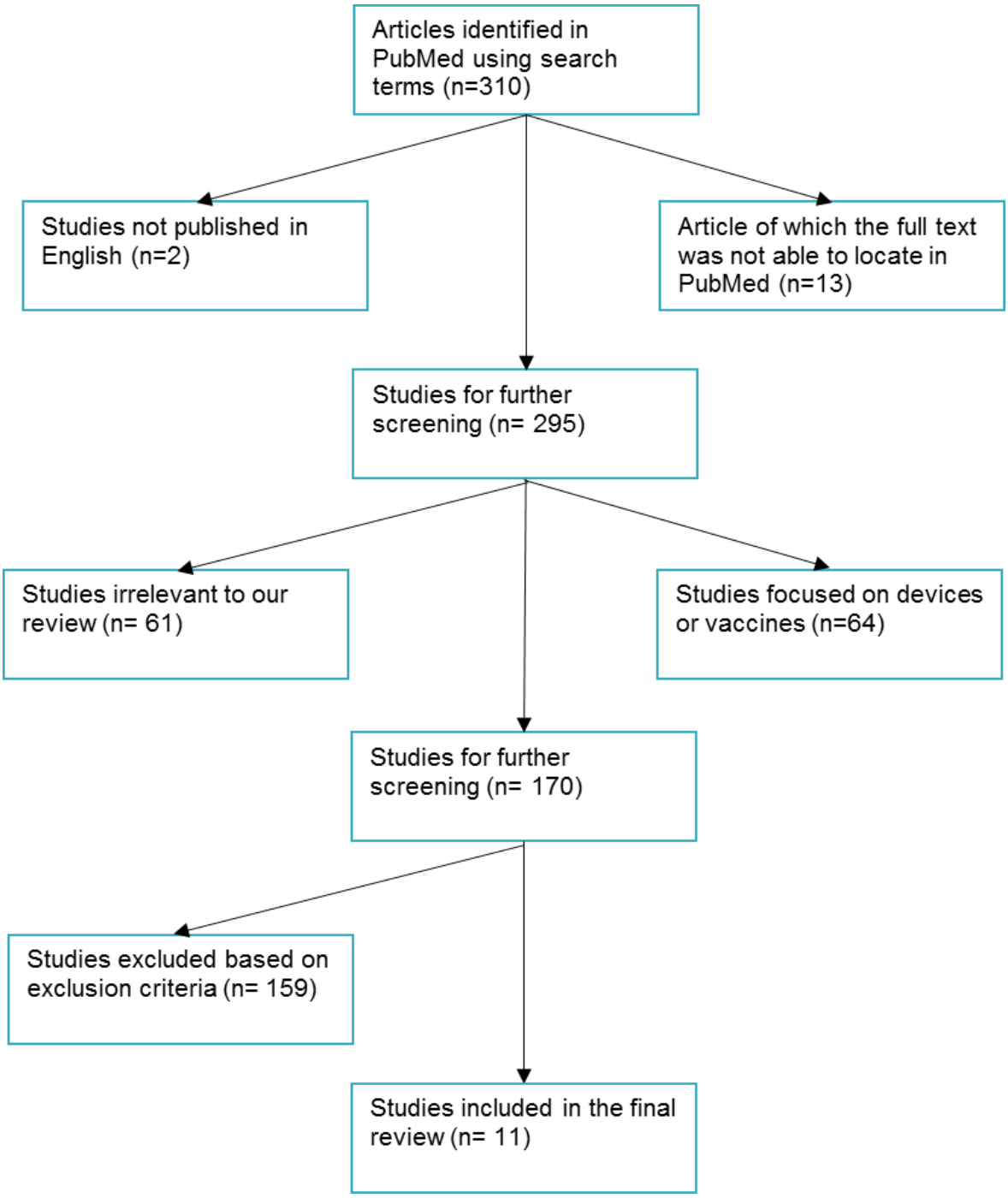
Review of Studies Comparing FAERS Data and Findings from Observational Studies

A literature review was performed in PubMed to identify studies that compared spontaneous reported data from FAERS with evidence from observational studies. The purpose of this review was to assess the findings from previous studies that either qualitatively or quantitatively examined the quality and applicability of FAERS data through comparison with data from observational studies. We utilized related terms of FAERS, combined with a series of terms regarding other approaches for post-marketing surveillance. The search terms that we used included: (FDA Adverse event reporting system OR MedWatch) AND (published studies OR literature OR epidemiological OR observational OR clinical trials OR case series OR registry OR electronic data) AND (rate OR incidence OR number OR ratio OR rank).

The inclusion criteria for the literature review included: (1) analyses using FAERS data and other post-marketing surveillance approaches, (2) review and comparison of evidence generated from FAERS and other study designs, and (3) published in English. The exclusion criteria for studies were: (1) solely focused on adverse events detection using FAERS, (2) used FAERS as supplementary evidence and no comparisons were made, (3) focused on devices and vaccines, (4) linked evidence from FAERS to biomedical mechanisms, and (5) the full text was not available.

The initial search generated a total of 310 articles (as of July 2016) using our search terms. There were two articles that were not published in English and 13 articles of which full text was not available in PubMed. The abstracts of studies were then examined to determine relevance to the purpose of our review. After the examination, a total of 11 studies remained after applying exclusion criteria and were included in our final review (Figure 2). Although none of these studies quantitatively compared FAERS data with results from other sources of post-marketing surveillance, these studies rendered evidence of relative comparability and consistency of findings between FAERS data and other approaches.

Figure 2 Flow Diagram of Literature Review of Comparison on FAERS Data and Observational Studies



Four studies utilized and compared multiple databases. Mammo et al. published an article in 2016 on their findings on the risk of age related macular degeneration (AMD) with oral bisphosphonates (alendronate, ibandronate, and risedronate).[98] They utilized the FAERS database and 2 patient cohorts, and employed 3 distinct study designs: disproportionality analysis (RORs were computed), case-control study, and a self-controlled case series (SCCS). Higher ROR was observed in the disproportionality analysis for alendronate and had the highest number of cases with greater than 3 years of bisphosphonates use. This indicated a potential association between higher risk of AMD and longer duration of bisphosphonates use, which was also demonstrated in the case control and SCCS studies.

Fujimoto et al. examined the association of stain use and cancer using FAERS database and a claims database.[99] Reported cases of atorvastatin, fluvastatin, simvastatin, rosuvastatin, pitavastatin, and pravastatin were searched and around 8,000 preferred terms of adverse events were identified. Consistent findings were seen in analyses using both databases – statins, as a class, were significantly associated with two types of cancers: colorectal cancer and pancreatic cancer.

Edwards and her colleagues compared the strengths and limitations of three databases through evaluating the completeness and accuracy of safety information regarding nephrogenic systemic fibrosis (NSF).[100] The three databases studied were: the International Centre for Nephrogenic Systemic Fibrosis Registry (ICNSFR), FAERS, and a legal data set. The FAERS offered

the largest number (n = 1,395) of NSF reports, however, shared the limitations that were inherent to spontaneous report data such as incompleteness and inability to avoid redundant reporting. A similar study was also conducted to examine pediatric cases of NSF in FAERS, ICNSFR, and published literature. Data mining of three data sources gave the consistent conclusion that NSF is rare in children.[101] Both studies emphasized the necessity of looking into multiple data sources to identify more information on rare but important adverse events.

Other studies examined evidence from FAERS by comparing it with published literature or clinical findings. Edwards et al. published a study in 2013 on their findings on the association between bisphosphonates and non-healing femoral fractures.[102] They utilized FAERS data to detect significant signals between bisphosphonates and non-healing femoral fractures and found strong association with a PRR of 4.51. Additionally, they performed a systematic review to support the findings from FAERS and made similar conclusions.

Sakaeda et al. reviewed FAERS cases and detected signals using multiple algorithms to examine platinum agents related adverse events and to compare the rank of studied agents (cisplatin, carboplatin, and oxaliplatin) based on signals for each adverse event with clinical findings.[103] The results demonstrated that platinum agents might cause adverse events such as nausea, vomiting, and neutropenia. The rank-order of studied agents in terms of many adverse events were all confirmed to be consistent with clinical findings, suggesting the usefulness of FAERS data and reproducibility of clinical findings.

Evens et al. looked into rituximab related hepatitis B virus reactivation (HBV-R) cases from published literature and the FAERS database, and compared the completeness of FAERS and literature cases based on pre-specified covariates.[104] Evidence from both FAERS and literature indicated strong association between rituximab and HBV-R; however, cases identified from literature tended to be much more complete. Belknap et al. investigated clinical features of gemcitabine related lung injury through clinical trial reports, literature case reports and FAERS.[105] McKoy JM and her colleagues summarized information on gemtuzumab ozogamicin associated sinusoidal obstructive syndrome from variable sources, including peer-reviewed articles, an observational registry and FAERS database.[106] Evidence from FAERS provided relatively consistent findings as well.

Reese et al. employed three different methods to identify drugs that may contribute to drug-induced immune thrombocytopenia.[107] The three methods included: (1) case reports from published literature, (2) serum samples tests, and (3) FAERS data mining. Five hundred seventy-three drugs were found to have significant signals with thrombocytopenia in FAERS. Drugs identified in FAERS covered 327 (93%) of 351 drugs described in literature and or serum sample tests. However, only 16% of these 573 drugs were reported to be associated with thrombocytopenia in literature or serum tests. This indicated the superior ability of FAERS database to identify potentially related drugs in a more comprehensive manner.

Not all studies found consistent results. A review study by Suarez et al. examined evidence from observational studies on the association between incretin-based therapies and potential increased risk of acute pancreatitis and pancreatic cancer.[108] Although signals detected from FAERS database suggested GLP-1 receptor agonist and DPP-4 inhibitor use may lead to acute pancreatitis and pancreatic cancer, the findings of their review showed conflicting evidence. However, as mentioned in the article, it is noteworthy that the studies reviewed by Suarez and colleagues provided limited evidence to make any conclusions.

In summary, findings from these 11 studies demonstrate relative consistency between the evidence from FAERS data and evidence from observational studies (either through databases or clinical trials), although one study (Suarez et al.) suggests potential conflicting evidence between FAERS and observational studies. Of note, only one study searched for specific adverse event terms (preferred terms) and compared evidence from the FAERS database and a claims database with that information (Fujimoto et al.). Our literature review identified consistency between evidence from FAERS and observational studies regarding adverse events related to specific drugs. The review also indicated a need for quantitative examination and comparison of FAERS data to observational studies.

Additional Analyses for FAERS Data

Common data mining in spontaneous reported data only generates descriptive statistics and reporting signals, which often ignore individual-level variations. Researchers have been trying to develop additional analytic methods that can be applied to FAERS data to help better understand and compare the effect of drugs in question and to adjust for issues in spontaneously reported data. One important element to incorporate is the time to onset of adverse events.

Maignen F et al. proposed a method to employ hazard functions using time to onset of adverse events.[24] Their idea was based on the assumption that "the estimation of the hazard of occurrence of a reaction is directly connected to the underlying mechanism of the toxicity". They examined both non-parametric analysis using Kaplan-Meier estimates and parametric distributions to model the time to onset of event and develop the hazards functions. They selected two drug-adverse events combinations to assess their models: (1) bosentan and liver injuries, (2) TNF inhibitors and infections. Their study found some consistency of the associations between TNF inhibitors and occurrences of infections, suggesting that their parametric modeling might be a potentially useful tool to detect a casual association between drugs and adverse events. However, the parametric method was limited in that it required a minimum number of reports, which were sufficiently complete to satisfy an acceptable fit of distributions. They also reinforced that the results should be interpreted with caution due to limitations in the data and lack of comparators.

Another study by Van Holle L and Bauchau V looked into an approach to predict adverse events following the initiation of immunization.[109] They also included the time to onset of event distributions as a predictive variable along with stratified PRR, and found that the relative unexpectedness of the time-to-onset of event seemed to be the best predictor of a potential safety alert. However, the study was conducted using VAERS data, which focused on vaccines, and set a 60-day post-vaccination window for assessment, the method developed in this study is not applicable to our project since we are looking at long-term safety and the time to onset of event varies widely between cases and events.

Another novel method that addressed potential biases in FAERS data is a likelihood ratio test-based method, developed by Huang and colleagues.[110] This method aims to control for family-wise type 1 error and offer a way to, as the authors stated, "(1) identify the AEs with high reporting rates compared with other AEs associated with a particular drug, (2) identify drugs associated with high reporting rates of a particular AE compared to the other drugs."[110] However, the methodology proposed in this article was very experimental and beyond the scope of our study, thus such methods were not be examined here.

Summary

Spontaneous reporting systems often raise a controversy due to their inherent issues and limitations. Issues or limitations that have been discussed in this chapter include underreporting, stimulated reporting, the Weber effect,

duplication of reports, inability to provide incidence rates, and incompleteness. The FAERS database is very likely also subject to such issues, which need to be taken into account when conducting data mining in FAERS.

In our study, we examined some of the issues in FAERS cases on infections related to TNF inhibitors, since they may introduce bias or lead to misinterpretation to our study results. However, we did not assess stimulated reporting and the Weber effect because such issues are not pertinent to the purpose of this study. Stimulated reporting is often assessed when there is a new boxed warning on a specific adverse event for a drug, while the focus of our study is to identify more infections instead of studying one specific infection type. The Weber effect is irrelevant to our study purpose as well because it is a proposed trend describing an overall reporting pattern while our study is to identify specific infections in order to facilitate clinical practice.

