Retrospective cohort study of anti-tumor necrosis factor agent use in a Veteran Population

Introduction: Anti-tumor necrosis factor (TNF) agents are effective for several immunologic conditions (rheumatoid arthritis (RA), Crohn's disease (CD), and psoriasis). The purpose of this study was to evaluate the efficacy and safety of anti-TNF agents via chart review. **Methods:** Single-site, retrospective cohort study that evaluated the efficacy and safety of anti-TNF agents in veterans initiated between 2010-2011. Primary aim evaluated response at 12 months post-index date. Secondary aims evaluated initial response prior to 12 months post-index date and infection events. **Results:** A majority of patients were prescribed anti-TNF agents for CD (27%) and RA (24%). Patients were initiated on etanercept (41%), adalimumab (40%), and infliximab (18%) between 2010-2011. No differences in patient demographics were reported. Response rates were high overall. Sixty-five percent of etanercept patients, 82% of adalimumab patients, and 59% of infliximab patients were either partial or full responders, respectively. Approximately 16% 11%, and 12% of etanercept, adalimumab, and infliximab were non-responders, respectively. Infections between the groups were non-significant. Etanercept and adalimumab patients had higher but non-significant odds of being a responder relative to infliximab. **Conclusions:** Most patients initiated with anti-TNF agent were responders at 12 months follow-up for all indications in a veteran population.

Title:

Retrospective cohort study of anti-tumor necrosis factor agent use in a Veteran Population

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Disclosures

Dr. Bounthavong has received a grant from UCB pharmaceuticals, which is the manufacturer of Cimzia (certolizumab pegol). IIS #: 002296

Drs. Madkour and Kazerooni declare that there are no conflicts of interest regarding the publication of this article.

Abstract:

Introduction: Anti-tumor necrosis factor (TNF) agents are effective for several immunologic conditions (rheumatoid arthritis (RA), Crohn's disease (CD), and psoriasis). The purpose of this study was to evaluate the efficacy and safety of anti-TNF agents via chart review.

Methods: Single-site, retrospective cohort study that evaluated the efficacy and safety of anti-TNF agents in veterans initiated between 2010-2011. Primary aim evaluated response at 12 months post-index date. Secondary aims evaluated initial response prior to 12 months post-index date and infection events.

Results: A majority of patients were prescribed anti-TNF agents for CD (27%) and RA (24%). Patients were initiated on etanercept (41%), adalimumab (40%), and infliximab (18%) between 2010-2011. No differences in patient demographics were reported. Response rates were high overall. Sixty-five percent of etanercept patients, 82% of adalimumab patients, and 59% of infliximab patients were either partial or full responders, respectively. Approximately 16% 11%, and 12% of etanercept, adalimumab, and infliximab were non-responders, respectively. Infections between the groups were non-significant. Etanercept and adalimumab patients had higher but non-significant odds of being a responder relative to infliximab.

Conclusions: Most patients initiated with anti-TNF agent were responders at 12 months follow-up for all indications in a veteran population.

Introduction:

In the past two decades, biologic therapies have reshaped how clinicians approached chronic disease management (Agarwal, 2011a, 2011b; Ford et al., 2011; Lichtenstein et al., 2009; Mayberry et al., 2013; Singh and Cameron, 2012). Immunologic disorders such as rheumatoid arthritis (RA) and Crohn's disease (CD) have traditionally relied on oral pharmacotherapy for treatment of acute symptoms, management, and remission. However, oral therapies were unable to provide long-term control and disease progression resulting in relapse and hospital admission/surgery. Biologic agents, such as monoclonal antibodies, target the host's immune system to attenuate the self-destructive immune response, which is the cause of RA and CD. Clinical efficacy with biologics has been reported in RA and CD as well as a reduction in hospital admission/surgery (Bodger, 2002; Lundkvist et al., 2008). More importantly, biologic therapy has improved the quality of life for patients suffering with these chronic diseases (Feagan et al., 2009; Staples et al., 2011).

Monoclonal antibodies, in particular, the anti-tumor necrosis factor (TNF) agents, have demonstrated significant reductions in disease symptoms, progression, and improvement in patient quality of life (Feagan et al., 2009; Ford et al., 2011; Lundkvist et al., 2008; Nixon et al., 2007; Ordás et al., 2011). In several studies, anti-TNF agents have increased the proportion of patients who experience remission; thereby, controlling the disease and limiting permanent damage. In some studies, remission duration has been reported for several years (Ancuța et al., 2009; Emery et al., 2010; van der Heijde et al., 2006).

RA is a systemic autoimmune disorder which is characterized by inflammation of the synovial joints (Segal et al., 2008). RA affects about 0.5% to 1.0% of the US population with a prevalence of 1.3 million (Gabriel and Michaud, 2009; Helmick et al., 2008). The health burden of RA in the

US was estimated to be 98 Disability Adjusted Life Years (DALYS) lost per 100,000 population; and 1 RA-related death per 100,000 population (Lundkvist et al., 2008). In the VA, there were a total of 1,694 RA-related mortalities from 1999 to 2004 (Lee et al., 2007). The age-adjusted 5-year RA-related mortality rate among patients with a single condition relative to no other condition was 6.05 (95% confidence interval [CI]: 4.90, 7.20) (Lee et al., 2007). The average annual costs of RA per person in the US was $12,558 (adjusted for 2006 $US) (Lundkvist et al., 2008).

