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Medication Adherence, Persistence, Switching and Dose Escalation with the Use of Tumor Necrosis Factor (TNF) Inhibitors among Texas Medicaid Patients Diagnosed with Rheumatoid Arthritis

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by

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Dedication

To my lovely wife, Ayoade, for helping to make this dream come true.

(Prov 31:10-31)

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Medication Adherence, Persistence, Switching and Dose Escalation with the Use of Tumor Necrosis Factor (TNF) Inhibitors among Texas Medicaid Patients Diagnosed with Rheumatoid Arthritis

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The main purpose of this study was to evaluate medication use patterns (i.e., dose escalation, medication adherence, persistence, and switching) of rheumatoid arthritis (RA) patients on etanercept (ETN), infliximab (IFX) or adalimumab (ADA) and the associated healthcare utilization costs using Texas Medicaid data. Study participants were Medicaid beneficiaries (18-63 years) with an RA diagnosis (ICD-9-CM code 714.0x) who had no claim for a biologic agent in the 6-month pre-index period (July 1, 2003 - Dec 31, 2010). The index date was the first date when the patient had the first fill for any of the study TNF inhibitors (ETN, ADA or IFX) within the study identification period (Jan 1, 2004 – Aug 31, 2010). Data were extracted from July 1, 2003 to August 31, 2011. Prescription and medical claims were analyzed over an 18-month study period (i.e., 6-month pre-index and 12-month post-index periods). The primary study outcomes were adherence, persistence, dose escalation, switching

and cost (i.e., total healthcare, RA-related and TNF inhibitor therapy cost). The study covariates were demographic factors (age, gender, race/ethnicity), pre-index use of other RA-related medications (pain, glucocorticoids and disease modifying antirheumatic drugs), total number of non-study RA-related medications used at index, pre-index RA and non-RA related visits, pre-index healthcare utilization cost and Charlson Comorbidity Index score. Conditional regression analyses, which accounts for matched samples, were used to address the study objectives.

After propensity score matching, 822 patients (n=274/group) comprised the final sample. The mean age (±SD) was 48.9(±9.8) years, and the majority of the subjects were between 45 and 63 years (69.2%), Hispanic (53.7%) and female (88.0%). Compared to patients on ETN, the odds of having a dose escalation were ≈ 5 [Odds Ratio= 4.605 [95% CI= 1.605-12.677], p=0.0031] and ≈ 8 [Odds Ratio=7.520, [95% CI= 2.461-22.983], p=0.0004] times higher for IFX and ADA patients, respectively, while controlling for other variables in the model. Compared to ETN, patients on IFX (p=0.0171) were more adherent while adherence was comparable with patients on ADA (p=0.1144). Compared to patients on ETN, the odds of being adherent (MPR ≥ 80%) to IFX was ≈ 2 times higher [Odds Ratio= 2.437, [95% CI=1.592-3.731], p < 0.0001] while controlling for other variables in the model. Persistence to index TNF inhibitor therapy and likelihood to switch or discontinue index TNF inhibitor therapy were comparable among the 3 study groups. In addition, the duration of medication use (i.e., persistence) prior to switching or discontinuation of index therapy was comparable among the 3 study groups. Furthermore, for each

of the cost variables (total healthcare, RA-related and TNF inhibitor therapy cost), costs incurred by patients on ETN were significantly lower ($p < 0.01$) than those incurred by ADA patients but significantly higher ($p < 0.01$) than those incurred by IFX patients. Finally, a positive and significant relationship ($p < 0.0001$) was found between RA-related healthcare cost, adherence and persistence to TNF inhibitor therapies.

In conclusion, ETN was associated with lower rates of dose escalation compared to ADA or IFX. However, adherence was better and associated healthcare costs were lower with IFX. Clinicians should endeavor to work with each individual patient to identify patient-specific factors responsible for poor medication use behaviors with TNF-inhibitor therapies. Reducing the impact of these factors and improving adherence should be included as a major part of the treatment plan for each RA patient. RA patients need to be adequately educated on the importance of adhering and persisting to their TNF-inhibitor therapy as poor medication adherence/persistence negatively impacts the RA disease process.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Chapter 1: INTRODUCTION

1.1 BACKGROUND/STUDY RATIONALE

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation of the joints.[1] RA is a leading cause of disability and affects about 1 percent of the adult United States (US) population with a higher prevalence, incidence and lifetime risk in women compared to men.[2,3] The direct medical cost related to management of RA in the US has been estimated to exceed $4 billion annually.[4] RA negatively impacts patients' health related quality of life causing significant joint pain, disability and limited mobility.[3] RA has also been associated with increased mortality as it predisposes patients to increased risk for cardiovascular-related diseases, cancer, infections and mental health conditions.[3] Overall, RA contributes to a reduction in a patient's lifespan by 5 to 10 years.[3] Although the etiology of RA remains unknown, it has been speculated that its occurrence may result from an interaction between environmental exposures and genetic factors. Risk factors for RA include age (incidence increases with age and is highest among those between 65 and 74 years), being female (incidence is 2 to 3 times higher in women than men), presence of specific human leukocyte antigen (HLA) class II genotypes, tobacco use, dietary factors, reproductive hormonal and microbial exposures.[3]

While a cure for RA is yet to be developed, current treatment goals lie in slowing or stopping the progression (i.e., remission) of the disease. Among the available treatment options, the tumor necrosis factor (TNF) inhibitors, which are

referred to as biologic agents or biological response modifiers (BRMs), have generally been recognized to have revolutionized the management of RA as they have been shown through randomized clinical trials (RCTs) to significantly improve patients' symptoms as well as retard disease progression.[5-9] TNF inhibitors are recommended for use in patients who failed to achieve remission or satisfactory response following treatment with traditional or conventional disease modifying antirheumatic drugs (DMARDs) (e.g., methotrexate). TNF inhibitors have been found to be even more effective when used in combination with traditional DMARDs.[3,6-11] Among the available TNF inhibitors, three agents (Enbrel® (etanercept), Remicade® (infliximab) and Humira® (adalimumab) have been extensively studied and used with remarkable results. While no clinical trial has been conducted to directly compare (i.e., head to head comparison) the three agents, results from the majority of the indirect treatment comparison studies suggest that the agents have comparable efficacy and safety profiles.[12-17] However, they differ in their method of administration and flexibility of dosing (see Table 1.1) and these differences may possibly result in differences in medication use profiles (adherence, persistence, discontinuation, switching and dose escalation) and cost of care for RA patients on medications.[18-20]

Table 1.1 Dosing Recommendations for Etanercept, Infliximab and Adalimumab in RA Management[18-20]

Drug (Brand Name)	Dose & Administration Route
Etanercept (Enbrel®)	25mg SC twice weekly or 50mg once weekly (self-administered)[a,b]
Infliximab[c] (Remicade®)	3mg/kg IV over 2 hours at week 0, 2, 6, then every 8 weeks [d], with dose adjustment up to 10mg/kg
Adalimumab‡ (Humira®)	40mg SC every 2 weeks (self-administered)[a, e]

IV = Intravenous; **RA** = Rheumatoid arthritis; **SC** = Subcutaneous;
[a] Administered as monotherapy or in combination with other RA therapies (e.g., methotrexate, leflunomide, glucocorticoids, salicylates, analgesics, or NSAIDs);
[b] Higher doses of etanercept are not recommended since they do not provide any additional benefit and due to increased risk of adverse events
[c] Infliximab was approved to be administered in combination with methotrexate
[d] frequency of administration can also be shortened from every 8 weeks to every 4 weeks; [e] Can be administered at a dose of 40mg weekly

All available studies in the literature which used administrative claims data to evaluate RA patients' adherence to etanercept, infliximab and adalimumab were conducted in the US. Studies on medication adherence (measured using varying definitions of medication possession ratio [MPR] or proportion of days covered [PDC]) reported varied mean adherence (mean MPR) values for each of the TNF inhibitors.[2,21-25] Curkendall et al. reported an overall mean MPR of 0.52 (±0.31) for etanercept and adalimumab users.[22] Borah et al. reported mean MPR values ranging from 0.65 (±0.31) to 0.73 (±0.26) for patients on etanercept and mean MPR values ranging from 0.63 (±0.32) to 0.70 (±0.28) for patients on adalimumab.[2] Grijalva et al. reported mean MPR (SD not provided) values of 0.83, 0.85 and 0.90 for etanercept, adalimumab and infliximab users, respectively.[23] A second study by Grijalva et al., reported median MPR values of 0.73, 0.72 and 0.68 for etanercept, adalimumab and

infliximab use, respectively.[24] Li et al. reported mean PDC values (SD not provided) of 0.57 and 0.64 for etanercept and infliximab patients, respectively.[25] When proportion of adherent patients (MPR≥0.8 or 80%) were considered, Borah et al. reported 42.0 to 51.3 percent of etanercept users and 41.0 to 47.1 percent of adalimumab users, as being adherent.[2] Harley et al. reported 68.4 and 80.9 percent of patients on etanercept and infliximab, respectively, as being adherent (MPR>0.80).[21] Furthermore, among new users, the likelihood of being adherent (MPR≥0.8) to etanercept was reportedly lower (OR=0.462, 95% CI=0.290-0.736, $p < 0.05$) compared to infliximab, while among existing users, patients were more likely to be non-adherent to adalimumab compared to etanercept (OR=1.25, 95% CI=1.05-1.49, p=0.01).[2,21]

The literature on medication persistence to etanercept, infliximab and adalimumab presents conflicting results, and only a few of the US studies[2,22,23,25-27] specified the gap period(s) used in the analyses. Tang et al. and Yazici et al. reported significantly higher mean (p=0.005) and median ($p < 0.0001$) persistence rates, respectively, for infliximab compared to etanercept and adalimumab.[4,27] Harrison et al. found significantly ($p < 0.05$) higher mean persistence rates among new users of etanercept compared to new users of infliximab and adalimumab, but comparable (p>0.05) mean duration of therapy and persistence rates among continuing users on the 3 drugs.[28] Wu et al. and Li et al. reported comparable (p>0.05) discontinuation rates among users of the 3 drugs [25,26] while Borah et al. found no significant difference

in the likelihood (HR=1.11 p=0.06 CI=1.00-1.23) of medication discontinuation among existing patients on adalimumab compared to etanercept.[2]

Studies on dose escalation and cost of TNF inhibitor therapy consistently indicated that etanercept use was associated with significantly lower rates of dose escalation and lower TNF inhibitor therapy cost compared with the use of adalimumab and infliximab.[26,28-33] Evidence supporting switching effectiveness between TNF inhibitors is limited to results obtained from small case series and open-label studies (non-controlled studies), the majority of which are non-US studies.[34-49] Results from these studies consistently showed that treatment response following a switch between TNF inhibitors was comparable with, or better than the response observed with the initial TNF inhibitor agent. Furthermore, results from systematic reviews/meta-analyses also supported the effectiveness of switching between TNF inhibitors (i.e., adalimumab, infliximab and etanercept) irrespective of the reason for switching (either due to inefficacy or adverse events) and order of switching.[50] However, treatment response was reported to be slightly better if switching was as a result of adverse events rather than inefficacy.[50,51]

The majority of the studies reported earlier were conducted using data from patients enrolled in private health plans or managed care organizations. Only 3 studies were identified to have utilized data from patients enrolled under Medicaid programs, many of whom are not the typical patients enrolled in clinical trials.[23-25] These patients are of poor socioeconomic status and are more likely to present with

more comorbid disease conditions when compared to the general population. Furthermore, of the 3 studies which utilized Medicaid data, only one evaluated medication adherence and persistence across the three TNF inhibitors of interest (i.e., etanercept, infliximab and adalimumab) and none examined dose escalation and the healthcare utilization costs associated with the use of these agents.

1.2 STUDY AIM

The present study aims to evaluate medication use patterns (e.g., medication adherence, persistence, switching and dose escalation) of RA patients on etanercept, infliximab or adalimumab and the associated healthcare utilization costs using Texas Medicaid data. Etanercept, infliximab and adalimumab were the only biologics chosen for this study because they have been widely used and extensively studied.

1.3 STUDY RELEVANCE

The cost of managing chronic disease conditions is one of the major drivers of increasing healthcare costs in the U.S. RA treatment contributes to this with direct costs estimated to exceed $4 billion annually.[4] Poor medication use behaviors can further increase the cost of care as they can undermine the potential benefits of these expensive, but effective RA treatments (i.e., TNF inhibitors). Suboptimal medication use causes suboptimal treatment response, rapid disease progression and occurrence of complications, requiring even more aggressive treatment options. In the face of limited healthcare resources, the need therefore arises to assess RA patients' TNF

inhibitors medication use patterns (e.g., medication adherence, persistence, discontinuation, dose escalation and switching) as well as the associated healthcare utilization cost. This information can be used to promote better medication use behavior, improve treatment outcomes and optimize treatment costs among RA patients.

Chapter 2: LITERATURE REVIEW

2.1 CHAPTER OVERVIEW

This chapter provides a discussion of the literature relevant to the present study. The literature review covers the following topics as it relates to rheumatoid arthritis (RA): epidemiology, humanistic and economic burden, etiology and risk factors, clinical classification and diagnosis, clinical assessments and outcomes. Other topics covered include treatment goals, management options, clinical practice guidelines and medication use patterns of tumor necrosis factor (TNF) inhibitors among RA patients. The chapter concludes with a summary of the literature review, study objectives and hypotheses.

2.1.1 Definition, Morbidity and Mortality of RA

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation and progressive destruction of the joints.[1] RA is also associated with disabling pain, tenderness, swelling and stiffness in the joints. RA causes progressive decline in functional ability and it limits performance of social roles and other activities.[3,52,53] Untreated or improperly treated RA also increases the risk for permanent joint damage and deformity.[54] Overall, RA contributes to a mean reduction in a patient's lifespan by 5 to 10 years.[3] Compared to the general population, RA patients have an increased mortality with standardized mortality ratios varying from 1.29 to 2.98.[55] RA accounts for about 22 percent of all arthritis-related deaths

including deaths due to rheumatic conditions.[3] Patients with RA are at risk for developing cardiovascular events (e.g., ischemic heart diseases, stroke and heart failure), gastrointestinal, hematologic and respiratory infections, cancer (e.g., skin and lung cancer), skeletal disorders as well as mental health conditions (e.g., depression).[55-58] RA patients also present with fatigue, sleep disturbances and sexual dysfunction.[52,59]

2.1.2 Prevalence and Incidence of RA

In the developed world (i.e., Europe and the United States (US)), the estimated prevalence rate of RA ranges between 0.5 and 1 percent, with a higher prevalence rate reported among women compared to men.[55] Based on 2005 data from the National Health Interview Survey (NHIS) and the Rochester project, an estimated 1.3 to 1.5 million people in the US present with RA.[60,61] The Rochester project indicated a 16.1 percent increase in RA prevalence rates per 100,000 population between 1995 and 2005 among the US adult population (≥18 years).[61] Incidence rates for RA declined from 61.2 per 100,000 population in the period 1955-1964 to 32.7 per 100,000 population in the period 1985-1994, but increased to 40.9 per 100,000 population in the period 1995-2007.[61,62] The increase in prevalence and incidence of RA in recent years have largely been attributed to changes in the incidence of RA among women, which has increased by an annual rate of 2.5 percent from 1995 to 2007, while incidence rates among men decreased by 0.5 percent.[61] Likewise, RA prevelance rates among women have increased significantly by about 27.3 percent

from 1995 to 2005.[61] Furthermore, data from 1980 to 2007 indicated that for both men and women, the distribution of RA incidence across different age groups has remained relatively stable with the lowest incidence observed among ages 18-34 (8.7 per 100,000 people) and the highest incidence seen among ages 65-74 (89 per 100,000). Interestingly, a decline in RA incidence was observed among adults above the age of 74.[61,62] Limited information exists in the literature on the distribution of RA prevalence and incidence by race and it is important to know that the population involved in the Rochester project was primarily white (over 90 percent). [61,62] However, the prevalence rates of arthritis (RA inclusive) by race and ethnicity based on a combination of data from the 2002, 2003 and 2006 National Health Interview Survey are presented below in Table 2.1.[63]

Table 2.1 Prevalence of Arthritis By Race/Ethnicity

Race/ Ethnicity	Prevalence (%)
American Indian/Alaska Native	25.2
Non-Hispanic White	23.8
Multiracial/Other	20.7
Non-Hispanic Black	19.4
Hispanic	11.1
Asian/Pacific Islander	8.4

Source: National Health Interview Survey 2002, 2003 and 2006.
Centers for Disease Control and Prevention. Racial/Ethnic differences: Differences in the prevalence and impact of arthritis among racial/ethnic groups in the Unites States. 2011;
http://www.cdc.gov/arthritis/data_statistics/race.htm. Accessed March 3, 2012

2.1.3 Humanistic and Economic Burden of RA

Due to the chronic nature of RA, the comorbidities (especially cardiovascular and depressive diseases) that occur as the disease progresses and the negative impact of RA on patients' health-related quality of life (HRQoL) and productivity, the burden associated with the management of RA is significant. HRQoL parameters affected by RA include mental wellbeing, physical and social functioning. RA patients also present with pain, stiffness, fatigue and sleep disturbances.[64] The impact of RA on these HRQoL parameters directly or indirectly negatively influences patients' productivity.

In the past two decades, the estimated prevalence of work disability among RA patients (based on results from clinical studies) ranged from 22 to 44 percent.[65] Compared to individuals without RA, patients with RA are at increased risk of being employed for fewer years or being without a paid job (odds range between 1.2 and 3.4). [55,65] Among patients with early RA (< 1 year), about 33 percent are at risk of losing their jobs in the first 2 years and about 53 percent will lose their jobs within 6 years.[55] Yearly incidence rates for ending employment and ending without resuming

employment have also been reported to be about 8.7 and 4 percent, respectively.[55] Given a population average of approximately 11 sick leave days per year, patients with established RA reportedly used an average of 46 days, with some using as many as 118 sick leave days per year.[55]

Birnhaum et al., using administrative databases of both privately- and publicly- insured patients (Medicare and Medicaid beneficiaries), estimated the direct and indirect costs (i.e., productivity costs or income lost due to presenteeism, absenteeism, unpaid work, productivity loss and/or change in employment status (see Table 2.2 for definitions)) associated with RA to be about $8.4 billion and $10.9 billion, respectively.[66] RA patients have been reported to incur about 2 to 3 times more in average direct medical expenditures per year than individuals of similar age and gender without RA.[67] Also, RA patients with comorbidities (e.g., cardiovascular disease and/or depression) were reported to spend an average of $2,000 to $3,000 more in annual healthcare costs than similar RA patients with no comorbid conditions.[68] Wolfe et al. estimated an annual median income loss of between $2,319 and $3,407 (i.e., 9.3% to 10.0% loss) among employed US RA patients.[69] Li et al. reported an average annual productivity cost per patient of CAN$11,553 (≈US$8,665) among employed Canadian patients with arthritis with loss due to reduced performance at work (i.e., presenteeism) being the major contributor (see Table 2.3).[70]

Table 2.2 Types of Productivity Loss

Productivity Categories	Definition
Absenteeism	Days absent from work due to illness
Presenteeism	Reduced or impaired performance at work due to illness
Unpaid work	Production losses when not paid
Productivity loss	Activities postponed or taken over due to illness
Change in employment status	Reduced work hours or having to work part-time, unemployment or early retirement due to illness

Source: Zhang W, Anis AH. The economic burden of rheumatoid arthritis: beyond health care costs. *Clin Rheumatol*. 2011; 30 (Suppl 1):S25-S32.

Table 2.3 Productivity Loss Associated with Arthritis

Productivity Categories	Cost[a]/person/year	% of Total
Reduced performance at work (Presenteeism)	$4,724	41.0
Wage loss from stopping or changing jobs	$4,309	37.0
Decreased hours	$1,398	12.0
Absenteeism	$1,212	10.0
Total lost productivity	$11,553	100.0

[a] Costs are in Canadian dollars

Source: Li X, Gignac MA, Anis AH. The indirect costs of arthritis resulting from unemployment, reduced performance, and occupational changes while at work. *Med Care*. 2006; 44(4):304-310.

2.1.4 Etiology and Risk Factors for RA

While the etiology of RA remains unknown, it has been speculated that it may be caused by an interaction between environmental exposures, genetic factors and chance.[58] Genetic factors have been reported to account for about 50 percent of the risk of developing RA.[71] The presence of specific human leukocyte antigen (HLA) class II genotype (e.g., HLA-DRB1 alleles) has been confirmed in patients who tested positive for rheumatoid factor (RF) or anti-citrullinated protein antibodies.[58] Factors that cause bronchial distress (e.g., smoking and exposure to silica) also increase patients' risk of developing RA, especially if the patient is susceptible to HLA-DR4 alleles.[58] Smoking has been associated with the development of erosive disease and

vasculitis which are part of the joint destruction process.[72] Furthermore, citrulline-producing cells, which are indicative that a citrullination process is occurring, have been identified in the bronchoalveolar lavage fluid of smokers.[72] The citrullination process is an early step in the cell death process involving the modification of the amino acid arginine into citrulline.[72,73] It is an important process as the presence of anti-citrullinated protein antibodies or anti-cyclic citrullinated peptide (anti-CCP) is predictive of both the presence and severity of RA.[72] Smoking and HLA-DRB1 alleles (especially homozygotes) act synergistically, increasing a patient's risk of developing anti-citrullinated protein antibodies.[58,71,73] A combination of rheumatoid factor (RF) and anti-citrullinated protein antibodies has been reported to yield a better diagnosis of RA.[74]

Exposure to microbial agents (e.g., *Escherichia coli,* proteus species, cytomegalovirus and Epstein-Barr virus) and their products (heat-shock proteins) have also been associated with the development of RA. Complexes formed during infection may activate the release of rheumatoid factor which is a biomarker for the diagnosis of RA and is associated with its development.[58] Other associated risk factors for the development of RA include: presence of periodontal diseases due to *Porphyromonas gingivalis*, dietary factors, age (incidence increases with age and highest among those between 65 and 74 years), being female (incidence is 2-3 times higher in women than men) and exposures to specific reproductive hormones.[3,58] Other reported potential environmental risk factors for which available supporting

evidence is weak include low socioeconomic status, coffee intake, vitamin D status, alcohol intake and oral contraceptive use.[71]

2.1.5 Classification and Diagnosis of RA

RA has generally been classified as either early or established RA. RA is considered to be early during the first 24 months of diagnosis, but greater emphasis is placed on the first 12 months.[72] Identifying RA early is critical for early suppression of the inflammatory process, as undiagnosed or untreated RA increases the risk of persistent inflammation and progressive damage to the joints.[72] On the other hand, patients with a mild form of early RA may not benefit from treatment if the disease is unlikely to progress. This is because patients with early RA tend to enter a period of remission (Figure 2.1) regardless of whether they receive treatment or not, and the likelihood of achieving spontaneous remission is even higher among patients with mild early RA disease.[72]

Figure 2.1 ACR Criteria for Defining Remission

At least 5 of the following conditions below must be met for ≥ 2 consecutive months

- Morning stiffness for a duration ≤ 15 minutes
- No fatigue
- No joint pain
- No joint tenderness or pain with motion
- No soft-tissue swelling in joints or tendon sheaths
- An ESR level of ≤ 30 mm/hr (females) or ≤ 20mm/hr (males)

ACR= American College of Rheumatology; **ESR**= Erythrocyte sedimentation rate.
Source: Goetz I, Carter GC, Lucero M, et al. Review of treatment response in rheumatoid arthritis: assessment of heterogeneity. *Curr Med Res Opin.* 2011;27(4):697-711.

In 1987, the American College of Rheumatology (ACR) introduced criteria for classifying RA (Figure 2.2).[75] However, the criteria performed poorly in classifying patients with early inflammatory arthritis as having RA. It was also ineffective in identifying patients with early RA who subsequently developed established RA.[71] The criteria were believed to have failed in classifying/identifying early RA primarily due to the process through which they were developed (i.e., from studies of patients with established RA).[72,76] The criteria also relied solely on 'physician's opinion' as the 'gold standard' but physicians have been reported to have difficulty identifying early RA solely on clinical criteria.[72,75] Furthermore, two (i.e., rheumatoid nodules and severe erosive joint damage) of the seven ACR criteria necessary for establishing an RA diagnosis take months or even years to appear after the onset of synovitis.[71,76]

In an approach to address the difficulty in classifying early RA, a review by Dixon et al. suggested that immediate classification of patients with early inflammatory arthritis be avoided given that a considerable follow-up period is required to determine if these patients will have a seropositive or seronegative RA and/or present with other disorders.[77] They classified the development of RA into four stages which include: (a) the period leading to the onset of arthritis; (b) the period during which persistence or remission occurs; (c) the period when the arthritis evolves into a specific form of arthritis; and (d) finally the outcome of the arthritis.[77] Since the duration of these stages varies across patients, with some patients having the stages follow a rapid succession and others having them

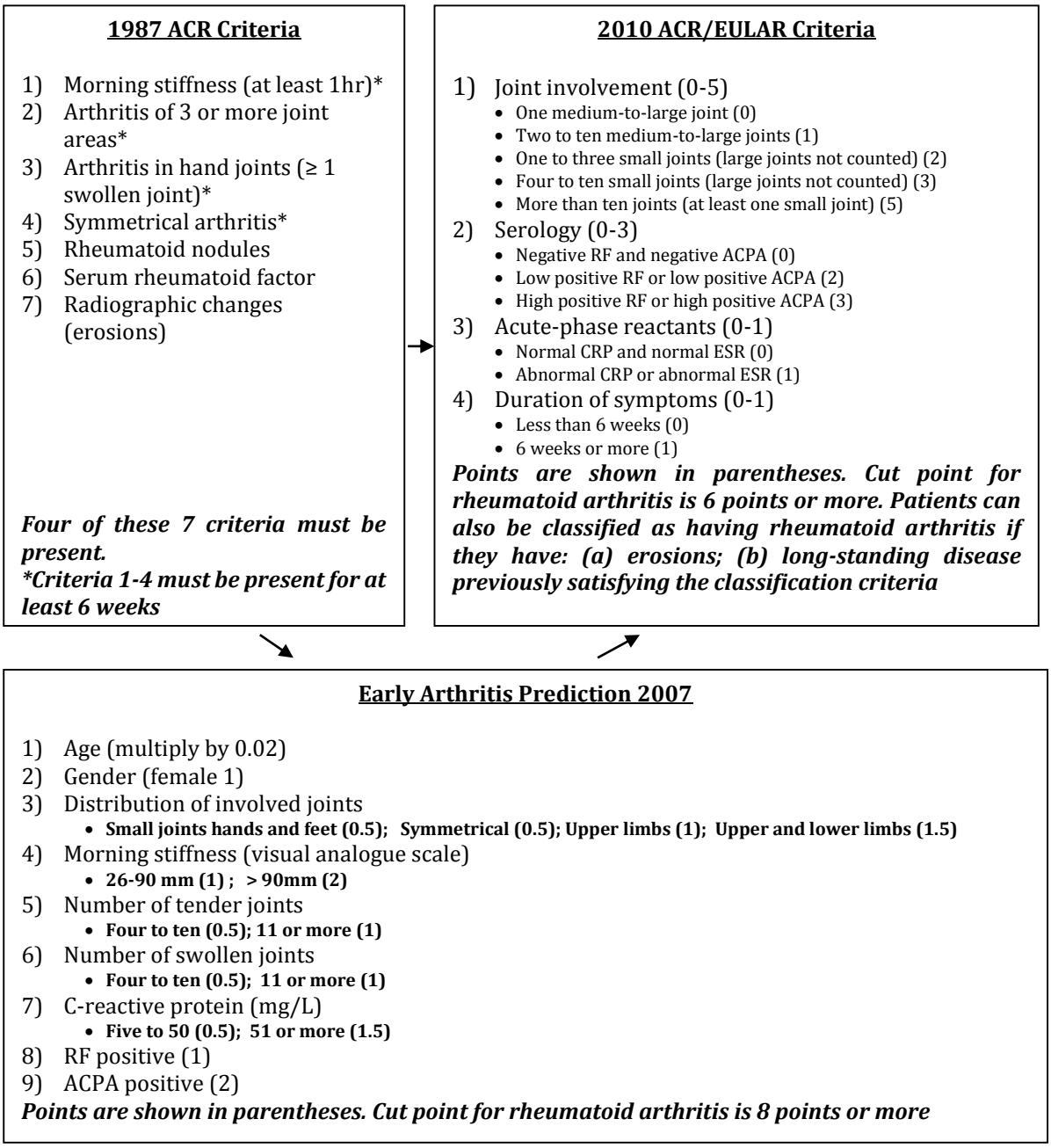
prolonged over several months or years, they further suggested that the concept of early arthritis be discontinued and patients be classified as either having an undifferentiated inflammatory arthritis or established RA.[77]

Over the past few years, prediction models have been designed with the aim of predicting outcomes in patients with early arthritis who do not currently meet the 1987 ACR criteria.[78-81] However, these models were found to be somewhat complicated.[71] In 2010, the ACR and European League Against Rheumatism (EULAR) developed new criteria intended to classify/diagnose both early and established RA.[82] The new criteria (2010 ACR/EULAR criteria) were developed using a three-phase approach. The first phase involved collecting data from patients with early RA regarding the factors associated with their physicians' decisions to start methotrexate therapy. This was followed by a consensus-driven approach to refine these factors based on input from current clinical thinking. The final phase involved summarizing all the data to develop a prediction model and cut-off value for the probability score.[71]

The 2010 ACR/EULAR criteria for classifying/diagnosing both early and established RA are based on an assessment of the patient's joint involvement, autoantibody status, acute-phase reactants, and symptom duration (Figure 2.2).[82] The diagnostic accuracies of the 2010 ACR/EULAR criteria have been compared with those of the 1987 ACR criteria.[83,84] While no statistically significant differences were observed between the two criteria, the 2010 ACR/EULAR was reported to show some

improvements and was also slightly more sensitive when compared to the 1987 ACR criteria.[83,84]

Figure 2.2 Conventional (1987), Early (2007) and New Classification (2010) Criteria for Rheumatoid Arthritis



ACPA= anti-citrullinated protein antibodies; **ACR**= American College of Rheumatology; **CRP**= C-reactive protein; **EULAR**= European League Against Rheumatism; **ESR**= erythrocytes sedimentation rate; **RF**= rheumatoid factor. ACR 1987 criteria (left panel) were designed to classify established rheumatoid arthritis (RA). ACR/EULAR 2010 criteria (right panel) are intended to classify both early and established RA. Prediction models such as the van de Helm model (lower panel) represent an intermediate phase designed to identify patients with early undifferentiated arthritis who are most likely to subsequently meet criteria for RA; such models are somewhat more complex than the new criteria.
Source: Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. *Lancet*. 2010; 376 (9746):1094-1108.