CHAPTER THREE: METHODS

This chapter discusses the main data sources that were used for the assessment of FAERS reports and the comparison between evidence from FAERS and observational approaches on TNF inhibitor related infections. Data extraction methods and relevant statistical analyses are presented as well.

Overall Research Design

Our study examined the features and consistency in the evidence of common TNF inhibitors related infections from FAERS and observational studies. We compared evidence from different data sources through evaluation of summarized data and generated rankings of most commonly reported infections related to TNF inhibitors. We performed statistical analyses to examine the applicability of additional analyses for FAERS data. All statistical analyses were conducted using Stata (version 14, Stata Corp, College Station, Texas, USA).

Data Source

FAERS

We accessed the FAERS database through Evidex™, a web-based platform, provided by Advera Health Analytics, Inc. (http://www.adverahealth.com/). Evidex™ contains information on adverse event reports to FAERS, and provides detailed case reports and data mining signals. Case reports in FAERS contained information on report/case identification

(individual safety report number, case number, report date), patients' demographic characteristics including age, gender and weight, patients' conditions, adverse events defined by different levels and outcomes, information regarding primary suspect drug such as brand name, verbatim dosage (exactly as entered in the report), route of administration, primary suspect therapy start date, date adverse event began and manufacturer, brand names of secondary suspect drug and concomitant drugs, and information about report/reporter (report code, date manufacturer received report, date report sent, and reporter occupation and country). We searched infection cases by using System Organ Class level term "infections and infestations" for each TNF inhibitor.

Post-marketing Observational Studies

Literature Review

PubMed was searched for post-marketing studies that reported observational data on infections related to any of the studied TNF inhibitors: etanercept, infliximab, adalimumab, certolizumab pegol, and golimumab. Search terms combined generic names of the five TNF inhibitors and terms relevant to post-marketing observational studies, specified as: ("Observational Study" [Publication Type]) OR ("Clinical Trial, Phase IV" [Publication Type]) and (adalimumab OR etanercept OR infliximab OR golimumab OR certolizumab pegol). Identified articles were then screened on their titles and abstracts for eligibility.

Inclusion/Exclusion Criteria: Articles that were included in our final review must meet all of the following requirements: (1) a peer-reviewed article, (2) phase 4 trials or observational/epidemiological studies on one or more of the five TNF inhibitors, (3) studies reporting data on TNF inhibitor-associated infections and (4) articles that were written in English. No restriction on publication date was applied. If findings from one study were reported in multiple publications, only latest data were used. Articles were filtered out if any of the following exclusion criteria were present: (1) study that was irrelevant to our review objective, (2) studies that only focuses on one specific infection, (3) studies of which the type was misclassified (such as reviews or pre-marketing studies) and (4) studies of which full text could not be retrieved.

ClinicalTrials.gov

ClinicalTrials.gov was also searched for observational studies on TNF inhibitors. This website is a service of the National Institutes of Health (NIH) and maintained by the National Library of Medicine at the NIH. It contains information on registered clinical trials, either publicly or privately funded.[111] All information from this website is up-to-date along with the progress of each clinical trial and can be freely accessed by the public. The search in this website for eligible studies was conducted through the Advanced Search webpage (https://clinicaltrials.gov/ct2/search/advanced). Search terms that were used included “adalimumab OR etanercept OR infliximab OR golimumab OR certolizumab”. Search results were then narrowed down by selecting only observational studies and studies with results. We only included studies with

reported results because adverse events were displayed on the website as part of study results. Studies identified from the search were first checked for related publications though reviewing the “study results” section. Data on infections were extracted directly from the “study results” section in the website.

Inclusion/Exclusion Criteria: Studies that were included in our final review must meet all of the following requirements: (1) observational studies on one or more of the five TNF inhibitors, (2) studies reporting data on specific infections related to TNF inhibitors and (3) study purpose was pertinent to evaluation of TNF inhibitor treatments. Studies were filtered out if any of the following exclusion criteria were present: (1) study that was irrelevant to our review objective, (2) studies of which the study population was already included in another study (in this case, we used data from the most recent study or the study with a bigger sample size).

For each study included in the final review, information extracted for our summary purpose included (if available): author, year, country, study type, study size, disease condition, follow-up period, study treatment and data on reported infections. Summary tables were created for each data source on distribution of included studies by different TNF inhibitor and disease condition.

Analyses

For each data source, we summarized included studies (cases in FAERS) by TNF inhibitor and indication. We also examined the distribution of cases in FAERS before and after 4/22/2008 (approval date of certolizumab pegol) based

on each case's primary suspect therapy start date, as infliximab, adalimumab and etanercept were approved almost 10 years earlier than certolizumab pegol and golimumab, which may have masked the current distribution with large amount cases from period before certolizumab pegol and golimumab were approved.

Specific Aim 1: Specific Aim 1 was to describe and contrast features of FAERS and observational studies in post-marketing surveillance for TNF inhibitor related infections. We hypothesized that we would observe differences between FAERS data and observational studies data regarding infections related to TNF inhibitors in terms of duplication of cases, incompleteness and timeliness. General issues with spontaneous reporting systems stated in Chapter 2 were addressed and examined for FAERS data and for observational studies if feasible.

Duplication of Cases

FAERS: Duplicates were excluded from the summary of case reports. A case was considered as a duplicate if it had identical information with another case on patient characteristics (such as age, gender, weight, and country), product names and treatment date and/or date adverse event began.

Observational studies: Duplicates were considered as same study cohorts. If multiple articles were published on the results from the same study cohort (often seen in extended study or follow up study), only the latest data were used in our analysis. If a published report only used a subgroup of the data of

another published study, we used the one with the bigger study population in our final analysis.

Timeliness

In order to compare the timeliness of FAERS reports and observational findings, we searched in PubMed for articles published on TNF inhibitor-associated infections with FAERS data. Search terms used were: (adalimumab OR etanercept OR infliximab OR golimumab OR certolizumab pegol) and (Medwatch or FDA adverse event reporting system or Food and Drug administration adverse event reporting system). Inclusion Criteria were: (1) a peer-reviewed article, (2) published in English and (3) studies used FAERS evidence and examined TNF inhibitor-associated infections. No restriction on publication date was applied. Exclusion criteria were: (1) study that was irrelevant to our review objective, (2) study that was based on cases from non-US country and (3) studies of which the full text could not be retrieved.

First online availability or the publication dates of studies using FAERS data and observational studies included in our systematic literature review were extracted for comparison based on the median of publication year. Although the publication date is usually months after the completion of a study and often subject to delays due to factors such as manuscript revisions, we still used the publication date as the measure to examine timeliness, as studies can only make an impact after being published. If multiple publications were found on the same study, only the earliest publication date was used for comparison.

Incompleteness and Inaccuracy in FAERS

Any information that was vacant in a report was considered as missing data. The rates of missing data were calculated for cases' demographic information, such as age, gender, and weight. The rates of missing values in primary suspect therapy start date and event began date were also examined.

Specific Aim 2: Specific aim 2 was to examine and compare the number of TNF inhibitor related infections identified and the specific level of identified TNF inhibitor related infections using FAERS and observational approach. We hypothesized that we would observe differences in the number and the specific level of identified TNF inhibitor related infections using FAERS and observational studies identified in the literature or ClinicalTrials.gov.

In FAERS, we searched for all primary suspect cases of infections related to each TNF inhibitor. We excluded cases for which the MedDRA® preferred term coded as "Infection" as this term was not specific and compromised large proportion of our total cases, which would bias our summary of preferred terms and our analyses for specific aim 3. We then filtered through the preferred terms reported for all cases and identified unique terms in Excel.

For each observational study included in our literature review, we extracted all reported infection terms from the body of text of individual article and recorded the terms for each article in Excel in a cumulative manner with the same term only recorded once.

For each observational study identified from ClinicalTrials.gov, we extracted all reported infection terms from the “Serious Adverse Events” and “Other Adverse Events” sections for each study and the terms for each study in Excel in a cumulative manner as well with the same term only recorded once

The total number of all identified unique infection terms were then summarized for each data source and compared for its number and specificity.

Specific Aim 3: Specific aim 3 was to examine the consistency between FAERS and an observational approach in the type and reporting rates of common infections associated with TNF inhibitors. We hypothesized that we would observe a difference in the type of most common infections reported in FAERS and observational studies. The reporting rates of cases (patients) for the same TNF inhibitor-infection combination would differ as well.

For each approach, 5 rankings were generated for identified infections related to each TNF inhibitor (adalimumab, etanercept, infliximab, certolizumab pegol and golimumab) respectively. Rankings from observational studies were based on the rate of each infection using pooled frequency of each infection divided by the total number of patients with any infection. The ranking of infections from FAERS data was based on the percentage of primary suspect cases for each infection among all TNF inhibitor related infection cases after eliminating “Infection” cases.

The generated rankings were then compared to examine whether these data sources provided relatively consistent findings by subjective examination.

For infections that were among top 10 on both rankings, we further checked if the reporting rates were similar.

Specific Aim 4: Specific aim 4 was to examine the applicability of additional analyses using FAERS data. Analyses were performed on all infections cases related to TNF inhibitors.

Only cases that were appropriately documented were used in our analyses. That is, any missing values or values that did not make sense were excluded from our analyses. For instance, age or weight was documented less than or equals to 0, or primary suspect therapy start date was later than the infection event began date. We also excluded patients who were older than 80 years old, as age older than this would highly confound our analyses results.

Descriptive statistics were summarized on patient age, gender, TNF inhibitor, weight, and time to onset of adverse events. Time to onset of adverse events was calculated in days using “Date Adverse Event Began” minus “Primary Suspect Therapy Start Date”. Age and time to onset of adverse events were kept as continuous variables and the mean and median value for each TNF inhibitor was calculated (Table 3).

Multiple logistic regressions were performed to explore the relationship between case endpoint outcome (death, life-threatening, hospitalization or other) and patient demographic and treatment characteristics (Table 4). Patient demographic characteristics included age (years), gender (male/female) and weight (lbs.); treatment characteristics included TNF inhibitors (etanercept,

infliximab, adalimumab, certolizumab pegol, or golimumab), and time to onset of adverse event (days). Bivariate logistic regression analyses were conducted by taking each independent variable, one at a time, to examine its impact on case outcomes. Four regression models with different case outcomes were used to examine the influence of independent variables. A p-value < 0.2 was the criterion for a variable to be included in the multiple logistic regression model. A p-value <0.05 was considered of statistical significance in the multiple logistic regression analyses.

Table 3 Independent Variables for Multiple Logistic Regression Models

	Variable Type	Levels
Age	Continuous	Years (0-80)
Gender	Categorical	Male, female
Weight	Continuous	Lbs.
TNF inhibitors	Categorical	Etanercept, adalimumab, infliximab, certolizumab pegol, golimumab
Time to onset of adverse event	Continuous	Days

Table 4 Dependent Variables for Multiple Logistic Regression Models

	Dependent variable	Case Definition
Regression 1	Death	All death cases
Regression 2	Life-threatening	All cases reported with an outcome labeled as life-threatening, excluding death cases
Regression 3	Death or life-threatening	Cases with an outcome of death or life–threatening or both.
Regression 4	Hospitalization	Cases with an outcome of hospitalization, excluding any case with a outcome record of death or life-threatening

Time to onset analysis was conducted to examine differences in survival distributions between TNF inhibitors. For the purpose of the analysis, reports without adverse event began date or therapy start date were excluded from analysis; reports with a therapy start date before drug approval date was excluded as well. In our case, the event time was the infection began date, thus all of the people in our analysis had the event.

The analysis was performed for each TNF inhibitor for all infections (defined by SOC “infections and infestations”, as a whole class) first and differences between drugs for all infections were examined. The survival distribution was estimated using Kaplan-Meier method. The estimates of survival functions from Kaplan-Meier method for five TNF inhibitors were then compared using the log-rank test to examine whether there was a significant difference (p-value < 0.05) in the survival across the five groups.

Human Research Review Committee (HRRC) Approval

Analyses proposed in this study do not require UNM HRRC approval as the FAERS database is available for public inquiries and no identifiable private information can be obtained. According to the federal regulations for human subject research (45 CFR Part 46), IRB review of analysis of publicly available de-identified data is not required.

CHAPTER FOUR: RESULTS

This chapter presents the results from our analyses for each of the specific aims of the study. Descriptions and general summaries of the data retrieved from FAERS, literature and ClinicalTrials.gov are first displayed. Detailed description and comparisons of evidence from each type of data source are then presented, followed by results of rankings for assessing consistency in reported infections between the three data sources. Lastly, we report results from logistic regressions on predictors and outcomes of infection cases, as well as the results of Kaplan-Meier functions comparing the time to onset of event between different TNF inhibitors.

Description of Retrieved Data

FAERS Cases

A total of 163,789 primary suspect cases of infections and infestations were identified in FAERS database for all TNF inhibitors of interest as of November 2016. The number of retrieved cases and retrieval dates are summarized in Table 5 for each TNF inhibitor. Etanercept has the largest number of cases (n=68,807), while golimumab has the least number of cases (n=4,884).