The goal of therapy for patients with RA is to control and reduce the rate of degeneration of the joints due to immunologic destruction by the host's immune system (Agarwal, 2011a). In addition, quality of life and increased productivity are important milestones for treatment. Anti-TNF agents have been reported to reduce the rate of radiographic progression and improve short-term inflammatory symptoms (Bathon et al., 2000; Breedveld et al., 2006; Choy et al., 2012; Emery et al., 2009; Keystone et al., 2008, 2009, 2004; Klareskog et al., 2004; Maini et al., 1999; Moreland et al., 1999; St Clair et al., 2004; van de Putte et al., 2004; Weinblatt et al., 2003, 1999). Consequently, improvement in clinical outcomes has resulted in improved quality of life for RA patients. To date, there are five FDA-approved anti-TNF agents for RA: adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®), golimumab (Simponi®), and infliximab (Remicade®) (Agarwal, 2011b).

Crohn's disease is a chronic inflammation of the gastrointestinal tract that is characterized by abdominal pain, diarrhea, gastrointestinal bleeding, bowel perforations, and fistulas (Baumgart and Sandborn, 2012). The incidence of Crohn's disease in the United States (US) was 7.9 cases per 100,000 population (1990-2000); and the adjusted prevalence was 174 per 100,000 population (2001) (Loftus et al., 2007, 2002). In 2009, the average annual age- and gender-

adjusted incidence rate of CD among veterans was 33 per 100,000 population (range: 27 to 40) (Hou et al., 2013). The age- and gender-adjusted point prevalence of CD among veterans was 287 per 100,000 population (Hou et al., 2013). Prior to the wide-spread use of anti-TNF agents, the average annual cost per patient in the US was estimated to be $19,237 (adjusted for 2012 $US) with surgery responsible for a majority of direct costs (55.8%) (Bodger, 2002). However, after the widespread use of anti-TNF agents, the average annual cost per patient with CD was $13,699 per year (adjusted for 2012 $US) (Kappelman et al., 2008).

Biologic therapies, such as anti-TNF agents, for Crohn's disease have provided clinically meaningful improvement in patient reported outcomes while maintaining remission (Ford et al., 2011; Hanauer et al., 2006; Louis et al., 2013; Sandborn et al., 2007a, 2007b). As a result, the increased utilization of anti-TNF therapy has shifted costs from hospitalizations and surgeries to medications. Van der Valk, et al. (2012) reported that medication costs were responsible for 70.9% of total direct costs compared to hospitalizations- (19.4%) and surgery-related costs (0.6%) in the Netherlands (van der Valk et al., 2012). Loomes, et al. (2011) reported that total direct costs increased from $3,930 to $25,346 (difference of $21,416, $P<0.005$) after the introduction of infliximab therapy (adjusted for 2010 $CAN) (Loomes et al., 2011). Currently, there are three anti-TNF agents FDA-approved for the treatment and management of CD: adalimumab (Humira), certolizumab pegol (Cimzia), and infliximab (Remicade) (FDA Office of the Commissioner, 2008; NIDDK National Digestive Diseases Information Clearinghouse, n.d.).

The Department of Veterans Affairs has a national formulary that is shared with all the VA medical centers around US and its territories. However, none of the anti-TNF agents are listed on the VA National Formulary (VANF) as of August 2013. This is important because the burden of

111 disease in the VA is significant. There have been no reports that currently investigated the
112 efficacy and safety of anti-TNF agents in the veteran population for all indications.

113 The purpose of this study was to evaluate the efficacy and safety of anti-TNF agent use in the
114 Veterans Affairs San Diego Healthcare System (VASDHS) who initiated therapy in 2010 and
115 2011 for all prescribed indications. Particular attention was focused on RA and CD due to early
116 approvals in these therapeutic areas.

Methods:

This was a single-site, retrospective cohort study that evaluated the efficacy and safety of anti-TNF agents in a veteran population who initiated treatment between 2010 and 2011 and followed-up for 12 months. The study site was at VASDHS, a 296-bed medical facility in the San Diego County, California with a regional patient membership of approximately 232,000 veterans. VASDHS is part of the Veterans Health Administration (VHA), an integrated healthcare system in the US.

Patients were eligible for inclusion if they were 18 years old or greater and initiated on an anti-TNF agent at VASDHS between 2010 and 2011. The index date was determined to be the first fill-date of the anti-TNF agent at VASDHS.

Clinical efficacy was categorized as responder, partial responder, and non-responder which were determined from chart notes as defined by the provider. Responders were defined as any documented report of improvement from baseline based on resolution of symptoms and clinical assessment by the provider. Partial responders were defined as any documented report of partial improvement from baseline based on attenuated but continued symptoms and clinical assessment by the provider. Non-responders were defined as any documented report of no improvement from baseline based on continued or worsening of symptoms and clinical assessment by the provider. Two reviewers independently performed the chart reviews (MB and NM) and any disagreements on clinical response were resolved through group discussion.

Primary indication for the anti-TNF agent was determined through the submission of non-formulary (or prior authorization) consults which were reviewed by the VASDHS pharmacy service pharmacoeconomics/formulary group. Anti-TNF agents are listed as non-formulary in the

VHA; therefore, requests for these agents in VASDHS require a submission of a non-formulary consult. Providers were required to list the primary indication for anti-TNF agent use. If more than one indication was listed, then the primary indication was categorized according to the specialty field of the submitting provider. For example, a rheumatology provider who submitted a non-formulary consult for both arthritis and psoriasis will have the indication categorized for RA.

Primary aim evaluated response at 12 months post-index date. A majority of clinical trails evaluated response at 12 months; therefore, we also followed this convention. Secondary aims evaluated initial response to anti-TNF agents prior to the 12 months post-index date, alternative strategy after failure to respond or development of an adverse drug event to the initial anti-TNF agent, and infection events. Reporting was further stratified into the top three indications: RA, CD, and psoriasis. Infection events included any infection that occurred after the index date up to 12 months post-index date.