2.1.6 Clinical Assessments and Outcomes in the Management of RA

Clinical assessment in the management of RA entails an evaluation of the patient's disease activity, extra-articular disease and comorbidities.[71] Disease activity assessments involve evaluation of: (1) core measures; (2) fatigue and radiographical damage; (3) combined status indices; and (4) change in status.[71] *Core measures* assessed include: (a) tender and swollen joint counts (e.g., counts of the 28 joints in the hands, knees and upper limbs); (b) laboratory measures (e.g., erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]); (c) patient-based measures (e.g., global assessment, pain appraisal, measures of fatigue and disability).[71] *Radiographical techniques* (e.g., ultrasound and magnetic resonance imaging) are used in assessing both reversible and irreversible structural changes (e.g., justa-articular erosions). *Combined status indices* (e.g., the disease activity score (DAS); disease activity score 28 (DAS28); clinical disease activity score; and simple disease activity score) use a combination of information from 2 or more of the core measures described above in assessing patients' disease activity status.[71] For example the DAS28 combines information from patient's global assessment, ESR and counts of the 28 tender and swollen joints of the arms, hands and knees. DAS28 values 2.6-3.2; 3.3-5.1; and >5.1 refers to low, moderate and high disease activity levels, respectively, while a DAS28 <2.6 refers to a state of remission.[85] *Change in status measures* are used in clinical trials to determine improvement in patients' disease activity status based on ACR improvement criteria. They are also used to measure the efficacy of the treatment agents. They are expressed as ACR20, ACR50 and ACR70, which indicates

a 20, 50, and 70 percent, respectively, improvement from baseline in swollen joint count, tender joint count, and at least three of the following five measures (patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of pain, acute phase reactant and disability).[71,86] In addition, some clinical trials also use response criteria developed by EULAR to determine the efficacy of therapeutic agents.[86] The EULAR response criteria are based on patients' performance on the DAS or DAS28. The DAS consists of the Ritchie articular index, the 44 swollen joint counts, the ESR and a general health assessment on a Visual Analog Scale (VAS). Based on EULAR response criteria, achieving a DAS ≤ 2.4 is indicative of a 'good response'; a DAS > 2.4 but ≤ 3.7 is indicative of a 'moderate response'; while a DAS > 3.7 shows a 'lack of response' to therapy.[86] See Table 2.4 for the response criteria for the DAS28.

Table 2.4 EULAR Response Criteria Based on the DAS28

Current DAS28	**Improvement in DAS28**		
	>1.2	0.6-1.2	< 0.6
<3.2	Good response	Moderate response	No response
3.2-5.1	Moderate response	Moderate response	No response
>5.1	Moderate response	No response	No response

DAS28= Disease Activity Score 28.
Source: Lutt JR, Deodhar A. Rheumatoid arthritis - Strategies in the management of patients showing an inadequate response to TNF alpha antagonists. *Drugs*. 2008; 68(5):591-606.

Extra-articular diseases and comorbidities assessed in RA are presented in Figure 2.3. Important outcomes in RA management include persistent joint inflammation, progressive joint damage and functional decline. Others include patient-related factors (e.g., fatigue, work disability), presence of comorbidities (e.g., cardiovascular, infection, cancer), extra-articular diseases (e.g., vasculitis, lung disease, rheumatoid nodules and Sjögren's syndrome) and premature mortality.[71]

Figure 2.3 Extra-articular Diseases and Comorbidities Assessed in RA†

Extra-articular Diseases

a) *Cutaneous*
- Leg ulceration
- Vasculitic rashes
- Palmar erythema
- Pyoderma gangrenosum

b) *Cardiac*
- Pericarditis
- Conduction defects
- Valvular heart diseases

c) *Vasculitis*
- Systemic
- Nail fold

d) *Neurological*
- Mononeuritis muitiplex
- Nerve entrapment
- Cervical myelopathy
- Peripheral neuropathy

e) *Ocular*
- Scleritis
- Keratoconjunctivitis sicca
- Episcleritis

f) *Pulmonary*
- Fibrosing alveolitis
- Pleural effusion
- Pulmonary nodules

g) *Amyloidosis & Nodules*

Comorbidities‡

a) *Cardiovascular*
- Myocardial infarction
- Stroke
- Hypertension
- Heart failure
- Peripheral vascular disease

b) *Infection*
- Bacterial
- General

c) *Cancer*
- Skin cancer
- Lung cancer
- Lymphoma and lympho-proliferative diseases

d) *Others*
- Depression
- Gastrointestinal disease
- Renal disease
- Psoriasis
- Osteoporosis

‡Some of the diseases are associated mainly with rheumatoid arthritis (e.g., cardiovascular); some are associated with the treatment (e.g., gastrointestinal diseases); and some with both the disease and the treatment (e.g., infection)

† Rheumatoid Arthritis
Source: Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. *Lancet*. 2010; 376 (9746):1094-1108.

2.1.7 Disease Progression in RA

The clinical course of RA can range from a mild and self-limiting disease to one that is severe and progressive, causing significant disability. The progression and disease activity of RA vary widely among patients, thereby necessitating the need for early identification.[87] Early identification presents patients with the opportunity of benefitting from intensive or aggressive therapy with a high likelihood of changing the course of the disease.[87] While the presence of bone and cartilage erosions are useful predictors of disease progression to severe RA in patients with established RA, they have not been helpful in predicting disease progression among patients with early RA.[87] Monitoring for the presence of serum RF, anti-CCP antibodies, elevated levels of acute phase reactants (e.g., ESR and CRP levels) and markers of bone and cartilage turnover have also been proposed to better predict the destructive course of RA.[87] However, the diagnostic sensitivity and specificity of these biomarkers have been reported to be insufficient in providing guidance for therapeutic decision making.[87] In an approach to address this limitation, a suggestion to use a group of multiple biomarkers that enables detailed stratification of the disease was proposed. According to Lindstrom et al., these biomarkers need to be improved to have the required specificity and sensitivity necessary to accurately identify patients who are at risk of developing erosive RA.[87]

In determining the progression of RA disease in affected patients, the ACR developed classification criteria based on patients' global functional status and the radiographical appearance of their joints on X-ray (see Table 2.5).[86]

Table 2.5 ACR Classification of RA Severity

Class/Stage	Based on Global Functional Status	Based on X-ray Appearance of Joints
I	Completely able to perform usual activities of daily living (self-care, vocational and avocational)	No damages seen on X-rays, although there may be signs of bone thinning
II	Able to perform usual self-care and vocational activities, but limited in avocational activities	**1)** On X-ray, evidence of bone thinning around a joint with or without slight bone damage **2)** Slight cartilage damage possible **3)** Joint mobility may be limited; no joint deformities observed **4)** Atrophy of adjacent muscle **5)** Abnormalities of soft tissue around joint possible
III	Able to perform usual self-care activities, but limited in vocational and avocational activities	**1)** On X-ray, evidence of cartilage and bone damage and bone thinning around the joint **2)** Joint deformity without permanent stiffening or fixation of the joint **3)** Extensive muscle atrophy **4)** Abnormalities of soft tissue around joint possible

Table 2.5 ACR Classification of RA Severity (Contd)

Class/Stage	Based on Global Functional Status	Based on X-ray Appearance of Joints
IV	Limited in ability to perform usual self-care, vocational and avocational activities	**1)** On X-ray, evidence of cartilage and bone damage and osteoporosis around joint **2)** Joint deformity with permanent fixation of the joint (referred to as ankylosis) **3)** Extensive muscle atrophy **4)** Abnormalities of soft tissue joint possible

ACR= American College of Rheumatology
Usual self-care activities include dressing, feeding, bathing, grooming, and toileting.
Avocational (recreation and/or leisure) and **vocational activities** (work, school, homemaking) are patient-desired and age-and gender-specific
Source: Goetz I, Carter GC, Lucero M, et al. Review of treatment response in rheumatoid arthritis: assessment of heterogeneity. *Curr Med Res Opin.* 2011;27(4):697-711.

2.1.8 Management of RA

RA like many chronic disease conditions presently has no cure. A multidisciplinary team approach involving rheumatologists, nurse specialists, occupational therapists, podiatrists, dieticians, pharmacists, physical therapists, psychologists, occupational therapists, rehabilitation specialists and orthopedic surgeons is highly recommended in RA management.[88,89] Current treatment goals are focused on slowing or stopping disease progression (i.e., achieving clinical remission) while controlling associated inflammatory symptoms (e.g., pain, tenderness, swelling and stiffness in the joints as well as fatigue) and halting joint erosions. Treatments are also geared towards improving joint function, work productivity and health-related quality of life, preventing joint destruction and disabilities as well as reducing

morbidity and mortality.[74] Management of RA can be broadly classified into non-pharmacological and pharmacological interventions.

2.1.8.1 Non-Pharmacological Therapies in the Management of RA

Non-pharmacological therapies used in the management of rheumatoid arthritis (RA) are generally recommended as adjunct or supportive therapies to pharmacological treatment.[71,90] Their use varies depending on the stage and progression of the disease, both of which are functions of regular clinical assessment of the disease.[90] Other factors considered include patient's personality, treatment objectives and the environment.[90] Examples of these non-pharmacological therapies include physical therapy, psychotherapy/mind-body medicine, therapeutic patient education, physiotherapy, occupational therapy, exercise/aerobic activities, diet, balneotherapy/hydrotherapy/spa treatment, acupuncture, massage, foot care, joint protection, thermotherapy, transcutaneous electric nerve stimulation (TENS), splints, use of assistive devices and adaptations of the environment.[71,90-92] Finally, surgical treatments or reconstructive surgery (e.g., joint replacement procedures), which are also non-pharmacological options, are used in maintaining or restoring function in situations of significant functional impairment or unacceptable level of pain.[71,74]

2.1.8.2 Pharmacological Therapies in the Management of RA

Pharmacological therapies for the management of RA can be broadly classified into symptomatic/supportive treatment and disease modifying therapies.

Symptomatic/Supportive Treatment Therapies in RA Management

As discussed earlier, patients with RA experience pain, tenderness, swelling and stiffness of the joints due to the on-going inflammatory process. RA patients have over the years benefitted from the use of analgesic and non-steroidal anti-inflammatory drugs (NSAIDs). Analgesic agents only reduce pain while NSAIDs including cyclooxygenase-2 inhibitors effectively improve inflammatory symptoms. However, they have been of limited use in the management of RA due to their inability to modify the disease process (i.e., stop or slow disease progression) in the long term and there are concerns about their safety because these therapies predispose patients to renal damage, gastrointestinal toxicity and cardiovascular morbidities.[71,74,93-95]

Low-dose glucocorticoids (e.g., ≤10mg of prednisone or equivalent) have also been found to be effective due to their potent anti-inflammatory and immunomodulatory effects.[74] They have been reported to reduce the rate of joint erosion and vasculitis in early RA and are recommended as beneficial for short-term treatment in combination with a standard therapy.[71,96,97] Higher does can also be administered over a short period of time either orally or via intramuscular injection as 'bridge therapy' pending the onset of action of disease modifying antirheumatic drugs.[74] In addition, they are also highly effective as local treatment for individual

active joints when administered via intra-articular injection.[71] They have also been of limited use due to their serious side effects, examples of which include blood glucose abnormalities, osteoporosis, Cushingoid manifestations, infections, cataracts and elevated cardiovascular risks.[74]

Disease Modifying Therapies in the Management of Rheumatoid Arthritis

Disease modifying therapies administered in the management of RA can be broadly classified into traditional or conventional disease modifying antirheumatic drugs (DMARDs) and biologic agents or biological response modifiers (BRM).

Traditional or Conventional Disease Modifying Antirheumatic Drugs (DMARDs)

The DMARD class is a heterogeneous collection of drugs with diverse mechanisms of action.[71] These medications have been used in the treatment of RA for decades and have been found to be effective at reducing inflammatory symptoms (e.g., pain and swelling) and acute-phase markers.[71] They modify the disease process by limiting the progression of joint damage and also improve joint function. DMARDs generally have slow onset of action which range from several weeks to months. Examples include methotrexate (MTX), sulfasalazine, leflunomide, hydroxychloroquine, chloroquine, gold (rINN sodium aurothiomalate), cyclosphosphamide, cyclosporine, azathioprine and minocycline.[71,74]

Of these drugs, MTX is the most widely used due to its long-term effectiveness, acceptable safety profile and low cost. MTX remains the standard by which newer

DMARDs are evaluated.[71,74] Other commonly used DMARDs include sulfasalazine, leflunomide and hydroxychloroquine (see Table 2.6).[71,74] While these agents have been shown to be efficacious (e.g., improvement in clinical and radiographic outcomes) when administered as either mono- or combination therapies, limited evidence exists to support the effectiveness of one particular DMARD over the other.[16,98-103] Commonly reported adverse events with the use of MTX (at its usual dose of ≤ 25mg/week) include hepatotoxicity, gastrointestinal toxicities and myelosuppresion.[74] Pulmonary and renal toxicity have also been observed at higher doses of MTX and, as such, periodic monitoring of peripheral blood cell count, liver and kidney function is required.[74] Leflunomide use is associated with alopecia, headache, gastrointestinal symptoms and elevated liver enzymes. Adverse events associated with sulfasalazine use include photosensitivity, myelosuppresion, hematological and gastrointestinal toxicities.[74] Patients on hydroxychloroquine present with skin reactions, alopecia, dizziness, myopathy, headache, central nervous system toxicity and gastrointestinal reactions and in rare situations, ocular toxicity including retinopathy may occur.[74] Due to the severity of the adverse events associated with the use of DMARDs, the American College of Rheumatology (ACR) in 2008 issued recommendations regarding safety monitoring of these agents (Table 2.7).[104]

Table 2.6 Overview of DMARDs Commonly Used in RA Management

Drug Class	Drug (Brand Name) & FDA Approval Date	Mode of Action	Dose and Administration Route	Half life ($t^{1/2}$)
Dihydrofolate reductase inhibitor	Methotrexate (Trexall®) (1988)*	Inhibits metabolism of folic acid	7.5-25mg weekly oral or in subcutaneous injections	3- 15 hours (dose dependent)
Sulfa	Sulfasalazine (Azulfidine®) (1950)*	Not completely clear	1-3g daily oral in divided doses	5-10 hours
Pyrimidine synthesis inhibitor	Leflunomide (Arava®) (1998)*	Inhibits mitochondrial enzyme dihydroorotate dehydrogenase (DHODH)	10-20mg daily oral	14 days
Anti-malaria	Hydroxychloroquine (Plaquenil®; Quineprox®) (1955)*	Inhibits stimulation of the toll-like receptor (TLR) 9 family receptors	200-400mg daily oral	1-2 months

DMARDs= disease modifying antirheumatic drugs; **FDA**= Food and Drug Administration; **RA**= rheumatoid arthritis.

*The approval date indicated is the approval date for the agent's primary indication. For all the agents, RA was not the primary indication for which they were originally approved.

Table 2.7 ACR 2008 Recommendations for Optimal Laboratory Monitoring Intervals* for Complete Blood Count, Liver Transaminase Levels and Serum Creatinine Levels for RA Patients Receiving DMARDs

Agent	Monitoring Interval Based on Duration of Treatment		
	< 3 Months	3-6 Months	> 6 Months
Methotrexate	2-4 weeks	8-12 weeks	12 weeks
Sulfasalazine	2-4 weeks	8-12 weeks	12 weeks
Leflunomide	2-4 weeks	8-12 weeks	12 weeks
Hydroxychloroquine	None after baseline	None	None

ACR= American College of Rheumatology; **DMARDs**= disease modifying antirheumatic drugs; **RA** = rheumatoid arthritis.
*More frequent monitoring is recommended within the first 3 months of therapy or after increasing the dose.
Source: Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of non-biologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum*. 2008; 59(6):762-784.

Biologic Agents or Biological Response Modifiers (BRM)

Biologic agents act by targeting specific inflammatory proteins, cytokines and cellular interactions involved in the pathophysiology of RA.[54,105] Their introduction has generally been recognized to have revolutionized the management of RA as they have been shown to significantly improve patients' symptoms, physical functioning and quality of life while slowing the progression of the disease. [5-10,106-126] Furthermore, the biologic agents' clinical responses are rapid with improvements observed within a few weeks of therapy initiation.[7,111,117,118] While biologics are effective in early RA management, their use is recommended in patients with moderate or severe RA who failed to achieve remission or satisfactory response following treatment with traditional DMARDs (e.g., methotrexate).[74] This is primarily due to their substantial cost impact and long-term safety concerns.[74] Biologics also differ in their mode of administration, mechanism of action and frequency of dosing (Table 2.8).[54] These differences, together with other factors (e.g., cost, insurance

coverage, patient and physician preferences) impact the choice of biologic agent used in clinical practice. Examples of these agents include anakinra, etanercept, adalimumab, infliximab, golimumab, certolizumab, rituximab, abatacept and tocilizumab.[54]

Among the available biologic agents, the tumor necrosis factor (TNF) inhibitors are the most widely used because of their remarkable efficacy. They act by preventing TNF-α, a proinflammatory cytokine, from binding to its receptor.[54] Of the five currently available TNF inhibitors, four (i.e., adalimumab, infliximab, certolizumab and golimumab) are monoclonal antibodies (MAbs) that bind directly to TNF-α while one (etanercept) is a synthetic TNF-receptor immunoglobulin (IgG1) fusion protein that binds specifically to TNF-α and TNF-β (lymphotoxin).[54] They have been shown through randomized controlled trials (RCTs) to be efficacious in the management of RA patients.[5-10,106-116] These agents demonstrated better outcomes (clinical and radiographic benefit) when administered in combination with traditional or conventional DMARDs (e.g., methotrexate or leflunomide) compared to monotherapy. [3,6-11,112] While there is no direct head-to-head comparison among the available TNF inhibitors, results from the majority of indirect treatment comparison studies suggested that the agents have comparable efficacy and safety profiles.[12-17,127] Commonly reported adverse events with the use of TNF inhibitors include injection-site or infusion reactions (e.g., stinging and burning) and infections (e.g., tuberculosis (TB)).[71,74,127] Long-term safety concerns of TNF inhibitors include increased risks for

serious bacteria (e.g., abscesses, sepsis and cellulites), fungal (e.g., candidiasis) and viral (e.g., herpes zoster) infections.[71,127] Other serious but rare events of concern that may occur include autoimmunity, demyelinating disease and hepatotoxicity.[71,74] Cancer/ increased risk for lymphoma have also been associated with TNF inhibitor use.[71,74] However, evidence substantiating this relationship is weak as patients with severe RA are at high risk of developing lymphoma due to the RA inflammatory disease process.[54,58,71,128] Due to the risk for TB and hepatitis (B and C) infections, regular and appropriate screening is required for patients on TNF inhibitors.[71,74] Patients should also be screened for latent TB and be given preventive TB therapy if found to be positive prior to initiating TNF inhibitor therapy.[74]

The other biologic agents include anakinra, abatacept, rituximab and tocilizumab. Anakinra is a recombinant protein that binds to the interleukin (IL) -1 type-1 receptors, thereby preventing IL-1-mediated signal transduction in target cells.[54] Although it is efficacious in the treatment of RA,[119,120] it is not frequently used due to the availability of better therapies.[74] Compared to the TNF inhibitors, it has fewer clinical benefits and more frequent injection site reactions.[74,129] Abatacept is a cyctotoxic T lymphocyte-associated antigen-4 immunoglobulin (CTLA-4Ig) G1 fusion protein that affects T-cell activation due to its blockage of the co-stimulatory signal required for the activation process.[54] Rituximab is an anti-CD20 antibody that causes selective depletion of CD20+ B cells.[54] Abatacept and rituximab, usually in combination with MTX, are mostly reserved for patients who fail to respond

adequately to TNF inhibitors.[54,74] Efficacy of these agents has also been demonstrated through RCTs.[117,118,121] Furthermore, combining abatacept (due to its unique mechanism of action) with TNF inhibitors is discouraged as such combinations have no significant incremental benefit over TNF monotherapy.[130] The side effect profile of abatacept and rituximab is comparable with those of TNF inhibitors.[54] However, patients on rituximab with concurrent or prior usage of other immunosuppressive therapies are at risk of developing John Cunningham (JC) virus infection which causes progressive multifocal leukoencephalopathy.[54]

Tocilizumab is the newest biologic agent[a] approved by the FDA for management of RA.[74] It is an anti IL-6 receptor monoclonal antibody with efficacy and safety/tolerability profiles comparable to other biologic agents.[74] Biologic agents in development include: denosumab, which is an inhibitor of the receptor-activator of NF-κB ligand (RANKL); ocrelizumab and oftatumumab which are anti-CD20 B-cell blockers; and the kinase inhibitors (i.e., Janus Kinase inhibitors (JAK) and Spleen Tyrosine Kinase (SYK) inhibitors) which target specific inflammatory pathways. Others include agents targeting alternative inflammation/T-cells activation pathways and those blocking other B-cell targets (i.e., toll-like receptors, B lymphocyte stimulator and other surface receptors and markers).[74]

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[a] Tofacitinib (Xeljanz® by Pfizer) recently approved (2013) for moderate to severe RA is not a biologic. It is an orally administered JAK inhibitor which works differently from the biologics.

Table 2.8 Overview of Biologic Agents Used in the Management of RA

Drug Class	Drug (Brand Name) & FDA Approval Date	Structure	Mode of Action	Dose and Administration Route	Half life ($t_{1/2}$)
TNF Inhibitors	Etanercept (Enbrel®) (1998)	Soluble fusion protein (dimer) of 2 recombinant p75 TNF-α receptor proteins, with each molecule linked to the Fc portion of human IgG1	Prevent binding of TNF-α to its receptor	25mg SC twice weekly or 50mg once weekly (self-administered	4 days
	Infliximab (Remicade®) + MTX (1999)	Chimeric MAb with Fc region of human IgG1 joined to variable region of mouse anti-TNF-α antibody		3mg/kg IV over 2 hours at week 0, 2, 6, then every 8 weeks, with dose adjustment up to 10mg/kg, if necessary	8-10 days
	Adalimumab (Humira®) (2003)	Recombinant human IgG1 MAb to TNF-α		40mg SC every 2 weeks (self-administered)	≈ 14 days
	Certolizumab pegol (Cimza®) (2009)	Pegylated humanized monoclonal anti-TNF Fab' fragment		400 mg SC (liquid or lyophilized) at week 0, 2 and 4, followed by 200mg every other week (or 400mg every 4 weeks)	14 days
	Golimumab (Simponi®)+ MTX (2009)	Human anti-TNF receptor MAb		50mg SC once a month	≈ 14 days

Drug Class	Drug (Brand Name) & FDA Approval Date	Structure	Mode of Action	Dose and Administration Route	Half life ($t_{1/2}$)
IL-1 inhibitor	Anakinra (Kineret®) (2001)	Recombinant IL-1 inhibitor	Prevents IL-1 from binding to its receptor	100mg SC daily	≈ 14 days
T-cell co-stimulation blocker	Abatacept (Orencia®) (2005)	Recombinant fusion protein consisting of the extracellular domain of human CTLA-4 and part of the Fc domain of human IgG1	Prevents the co-stimulatory signal required for T-cell activation	500-1000mg IV over 300 minutes, depending on body weight at week 0, 2 and 4, then every 4 weeks	17 days
B-cell targeted therapy	Rituximab (Rituxan®) + MTX (2006)	Chimeric human/mouse anti-CD20 MAb	Binds to CD20, a cell marker expressed on mature- and pre-B-cells, but not on other cells, including plasma cells; leads to selective depletion of CD20+B cells via several mechanisms	Two separate 1000mg IV infusions, 2 weeks apart (IV methylpredisolone 100mg or equivalent is recommended 30 minutes before administering rituximab to prevent serious reaction)	19 days

Drug Class	Drug (Brand Name) & FDA Approval Date	Structure	Mode of Action	Dose and Administration Route	Half life (t1/2)
Biologics newly approved in the US					
IL-6 inhibitor	Tocilizumab (Actemra®) (2010)	Humanized anti-IL-6 receptor MAb	Prevents IL-6 from binding to both membrane-expressed and soluble IL-6 receptors	4mg/kg IV or 8mg/kg IV every 4 weeks as monotherapy or in combination with DMARDs	
RANKL inhibitor	Denosumab (phase II)†	Human anti-RANKL MAb	Binds RANKL and inhibits RANKL action	Twice yearly SC injections of denosumab plus MTX	

CTLA-4=cyctotoxic T lymphocyte-associated antigen-4; **DMARDs**= disease modifying antirheumatic drugs; **FDA**= US Food and Drug Administration. †Denosumab is approved in the United States for the treatment of postmenopausal osteoporosis (approved as Prolia® June 2010) and for the prevention of skeletal-related events in patients with bone metastases from solid tumors (approved as Xgeva® November 2010) but it is not currently indicated for the treatment of RA; **IgG**= immunoglobulin; **IL**= interleukin; **IV**= intravenous; **MAb**= monoclonal antibody; **MTX**= methotrexate; **RA**=rheumatoid arthritis; **RANKL**= receptor-activator of NF-κB ligand; **SC**= subcutaneous; **TNF**= tumor necrosis factor.

Source: Curtis JR, Singh JA. Use of biologics in rheumatoid arthritis: current and emerging paradigms of care. *Clin Ther.* 2011; 33 (6):679-707.

2.1.9 Clinical Practice Guidelines for the Management of RA

A number of clinical practice guidelines have been developed over the years to help in the effective management of RA. Among those commonly used are recommendations by the British Society for Rheumatology (BSR), British Health Professionals in Rheumatology (BHPR), the American College of Rheumatology (ACR), the European League Against Rheumatism (EULAR), and the UK's National Institute for Health and Clinical Excellence (NICE). While there are variations in the recommendations, all organizations supported the following key messages: 1) early referral of patients to specialists; 2) rapid control of inflammatory symptoms using the lowest effective dose of NSAIDs or short-term low dose glucocorticoids; 3) early initiation of traditional DMARD therapy for active disease; and 4) use of biologic agents in situations of suboptimal response to traditional DMARD therapy.[74] Further discussions in this section will be limited to the recommendations by ACR and EULAR because they have been the most commonly used clinical practice guidelines.

ACR Recommendations

The recommendations provided by ACR to guide therapeutic decisions were based on three important clinical features: (1) disease activity which is categorized as low, moderate or high; (2) presence of predetermined relevant prognostic factors (e.g., functional limitation, presence of RF or anti-CCP antibodies, extra-articular disease and bony erosions on radiography); and (3) the duration of the disease [(i.e., short (< 6 months), intermediate (6-24 months), or long (> 24 months) for non-

biologic DMARD therapies and < 6 months or ≥ 6 months for biologic DMARD therapies)].[104] Table 2.9 presents a summary of ACR recommendations for the use of traditional DMARDs in RA. Recommendations regarding the use of biologic DMARD therapies restrict TNF inhibitor use to the following situations: (a) early RA, in combination with MTX in patients who present with high disease activity for 3-6 months and have not received any prior DMARD therapy; (b) early RA, in combination with MTX in patients who present with high disease activity for less than 3 months and poor prognosis. In addition, such patients should have no cost or insurance coverage limitations; (c) intermediate and longer duration RA, in patients with either a moderate disease activity and poor prognosis or high disease activity, who responded poorly to MTX monotherapy; and (d) intermediate and longer duration RA, in patients with moderate or high disease activity, who had prior treatment failure with MTX combination therapy or sequential administration of other non-biologic DMARD. [104] Abatacept and rituximab are recommended for patients with moderate or high disease activity, poor prognosis and suboptimal response to combinations of MTX with other DMARDs or sequential administration of other non-biologic DMARDs.[104] Combinations among biologic DMARDs are not recommended due to risk of increased adverse events and lack of evidence regarding incremental benefits.

The 2012 update of the 2008 ACR recommendation included newer TNF-inhibitors (e.g., golimumab, certolizumab pegol and tocilizumab) to its list of

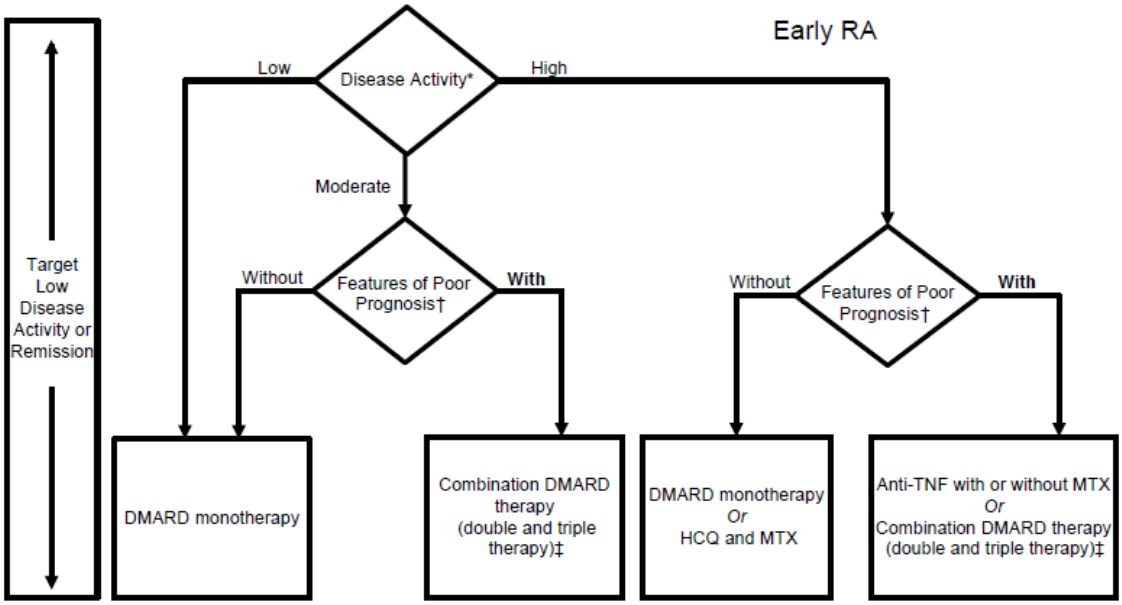
recommended biologics and provided more details as regard switching between therapies in management of established RA.[131] Figures 2.4 and 2.5 provides a summary of the 2012 update of the 2008 ACR recommdendations in management of early and established RA.