We further checked the proportion of each TNF inhibitor related infection cases before 4/22/2008 (the approval date of certolizumab) and after 4/22/2008, based on the reported primary suspect therapy start date (cases with available

therapy start date and event began date, n=68,881). The number and proportion of each TNF inhibitor are displayed in Table 6. The proportion of available cases among all cases for each TNF inhibitor is also presented in Table 6. Etanercept still had the largest number of cases (n=14,770, 53.3%) for the period before 4/22/2008, while adalimumab was the dominant one (n=17,383, 42.2%) after 4/22/2008. The combined proportion of certolizumab pegol and golimumab increased to 12.7% for the period after 4/22/2008.

Data Extracted from Systematic Literature Review

We identified a total of 225 articles from our initial search in PubMed in November 2016. After applying inclusion and exclusion criteria, thirty articles remained for our final analysis. The reference lists of included articles were reviewed for additional relevant articles and 23 articles were considered eligible for our final review. Thus, we have a total of 53 articles in our final data synthesis. The PRISMA flow diagram of included articles is presented in Figure 3.

Among included studies, two were extended phase 4 studies of randomized clinical trials and fifteen studies used registry data or chart records. The number of participants in each individual study ranged from 12 to 1879 and the length of study period ranged from 8 weeks to 72 months. Eight studies reported adverse events on multiple TNF inhibitors. The number of included studies on each disease condition and TNF inhibitor is presented in Table 7.

Data Extracted from ClinicalTrials.gov

We located 78 observational studies in the ClinicalTrials.gov website in December 2016, of which 18 studies were excluded for having irrelevant study purposes (such as focusing on patients' work productivity) and not reporting any infection adverse events (n=5). Another 3 studies were further excluded because their study populations were contained in included studies. A total of 52 studies were included in our final review. Seven of the included studies were found with related publications on study results, among which 5 were included in our systematic literature review in PubMed. Of included studies from ClinicalTrials.gov, one study was on three TNF inhibitors (adalimumab, infliximab and etanercept). Besides that study, twenty-four studies were on adalimumab, sixteen studies were on etanercept and eleven studies were on infliximab. Two studies were on certolizumab pegol and only one study was on golimumab. The study population of included studies ranged from 25 to 7740 and the length of study period ranged from 14 weeks to 72 months. The number of included studies on each disease condition and TNF inhibitor is presented in Table 8.

Table 5 Data Retrieval Dates and Number of Primary Suspect Cases in FAERS by Each TNF Inhibitor

	Data retrieval date	Number of primary suspect cases	%
Etanercept	11/05/2016	68807	42.0%
Adalimumab	11/01/2016	60649	37.0%
Infliximab	11/02/2016	22499	13.7%
Certolizumab Pegol	11/03/2016	6950	4.2%
Golimumab	11/03/2016	4884	3.0%
Total		163789	100%

Table 6 Distribution of Primary Suspect Cases by Each TNF Inhibitor Before/After 4/22/2008

	Before 4/22/2008		After 4/22/2008		Total (% of All Extracted Cases)
	n	%	n	%	
Etanercept	14,770	53.3%	15,440	37.5%	30,210 (43.9%)
Adalimumab	9,401	33.93%	17,383	42.22%	26,784 (44.2%)
Infliximab	3,539	12.77%	3,138	7.62%	6,677 (29.7%)
Certolizumab Pegol	0	0	3,874	9.41%	3,874 (55.7%)
Golimumab	0	0	1,336	3.25%	1,336 (27.4%)
Total (n=68,881)*	27,710	100%	41,171	100%	68,881 (42.1%)

*Total number is different due to limited number of cases with information on primary suspect therapy date and event began date

Figure 3 PRISMA Flowchart of Included Studies from PubMed

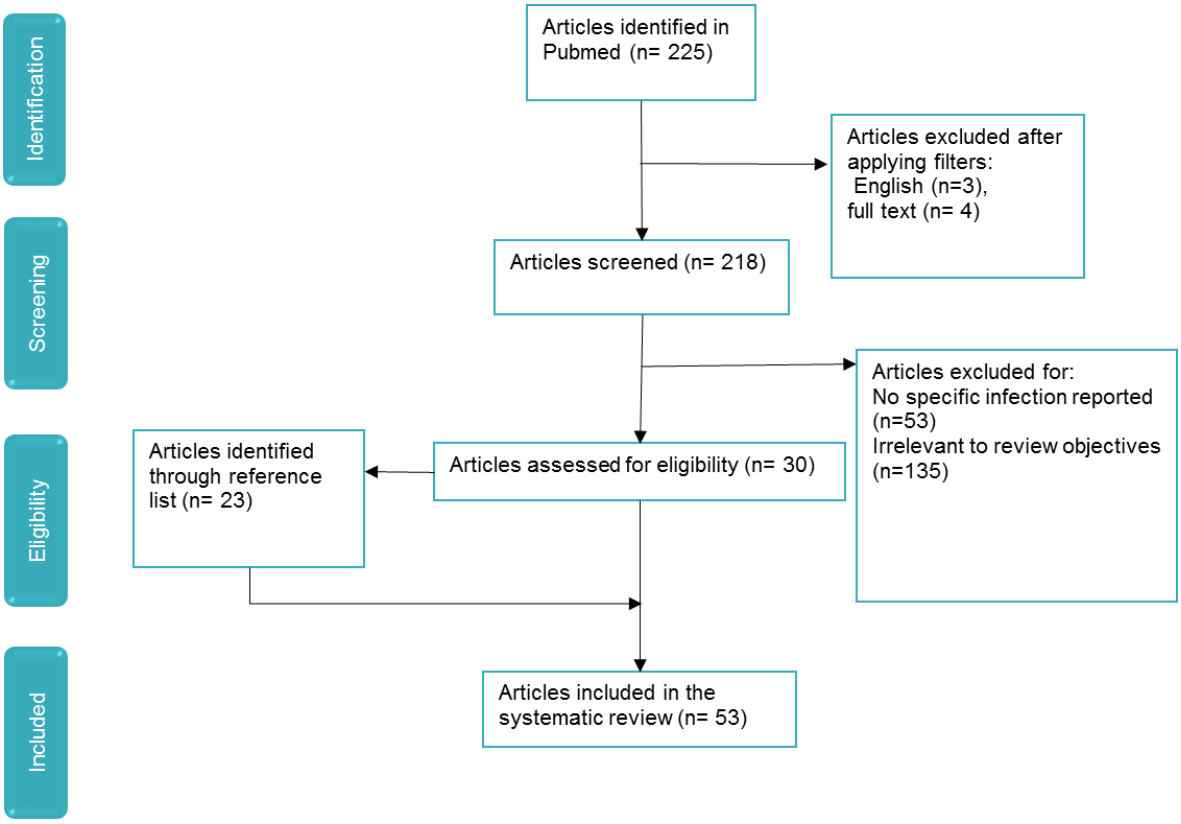


Table 7 Distribution of Included Studies from PubMed by TNF Inhibitor and Indication

	Etanercept (n=22)	Adalimumab (n=17)	Infliximab (n=23)	Certolizumab Pegol (n=1)	Golimumab (n=0)
Crohn's Disease	0	7[112–118]	3[60,119,120]	1[121]	0
Rheumatoid Arthritis	6[63,122–126]	2[125,126]	9[57,63,125–131]	0	0
Lupus Arthritis	1[132]	0	0	0	0
Ulcerative Colitis	0	3[133–135]	4[136–139]	0	0
Uveitis	0	2[140,141]	1[141]	0	0
Psoriasis	8[61,142–148]	1[142]	3[142,149,150]	0	0
Juvenile Idiopathic Arthritis	5[151–155]	2[153,155]	1[155]	0	0
Hidradenitis Suppurativa	0	0	0	0	0
Ankylosing spondylitis	2[156,157]	0	0	0	0
Behçet's Disease	0	0	2[158,159]	0	0
Total	22	17	23	1	0

Table 8 Distribution of Included Studies from ClinicalTrials.gov by TNF Inhibitor and Indication

	Etanercept (n=16)	Adalimumab (n=24)	Infliximab (n=11)	Certolizumab Pegol (n=2)	Golimumab (n=1)
Crohn's Disease	0	2[160,161]	3[162–164]	0	0
Rheumatoid Arthritis	7[165–171]	14[160,171–183]	5[171,184–187]	2[188,189]	1[190]
Lupus Arthritis	0	0	0	0	0
Psoriatic Arthritis	3[191–193]	8[160,175,177,182,183,194–196]	2[186,187]	0	1[190]
Ulcerative Colitis	0	0	0	0	0
Uveitis	0	0	0	0	0
Psoriasis	5[191,192,197–199]	7[160,195,200–204]	3[187,205,206]	0	0
Juvenile Idiopathic Arthritis	1[207]	0	0	0	0
Hidradenitis Suppurativa	0	0	0	0	0
Ankylosing spondylitis	2[208,209]	7[160,175,177,182,183,194,210]	3[186,187,211]	0	1[190]
Behçet's Disease	0	0	0	0	0
Total*	18	37	16	2	3

*Total number exceeds n due to some articles included multiple indications.

Issues of FAERS and Observational Studies Data

Duplication of Cases

FAERS: Our retrieved data from Evidex™ did not contain duplicates, as we were notified that the data on the Evidex™ platform had duplicate case reports removed (more details can be found at http://www.adverahealth.com/assets/pdf/rxfilter_publication_min.pdf).

Literature Review: After applying inclusion and exclusion criteria, we identified two studies that published multiple articles on the same study cohorts.[121,144,212,213] One study published before and after the long-term follow-up results; another study published results on its interim analysis and its final results.

ClinicalTrials.gov: After applying inclusion and exclusion criteria, we identified three observational studies of which the study cohort was already included in other two studies (NCT01077258 was included in NCT01078090; NCT01163318 and NCT01163292 was included in NCT01346501). NCT01077258 was a 2-year prospective observational study on patients from 303 clinics in German and NCT01078090 was a 5-year prospective observational study on patients from 370 clinics in German, which included the clinics in NCT01077258 and overlapped with the study period of NCT01077258.

Timeliness

We identified a total of 38 articles from our initial search with the search terms. Two of these articles were first excluded for not having full text available in PubMed. After applying inclusion and exclusion criteria, a total of 6 articles remained in our analysis.[214–219] The publication dates (first online availability dates) of articles on FAERS evidence ranged from 2001 to 2013 with a median of 2007. The publication dates (first online availability dates) of articles included in our systematic review of observational studies ranged from 2005 to 2016 with a median of 2012.

Incompleteness and Inaccuracy

We checked the amount of missing values for cases' demographic information, such as age, gender and weight, as well as some unreasonable values (e.g. age≤0 years or weight≤0 lbs.). For age variable, we identified 27.4% of the total cases with a missing value or an unreasonable value. For gender, we identified 4.1% of total cases with a missing value. For weight, we identified 29.9% of total cases with a missing value. The rates of missing values for primary suspect therapy start date and event began date were higher (48.3% and 51.7%).

Comparison of the Number and Specificity of Infection Terms

The number of eliminated “infection” (preferred term level) cases for each TNF inhibitor in FAERS is summarized in Table 9. The number of unique identified infection terms from each approach (FAERS, published articles and ClinicalTrials.gov) for each TNF inhibitor is presented in Table 10. For all TNF inhibitors, the FAERS data contains the largest amount of identified terms (ranged from 399 to 824), followed by ClinicalTrials.gov (ranged from 23 to 271) and literature review (ranged from 0 to 90). Adalimumab was found to be associated with the largest number of reported infection types based on the evidence from FAERS (n=824) and ClinicaTrials.gov (n=271), but had the third largest number based on literature review (n=52). Infliximab was associated with the largest number of types of infections based on literature review (n=90), but had the second largest number in FAERS data (n=798) and the third largest number in ClinicalTrials.gov (n=122). Etanercept was associated with the second largest number of types of infections based on evidence from both literature review (n=87) and ClinicalTrials.gov (n=238). Certolizumab pegol had the fourth largest number of infections types from all three data sources, although the numbers were much smaller compared to adalimumab, infliximab and etanercept (FAERS: n=423, literature review: n=3 and ClinicalTrials.gov: n=34). For golimumab, we didn’t find any study reporting specific infections in PubMed. Since certolizumab pegol and golimumab received US FDA approval in 2008 and 2009, respectively, which was less than 10 years from today, there has been very limited number of observational studies published or completed. Despite a

short period of the marketing of certolizumab pegol and golimumab, FAERS database still rendered many more specific infection types than observational studies – the number was over 10 times more than that from observational studies (either literature review or ClinicalTrials.gov).

Most of the observational studies identified from the ClinicalTials.gov website reported adverse events in a standardized manner and often used MedDRA® preferred terms. The number of non-serious infection terms may have been underreported in ClinicalTrials.gov, because some studies only reported serious adverse events and some reported non-serious adverse events that occurred in more than 1%, 2% or 5% of study population. Among studies included from ClinicalTrial.gov, one study had a threshold of 0.5% (NCT01298648), one study had a threshold of 2% (NCT01558089) and 15 studies had a threshold of 5% in reporting non-serious adverse events (NCT01083121, NCT01078402, NCT01316224, NCT01155570, NCT00725452, NCT00988832, NCT00705289, NCT00727298, NCT00779675, NCT00725621, NCT00725543, NCT00724958, NCT00705614, NCT00322439 and NCT01313858). One study measured non-serious adverse events at >1% frequency level but no non-serious adverse event had a frequency above this threshold, thus no non-serious adverse events were reported (NCT01111240). Two studies specifically stated that non-serious adverse events were not collected (NCT01646385 and NCT01557322).