This study received appropriate approvals from the UCSD/VASDHS Institutional Review Board and the Research and Development Committee (Protocol #: H120150).

Statistical analysis:

Normality testing was performed using Shapiro-Wilk's test for continuous data. Descriptive analyses for continuous data were presented as mean, standard deviation, and median. Discrete data were presented as frequency and percentage. One-way analysis of variance and Kruskal-Wallis tests were performed for continuous data where appropriate. Pearson's chi-squared and Fisher's exact tests were performed for discrete data.

Logistic regression was performed to evaluate the association between anti-TNF agents and response controlling for potential confounders. The outcome variable was transformed into a binary variable in order to perform the logistic regression. Responders and partial responders were collapsed into "Responders." Non-responder and patients who experienced an adverse drug event were categorized as "Non-responders." Model fit was assessed using Hosmer-Lemeshow test. Statistical significance was defined as $P<0.05$, two-tailed. All analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (Armonk, NY: IBM Corp).

166 **Results:**

167 Baseline

168 A total of 92 patients met the inclusion criteria. Table 1 summarizes the demographic variables of
169 the cohort. The average patient was 50 (SD, 16.2) years old, male (N=77, 84%), non-Hispanic
170 (N=78, 85%), and white (N=68, 74%). CD was the most common indication for an anti-TNF
171 agent (N=25, 27%) followed by RA (N=22, 24%), psoriasis (N=19, 21%), psoriatic arthritis
172 (N=13, 14%), other conditions (N=8, 9%), and ankylosing spondylitis (N=5, 5%). The most
173 common comorbid conditions were hypertension (N=39, 42%), dyslipidemia (N=36, 39%),
174 gastrointestinal conditions excluding CD (N=24, 26%), cardiovascular disease (N=11, 12%), and
175 diabetes (N=11, 12%). Several patients were on prednisone (N=18, 20%) or methotrexate (N=15,
176 16%) at baseline. Less than half of the study patients had previous experience with an anti-TNF
177 agent (N=42, 46%), most commonly adalimumab (N=22) followed by etanercept (N=11) and
178 infliximab (N=9).

179 A majority of patients were started on adalimumab (N=37) and etanercept (N=38) followed by
180 infliximab (N=17) between 2010 and 2011 at VASDHS (Table 2). There were no differences in
181 age (P=0.141), gender (P=0.480), ethnicity (P=0.132), and race (P=0.726) between the three anti-
182 TNF agents. No difference in primary diagnosis for anti-TNF agent use was reported with RA
183 (P=0.119), psoriatic arthritis (P=0.167), ankylosing spondylitis (P=0.474), and other conditions
184 (P=0.157) between the three anti-TNF agents. Infliximab and adalimumab were often used in CD
185 compared to etanercept (P<0.0001). Conversely, a majority of patients received adalimumab to
186 treat psoriasis relative to the other agents (P<0.0001). There were no statistically significant
187 difference in comorbidities between the three anti-TNF agents except for hypertension (P=0.023),
188 other gastrointestinal conditions other than CD (P=0.016), and hypothyroidism (P=0.020). A

majority of patients had tuberculosis screening (N=83, 90%) and hepatitis B screening (N=73, 79%) performed at baseline.

At baseline, methotrexate was only reported by patients who started on etanercept (N=8) and adalimumab (N=7). A small number of prednisone prescriptions were written at baseline during initiation of etanercept (N=6), adalimumab (N=8), and infliximab (N=4). Among patients who started on etanercept at the VASDHS, six had previous experience with it. Similarly, among patients who were initiated on adalimumab and infliximab at VASDHS, eleven and two patients had a previous history with those agents, respectively.

Clinical Response

The average time to first follow-up visit was 86 (SD, 120) days. At the initial follow-up, 73 (83%) patients responded (responder and partial responder) to therapy (Table 3). At 12 months follow-up, a majority of patients responded (responder and partial responder) to therapy (N=65, 71%). After 12 months of follow-up, there were 15 unique cases (16%) of infections that did not require hospital admissions, and three adverse drug events were reported which resulted in discontinuation of anti-TNF agent therapy. Two of the drug events that resulted in discontinuation were infection-related (abscess and surgical wound); the other was for myelosplastic syndrome.

At 12 months follow up, there was no significant differences in responses between anti-TNF agents (P=0.904). In patients initiated on etanercept, 18 (49%) were responders, 6 (16%) were partial responders, 6 (16%) were non-responders, and 2 (5%) had an adverse drug event (myelospastic syndrome and surgical wound infection) at 12 months (Figure 1). In patients initiated on adalimumab, 23 (61%) were responders, 8 (21%) were partial responders, 4 (11%) were non-responders, and 1 (3%) had an adverse drug event (abscess) at 12 months. In patients

initiated on infliximab, 8 (47%) were responders, 2 (12%) were partial responders, 2 (12%) were non-responders, and 0 had an adverse drug event at 12 months. There were missing data for 5, 2 and 5 patients in the etanercept, adalimumab, and infliximab groups, respectively. These missing data were considered missing completely at random; therefore complete-case analysis was appropriate.(Little and Rubin, 2002)

Responders were stratified by RA, CD, and psoriasis for each anti-TNF agent (Figure 2). In RA, 91% of patients receiving adalimumab were responders compared to 78% with etanercept. In CD, 89% of patients receiving infliximab were responders compared to 73% with adalimumab. In psoriasis, 100% of patients receiving adalimumab were responders compared to 64% receiving etanercept.

Infections were reported for 5 (14%), 10 (26%), and 0 (0%) patients in the etanercept, adalimumab, and infliximab groups, respectively. This difference in infection rates between all three anti-TNF agents was statistically significant (P=0.043).