Table 2.9 2008 ACR Recommendations for the Use of DMARDs

Disease Duration < 6 Months		
Disease Activity	**Poor Prognostic Features**	
	Present	**Absent**
Low	LEF or MTX	MTX, LEF, SSZ, HCQ or MIN
Moderate or High	LEF, MTX or combinations of DMARDs† including MTX	MTX, LEF, SSZ, or combinations of DMARDs including MTX
Disease Duration 6-24 Months		
Disease Activity	**Poor Prognostic Features**	
	Present	**Absent**
Low	LEF, MTX or combinations of DMARDs including MTX	MTX, LEF, SSZ or HCQ
Moderate or High	LEF, MTX or combinations of DMARDs‡ including MTX	MTX, LEF, SSZ, or combinations of DMARDs‡#§
Disease Duration > 24 Months		
Disease Activity	**Poor Prognostic Features**	
	Present	**Absent**
Low or Moderate	LEF, MTX or combinations of DMARDs including MTX	MTX, LEF, SSZ, or combinations of DMARDs including MTX
High	LEF, MTX or combinations of DMARDs including MTX	MTX, LEF, SSZ, or combinations of DMARDs including MTX

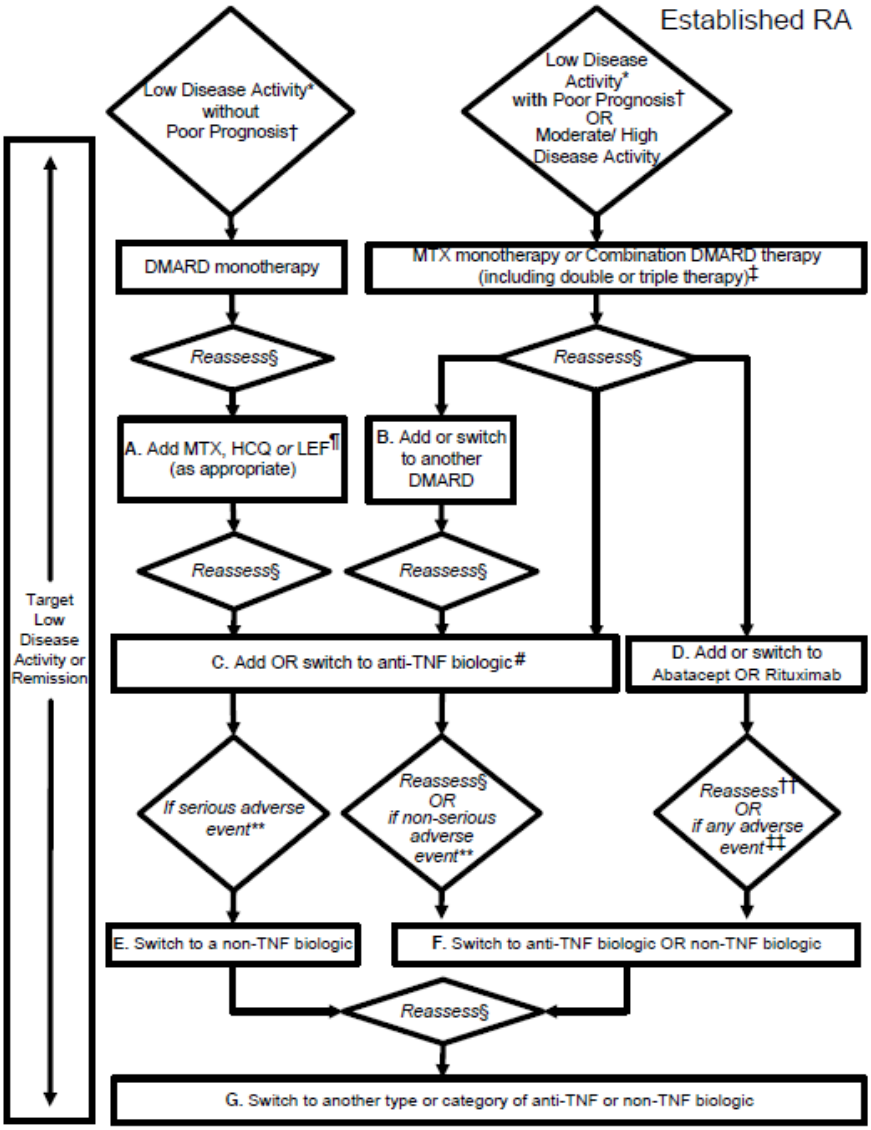
DMARDs= disease modifying antirheumatic drugs; **HCQ**=hydroxychloroquine **LEF**= leflunomide; **MIN**= minocycline; **MTX**= methotrexate; **SSZ**= sulfasalazine.
Combinations of DMARDs including SSZ are also recommended for the following: (1) †patients with high disease activity with features of poor prognosis; (2) ‡patients with moderate disease activity regardless of prognostic features; and (3) #patients with high disease activity without features of poor prognosis.
§Combinations of DMARDs including HCQ are recommended for patients with high disease activity without features of poor prognosis
Source: Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of non-biologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum*. 2008; 59(6):762-784.

Figure 2.4 2012 Update of the 2008 ACR Recommendations for the Management of Early RA (Disease Duration < 6 Months)



DMARDs= disease modifying antirheumatic drugs; **HCQ**=hydroxychloroquine; **MTX**= methotrexate
†Patients were catergorized based on the presence or absence of ≥ 1 of the following poor prognostic features: functional limitation (e.g., Health Assessment Questionnaire score or similar valid tools), extraarticular disease (e.g. Felty's syndrome, presence of rheumatoid nodules, RA vasculitis), bony erosions by radiography and positive rheumatoid factor or anti-cyclic citrullinated peptide antibodies.
‡Combination DMARD therapy with 2 DMARDs, which is most commonly MTX based, with some exceptions (e.g., MTX + HCQ, MTX+ Leflunomide, MTX + Sulfasalazine (SSZ) and SSZ + HCQ), and triple therapy (MTX + HCQ + SSZ).
Source: Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken).* 2012; 64(5):625-639.

Figure 2.5 2012 Update of the 2008 ACR Recommendations for the Management of Established RA (Disease Duration ≥ 6 Months)



DMARDs=Disease modifying antirheumatic drugs; **HCQ**=Hydroxychloroquine; **LEF**=Leflunomide; **MTX** =Methotrexate

Depending on a patient's current medication regimen, the management algorithm may begin at an appropriate rectangle in the figure, rather than only at the top of the figure. DMARDs include HCQ, LEF, minocycline (MIN), MTX and sulfasalazine (SSZ). Azathioprine and cyclosporine were considered but not included. DMARD monotherapy refers to treatment in most instances with HCQ, LEF, MTX or SSZ. In few instances, where appropriate, MIN may also be used as DMARD monotherapy. Anti-tumor necrosis factor (anti-TNF) biologics include adalimumab, certrolizumab pegol, etanercept, infliximab and golimumab. Non-TNF biologics include abatacept, rituximab and tocilizumab.

†Patients were catergorized based on the presence or absence of ≥ 1 of the following poor prognostic features: functional limitation (e.g., Health Assessment Questionnaire score or similar valid tools), extraarticular disease (e.g., Felty's syndrome, presence of rheumatoid nodules, RA vasculitis), bony erosions by radiography and positive rheumatoid factor or anti-cyclic citrullinated peptide antibodies.
‡Combination DMARD therapy with 2 DMARDs, which is most commonly MTX based, with some exceptions (e.g., MTX + HCQ, MTX+ LEF, MTX + SSZ and SSZ + HCQ), and triple therapy (MTX + HCQ + SSZ).
§ Reassess after 3 months and proceed with escalating therapy if moderate or high disease activity in all instances except after treatment with a non-TNF biologic (rectangle D), where reassessment is recommended at 6 months due to a longer abticipated time to peak effect.
¶ Lef can be added in patients with low disease activity after 3-6 months of MIN, HCQ, MTX or SSZ.
# If after 3 months of intensified DMARD combination therapy or after a second DMARD has failed, the option is to ass or switch to an anti-TNF biologic.
** Serious adverse events were defined per the US Food and Drug Administration (FDA; see below); all other adverse events were considered nonserious adverse events.
†† Reassessment after treatment with a non-TNF biologic is recommended at 6 months due to anticipation that a longer time to peak effect is needed for non-TNF compared to anti-TNF biologics.
‡‡ Any adverse event was defined as per the US FDA as any undesirable experiences associated with the use of a medical product in a patient. The FDA definition of serious adverse event includes death, life-threatening event, imitial or prolonged hospitalization, disability, congenital anomaly, or an adverse event requiring intervention to prevent impairment or damage.
Source: Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken).* 2012; 64(5):625-639.

EULAR Recommendations

The latest recommendations by EULAR were based on 3 overarching principles. These principles identified: (1) the need for rheumatologists to be the primary care provider for RA patients; (2) the importance of having a treatment approach that is aimed at providing the best care and based on a shared decision between the patient and the rheumatologist; and (3) the need for the rheumatologist to consider both the medical costs and productivity costs associated with the management of RA.[132] While the previously published EULAR recommendations focused on management of patients with early RA or undifferentiated arthritis, the latest EULAR recommendations apply to all patients with RA and also provided detailed guidance on the use of pharmacological compounds.[132,133] However, both

sets of recommendations recognize the importance of initiating DMARD therapy as soon as RA is diagnosed.[132,133] Figure 2.6 presents the current EULAR recommendations for the management of RA.

Figure 2.6 EULAR Recommendations for the Management of RA

- Treatment with synthetic DMARDs should be started as soon as the diagnosis of RA is made
- Treatment should be aimed at reaching a target of remission or low disease activity as soon as possible in every patient; as long as the target has not been reached, treatment should be adjusted by frequent (every 1 to 3 months) and strict monitoring
- MTX should be part of the first treatment strategy in patients with active RA
- When MTX contraindications (or intolerance) are present, the following DMARDs should be considered as part of the (first) treatment strategy: LEF, SSZ or injectable gold
- In DMARD naïve patients, irrespective of the addition of GCs, synthetic DMARD monotherapy rather than combination therapy of synthetic DMARDs may be applied
- GCs added at low to moderately high doses to synthetic DMARD monotherapy (or combinations of synthetic DMARDs) provide benefit as initial short-term treatment but should be tapered as rapidly as clinically feasible
- If the treatment target is not achieved with the first DMARD strategy, addition of a biological DMARD should be considered when poor prognostic factors are present; in the absence of poor prognostic factors, switching to another synthetic DMARD strategy should be considered

Figure 2.6 EULAR Recommendations for the Management of RA (Contd)

- In patients responding insufficiently to MTX and/or other synthetic DMARDs with or without GCs, biological DMARDs should be started; current practice would be to start a TNF inhibitor (adalimumab, certolizumab, etanercept, golimumab, infliximab) which should be combined with MTX
- Patients with RA for whom a first TNF inhibitor has failed, should receive another TNF inhibitor, abatacept, rituximab or tocilizumab
- In cases of refractory severe RA or contraindications to biological agents or the previously mentioned synthetic DMARDs, the following synthetic DMARDs might be also considered, as monotherapy or in combination with some of the above: azathioprine, cyclosporin A (or exceptionally cyclosphosphamide)
- Intensive medication strategies should be considered in every patient, although patients with poor prognostic factors have more to gain
- If a patient is in persistent remission, after having tapered GCs, one can consider tapering DMARDs, especially if this treatment is combined with a synthetic DMARD
- In cases of sustained long-term remission, cautious titration of synthetic DMARD dose could be considered, as a shared decision between patient and doctor
- DMARD naïve patients with poor prognostic markers might be considered for combination therapy of MTX plus a biological agent
- When adjusting treatment, factors apart from disease activity, such as progression of structural damage, comorbidities and safety concerns should be taken into account

DMARD= disease modifying antirheumatic drug; **EULAR=** European League Against Rheumatism**; GCs**= glucocorticoids; **LEF**= leflunomide**; MTX**= methotrexate; **RA**= rheumatoid arthritis; **SSZ**= sulfasalazine; **TNF**= tumor necrosis factor

Source: Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis.* 2010;69(6):964-975.

2.1.10 Medication Use Patterns in the Management of RA

2.1.10.1 Medication Adherence: Brief Overview

The World Health Organization (WHO) defined adherence as "the extent to which a person's behavior (i.e., taking medication, following a diet and/or executing lifestyle changes) corresponds with agreed recommendations from a health care provider."[134] A patient's adherence (or compliance) to medication can be defined as the extent to which the patient takes his/her medications as prescribed (with respect to the interval, dose and dosing regimen) by his/her health care provider.[135,136] Medication persistence on the other hand is defined as the duration or length of time a patient consistently takes a prescribed medication from initiation to discontinuation of therapy.[136,137] Medication adherence and persistence captures two important aspects of a patient medication taking behavior, namely regularity and continuity.[138]

Poor medication adherence has been reported as a factor responsible for therapeutic failures or poor health outcomes in patients, especially among those with chronic medical conditions (e.g., RA) who require a lifetime use of medications.[138] Generally, patients with chronic conditions (especially after the first six months of therapy) tend to present with lower adherence rates when compared to those with acute disease conditions.[135,137] Poor or suboptimal adherence to prescribed medications has also been associated with increases in healthcare utilization and healthcare costs. [135] It is responsible for approximately 33 to 69 percent of

medication-related hospital admissions at an estimated at $100 billion per year in avoidable/preventable healthcare costs.[135] This is because non-adherence increases the risk for rapid disease progression, development of complications, occurrence of preventable hospitalizations and emergency department visits, ambulatory care visits, increased visits to physicians and other healthcare providers, unnecessary change in treatment regimens, further diagnostic processes, premature disability and ultimately death.[135,138,139] Factors associated with poor or suboptimal medication adherence include the patient's lack of adequate understanding of the disease and its complications, the asymptomatic nature of some diseases, unpleasant side effects of medications, complexity of treatment, high medication cost, missed appointments, the patient's lack of confidence in immediate or future benefits of treatment, cognitive impairment, inadequate follow-up or discharge planning, psychological problems (especially depression), barriers to care or medication and poor relationship with health care provider. Other factors include poor socioeconomic status, gender and race.[135] Commonly used methods for measuring patients' adherence to prescribed medications are presented in Table 2.10.

Table 2.10 Methods for Measuring Medication Adherence

Methods	Examples
Direct measurement methods	• Directly observed therapy (DOT) • Drug levels or metabolites in blood • Blood biomarkers
Indirect measurement methods	• Patient self-reports • Pill counts • Prescription refill rates • Patient clinical response • Electronic medication monitors • Patient diaries • Physiologic markers

Source: Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med.* 2005;353(5):487-497.

2.1.10.2 Medication Adherence and Persistence in the Management of RA

As in all disease conditions (most especially chronic diseases), the importance of adherence and persistence to prescribed therapies in the management of RA cannot be overemphasized. Despite the risk for increased joint pain and functional impairment, RA patients have been generally reported to have problems adhering to their prescribed RA therapies (i.e., pharmacological regimens). Reported adherence and persistence rates to prescribed RA therapies ranged between 20 and 80 percent.[137,138] Factors identified to be associated with poor medication taking behavior among RA patients include low socioeconomic status (i.e., education and income level), younger age, lack of social support, medication side-effects, presence of comorbidities, increased disability, inadequate knowledge/understanding of the disease and its treatment, poor quality of contact with healthcare provider, being of ethnic minority descent, as well as poor prior medication-taking behaviors and beliefs.[137]

Among the RA therapies discussed earlier, more attention has increasingly been focused on use of biologic agents (especially TNF inhibitors) in clinical settings, as poor medication use behaviors among patients can significantly undermine the potential benefits of these RA treatments. Among the available TNF inhibitors, three agents (Enbrel® (etanercept); Remicade® (infliximab); and Humira® (adalimumab)) have been extensively studied and due to their importance in RA management, further discussions in this section will be limited to these three biologic agents.

All available studies in the literature which used administrative claims data to evaluate RA patients' adherence to etanercept, infliximab and adalimumab were conducted in the US, with adherence measured using varying definitions of medication possession ratio (MPR) or proportion of days covered (PDC).[2,21-23,25] MPR is defined as the sum of total days' supply for all fills divided by the number of days in the study period. PDC is defined as the proportion of days a patient has a drug available in the specified interval or study period. Three of the available studies utilized Medicaid data,[23-25] while the other 3 studies were conducted using data from patients enrolled in private health plans or managed care organizations.[2,21,22]

For studies conducted with Medicaid data, Li et al. reported significantly ($p < 0.05$) higher mean adherence among infliximab users compared to etanercept users, with mean PDC (SD not provided) values of 0.64 and 0.57 reported for infliximab and etanercept users, respectively.[25] The other two Medicaid studies used methotrexate

(MTX) as the reference agent with no comparison made among the 3 TNF inhibitors.[23,24] Grijalva et al. reported mean MPR (SD not provided) values of 0.83, 0.85 and 0.90 for etanercept, adalimumab and infliximab users, respectively.[23] Lower mean MPR values were observed when etanercept, adalimumab and infliximab were individually administered in combination with MTX (mean MPR (SD not provided) values were 0.64, 0.66 and 0.72, respectively).[24] The second study by Grijalva et al., reported median MPR values of 0.73, 0.72 and 0.68 for etanercept, adalimumab and infliximab use, respectively.[24]

For studies that utilized commercial databases, Curkendall et al. reported an overall mean MPR of 0.52 (±0.31) for etanercept and adalimumab users.[22] Borah et al. reported mean MPR values ranging from 0.65 (±0.31) to 0.73 (±0.26) for patients on etanercept and mean MPR values ranging from 0.63 (±0.32) to 0.70 (±0.28) for patients on adalimumab.[2] In addition, the proportion of adherent patients (MPR>0.80) ranged from 42.0 to 51.3 percent among etanercept users and 41.0 to 47.1 percent among adalimumab users.[2] Harley et al. reported 68.4 and 80.9 percent of patients on etanercept and infliximab, respectively, as being adherent (MPR>0.80).[21] Furthermore, among new users, the likelihood of being adherent (MPR≥0.8) to etanercept was reportedly lower (OR=0.462, 95% CI=0.290-0.736, $p < 0.05$) compared to infliximab, while among existing users, patients were more likely to be non-adherent to adalimumab compared to etanercept (OR=1.25, 95% CI=1.05-1.49, p=0.01).[2,21]

Commonly used terms for describing medication persistence across studies include persistence, treatment retention, treatment continuation, drug survival and time to drug discontinuation.[138] The literature on medication persistence to etanercept, infliximab and adalimumab presents conflicting results and only a few studies[2,22,23,25-27] specified the gap period(s) used in the analyses. A brief overview of the results of the persistence studies conducted in the US is presented in the subsequent paragraphs.

For studies conducted with Medicaid data, Li et al. found comparable ($p>0.05$) 12-month discontinuation rates between infliximab (48.3%) and etanercept (50.0%) users using a 60-day gap.[25] Sensitivity analyses using 30-, 90- and 120-day gaps also yielded comparable discontinuation rates between infliximab (65.3%, 40.9% and 33.6%, respectively) and etanercept users (67.9%, 40.7%, and 34.5%, respectively).[25] Grijalva et al. reported median persistence of 175 days, 134 days and 85 days for etanercept, adalimumab and infliximab users, respectively, based on a 12-month follow-up period, using a 90-day gap period. MTX was the reference agent and no comparison was made among the 3 TNF inhibitors.

Regarding commercial data studies, Tang et al. reported significantly ($p=0.005$) higher mean persistence rates among infliximab patients (78.0%) compared to patients on etanercept (72.8%) and adalimumab (70.8%) based on a 1-year follow-up period.[4] Harrison et al. found a significantly ($p < 0.05$) higher mean duration of therapy (in days) and persistence rate among naïve users of etanercept

(301 days ± 91; 82.5%) compared to naïve users of infliximab (281 days ± 106; 77.0%) and adalimumab (280 days ± 102; 76.7%), but comparable mean durations of therapy (in days) and persistence rates among continuing users on the 3 drugs based on a 1-year follow-up period.[28] Wu et al. reported comparable (p>0.05) 12-month discontinuation rates among users of infliximab (37.8%), etanercept (44.6%) and adalimumab (44.4%) using a 60-day gap.[26] Borah et al. reported comparable mean time (SD not provided) to discontinuation of therapy between drug-naïve patients on either etanercept (211 days) or adalimumab (211 days), as well as between existing patients on either etanercept (237 days) or adalimumab (232 days) based on a one-year follow-up period using a 30-day gap.[2] In addition, the likelihood of discontinuing medication use was not significantly different (HR=1.11 p=0.06 95% CI=1.00-1.23) between existing adalimumab users compared to etanercept users.[2] Yazici et al., in a subanalysis, reported a significantly ($p < 0.0001$) higher median persistence in days among infliximab users (464 days) compared to etanercept (347.5 days) and adalimumab (365 days) users based on an 18-month follow-up period using a 30-day gap.[27]

For studies conducted in Europe, continuation rates for infliximab (administered with or without traditional DMARDs) ranged from 48.0 to 90.9 percent based on a 12-month follow-up period [41,140-151] and from 47.5 to 80.7 percent based on a 24-month follow-up period.[142,145-147,151] Similarly, continuation rates for etanercept (administered with or without traditional DMARDs) ranged from 42.0 to

89.0 percent based on a 12-month follow-up period [34,41,141,142,144,148,149,152] and from 50.8 to 79.0 percent based on a 24-month follow-up period.[142,153] Studies on adalimumab (administered with or without traditional DMARDs) reported continuation rates ranging from 60.0 to 87.4 percent based on a 12-month follow-up period[41,142,144,152] and 60.2 percent based on a 24-month follow-up period.[142] Furthermore, a study by Punzi et al. which used a 36-month follow-up period reported significantly ($p < 0.001$) lower continuation rates among infliximab patients (57.5%) compared to patients on etanercept (74.7%) and adalimumab (72.0%).[1]

A summary of studies conducted in the US and Europe on medication adherence and persistence to etanercept, adalimumab and infliximab is presented in Table 2.11. Overall, the results from the adherence and persistence studies suggest the following: (1) mean adherence values vary widely acrossed studies depending on how adherence was measured; (2) adherence to etanercept and adalimumab is comparable among biologic-naïve or new patients; (2) biologic-naïve patients tend to adhere better to infliximab compared to etanercept; (3) existing or continuing patients on biologics tend to adhere better to etanercept compared to adalimumab; (4) persistence/discontinuation rates vary widely depending on the follow-up periods and the allowable gap periods used in the study; (5) results on persistence/discontinuation remain largely inconsistent with some of the studies indicating comparable persistence/discontinuation rates among users of the 3 TNF

inhibitors, while others showed either infliximab or etanercept having a better outcome.

Table 2.11 Summary of Studies[a] on Adherence and Persistence to Etanercept, Adalimumab and Infliximab

Study	Study Agents	Datasource/ Analysis/ Country	Sample size/ Brief description of sample	Adherence/ Compliance Measurement	Adherence/ Compliance Results	Persistence Measurement	Persistence Results
Claims Data							
Borah et al.[2]	ADA and ETN	Claims data (private commercial) Retrospective US	3,829/ mean age (±SD) was 49.9 years (SD not provided) and females (77.1%) made up the majority of the sample.	MPR was defined as total day's supply divided by 365. Adherence was defined as MPR ≥80%.	**For naïve users**: Mean MPR was 63.0% (±0.32) for ADA and 65% (±0.31) for ETN (p=0.3855). The proportion of adherent patients was 41.0% for ADA and 42.0% for ETN (p=0.7312). **For existing users**: Mean MPR was 70.0% (±0.28) for ADA and 73.0% (±0.26) for ETN (p=0.0066). The proportion of adherent patients was 47.0% and 51.3% for ADA and ETN users, respectively (p=0.0514). ADA users were more likely to be non-adherent compared to ETN users (OR=1.25, 95% CI=1.05-1.49, p=0.01).	Time to treatment discontinuation[b] from index based on a 12-month follow-up period. A 60-day gap period was used.	Mean time (SD not provided) to discontinuation of therapy was comparable between naïve users on either ETN (211 days) or ADA (211 days) as well as between existing users on either ETN (237 days) or ADA (232 days).The likelihood to discontinue medication use was not significantly different (HR=1.11 p=0.06 95% CI=1.00-1.23) between existing ADA and ETN users.

Study	Study Agents	Datasource/ Analysis/ Country	Sample size/ Brief description of sample	Adherence/ Compliance Measurement	Adherence/ Compliance Results	Persistence Measurement	Persistence Results
Tang et al.[4]	ADA+MTX, ETN+MTX and IFX+MTX	Claims data (majority (90.3%) private commercial and Medicare) Retrospective US	1,242/ mean age was 50.0 years (SD not provided) and females (77.7%) comprised the majority of the sample.	N/A	N/A	Treatment persistence[b] was defined as the number of days between the first and last filled prescriptions or administered drugs and reported as a percentage of the 1-year period after treatment inititiation. No gap period was specified.	The IFX group had significantly (p=0.005) higher mean persistence days and rates (284.8 days (*95% CI=276.2-293.4)*; 78.0%) compared to patients on ETN (265.6 days (*95% CI=256.1-275.1)*; 72.8%) and ADA (258.5 days (*95% CI=238.0-279.0)*; 70.8%).
Wu et al.[26]	ADA, ETN and IFX	Claims data (private commercial) Retrospective US	808/ mean age (±SD) was 50.1 years (SD not provided) and females (75.4%) comprised the majority of the sample.	N/A	N/A	Treatment discontinuation was defined as the first occurrence of a gap in the index medication administration of more than 60 days during the 12-month study period.	ADA (44.4%), ETN (44.6%) and IFX (37.8%) had comparable (p>0.05) discontinuation rates.

Study	Study Agents	Datasource/ Analysis/ Country	Sample size/ Brief description of sample	Adherence/ Compliance Measurement	Adherence/ Compliance Results	Persistence Measurement	Persistence Results
Grijalva et al.[23]	12 regimens including biologic (e.g., ADA, ETN and IFX) and traditional DMARDs in mono- and combination therapy	Claims data (Medicaid) Retrospective US	14,932/ median age (range) was 54 years (41-66) and females (79.4%) comprised the majority of the sample.	MPR was defined as aggregated number of days supply obtained during an episode divided by the length of the episode, excluding the last prescription fill.	**Monotherapy:** Mean MPR was 83.0% for ETN, 85.0% for ADA and 90.0% for IFX. Compared to MTX (mean MPR=0.80), each agent showed significantly higher mean MPR ($p < 0.01$). **Combination therapy with MTX**: Mean MPR was 64.0% for ETN, 72.0% for ADA and 66.0% for IFX. Compared with MTX (monotherapy), individual combinations with MTX showed significantly lower mean MPR ($p < 0.01$).	Time to treatment discontinuation[b] from index based on a 12-month follow-up period. A 90-day gap period was used.	**Monotherapy:** Median persistence was 175 days for ETN, 134 days for ADA and 85 days for IFX. Compared to MTX *(median persistence=150 days),* only IFX use was associated with a higher likelihood of discontinuation (adjusted HR=1.37; 95% CI=1.09-1.73; p=0.007). **Combination with MTX:** Median persistence was 147 days with ETN, 219 days with ADA and 155 days with IFX. Compared with MTX (monotherapy), only the combination of ADA with MTX showed lower likelihood of discontinuation (adjusted HR=0.63; 95% CI=0.48-0.84; p=0.002).

Study	Study Agents	Datasource/ Analysis/ Country	Sample size/ Brief description of sample	Adherence/ Compliance Measurement	Adherence/ Compliance Results	Persistence Measurement	Persistence Results
Li et al.[25]	IFX, ETN and ANA	Claims data (Medicaid) Retrospective US	2,638/ mean age (±SD) was 58.0 years (SD not provided) and females (88.4%) comprised the majority of the sample.	PDC was defined as the number of days covered with biologic divided by the fixed time interval of 365 days from date of index biologic therapy initiation (i.e., 12-month post-index). Adherence was defined as PDC≥ 0.8.	Mean PDC (SD not provided) values were 0.57 for ETN users and 0.64 for IFX users ($p < 0.05$); 32.0% of ETN users and 43.0% of IFX users were adherent ($p < 0.05$).	Treatment discontinuation rates at 12 months using a 90-day gap period. Sensitivity analyses were conducted for 30, 60 and 120-day gap periods.	Discontinuation rates were comparable ($p>0.05$) for ETN (40.7%) and IFX (40.9%) users using a 90-day gap period. Sensitivity analyses using 30, 60 and 120-day gaps were robust.
Yazici et al.[27]	ETN, IFX and ADA	Claims data (private commercial) Retrospective US	9,074/ mean age (±SD) was 49.0 years (±11.97) and females (74.1%) comprised the majority of the sample.	N/A	N/A	Treatment persistence was defined as days of continous therapy from the date of first TNF claim. A 30-day gap period was used.	Persistence with IFX was significantly greater than that of ETN or ADA. In a subanalysis of 4,260 patients, median persistence was significantly higher ($p < 0.0001$) for IFX users (464.0 days) compared to ETN (347.5 days) and ADA (365.0 days) users

Study	Study Agents	Datasource/ Analysis/ Country	Sample size/ Brief description of sample	Adherence/ Compliance Measurement	Adherence/ Compliance Results	Persistence Measurement	Persistence Results
Harrison et al.[28]	ETN, IFX and ADA	Claims data (private commercial) Retrospective US	4,628/ mean age (±SD) was 55.2 years (±5.0) for naïve patients and 56.6 years (±4.4) for continuing patients and females (76.6%) comprised the majority of the sample.	N/A	N/A	Duration of therapy in days from index based on 12-months follow-up period. No gap period was specified.	**For naïve users**: The mean duration of therapy was significantly higher ($p < 0.05$) for ETN users (301 days ±91) compared to IFX (281 days ±106) and ADA (280 days ±102) users. **For continuing users**: Mean duration of therapy was comparable ($p>0.05$) among ETN (333 days ±39), IFX (332 days ±42) and ADA (335 days ±41) users.
Grijalva et al.[24]	ETN, IFX, ADA, MTX, LEF, SSZ, HCQ and GC	Claims data (Medicaid) Retrospective US	14,586 (28,906 new episodes of medication use)/ median age was 55.0 years and females (76%) comprised the majority of the sample	MPR was defined as percentage of person-time exposed to the initial regimen during episodes. MPR was calculated for episodes with 180 person-days of available follow-up.	Median MPR values of 0.73, 0.72 and 0.68 were reported for ETN, ADA and IFX initiation, respectively. Compared to MTX (0.59), none of the TNF inhibitors increased hospitalization risk for the PER analyses. However, IFX increased hospitalization risk in the PEI analyses (HR 1.46; 95% CI 1.19-1.80).	N/A	**N/A**

Study	Study Agents	Datasource/ Analysis/ Country	Sample size/ Brief description of sample	Adherence/ Compliance Measurement	Adherence/ Compliance Results	Persistence Measurement	Persistence Results
Curkendall et al.[22]	ETN and ADA	Claims data (private commercial) Retrospective US	2,285/ mean age (±SD) was 54.0 years (±12.00) and females (75.0%) comprised the majority of the sample.	MPR was defined as total days supply of the medication divided by total days of follow-up.	Individual mean drug MPR was not reported. However, an overall mean MPR of 0.52 (±0.31) was reported.	Time to treatment discontinuation from index based on a 12-month follow-up period. A 30-day gap period was used.	No individual drug or overall persistent rate was reported. Persistence was used as a factor in the regression analysis.
Harley et al.[21]	ETN, IFX and MTX	Claims data (Medicare and private commercial) Retrospective US	2,662 (62.7% of sample were MTX users)/ mean age (±SD) was 52.3 years (SD not provided) and females (73.3%) comprised the majority of the sample.	Actual number of therapy administrations or filled prescriptions divided by the expected number.	Adherence (≥80%) of the expected dosages was significantly lower for ETN (OR=0.462; 95% CI=0.290-0.736) compared to IFX.	N/A	N/A
Chart review							
Punzi et al.[1]	ADA, ETN and IFX	Chart review (Rheumatology center) Retrospective Italy	703/ mean age (±SD) was 53.4 years (±13.09) and females (80.8%) comprised the majority of the sample.	N/A	N/A	Treatment discontinuation rates[b] at 36 months	At 36 months, 74.7%, 72.0% and 57.7% of ETN, ADA and IFX users, respectively, were still on therapy. The discontinuation rate of IFX (42.5%) was significantly higher ($p < 0.001$) compared with either ETN (25.3%) or ADA (28.0%).