Underreporting of non-serious events also existed in observational studies identified through our PubMed search. Some articles only reported serious

infections cases or adverse events of interest. Two articles reported infection cases by infection sites.[125,126] Infection sites reported in these articles include lower respiratory tract, skin and soft tissue, musculoskeletal, neurological, osteoarticular, upper respiratory tract, cardiovascular, intra-abdominal, urinary tract, and ear, nose, throat. The most reported site is skin and soft tissue.

A comparison of reported infection cases in the same study identified in both literature and ClinicalTrials.gov demonstrated that overall, even for the same observational studies, ClinicalTrials.gov rendered more specific infection terms but had a greater number of cases not reported (Table 11).

FAERS database contains all spontaneously reported cases, regardless of serious adverse events or non-serious adverse events. Serious adverse event cases can be determined in FAERS based upon the reported case outcomes (i.e. hospitalization, disable and death). FAERS data contain individual-level information on demographics and suspect medications but of relatively poor quality (missing, incomplete or inaccurate values); clinicaltials.gov provides no info on demographics; literature usually contains tables on demographics and other confounding factors but were descriptive statistics and for all participants.

To sum, FAERS provided the largest number of specific terms. Terms regarding infections extracted from FAERS were at a more specific level. Terms from ClinicalTrials.gov are more specific compared to those reported in literature and more aligned with FAERS terms (MedDRA® preferred terms level).

Table 9 Distribution of Primary Suspect Cases in FAERS by TNF Inhibitor after Eliminating "Infection" Cases

	Number of dropped "infection" cases	Number of primary suspect cases (excluding "infection" cases)	
	N	N	%
Etanercept	3528	65279	41.8%
Adalimumab	2637	58012	37.1%
Infliximab	854	21645	13.9%
Certolizumab Pegol	363	6587	4.2%
Golimumab	216	4668	3.0%
Total	7598	156191	100%

Table 10 Number of Identified Infection Terms by TNF Inhibitor and Data Source

	FAERS	Literature	ClinicalTrials.gov
Adalimumab	824	52	271
Infliximab	798	90	122
Etanercept	788	87	238
Certolizumab Pegol	423	4	34
Golimumab	399	NA	23

Table 11 Comparison of the Number of Infection Cases and Infection Terms Reported in the Literature and ClinicalTrials.gov for the Same Study

Literature			ClinicalTrials.gov		
Author (Year)	**Number of reported infection cases**	**Number of identified terms**	**Registry Number**	**Number of reported infection cases**	**Number of identified terms**
Shear et al. (2014)	16	7	**NCT00779675**	13	11
Westhovens et al. (2014)	52	10	**NCT00705289**	13	12
Kimball et al. (2015)	231	11	**NCT00322439**	149	58
de Vlam et al. (2015)	66	3	**NCT00938015**	225	65

Consistency in the Types and Reporting Rates of the Most Common Infections

We generated rankings of reported infections with most cases for each TNF inhibitor based on the pooled frequency of each type of infection from data source (FAERS, literature and ClinicalTrials.gov). The top 10 infection types from each approach are summarized in Table 12-16 for each TNF inhibitor (top 5 for certolizumab pegol and golimumab due to limited data for these two TNF inhibitors from observational studies included from the literature and ClinicalTrials.gov). The rankings and comparisons between different data sources are summarized below.

Etanercept (Table 12)

In FAERS, 65,279 infection cases were found for etanercept. The 10 most frequently reported preferred terms related to infections in FAERS were nasopharyngitis (n=9,128, 13.9%), sinusitis (n=6,673, 10.2%), bronchitis (n=4,504, 6.9%), pneumonia (n=3,960, 6.1%), influenza (n=3,615, 5.5%), upper respiratory tract infection (n=2,380, 3.7%), urinary tract infection (n=2,322, 3.6%), herpes zoster (n=2,282, 3.5%), cellulitis (n=1,731, 2.7%) and lower respiratory tract infection (n=1,389, 2.1%). The top 10 reported infections compromised 58.2% of all patients with any type of infections.

In the literature review, a total of 1,376 infection cases were pooled for our evaluation of most frequently reported infection terms. The 10 most frequently reported terms regarding infections were upper respiratory tract infection (n=297,

21.6%), pneumonia (n=284, 20.6%), cellulitis (n=76, 5.5%), viral infection (n=69, 5.0%), nasopharyngitis (n=59, 4.3%), herpes zoster (n=42, 3.1%), flu syndrome (n=38, 2.8%), gastroenteritis (n=33, 2.4%), diverticulitis (n=33, 2.4%), varicella zoster (n=32, 2.3%) and otitis media (n=32, 2.3%). The top 10 reported infections compromised 72.3% of all patients with any type of infections.

For observational studies identified in ClinicalTrials.gov, a total of 1,998 infection cases were pooled for our evaluation of most frequently reported infection terms. The 10 most frequently reported infections were nasopharyngitis (n=354, 17.7%), bronchitis (n=191, 9.6%), upper respiratory tract infection (n=130, 6.5%), pneumonia (n=85, 4.3%), sinusitis (n=82, 4.1%), respiratory tract infection (n=81, 4.1%), urinary tract infection (n=66, 3.3%), herpes zoster (n=57, 2.9%), cystitis (n=36, 1.8%), gastrointestinal infection (n=32, 1.6%) and gastroenteritis (n=32, 1.6%). The top 10 reported infections compromised 57.4% of all patients with any type of infections.

To sum, 4 of 10 infection terms matched between all three data sources (nasopharyngitis, pneumonia, upper respiratory tract infection, and herpes zoster), among which herpes zoster was reported at rates within 1% of each other. Seven of the top 10 infection terms matched between evidence from FAERS and ClinicalTrials.gov (nasopharyngitis, sinusitis, bronchitis, pneumonia, upper respiratory tract infection, urinary tract infection and herpes zoster); 2 were reported at rates within 1% of each other (urinary tract infection and herpes zoster). Respiratory cases accounted for 6 of the top 10 infection terms in both

FAERS and observational studies from ClinicalTrials.gov. Nasopharyngitis was ranked the first place in both as well.

Table 12 Top 10 Reported Infections Related to Etanercept from Each Data Source

Rank	FAERS (n=65,279)		Literature (n=1,376)		ClinicalTrials.gov (n=1,998)	
1	Nasopharyngitis	9,128 (13.9%)	Upper Respiratory Tract Infection	297 (21.6%)	Nasopharyngitis	354 (17.7%)
2	Sinusitis	6,673 (10.2%)	Pneumonia	284 (20.6%)	Bronchitis	191 (9.6%)
3	Bronchitis	4,504 (6.9%)	Cellulitis	76 (5.5%)	Upper Respiratory Tract Infection	130 (6.5%)
4	Pneumonia	3,960 (6.1%)	Viral Infection	69 (5.0%)	Pneumonia	85 (4.3%)
5	Influenza	3,615 (5.5%)	Nasopharyngitis	59 (4.3%)	Sinusitis	82 (4.1%)
6	Upper Respiratory Tract Infection	2,380 (3.7%)	Herpes Zoster	42 (3.1%)	Respiratory Tract Infection	81 (4.1%)
7	Urinary Tract Infection	2,322 (3.6%)	Flu Syndrome	38 (2.8%)	Urinary Tract Infection	66 (3.3%)
8	Herpes Zoster	2,282 (3.5%)	Gastroenteritis	33 (2.4%)	Herpes Zoster	57 (2.9%)
9	Cellulitis	1,731 (2.7%)	Diverticulitis	33 (2.4%)	Cystitis	36 (1.8%)
10	Lower Respiratory Tract Infection	1,389 (2.1%)	Varicella Zoster Infection	32 (2.3%)	Gastrointestinal Infection	32 (1.6%)
			Otitis Media	32 (2.3%)	Gastroenteritis	32 (1.6%)

*n is the total number of patients with any infection

Adalimumab (Table 13)

In FAERS, 58,012 infection cases were found for adalimumab. The 10 most frequently reported preferred terms related to infections in FAERS were nasopharyngitis (n=8,992, 15.5%), sinusitis (n=4,540, 7.8%), pneumonia (n=3,613, 6.2%), bronchitis (n=3,251, 5.6%), influenza (n=2,583, 4.5%), urinary tract infection (n=2,286, 3.9%), herpes zoster (n=1,918, 3.3%), upper respiratory tract infection (n=1,514, 2.6%), cellulitis (n=1,278, 2.2%) and ear infection (n=1,062, 1.8%). The top 10 reported infections compromised 53.5% of all patients with any type of infections.

In the literature review, a total of 193 infection cases were pooled for our evaluation of most frequently reported infection terms. The 10 most frequently reported terms regarding infections upper respiratory tract infection (n=43, 22.3%), lower respiratory tract infection (n=22, 11.4%), bacterial infection (n=15, 7.8%), bacteremia (n=12, 6.2%), viral infection (n=8, 4.1%), otitis media (n=7, 3.6%), pneumonia (n=5, 2.6%), tonsillitis (n=5, 2.6%), sinusitis (n=5, 2.6%), sepsis (n=4, 2.1%) and herpes zoster (n=4, 2.1%). The top 10 reported infections compromised 67.4% of all patients with any type of infections.

For observational studies identified in ClinicalTrials.gov, a total of 2,284 infection cases were pooled for our evaluation of most frequently reported infection terms. The 10 most frequently reported infections were nasopharyngitis (n=359, 15.7%), bronchitis (n=314, 13.7%), urinary tract infection (n=246, 10.8%), pneumonia (n=131, 5.7%), respiratory tract infection (n=97, 4.2%), upper

respiratory tract infection (n=64, 2.8%), herpes zoster (n=51, 2.2%), sinusitis (n=44, 1.9%), sepsis (n=39, 1.7%) and pharyngitis (1.7%). The top 10 reported infections compromised 60.6% of all patients with any type of infections.

To sum, 4 of 10 infection terms matched between all three data sources (sinusitis, pneumonia, upper respiratory tract infection, and herpes zoster), among which none was reported at rates within 1% of each other. Seven of the top 10 infection terms matched between evidence from FAERS and ClinicalTrials.gov (nasopharyngitis, sinusitis, pneumonia, bronchitis, urinary tract infection, upper respiratory tract and herpes zoster); 3 were reported at rates within 1% of each other (nasopharyngitis, pneumonia and upper respiratory tract infection). Respiratory cases accounted for 6 and 7 of the top 10 infection terms in FAERS and observational studies from ClinicalTrials.gov, respectively, and nasopharyngitis was ranked the first place in both.

Table 13 Top 10 Reported Infections Related to Adalimumab from Each Data Source

Rank	FAERS (n=58,012)		Literature (n=193)		ClinicalTrials.gov (n=2,284)	
1	Nasopharyngitis	8,992 (15.5%)	Upper Respiratory Tract Infection	43 (22.3%)	Nasopharyngitis	359 (15.7%)
2	Sinusitis	4,540 (7.8%)	Lower Respiratory Tract	22 (11.4%)	Bronchitis	314 (13.7%)
3	Pneumonia	3,613 (6.2%)	Bacterial Infection	15 (7.8%)	Urinary Tract Infection	246 (10.8%)
4	Bronchitis	3,251 (5.6%)	Bacteremia	12 (6.2%)	Pneumonia	131 (5.7%)
5	Influenza	2,583 (4.5%)	Viral Infection	8 (4.1%)	Respiratory Tract Infection	97 (4.2%)
6	Urinary Tract Infection	2,286 (3.9%)	Otitis Media	7 (3.6%)	Upper Respiratory Tract Infection	64 (2.8%)
7	Herpes Zoster	1,918 (3.3%)	Pneumonia	5 (2.6%)	Herpes Zoster	51 (2.2%)
8	Upper Respiratory Tract Infection	1,514 (2.6%)	Tonsillitis	5 (2.6%)	Sinusitis	44 (1.9%)
9	Cellulitis	1,278 (2.2%)	Sinusitis	5 (2.6%)	Sepsis	39 (1.7%)
10	Ear Infection	1,062 (1.8%)	Sepsis	4 (2.1%)	Pharyngitis	38 (1.7%)
			Herpes Zoster	4 (2.1%)		

*n is the total number of patients with any infection

Infliximab (Table 14)

In FAERS, 21,645 infection cases were found for infliximab. The 10 most frequently reported preferred terms related to infections in FAERS were pneumonia (n=1,664, 7.7%), tuberculosis (n=1,332, 6.2%), herpes zoster (n=1,022, 4.7%), pulmonary tuberculosis (n=547, 2.5%), sepsis (n=539, 2.5%), abscess (n=496, 2.3%), disseminated tuberculosis (n=492, 2.3%), pneumocystis jirovecii pneumonia (n=481, 2.2%), cellulitis (n=473, 2.2%) and urinary tract infection (n=431, 2.0%). The top 10 reported infections compromised 34.5% of all patients with any type of infections.

In the literature review, a total of 704 infection cases were pooled for our evaluation of most frequently reported infection terms. The 10 most frequently reported terms regarding infections upper respiratory tract infection (n=200, 28.4%), bronchitis (n=55, 7.8%), lower respiratory tract infection (n=37, 5.3%), nasopharyngitis (n=36, 5.1%), tonsillitis (n=31, 4.4%), otitis media (n=31, 4.4%), pneumonia (n=29, 4.1%), sinusitis (n=27, 3.8%), urinary tract infection (n=26, 3.7%), gastroenteritis (n=23, 3.3%) and bacterial infection (n=23, 3.3%). The top 10 reported infections compromised 73.6% of all patients with any type of infections.