Unadjusted odds of being a responder were 0.60 (95% CI: 0.11, 3.34) and 1.24 (95% CI: 0.21, 7.41) for patients initiated on etanercept and adalimumab relative to infliximab, respectively (Table 4). Controlling for age, gender, and previous history of anti-TNF agent use, the odds of being a responder was 0.91 (95% CI: 0.13, 6.23) and 1.85 (95% CI: 0.26, 13.10) for patients initiated on etanercept and adalimumab relative to infliximab, respectively.

Discussion:

At VASDHS, patients initiated on an anti-TNF agent had a high proportion classified as responder (responder and partial responder) after 12 months of therapy. Reports from several clinical studies support this observation. Weinblatt, et al. (2003) reported that 67% of patients randomized into adalimumab 40 mg every 2 weeks plus methotrexate for RA achieved American College of Rheumatology 20% (ACR20) at 24-week follow-up (Weinblatt et al., 2003). Kameda, et al. (2010) reported that 90% of patients randomized into etanercept 25 mg twice weekly for RA achieved ACR20 at 24-week follow-up (Kameda et al., 2010). Colombel, et al. (2010) investigated the efficacy of infliximab 5 mg per kg plus azathioprine in CD over a 30 week period and reported a remission rate of 57% (Colombel et al., 2010). Sandborn, et al. (2007) evaluated the long-term effectiveness of adalimumab 40 mg weekly and 40 mg every other week over 56 weeks in moderate-to-severe CD (Sandborn et al., 2007b). Remission was maintained in 83% and 79% of patients taking adalimumab 40 mg weekly and adalimumab 40 mg every other week, respectively (Sandborn et al., 2007b).

Ng, et al. (2013) performed a retrospective cohort study of biologic utilization for RA in the VA population from 1999 to 2009 (Ng et al., 2013). Biologics used as the first DMARD increased from 3% in 1999-2001 to 6.7% in 2006-2007 ($P<0.001$) (Ng et al., 2013). However, the proportion of patients who had a biologic dispensed for RA was stable over the years ranging from 18.6% to 26.7% (Ng et al., 2013). We reported that 17% of patients who initiated etanercept previously had been on an anti-TNF agent; and 90% of patients who were initiated on adalimumab at VASDHS had previous experience with an anti-TNF agent. We adjusted for this in the logistic regression model and found that there was no significant confounding with previous history of anti-TNF agent use on the exposure-outcome relationship. A concern with previous anti-TNF agent use is confounding by indication where patients are inherently different due to

253 severity of their disease which results in residual confounding (Salas et al., 1999). Future studies
254 will need to address whether previous history of anti-TNF therapy have an impact on outcomes at
255 12 months follow up.

256 Utilization of anti-TNF agents in the CD veteran population has not been previously performed.
257 However, an evaluation of hospitalization associated with CD in veterans was performed by
258 Sonnenberg and colleagues (Sonnenberg et al., 2009). From 1975 to 2006, the total number of
259 hospitalizations associated with CD among veterans was 54,271 with the highest proportion in
260 the 54-64 year age group (N=22,551) (Sonnenberg et al., 2009). The incidence rate for
261 hospitalization was 11.63 per 1 million population.(Sonnenberg et al., 2009) Among veteran
262 population, CD is a moderately severe chronic disease that has modest resource consumption.
263 However, the use of anti-TNF agents increases the overall direct costs associated with CD. Our
264 results provide real world effectiveness of anti-TNF agents on CD in the veteran population;
265 however, we did not evaluate whether the strategy was based on a top-down or step-up approach
266 (D'Haens, 2009; Hanauer, 2003; Lin et al., 2010). Debate continues on whether a top-down
267 approach is more effective and efficient relative to a step-up approach for CD treatment and
268 management (D'Haens, 2009; Hanauer, 2003; Lin et al., 2010).

269 We reported on anti-TNF agent use across a wide spectrum of different indications. We also
270 presented the effectiveness of anti-TNF agents for the top three indications: RA, CD, and
271 psoriasis, but small sample size prevented us from performing additional statistical tests. The
272 high proportion of patients who were responders for RA, CD, and psoriasis provide some support
273 for the effectiveness of anti-TNF agents at 12 months which parallels the results of other studies
274 (Breedveld et al., 2006; Colombel et al., 2010, 2007; Kameda et al., 2010; Sandborn et al., 2007b;
275 Weinblatt et al., 2003, 1999). Justification for using anti-TNF agents for these three indications

will require a more robust analysis with a larger veteran population along with cost-effectiveness analyses.

Developing infection is a risk associated with using anti-TNF agents. Lane, et al. reported that VA patients using anti-TNF agents for RA from 1998 to 2005 were at risk of being hospitalized for an infection [Hazard Ratio (HR)=1.24; 95% CI; 1.02, 1.50] (Lane et al., 2011). Ford and Peyrin-Biroulet (2013) reported that patients using anti-TNF agents for CD had higher risk of developing an opportunistic infection compared to placebo [Relative Risk (RR)=2.05; 95% CI: 1.10, 3.85] (Ford and Peyrin-Biroulet, 2013). The risk of developing *Mycobacterium tuberculosis* was higher but not significant in patients receiving anti-TNF agents compared to placebo (RR=2.52; 95% CI: 0.62, 10.21) (Ford and Peyrin-Biroulet, 2013). We reported that patients on etanercept and adalimumab developed infections; however, these did not require hospitalizations and were treated with oral antibiotics in the outpatient setting. Furthermore, two infection-related adverse events resulted in discontinuation of the anti-TNF agents. Lane, et al. (2011) reported that patients receiving infliximab for RA had a higher hazard of hospitalized infections relative to etanercept (HR=1.51; 95% CI: 1.14, 2.00); and patients receiving adalimumab had a lower but non-significant hazard of hospitalized infections relative to etanercept (HR=0.95; 95% CI: 0.68, 1.33) (Lane et al., 2011). In our study, we reported that patients in the adalimumab group had more infections compared to the etanercept group; and no infections were reported in the infliximab group. This conflict may be due to the small sample size which potentially introduces type II error. Furthermore, Lane, et al (Lane et al., 2011) focused on hospitalized infections in RA while our report described non-hospitalized infection events for all anti-TNF agent indications. In our study, stratifying by RA, we observed that 2 out of 7 patients receiving adalimumab developed an infection; however, infections were not observed in the other groups for RA (data not presented). Future studies will need to incorporate a larger sample size in order to capture any