Study	Study Agents	Datasource/ Analysis/ Country	Sample size/ Brief description of sample	Adherence/ Compliance Measurement	Adherence/ Compliance Results	Persistence Measurement	Persistence Results
Duclos et al.[142]	IFX, ETN and ADA	Chart review (Rheumatology unit) Retrospective France	770[c] / mean age (±SD) for the entire sample was 49.3 years (±15.00) and females (60.4%) were the majority. For the RA population (n=440), mean age (±SD) was 55.1 years (±13.90) and the proportion of females was 80.5%.	N/A	N/A	Treatment continuation rates at 12, 24 and 36 months	Overall, the percentage of patients receiving the same treatment at month 12, 24 and 36 was 64.0%, 50.3% and 39.4%, respectively. Retention rates were comparable (p=0.48) among the 3 TNF inhibitors. Retention rates were 63.2%, 63.9% and 68.2% at 12 months and 47.5%, 50.8% and 60.2% at 24 months for IFX, ETN and ADA, respectively.
Wendling et al.[146]	IFX	Chart review (Rheumatology unit) Retrospective France	41/ mean age (±SD) was 54.0 years (SD not provided) and females (73.2%) comprised the majority of the sample.	N/A	N/A	Treatment continuation rates[b] at 6, 12, 24 and 36 months	The proportions of patients still on IFX were 82%, 74%, 67% and 20% after 6, 12, 24 and 36 months, respectively.[d]
Levalampi et al.[152]	ETN and ADA	Chart review (Rheumatology center) Retrospective Finland	96[e] / mean age (±SD) was 48.0 years (SD not provided but range was 17-75 years) and females (64.6%) comprised the majority of the sample.	N/A	N/A	Treatment continuation rates at 12 months	The continuation rate was 74% with ETN users and 60% with ADA users at 12 months of follow-up.[d]

Study	Study Agents	Datasource/ Analysis/ Country	Sample size/ Brief description of sample	Adherence/ Compliance Measurement	Adherence/ Compliance Results	Persistence Measurement	Persistence Results
Brocq et al.[154]	ETN, ADA and IFX	Chart review (Teaching hospital) Retrospective France	304/ mean age (±SD) was 58.0 years (SD not provided) and females (81.3%) comprised the majority of the sample	N/A	N/A	Treatment continuation rates[b] at 12 and 24 months	Continuation rates were high with ETN (87% after 12 months and 68% after 24 months) and ADA (83% and 66%) but significantly lower with IFX (68% and 46%; p=0.0001 vs. ETN and p < 0.01 vs. ADA).
Agarwal et al.[155]	IFX	Chart review (Rheumatology center) Retrospective US	183/ mean age (±SD) was 59.3 years (±14.4) and females (87.0%) comprised the majority of the sample.	N/A	N/A	Treatment discontinuation rates	Discontinuation rate for IFX was 48% after 12 months and 67% after the entire study period.[d]
Clinical follow-up (Prospective)							
Figueiredo et al.[143]	IFX	Clinical follow-up Prospective France	152/ mean age (±SD) was 53.3 years (SD not provided but range was 24-82 years) and females (79.0%) comprised the majority of the sample.	N/A	N/A	Treatment continuation rates[b]	The continuation rate (survival) was 78% at 12 months of follow-up.
Voulgari et al.[145]	IFX	Clinical follow-up Prospective Greece	84/ mean age (±SD) was 59.0 years (±8.00) and females (72.6%) comprised the majority of the sample.	N/A	N/A	Treatment discontinuation rates[b] at 12, 24 and 36 months	Discontinuation rates were 15.5%, 27.0% and 41.0% at 12, 24 and 36 months, respectively.[d]

Study	Study Agents	Datasource/ Analysis/ Country	Sample size/ Brief description of sample	Adherence/ Compliance Measurement	Adherence/ Compliance Results	Persistence Measurement	Persistence Results
Kristensen et al.[148]	ETN and IFX monotherapy or in combination with either MTX or other DMARDs.	Clinical follow-up Prospective Sweden	1,161/ mean age (±SD) was 56.4 years (SD not provided) and females (77.3%) comprised the majority of the sample.	N/A	N/A	Level of drug adherence defined as proportion of patients remaining on therapy during observation period. [b]	**For Monotherapy users**: The level of adherence to therapy at 4 years (1 year) was 18% (47%) for IFX and 53% (74%) for ETN. **For combinations with MTX**: The level of adherence to therapy at 5-year (4-year; 1-year) was 36% (38%; 69%) for IFX and 65% (75%; 89%) for ETN. *The values for the 4-year and 1-year periods were significantly ($p < 0.001$) higher when compared to monotherapy users for both IFX and ETN.* **For combinations with other DMARDs**: The level of adherence to therapy at 4 years (1 year) was 27% (58%) for IFX and 71% (85%) for ETN. *The values for the 4-year and 1-year periods were significantly lower ($p=0.002$) when compared to combination with MTX for IFX users but higher ($p=0.015$) when compared to monotherapy for ETN users.*

Study	Study Agents	Datasource/ Analysis/ Country	Sample size/ Brief description of sample	Adherence/ Compliance Measurement	Adherence/ Compliance Results	Persistence Measurement	Persistence Results
Buch et al.[150]	IFX	Clincal follow-up Prospective UK	309/ mean age (±SD) was 57.0 years (±15.82) and females (73.0%) comprised the majority of the sample.	N/A	N/A	Treatment discontinuation rate	Discontinuation rate was over 55% at 12 months among primary responders to IFX (n=117).
Vander Cruyssen et al.[151]	IFX	Clinical follow-up Prospective Belgium	511/ no information on patients' characteristics was provided.	N/A	N/A	Treatment continuation rates[b] at 48 months	Among the initial 511 patients included in the study, 479 could be evaluated; of these, 295 (61.6%) were still receiving IFX treatment at year 4 of follow-up.
Lass et al.[34]	ETN	Clinical follow-up Prospective Finland	49/ mean age (±SD) was 52.3 years (SD not provided) and females (87.8%) comprised the majority of the sample.	N/A	N/A	Treatment discontinuation rates[b]	Of the 49 patients that were switched from IFX to ETN, 20 (40.8%) discontinued therapy. The mean duration of follow-up was 16 months (±3) and the mean time to discontinuation was 4 months (±2).

Study	Study Agents	Datasource/ Analysis/ Country	Sample size/ Brief description of sample	Adherence/ Compliance Measurement	Adherence/ Compliance Results	Persistence Measurement	Persistence Results
Du Pan et al.[156]	ADA, ETN and IFX	Clinical follow-up Prospective Switzerland	2,364/ mean age (±SD) was 54.0 years (SD not provided) and females (77.9%) comprised the majority of the sample.	N/A	N/A	Drug survival rates[b] at 12 and 24 months	A statistically significant difference (adjusted p < 0.001) was noted in the discontinuation rates between the 3 anti-TNF agents. After 1 (2) years, 78% (58%); 82% (65%) and 84% (66%) were still receiving IFX, ETN and ADA, respectively. There was a trend in favor of a lower risk of discontinuation of anti-TNF agents in combination with MTX (HR=0.85, 95% CI= 0.70-1.02).
Ostergaard et al.[157]	IFX and ETN	Clinical follow-up Prospective Denmark	417/ mean age (±SD) was 53.5 years (SD not provided) and females (74.3%) comprised the majority of the sample.	N/A	N/A	Median drug survival time[b]	Median drug survival time for IFX and ETN was 127 and 197 weeks, respectively. Survival at 1 year for IFX and ETN was 71% and 73%, respectively (p=0.04).
Agarwal et al.[158]	IFX, ADA and ETN	Clinical follow-up Prospective US	503/ mean age (±SD) was 55.4 years (±13.5) and females (85.0%) comprised the majority of the sample.	N/A	N/A	Treatment discontinuation rates	Overall, 42% of the patients discontinued treatment with TNF inhibitors, with a mean length of follow-up of roughly 39 months. Discontinuation rates to individual TNF inhibitor were not reported.

Study	Study Agents	Datasource/ Analysis/ Country	Sample size/ Brief description of sample	Adherence/ Compliance Measurement	Adherence/ Compliance Results	Persistence Measurement	Persistence Results
Clinical follow-up (Retrospective)							
Gomez-Reino et al.[41]	IFX, ETN and ADA	Clinical follow-up Retrospective Spain	488/ paient characteristics were not provided for this sample	N/A	N/A	Treatment discontinuation rates[b]	Survival of the second TNF antagonist decreased to 0.68 and 0.60 at 12 and 24 months, respectively. Survival was greater in patients treated with IFX (HR=3.22; 95% CI=2.13-4.87).
Zink et al.[141]	ETN, IFX and ANA as monotherapy or in combination with either MTX or other DMARDs. There was also a control group comprising of patients on mono and combination DMARDs therapy	Clinical follow-up Retrospective Germany	1,523(39.3% of sample was in the control group) / mean age (±SD) was 53.8 years (SD not provided) for patients on biologics and 56.5 years (±11.4) for the control group. Females (78.3%) comprised the majority of the sample.	N/A	N/A	Treatment continuation rates[b] after 12 months	Treatment continuation rates between ETN (69%; 95% CI=62%-75%) and IFX (65%; 95% CI=58%-73%) were found to be comparable (p>0.05) in the first 12 months of observation.

Study	Study Agents	Datasource/ Analysis/ Country	Sample size/ Brief description of sample	Adherence/ Compliance Measurement	Adherence/ Compliance Results	Persistence Measurement	Persistence Results
Geborek et al.[159]	ETN, IFX and LEF	Clinical follow-up Retrospective Sweden	369 (33 of these patients were on 2 TNF-inhibitors and 1 was on 3 drugs) / mean age (±SD) was 56.9 years (SD not provided) and females (79.4%) comprised the majority of the sample.	N/A	N/A	Drug survival rates[b] (or continuation rates)	There were no significant differences (p>0.05) in treatment continuation rates between ETN (79%) and ADA patients (75%) after 20 months.
Favalli et al.[160]	IFX	Clinical follow-up Retrospective Italy	95/ mean age (±SD) was 57.3 years (±7.8) and females (86.3%) comprised the majority of the sample.	N/A	N/A	Treatment discontinuation rates	Overall discontinuation rate at 12 months was 17%.
Levalampi et al.[161]	IFX	Clinical follow-up Retrospective Finland	104[e] / mean age (±SD) was 45.0 years (SD not provided but range was 18-75 years) and females (62.0%) comprised the majority of the sample.	N/A	N/A	Treatment continuation rates	Overall continuation rate at 6 months was 71%.
Registry							
Chevillotte-Maillard et al.[140]	IFX	Registry Retrospective France	83 (72.3% of sample had RA) / mean age (±SD) was 53.9 years (±13.00) and females (66.3%) comprised the majority of the sample.	N/A	N/A	Withdrawal rate[b] based on a 12-month follow-up period	Withdrawal rate was 36.1%.

Study	Study Agents	Datasource/ Analysis/ Country	Sample size/ Brief description of sample	Adherence/ Compliance Measurement	Adherence/ Compliance Results	Persistence Measurement	Persistence Results
Flendrie et al.[144]	ETN, IFX and ADA	Registry Retrospective Netherlands	230/ mean age (±SD) was 55.5 years (±12.40) and females (67.0%) comprised the majority of the sample.	N/A	N/A	Drug survival rates[b]	Median survival time was 37 months and maximum follow-up time for ADA, IFX and ETN was 69, 35 and 30 months, respectively. One year survival rate was comparable (p>0.05) among ADA (73%), IFX (66%) and ETN (74%) users.
Strangfeld et al.[149]	ETN, ADA and IFX in combination with either MTX or LEF	Registry Retrospective Germany	1,769/ mean age (±SD) was 53.5 years (SD not provided) and females (75.5%) comprised the majority of the sample.	N/A	N/A	Treatment discontinuation rate[b] at 36 months	After 36 months, the discontinuation rates between combinations of ETN with MTX (46.3%) and ETN with LEF (53.4%) were comparable (p>0.05). Similar results were obtained between combinations of ADA with MTX (51.3%) and ADA with LEF (63.1%); as well as between combinations of IFX with MTX (61.5%) and IFX with LEF (67.1%).
Feltelius et al.[153]	ETN	Registry Prospective Sweden	1,073 (76.4% of the sample was recruited in the first year) / mean age (±SD) was 52.0 years (SD not provded) and females (76.6%) comprised the majority of the sample.	N/A	N/A	Treatment discontinuation rate at 24 months	After two years, 21% (n = 172) of the patients recruited in the first year had discontinued the treatment.

Study	Study Agents	Datasource/ Analysis/ Country	Sample size/ Brief description of sample	Adherence/ Compliance Measurement	Adherence/ Compliance Results	Persistence Measurement	Persistence Results
Hetland et al.[162]	ADA, ETN and IFX	Registry Retrospective Denmark	2,326/ median age (range) was 57.0 years (15-89) and females (73.7%) comprised the majority of the sample.	N/A	N/A	Adherence rate was defined in terms of drug survival rates[b]	The drug survival rate (or continuation rates) was highest for ETN and lowest for IFX. At 48 months, the unadjusted drug adherence rates were as follows: For ADA, 52% (95% CI=46-57%); for ETN, 56% (95% CI=51-62%); and for IFX, 41% (95% CI=37-44%) ($p < 0.0001$)
Marchesoni et al.[163]	ADA, ETN and IFX	Registry Retrospective Italy	1,064 / mean age (±SD) was 55.8 years (±12.96) and females (83.2%) comprised the majority of the sample.	N/A	N/A	Drug survival rates[b]	After 36 months, the likelihood of survival (or continuation rates) on ETN (62.5%) was significantly ($p=0.027$) higher than the likelihood of survival (or continuation) on IFX (49.1%) or ADA (53.6%).

Study	Study Agents	Datasource/ Analysis/ Country	Sample size/ Brief description of sample	Adherence/ Compliance Measurement	Adherence/ Compliance Results	Persistence Measurement	Persistence Results
Finckh et al.[164]	IFX, ADA and ETN	Registry Retrospective Switzerland	1,198/ mean age (±SD) was 53.5 years (SD not provided) and females (74.3%) comprised the majority of the sample.	N/A	N/A	Treatment discontinuation rates[b]	The discontinuation rates were not significantly different between the treatments (p=0.67) The HR of discontinuing treatment was 1.11 (99% CI= 0.89 to 1.40) for IFX compared with ETN and ADA; 0.97 (99% CI= 0.71 to 1.15) for ADA compared with IFX and ETN; and 0.91 (99% CI= 0.71 to 1.15) for ETN compared with IFX and ADA. Actual discontinuation percentages were not provided.
Genta et al.[165]	IFX, ADA and ETN	Registry Retrospective Switzerland	66/ mean age (±SD) was 60.5 years (±13.00) and females (65.0%) comprised the majority of the sample.	N/A	N/A	Treatment discontinuation rates	Overall discontinuation rate at 6 months was 24%. Discontinuation rates to individual TNF inhibitor were not reported.

Study	Study Agents	Datasource/ Analysis/ Country	Sample size/ Brief description of sample	Adherence/ Compliance Measurement	Adherence/ Compliance Results	Persistence Measurement	Persistence Results
Others							
Ducoulombier et al.[147]	IFX	Open label trial Prospective France	50/ mean age (±SD) was 49.1 years (±11.1) and females (78.0%) comprised the majority of the sample.	N/A	N/A	Treatment continuation rates at 24 months	The 2-year continuation rate for IFX was 70%.

ADA = Adalimumab; **ETN** = Etanercept; **GC** = Glucocorticoid; **HCQ** = Hydroxychloroquine; **HR** = Hazard Ratio; **IFX** = Infliximab; **LEF** = Leflunomide; **MPR** = Medication possession ratio; **MTX** = Methotrexate; **PEI** = Persistent exposure ignored; **PER** = Persistent exposure required; **PDC** = Proportion of days covered; **RA** = Rheumatoid arthritis; **SD** = Standard deviation; **SSZ** = Sulfazalazine; **TNF** = Tumor necrosis factor; [a] US and European RA studies only; [b]Obtained by conducting survival analysis; [c]Inflammatory arthritis including rheumatoid arthritis; [d]No statistical comparison was conducted; [e]Includes patients with rheumatoid arthritis and spondylarthropathies.

Summary pattern was adapted from: Koncz T, Pentek M, Brodszky V, Ersek K, Orlewska E, Gulacsi L. Adherence to biologic DMARD therapies in rheumatoid arthritis. *Expert Opinion on Biological Therapy*. 2010; 10(9):1367-1378.

2.1.11 Medication Switching among TNF Inhibitors in RA Management

Due to the complexity of the disease process as well as differences in patient characteristics, responses to TNF inhibitors tend to vary across patients. Some patients may: completely fail to respond to therapy (primary lack of efficacy), exhibit a suboptimal response (partial response), have difficulty maintaining an initially good response over the course of treatment (secondary loss of efficacy or acquired drug resistance), or experience intolerable adverse events.[166,167] These unfavorable outcomes may necessitate the need to discontinue current therapy and switch to another. However, a major challenge lies in the limited range of options clinicians may have to choose from since in many instances the initiation of TNF inhibitor therapy will have occurred following treatment failure with multiple traditional DMARDs.[35] While the newer biological agents (e.g., abatacept, rituximab, tocilizumab and golimumab) have been shown through RCTs to be efficacious compared to placebo in RA patients who failed to respond to prior TNF inhibitor therapy, [114,117,118,168,169] there has been no direct (head-to-head) comparison among these agents to help clinicians decide on the most appropriate option regarding both efficacy and safety.[127] An indirect pair-wise comparison (meta-analysis) conducted by Schoels et al. suggested similar ACR20 response rates at 24 weeks for abatacept, rituximab and tocilizumab but lower rates for golimumab.[170] ACR50 and ACR70 response rates were reported to be similar across the four agents, suggesting that they have comparable efficacy in RA patients who failed to respond to prior TNF inhibitor therapy.[170]

Due to the differences in the pharmacokinetic profiles and specific characteristics (e.g., molecular structures, sites of action, dosing regimens, drug neutralizing autoantibody induction, type and frequency of adverse events) of TNF inhibitors, medication switching across TNF inhibitors has been recommended. However, evidence supporting switching effectiveness between TNF inhibitors is limited to results obtained from small case series and open-label studies (non-controlled studies).[34-40,42-49,171,172] Results from these studies consistently showed that treatment response following a switch between TNF inhibitors was comparable with, or better than the response observed with the initial TNF inhibitor agent. In addition, treatment responses were found to be comparable with the response observed among patients naïve to TNF inhibitor therapy.[85] Results from systematic reviews/meta-analyses also supported the effectiveness of switching between TNF inhibitors (i.e., adalimumab, infliximab and etanercept) irrespective of the reason for switching (either due to inefficacy or adverse events) and order of switching.[50,51] However, treatment response was reported to be slightly better if switching was as a result of adverse events rather than inefficacy.[50,51]

According to the systematic review/meta-analysis (n= 32 studies) by Remy et al., the pooled proportions of responders following a switch to a second TNF inhibitor were 55.1 percent (95% CI= 48.2-62) and 74.9 percent (95% CI=72.3-77.5), respectively, based on ACR20 and EULAR response criteria. Response rates with ACR50 and ACR70 were 31.5 percent (95% CI=29-34.1) and 13.8 percent (95%

CI=10.1-18.1), respectively. When the efficacy of a switch was analyzed (n=19 studies) based on the reason to switch, the pooled proportions of responders based on ACR20 and EULAR response criteria were 62.4 percent (95% CI=57.0-67.7) and 69.4 percent (95% CI=46.7-88.0), respectively for patients who switched due to adverse events and 52.6 percent (95% CI=43.9-61.1) and 66.3 percent (95% CI=55.8-76.1), respectively for those who switched due to lack of efficacy. Overall survival rate (persistence) on a second TNF inhibitor was reported to be 80.4 percent (95% CI=65.8-91.7) at 3 months, 84.6 percent[b] (95% CI=76.2-91.5) at 6 months and 61.8 percent[c] (95% CI=50.8-72.3) at 12 months. Survival rates at 3 months were slightly higher if the switch was due to inefficacy rather than due to adverse events, but were comparable at 12 months. In addition, analyses involving switches between specific TNF inhibitors showed a higher proportion of responders among those who switched from infliximab to adalimumab (ACR20=63.9% (95% CI=60.2-67.4) and EULAR=74.0% (95% CI=62.1-84.3)) compared to those who switched from infliximab to etanercept (ACR20=45.6% (95% CI=40.3-51.1) and EULAR=59.3% (95% CI=52.7-65.7)). However, at ACR50 and 70, the proportions of responders were similar regardless of whether the switch was to etanercept or adalimumab. For patients who switched from etanercept to either infliximab or adalimumab, the

[b] Of those that persisted at 3 months

[c] Of those that persisted at 6 months

pooled proportions of responders based on ACR20 and EULAR criteria were 58.6% (95% CI=52.2-64.9) and 76.7% (95% CI=34.1-99.6), respectively.[50]

2.1.12 Dose Escalation and Impact on Cost of TNF Inhibitor Therapy in RA Management

An approach to addressing inadequate treatment response (partial or secondary loss of efficacy) to TNF inhibitors may require escalating the administered dose. This may be achieved by either increasing the infused dose or reducing the dosing interval (increasing frequency of dosing) or both. The rationale for dose escalation has been partly explained based on the premise that inadequate treatment responses (partial or secondary loss of efficacy) occur due to the development of autoantibodies to TNF inhibitors, which, over the course of treatment, reduces their efficacy. However, the literature lacks sufficient evidence to support this claim. A higher likelihood of development of autoantibodies to infliximab and adalimumab compared to etanercept have also been reported.[173]

A major implication of dose escalation in the management of RA actually lies in its impact on the cost of the TNF inhibitor therapy (which impacts the overall cost of care of the RA patient) and patient safety.[174] While dose escalation is recommended[18,19,175] and occurs more often with the use of infliximab and adalimumab in improving treatment response, [26,28-30,176,177] it is not recommended for patients on etanercept as it has not been associated with any significant improvement in treatment response rates.[20,178] Studies on dose escalation and cost of TNF inhibitor

therapy showed that etanercept use was associated with significantly lower rates of dose escalation and lower TNF inhibitor therapy cost compared with the use of adalimumab and infliximab.[26,28-33,177] Furthermore, Gu et al. reported that the difference in total cost of care between patients who had higher starting doses (or escalated doses) and those who did not was significantly ($p < 0.001$) higher for adalimumab users compared to etanercept users ($4,154 vs. $683) (SD not provided).[31] Similarly, Moot et al. found a significant ($p < 0.001$) difference in total cost of care between dose escalators and non-escalators treated with either adalimumab (€5,872 (95% CI=3,862 - 7,882) ≈ $9,248 (95% CI= 6,079 - 12,414)) or infliximab (€2,126 (95% CI= 411-3,840) ≈ $3,348 (95% CI= 647 – 6,047)) but not for etanercept (€2,266 (95% CI= -878 – 5410) ≈ $3,568 (95% CI= -1,382 – 8,518)).[177]

2.1.13 Summary of Literature Review

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation of the joints.[1] RA remains a leading cause of disability and affects about 1 percent of the adult United States (US) population with a higher prevalence, incidence and lifetime risk in women compared to men.[2,3] Current treatment goals involve slowing or stopping the progression (i.e., remission) of the disease. Among the available treatment options, the TNF inhibitors have generally been recognized to have revolutionized the management of RA as they have been shown through RCTs to significantly improve patients' symptoms as well as retard the progression of the disease.[5-9] Among the available TNF inhibitors, three agents (Enbrel® [etanercept],

Remicade® [infliximab] and Humira® [adalimumab]) have been extensively studied and used in clinical practice with remarkable results. While clinical trials that directly compare these agents are lacking, results from the majority of the indirect treatment comparison studies suggested they have comparable efficacy and safety profiles.[12-14] However, they differ in their method of administration and flexibility of dosing and these differences may possibly result in differences in their medication use profiles (e.g., medication adherence, persistence, discontinuation, and dose escalation) and cost of care of RA patients on these medications.[18-20] Studies have been conducted in the US to evaluate the medication use patterns of RA patients on these TNF inhibitors (etanercept, infliximab and adalimumab).[2,4,21-31] However, only 3 of these US studies[23-25] utilized data from patients enrolled under Medicaid programs, many of whom are not the typical patients enrolled in RCTs. These patients are of poor socioeconomic status and usually present with comorbid disease conditions. Furthermore, none of the 3 studies examined dose escalation and the associated healthcare utilization costs.

2.1.14 Study Objectives and Hypotheses

The present study aims to evaluate medication use patterns (medication adherence, persistence, discontinuation, switching and dose escalation) of RA patients on etanercept, infliximab or adalimumab and the associated healthcare utilization costs using Texas Medicaid data. Etanercept, infliximab and adalimumab

were the only biologics chosen for this study because they have been widely used and extensively studied.

The covariates considered in the study include demographic factors (age, gender, race/ethnicity), pre-index use of other RA-related medications (e.g., NSAIDs, cyclooxygenase-2-inhibitors, narcotic analgesics, tramadol, glucocorticoids and traditional DMARDs), total number of non-study RA-related medications used at index, Charlson Comorbidity Index score, pre-index RA and non-RA related visits, pre-index healthcare utilization cost and specialty of prescribing physician.

2.1.14.1 Specific Research Objectives and Hypotheses

1) To describe and compare baseline socio-demographics and clinical characteristics of Texas Medicaid RA patients on etanercept (ETN), adalimumab (ADA) or infliximab (IFX).

2) To describe medication dosing patterns among ETN, ADA and IFX users.

3) To determine if the likelihood of having a dose escalation among ETN users differs significantly compared to ADA and IFX users while controlling for covariates.

> *H_1: The **likelihood of having a dose escalation** is significantly lower among RA patients on ETN compared to patients on ADA and IFX while controlling for covariates.*

4) To determine if medication use patterns (adherence, persistence, discontinuation, and switching) among ETN users differ significantly compared to ADA and IFX users while controlling for covariates.

*H_{o2A}: There is no significant difference in **medication adherence** to ETN compared to ADA and IFX while controlling for covariates.*

*H_{o2B}: The **likelihood of being adherent*** (MPR≥0.80 or 80%) *to ETN does not differ significantly compared to ADA and IFX while controlling for covariates.*

*H_{o3}: There is no significant difference in **medication persistence** to ETN compared to ADA and IFX while controlling for covariates.*

*H_{o4}: The **likelihood of discontinuing** ETN does not differ significantly compared to ADA and IFX while controlling for covariates.*

*H_{o5}: There is no significant difference in **duration of medication use** (i.e., persistence) **prior to discontinuation** of ETN compared to ADA and IFX while controlling for covariates.*

*H_{o6}: There is no significant difference in the **likelihood of switching** from index TNF inhibitor therapy to another biologic agent among ETN users compared to ADA and IFX users while controlling for covariates.*

*H_{o7}: There is no significant difference in **duration of medication use** (i.e., persistence) **prior to switching** from index TNF inhibitor therapy among ETN users compared to ADA and IFX users while controlling for covariates.*

5) To determine if total healthcare utilization cost (medical and medication costs) for ETN users differs significantly compared to ADA and IFX users while controlling for covariates.

*H_8: **Total healthcare utilization cost** is significantly lower for ETN patients compared to patients on ADA and IFX while controlling for covariates.*

6) To determine if RA-related healthcare utilization cost (medical and medication costs) for ETN users differs significantly compared to ADA and IFX users while controlling for covariates.

*H_9: **RA-related healthcare utilization cost** is significantly lower for ETN patients compared to patients on ADA and IFX while controlling for covariates.*

*H_{11}: **TNF inhibitor therapy cost** is significantly lower for ETN patients compared to patients on ADA and IFX while controlling for covariates.*

7) To determine if RA-related healthcare utilization cost is associated with adherence/persistence to TNF inhibitors (ETN, ADA or IFX) while controlling for covariates.

*H_{15}: **RA-related healthcare utilization cost** is significantly and positively related to **TNF medication adherence** while controlling for covariates.*

*H_{16}: **RA-related healthcare utilization cost** is significantly and positively related to **TNF medication persistence** while controlling for covariates.*

CHAPTER 3: METHODOLOGY

3.1 CHAPTER OVERVIEW

This chapter provides a detailed description of the study methodology. Information provided covers the following: study design; data source; study population; data extraction and study timeframe; the inclusion and exclusion criteria for developing the study cohort; and the study variables. Also presented are the operational definitions of the study variables, statistical analytical methods that were employed to address the study objectives as well as the sample size calculations.

3.1.1 Institutional Review Board Approval

Approval for the present study was obtained from the Institutional Review Boards (IRB) of The University of Texas at Austin (IRB protocol number: 2012-02-0110) and Texas Health and Human Services Commission prior to its commencement. A waiver of informed consent was obtained because this is a retrospective database study containing de-identified data which presents no more than a minimal risk to the welfare and privacy of subjects.

3.1.2 Study Design and Data Source

This was a retrospective study involving the use of a secondary database. Demographic, medical and prescription claims records of Texas Medicaid RA patients between the ages of 18 and 63 years on TNF inhibitors (etanercept, adalimumab and infliximab) within the timeframe ranging from July 2003 to August 2011 was

obtained from the Texas Medicaid prescription and medical claims data files. The next paragraph provides a brief description of the Medicaid program.

The Medicaid program is a healthcare program jointly sponsored by the state and federal governments.[179] The program was established through Title XIX of the Social Security Act on July 30, 1965 and provides health insurance coverage especially for low-income families, individuals with chronic disabilities, blind persons, low-income pregnant women, elderly people or seniors, non-disabled children and caretakers of dependent children.[179] The Medicaid program is administered by the states, with federal oversight through the Centers for Medicare and Medicaid Services (CMS). Participating states are mandated by the CMS to provide a set of basic healthcare services to enrollees and since it is an entitlement program, there is no restriction to the number of people who can be enrolled provided they meet the eligibility criteria for the program.[179] Based on the most recent available data (i.e., 2009-2010 data), the Texas Medicaid program provided health insurance coverage for approximately 3.7 million (≈14.8%) non-elderly residents (i.e., 64 years of age and below).[180] Among these non-elderly beneficiaries of the Texas Medicaid program, children (i.e., ≤ 18 years of age) constitute the majority (74.5%).[180] Examples of services provided by the Texas Medicaid program include: physician services, inpatient and outpatient hospital services, long-term care, lab and X-ray services and pharmacy services.

3.1.2.1 Inclusion/Exclusion Criteria

Texas Medicaid recipients who met the following eligibility criteria were included in the study: (a) subjects between the ages of 18 and 63 years at the index date; (b) continuously enrolled for at least 6 months before and 12 months after the index date; (c) have a diagnosis for RA in the 6-month pre-index period (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 714.0x); (d) have no claim for a biologic agent (e.g., abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab) indicated for RA within the 6-month pre-index period; and (e) have at least one claim for any of the study TNF inhibitors (etanercept, adalimumab or infliximab) indicated for the treatment of RA within the 12-month post-index period.