For observational studies identified in ClinicalTrials.gov, a total of 419 infection cases were pooled for our evaluation of most frequently reported infection terms. The 10 most frequently reported infections were anal abscess (n=65, 15.5%), pneumonia (n=23, 5.5%), abdominal abscess (n=20, 4.8%),

gastroenteritis (n=20, 4.8%), abscess (n=13, 3.1%), cellulitis (n=11, 2.6%), sepsis (n=11, 2.6%), subcutaneous abscess (n=8, 1.9%), urinary tract infection (n=8, 1.9%), herpes zoster (n=8, 1.9%) and nasopharyngitis (n=8, 1.9%). The top 10 reported infections compromised 46.5% of all patients with any type of infections.

To sum, 2 of 10 infection terms matched between all three data sources (pneumonia and urinary tract infection), among which none was reported at rates within 1% of each other. Six of the top 10 infection terms matched between evidence from FAERS and ClinicalTrials.gov (pneumonia, herpes zoster, sepsis, abscess, cellulitis and urinary tract infection); 4 were reported at rates within 1% of each other (abscess, cellulitis, sepsis and urinary tract infection). Respiratory cases accounted for 5 and 2 of the top 10 infection terms in FAERS and observational studies from ClinicalTrials.gov, respectively.

Table 14 Top 10 Reported Infections Related to Infliximab from Each Data Source

Rank	FAERS (n=21,645)		Literature (n=704)		ClinicalTrials.gov (n=419)	
1	Pneumonia	1,664 (7.7%)	Upper Respiratory Tract Infection	200 (28.4%)	Anal Abscess	65 (15.5%)
2	Tuberculosis	1,332 (6.2%)	Bronchitis	55 (7.8%)	Pneumonia	23 (5.5%)
3	Herpes Zoster	1,022 (4.7%)	Lower Respiratory Tract	37 (5.3%)	Abdominal Abscess	20 (4.8%)
4	Pulmonary Tuberculosis	547 (2.5%)	Nasopharyngitis	36 (5.1%)	Gastroenteritis	20 (4.8%)
5	Sepsis	539 (2.5%)	Tonsillitis	31 (4.4%)	Abscess	13 (3.1%)
6	Abscess	496 (2.3%)	Otitis Media	31 (4.4%)	Cellulitis	11 (2.6%)
7	Disseminated Tuberculosis	492 (2.3%)	Pneumonia	29 (4.1%)	Sepsis	11 (2.6%)
8	Pneumocystis Jirovecii Pneumonia	481 (2.2%)	Sinusitis	27 (3.8%)	Subcutaneous Abscess	8 (1.9%)
9	Cellulitis	473 (2.2%)	Urinary Tract Infection	26 (3.7%)	Urinary Tract Infection	8 (1.9%)
10	Urinary Tract Infection	431 (2.0%)	Gastroenteritis	23 (3.3%)	Herpes Zoster	8 (1.9%)
			Bacterial Infection	23 (3.3%)	Nasopharyngitis	8 (1.9%)

*n is the total number of patients with any infection

Certolizumab Pegol (Table 15)

In FAERS, 6,587 infection cases were found for certolizumab pegol. The 10 most frequently reported preferred terms related to infections in FAERS were pneumonia (n=635, 9.6%), nasopharyngitis (n=384, 5.8%), herpes zoster (n=384, 5.8%), urinary tract infection (n=313, 4.8%), bronchitis (n=292, 4.4%), sinusitis (n=251, 3.8%), influenza (n=194, 3.0%), lower respiratory tract infection (n=183, 2.8%), abscess (n=180, 2.7%) and cellulitis (n=177, 2.7%). The top 10 reported infections compromised 45.4% of all patients with any type of infections.

For observational studies identified in ClinicalTrials.gov, a total of 166 infection cases were pooled for our evaluation of most frequently reported infection terms. The 5 most frequently reported infections were nasopharyngitis (n=111, 66.9%), pneumonia (n=10, 6.0%), pulmonary tuberculosis (n=4, 2.4%), sepsis (n=4, 2.4%) and Urinary tract infection (n=3, 1.8%). The top 5 reported infections compromised 79.5% of all patients with any type of infections.

Because only 1 study reported information on infection cases from the literature review, a total of 4 infection cases were pooled. These 4 infection cases included 2 urinary tract infections, 1 case with clostridium difficile colitis and 1 case with skin infection. Urinary tract infection compromised half of the total cases.

To sum, 1 of the top 5 infection terms matched all three data sources (urinary tract infection). Three of the top 5 infection terms matched between evidence from FAERS and ClinicalTrials.gov (pneumonia, nasopharyngitis,

urinary tract infection); nasopharyngitis was reported at rates within 1% of each other. Respiratory cases accounted for 3 of the top 5 infection terms in both FAERS and observational studies from ClinicalTrials.gov.

Table 15 Most Frequently Reported Infections Related to Certolizumab Pegol from Each Data Source

Rank	FAERS (n=6,587)		Literature (n=4)		ClinicalTrials.gov (n=166)	
1	Pneumonia	635 (9.6%)	Urinary Tract Infection	2 (50.0%)	Nasopharyngitis	111 (66.9%)
2	Nasopharyngitis	384 (5.8%)	Clostridium Difficile Colitis	1 (25.0%)	Pneumonia	10 (6.0%)
3	Herpes Zoster	384 (5.8%)	Skin Infection	1 (25.0%)	Pulmonary tuberculosis	4 (2.4%)
4	Urinary Tract Infection	313 (4.8%)			Sepsis	4 (2.4%)
5	Bronchitis	292 (4.4%)			Urinary tract infection	3 (1.8%)
6	Sinusitis	251 (3.8%)				
7	Influenza	194 (3.0%)				
8	Lower Respiratory Tract Infection	183 (2.8%)				
9	Abscess	180 (2.7%)				
10	Cellulitis	177 (2.7%)				

*n is the total number of patients with any infection

Golimumab (Table 16)

In FAERS, 4,668 infection cases were found for golimumab. The 10 most frequently reported preferred terms related to infections in FAERS were pneumonia (n=620, 13.3%), lower respiratory tract infection (n=399, 8.6%), influenza (n=226, 4.8%), urinary tract infection (n=221, 4.7%), cellulitis (n=181, 3.9%), herpes zoster (n=156, 3.3%), bronchitis (n=150, 3.2%), nasopharyngitis (n=126, 2.7%), sinusitis (n=77, 1.7%) and diverticulitis (n=65, 1.4%). The top 10 reported infections compromised 47.6% of all patients with any type of infections.

Because only 1 observational study reported information on infection cases included from ClinicaTrials.gov, a total of 35 infection cases were pooled. The 5 most frequently reported infections were pneumonia (n=7, 20.0%), subcutaneous abscess (n=4, 11.4%), bronchitis (n=2, 5.7%), bronchopneumonia (n=2, 5.7%) and cellulitis (n=2, 5.7%). The top 5 reported infections compromised 48.6% of all patients with any type of infections. Because no study reported infection cases for golimumab in our literature review, no ranking was generated for golimumab for this data source.

To sum, two of the top 5 infection terms matched between evidence from FAERS and ClinicalTrials.gov (pneumonia and cellulitis); none was reported at rates within 1% of each other. Respiratory cases accounted for 2 and 3 of the top 5 infection terms in FAERS and observational studies from ClinicalTrials.gov, respectively.

Table 16 Most Frequently Reported Infections Related to Golimumab from Each Data Source

Rank	FAERS (n=4,668)		ClinicalTrials.gov (n=35)	
1	Pneumonia	620 (13.3%)	Pneumonia	7 (20.0%)
2	Lower Respiratory Tract Infection	399 (8.6%)	Subcutaneous abscess	4 (11.4%)
3	Influenza	226 (4.8%)	Bronchitis	2 (5.7%)
4	Urinary Tract Infection	221 (4.7%)	Bronchopneumonia	2 (5.7%)
5	Cellulitis	181 (3.9%)	Cellulitis	2 (5.7%)
6	Herpes Zoster	156 (3.3%)		
7	Bronchitis	150 (3.2%)		
8	Nasopharyngitis	126 (2.7%)		
9	Sinusitis	77 (1.7%)		
10	Diverticulitis	65 (1.4%)		

*n is the total number of patients with any infection

Multiple Logistic Regressions and Time to Onset of Event Analysis

Table 17 presents the characteristics of the study sample after checking for missing values and unreasonable values. The total sample included persons with a mean age of 51.9 years (SD=15.4) and the interquartile range of the sample aged from 43 to 63 years, which suggested that our sample were mainly middle-aged patients. Cases with golimumab as the primary suspect therapy had the highest mean age (56.5 years old, SD=14.5) of all cases with TNF inhibitors and certolizumab pegol cases had the youngest mean age (49.1 years old, SD=16.0). The result of ANOVA showed a significant difference age between different TNF inhibitor groups (p-value<0.001).

Females were the majority of the study sample (72.3%) and were dominant across all TNF inhibitor groups. Etanercept had the largest proportion of females (75.0%), while infliximab has the smallest proportion of females (60.8%). For all the other 3 TNF inhibitors, females constituted more than 70% of the sample. The result of chi-square test suggested a significant difference in the proportions of gender between different TNF inhibitors (p-value<0.001).

The mean weight in our study sample was 163.4 lbs. (SD=48.2), with the first quartile being 129.8 lbs. and the third quartile being 189.2 lbs. Cases on golimumab had the lowest mean weight of 148.2 lbs. (SD=41.9) and cases on etanercept had the highest mean weight of 165.6 lbs. (SD=52.5). A statistically significant difference was also observed in the mean weight for different TNF inhibitors (p-value<0.001).

We calculated the time period between primary suspect therapy start date and the date when adverse event began, after checking the accuracy and completeness of dates. The median of time to onset of event was 160 days in the total sample. However, the data was quite skewed for the whole sample and also for each TNF inhibitor. Cases related to etanercept was found to have the longest median time to onset of infection event (214 days), which was 3 months longer compared to cases related to adalimumab (median=122 days). Etanercept also had the largest number for its third quartile (879 days), which was almost twice as many as that for adalimumab group and golimumab group. The result of t-test indicated a significant difference in the time to onset of event between different TNF inhibitor groups (p-value<0.001).

Table 17 Demographic Characteristics and Time to Onset of Event of the Study Sample in FAERS

	All (n=68,881)	Etanercept (n=30,210)	Adalimumab (n=26,784)	Infliximab (n=6,677)	Certolizumab pegol (n=3,874)	Golimumab (n=1,336)	p-value
Age (Years)							<0.001
Mean (SD)	51.9 (15.4)	53.4 (14.0)	51.3 (15.5)	48.5 (19.2)	49.1 (16.0)	56.5 (14.5)	
Q1 (25%)	43	46	41	34	37	48	
Q2 (50%)	54	55	53	52	51	59	
Q3 (75%)	63	63	63	64	61	67	
NA	18020 (26.2%)	8600 (28.5%)	6991 (26.1%)	1077 (16.1%)	1009 (26.0%)	343 (25.7%)	
Gender							<0.001
Female	47777 (63.4%)	20869 (69.1%)	19083 (71.2%)	4014 (60.1%)	2829 (73.1%)	982 (74.3%)	
Male	18319 (26.6%)	6940 (23.0%)	7438 (27.8%)	2587 (38.8%)	1015 (26.2%)	339 (25.7%)	
NA	2785 (4.0%)	2401 (7.9%)	263 (1.0%)	76 (1.1%)	30 (0.7%)	15 (1.1%)	
Weight (lbs.)							<0.001
Mean (SD)	163.4 (48.2)	165.6 (52.5)	165.8 (46.7)	157.6 (48.8)	160.1 (50.0)	148.2 (41.9)	
Q1 (25%)	129.8	132	132	125.4	125.4	116.6	
Q2 (50%)	157	162.8	160	151.8	151.8	143	
Q3 (75%)	189.2	195.8	191.4	184.8	184.8	174.9	
NA	46937 (68.1%)	(90.7%)	13972 (52.2%)	2608 (39.1%)	2168 (55.9%)	780 (58.4%)	
Time to onset of event							<0.001
Mean (SD)	466.3 (690.5)	598.5 (821.2)	343.1 (514.3)	526.3 (752.3)	295.1 (400.9)	299.1 (376.9)	
Q1 (25%)	31	32	26	39	42	31	
Q2 (50%)	160	214	122	197	153	149	
Q3 (75%)	611	879	435	690.5	365	441	

*P-value from ANOVA or chi-square tests; Total number of females and males may not add up to the total number of cases for all/each TNF inhibitor due to missing values.

Table 18 shows the distribution of primary suspect TNF inhibitors by disease condition. Overall, rheumatoid arthritis was the most common condition for all TNF inhibitor groups (49.7%), followed by Crohn's disease (14.5%) and Psoriasis (12.9%). Hidradenitis Suppurativa was the least common condition identified across all TNF inhibitor groups and was only 0.06% of our study sample. The distribution was overall consistent with the labeled indications for each TNF inhibitor (see Table 1 for labeled indications). For example, according to the labeling information, only etanercept and adalimumab have been approved for juvenile idiopathic arthritis, which was reflected in the distribution table as well. Etanercept and adalimumab compromised 93.2% of all cases related to juvenile idiopathic arthritis. Although all TNF inhibitors have been approved for treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, etanercept was the most common primary suspect drug.