300 infection events stratified by disease.

301 Our study has limitations that are inherent to observational studies and studies involving chart
302 reviews. This was a retrospective study that used manual chart reviews to abstract the relevant
303 data. Consequently, there may be some validity issues with how responders and non-responders
304 were determined. Published studies use standardized and validated criteria (ACR, DAS, and
305 CDAI) to generate an objective score for a disease (e.g., RA and CD). However, in practice, these
306 criteria may not always be used or may be impractical. As a result, manual chart reviews are often
307 necessary to determine response to therapy. Previous studies have demonstrated that manual chart
308 reviews may be more sensitive in identifying cases of RA compared to using electronic medical
309 record or ICD-9 coding (Liao et al., 2010; Love et al., 2011; Tinoco et al., 2011). However,
310 interpretation of the meaning and intention of the chart notes require careful attention to the signs
311 and symptoms of disease and improvement in patient functionality. Misclassification may pose a
312 potential source of internal validity; therefore, we took precautions and used two independent
313 chart reviewers to mitigate this problem. This example highlights an important limitation with
314 using chart review in determining response. Due to a lack of objective reporting, evaluation of
315 success with anti-TNF agents would be reduced to evaluation based on a case definition of
316 response. We acknowledge that misclassification is an important bias that cannot be truly ruled
317 out. Ideally, an objective measurement should be recorded in the patient's chart; however, this has
318 not been a requirement for reimbursement or continuation of anti-TNF agents. Future policy
319 development may consider this as a need in order to accurately report response in patients
320 receiving these costly agents.

321 We focused on a single site, which may not be generalizable to other VA institutions. Although
322 each VA medical center abides by the VHA National Formulary, differences in practice may exist

at individual sites. A lack of a VA national criteria or guideline for anti-TNF agents in RA and CD has led some sites to develop their own local criteria for use. These criteria may differ resulting in a variety of methods for providers to get access to anti-TNF agents for prescribing. In addition, our study focused on a single VA medical center population which limits generalizability to the general veteran population. Future studies will need to incorporate the entire VA population using anti-TNF agents to confirm our findings.

This study had missing data, which is a concern, especially if the missing data is informative. We chose to assume that the missing data was not informative. This does not rule out the possibility that bias exists. Caution should be applied when extrapolating what potential effect these missing data would have on the overall conclusion of this observational study.

Patients who were categorized as non-responders could have been switched to another anti-TNF agent, continued on the anti-TNF agent, or discontinued altogether. It was not possible to establish the average time that these patients were on an anti-TNF agent due to these issues. We reported that the average time to follow up was 86 days, which may not reflect the average follow up in the community. Further observational studies should evaluate the average time to follow up with anti-TNF agents in order to establish the optimal time to measure efficacy and safety.

We reported that several patients were on DMARDs at baseline. However, due to the small sample size, we were unable to evaluate whether they were meaningful differences with this population in terms of effectiveness and safety. Future studies should investigate this population and whether increased effectiveness or worsening side effect profile is reported.

Finally, patients at the VA may have dual care with non-VA medical centers and providers. These

patients may have experienced changes in their therapy and received treatment for infections that were not captured with the VA electronic records. Clinical trials have reported the proportion of patients with infections ranging from 5.7% (Emery et al., 2009) to 46% (Colombel et al., 2010). To complicate matters, patient healthcare benefits may not be restricted to the VA resulting in patients "shopping" for different providers. This may lead to vital information about the patient's disease and status that are not shared with the VA (Nayar et al., 2013a, 2013b; Weeks et al., 2002). As a result, there may be some underreporting of infection events with our analysis.

We did not observe golimumab and certolizumab pegol utilization at VASDHS between 2010 and 2011, despite their availability. We speculate that this was due to their novelty, lack of provider experience, and availability of alternative biologic agents (e.g., IL-6 inhibitors and integrin inhibitors). Although these other anti-TNF agents were not used at VASDHS, it is possible that they may have been utilized at different VA facilities. Future studies will need to expand this investigation to include more VA facilities in order to capture golimumab and certolizumab pegol utilization.

358 **Conclusion:**

359 A majority of patients who were initiated with an anti-TNF agent in the VA were categorized as
360 responders at 12 months follow-up. This was observed for RA and CD indications. Infections
361 were only observed in etanercept and adalimumab patients; however, low sample size in the
362 infliximab subgroup may introduce type II error. Future studies will need to investigate the entire
363 VA population using anti-TNF agents to determine if response is consistent with those reported at
364 VASDHS.

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Figure 1

Outcome with tumor necrosis factor use at 12 months, 2010-2011.