Subjects with a diagnosis for psoriasis (ICD-9-CM 696.1x), psoriatic arthritis (ICD-9-CM 696.0x), ankylosing spondylitis (ICD-9-CM 720.0x), ulcerative colitis (ICD-9-CM 556.0, 556.1, 556.2, 556.3, 556.5, 556.6, 556.8 or 556.9), Crohn's diseases (ICD-9-CM 555.0x, 555.1x, 555.2x, 555.9x, 565.1x, or 569.81), juvenile idiopathic arthritis (ICD-9-CM 714.3x), non-Hodgkin's lymphoma (ICD-9-CM 200.xx or 202.xx) or chronic lymphocytic leukemia (ICD-9-CM 204.1x) were excluded as the TNF inhibitors are also used to treat these indications. The age range was restricted to 63 years to avoid including patients with dual eligibility status (i.e., Medicaid and Medicare).

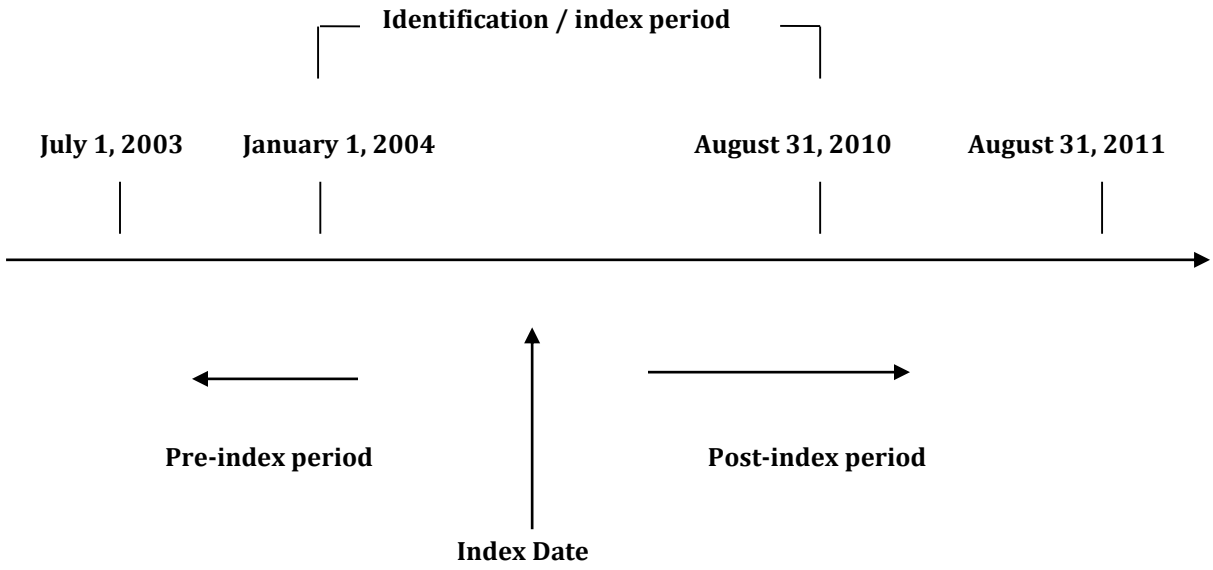
3.1.2.2 Index Date

The index date was defined as the date within the identification period (Figure 3.1) when the patient had the first fill for any of the study TNF inhibitors (etanercept, adalimumab or infliximab) without any fills during the prior 6 months. The index date was unique for each subject and falls within January 1, 2004 and August 31, 2010.

3.1.2.3 Data Collection/ Study Timeframe

Information extracted from the Texas Medicaid medical and prescription claims files include: de-identified unique patient identification numbers, gender, race/ethnicity, date of enrollment, date of end of enrollment, ICD-9-CM codes (diagnostic codes), the National Drug Code (NDC), the Generic Sequencing Number (GCN), the American Hospital Formulary Service (AHFS) number, the date a prescription was dispensed, the quantity of drug supplied, the number of days for which the drug was supplied and the amount paid for drug supplied. Data was extracted within the time frame of July 1, 2003 to August 31, 2011. Subjects were identified during the index period from January 1, 2004 to August 31, 2010 (Figure 3.1). Prescription claims data for each subject was analyzed over an 18-month study period (i.e., the 6-month pre-index and 12-month post-index periods).

Figure 3.1 Data Extraction and Subject Identification Period



3.1.3 Study Variables

3.1.3.1 Dependent Variables

The dependent variable categories for the study include: (1) dose escalation; (2) medication use patterns (i.e., adherence, persistence, discontinuation, and switching); (3) medication dosing patterns; (4) total healthcare utilization costs (medical and medication costs) (5) RA-related healthcare utilization costs (medical and medication costs) and (6) TNF inhibitor therapy costs. These categories are further described below.

Dose Escalation

Dose escalation can be assessed using a variety of methods. These include: (1) last prescription dose versus index prescription dose;[28,30,174 181-183] (2) average actual dose versus recommended dose;[30,184] (3) multiple (>2) instances of a subsequent dose exceeding the index dose;[30,185] (4) when average of all subsequent doses exceed a predetermined percentage (e.g., 115%, 130% or 150%) of the index dose;[30,186] and (5) the time-trend method.[28,30,31] The advantages as well as the disadvantages of each method are discussed in the subsequent paragraphs.

The *first method* (i.e., last prescription dose versus index prescription dose) compares the weekly dose of the last prescription with that of the index prescription. While this has the advantage of ease of computation, it fails to utilize the entire data in its analysis of dose escalation and as such the result may not be representative of the "actual medication use pattern" across the course of treatment.[30] The *second method* (i.e., average actual dose versus recommended dose) measures the average weekly dose (i.e., (total dispensed quantities in the study period in mg/ total days supply) x 7) and compares with the manufacturer recommended weekly dose.[30] While this method has the advantage of ease of computation, it overestimates dose escalation especially in patients who started therapy on a high dose. In addition, it does not necessarily measure dose escalation, but rather dose deviation from manufacturer's recommended dose. It also fails to incorporate the time component necessary to understand changes that occur in the course of therapy.[30]

The *third method* estimates dose escalation by identifying 2 or more instances when the patient's weekly dose of subsequent prescriptions exceeds that of the index prescription. This has the advantage of using all the available data as well as capturing dose changes over the course of treatment. The drawbacks of this method of estimating dose escalation include: failure in distinguishing between changes over time and true dose escalation; the complexity of the analysis and the subjectivity involved in deciding the number of incidences.[30] The *fourth method* of estimating dose escalation calculates the ratio between the average weekly dose of all subsequent prescriptions and the weekly dose of the index prescription to determine if it exceeds a predetermined percentage (e.g., 115%, 130% or 150%). While this approach has the advantage of using all the available data as well as capturing dose changes over the course of treatment based on a predetermined threshold, it presents challenges similar to those discussed under the third method.[30] The last and *fifth method* (i.e., time-trend approach) computes patient's weekly dose and compares each week's dose with the subsequent week's dose or a recommended or index dose. It allows the use of the entire available data as well as provides information on dose escalation over a specified period of time. Its drawback lies in the complexity of the analytical process. This approach is highly recommended since it provides a more transparent and comprehensive picture of medication use pattern in clinical practice.[30]

For the present study, the *fourth* method was used to assess dose escalation. Based on the fourth method, patients were classified as having a dose escalation if the

average weekly dose for all their subsequent prescriptions exceeds the weekly dose of their index prescription by 150 percent. The cut-off value of 150 percent was chosen as it is the most conservative of all the recommended values (e.g., 115%, 130% or 150%). [30]

Medication Adherence

Two commonly employed approaches in estimating medication adherence with the use of quantitative data are the medication possession ratio and proportion of days covered. Medication possession ratio (MPR) can be defined as the sum of total days' supply for all fills divided by the number of days in the study period (Figure 3.2). The proportion of days covered (PDC) can be defined as the proportion of days a patient has a drug available in the specified interval or study period. The PDC method involves evaluating each day in the specified interval or study period to determine if a patient has the dispensed study drug(s) based on the initial prescription fill date(s) and the days' supply, and then assigns a value of 1 or 0 indicating the presence or absence of the study drug(s) for each study day. The PDC is calculated by counting each day within the study period for which the study drug(s) was available and then divide the sum by the number of days in the study period (Figure 3.3).[187]

Studies have shown that MPR and PDC result in similar adherence values for cases of simple drug use (i.e., use of one drug); however, MPR may overestimate adherence in cases of drug switches, therapeutic duplication, or multiple drug use within the same therapeutic class. [187,188] Since the former (simple drug use) is the case

for the present study, MPR was utilized in estimating medication adherence across the study TNF inhibitors. Based on the obtained MPR values, mean adherence (mean MPR) and proportion of adherent and non-adherent patients (using a 0.80 cut-off point with MPR ≥ 0.80 referred to as adherent) was determined for each TNF inhibitor. Sensitivity analyses were conducted using 0.70 and 0.90 percent cut-off values.

Figure 3.2 Formula for Calculating Medication Possession Ratio (MPR)

MPR = Sum of total days supply for all fills [a] x 100 / Number of days in study period [b,c]

[a] For dual or triple therapy the numerator is divided by 2 or 3, respectively
[b] It is typically a clinically meaningful number of days and should be the same for all intervals and patients
[c] The denominator may be substituted with [(last dispense date – first dispense date) + last days supply]

Figure 3.3 Formula for Calculating Proportion of Days Covered (PDC)

†PDC = Number of days when drug(s) was available / Number of days in the study period
†PDC value is always between 0 and 1

Medication Persistence, Discontinuation and Switching

Medication persistence can be defined as the number of days of continuous therapy during the follow-up period (i.e., post-index period).[137] Pre-specified gap periods were allowed between prescriptions to account for early or delayed refills of prescriptions. Since there is no standard gap period, a 60-day gap period was used but sensitivity analyses were conducted using 30-, 45-, 90- and 120-day gap periods. These gap periods have been used in previous studies involving TNF inhibitors medication use.[2,22,23,25-27] Using a 60-day gap period, a patient was considered to be persistent for the period of time (in days) when there was no more than a 60-day gap between two consecutive prescriptions. Other parameters of interest include rates at which patients discontinue or switch from index TNF inhibitor therapy.

Medication discontinuation of index TNF inhibitor therapy was assumed to have occurred if there was greater than a 60-day gap period following a prescription or presence of a switch from the index TNF inhibitor therapy. Sensitivity analyses were conducted using 30-, 45-, 90- and 120-day gap periods. *Medication switching* was assumed to have occurred if a patient had a RA biologic agent that was different from the index TNF inhibitor therapy. Since these agents can not be used concomitantly, patients were assumed to be on one TNF inhibitor therapy at a specific point in time. Table 3.1 illustrates the use of the parameters discussed under this section.

Table 3.1 An Example Illustrating the Calculation of Medication Persistence, Discontinuation and Switching

Patient	Months (30 days/month)											
	1	2	3	4	5	6	7	8	9	10	11	12
A	D1	D1				D1	D1	D1	D1	D1	D1	
B	D1	D1	D1	D1	D1	D1			D2	D2	D2	
C	D2	D2	D2	D2	D2		D1	D1	D1	D1	D1	D1
D	D2	D2	D2		D1	D1	D1					
E	D1	D1	D1	D1		D2	D2	D2	D2	D2	D2	D2
F	D1		D2	D2	D2							
G	D2	D2					D2	D2	D2	D2	D2	D2

Days persistent (continous days) without greater than a 60-day gap for the index drug based on a 180-day follow-up period

- For D1 (index): A = 60 days; B = 180 days; E = 120 days; and F = 30 days.
- For D2 (index): C =150 days; D = 90 days; and G = 60 days.
- Mean persistence for patients on D1 = (60+180+120+30)/4 = 97.5 days.
- Mean persistence for patients on D2 = (150+90+60)/3 = 100.0 days.

Medication discontinuation over a 180-day period (Greater that a 60-day gap following index drug or introduction of a new drug*†)

- For D1 (index): Patients A, B, E and F discontinued therapy (4 out of 4 patients)
- For D2 (index): Patients C, D and G discontinued therapy (3 out of 3 patients)

Switching§ from index medication to another study medication during a 180-day study period

- Patients B, E and F switched from D1(index) to D2 (3 out of 4 patients)
- Patients C and D switched from D2(index) to D1 (2 out of 3 patients)

A, B, C, D, E, F and G are the patients; D1 and D2 are the study drugs; *Index drug is the first study drug the patient was placed on; †Drugs D1 and D2 can not be used concomitantly; §Starting a new study drug that is different from the index drug

Total Healthcare Utilization Costs

Total healthcare utilization costs were the direct costs (i.e., medical and medication costs combined) to Texas Medicaid in the post-index period for users on each of the study TNF inhibitors, adjusted to 2011 US dollars (using the medical consumer price index from the U.S. Bureau of Labor Statistics current data).

RA-related Healthcare Utilization Costs

RA-related healthcare costs were the total RA-related direct costs (i.e., medical and medication costs combined associated with ICD-9-CM code 714.0x) to Texas Medicaid in the post-index period for users on each of the study TNF inhibitor, adjusted to 2011 US dollars (using the medical consumer price index from the U.S. Bureau of Labor Statistics current data).

3.1.3.2 Independent Variables and Covariates

The main independent variable for the study was the type of TNF inhibitor (etanercept, adalimumab and infliximab). The study covariates controlled for in the multivariate analysis included demographic factors (age, gender, race/ethnicity), pre-index use of other RA-related medications (e.g., NSAIDs, cyclooxygenase-2-inhibitors, narcotic analgesics, tramadol, corticosteroids and non-biologic agents), total number of non-study RA-related medications at index, Charlson Comorbidity Index score, pre-index RA and non-RA related visits, pre-index healthcare utilization cost and specialty of prescribing physician.

Charlson Comorbidity Index (CCI) Score

The pathogenesis (disease process) of RA as well as its treatment often predisposes patients to developing comorbidities (see Figure 2.3 for examples of RA-related comorbidities).[71] Comorbidities are frequently measured in epidemiological studies as they often reflect the severity of the disease as well as the overall health status of the patient.[4,189] In outcome research studies involving the use of administrative databases, comorbidities can be measured using either diagnosis- or prescription medication-based scores.[189,190] Prescription medication-based scores (e.g., chronic disease score (CDS)) are used when only prescription claims data are available.[189] Diagnosis-based scores (e.g., Charlson Comorbidity Index (CCI) and its adaptations (e.g., Deyo, Ghali, Dartmouth-Manitoba and D'Hoores)) are used if diagnosis records or data (e.g., ICD-9 CM or ICD-10 CM codes) are available along with prescription claims data.[191-195] While the CCI was developed based on review of medical records, adaptations of the CCI (e.g., Deyo, Ghali, Dartmouth-Manitoba and D'Hoores) were developed by matching the diagnosis included in the CCI with similar ICD-9 diagnoses and procedures.[191-194] The CCI score is derived based on the sum of weights (from 1 to 6) assigned to a predefined set of comorbidities for which a patient has claims data available.[195,196] The assigned weights (see Table 3.2) were obtained from relative risk estimates associated with each comorbid condition in a Cox proportional hazards regression model using clinical data.[189,190,196]

Since the present study has diagnosis data (i.e., ICD-9 CM codes) along with prescription claims data, adaptations of the CCI were used to compute the comorbidity scores for the study population. The two most commonly used adaptations of the CCI are the Deyo and the Dartmouth-Manitoba adaptations.[196] They differ from each other based on how they translated the CCI to ICD-9-CM codes.[196] The Deyo adaptation is stricter in its interpretation of the Charlson's comorbidity definitions compared to the Dartmouth-Manitoba adaptation which included conceptually similar conditions not explicitly mentioned by Charlson et al.[191,194,196] However, both adaptations have been shown to demonstrate comparable agreement in identifying Charlson comorbidities and CCI score with comparable discriminative ability in predicting mortality.[193,196-198] The D'Hoores adaptation on the other hand differed from the Deyo and the Dartmouth-Manitoba adaptations as it only used the first 3 digits of the ICD-9 codes in its interpretation of the Charlson index.[192] Lastly, the adaption by Ghali et al. differed as it was based on assigning study-specific data-derived weights to the original Charlson comorbidity variables as interpreted by Deyo and colleagues.[191,193] For the present study the Dartmouth-Manitoba adaptation was used because it is the least restrictive of two commonly used CCI adaptations.[196]

A summary of the operational definitions of the independent variables and covariates is presented in Table 3.3.

Table 3.2 Charlson Comorbidity Index Components, Weights and Adaptations

Comorbid Conditions	Weights	Deyo et al. codes	Dartmouth-Manitoba codes	D'Hoore et al. codes
Myocardial infarction	1	410.xx, 412*	410.xx, 412*	410, 411
Congestive heart failure	1	428.x	402.01, 402.11, 402.91, 425.x, 428.x, 429.3, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93	398, 402, 428
Peripheral vascular disease	1	441.x*, 443.9*, 785.4*, V43.4*, 38.48(P)	440.x*, 441.x*, 442.x*, 443.1-443.9*, 447.1*, 785.4*, 38.13-38.14(P)*, 38.16(P)*, 38.18(P)*, 38.33-38.34(P)*, 38.36(P)*, 38.38(P)*, 38.43-38.44(P)*, 38.46(P)*, 38.48(P)*, 39.22-39.26(P)*	440-447
Cerebrovascular disease	1	430-437.x, 438*	362.34, 430-436, 437-437.1, 437.9, 438, 781.4, 784.3, 997.0, 38.12(P), 38.42(P)	430-433, 435
Dementia	1	290.x*	290.x*, 331-331.2*	290, 291, 294
Chronic pulmonary disease	1	490-496*, 500-505*, 506.4*	415.0*, 416.8-416.9*, 491.x-494*, 496*	491-493
Connective tissue disease	1	710.0-710.1*, 710.4*, 714.0-714.2*, 714.81*, 725*	710.x, 714.x	710, 714, 725
Ulcer disease	1	531.4x-531.7x*, 532.4x-532.7x*, 533.4x-533.7x*, 534.4x-534.7x*, 531.0x-531.3x, 532.0x-532.3x, 533.0x-533.3x, 534.0x-534.3x, 531.9, 532.9, 533.9, 534.9	531.xx-534.xx	531-534
Mild liver disease	1	571.2*, 571.4*, 571.5*, 571.6*	571.2*, 571.5-571.6*, 571.8-571.9*	571, 573
Diabetes	1	250.0x-250.3x*, 250.7x*	250.0x-250.3x*	250
Diabetes with end organ damage	2	250.4x-250.6x*	250.4x-250.9x*†	
Hemiplegia	2	342.x*, 344.1*	342.x, 344.x	342, 434, 436, 437

Comorbid Conditions	Weights	Deyo et al. codes	Dartmouth-Manitoba codes	D'Hoore et al. codes
Moderate or severe renal disease	2	582.x*, 583.0-583.7*, 585*, 586*, 588.x*	585-586*, V42.0*, V45.1*, V56.x*, 39.27(P)*, 39.42(P)*, 39.93-39.95(P)*, 54.98(P)*	403, 404, 580-586
Any tumor	2	140.x-172.x, 174.x-195.x, 200.xx-208.xx	140.x-171.x*, 174.x-195.x*, 200.xx-208.x*, 273.0*, 273.3*, V10.46*, 60.5(P)*, 62.4-62.41(P)	140-195
Leukemia	2			204-208
Lymphoma	2			200, 202, 203
Moderate or severe liver disease	3	572.2-582.8*, 456.0-456.2x*	572.2-572.4*, 456.0-456.2x*, 39.1(P)*, 42.91(P)*†	070, 570, 572
Metastatic solid tumor	6	196.x-199.x	196.x-199.x*†	196-199
AIDS	6	042.x-044.x	042.x-044.x	

(P) follows all ICD-9-CM codes that describe procedures rather than diagnoses (Vol.III).

* The codes with asterisks are included in the definition of a comorbidity if they are listed during either index or prior hospital discharges ; other codes are included only if recorded prior to the index discharge. Each asterisk applies to all codes within the indicated range.

†In the Dartmouth-Manitoba algorithm, these comorbidities take precedence over less severe comorbidities involving the same organ system.

Adapted from:

Needham DM, Scales DC, Laupacis A, Pronovost PJ. A systematic review of the Charlson comorbidity index using Canadian administrative databases: a perspective on risk adjustment in critical care research. *J Crit Care*. 2005; 20(1):12-19

Romano PS, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: differing perspectives. J Clin Epidemiol. 1993; 46(10):1075-1079; discussion 1081-1090

D'Hoore W, Bouckaert A, Tilquin C. Practical considerations on the use of the Charlson comorbidity index with administrative data bases. J Clin Epidemiol. 1996; 49(12):1429-1433

Table 3.3 Operational Definition of Study Variables

Variables	Operational Definition
Dependent Variable	
Dose escalation[1]	When average of all subsequent weekly dose (i.e., (total dispensed quantities for all subsequent prescriptions in mg/ total days supply for all subsequent prescriptions) x 7); is greater than the weekly dose of the index prescription by 1.5 (150%)
	1 = Dose escalation (if above criterion is met) 0 = No dose escalation (if above criterion is not met)
Medication adherence[2]	TNF[3] medication adherence in the post-index period[4] measured using MPR[5]
	1 = Non-Adherent (MPR< 0.8 or 80%) 0 = Adherent (MPR≥0.8 or 80%)
Medication persistence (MP)	Number of days of continuous therapy on index medication without a specified gap in the post-index period[4]. A 60-day gap period will be used but sensitivity analyses was conducted using 30-, 45-, 90- and 120-day gap periods
	1 = Non-persistent (MP <292 days)[6] 0 = Persistent (MP≥292 days)[6]
Medication discontinuation	Presence of greater than a 60-day gap period between consecutive prescriptions or a switch from an index TNF[3] inhibitor therapy. Sensitivity analyses was conducted using 30-, 45-, 90- and 120-day gap periods
	1 = Discontinued index medication 0 = Did not discontinue index medication
Medication switch	Starting a RA biologic agent that is different from the index TNF[3] inhibitor therapy
	1 = Switched from index medication 0 = Did not switch from index medication
Medication dosing patterns	Initial dose, dose category changes (i.e., patients moving to higher doses)
Post-index total healthcare utilization cost	Total direct medical and medication costs[7] in the post-index period[4], adjusted to 2011 US dollars
Post-index RA[8] related healthcare utilization cost	Total RA-related direct medical and medication costs[7] (associated with ICD-9-CM code 714.0x)[9] in the post-index period[4], adjusted to 2011 US dollars
TNF[3] medication cost	Total cost[7] of the index TNF inhibitor medication in the post-index period[4], adjusted to 2011 US dollars
Independent Variables	
Type of TNF[3] inhibitor prescribed	1 = Etanercept (ETN) 2 = Adalimumab (ADA) 3 = Infliximab (IFX)
Covariates	
Age[10]	Age of the subject at index date
Gender[10]	1 = Female 0 = Male

Variables	Operational Definition
Race/ Ethnicity[10]	1 = White 2 = Black 3 = Hispanic 4 = Others
Use of other RA[8] related medications[10]	Presence of a prescription for at least one medication in each group of non-study RA related medications in the pre-index period
	1 = DMARD[11] medication 0 = No DMARD[11] medication
	1 = Glucocorticoid medication 0 = No glucocorticoid medication
	1 = Pain medication 0 =No pain medication
Total number of non-study RA[8] related medications[10]	Total number of non-study RA[8] related medications (NSAIDs, cyclooxygenase-2-inhibitors, narcotic analgesics, tramadol, glucocorticoids and non-biologic DMARDs) at index date
Charlson Comorbidity Index score[10](Dartmouth-Manitoba codes)	The sum of weights related to each comorbid condition at index (See Table 3.2)
Pre-index RA[8]-related visits[10]	Visits associated with ICD-9-CM[9] code 714.0x
Pre-index non-RA[8] related visits[10]	Other visits not associated with ICD-9-CM[9] code 714.0x
Pre-index total healthcare utilization cost[7,10]	Total direct medical and medication costs[7] in the pre-index period[12], adjusted to 2011 US dollars
Specialty of prescribing physician[10,13]	1 = Rheumatologist 2 = General or Family practice practitioner 3 = Others

[1] In addition, the average weekly dose for all subsequent prescriptions must be greater than 50mg for patients on etanercept (ETN) or 20mg for patients on adalimumab (ADA)
[2] Based on the obtained MPR values, mean adherence (mean MPR), and proportion of adherent patients (using 0.80 or 80% cut-off point with MPR≥ 0.80 or 80% referred to as being adherent) were determined for each TNF inhibitor. Sensitivity analysis will be conducted at 70 and 90 percent cut-off values
[3]Tumor necrosis factor
[4]Twelve months follow-up period from the index date
[5]Medication possession ratio= Sum of days supply for all fills x 100 ÷ Number of days in study period
[6]Using a 80% cut-off as used with adherence (80% x 365days= 292 days)
[7]Costs to the Texas Medicaid program
[8]Rheumatoid arthritis
[9] International Classification of Diseases, Ninth Revision, Clinical Modification
[10] Included as variables for the propensity scoring matching
[11]Disease modifying antirheumatic drugs
[12]Six months period (July 1, 2003 to Dec., 31, 2003) prior to the index date (January 1, 2003 to August 31, 2010);
[13] Specialty of prescribing physician was dropped due to greater than 10 percent of subjects have missing information on this variable

3.1.4 Statistical Analysis

All data manipulation and statistical analyses were performed using SAS for Windows, Version 9.2 (SAS Institute, Cary, NC). All statistical analyses were two-tailed and the significance level was set a priori at $p < 0.05$. Frequencies, skewness, kurtosis and normality tests were computed to check for data abnormalities and normality distribution. Due to baseline differences in the study covariates among the study groups, a propensity score technique was used.[199] Propensity scores were generated using multinomial logistic regression and the study groups were matched using a 3-way match (nearest neighbor) with caliper set at 0.05.[200] To determine if a balance was achieved among the matched groups, differences between matched pairs were evaluated on each of the study covariates using the paired t-test or signed-rank test for continuous data and the McNemar's test for binary data.[199] Bonferroni correction was used to control for type 1 error due to multiple comparisons. Descriptive statistics (mean, standard deviation and frequency) were used to summarize baseline socio-demographics, clinical characteristics and healthcare utilization cost patterns. Based on the type (categorical or continuous) and the distribution of data, appropriate statistical tests, which accounted for the matched nature of the final study sample, were conducted. Specific analytical test(s) for each study objective/hypothesis are presented in Table 3.4.

Table 3.4 Summary of Hypotheses, Study Measure(s) and Statistical Techniques

Objectives/ Hypotheses	Dependent Variable[a]	Measurement Level	Independent Variable	Measurement Level	Statistical Analysis
Objective 1*: To describe and compare baseline socio-demographics and clinical characteristics of Texas Medicaid RA patients on etanercept (ETN), adalimumab (ADA) or infliximab (IFX)*	[b]Age	Continuous	Type of TNF inhibitor	Nominal	Descriptive statistics[‡] & ANOVA
	[b]Gender	Nominal			Descriptive statistics[c] & Pearson Chi-square (X^2)
	[b]Race	Nominal			Descriptive statistics[c] & Pearson Chi-square (X^2)
	[b]Use of other RA-related medications	Nominal			Descriptive statistics[c] & Pearson Chi-square (X^2)
	[b]Total number of non-study RA-related medications	Continuous			Descriptive statistics[c] & ANOVA
	[b]Charlson Comorbidity Index	Continuous			Descriptive statistics[c] & Kruskal-Wallis
	[b]Total number of RA-related visits	Continuous			Descriptive statistics[c] & Kruskal-Wallis
	[b]Total number of non RA-related visits	Continuous			Descriptive statistics[c] & Kruskal-Wallis
	[b]Pre-index total healthcare utilization cost	Continuous			Descriptive statistics[c] & Kruskal-Wallis
	[b]Speciality of prescribing physician	Nominal			Descriptive statistics[c] & Pearson Chi-square (X^2)
Objective 2*: To describe medication dosing patterns (initial or starting dose and dose category changes) among ETN, ADA and IFX users.*	Initial or starting dose	Nominal			Descriptive statistics[c]
	Dose category changes	Nominal			Descriptive statistics[c]
Objective 3*: To determine if the likelihood of having a dose escalation among ETN users differs significantly compared to ADA and IFX users while controlling for covariates[d]*					
H_1: The likelihood of having a dose escalation is significantly lower among RA patients on ETN compared to patients on ADA and IFX while controlling for covariates[d]	Dose escalation (dichotomous- i.e., Yes or No)	Nominal	Type of TNF inhibitor	Nominal	Conditional logistic regression[e] (Regression analysis)

Objectives/ Hypotheses	Dependent Variable[a]	Measurement Level	Independent Variable	Measurement Level	Statistical Analysis
Objective 4*: To determine if medication use patterns (adherence, persistence, discontinuation and switching) among ETN users differ significantly compared to ADA and IFX users while controlling for covariates[d]*					
H_{o2A}: There is no significant difference in medication adherence to ETN compared to ADA and IFX while controlling for covariates[d]	Medication adherence (MPR)	Continuous	Type of TNF inhibitor	Nominal	GLM model estimated with GEE[f] (Regression analysis)
H_{o2B}: The likelihood of being adherent (MPR≥80%) to ETN does not differ significantly compared to ADA and IFX while controlling for covariates[d]	Medication adherence (dichotomous- MPR< 0.80 or 80% and MPR≥ 0.80 or 80%)	Nominal	Type of TNF inhibitor	Nominal	Conditional logistic regression[e] (Regression analysis)
H_{o3}: There is no significant difference in medication persistence to ETN compared to ADA and IFX while controlling for covariates[d]	Medication persistence	Continuous	Type of TNF inhibitor	Nominal	GLM model estimated with GEE[f] (Regression analysis)
H_{o4}: The likelihood of discontinuing ETN does not differ significantly compared to ADA and IFX while controlling for covariates[d]	Medication discontinuation (dichotomous- Yes or No)	Nominal	Type of TNF inhibitor	Nominal	Conditional logistic regression[e] (Regression analysis)
H_{o5}: There is no significant difference in duration of medication use prior to discontinuation of ETN compared to ADA and IFX while controlling for covariates[d]	Medication persistence (Survival time)	Continuous	Type of TNF inhibitor	Nominal	Cox proportional hazards regression[g] (Regression analysis)
H_{o6}: There is no significant difference in the likelihood of switching from index TNF inhibitor therapy to another biologic agent among ETN users compared to ADA and IFX users while controlling for covariates. [d]	Medication switching (dichotomous- Yes or No)	Nominal	Type of TNF inhibitor	Nominal	Conditional logistic regression[e] (Regression analysis)
H_{o7}: There is no significant difference in duration of medication use prior to switching from index TNF inhibitor therapy among ETN users compared to ADA and IFX users while controlling for covariates[d]	Medication persistence	Continuous	Type of TNF inhibitor	Nominal	GLM model estimated with GEE[f] (Regression analysis)

Objectives/ Hypotheses	Dependent Variable[a]	Measurement Level	Independent Variable	Measurement Level	Statistical Analysis
Objective 5*: To determine if total healthcare utilization cost for ETN users differs significantly compared to ADA and IFX users while controlling for covariates*[d]					
H_8:Total healthcare utilization cost is significantly lower for ETN patients compared to patients on ADA and IFX while controlling for covariates[d]	Total healthcare cost	Continuous	Type of TNF inhibitor	Nominal	GLM model estimated with GEE[f] (Regression analysis)
Objective 6: *To determine if RA-related healthcare utilization cost for ETN users differs significantly compared to ADA and IFX users while controlling for covariates*[d]					
H_9:RA-related healthcare utilization cost[h] is significantly lower for ETN patients compared to patients on ADA and IFX while controlling for covariates[d]	RA-related healthcare cost	Continuous	Type of TNF inhibitor	Nominal	GLM model estimated with GEE[f] (Regression analysis)
H_{10}: TNF medication cost is significantly lower for ETN patients compared to patients on ADA and IFX while controlling for covariates[d]	TNF medication cost	Continuous	Type of TNF inhibitor	Nominal	GLM model estimated with GEE[f] (Regression analysis)
Objective 7*: To determine if RA-related healthcare utilization cost is associated with adherence/persistence to TNF inhibitors (ETN, ADA or IFX) while controlling for covariates*[d]					
H_{11}: RA-related healthcare utilization cost is significantly and positively related to TNF medication adherence while controlling for covariates[d]	RA-related healthcare utilization cost	Continuous	Medication adherence (MPR)	Continuous	GLM model estimated with GEE[f] (Regression analysis)
H_{12}: RA-related healthcare utilization cost is significantly and positively related to TNF medication persistence while controlling for covariates[d]	RA-related healthcare utilization cost	Continuous	Medication persistence	Continuous	GLM models estimated using GEE[f] (Regression analysis)

ADA= adalimumab; **ANOVA**= analysis of variance; **ETN**= etanercept; **GEE=** generalized estimating equation; **GLM**=generalized linear model; **IFX**= infliximab; **MPR**= Medication possession ratio; **RA**= rheumatoid arthritis; **TNF**= Tumor necrosis factor;

[a]Does not apply to the variables under the first objective; [b]These are baseline covariates and are not dependent variables; [c]Mean, standard deviation and frequency; [d]Covariates include age, gender, pre-index use of other RA-related medications, total number of other RA-related medications use at index, Charlson Comorbidity index, pre-index total RA-related visits, pre-index total non-RA related visits, pre-index RA-related healthcare utilization cost, specialty of prescribing physician; [e]Used instead of the traditional logistic regression to account for the matched nature of the sample; [f]Used instead of multiple regression to account for the matched nature of the sample; [g]Matched nature of the sample was accounted for using the strata statement. **Note**: For the GLM models a gamma distribution was assumed due to the violation of the normality assumption.