Table 18 Distribution of Primary Suspect Cases in FAERS by FDA-Approved Indication and TNF Inhibitor

	All	Etanercept	Adalimumab	Infliximab	Certolizumab pegol	Golimumab
Rheumatoid Arthritis	34267	17439 (58.6%)	12239 (46.4%)	2332 (41.4%)	1452 (44.7%)	805 (70.6%)
Juvenile Idiopathic Arthritis	775	539 (1.8%)	183 (0.7%)	33 (0.6%)	9 (0.3%)	11 (1. 0%)
Psoriatic Arthritis	7319	4633 (15.6%)	2301 (8.7%)	226 (4.0%)	41 (1.3%)	118 (10.4%)
Crohn's Disease	9965	6 (0.0 %)	6295 (23.9%)	1982 (35.0%)	1675 (51.6%)	7 (0.6%)
Ulcerative Colitis	1400	2 (0.0 %)	798 (3.0%)	555 (9.8%)	10 (0.3%)	35 (3.1%)
Psoriasis	8906	5378 (18.1%)	3313 (12.6%)	197 (3.5%)	7 (0.2%)	11 (1.0%)
Hidradenitis Suppurativa	44	4 (0.0 %)	30 (0.1%)	10 (0.2%)	0 (0.0%)	0 (0.0%)
Uveitis	65	3 (0.0 %)	46 (0.2%)	13 (0.2%)	2 (0.1%)	1 (0.1%)
Ankylosing Spondylitis	3437	1755 (5.9%)	1160 (4.4%)	320 (5.6%)	50 (1.5%)	152 (13.3%)
Total	66178	30210	26784	6677	3874	1336

*A patient may have multiple indications.

Table 19 presents the distribution of primary suspect TNF inhibitor by case outcome of interest reported in the FAERS database. We observed a significant difference between TNF inhibitor groups for all three types of outcomes studied (p-value<0.001). Adalimumab was associated with the highest number of death cases and also the highest proportion of death cases (n=1,366, 11.1%), followed by infliximab (n=611, 9.7%) and etanercept (n=788, 6.6%). Golimumab had the smallest number of death cases (n=45, 3.4%) and certolizumab had the lowest proportion of death cases (n=86, 3.2%).

The number of cases with a life-threatening outcome by TNF inhibitor (after excluding death cases) is also presented in Table 19. Adalimumab was associated with the highest number of cases with life-threatening outcomes (n=417), followed by infliximab (n=340) and etanercept (n=313). However, infliximab had the highest proportion of life-threatening cases (6.0%), followed by adalimumab (3.8%) and etanercept (2.8%). Golimumab had the smallest number of life-threatening cases (n=22) but certolizumab pegol had the lowest proportion (n=82, 1.7% (1.73% vs. 1.74% for golimumab)).

Distribution of cases with an outcome of hospitalization was also examined from each TNF inhibitor, after excluding death and life-threatening cases (Table 19). Adalimumab had the highest number of cases with an outcome of hospitalization (n=7,802), followed by etanercept (n=6,221) and infliximab (n=3,300). Adalimumab also had the largest proportion of hospitalization cases (74.4%), followed by infliximab (61.5%) and etanercept (57.4%). Golimumab had

the smallest number and smallest proportion of hospitalization cases (n=567, 45.5%).

Table 20 presents the distribution of primary suspect TNF inhibitor by case outcomes of interest reported in the FAERS database after excluding observations with a missing value in any of our covariates for multiple logistic regressions. We observed a significant difference between TNF inhibitor groups for all three types of outcomes studied (p-value<0.001). Etanercept was associated with the highest number of death cases and also the highest proportion of death cases (n=106, 9.4%), followed by adalimumab (n=373, 9.1%) and infliximab (n=168, 6.5%). Golimumab had the smallest number of death cases (n=11, 3.4%) and certolizumab had the lowest proportion of death cases (n=23, 2.3%).

Adalimumab was associated with the highest number of cases with life-threatening outcomes (n=163), followed by infliximab (n=155) and etanercept (n=102). However, etanercept had the highest proportion of life-threatening cases (10.0%), followed by infliximab (6.4%) and adalimumab (4.3%). Golimumab had the smallest number of life-threatening cases the lowest proportion (n=6, 1.9%). Adalimumab had the highest number of cases with an outcome of hospitalization the largest proportion of hospitalization cases (n=2,715, 75.7%), followed by infliximab (n=1,448, 63.7%) and certolizumab pegol (n=662, 68.1%). Golimumab had the smallest number of hospitalization cases (n=192, 61.9%).

Table 19 Distribution of Primary Suspect Cases in FAERS by Case Outcome and TNF Inhibitor

	Etanercept	Adalimumab	Infliximab	Certolizumab Pegol	Golimumab	p-value
Death						<0.001
Yes	788 (6.6%)	1366 (11.1%)	611 (9.7%)	86 (3.2%)	45 (3.4%)	
No	11161 (93.4%)	10911 (88.9%)	5702 (90.3%)	2607 (96.8%)	1268 (96.6%)	
Life-threatening						<0.001
Yes	313 (2.8%)	417 (3.8%)	340 (6.0%)	45 (1.7%)	22 (1.7%)	
No	10848 (97.2%)	10494 (96.2%)	5362(94.0%)	2562 (98.3%)	1246 (98.3%)	
Hospitalization						<0.001
Yes	6221 (57.4%)	7802 (74.4%)	3300 (61.5%)	1484 (57.9%)	567 (45.5%)	
No	4627 (42.6)	2692 (25.6%)	2062 (38.5%)	1078 (42.8%)	679 (54.5%)	

***** P-value from chi-square tests; most serious outcome was used if a case reported multiple outcomes (Death>Life-threatening>Hospitalization); “No” cases contain all cases with less serious outcomes.

Table 20 Distribution of Primary Suspect Cases in FAERS by Case Outcome and TNF Inhibitor (After Excluding Cases with Missing Values in Covariates for Multiple Logistic Regression)

	Etanercept	Adalimumab	Infliximab	Certolizumab Pegol	Golimumab	p-value
Death						<0.001
Yes	106 (9.4%)	373 (9.1%)	168 (6.5%)	23 (2.3%)	11 (3.4%)	
No	1020 (90.6%)	3748 (90.9%)	2428 (93.5%)	994 (97.7%)	316 (96.6%)	
Life-threatening						<0.001
Yes	102 (10.0%)	163 (4.3%)	155 (6.4%)	22 (2.2%)	6 (1.9%)	
No	918 (90.0%)	3585 (95.7%)	2273(93.6%)	972 (97.8%)	310 (98.1%)	
Hospitalization						<0.001
Yes	567 (61.8%)	2715 (75.7%)	1448 (63.7%)	662 (68.1%)	192 (61.9%)	
No	351 (38.2%)	870 (24.3%)	825 (36.3%)	310 (31.9%)	118 (38.1%)	

***** P-value from chi-square tests; most serious outcome was used if a case reported multiple outcomes (Death>Life-threatening>Hospitalization); “No” cases contain all cases with less serious outcome

Results of Multiple Logistic Regressions

Multiple Logistic Regression 1 (Outcome=Death)

The results of the multiple logistic regression on the association between case outcome death and predictors (TNF inhibitors, demographics and time to onset of event) are presented in Table 21. Compared to the reference TNF inhibitor group (etanercept), the odds of death was 0.251 with a p-value <0.001 in the certolizumab pegol group, which indicated a significant difference in the probability of death cases between certolizumab pegol group and etanercept group. A significant difference was also observed for the golimumab group. The odds of death was 0.282 with a p-value <0.001 in the golimumab group, compared to the etanercept group.

The logistic regression results also showed that there was a statistically significant difference in the odds of death between males and females. The odds of death in males was 1.499 times that in females with a p-value <0.001. Older age seemed to be associated with a higher odds of death, but the effect was very minimal (OR=1.048, p<0.001). With every unit (lbs.) increase in weight, the odds of death was 0.993, which was almost 1.0, meaning there is no difference as one unit change in weight (although the p-value is <0.001). No difference was observed in the odds of death as one-day change in time-to-onset of infection event (OR=1, p=0.304).

Table 21 Results of Multiple Logistic Regression 1 (n=9,187, Outcome=Death)

	Odds Ratio	95% CI	P-value
Intercept	0.017	(0.010, 0.028)	<0.001
TNF Inhibitors			
Etanercept	Ref.	-	-
Adalimumab	1.023	(0.811, 1.291)	0.846
Infliximab	0.818	(0.630, 1.061)	0.130
Certolizumab Pegol	0.251	(0.158, 0.401)	<0.001
Golimumab	0.282	(0.148, 0.536)	<0.001
Age (Years)	1.048	(1.042, 1.054)	<0.001
Gender			
Female	Ref.	-	-
Male	1.460	(1.229, 1.743)	<0.001
Weight (lbs.)	0.993	(0.991, 0.995)	<0.001
Time to onset of event (Days)	1.000	(0.999, 1.000)	0.304

Pseudo R^2=0.089

Multiple Logistic Regression 2 (Outcome=Life-Threatening, Excluding Death Cases)

The results of the multiple logistic regression on the association between life-threatening outcomes and predictors (TNF inhibitors, demographics and time to onset of event) are presented in Table 22. Compared to the reference TNF inhibitor group (etanercept), all other TNF inhibitors were associated with less severe outcomes. The odds of a life-threatening event (excluding death) was 0.404 with a p-value less than 0.001 in the adalimumab group, which indicated a significant difference in the probability of life-threatening cases between adalimumab group and etanercept group. Significant differences were also observed for the infliximab, certolizumab pegol and golimumab groups when comparing to the etanercept group (infliximab vs. etanercept: OR=0.620, p<0.001; certolizumab pegol vs. etanercept: OR=0.204, p<0.001; golimumab vs. etanercept: OR=0.155, p<0.001).

The logistic regression results also showed that there was a statistically significant difference in the odds of life-threatening cases between males and females. The odds of having a case with a life-threatening outcome was 1.775 with a p-value less than 0.001 in males when comparing that to females. Older age had a greater odds of death, but such difference was not clinically important in practice settings (OR=1.012, p<0.001). With every unit (lbs.) increase in weight, the odds of having a life-threating outcome was 0.996, which was also not very clinically meaningful, although the p-value is less than 0.001. A statistically significant difference was observed in the odds of having a life-

threatening outcome as one-day change in time-to-onset of infection event, although the odds ratio approached 1.0 (OR=0.999, p=0.021).

Table 22 Results of Multiple Logistic Regression 2 (n=8,506, Outcome=Life-Threatening)

	Odds Ratio	95% CI	P-value
Intercept	0.102	(0.064, 0.163)	<0.001
TNF Inhibitors			
Etanercept	Ref.	-	-
Adalimumab	0.404	(0.312, 0.524)	<0.001
Infliximab	0.620	(0.475, 0.810)	<0.001
Certolizumab Pegol	0.204	(0.127, 0.328)	<0.001
Golimumab	0.155	(0.067, 0.358)	<0.001
Age (Years)	1.012	(1.007, 1.018)	<0.001
Gender			
Female	Ref.	-	-
Male	1.775	(1.453, 2.168)	<0.001
Weight (lbs.)	0.996	(0.994, 0.998)	<0.001
Time to onset of event (Days)	0.999	(0.999, 1.000)	0.021

Pseudo R^2=0.039

Multiple Logistic Regression 3 (Outcome=Death or Life-threatening)

The results of the multiple logistic regression on the association between cases with either death or a life-threatening outcome and predictors (TNF inhibitors, demographics and time-to-onset of event) are presented in Table 23. Compared to the reference TNF inhibitor group (etanercept), all other TNF inhibitors were associated with less severe outcomes. The odds of death/life-threatening outcome was 0.676 with a p-value less than 0.001 in the adalimumab group, which indicated a significant difference in the probability of death/life-threatening cases between adalimumab group and etanercept group. Significant differences were also observed for the infliximab, certolizumab pegol and golimumab groups when comparing to the etanercept group (infliximab vs. etanercept: OR=0.713, p=0.001; certolizumab pegol vs. etanercept: OR=0.219, p<0.001; golimumab vs. etanercept: OR=0.206, p<0.001).

The logistic regression results also showed that there was a statistically significant difference in the odds of death/life-threatening outcome between males and females. The odds of having a case with an outcome being death or life-threatening was 1.632 with a p-value less than 0.001 in males when comparing to that of females. Older age seemed to have a greater odds of death/life-threatening outcome, but the effect was also negligible (OR=1.032, p<0.001). With every unit (lbs.) increase in weight, the odds of having a death/life-threating outcome was 0.994 (p-value<0.001). No statistically significant difference was observed in the odds of having a death/life-threatening

outcome as one-day change in time-to-onset of infection event (OR=1.0, p=0.623).