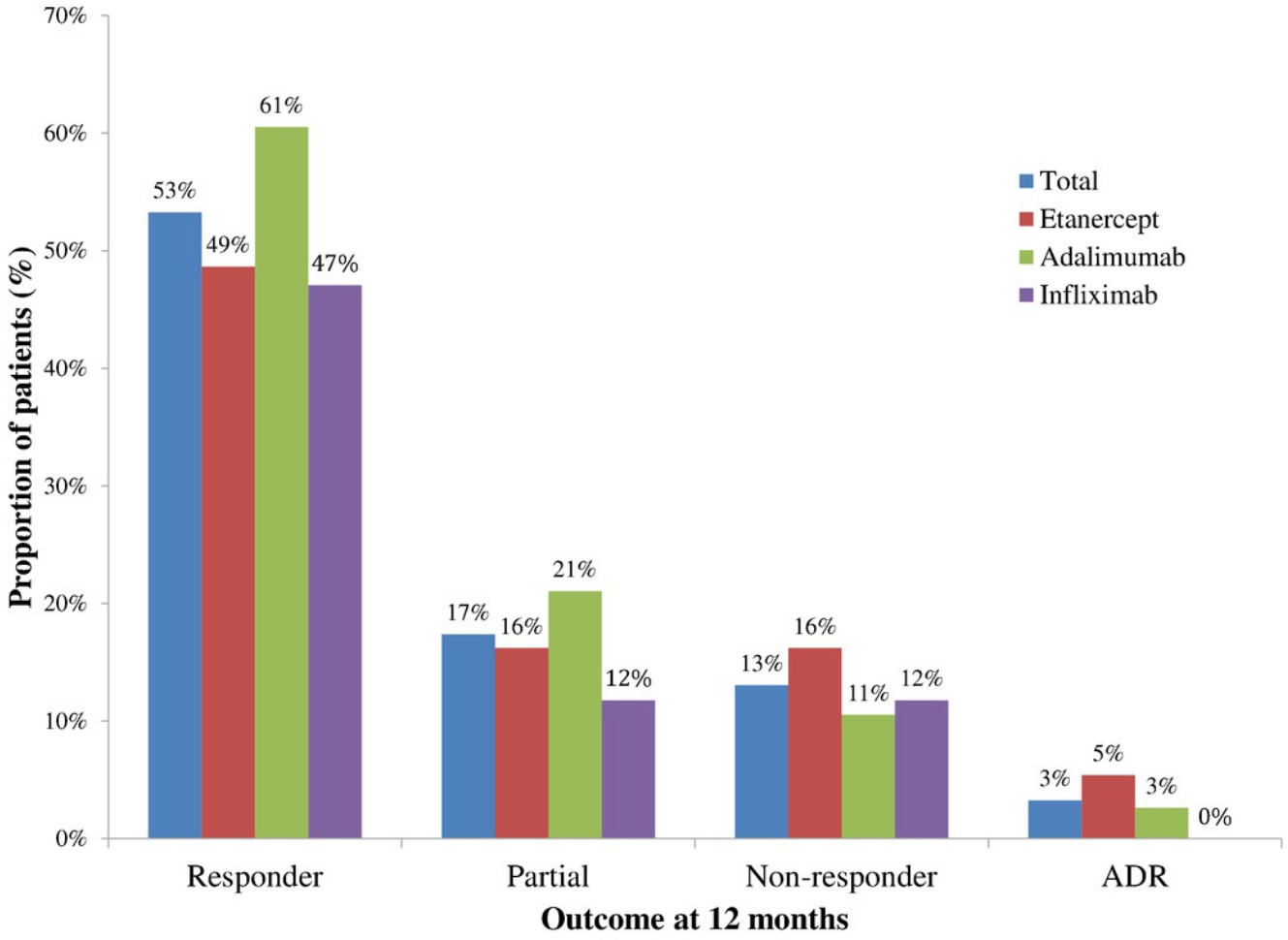

Figure 2

Outcomes of different anti-TNF agents stratified by the top three disease states, 2010-2011.