3.1.4.1 Statistical Tests Assumptions and Sample Size Calculations

This section discusses the test assumptions as well as sample size calculations for the statistical analyses presented in Table 3.4. Sample size calculations were not conducted for statistical tests under objectives 1 and 2 as they involved baseline comparisons and descriptive statistics.

Multiple Regression Analysis

Multiple regression analysis is an example of a general linear model. It requires that the data to be analyzed is a random sample from a population in which the following assumptions are met: (1) linear relationship between the dependent and independent variables; (2) homoscedasticity of variance – the variance of the residuals about the predicted dependent variable values must be the same or constant for all predicted values; (3) normal distribution of residuals about the predicted dependent variable values; (4) independence of errors of prediction; and (5) lack of multicollinearity (or correlations) among independent variables. The multiple regression model is presented in Figure 3.4. Using the G-Power software, an estimated total sample size of 850 patients (power = 0.8; $\alpha = 0.05$; small effect size (f) = 0.02; number of predictors = 11) were required for a multiple regression analysis.

4,201-203

Figure 3.4 Multiple Regression Model

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_n X_n$$

- *Y is the dependent or response variable*
- *β_0 is the intercept*
- *β_1 to β_n are the regression coefficients*
- *X_1 to X_n are the independent or predictor variables*

Cox Proportional Hazards Regression Analysis

To address part of objective 4, Cox proportional hazards regression analysis was employed. However, a strata statement was included to account for the matched nature of the study sample. The Cox proportional hazards regression is an example of a survival analysis (which is also an example of a general linear model) that allows for control of covariates. It is expressed in the form below in Figure 3.5. The Cox proportional hazards regression is a semi-parametric model with model assumptions similar to those for parametric models but it makes no assumptions about the form or shape of the underlying hazard (h(t)). It assumes parametric form for the effect of the predictors on the hazard and interprets parameter estimates in the same way as obtained in parametric models.

Figure 3.5 Cox Proportional Hazards Regression Model

$$h\,(t/X) = h\,(t)\ \exp\,(X_1\beta_1 + \ldots\ldots + X_n\beta_n)$$

- *h(t) is the hazard function and represents risk changes with time and it is the non-parametric part of the model*
- *exp represents the effect of covariates*
- *X_1 to X_n are the predictor variables and are assumed to act addictively on log h(t/x)*
- *β_1 to β_n are the regression coefficients*
- *log h(t/x) changes linearly with the βs*
- *The effect of the predictors is the same at all times t*

Using the PASS 11 software and varying the parameters required for sample size calculations over a range of values, the largest sample size obtained was chosen as the required sample size for the Cox proportional hazards regression. Table 3.5 presents the estimates of sample sizes required for the Cox proportional hazards regression analysis. Based on the estimates of sample size obtained, an estimated total sample size of 1,662 patients (power = 0.8; α = 0.05) was required for the Cox proportional hazards regression analysis.[31,204,205]

Table 3.5 Estimates of Sample Size for Cox-Proportional Hazard Regression Analysis

B (log Hazard ratio)[a]	1.5	1.5	1.5	1.5	1.5
P(Overall Event Rate)[b]	0.3	0.35	0.4	0.45	0.5
R-squared[c]	0.1	0.1	0.1	0.1	0.1
Total Sample Size	**1292**	**1108**	**969**	**862**	**776**
B (log Hazard ratio)[a]	1.5	1.5	1.5	1.5	1.5
P(Overall Event Rate)[b]	0.3	0.35	0.4	0.45	0.5
R-squared[c]	0.2	0.2	0.2	0.2	0.2
Total Sample Size	**1454**	**1246**	**1091** **1091**	**969**	**873**
B (log Hazard ratio)[a]	1.5	1.5	1.5	1.5	1.5
P (Overall Event Rate)[b]	0.3	0.35	0.4	0.45	0.5
R-squared[c]	0.3	0.3	0.3	0.3	0.3
Total Sample Size	**1662**	**1424**	**1246**	**1108**	**997**
B (log Hazard ratio)[a]	2.0	2.0	2.0	2.0	2.0
P(Overall Event Rate)[b]	0.3	0.35	0.4	0.45	0.5
R-squared[c]	0.1	0.1	0.1	0.1	0.1
Total Sample Size	**727**	**623**	**546**	**485**	**437**
B (log Hazard ratio)[a]	2.0	2.0	2.0	2.0	2.0
P(Overall Event Rate)[b]	0.3	0.35	0.4	0.45	0.5
R-squared[c]	0.2	0.2	0.2	0.2	0.2
Total Sample Size	**818**	**701**	**614**	**546**	**491**
B (log Hazard ratio)[a]	2.0	2.0	2.0	2.0	2.0
P (Overall Event Rate)[b]	0.3	0.35	0.4	0.45	0.5
R-squared[c]	0.3	0.3	0.3	0.3	0.3
Total Sample Size	**935**	**801**	**701**	**623**	**561**

Y = dependent variable; X = independent variables (IV); $\alpha = 0.05$ (two tailed), $\beta = 0.20$ (power = 80%)

[a] Known as the regression coefficient defined as the predicted change in log(base e) hazards at one unit change in X_1 when the other covariates are held constant

[b] Denotes the the proportion of subjects in which the event of interest occurs during the duration of the study (Based on values reported in the across studies in the literature). The modeled event was medication discontinuation over a 12-month follow-up period

[c] The value achieved when X_1 is regressed on the other IVs or covariates in the regression

Generalized Linear Models

Generalized linear models (GLMs) are flexible generalizations of ordinary linear regression. They are used to relate responses to linear combinations of predictor variables and can be used for analyses in which the response variables have either normal or non-normal distributions.[206] A general linear model (e.g., linear regression) can be defined as a GLM with a normal distribution and an identity link function.[206] GLMs consist of 3 components: the response or dependent variable distribution which is also called the exponential family; a linear predictor; and a link function.[206] The exponential family is the particular distribution (e.g., normal, exponential, gamma, inverse Gaussian, Poisson, binomial, categorical, multinomial and Bernoulli) from which the response variable (Y) is derived. The variance of the distribution of the response variable (Y) is a function (v) of the mean of the distribution (μ) and possibly, the dispersion parameter (ϕ).[207] The linear predictor (η) incorporates information about the independent variables (X) into the model while the link function (g) provides the relationship between the linear predictor (η) and the mean of the distribution function (μ). The relationship among the components of the GLMs is presented in Figure 3.6. Examples of commonly used distributions and their canonical link functions are also presented in Table 3.6.

Figure 3.6 Relationships across Components of Generalized Linear Models

$$\eta = X\beta$$

$$E(Y) = \mu = g\text{-}1(X\beta) = g\text{-}1(\eta)$$

$$Var\ (Y) = \phi\ w\text{-}1\ V\ (\mu) = \phi\ w\text{-}1\ V\ (g\text{-}1\ (X\beta)) = \phi\ w\text{-}1\ V\ (g\text{-}1(\eta))$$

- X = the independent variables
- β = the unknown parameters which can be estimated using maximum likelihood
- Xβ = the linear combination of unknown parameters and is equivalent to the link predictor (η)
- E(Y) = the expected value of the response or dependent variable (Y)
- μ = the mean of the distribution
- g = link function
- Var (Y) = the variance of the distribution (i.e., dependent variable (Y)) and this is a function (v) of the mean of the distribution and possibly, the dispersion parameter (ϕ)
- W is a prior weight that specifies the precision of Y

Adapted from: Breslow NE. Generalized linear models: checking assumptions and strengthening conclusions. http://biostat.georgiahealth.edu/~dryu/course/stat9110spring12/land16_ref.pdf. Accessed May 1, 2012

Table 3.6 Common Distributions, Uses and Canonical Link Functions

Distribution	Support of Distribution	Typical Uses	Link Name
Normal	Real : (- ∞, + ∞)	Linear-response data	Identity
Exponential	Real: (0, + ∞)	Exponential-response data, scale parameters	Inverse or log
Gamma			
Inverse Gaussian			Inverse squared
Poisson	Integer: (0, +∞)	Count of occurrences in fixed amount of time/space	Log
Bernoulli	Integer: (0,1)	Outcome of single yes/no occurrence	Logit
Binomial	Integer: (0,N)	Count of number of 'yes' occurrences out of N yes/no occurrences	
Categorical	Integer: (0, K)	Outcome of single K-way occurrence	
	K-vector of integer: (0,1), where exactly one element in the vector has the value 1		
Multinomial	K-vector of integer: (0, N)	Count of occurrences of different types (1…K) out of N total K-way occurrences	

In general, the key assumptions that underlie GLMs include: 1) statistical independence of the observations; 2) correct specification of the variance function (V); 3) correct specification of the dispersion effect ϕ; 4) correct specification of the link function (g); 5) correct form for the explanatory variables (X); and 6) lack of undue influence of individual observations.[207]

Logistic Regression Analysis

To address objective 3 and part of objective 4, a conditional logistic regression analysis was employed to account for the matched nature of the sample. Logistic

regression is an example of generalized linear regression with the response or dependent variable having a binomial distribution. The following assumptions are required in order to employ a logistic regression model: 1) observations have to be independent of one another; and 2) the dependent variable has to be a dichotomous variable. The logistic regression model is presented in Figure 3.7. Using the G-Power software, and varying the parameters required for sample size calculations over a range of values, the largest sample size obtained was chosen as the required sample size for the logistic regression. Table 3.7 presents the estimates of sample sizes required for the logistic regression analysis. Based on the estimates of sample size obtained, an estimated total sample size of 1,214 patients (power = 0.8; $\alpha = 0.05$) was required for the logistic regression analysis. [4,201-203]

Figure 3.7 Logistic Regression Model

Logit [Θ (x)] = log [Θ(x) / 1-Θ(x)] = $\beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots\ldots + \beta_n x_n$

- Θ (x) = Probability of success
- 1-Θ(x) = Probability of failure
- β_0 = Constant of equation
- β_1 to β_n = Regression coefficients
- X_1 to Xn = Independent or predictor variables

Table 3.7 Estimates of Sample Size for Logistic Regression Analysis

Odds Ratio	1.5	2.0	2.5	3.0
Pr(Y=1|X=1)H_o[a]	0.03	0.03	0.03	0.03
R-squared[b]	0.1	0.1	0.1	0.1
Total Sample Size	**944**	**226**	**112**	**74**
Odds Ratio	1.5	2.0	2.5	3.0
Pr(Y=1|X=1)H_o[a]	0.03	0.03	0.03	0.03
R-squared[b]	0.2	0.2	0.2	0.2
Total Sample Size	**1062**	**255**	**126**	**83**
Odds Ratio	1.5	2.0	2.5	3.0
Pr(Y=1|X=1)H_o[a]	0.03	0.03	0.03	0.03
R-squared[b]	0.3	0.3	0.3	0.3
Total Sample Size	**1214**	**291**	**144**	**95**

Y = dependent variable; X = independent variables (IV); α = 0.05 (two tailed), β = 0.20 (power = 80%), a Poisson distribution was assumed for the IV of interest (X_1)

[a] Denotes the the probability of an event under H_o (lowest possible value which translates to highest possible sample size after evaluating the values reported across studies in the literature). The modeled event was dose-escalation rate over a 12-month follow-up period

[b] The value achieved when X_1 is regressed on the other IVs or covariates in the regression

Generalized Linear Model with Gamma Distribution

Generalized linear model with gamma distribution is one of the recommended approaches for analyzing data with a response or dependent variable that is positive and continuous.[208] Unlike the transformation-based approaches, back transformation is not required as estimations are carried out directly on the scale of the raw data. They are more robust to outliers and more suitable for analyzing very heavy-tailed data.[208] For the present study, a GLM (with gamma distribution) estimated using generalized estimation equation (GEE) to account for the matched nature of the

sample was used to analyze part of objective 4, and objectives 5, 6 and 7. The following assumptions are required to be met: 1) observations have to be independent of one another; and 2) the dependent variable has to be continuous.

Little information exists in the literature with respect to sample size calculation for GLMs with gamma distribution. However, based on information from the literature, it can be assumed that the sample size required for a gamma distribution will not be greater than the required sample size for a normal distribution at any given power level.[209] In estimating the required sample size for a GLM with gamma distribution, one can estimate the required sample size for a linear multiple regression and assume that if this is met, the study will be adequately powered to detect significant differences. Using the G-Power software, for the linear multiple regression, an estimated total sample size of 850 patients (power = 0.8; α = 0.05; small effect size (f) = 0.02; number of predictors = 11) was required. A summary of the sample sizes required for each of the statistical analytical tests conducted is presented below in Table 3.8. Based on these values, a total sample size of 1,662 subjects was required to address the study objectives.

Table 3.8 Summary of Sample Sizes for the Statistical Analytical Tests

Statistical Analytical Tests	Cox Proportional Hazards Regression	Logistic Regression	Generalized Linear Models (with Gamma Distribution)
Required Sample Size	**1,662**	**1,214**	**850**

CHAPTER 4: RESULTS

4.1 CHAPTER OVERVIEW

This chapter presents a detailed description of the study results. First, the patients' selection process based on the inclusion criteria is presented. Then information on patients' demographic profile and other study covariates are shown. Finally, the study objectives and the results of all associated statistical analyses are presented.

4.2 EXTRACTION OF ELIGIBLE PATIENTS IN THIS STUDY

A total of 43,330 subjects had an RA diagnosis and of those, 38,404 (88.6%) had no prescriptions for a biologic agent during the study period. This left a sample size of 4,926 of which the remaining inclusion/exclusion criteria were applied to obtain the final sample. Of those, 1,542 met the study criteria. Approximately 13% (N = 194; 12.6%) of these subjects had only one claim for a study TNF inhibitor within the 12-month study period while 1,348 subjects had at least 2 claims for the same study TNF inhibitor. Table 4.1 shows the study's inclusion criteria with the corresponding sample sizes after implementation of each criterion.

Table 4.1: Patient Attrition in the Texas Medicaid Database

Criteria	Subjects Excluded		Subjects Remaining	
	N	%	N	%
Initial Sample			43,330	100.0
No prescription for a biologic agent within the study period[a]	38,404	88.6	4,926	11.4
No prescription for study TNF inhibitors (ETN, ADA or IFX) within the identification period[b]	474	1.1	4,452	10.3
Had any RA biologic in pre-index period	1,267	2.9	3,185	7.4
Had claims for 2 or more study TNF inhibitors (ETN, ADA or IFX) on the index date	0	0.0	3,185	7.4
Missing value for age	23	0.1	3,162	7.3
Age < 18 on index date	91	0.2	3,071	7.1
Age > 63 on index date	77	0.2	2,994	6.9
Not continuously enrolled 180 days prior to index date	436	1.0	2,558	5.9
Not continuously enrolled 365 days after index date	543	1.3	2,015	4.7
No diagnosis of RA in pre-index period (180 days prior to index date)	254	0.6	1,761	4.1
Had diagnosis for another disease indication (PsO, PsA, UC, Crohn's, AS, JIA, NHL and CLL) in addition to RA diagnosis	217	0.5	1,544	3.6
Subjects on a SC drug with a J-Code	2	0.0	1,542	3.6
Off-label use of drug prior to RA indication approval	0	0.0	1,542	3.6
Final sample			**1,542[c]**	

ADA = Adalimumab; **AS** = Ankylosing spondylitis; **CLL** = Chronic lymphocytic leukemia; **Crohn's** = Crohn's disease; **ETN** = Etanercept; **IFX** = Infliximab; **JIA** = Juvenile idiopathic arthritis; **NHL** = Non-Hodgkin's lymphoma; **PsA** = Psoriatic arthritis; **PsO** = Plaque psoriasis; **SC** = Subcutaneous; **TNF** = Tumor necrosis factor; **UC** = Ulcerative colitis

[a] July 1, 2003 to August 31, 2011

[b] January 1, 2004 to August 31, 2010

[c] 194 subjects had only one claim for a study TNF inhibitor within the 12-month study period while 1,348 subjects had at least 2 claims for the same study TNF inhibitor within the 12-month study period

4.3 DESCRIPTIVE STATISTICS

Baseline demographic and clinical characteristics of the entire study sample are presented below with full details shown in Table 4.2.

4.3.1 Demographic Characteristics

The majority of the sample (71.5%) was between 45-63 years of age, Hispanic (54.0%) and female (88.7%).

4.3.2 Clinical Characteristics

Among the three study TNF inhibitors, most of the subjects were prescribed ETN at index (37.5%), followed closely by IFX (36.5%), and then ADA (26.0%). Almost 70 percent (69.6%) of the sample used DMARDs in the pre-index period, with methotrexate (55.6%) being the most commonly prescribed DMARD therapy. Over 40 percent (42.9%) of the sample received glucocorticoids in the pre-index period. Over one-third received prednisone (34.4%). The remaining oral glucocorticoids were used by approximately 6 percent (5.8%) of the sample. Approximately 8 percent (8.1%) of the sample received injectable glucocorticoids in the pre-index period. Over 70 percent (71.7%) of the sample used pain medications with narcotic analgesics (47.4%) being the most commonly prescribed. The majority of the sample were on at least 2 non-study RA-related medications (70.9%) and had a Charlson Comorbidity Index score ranging from 1-2 (96.8%) in the pre-index period. Slightly over 40 percent (41.2%) of the sample had a rheumatologist who prescribed their

index medication, while less than 10 percent (9.8%) had a general for family practice physician as the prescriber. A large percentage of subjects were in the 'other' (42.8%) category, which included various specialties within internal medicine. Of the 9,086 total visits, the majority (83.6%) were for RA-related ambulatory care. Less than 1 percent (0.3%) of the sample had an inpatient visit (RA and non-RA related).

Table 4.2: Baseline Summary Statistics for Final Sample

Demographic & Clinical Characteristics	N	%
Age groups		
18-34	136	8.8
35-44	304	19.7
45-54	532	34.5
55-63	570	37.0
Total	**1,542**	**100.0**
Race/ethnicity		
Caucasians	420	27.2
African Americans	163	10.6
Hispanics	832	54.0
Others	127	8.2
Total	**1,542**	**100.0**
Gender		
Females	1,368	88.7
Males	174	11.3
Total	**1,542**	**100.0**
Index TNF inhibitor		
Etanercept	578	37.5
Adalimumab	401	26.0
Infliximab	563	36.5
Total	**1,542**	**100.0**
Pre-index DMARDs utilization		
Yes	1,074	69.6
No	468	30.4
Total	**1,542**	**100.0**
Types of DMARDs[a]		
Methotrexate	858	55.6
Leflunomide	138	8.9
Sulfasalazine	168	10.9
Hydroxychloroquine	287	18.6
Other DMARDs[b]	11	0.7
Pre-index glucocorticoid utilization		
Yes	662	42.9
No	880	57.1
Total	**1,542**	**100.0**
Types of oral glucocorticoids[a]		
Dexamethasone	3	0.2
Hydrocortisone	0	0.0
Methylprednisolone	84	5.4
Prednisolone	3	0.2
Prednisone	530	34.4
Cortisone	0	0

Table 4.2: Baseline Summary Statistics for Final Sample Contd.

Demographic & Clinical Characteristics	N	%
Types of glucocorticoid injections[a]		
Corticotropin	0	0.0
Dexamethasone	13	0.8
Hydrocortisone	0	0.0
Methylprednisolone	57	3.7
Prednisolone	0	0.0
Triamcinolone	55	3.6
Pain medications		
Yes	1,105	71.7
No	437	28.3
Total	**1,542**	**100.0**
Types of pain medications[a]		
NSAIDs	354	23.0
COXIBs	278	18.0
Narcotic analgesics	731	47.4
Tramadol	295	19.1
Total number of non-study RA-related medications		
0	181	11.7
1	268	17.4
2	402	26.1
3	378	24.5
≥4	313	20.3
Total	**1,542**	**100.0**
Charlson Comorbidity Index score		
1-2	1,493	96.8
3-4	47	3.0
≥5	2	0.1
Total	**1,542**	**99.9**[c]
Specialty of prescribing physician		
Rheumatologist	635	41.2
General or family practice	151	9.8
Others[d]	660	42.8
Missing	96	6.2
Total	**1,542**	**100.0**
Health care resource utilization (# of visits)		
RA-related ambulatory care[e]	7,593	83.6
RA-related inpatient care[e]	21	0.2
Non-RA related ambulatory care	1,462	16.1
Non-RA related inpatient care	10	0.1
Total visits	**9,086**	**100.0**

COXIB = cox-2 inhibitors; **DMARD** = disease modifying anti-rheumatic drugs; **NSAIDs** = non-steroidal anti-inflammatory drugs; **RA** = Rheumatoid arthritis; **TNF** = tumor necrosis factor

[a] Groups are not mutually exclusive as subjects may have used more than one medication

[b] Azathioprine, chloroquine, cyclosphosphamide, cyclosporine, minocycline, and sodium aurothiomalate (gold)

[c] Does not add up to 100.0% due to rounding error

[d] Different specialties within internal medicine
[e] Visits associated with ICD-9-CM code 714.0x

4.4 STUDY OBJECTIVES

4.4.1 Objective 1: Description and Comparison of Baseline Characteristics

Objective 1 was to describe and compare baseline socio-demographics and clinical characteristics of Texas Medicaid RA patients on etanercept (ETN), adalimumab (ADA) or infliximab (IFX). A description of the baseline socio-demographics and clinical characteristics have been presented in Table 4.2. A summary of baseline demographic and clinical characteristics comparisons are presented here with full details shown in Table 4.3. Overall, at baseline, there were no significant differences on all demographic characteristics among the 3 study groups (ETN, ADA & IFX). However, all clinical characteristics revealed significant differences. In general, IFX users seemed to be less severe. Although IFX users had more health care visits[d], their total costs at baseline were significantly lower.

Demographic Characteristics

When comparing ETN, ADA, and IFX, there were no statistically significant differences in age (p=0.1761), gender (p=0.5345) or race/ethnicity (p=0.8320).

[d] Primarily physician visits

Clinical Characteristics

A significantly ($p < 0.0001$) lower proportion of subjects on IFX (62.0%) used DMARDs in the pre-index period when compared to ETN (73.4%) and ADA (75.1%) users. A significantly ($p < 0.0001$) lower proportion of subjects on IFX used glucocorticoids (29.0%) when compared to ETN (49.7%) and ADA users (52.9%). Similarly, a significantly ($p < 0.0001$) lower proportion of subjects on IFX used pain medications (56.7%) when compared to ETN (81.5%) and ADA users (78.6%). Subjects on IFX also had a significantly ($p < 0.0001$) lower mean number of non-study RA-related medications (1.9±1.5) when compared to ETN (2.7±1.4) and ADA (2.5±1.3) users. Subjects on IFX had a significantly ($p < 0.0045$) higher Charlson score (1.3±0.6) compared to ETN (1.2±0.5) and ADA (1.2±0.5) users. A significantly ($p < 0.0001$) lower proportion of subjects on IFX (32.3%) had a rheumatologist prescribe the index medication when compared to ETN (46.0%) and ADA (46.6%) users. Regarding RA-related healthcare utilization[b] (i.e., physician visits), there was a significant ($p < 0.0001$) difference among all study medications, with subjects on IFX having significantly more visits (6.5±5.3) than ETN (4.0±4.0) or ADA (4.1±2.9). Regarding non RA-related health care utilization[e] (i.e., physician visits), IFX users had significantly ($p < 0.0001$) more visits (1.4±1.9) than ETN (0.7±1.3) or ADA (0.8±1.2).

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[e] For the healthcare utilization and costs means were reported but non-parametric tests were used

Regarding total healthcare utilization costs[a] (medical and medication costs), IFX users had significantly (p=0.0308) lower costs ($1,854±2,620) compared to ETN ($2,433±2,790) or ADA ($2,153±2,900).

Table 4.3: Comparison of Baseline Characteristics by Type of TNF Inhibitor (Unmatched Population)

	ETN (N=578)	ADA (N=401)	IFX (N=563)	p-value
Age, Mean(±SD)[a]	49.7(±10.0)	50.3(±10.0)	50.8(±9.3)	0.1761
Females (%)[b]	89.6	89.0	87.6	0.5345
Race/ethnicity (%)[b]				0.8320
Hispanics	53.5	53.6	54.7	
Caucasians	26.6	26.9	28.1	
African Americans	10.4	11.5	10.1	
Others	9.5	8.0	7.1	
DMARD utilization (%)[b]	73.4	75.1	62.0	< 0.0001
Glucocorticoid utilization (%)[b]	49.7	52.9	29.0	< 0.0001
Pain medication (%)[b]	81.5	78.6	56.7	< 0.0001
Total number of non-study RA-related medications, Mean(±SD)[a]	2.7(±1.4)[c]	2.5(±1.3)[c]	1.9(±1.5)	< 0.0001
Charlson Comorbidity Index[d]				0.0045
Median	1.0[e]	1.0[e]	1.0	
Mean(±SD)	1.2(±0.5)	1.2(±0.5)	1.3(±0.6)	
Specialty of prescribing physician (%)[b, f]				< 0.0001
Rheumatologist	46.0	46.6	32.3	
General/ family practice	8.7	9.0	11.6	
Others	45.3	44.5	39.1	
Missing	0.0	0.0	17.1	
RA-related health care utilization[d,g-i]				< 0.0001
Median	3.0	3.0	5.0	
Mean(±SD)	4.0(±4.0)	4.1(±2.9)	6.5(±5.3)	
Non-RA related health care utilization[d,e,i]				< 0.0001
Median	0.0[e]	0.0[e]	1.0	
Mean(±SD)	0.7(±1.3)	0.8(±1.2)	1.4(±1.9)	
Pre-index total health care utilization costs ($) [d,e,j]				0.0308
Median	1583[e]	1432[e]	1229	
Mean(±SD)	2433(±2790)	2153(±2900)	1854(±2620)	

ADA = adalimumab**; DMARD** = disease modifying anti-rheumatic drugs; **ETN** = etanercept; **IFX** = infliximab; **RA** = rheumatoid arthritis; **TNF** = tumor necrosis factor

[a] ANOVA

[b] Chi-square.

[c] Pairwise comparison test (i.e., Duncan); like letters were not significantly different

[d] Kruskal Wallis

[e] Pairwise comparison test (i.e., Wilcoxon test with Type 1 error correction using Bonferroni); like letters were not significantly different

[f] This variable was dropped in further analysis due to missing data on >10% of IFX patients

[g] Pairwise comparison test (i.e., Wilcoxon test with Type 1 error correction using Bonferroni) showed significant difference among each of the three groups

[h] Visits associated with ICD-9-CM code 714.0x

[i] Ambulatory and inpatient visits

[j] Total direct medical and medication costs in the pre-index period, adjusted to 2011 US dollars

4.4.1.2: Use of Propensity Score Matching

Propensity score matching is a method commonly used in observational studies to reduce the impact of treatment selection bias by balancing study covariates across the comparison groups. A subject's propensity score (PS) is defined as the probability of the subject receiving a specific treatment given the subject's observed covariates values. While PS matching is aimed at mimicking randomization, its effectiveness is highly dependent on the quality of the covariates introduced into the logistic regression model since PS matching only controls for known or overt biases. The procedure requires one to: 1) identify plausible covariates; 2) conduct a logistic regression to generate the PS scores; 3) conduct a PS match; and 4) test for balance between matched groups.[199]

For the present study, since the comparison groups differed on baseline clinical characteristics, PS matching was conducted.[199] PSs were generated using multinomial logistic regression[f] and the study groups were matched using a 3-way match (nearest neighbor) with caliper set at 0.05.[200] To determine if a balance was achieved among the matched groups, differences between matched pairs were

[f] Multinomial logistic regression is a regression model that generalizes logistic regression by allowing more than 2 discrete outcomes.

evaluated on each of the study covariates using a paired t-test or signed rank test for continuous data and the McNemar's test for binary data. Bonferroni correction was used to control for type 1 error due to multiple comparisons. Results of the matched groups are presented in Table 4.4. Based on the results obtained from the balance test (Table 4.4), it can be inferred that the PS matching balanced the covariates across the comparison groups. However, 46.7% of the original sample (N = 1542) was lost during the PS matching process with a final matched sample of 822 remaining.