Table 23 Results of Multiple Logistic Regression 3 (n=9,187, Outcome=Death or Life-Threatening)

	Odds Ratio	95% CI	P-value
Intercept	0.089	(0.063 0.127)	<0.001
TNF Inhibitors			
Etanercept	Ref.	-	-
Adalimumab	0.676	(0.565, 0.809)	<0.001
Infliximab	0.713	(0.586, 0.868)	0.001
Certolizumab Pegol	0.219	(0.156, 0.307)	<0.001
Golimumab	0.206	(0.123, 0.346)	<0.001
Age (Years)	1.032	(1.028, 1.036)	<0.001
Gender			
Female	Ref.	-	-
Male	1.632	(1.425, 1.869)	<0.001
Weight (lbs.)	0.994	(0.992, 0.995)	<0.001
Time to onset of event (Days)	1.000	(0.999, 1.000)	0.623

Pseudo R^2=0.064

Multiple Logistic Regression 4 (Outcome=Hospitalization, Excluding Death and Life-Threatening Cases)

The results of the multiple logistic regression on the association between the outcome hospitalization and predictors (TNF inhibitors, demographics and time to onset of event) are presented in Table 24. Compared to the reference TNF inhibitor group (etanercept), the odds of hospitalization was 1.925 with a p-value less than 0.001 in the adalimumab group, which indicated a significant difference in the odds of having an outcome of hospitalization between adalimumab group and etanercept group. A significant difference was also observed for the certolizumab pegol group. The odds of hospitalization was 1.341 with a p-value of 0.003 in the certolizumab pegol group, compared to the etanercept group.

The logistic regression results also showed that there was a statistically significant difference in the odds of hospitalization between males and females. The odds of having a case with an outcome being hospitalization was 1.634 with a p-value less than 0.001 in males when comparing that to females. With every unit (lbs.) increase in weight, the odds of having a hospitalization case was 0.996 (p-value<0.001). No statistical significant difference was observed in the odds of having a hospitalization case with one-year change in age (OR=1, p=0.877) or one-day change in time-to-onset of infection event (OR=1, p=0.784).

Table 24 Results of Multiple Logistic Regression 4 (n=8,058, Outcome=Hospitalization)

	Odds Ratio	95% CI	P-value
Intercept	2.607	(2.038, 3.335)	<0.001
TNF Inhibitors			
Etanercept	Ref.	-	-
Adalimumab	1.925	(1.649, 2.248)	<0.001
Infliximab	0.998	(0.849, 1.173)	0.976
Certolizumab Pegol	1.341	(1.106, 1.625)	0.003
Golimumab	0.976	(0.746, 1.277)	0.861
Age (Years)	1.000	(0.997, 1.003)	0.877
Gender			
Female	Ref.	-	-
Male	1.634	(1.466, 1.821)	<0.001
Weight (lbs.)	0.996	(0.995, 0.997)	<0.001
Time to onset of event (Days)	1.000	(0.999, 1.000)	0.784

Pseudo R^2=0.024

Time to Onset of Event Analysis

The Kaplan-Meier estimates (unadjusted) of survivor function of time to infection event reported in FAERS for the five TNF inhibitors are presented in Figure 4. We observed that cases related to etanercept had an overall longest time before an infection event occurred and the highest survival rate, followed by infliximab and adalimumab. The Kaplan-Meier curves for certolizumab pegol and golimumab cases were very close with golimumab having a better survival rate between 200 and 800 days and certolizumab pegol having a slightly better survival rate after 800 days. However, both certolizumab pegol and golimumab had the lowest survival rates compared to the other three TNF inhibitors.

The results of the log-rank test are displayed in Table 25. The p-value of the log-rank test was less than 0.001, which indicated that there is a statistically significant difference in survival between different TNF inhibitors. By comparing the number of observed events to the number of expected events, we can see that the etanercept and infliximab had fewer events than expected events, suggesting better survival probabilities than adalimumab, certolizumab pegol and golimumab.

Figure 4 Kaplan-Meier Estimates of Time to Onset of Infections Related to Each TNF Inhibitor

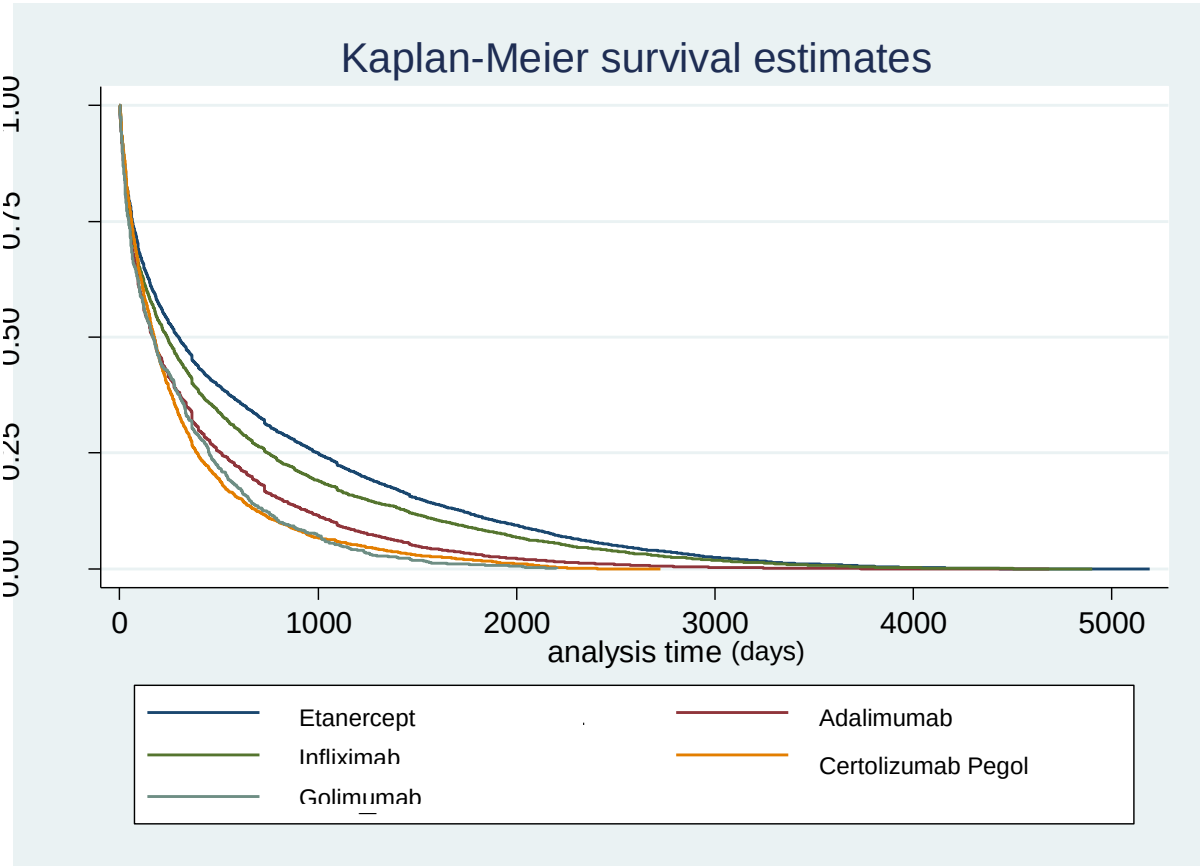


Table 25 Results of Log Rank Test

	Events Observed	Events Expected
TNF Inhibitors		
Etanercept	17926	21505.55
Adalimumab	17222	14139.26
Infliximab	4503	4767.53
Certolizumab Pegol	2210	1638.23
Golimumab	701	511.43
Total	42562	42562.00

Chi^2 (4) = 1629.32
$Pr>Chi^2$ = 0.0000

Table 26 Summary of Results for Each Specific Aim

Specific Aims	Results
Specific Aim 1	FAERS provided timelier evidence; differences were observed in terms of duplicated reports; incompleteness and inaccuracy exist in FAERS while it was not possible to assess in observational studies.
Specific Aim 2	FAERS rendered the greatest number and level of specificity of reported TNF inhibitor related infections; FAERS > ClinicalTrials.gov > Literature
Specific Aim 3	Moderate consistency was observed, especially between FAERS and ClinicalTrials.gov
Specific Aim 4	Multiple logistic regressions and time to onset of event analysis were applicable with FAERS data

CHAPTER FIVE: DISCUSSION

This chapter presents the discussion regarding the study results and our recommendations for future research on adverse events. The chapter begins with discussions of the results from analyses with respect to each of the study aims, followed the limitations in our study design. Lastly, we provide our recommendations for future research in our conclusions, along with the strengths of our study.

Features of FAERS and Observational Data

FAERS data and observational data (either from the literature or from ClinicalTrials.gov) demonstrated considerable differences in the method of extracting data, summarizing data and assessing data. Due to the spontaneous nature of FAERS, it provides many more adverse event terms and terms of higher specificity. Individual patient level data in FAERS also allow for additional analyses. Published articles usually serve as a venue for researchers to present their findings, convey their opinions and provide a direction for further research, thus they often do not present complete or detailed information on the data collected for individuals. ClinicalTrials.gov, compared to the literature, rendered much more detailed information on adverse events as safety information is a mandatory element to report for registered studies, although data are still not at the individual patient level. However, it is important to have comparable data

from each source for the most efficient data synthesis of information regarding adverse events. By using standardized terminology (such as MedDRA® terminology) and reporting specific adverse event terms (such as preferred terms in MedDRA®) in publications and records for registered studies, it would be more efficient to extract and compare data regarding adverse events from all data sources.

Issues of FAERS and Observational Studies Data

The difference in the number of publications between observational studies and studies using FAERS data was very significant in our summaries. Only 6 studies identified in PubMed reported TNF inhibitor related infections using FAERS. The initial search for any study on any TNF inhibitor using FAERS data also generated a limited number of articles (n=38), compared to 225 articles from the initial search for observational studies. This may reflect researcher's lack of awareness about the ability to use FAERS data or potential concerns that researchers may have with FAERS data.

FAERS data indeed are subject to several issues as we examined in our study, such as incompleteness and inaccuracy, which is an inherent issue from the special data collecting process used in FAERS. We examined the amount of missing values for cases' demographics and our findings on the completeness of demographics are consistent with the findings by Getz et al., however, the missing rates of dates are lower than the rates reported in their article.[92] Duplicated cases are another issue with FAERS or other spontaneous reporting

system. However, this issue may be addressed and solved through filtering process with the help of open source technologies.[220] Duplicated cohorts also exist in publications of observational studies. We identified a few publications in PubMed on the same study and a few registered studies on ClinicalTrials.gov that shared the same study cohort as well. Such issues need to be considered and examined carefully when conducting systematic reviews or meta-analysis.

Despite the issues with the quality of the FAERS data, we found that FAERS provided more timely evidence compared with observational studies. Although the assessment of timeliness of FAERS was based on only 6 articles identified in PubMed, both the range and the median of the publication dates suggest that FAERS may provide preliminary evidence on adverse events almost 4 years earlier than observational studies (range: 2001-2013 vs. 2005-2016; median: 2007 vs. 2012). Findings from studies using FAERS could potentially be reported in an even timelier manner as awareness and utilization of FAERS increases.

Number and Specific Level of Infection Terms Identified

In this study, we identified a total of 824 preferred terms related to infection for adalimumab, 798 preferred terms for infliximab, 788 preferred terms for etanercept, 423 preferred terms for certolizumab and 399 preferred terms for golimumab in FAERS. The number was on average 8 times more than that from ClinicalTrial.gov and 35 times more than that from the literature. FAERS

demonstrated its usefulness in identifying more types of and more on specific infections.

Compared to the literature, ClinicalTrials.gov, as another source of observational data, provided more detailed information on adverse event cases as an adverse event profile is a mandatory requirement for registered studies and often times the events are recorded in a more standardized manner (such as MedDRA® terminology). Comparisons of the reported infection cases for the same study between the literature and its record in ClinicalTrials.gov demonstrated that ClinicalTrials.gov could be a better data source to extract data on adverse events if specific adverse event terms were desired. It was out of our expectation that only 5 studies overlapped between studies from ClinicalTrials.gov and articles included in our review. Most of the registered studies in ClinicalTrials.gov did not publish their findings. Adverse events profiles from published observational studies could be potential supplementary materials to information extracted from ClinicalTrials.gov.

Of note, even among the preferred terms in FAERS data, which are of relatively high level of specificity, there still are terms that are more general and terms that are more specific. This issue also exists among observational studies. As healthcare professionals have different ways to record medical information and often times they need to make a judgment in a short period of time, the level of detail of the report or reported adverse event terms may largely vary. This issue reflects a lack of standardization in recording and reporting adverse events,

which poses potential difficulty for the most efficient data extraction and safety assessment.

Only 7 out of 52 (13.5%) observational studies that were identified from ClinicalTrials.gov were found to have been published. This percentage is much lower compared to the finding from Ross and colleagues on US National Institutes of Health (NIH) funded clinical trials.[221] The authors conducted a cross-sectional analysis to describe the publication patterns of clinical trials funded by NIH and registered on ClinicalTrials.gov. They identified 635 NIH funded clinical trials which were registered on or after September 13th, 2005 and were completed as of December 31st, 2008. These studies were then searched for publication in Medline and 68% of these studies were found to have been published. One explanation for the low publication rate of observational studies identified in our study is that most of the studies were funded by pharmaceutical companies rather than NIH. Funding source could be a factor influencing publication of research results and non-commercial funded studies were more likely to be published.[222,223] Publication bias could be another explanation for the low publication rate, however, a study found that publication bias more likely originates with investigators instead of journal editors.[222] Further investigation on the low rate of publication of observational studies identified in our study is needed as timely and informed decisions require public dissemination of research results and unbiased reporting of study outcomes. Share of research evidence prevents redundant efforts and is a commitment to the use of our limited medical and financial resources.