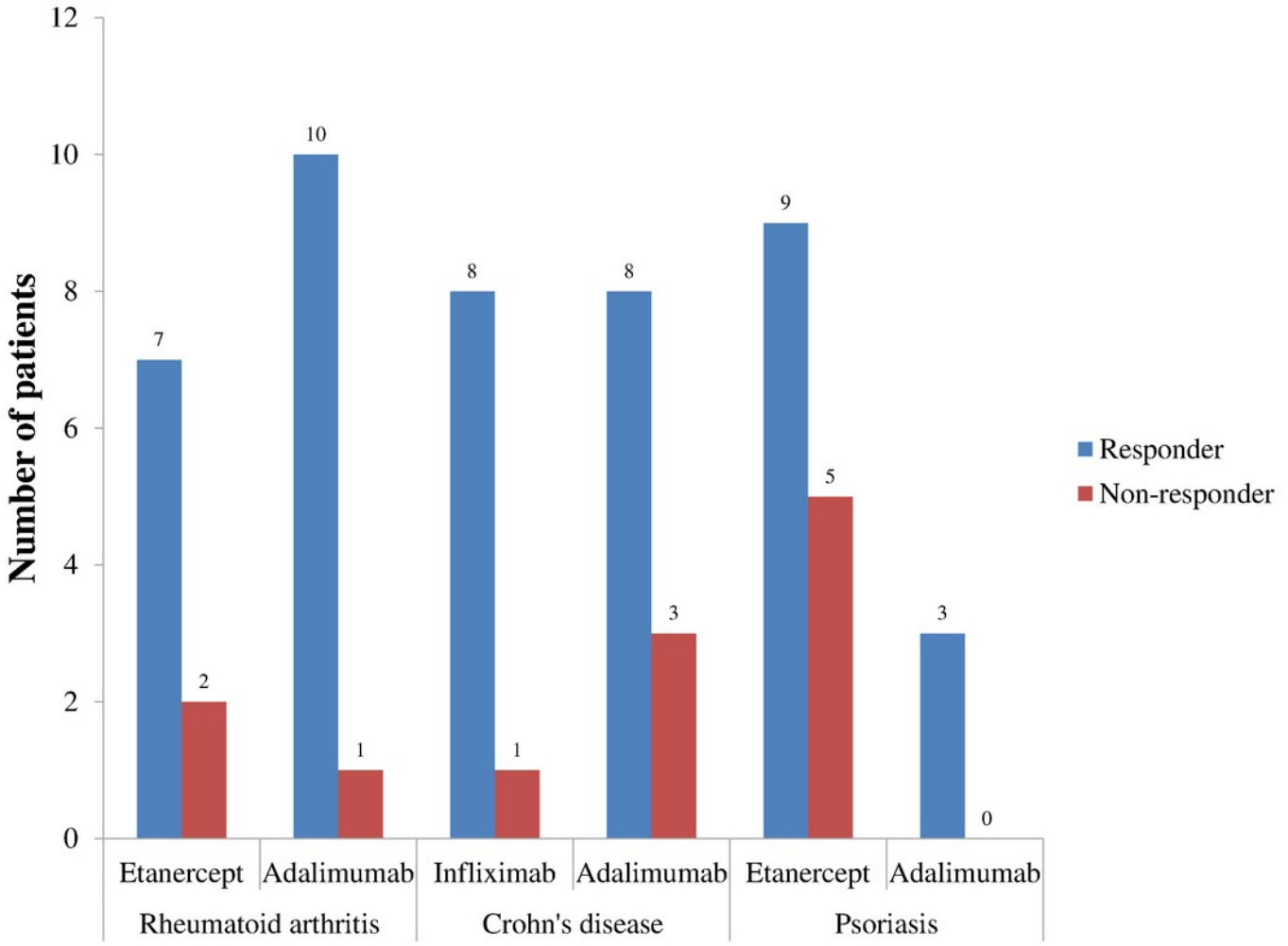

Table 1(on next page)

Demographics of entire cohort started in anti-tumor necrosis factor (TNF) agents, 2010-2011

N	92	
Variable	Mean	SD
Age	49.97	16.23
BMI	28.96	5.49
AST	24.88	20.35
ALT	28.13	25.71
	Number	Percent
Gender		
Male	77	84%
Female	15	16%
Ethnicity		
Hispanic	13	14%
Non-Hispanic	78	85%
Unknown	1	1%
Race		
White	68	74%
Black	11	12%
Asian	3	3%
Native American/Pacific Islander	2	2%
American Indian/Alaskan Native	1	1%
Unknown	5	5%
Declined	2	2%
Primary Diagnosis		
RA	23	25%
CD	24	26%
Psoriasis	19	21%
Psoriatic arthritis	13	14%
Other*	7	8%
Ankylosing spondylitis	5	5%
Comorbid conditions		
Diabetes	11	12%
Hypertension	39	42%
Arrhythmia	3	3%
Heart failure	3	3%
Malignancy	7	8%
Chronic lung disease	5	5%
CVD	11	12%
Hepatic disease	3	3%
Renal	5	5%

Gout	5	5%
Hepatitis C	4	4%
Dyslipidemia	36	39%
History of MI	2	2%
GI (other than CD)	24	26%
Hypothyroidism	5	5%
Baseline DMARDS		
MTX	15	16%
Prednisone	18	20%
SSZ	9	10%
Plaqguenil	4	4%
Previous TNF agent		
Yes	42	46%
No	50	54%
TNF history		
Adalimumab history	22	24%
Etanercept history	11	12%
Infliximab history	9	10%
TNF history origin		
Community provider	21	23%
Another VA facility	5	5%
Department of Defense	4	4%
Veterans Affairs San Diego Healthcare System	12	13%
RF result at baseline		
Positive	11	12%
Negative	14	15%
TB test performed		
Yes	83	90%
No	9	10%
TB result		
Positive	3	3%
Negative	79	86%
Hepatitis test performed		
Yes	73	79%
No	19	21%
HsAg (+)	27	29%
HsAb (+)	1	1%
HcAb(+)	7	8%

*"Other" includes ulcerative colitis (N=5), uveitis (N=1), and spondylarthropathy (N=1).

Table 2(on next page)

Demographics of patients initiated on etanercept, adalimumab, and infliximab, 2010-2011

	Etanercept			Adalimumab			Infliximab						
N	37			38			17						
Variable	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median	P-value			
Age	52.92	15.15	56.0	49.47	15.97	55.0	44.60	17.69	41.0	0.141			
BMI	30.44	6.02	30.2	28.30	4.92	28.5	27.02	4.79	26.7	0.108			
AST	28.57	28.06	22.0	24.00	13.43	21.0	18.31	6.02	18.0	0.122			
ALT	33.59	34.75	24.0	27.92	17.59	230	16.00	5.29	15.0	0.004			
	Number	Percent		Number	Percent		Number	Percent		Chi-square	df	P-value	
Gender													
Male	33	89%		30	79%		14	82%		1.469	2	0.480	
Female	4	11%		8	21%		3	18%					
Ethnicity													
Hispanic	4	11%		8	21%		1	6%		7.069	4	0.132	
Non-Hispanic	33	89%		30	79%		15	88%					
Unknown	0	0%		0	0%		1	6%					
Race													
White	29	78%		25	66%		14	82%		8.724	12	0.726	
Black	5	14%		5	13%		1	6%					
Asian	1	3%		1	3%		1	6%					
Native American/Pacific Islander	1	3%		1	3%		0	0%					
American Indian/Alaskan Native	0	0%		1	3%		0	0%					
Unknown	1	3%		4	11%		0	0%					
Declined	0	0%		1	3%		1	6%					
Primary Diagnosis													
Rheumatoid	10	27%		12	32%		1	6%		4.272	2	0.119	