Table 4.4: Comparison of Baseline Characteristics by Type of TNF Inhibitor: Propensity-Score (Caliper) 3-Way Matched[a]†

	ETN N=274	ADA N=274	p-value	ETN N=274	IFX N=274	p-value	ADA N=274	IFX N=274	p-value
Age, Mean(±SD)[b]	49.1 (±9.8)	48.9 (±9.9)	0.7638	49.1 (±9.8)	48.7 (±9.6)	0.6619	48.9 (±9.9)	48.7 (±9.6)	0.8710
Females (%)[c]	88.3	88.3	1.0000	88.3	87.2	0.7982	88.3	87.2	0.7914
Hispanics (%)[c]	54.0	52.6	0.7910	54.0	54.4	1.0000	52.6	54.4	0.7327
DMARD utilization (%)[c]	71.5	69.0	0.5341	71.5	75.9	0.2299	69.0	75.9	0.0558
Glucocorticoid utilization (%)[c]	43.8	45.3	0.7275	43.8	43.1	0.9022	45.3	43.1	0.5560
Pain medication (%)[c]	75.6	77.7	0.4885	75.6	80.3	0.1112	77.7	80.3	0.3916
Total number of non-study RA-related medications, Mean(±SD)[b]	2.4 (±1.3)	2.4 (±1.3)	1.0000	2.4 (±1.3)	2.5 (±1.3)	0.3297	2.4 (±1.3)	2.5 (±1.3)	0.3174
Charlson Comorbidity Index, Mean(±SD)[d]	1.2 (±0.5)	1.2 (±0.5)	0.3679	1.2 (±0.5)	1.2 (±0.5)	0.5508	1.2 (±0.5)	1.2 (±0.5)	0.7994
RA-related health care resource utilization,[d-f] Median Mean(±SD)	3.0 4.1(±3.3)	3.0 4.1(±2.7)	0.5188	3.0 4.1(±3.3)	4.0 4.5(±2.8)	0.0313	3.0 4.1(±2.7)	4.0 4.5(±2.8)	0.0430
Non-RA related health care resource utilization,[d-f] Median Mean(±SD)	0.0 0.8(±1.3)	0.0 0.8(±1.2)	0.9650	0.0 0.8(±1.3)	0.0 0.9(±1.3)	0.1679	0.0 0.8(±1.2)	0.0 0.9(±1.3)	0.2472
Pre-index total health care resource utilization cost ($),[d,g] Median Mean(±SD)	1477 2097 (±1955)	1376 1988 (±1890)	0.7230	1477 2097 (±1955)	1651 2210 (±2152)	0.2383	1376 1988 (±1890)	1651 2210 (±2152)	0.0747

ADA = adalimumab; **DMARD** = disease modifying anti-rheumatic drugs; **ETN** = etanercept; **IFX** = infliximab; **RA =** rheumatoid arthritis; **TNF** = tumor necrosis factor

[a] Caliper set at 0.05

[b] For the matched analysis, differences between matched pairs were evaluated using paired T test

[c] For the matched analysis, differences between matched pairs were evaluated using the McNemar's test

[d] For the matched analysis, differences between matched pairs were evaluated using the signed rank test

[e] Visits associated with ICD-9-CM code 714.0x

[f] Ambulatory and inpatient visits

[g] Total direct medical and medication costs in the pre-index period, adjusted to 2011 US dollars;

†Bonferroni correction was used to control for type 1 error due to multiple comparisons with a prior p value set at 0.0167 (0.05/n , where n=3 which is the number of comparisons)
Source of macros: Rassen JA, Doherty M, Huang W, Schneeweiss S. Pharmacoepidemiology Toolbox. Boston, MA. http://www.hdpharmacoepi.org
Article reference: Rassen JA, Shelat AA, Franklin JM, Glynn RJ, Solomon DH, Schneeweiss S. Matching by propensity score in cohort studies with three treatment groups. *Epidemiology (Cambridge, Mass.).* 2013; 24(3):401-409.

4.4.1.3 Demographic and Clinical Characteristics of the Matched Sample

Matched subjects' demographic and clinical characteristics at baseline are presented in Table 4.5. Subjects were within the ages of 18 and 63 years inclusive. The mean age (±SD) was 48.9(±9.8) years, and the majority of the subjects were between 45 and 63 years (69.2%), Hispanic (53.7%) and female (88.0%). Over 70 percent (72.1%) of the sample used DMARDs in the pre-index period, with methotrexate (58.2%) being the most commonly prescribed DMARD therapy. Over 40 percent (44.0%) of the matched sample received glucocorticoids in the pre-index period. Over one-third received prednisone (36.6%). The remaining oral glucocorticoids were used by approximately 6 percent (5.9%) of the sample. Approximately 7 percent (7.3%) of the sample received injection glucocorticoids in the pre-index period. Over 70 percent (77.9%) of the sample used pain medications with narcotic analgesics (53.2%) being the most commonly prescribed. The majority of the sample were on at least 2 non-study RA-related medications (75.9%) and had a Charlson score ranging from 1-2 (97.1%) in the pre-index period. The mean of total non_study RA-related medications used and mean Charlson score were 2.4 (±1.3) and 1.2 (±0.5) respectively. Of the 4,149 total pre-index clinical visits, the majority (84.1%) were for RA-related ambulatory and inpatient care. The mean visits for RA-related and non RA-related ambulatory and inpatient care were 4.2(±2.9) and

0.8(±1.2) visits, respectively. The mean pre-index healthcare utilization cost was $2,098(±2,001).

Table 4.5: Baseline Summary Statistics for Matched Sample

Demographic & Clinical Characteristics	N	%
Age groups		
18-34	77	9.4
35-44	176	21.4
45-54	292	35.5
55-63	277	33.7
Total	**822**	**100.0**
Race/ethnicity		
Caucasians	226	27.5
African Americans	84	10.2
Hispanics	441	53.7
Others	71	8.6
Total	**822**	**100.0**
Gender		
Females	723	88.0
Males	99	12.0
Total	**822**	**100.0**
Index TNF inhibitor		
Etanercept	274	33.3
Adalimumab	274	33.3
Infliximab	274	33.3
Total	**822**	**99.9**[a]
Pre-index DMARDs utilization		
Yes	593	72.1
No	229	27.9
Total	**822**	**100.0**
Types of DMARDs utilization[b]		
Methotrexate	478	58.2
Leflunomide	75	9.1
Sulfasalazine	79	9.6
Hydroxychloroquine	145	17.6
Other DMARDs[c]	6	0.7
Pre-index glucocorticoid utilization		
Yes	362	44.0
No	460	56.0
Total	**822**	**100.0**

Table 4.5: Baseline Summary Statistics for Matched Sample Contd.

Demographic & Clinical Characteristics	N	%
Types of Oral glucocorticoids[b]		
Dexamethasone	1	0.1
Hydrocortisone	0	0.0
Methylprednisolone	48	5.8
Prednisolone	0	0.0
Prednisone	301	36.6
Cortisone	0	0.0
Types of glucocorticoid injections[b]		
Corticotropin	0	0.0
Dexamethasone	7	0.9
Hydrocortisone	0	0.0
Methylprednisolone	25	3.0
Prednisolone	0	0.0
Triamcinolone	28	3.4
Pain medications		
Yes	640	77.9
No	182	22.1
Total	**822**	**100.0**
Types of pain medications[b]		
NSAIDs	212	25.8
COXIBs	161	19.6
Narcotic analgesics	437	53.2
Tramadol	138	16.8
Total number of non-study RA-related medications		
0	41	5.0
1	157	19.1
2	242	29.4
3	218	26.5
≥4	164	20.0
Total	**822**	**100.0**
Charlson Comorbidity Index score		
1-2	798	97.1
≥3	24	2.9
Total	**822**	**100.0**
Health care resource utilization (# of visits)		
RA-related ambulatory and Inpatient care[d]	3,489	84.1
Non-RA related ambulatory and Inpatient care	660	15.9
Total visits	**4,149**	**100.0**

COXIB = cox-2 inhibitors; **DMARD** = disease modifying anti-rheumatic drugs; **NSAIDs** = non-steroidal anti-inflammatory drugs; **RA** = Rheumatoid arthritis; **TNF** = tumor necrosis factor

[a] Does not add up to 100.0% due to rounding error

[b] Groups are not mutually exclusive as subjects may have used more than one medication

[c] Examples of other DMARDs: azathioprine, chloroquine, cyclosphosphamide, cyclosporine, minocycline, and sodium aurothiomalate (gold);

[d] Visits associated with ICD-9-CM code 714.0x

4.4.2 Objective 2: Description of Medication Dosing Patterns

Objective 2 was to describe medication dosing patterns (initial dose and dose category changes) among ETN, ADA and IFX users. For ADA and ETN, doses were calculated in terms of weekly doses by converting the days supply field into weeks and the quantity dispensed into milligrams. However, for IFX, dosing patterns could not be assessed due to lack of unit of service information needed to verify the quantity of vials administered (per Healthcare Common Procedure Coding System J-codes).

The average starting weekly dose for patients on ETN was 50.1mg (±6.2). Ninety-six percent of patients on ETN had a starting weekly dose equivalent to the manufacturer's recommended weekly dose of 50mg. A small percentage of patients (1.8%) on ETN had starting doses greater than 50mg. At the end of the 12-month follow-up period, the average weekly dose for patients on ETN was 52.1mg (±15.4) with 96 percent of patients receiving the manufacturer's recommended weekly dose of 50mg. A small percentage of patients (3.3%) received doses greater than 50mg weekly at the end of the follow-up period. However, this was an 80 percent increase over the proportion of patients who started at doses greater than 50mg weekly. The average starting weekly dose for patients on ADA was 22.6mg (±7.8). A total of 87.6 percent of patients on ADA had a starting weekly dose of 20mg equivalent to the manufacturer's recommended dose of 4omg every other week. Twelve percent of patients on ADA had starting doses greater than 20mg. At the end of the 12-month

follow-up period, the average weekly dose for patients on ADA was 24.5mg (±9.7) with 79.6 percent of patients receiving a weekly dose of 20mg equivalent to the manufacturer's recommended dose of 4omg every other week. Approximately 20.4 percent of patients on ADA had doses greater than 20mg at the end of the follow-up period. This was a 70 percent increase over the proportion of patients who started at doses greater than 20mg weekly. Table 4.6 shows the descriptive statistics relating to the starting and ending weekly doses of patients on ETN and ADA.

Table 4.6: Medication Starting Doses by Type of TNF Inhibitor (N = 548)

	Starting Weekly Doses		Ending Weekly Doses	
Doses in Mg	**N**	**%**	**N**	**%**
Etanercept (ETN)				
25	6	2.2	2	0.7
50	263	96.0	263	96.0
75	3	1.1	3	1.1
100	2	0.7	3	1.1
150	0	0.0	1	0.4
200	0	0.0	2	0.7
Total	**274**	**100.0**	**274**	**100.0**
≤ 50	269	98.2	265	96.7
>50	5	1.8	9	3.3
Total	**274**	**100.0**	**274**	**100.0**
Adalimumab (ADA)				
10	1	0.4	0	0.0
20	240	87.6	218	79.6
30	3	1.1	5	1.8
40	25	9.1	44	16.1
60	5	1.8	6	2.2
80	0	0.0	1	0.4
Total	**274**	**100.0**	**274**	**100.0**
≤20	241	88.0	218	79.6
>20	33	12.0	56	20.4
Total	**274**	**100.0**	**274**	**100.0**
Infliximab (IFX)*				

TNF= tumor necrosis factor

*IFX dose pattern could not be assessed

4.4.3 Objective 3: Dose Escalation

Objective 3 was to determine if the likelihood of having a dose escalation among ETN users differs significantly compared to ADA and IFX users while controlling for covariates. A patient was classified as having a dose escalation if the average weekly dose for all the subsequent prescriptions for the index TNF therapy exceeded the weekly dose of their index prescription by 150 percent. In addition, the average weekly dose for all subsequent prescriptions must be greater than 50mg for ETN or 20mg for ADA. For IFX, since the unit of service information was not available in the medical claims to determine the quantity of vials administered, cost information associated with the Healthcare Common Procedure Coding System J-code 1745 (J-code for infliximab) was used as a proxy. All J-code 1745 costs were adjusted to 2011 US dollars using the medical consumer price index from the U.S. Bureau of Labor Statistics current data. Then average of all J-code 1745 subsequent costs was compared to the index J-code 1745 cost and if the average cost exceeded the index cost by 150 percent the patient was assumed to have a dose escalation. Overall 6.8 percent of the study sample[g] had a dose escalation. A total of 2.2 percent of patients on ETN had a dose escalation while 8.4 percent and 9.9 percent on IFX and ADA respectively, had a dose escalation. Based on unadjusted pair-wise comparison (McNemar's test), the proportion of patients who had a dose escalation was

[g] See Appendix A for detailed result

significantly lower for patients on ETN compared to patients on ADA (S = 14.2258; df = 1; p < 0.0001) or IFX (S = 10.7037; df = 1; p = 0.0015).

4.4.3.1 Dose Escalation (Conditional Logistic Regression Model)

To determine if the likelihood of having a dose escalation among ETN users differs significantly compared to ADA and IFX users while controlling for covariates, a conditional logistic regression was conducted. The dependent variable was dose escalation status and the probability modeled was that of having a dose escalation. The independent variable was type of TNF inhibitor (ADA, ETN and IFX) therapy and ETN was selected as the reference therapy. The study covariates introduced into the model were age, gender, race/ethnicity, pre-index use of other RA-related medications (DMARDs, glucocorticoids and pain medications), total number of non-study RA-related medications used at index, Charlson Comorbidity Index score, pre-index RA and non-RA related visits, pre-index healthcare utilization cost. Multicollinearity among the covariate variables (i.e., continuous variables) was assessed using a multiple linear regression model. Tolerance coefficients for the predictor variables ranged from 0.885 (pre-index RA related visits) to 0.954 (Charlson Comorbidity Index score). The variance inflation factor (VIF), which is the inverse of tolerance, ranged from 1.048 (Charlson Comorbidity Index score) to 1.130 (pre-index RA related visits). Tolerance coefficient values greater than 0.1 and VIF

values less than 10 is an indication that there was no multicollinearity amongst the covariates.

Table 4.7 shows the detailed results of the conditional logistic regression model comparing the likelihood of having a dose escalation by type of TNF inhibitor therapy while controlling for covariates. The results of the model fit with or without the model parameters (explanatory) variables was inconclusive with the likelihood ratio test ($p = 0.0215$) indicating a rejection of the null hypothesis that all slope parameters are equal to zero while the Wald test (0.2735) and the score test ($p = 0.0908$) result failed to reject the null. A rejection of the null indicates that removing the explanatory variables will reduce the fit of the model while failing to reject the null indicates that removing the explanatory variables will not impact the model fit. Since leaving all the explanatory variables in the model will not impact the model fit, they were retained. Compared to patients on ETN, the odds of having a dose escalation were ≈ 5 [Odds Ratio (OR) = 4.605 [95% CI = 1.605-12.677], $p = 0.0031$] and ≈ 8 [Odds Ratio (OR) = 7.520, [95% CI = 2.461-22.983], $p = 0.0004$] times higher for IFX and ADA patients, respectively, while controlling for other variables in the model. None of the covariates was significantly related to the dependent variable.

H_1: *The **likelihood of having a dose escalation** is significantly lower among RA patients on ETN compared to patients on ADA and IFX while controlling for covariates.*

(Not Rejected)

Table 4.7: Conditional Logistic Regression Analysis Comparing the Likelihood of Dose Escalation among TNF Inhibitors (N = 822)

	Odds Ratio	95% CI		Wald X^2	p-value
Medication Type†					
Adalimumab	7.520	2.461	22.983	12.5286	0.0004*
Infliximab	4.605	1.673	12.677	8.7343	0.0031*
Covariates					
Age	1.016	0.964	1.071	0.3589	0.5491
Male†	1.001	0.216	4.635	0.0000	0.9994
Non-Whites†	0.605	0.124	2.939	0.3883	0.5332
Pre-index DMARD non-use	0.181	0.009	3.507	1.2777	0.2583
Pre-index pain medications non-use	0.733	0.009	61.360	0.0190	0.8905
Pre-index glucocorticoids non-use	0.191	0.006	5.963	0.8890	0.3458
Pre-index RA related visits	1.223	0.499	3.000	0.1934	0.6601
Pre-index non-RA related visits	1.526	0.380	6.128	0.3546	0.5515
Total number of non-study RA-related medications	0.347	0.079	1.525	1.9631	0.1612
Pre-index total utilization cost	1.000	0.999	1.001	0.0501	0.8229
Charlson Comorbidity Index	1.599	0.529	4.837	0.6907	0.4059

RA = rheumatoid arthritis; **TNF** = tumor necrosis factor
†Reference categories: Etanercept, females, whites, DMARD users, glucocorticoid users and pain medication users. Note: Race was dichotomized into two groups (Whites and others) due to small cell sizes.
Model Fit Statistics: likelihood ratio = 25.2373, df = 13, p = 0.0215; Score = 20.1803, df = 13, p = 0.0908; Wald = 15.5630, df = 13, p = 0.2735
*significant at $p < 0.05$

4.4.4 Objective 4: Medication Use Patterns

Objecive 4 was to determine if medication use patterns (adherence, persistence, discontinuation, and switching) among ETN users differ significantly compared to ADA and IFX users while controlling for covariates. Adherence was assessed both continuously and dichotomously.

4.4.4.1 Medication Adherence

To determine if medication adherence (continuous MPR) to ETN differs significantly compared to ADA and IFX, MPR was computed as a proxy for adherence for all the study subjects. For IFX users, the medical claims file lacked information on days supply but it contained information on date of service. Days supply information was computed based on the time interval expected between subsequent drug infusions as specified by the manufacturer and adjustments were made to avoid overlap between subsequent infusions. Table 4.8 shows the manufacturer recommended infusion intervals for IFX.

Table 4.8 Expected Number of Infusions in 1 year for Infliximab (Remicade®)

Infusion #	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Week	0	2	6	14	22	30	38	46	54
Day	0	14	42	98	154	210	266	322	378

Since the study subjects were biologic-naïve (no biologic in the 6-month pre-index period), their first date of service associated with the J-code 1745 was assumed to be day 0 and the week was assumed to be week 0 with the infusion as their first infusion for IFX

4.4.4.1a Medication Adherence (Unadjusted Analysis- Paired T-Test)

Overall mean adherence (±SD) to the study TNF inhibitor therapies was 52.5 percent (±29.5). Results of unadjusted pair-wise comparison)[h] showed that mean MPR (±SD) was significantly lower for ETN users (48.8%±28.7) compared to IFX users (55.7%±31.9; p = 0.0045) but not significantly different compared to ADA users (53.0%±27.3; p = 0.0779).

4.4.4.1b Medication Adherence (GLM-GEE Model)

To determine if medication adherence to ETN differs significantly compared to ADA and IFX while controlling for covariates, a generalized linear model (GLM), which was estimated using a generalized estimating equation (GEE), was used. The dependent variable was TNF inhibitor medication adherence (continuous MPR) and the independent variable was type of TNF inhibitor therapy. The same covariates used in the conditional logistic regression for dose escalation were introduced in the GLM. For the GLM, a gamma distribution and a log link was specified as the normality assumption was rejected based on the significance of the KS test ($p < 0.01$). Table 4.9 shows the detailed results of the GLM model estimated using a GEE. The GEE parameter estimate results showed that compared to patients on ETN, patients on IFX were significantly (p =c 0.0171) more adherent to their TNF inhibitor therapy

[h] See Appendix B for detailed result

while controlling for other variables in the model. There was no significant difference in adherence to TNF inhibitor therapy between ETN and ADA users while controlling for other variables in the model. Regarding the covariates, age (p = 0.0265), gender (p = 0.0026), pre-index RA-related visits (p = 0.0038) and Charlson Comorbidity Index score-CCI (p = 0.0232) were statistically significant related to TNF inhibitor medication adherence while controlling for other variables in the model. Older age and increase in pre-index RA-related visits were significantly associated with an increase in TNF inhibitor therapy medication adherence. An increase in the CCI score was significantly associated with a decrease in TNF inhibitor therapy medication adherence. Compared to female subjects, male subjects were significantly (p = 0.0026) more adherent to their TNF inhibitor therapy while controlling for other variables in the model.

H_{o2A}: *There is no significant difference in* ***medication adherence*** *to ETN compared to ADA and IFX while controlling for covariates.* **(Rejected)**

Table 4.9: Generalized Linear Regression Analysis Comparing Medication Adherence among TNF Inhibitors (N = 822)

	Estimate	95% CI		Z	p-value
Medication Type†					
Adalimumab	0.0744	-0.0180	0.1669	1.58	0.1144
Infliximab	0.1109	0.0198	0.2020	2.39	0.0171*
Covariates					
Age	0.0051	0.0006	0.0095	2.22	0.0265*
Male†	0.1494	0.0520	0.2467	3.01	0.0026*
Non-Whites†	-0.0664	-0.1519	0.0191	-1.52	0.1277
Pre-index DMARD non-use	-0.1195	-0.2396	0.0007	-1.95	0.0513
Pre-index pain medications non-use	0.0060	-0.1088	0.1208	0.10	0.9183
Pre-index glucocorticoids non-use	-0.0717	-0.1653	0.0220	-1.50	0.1335
Pre-index RA related visits	0.0187	0.0060	0.0314	2.89	0.0038*
Pre-index non-RA related visits	-0.0198	-0.0561	0.0165	-1.07	0.2845
Total number of non-study RA-related medications	-0.0169	-0.0654	0.0316	-0.68	0.4938
Pre-index total utilization cost	0.0000	-0.0000	0.0000	0.52	0.6002
Charlson Comorbidity Index	-0.0989	-0.1843	-0.0135	-2.27	0.0232*

RA = rheumatoid arthritis; **TNF** = tumor necrosis factor
†Reference categories: Etanercept, females, whites, DMARD users, glucocorticoid users and pain medication users. Note: Race was dichotomized into two groups (Whites and others) due to small cell sizes.
*significant at $p < 0.05$

4.4.4.1c Medication Adherence (Unadjusted Analysis-McNemar's Test)

Overall, 23.5 percent of the study sample were adherent (MPR ≥80%). A total of 21.2 percent of patients on ETN were adherent while 32.9 percent and 16.4 percent on IFX and ADA respectively, were adherent.[i] Based on unadjusted pair-wise comparison, the proportion of adherent patients was significantly lower for patients on ETN compared to patients on IFX ($S = 18.5780$; $df = 1$; $p < 0.0001$) but not significantly different compared to ADA ($S = 2.1392$; $df = 1$; $p = 0.1766$).

4.4.4.1d Medication Adherence (Conditional Logistic Regression Model)

To determine if the likelihood of adhering (dichotomous MPR) to ETN differs significantly compared to ADA and IFX while controlling for covariates, a conditional logistic regression was conducted. The dependent variable was medication adherence status based on patients' adherence (MPR values). The probability modeled was that of being adherent (MPR ≥ 80%). The independent variable was type of TNF inhibitor (ADA, ETN and IFX) therapy and ETN was selected as the reference therapy. The same covariates used in the prior analysis were used in the conditional logistic regression model. Table 4.10 shows the detailed results of the conditional logistic regression model comparing the likelihood of being adherent by type of TNF inhibitor therapy while controlling for covariates. The results of the model fit with or

[i] See Appendix A for detailed result

without the model parameters (explanatory) variables was significant ($p < 0.05$), indicating a rejection of the null hypothesis that all slope parameters are equal to zero. Results of maximum likelihood estimates showed that compared to patients on ETN, the odds of being adherent to IFX was ≈ 2 times higher [Odds Ratio (OR) = 2.437, [95% CI = 1.592-3.731], $p < 0.0001$] while controlling for other variables in the model. There was no significant difference in the likelihood of being adherent to TNF inhibitor therapy between ETN and ADA users while controlling for other variables in the model. None of the covariates was significantly related with the dependent variable. Results were robust when sensitivity analyses were conducted at 70 and 90 percent cut-off values for MPR.

H_{o2B}: *The **likelihood of being adherent** (MPR≥0.80 or 80%) to ETN does not differ significantly compared to ADA and IFX while controlling for covariates.* **(Rejected)**

Table 4.10: Conditional Logistic Regression Analysis Comparing the Likelihood of being Adherent among TNF Inhibitors (N = 822)

	Odds Ratio	95% CI		Wald X^2	p-value
Medication Type†					
Adalimumab	1.328	0.853	2.066	1.5800	0.2088
Infliximab	2.437	1.592	3.731	16.8140	<.0001*
Covariates					
Age	1.000	0.973	1.028	0.0001	0.9931
Male†	1.431	0.679	3.012	0.8886	0.3458
Non-Whites†	1.156	0.530	2.522	0.1329	0.7155
Pre-index DMARD non-use	0.897	0.208	3.861	0.0215	0.8835
Pre-index pain medications non-use	1.026	0.105	10.053	0.0005	0.9826
Pre-index glucocorticoids non-use	0.936	0.155	5.643	0.0053	0.9421
Pre-index RA related visits	0.981	0.637	1.511	0.0076	0.9305
Pre-index non-RA related visits	0.847	0.424	1.694	0.2204	0.6387
Total number of non-study RA-related medications	1.015	0.502	2.053	0.0017	0.9667
Pre-index total utilization cost	1.000	1.000	1.000	0.8375	0.3601
Charlson Comorbidity Index	0.690	0.337	1.410	1.0357	0.3088

RA = rheumatoid arthritis; **TNF** = tumor necrosis factor

†Reference categories: Etanercept, females, whites, DMARD users, glucocorticoid users and pain medication users. Note: Race was dichotomized into two groups (Whites and others) due to small cell sizes.

Model Fit Statistics: likelihood ratio = 28.7376, df = 13, p = 0.0071; Score = 28.3537, df = 13, p = 0.0081; Wald = 25.7999, df = 13, p = 0.0181

*significant at $p < 0.05$

4.4.4.2a Medication Persistence (Unadjusted Analysis- Paired T-Test)

To determine if medication persistence to ETN differs significantly compared to ADA and IFX, a gap period of 60 days was specified with sensitivity analysis conducted using 30-, 45-, 90- and 120-day gap periods. Overall, based on a 60-day gap period, mean persistence (±SD) to the study TNF inhibitor therapies was 203.9 days (±132.8). Results of unadjusted pair-wise comparison[j] showed that based on a 60-day gap, mean persistence (±SD) for ETN users (196.7±134.0 days) was not significantly different compared to IFX (215.6±133.5 days; p = 0.0730) and ADA users (199.4±130.5 days; p = 0.8132). Results of the sensitivity analysis were robust at 30-, 45-, 90- and 120-day gap periods.

4.4.4.2b Medication Persistence (GLM-GEE Model)

To determine if medication persistence to ETN differs significantly compared to ADA and IFX while controlling for covariates, a generalized linear model (GLM), which was estimated using a generalized estimating equation (GEE), was used. The dependent variable was TNF inhibitor medication persistence and the independent variable was type of TNF inhibitor therapy. The same covariates used in the previous analyses were used in the GLM. For the GLM, a gamma distribution and a log link was specified as the normality assumption was rejected based on the significance of the

[j] See Appendix B for detailed result

KS test ($p < 0.01$). Table 4.11 shows the detailed results of the GLM model estimated using a GEE. The GEE parameter estimate results showed that compared to patients on ETN, there was no significant difference in ADA or IFX users' persistence to TNF inhibitor therapy while controlling for other variables in the model.

Regarding the covariates, age ($p = 0.0206$), pre-index RA-related visit ($p = 0.0009$), gender ($p = 0.0043$) and Charlson comorbidity index (CCI) score ($p = 0.0291$) were significantly related to persistence to TNF inhibitor therapy while controlling for other variables in the model. Older age and increase in pre-index RA-related visits were associated with increase in persistence to TNF inhibitor therapy. An increase in the CCI score was associated with a significant decrease in persistence on TNF inhibitor therapy. Compared to female subjects, male subjects were significantly more persistent to their TNF inhibitor therapy while controlling for other variables in the model. Results were robust when sensitivity analyses were conducted using 90- and 120-day gap periods. Only pre-index RA-related visit was significantly related to persistence when a 30-day gap period was specified. With the 45-day gap period, only pre-index RA-related visit and gender were significantly related to persistence with male subjects being more persistent compared to female subjects.

H_{o3}: *There is no significant difference in* ***medication persistence*** *to ETN compared to ADA and IFX while controlling for covariates.* (**Not Rejected**)

Table 4.11: Generalized Linear Regression Analysis Comparing Medication Persistence among TNF Inhibitors (N=822)

	Estimate	95% CI		Z	p-value
Medication Type†					
Adalimumab	0.0040	-0.1075	0.1154	0.07	0.9443
Infliximab	0.0721	-0.0298	0.1739	1.39	0.1656
Covariates					
Age	0.0061	0.0009	0.0113	2.32	0.0206*
Male†	0.1715	0.0538	0.2892	2.86	0.0043*
Non-Whites†	-0.0564	-0.1577	0.0449	-1.09	0.2748
Pre-index DMARD non-use	-0.0871	-0.2159	0.0416	-1.33	0.1847
Pre-index pain medications non-use	-0.0043	-0.1345	0.1259	-0.06	0.9482
Pre-index glucocorticoids non-use	-0.0601	-0.1700	0.0499	-1.07	0.2845
Pre-index RA related visits	0.0203	0.0050	0.0356	2.61	0.0092*
Pre-index non-RA related visits	-0.0199	-0.0600	0.0203	-0.97	0.3320
Total number of non-study RA-related medications	0.0009	-0.0522	0.0539	0.03	0.9741
Pre-index total utilization cost	0.0000	-0.0000	0.0000	0.97	0.3298
Charlson Comorbidity Index	-0.1094	-0.2077	-0.0111	-2.18	0.0291*

RA= Rheumatoid arthritis; **TNF**= tumor necrosis factor

†Reference categories: Etanercept, females, whites, DMARD users, glucocorticoid users and pain medication users. Note: Race was dichotomized into two groups (Whites and others) due to small cell sizes.

*significant at $p < 0.05$

4.4.4.3 Medication Discontinuation

Discontinuation was defined as the presence of greater than a 60-day gap period between consecutive prescriptions or a switch from an index TNF inhibitor therapy. Sensitivity analyses were conducted using 30-, 45-, 90- and 120-day gap periods. Medication discontinuation was assessed dichotomously using conditional logistic regression and continuously using Cox-proportional hazard regression.

4.4.4.3a Medication Discontinuation (Unadjusted Analysis- McNemar's Test)

Overall 64.8 percent of the study sample discontinued their index TNF inhibitor therapy. Approximately 67 percent (66.8%), 62.0 percent and 65.7 percent of patients on ETN, IFX and ADA respectively, discontinued their therapy.[k] Based on unadjusted pair-wise comparison, the proportion of patients on ETN who discontinued index TNF inhibitor therapy was not significantly different compared to those on IFX (S = 1.4956; df = 1; p = 0.2589) and ADA (S = 0.0720; df = 1; p = 0.8581). Results of sensitivity analysis were robust at 30-, 45-, 90- and 120-day gap periods.

4.4.4.3b Medication Discontinuation (Conditional Logistic Regression Model)

To determine if the likelihood of discontinuing ETN differs significantly compared to ADA and IFX while controlling for covariates, a conditional logistic

[k] See Appendix A for detailed result

regression was conducted. The dependent variable was medication discontinuation status. The probability modeled was discontinuation of the index TNF inhibitor therapy. The independent variable was type of TNF inhibitor (ADA, ETN and IFX) therapy and ETN was selected as the reference therapy. The same covariates as used in prior analyses were used in the conditional logistic regression model.