The difference observed in our study in the reporting of infections between ClinicalTrials.gov and the published paper on the same study suggested a disconnect in the reporting of adverse events between study profiles and publications. According to the FDA's *Guideline for Industry on the Structure and Content of Clinical Study Reports*, it is required for investigators to report all adverse events for each patient in both preferred term and the reported term (original term used by investigator) as well as the rate for each observed adverse event. However, it is rare to find a published article that provides a list of all specific adverse events or reports adverse events using preferred terms. Such disconnect between clinical trial archived data and published data impedes efficient data synthesis and examination of adverse events and keeps the public from getting comprehensive and transparent information from studies, which is contradictory to the purpose of making informed decisions. Thus, we recommend the use of a standardized terminology system of adverse events (e.g. MedDRA®) as well as a full report on observed adverse events along with the publication of study results in any journal.

Effects of Difference in Approval Dates and Market Share on Our Summary Results

In this study, we identified a total of 163,789 primary suspect cases of infections and infestations in the FAERS database for all TNF inhibitors (Table 5 & 6). Etanercept had the largest number of cases (n=68,807), which accounted for 42% of our total cases, while golimumab had the smallest number of cases (n=4,884), accounting for 3%. Etanercept (Enbrel®), adalimumab (Humira®) and

infliximab (Remicade®), which were the first three TNF inhibitors approved in the US, together accounted for 92.8% of our total cases. Certolizumab pegol (Cimzia®) and golimumab (Simponi®), which are the most recently approved TNF inhibitors (approval date: 4/22/2008 and 4/24/2009), accounted for only 7.2% of our cases of infections and infestations data. It was not unexpected that etanercept, adalimumab and infliximab were related to a higher number of cases as they were approved prior to the other two TNF inhibitors by almost a decade. Additionally, these three earlier approved TNF inhibitors have been used for the treatment of more disease conditions than the other two. After examination of the proportions of each TNF inhibitor related infection cases before 4/22/2008 (the approval date of certolizumab) and after 4/22/2008, we observed some changes in the proportions of earlier approved TNF inhibitors and a larger proportion of certolizumab pegol and golimumab. The proportion of etanercept cases decreased by 15% (although the number of cases was close to the number before the cut-off date) and adalimumab cases increased by almost 10%, representing a doubling of cases. This could be potentially explained by the increased number of patients' uptake of adalimumab a few years after it was approved for multiple indications. The current sales and market shares of TNF inhibitors also suggests the leading position of adalimumab, followed by etanercept and infliximab.[224,225] The large difference in the case numbers between TNF inhibitors was directly associated with the difference in the number of infection terms reported. The number of infection terms identified for adalimumab in FAERS was over as twice as many as that for golimumab.

Imbalance in the number of identified observational studies and reported infection terms was also evident. Only one observational study was identified for certolizumab pegol with 4 reported infection terms and none for golimumab from our literature review. Two studies were identified for certolizumab pegol 34 reported infection terms) and 1 study for golimumab (23 reported infection terms) from ClinicalTrials.gov.

Consistency in the Most Commonly Reported Infections

Our study found that 20-40% of the most reported infections summarized in the rankings matched between all three data sources. FAERS and ClinicalTrials.gov rankings have a better consistency in the top reported infections compared to either FAERS vs. literature or literature vs. ClinicalTrials.gov. Respiratory infections accounted for the majority of the terms listed in the ranking for all three data sources. The lack of consistency between the literature vs. FAERS or literature vs. ClinicalTrials.gov was probably due to the limited number of observational studies identified and the limited sample size in individual observational study. The majority of the included articles only reported serious infections or infections of their study's interest, which led to the underreporting of infection cases. FAERS and ClinicalTrials.gov require standardized reporting using MedDRA terms, which helps with a more complete safety profile.

The relative consistency between FAERS evidence and evidence from observational studies registered on ClinicalTrials.gov shows that both data

source provide reliable evidence. It also indicates the utility of using FAERS data as a primary source of examining drug associated adverse events and the potential important role that ClinicalTrials.gov could play in tracking the safety profile from observational studies.

Application of Additional Analyses

The individual patient level information for each adverse event case in FAERS allows researchers to perform quantitative analyses identify potential risk factors for different types of adverse events and different adverse event outcomes. We performed logistic regression on the predictors of interest and case outcomes (death, life-threatening outcome, hospitalization and other less severe outcomes). Specific TNF inhibitor, gender and age were associated with the case outcome in all of our logistic regression models. Certolizumab pegol and golimumab, younger age and being female were found to be associated with less severe event outcomes. However, the pseudo R-squared values for our regression models were very small, varying from 0.024 to 0.089, which means a limited model fit and that only 2.4% to 8.9% of the variation in the outcome could be explained by our models. One important confounder that we did not include in these models was the groups of infections based on the severity of infections. A patient may have developed a serious infection such as pneumonia, which was often associated with hospitalization or more sever outcome, while another patient may have had rhinitis, which usually only requires medications. Such variety in the severity of infections may have significant implications regarding differences in case outcomes.

Of note, almost 90% of the included cases were eliminated in the multiple logistic regressions due to missing values in the covariates, especially the weight variable (Table17). Among all 5 TNF inhibitors, etanercept was the one with the largest proportion and number of cases with missing values. Such large amount of missing values in our data may have resulted in the odds ratios of having a life-threatening outcome for TNF inhibitors not aligning with the distribution shown in Table 19 but aligning with Table 20 where we presented the distribution by outcome and TNF inhibitor after removing cases with any missing value in the covariates. In Table 19, we observed that infliximab is associated with the largest proportion of cases with a life-threatening outcome, however, after removing cases with missing values in the covariates, etanercept became the one with the largest proportion of cases with a life-threatening outcome (Table 20). The odds ratios for TNF inhibitors from our second multiple logistic regression model showed that etanercept is significantly associated with a life-threatening outcome compared to other TNF inhibitors while controlling for covariates (Table 22). This finding was more aligned with the distribution presented in Table 20. We acknowledge the effect of elimination of cases with missing values as well as adjustment of covariates.

We also conducted the time to onset of event analysis. We employed survival analysis and plotted the Kaplan-Meier curves for all infection cases by TNF inhibitor. A statistically significant difference in the survival rates was observed between different TNF inhibitors ($p<0.001$). Etanercept and infliximab had better survival rates. However, considering the approval dates of

certolizumab pegol and golimumab were almost a decade later than the approval of infliximab, etanercept and adalimumab, our analysis might not be “unbiased” to certolizumab pegol and golimumab, as cases related to these two TNF inhibitors with long time to onset of event may have not even been reported yet in FAERS data. Additionally, all cases were spontaneously reported when an infection event occurred, which means all cases had an “event”. The survival analysis conducted using FAERS data was not a typical survival analysis and may not provide unbiased information. Log rank test was performed in our study and a significant difference in the survival rates was observed between TNF inhibitors, however, the log rank test was an overall test and could not provide information on between which TNF inhibitors the significant difference existed. Further analyses are needed to break down results to specific TNF inhibitors. Besides, the survival rates obtained in our analysis were not adjusted for determining factors such as demographic characteristics and infection types. The results may differ if adjusted for potential confounders and etanercept and infliximab may not be associated with better survival rates when comparing with adalimumab, certolizumab pegol and golimumab.

Our study shows that it is feasible to perform advanced analyses with FAERS data but the advanced methodology needs to be applied to adjust for the limitations in FAERS database and unique features of spontaneously reported information.

Limitations of our study

Our study results should be considered in light of several limitations. First, we did not further check potential duplicate cases in the FAERS dataset. Duplicate cases are very common in FAERS data, however, to our knowledge, there is no standardized systematic way to check duplicate cases or control for duplicate cases that can be performed by individual researchers. We were also informed that all cases from the web platform where we retrieved our data have been de-duplicated. Duplicate cases are often checked though individual detailed objective review on available information in the case report, which is only feasible if the data contained small number of cases. Our data set contained 167,389 infection cases and it was not feasible to check the details of all these cases. The existence of duplicate cases may bias our ranking results of most frequently reported infection terms, as well as the results of our additional analyses. However, based on our previous experience, the issue of duplicate cases exists regardless of the drug or the type of adverse events, thus its effect may have balanced out across all infection terms and TNF inhibitors.

The second limitation of our study exists in process of data extraction and synthesis. The literature review results are subject to the reviewer's knowledge and judgment. Other eligible studies may have not been included in our literature review and data synthesis. This limitation also applies to results based on the observational studies identified from ClinicalTrials.gov.

The third limitation in our study is that we did not examine the difference between the most commonly reported infections for TNF inhibitors between patients with different indications, as the mechanism of TNF inhibitor related infections may differ between patients with different conditions.[226] However, due to the limited number of observational studies identified in either literature or ClinicalTrials.gov, we had limited number of reported infection cases, among which the majority were on patients with the most common indications, such as rheumatoid arthritis, Crohn's disease and psoriasis. The sample size would be too small for us to generate meaningful summaries and rankings if we further divide our analysis by disease condition. We did not identify any observational studies in which the participants were with hidradenitis Suppurativa, due to the limited number of cases with this condition.

Besides controlling for different indications, our study is also limited in that we did not take into account the effect of different dosing, activity of disease, patients' previous experience with TNF inhibitors and concomitant drugs, which are also important predictors for infections.[226] Although in FAERS dataset, information on the dosage of primary suspect drug was available, such information was recorded verbatim (exactly the same as entered in the individual report) and with a large proportion of missing values (70%).[92] Information on secondary suspect drug and concomitant drug was also available in FAERS, however, given the large number of cases in FAERS, it was very challenging to summarize all secondary suspect drugs and concomitant drugs.

Another limitation of our study is that in the logistic regression analyses and time to onset of event analysis, we did not specify general infection types (higher level than preferred terms). Firstly, different types of infections have different etiology, which is also directly associated with infection outcome. Secondly, different TNF inhibitors are also likely to be associated with different types of infections or incidence of a certain infection type. The time to onset of event also differ by infection type.

Our study did not examine the potential effect from stimulated reporting associated with factors such as FDA boxed warnings. The FDA updated the boxed warning in September 2007 on all TNF inhibitors regarding the risk of infections from two bacteria: *Legionella* and *Listeria*.[227] Stimulated reporting of infection cases in FAERS associated with these two bacteria or even other infection types could be possible after the boxed warning was issued. However, we do not think that this boxed warning would have significant impact on the reported number of cases of specific infections nor biased our study results because (1) the information of the boxed warning was specific to two bacteria not to infections, while preferred terms on infections are usually not specified by type of bacteria, (2) multiple infections can be related to these two bacteria and this boxed warning would not lead to an increase of the number of reported cases with any particular infection and (3) even if the stimulated reported existed, the effect would not have been pronounced in our data as the FDA boxed warning was issued 10 years ago.

Strengths of Our Study

Our study provides valuable information and adds a unique contribution to current knowledge on TNF inhibitors related infections and post-marketing surveillance approaches on adverse events. To our knowledge, our study was the first study that examined the consistency in the evidence from different post-marketing surveillance approaches through systematic review and detailed summaries.

Our study is also one of the few studies that employed FAERS data to assess common infections related to TNF inhibitors. Despite the over two decades' existence of the FAERS database, few studies have been published on the potential association between TNF inhibitors and infections using FAERS data, which also indicates that FAERS has been underused by researchers. Our study demonstrates the utility of FAERS in terms of providing specific level information regarding adverse events and consistency in its evidence compared to findings from observational studies.

Our study also assessed the feasibility of multiple logistic regression and survival analyses using the individual level information in FAERS. Despite the general issues with FAERS data, such as large amount of missing values, the results from both analyses rendered interesting preliminary findings and suggest the potential of employing additional statistical analyses to FAERS data.

The findings in our study provide support regarding the reliability and use of FAERS data. We hope our findings would enhance the understanding of how

to use FAERS data, what to expect from FAERS data and what to take into account when conducting data mining in FAERS.

Conclusion

These analyses demonstrated the beneficial attribute of FAERS to provide specific infection terms regarding the amount and specific level of terms. Our analyses also showed the usefulness of ClinicalTrials.gov, as one of the data source of observational studies, of offering much detailed information on adverse events compared to studies identified in the literature. Overall, the literature was not an optimal source for extracting information regarding specific infections as it contained much fewer reported terms and very limited studies on certain indications and relative newly approved TNF inhibitors (certolizumab pegol and golimumab).

Overall, the evidence of most commonly reported infections were somewhat consistent between FAERS and observational studies. The evidence was more similar between FAERS and ClinicalTrials.gov. Among the top ranked (most frequently reported) infections, respiratory infections accounted for the majority. Other frequently reported infections included urinary tract infection, herpes zoster and abscess, etc.

The individual level information on each case in FAERS distinguished itself from observational studies and allows for additional statistical analysis such as regressions and survival analysis. It is feasible to perform such analyses but advanced methodology may be needed to control for limitations inherent in the FAERS data.

Researchers that are interested in drugs' adverse events profile should consider using FAERS as a primary source to identify adverse events if specificity was desired. ClinicalTrial.gov could be a valuable resource for obtaining evidence on adverse events from observational studies. Researchers should always consider limitations of each data source. When using FAERS, incompleteness and inaccuracy should be examined first. Underreporting issue should be in mind when using data from either source.

Future studies should further examine the consistency of evidence on most common infections related to TNF inhibitors when stratifying the cases by indication. Multiple logistic regressions and time to onset of event analysis should also be further stratified by indication as well as infection type. It would also be interesting to examine the survival function between TNF inhibitors by year so that we can control for the bias introduced by different approval dates of TNF inhibitors and predict the occurrence of infections based on previous trends.

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