arthritis									
Crohn's disease	0	0%	12	32%	12	71%	31.113	2	<0.0001
Psoriatic arthritis	7	19%	6	16%	0	0%	3.583	2	0.167
Ankylosing spondylitis	3	8%	2	5%	0	0%	1.494	2	0.474
Psoriasis	16	43%	3	8%	0	0%	19.722	2	<0.0001
Other*	1	3%	3	8%	3	18%	3.708	2	0.157
Comorbid conditions									
Diabetes	7	19%	4	11%	0	0%	4.086	2	0.130
Hypertension	21	57%	15	39%	3	18%	7.521	2	0.023
Arrhythmia	1	3%	2	5%	0	0%	1.093	2	0.579
Heart failure	0	0%	3	8%	0	0%	4.407	2	0.110
Malignancy	2	5%	5	13%	0	0%	3.32	2	0.190
Chronic lung disease	1	3%	3	8%	1	6%	0.991	2	0.609
Cardiovascular disease	5	14%	6	16%	0	0%	2.924	2	0.232
Hepatic disease	3	8%	0	0%	0	0%	4.61	2	0.100
Renal disease	2	5%	3	8%	0	0%	1.425	2	0.491
Gout	3	8%	2	5%	0	0%	1.494	2	0.474
Hepatitis C	2	5%	1	3%	1	6%	0.465	2	0.793
Dyslipidemia	16	43%	17	45%	3	18%	4.058	2	0.131
History of MI	1	3%	1	3%	0	0%	0.464	2	0.793
GI (other than CD)	10	27%	14	37%	0	0%	8.297	2	0.016
Hypothyroidism	5	14%	0	0%	0	0%	7.86	2	0.020
Baseline DMARDS									
MTX	8	22%	7	18%	0	0%	4.203	2	0.122
Prednisone	6	16%	8	21%	4	24%	0.487	2	0.784
SSZ	5	14%	2	5%	2	12%	4.013	2	0.134
Plaguenil	2	5%	2	5%	0	0%	0.949	2	0.622

Previous TNF agent									
Yes	13	35%	20	53%	9	53%	2.76	2	0.252
No	24	65%	18	47%	8	47%			
Origin									
Community provider	8		9		4	24%	3.317	6	0.768
Another VA facility	1		2		2	12%			
DoD	1		3		0	0%			
VASDHS	3		6		3	18%			
RF result at baseline									
Positive	7	19%	3	8%	1	6%	2.279	2	0.320
Negative	5	14%	8	21%	1	6%			
TB test performed									
Yes	35	95%	33	87%	15	88%	1.369	2	0.504
No	2	5%	5	13%	2	12%			
TB result									
Positive	1	3%	1	3%	1	6%	0.475	2	0.789
Negative	34	92%	31	82%	14	82%			
Hepatitis test performed									
Yes	31	84%	31	82%	11	65%	2.784	2	0.249
No	6	16%	7	18%	6	35%			
HsAg (+)	9	24%	12	32%	6	35%	0.449	2	0.799
HsAb (+)	1	3%	0	0%	0	0%	1.33	2	0.514
HcAb(+)	5	14%	2	5%	0	0%	2.457	2	0.293

*"Other" includes ulcerative colitis (N=5), uveitis (N=1), and spondylarthropathy (N=1).

Table 3(on next page)

Outcomes at the first follow-up visit and at 12 months for patients started on etanercept, adalimumab, and infliximab at the VASDHS, 2010-2011

	All groups		Etanercept		Adalimumab		Infliximab			
Initial outcome at first follow-up visit	Number	%	Number	%	Number	%	Number	%	Chi-square	df
Responder	65	71%	23	62%	27	71%	15	88%	7.764	4
Partial	11	12%	7	19%	4	11%	0	0%		
Non-responder	10	11%	4	11%	6	16%	0	0%		
Outcome at 12 months	Number	%	Number	%	Number	%	Number	%	Chi-square	df
Responder	49	53%	18	49%	23	61%	8	47%	2.169	6
Partial Responder	16	17%	6	16%	8	21%	2	12%		
Non-responder	12	13%	6	16%	4	11%	2	12%		
ADR	3	3%	2	5%	1	3%	0	0%		
Infections after anti-TNF agent initiation	Number	%	Number	%	Number	%	Number	%	Chi-square	df
Yes	15	16%	5	14%	10	26%	0	0%	6.314	2
No	77	84%	32	86%	28	74%	17	100%		

Table 4(on next page)

Odds of responder relative to infliximab

Crude analysis

Variable	B	SE	OR	95% CI
Etanercept	-0.511	0.876	0.60	0.108, 3.338
Adalimumab	0.215	0.912	1.24	0.207, 7.412

*Referent is Infliximab

**Hosmer-Lemeshow test, Chi-square<0.0001, df=1, P=1.000

Odds of responder adjusted for age, gender, and TNF history relative to infliximab.

Variable	B	SE	OR	95% CI
Etanercept	-0.090	0.979	0.91	0.134, 6.225
Adalimumab	0.613	1.000	1.85	0.260, 13.098
Age, years	-0.064	0.024	0.94	0.895, 0.983
Male	0.351	0.919	1.42	0.234, 8.600
TNF history	-0.161	0.646	0.85	0.240, 3.023

*Referent is Infliximab

**Hosmer-Lemeshow test, Chi-square=9.670, df=8, P=0.289