Table 4.12 shows the detailed results of the conditional logistic regression model comparing the likelihood of discontinuing index TNF inhibitor therapy by type of TNF inhibitor therapy while controlling for covariates. The results of the model fit with or without the model parameters (explanatory) variables was not significant ($p>0.05$) indicating a failure to reject the null hypothesis that all slope parameters are equal to zero. Results of maximum likelihood estimates showed that compared to patients on ETN, there was no significant difference in ADA or IFX users likelihood to discontinue index TNF inhibitor therapy while controlling for other variables in the model. Regarding the covariates, only CCI was significantly related to the likelihood of discontinuing index TNF inhibitor therapy and for every unit increase in CCI score, the odds to discontinue index TNF inhibitor therapy were ≈2 times higher while controlling for other variables in the model [Odds Ratio (OR) = 1.931, [95% CI = 1.028-3.629], p = 0.0409]. Results were robust when sensitivity analyses were conducted using 45, 90- and 120-day gap periods with none of the covariates significantly related to the dependent variable. When a 30-day gap period was specified, the odds to discontinue index TNF inhibitor therapy was 36.2 percent lower for IFX patients compared to ETN patients while controlling for other variables in the model [Odds Ratio (OR) = 0.638, [95% CI = 0.420-0.970], p = 0.0356]. There was no

significant difference in the likelihood to discontinue index TNF inhibitor therapy between ETN and ADA users while controlling for other variables in the model. None of the covariates was significantly related to the dependent variable.

H_{o4}: *The likelihood of discontinuing ETN does not differ significantly compared to ADA and IFX while controlling for covariates*. (**Not Rejected**)

Table 4.12: Conditional Logistic Regression Analysis Comparing the Likelihood of Discontinuing Index TNF Inhibitor Therapy (N = 822)

	Odds Ratio	95% CI		Wald X^2	p-value
Medication Type†					
Adalimumab	0.957	0.660	1.387	0.0543	0.8158
Infliximab	0.854	0.595	1.228	0.7226	0.3953
Covariates					
Age	0.998	0.975	1.021	0.0313	0.8597
Male†	0.793	0.410	1.535	0.4728	0.4917
Non-Whites†	0.709	0.344	1.463	0.8645	0.3525
Pre-index DMARD non-use	1.325	0.360	4.875	0.1791	0.6722
Pre-index pain medications non-use	3.894	0.494	30.718	1.6642	0.1970
Pre-index glucocorticoids non-use	1.342	0.267	6.751	0.1270	0.7215
Pre-index RA related visits	1.276	0.857	1.900	1.4360	0.2308
Pre-index non-RA related visits	1.815	0.961	3.427	3.3730	0.0663
Total number of non-study RA-related medications	0.545	0.285	1.041	3.3839	0.0658
Pre-index total utilization cost	1.000	0.999	1.000	4.7213	0.0298
Charlson Comorbidity Index	1.931	1.028	3.629	4.1803	0.0409*

TNF = tumor necrosis factor

†Reference categories: Etanercept, females, whites, DMARD users, glucocorticoid users and pain medication users. Note: Race was dichotomized into two groups (Whites and others) due to small cell sizes.

Model Fit Statistics: likelihood ratio = 17.0324, df = 13, p = 0.1978; Score = 16.8305, df = 13, p = 0.2072; Wald = 15.7274, df = 13, p = 0.2642

*significant at $p < 0.05$

4.4.4.3c Medication Discontinuation (Cox-Proportional Hazards Regression Model)

To determine if duration of medication use (i.e., persistence) prior to discontinuation of ETN differs significantly compared to ADA and IFX while controlling for covariates, a Cox proportional hazards regression model was used. An important step in utilizing a Cox proportional hazards regression model lies in ensuring that appropriate covariates and censoring mechanisms are selected and that the assumption of proportionality of hazards is not violated.[210,211] The proportionality of hazards assumption suggests that the shapes of the survival functions are similar for all the treatment groups and that the effect of each covariate is independent of time. A violation of this assumption implies that the coefficient of the variable being estimated by the model is an average effect of the variable over the range of times observed in the data.[210] A commonly used approach in testing for the assumption lies in introducing an interaction of each study covariate and the natural logarithm of time (survival time) into the model and check for the significance of each interaction term.[210] Other approaches to test for the proportionality assumption involve visually checking the lines (shapes) of the survival functions for each treatment level to see if they are parallel or plotting scaled Schoenfield residuals against time to determine if a relationship exists between the covariate and time. [211]

Results of the proportionality assumption test are presented in Table 4.13. The exposure variable was independent of time since it was defined at the point of entry into the cohort. Patients were censored if they did not discontinue index TNF therapy within the follow-up period. Discontinuation was defined as presence of greater than a 60-day gap period between two consecutive prescriptions or a switch from an index TNF inhibitor therapy. The survival time was the duration of time of continuous therapy on index TNF inhibitor therapy without switching or having greater than a 60-day gap period between consecutive prescriptions.

Table 4.13: Test for Proportionality of Hazards for Covariates

Covariates‡	Wald Chi-Square	Hazard Ratio	95% Hazard Ratio CI		P-Value
Age	6.5029	0.848	0.747	0.963	0.0108*
Male†	1.5757	0.109	0.003	3.470	0.2094
Non-Whites†	2.8815	29.864	0.591	1507.956	0.0896
Pre-index DMARD non-use	6.3923	0.000	0.000	0.131	0.0115*
Pre-index pain medications non-use	5.7331	0.000	0.000	0.105	0.0166*
Pre-index glucocorticoids non-use	4.1045	0.000	0.000	0.693	0.0428*
Pre-index RA related visits	4.2765	3.220	1.063	9.756	0.0386*
Pre-index non-RA related visits	4.7194	13.678	1.292	144.856	0.0298*
Total number of non-study RA-related medications	0.0713	0.673	0.037	12.317	0.7895
Pre-index total utilization cost	0.0546	1.000	0.999	1.001	0.8152
Charlson Comorbidity Index	6.5341	0.000	0.000	0.129	0.0106*

‡Interaction with the natural logarithm of survival time have been tested for each variable.
†Reference categories: Etanercept, females, whites, DMARD users, glucocorticoid users and pain medication users. Note: Race was dichotomized into two groups (Whites and others) due to small cell sizes.
Model Fit Statistics: likelihood ratio = 799.6396, df = 24, p < 0.0001; Score = 443.6858, df = 24, p < 0.0001; Wald = 14.9826, df = 24, p = 0.9213; Proportionality test X^2 *= 11.8434, df = 11, p = 0.3755*
*significant at $p < 0.05$

The proportionality assumption was not met for age, pre-index use of other RA-related medications (DMARDs, glucocorticoids and pain medications), Charlson Comorbidity Index score, pre-index RA and non-RA related visits. None of these interactions were expected because all of these variables were defined at index. Despite the interactions observed with each of these variables and survival time, they were all retained in their original forms during the Cox regression analysis since an interpretation of significant effects in terms of "average effects" is acceptable when variable effects are independent of time.[210] However, in sensitivity analysis, interaction terms of age, pre-index use of other RA-related medications (DMARDs, glucocorticoids and pain medications), Charlson Comorbidity Index score, pre-index RA and non-RA related visits and natural logarithm of survival time were entered into the model to estimate the effect of exposure. Overall, mean survival time (±SD) on the study TNF inhibitor therapies prior to discontinuation was 120.4 days (±84.9).[l] The mean survival times (±SD) prior to discontinuation were 116.5±85.5 days, 127.5±90.1 days and 117.7±78.9 days, respectively, for ETN, IFX and ADA users.

Table 4.14 shows the results of the Cox-proportional hazards regression model comparing the duration of medication use (i.e., persistence) prior to discontinuation of index therapy among ETN, ADA and IFX users while controlling for

[l] See Appendix B for detailed result

covariates. The results of the model fit with or without the model parameters (explanatory) variables was significant ($p < 0.05$) indicating a rejection of the null hypothesis that all slope parameters are equal to zero. Results of maximum likelihood estimates showed that there was no significant difference in the duration of medication use prior to discontinuation (survival time) when ETN users were compared to either ADA or IFX users while controlling for other variables in the model. None of the covariates was significantly related with the dependent variable. For the sensitivity analysis, when interaction terms of age, pre-index use of other RA-related medications (DMARDs, glucocorticoids and pain medications), Charlson Comorbidity Index score, pre-index RA and non-RA related visits and natural logarithm of survival time were entered into the model, the hazard ratios of ADA vs ETN [Hazard Ratio (HR) = 0.818 [95% CI = 0.566-1.183], p = 0.2865] and IFX vs ETN [Hazard Ratio (HR) = 0.776 [95% CI = 0.533-1.131], p = 0.1876] remained non-significant.

H_{o5}: *There is no significant difference in* ***duration of medication use*** *(i.e., persistence)* ***prior to discontinuation*** *of ETN compared to ADA and IFX users while controlling for covariates*. (**Not Rejected**)

Table 4.14: Cox Proportional Hazards Regression Model Comparing Survival Time Prior to Discontinuation of Index Therapy among TNF Inhibitors Users

	Hazard Ratio	95% Hazard Ratio CI		Wald X^2	p-value
Medication Type†					
Adalimumab	0.867	0.682	1.100	1.3812	0.2399
Infliximab	0.784	0.612	1.004	3.7278	0.0535
Covariates					
Age	0.991	0.977	1.006	1.4358	0.2308
Male†	0.674	0.435	1.045	3.1087	0.0779
Non-Whites†	1.048	0.644	1.705	0.0349	0.8518
Pre-index DMARD non-use	0.947	0.393	2.283	0.0145	0.9043
Pre-index pain medications non-use	0.994	0.251	3.932	0.0001	0.9934
Pre-index glucocorticoids non-use	0.802	0.272	2.364	0.1605	0.6887
Pre-index RA related visits	0.976	0.748	1.273	0.0319	0.8582
Pre-index non-RA related visits	1.001	0.659	1.521	0.0000	0.9953
Total number of non-study RA-related medications	0.822	0.534	1.264	0.7998	0.3712
Pre-index total utilization cost	1.000	1.000	1.000	0.3703	0.5429
Charlson Comorbidity Index	1.167	0.784	1.739	0.5789	0.4468

TNF = tumor necrosis factor

†Reference categories: Etanercept, females, whites, DMARD users, glucocorticoid users and pain medication users. Note: Race was dichotomized into two groups (Whites and others) due to small cell sizes.

Model Fit Statistics: likelihood ratio = 24.6730, df = 13, p = 0.0255; Score = 23.9996, df = 13, p = 0.0311; Wald = 23.1066, df = 13, p = 0.0404

*significant at $p < 0.05$

4.4.4.4a Medication Switching (Unadjusted Analysis- McNemar's Test)

Medication switching was defined as starting a RA biologic agent that is different from the index TNF inhibitor therapy. Overall 11.9 percent of the study sample switched from their index TNF inhibitor therapy. A total of 10.6 percent, 11.7 percent and 13.5 percent of patients on ETN, IFX and ADA respectively, switched from index TNF inhibitor therapy.[m] Based on unadjusted pair-wise comparison, the proportion of patients on ETN who switched from index TNF inhibitor therapy was not significantly different compared to those on IFX (S = 0.1636; df = 1; p = 0.7877) and ADA (S = 1.0323; df = 1; p = 0.3742).

4.4.4.4b Medication Switching (Conditional Logistic Regression Model)

To determine if the likelihood of switching from ETN to another biologic agent differs significantly compared to ADA and IFX while controlling for covariates, a conditional logistic regression was conducted. Medication switching was defined as starting an RA biologic agent that is different from the index TNF inhibitor therapy. The dependent variable was medication switch status. The probability modeled was switching from the index TNF inhibitor therapy. The independent variable was type of TNF inhibitor (ADA, ETN and IFX) therapy and ETN was selected as the reference

[m] See Appendix A for detailed result

therapy. The same covariates used in prior analysis were used in the conditional logistic regression model.

Table 4.15 shows the detailed results of the conditional logistic regression model comparing the likelihood of switching from index TNF inhibitor therapy by type of TNF inhibitor therapy while controlling for covariates. The results of the model fit with or without the model parameters (explanatory) variables were inconclusive with the likelihood ratio test ($p = 0.0150$) and score test ($p = 0.0468$) indicating a rejection of the null hypothesis that all slope parameters are equal to zero while the Wald test ($p = 0.0980$) result failed to reject the null. Since leaving all the explanatory variables in the model would not reduce the model fit, all the explanatory variables were retained in the model. Results of maximum likelihood estimates showed that compared to patients on ETN, there was no significant difference in ADA or IFX users' likelihood to switch from index TNF inhibitor therapy while controlling for other variables in the model. Regarding the covariates, age, race, pre-index pain medication use, pre-index RA-related visit, pre-index non RA-related visit and total number of non-study RA-related medications were significantly related to the likelihood to switch from index TNF inhibitor therapy while controlling for other variables in the model. For every year increase in age, the odds of switching from index TNF inhibitor therapy was 3.3 percent lower while controlling for other variables in the model [Odds Ratio (OR) = 0.967, [95% CI = 0.937-0.997], $p = 0.0341$]. For every unit increase in RA-related visits, the odds of switching from index TNF

inhibitor therapy was ≈ 3 times higher while controlling for other variables in the model [Odds Ratio (OR) = 2.661, [95% CI = 1.243-5.698], p = 0.0117]. For every unit increase in non RA-related visits, the odds of switching from index TNF inhibitor therapy was ≈ 5 times higher while controlling for other variables in the model [Odds Ratio (OR) = 4.689, [95% CI = 1.431-15.363], p = 0.0107]. For every unit increase in total number of non-study RA-related medications, the odds of switching from index TNF inhibitor therapy was 76.7 percent lower while controlling for other variables in the model [Odds Ratio (OR) = 0.233, [95% CI = 0.075-0.723], p = 0.0117]. Compared to White subjects, the odds of switching from index TNF inhibitor therapy was 82.1 percent lower for non-White subjects while controlling for other variables in the model [Odds Ratio (OR) = 0.179, [95% CI = 0.044-0.725], p = 0.0159]. Compared to those who used pain medications in the pre-index period, the odds of switching from index TNF inhibitor therapy was 88 times higher for non-pain medication users while controlling for other variables in the model[Odds Ratio (OR) = 88.40, [95% CI =1.889->999.999], p = 0.0224].

H_{o6}: *There is no significant difference in the **likelihood of switching** from index TNF inhibitor therapy to another biologic agent among ETN users compared to ADA and IFX users while controlling for covariates.* **(Not Rejected)**

Table 4.15: Conditional Logistic Regression Analysis Comparing the Likelihood of Switching from Index TNF Inhibitor Therapy (N = 822)

	Odds Ratio	95% CI		Wald X^2	p-value
Medication Type†					
Adalimumab	1.533	0.858	2.742	2.0784	0.1494
Infliximab	1.107	0.623	1.967	0.1204	0.7286
Covariates					
Age	0.967	0.937	0.997	4.4892	0.0341*
Male†	1.249	0.488	3.194	0.2153	0.6427
Non-Whites†	0.179	0.044	0.725	5.8125	0.0159*
Pre-index DMARD non-use	2.784	0.298	26.034	0.8059	0.3693
Pre-index pain medications non-use	88.400	1.889	>999.999	5.2173	0.0224*
Pre-index glucocorticoids non-use	4.965	0.283	87.023	1.2027	0.2728
Pre-index RA related visits	2.661	1.243	5.698	6.3494	0.0117*
Pre-index non-RA related visits	4.689	1.431	15.363	6.5112	0.0107*
Total number of non-study RA-related medications	0.233	0.075	0.723	6.3622	0.0117*
Pre-index total utilization cost	0.999	0.999	1.000	6.2065	0.0127
Charlson Comorbidity Index	2.301	0.768	6.893	2.2139	0.1368

RA = rheumatoid arthritis; **TNF** = tumor necrosis factor

†Reference categories: Etanercept, females, whites, DMARD users, glucocorticoid users and pain medication users. Note: Race was dichotomized into two groups (Whites and others) due to small cell sizes.

Model Fit Statistics: likelihood ratio = 26.3961, df = 13, p = 0.0150; Score = 22.5955, df = 13, p = 0.0468; Wald = 19.8892, df = 13, p = 0.0980

*significant at $p < 0.05$

4.4.4.4c Medication Switching (GLM-GEE Model)

To determine if duration of medication use (i.e., persistence) prior to switching from index TNF inhibitor therapy among ETN users differs significantly compared to ADA and IFX users while controlling for covariates, a generalized linear model (GLM), which was estimated using a generalized estimating equation (GEE), was used. The dependent variable was TNF inhibitor medication persistence prior to switch and the independent variable was type of TNF inhibitor therapy. The same covariates used in the previous analyses were used in the GLM. Overall, based on a 60-day gap period, mean persistence (±SD) to the study TNF inhibitor therapies prior to switching was 140.3 days (±93.7). The mean persistence values (±SD) prior to switch were 138.7±90.4 days, 142.5±103.9 days and 139.6±89.5 days, respectively, for ETN, IFX and ADA users.[n]

For the GLM, a gamma distribution and a log link was specified as the normality assumption was rejected based on the significance of the KS test ($p < 0.01$). Table 4.16 shows the detailed results of the GLM model estimated using a GEE. The GEE parameter estimate results showed that compared to patients on ETN, there was no significant difference in ADA or IFX users' persistence to TNF inhibitor therapy prior to switch while controlling for other variables in the model. Regarding the

[n] See Appendix B for detailed result

covariates, only gender (p = 0.0242) and CCI were significantly (p = 0.0414) related to persistence to TNF inhibitor therapy prior to switch. An increase in CCI score was associated with a significant decrease in persistence to TNF inhibitor therapy prior to switching while controlling for other variables in the model. Compared to female subjects, male subjects were significantly more persistent on TNF inhibitor therapy prior to switch while controlling for other variables in the model. Results were robust when sensitivity analyses were conducted using 45, 90- and 120-day gap periods. When a 30-day gap period was specified, in addition to the above, healthcare utilization was significantly and positively related to persistence to TNF inhibitor therapy prior to switch.

H_{o7}: *There is no significant difference in* ***duration of medication use*** *(i.e., persistence)* ***prior to switching*** *from index TNF inhibitor therapy among ETN users compared to ADA and IFX users while controlling for covariates.* (**Not Rejected**)

Table 4.16: Generalized Linear Regression Analysis Comparing Medication Persistence among TNF Inhibitors prior to Switch (N = 98)

	Estimate	95% CI		Z	p-value
Medication Type†					
Adalimumab	0.0273	-0.2748	0.3294	0.18	0.8592
Infliximab	0.0274	-0.3180	0.3729	0.16	0.8763
Covariates					
Age	0.0069	-0.0047	0.0186	1.16	0.2448
Male†	0.4419	0.0576	0.8262	2.25	0.0242*
Non-Whites†	0.1117	-0.1875	0.4109	0.73	0.4643
Pre-index DMARD non-use	-0.0154	-0.3329	0.3020	-0.10	0.9240
Pre-index pain medications non-use	0.0232	-0.3070	0.3534	0.14	0.8903
Pre-index glucocorticoids non-use	-0.2000	-0.5023	0.1024	-1.30	0.1949
Pre-index RA related visits	0.0231	-0.0190	0.0651	1.08	0.2822
Pre-index non-RA related visits	-0.0184	-0.1398	0.1029	-0.30	0.7659
Total number of non-study RA-related medications	-0.0105	-0.1363	0.1154	-0.16	0.8704
Pre-index total utilization cost	0.0000	-0.0001	0.0001	0.29	0.7744
Charlson Comorbidity Index	-0.3095	-0.6069	-0.0121	-2.04	0.0414*

RA = rheumatoid arthritis; **TNF** = tumor necrosis factor
†Reference categories: Etanercept, females, whites, DMARD users, glucocorticoid users and pain medication users. Note: Race was dichotomized into two groups (Whites and others) due to small cell sizes.
*significant at $p < 0.05$

4.4.5 Healthcare Utilization Cost

Objective 5 was to determine if total healthcare utilization cost for ETN users differs significantly compared to ADA and IFX users while controlling for covariates. Total healthcare cost was defined as the total direct costs (i.e., medical and medication costs combined) to the Texas Medicaid program in the post-index period for users on each of the study TNF inhibitors, adjusted to 2011 US dollars using the medical consumer price index from the U.S. Bureau of Labor Statistics current data.

4.4.5.1a Healthcare Utilization Cost (Unadjusted Analysis- Signed-Ranked Test)

Overall, the median total healthcare cost (mean±SD) incurred by the study subjects in the post-index period was $16,488 ($16,477±9,228). Median total healthcare costs (mean±SD) were $18,670 ($18,299±9,074), $16,575 ($16,325±8,469) and $13,171 ($14,808±9,792) for ADA, ETN and IFX users, respectively.[o] Result of unadjusted analysis indicated that compared to ETN users, median overall cost was significantly higher (p = 0.0170) for ADA users and was significantly lower (p = 0.0175) for IFX users.

[o] See Appendix C for detailed result

4.4.5.1b Total Healthcare Utilization Cost (GLM-GEE Model)

To determine if total healthcare utilization cost for ETN users differs significantly compared to ADA and IFX users while controlling for covariates, a generalized linear model (GLM), which was estimated using a generalized estimating equation (GEE), was used. The dependent variable was total healthcare utilization cost and the independent variable was type of TNF inhibitor therapy. The same covariates used in the previous analyses were used in the GLM. A gamma distribution and a log link was specified for the model as the normality assumption was rejected based on the significance of the KS test ($p < 0.01$). Table 4.17 shows the detailed results of the GLM model estimated using a GEE. The GEE parameter estimate results showed that total healthcare cost in the post-index period was significantly higher ($p = 0.0049$) for ADA users compared to ETN users while controlling for other variables in the model. Total healthcare cost in the post-index period was significantly lower ($p = 0.0005$) for IFX users compared to ETN users while controlling for other variables in the model. Regarding the covariates, only pre-index DMARD use ($p = 0.0038$), pre-index RA-related visit ($p = 0.0155$) and pre-index total utilization cost ($p <.0001$) were significantly related to total healthcare cost in the post-index period. An increase in pre-index RA-related visit or pre-index total utilization cost was associated with a significant increase in total healthcare cost in the post-index period while controlling for other variables in the model. Compared to subjects on DMARDs, subjects who were not on DMARDs in the pre-index period had significantly lower

total healthcare cost in the post-index period while controlling for other variables in the model.

H_8: *Total healthcare utilization cost is significantly lower for ETN patients compared to patients on ADA and IFX while controlling for covariates*. (**Rejected**)

Table 4.17: Generalized Linear Regression Analysis Comparing Total Healthcare Utilization Cost among TNF Inhibitors (N = 822)

	Estimate	95% CI		Z	p-value
Medication Type†					
Adalimumab	0.1215	0.0369	0.2061	2.81	0.0049*
Infliximab	-0.1625	-0.2543	-0.0707	-3.47	0.0005*
Covariates					
Age	-0.0018	-0.0061	0.0026	-0.80	0.4244
Male†	0.0523	-0.0485	0.1530	1.02	0.3092
Non-Whites†	-0.0483	-0.1294	0.0329	-1.17	0.2438
Pre-index DMARD non-use	-0.1383	-0.2321	-0.0446	-2.89	0.0038*
Pre-index pain medications non-use	-0.0851	-0.1916	0.0215	-1.56	0.1176
Pre-index glucocorticoids non-use	-0.0114	-0.0933	0.0705	-0.27	0.7854
Pre-index RA related visits	0.0137	0.0026	0.0248	2.42	0.0155*
Pre-index non-RA related visits	-0.0125	-0.0423	0.0173	-0.82	0.4106
Total number of non-study RA-related medications	0.0266	-0.0093	0.0626	1.45	0.1468
Pre-index total utilization cost	0.0001	0.0001	0.0001	9.54	<.0001*
Charlson Comorbidity Index	-0.0286	-0.1036	0.0464	-0.75	0.4547

RA = rheumatoid arthritis; **TNF** = tumor necrosis factor
†Reference categories: Etanercept, females, whites, DMARD users, glucocorticoid users and pain medication users. Note: Race was dichotomized into two groups (Whites and others) due to small cell sizes.
*significant at $p < 0.05$

4.4.6 RA-related Healthcare Utilization Cost

The first part of objective 6 was to determine if RA-related healthcare utilization cost for ETN users differs significantly compared to ADA and IFX users while controlling for covariates. RA-related healthcare cost was total RA-related direct medical and medication costs (associated with ICD-9-CM code 714.0x) in the post-index period, adjusted to 2011 US dollars using the medical consumer price index from the U.S. Bureau of Labor Statistics current data.

4.4.6.1a RA-related Healthcare Utilization Cost (Signed Rank Test)

Overall, the median RA-related healthcare cost (mean±SD) incurred by the study subjects in the post-index period was $13,921 ($13,713±8309). Median total RA-related healthcare costs (mean±SD) were $15,987 ($15,777±8005), $13,894 ($13,391±7,421) and $10,283 ($11,972±9,002) for ADA, ETN and IFX users, respectively.[p] Result of unadjusted analysis indicated that compared to ETN users, median overall RA-related healthcare cost was significantly higher ($p = 0.0010$) for ADA users and was significantly lower ($p = 0.0116$) for IFX users.

[p] See Appendix C for detailed result

4.4.6.1b RA-related Healthcare Utilization Cost (GLM-GEE Model)

To determine if RA-related healthcare utilization cost for ETN users differs significantly compared to ADA and IFX users while controlling for covariates, a generalized linear model (GLM), which was estimated using a generalized estimating equation (GEE), was used. The dependent variable was RA-related healthcare utilization cost and the independent variable was type of TNF inhibitor therapy. The same covariates used in the previous analyses were used in the GLM. A gamma distribution and a log link was specified for the model as the normality assumption was rejected based on the significance of the KS test ($p < 0.01$). Table 4.18 shows the detailed results of the GLM model estimated using a GEE. The GEE parameter estimate results showed that RA-related healthcare cost in the post-index period was significantly higher ($p = 0.0009$) for ADA users compared to ETN users while controlling for other variables in the model. RA-related healthcare cost in the post-index period was significantly lower ($p = 0.0003$) for IFX users compared to ETN users while controlling for other variables in the model. Regarding the covariates, gender ($p = 0.0414$), pre-index DMARD use ($p = 0.0023$), pre-index RA-related visit ($p < 0.0001$), pre-index total utilization cost ($p = 0.0011$) and CCI ($p = 0.0249$) were significantly related to RA-related healthcare cost in the post-index period. An increase in pre-index RA-related visit or pre-index total utilization cost was associated with significant increase in RA-related healthcare cost in the post-index period while controlling for other variables in the model. An increase in CCI score was

significantly associated with a decrease in RA-related healthcare cost in the post-index period. Compared to subjects on DMARDs, subjects who were not on DMARDs in the pre-index period had significantly lower RA-related healthcare cost in the post-index period while controlling for other variables in the model. Compared to female subjects, male subjects had significantly higher RA-related healthcare cost in the post-index period while controlling for other variables in the model.

H_9: *RA-related healthcare utilization cost is significantly lower for ETN patients compared to patients on ADA and IFX while controlling for covariates*. (**Rejected**)

Table 4.18: Generalized Linear Regression Analysis Comparing RA-related Healthcare Utilization Cost among TNF Inhibitors (N = 822)

	Estimate	95% CI		Z	p-value
Medication Type†					
Adalimumab	0.1576	0.0642	0.2510	3.31	0.0009*
Infliximab	-0.1929	-0.2965	-0.0893	-3.65	0.0003*
Covariates					
Age	-0.0033	-0.0081	0.0014	-1.38	0.1678
Male†	0.1119	0.0044	0.2194	2.04	0.0414*
Non-Whites†	-0.0589	-0.1493	0.0316	-1.28	0.2020
Pre-index DMARD non-use	-0.1650	-0.2712	-0.0588	-3.04	0.0023*
Pre-index pain medications non-use	-0.0719	-0.1894	0.0455	-1.20	0.2299
Pre-index glucocorticoids non-use	-0.0270	-0.1208	0.0667	-0.57	0.5717
Pre-index RA related visits	0.0290	0.0164	0.0416	4.50	<.0001*
Pre-index non-RA related visits	-0.0201	-0.0539	0.0137	-1.17	0.2429
Total number of non-study RA-related medications	0.0247	-0.0176	0.0671	1.14	0.2525
Pre-index total utilization cost	0.0000	0.0000	0.0001	3.26	0.0011*
Charlson Comorbidity Index	-0.0993	-0.1861	-0.0125	-2.24	0.0249*

RA = rheumatoid arthritis; **TNF**= tumor necrosis factor
†Reference categories: Etanercept, females, whites, DMARD users, glucocorticoid users and pain medication users. Note: Race was dichotomized into two groups (Whites and others) due to small cell sizes.
*significant at $p < 0.05$

4.4.7 TNF-Inhibitor Therapy Cost

The second part of objective 6 was to determine if TNF inhibitor therapy cost for ETN users differs significantly compared to ADA and IFX users while controlling for covariates. TNF inhibitor therapy cost was defined as total cost of the index TNF inhibitor therapy in the post-index period, adjusted to 2011 US dollars using the medical consumer price index from the U.S. Bureau of Labor Statistics current data.

4.4.7.1a TNF-Inhibitor Therapy Cost (Unadjusted Analysis- Signed Rank Test)

Overall, the median TNF inhibitor therapy cost (mean±SD) incurred by the study subjects in the post-index period was $9,512 ($10,879±7,543). Median TNF inhibitor therapy costs (mean±SD) were $13,190 ($12,999±7,517), $10,209 ($10,647±6,714) and $6,279 ($8,992±7,834) for ADA, ETN and IFX users, respectively.[q] Result of unadjusted analysis indicated that compared to ETN users, median overall cost was significantly higher (p = 0.0003) for ADA users and was significantly lower (p = 0.0005) for IFX users.

4.4.7.1b TNF-Inhibitor Therapy Cost (GLM-GEE Model)

To determine if TNF inhibitor therapy cost for ETN users differs significantly compared to ADA and IFX users while controlling for covariates, a generalized linear

[q] See Appendix C for detailed result

model (GLM), which was estimated using a generalized estimating equation (GEE), was used. The dependent variable was TNF inhibitor therapy cost and the independent variable was type of TNF inhibitor therapy. Same covariates used in the previous analyses were introduced in the GLM. A gamma distribution and a log link was specified for the model as the normality assumption was rejected based on the significance of the KS test ($p < 0.01$). Table 4.19 shows the detailed results of the GLM model estimated using a GEE. The GEE parameter estimate results showed that TNF inhibitor therapy costs were significantly higher ($p = 0.0004$) for ADA users compared to ETN users while controlling for other variables in the model. TNF inhibitor therapy cost was significantly lower ($p < 0.0001$) for IFX users compared to ETN users while controlling for other variables in the model. Regarding the covariates, gender ($p = 0.0031$), pre-index DMARD use ($p = 0.0003$), pre-index RA-related visit ($p = 0.0006$) were significantly related to TNF inhibitor therapy cost. An increase in pre-index RA-related visit was associated with significant increase in TNF inhibitor therapy cost while controlling for other variables in the model. Compared to subjects on DMARDs, subjects who were not on DMARDs in the pre-index period had significantly lower TNF inhibitor therapy cost while controlling for other variables in the model. Compared to female subjects, male subjects had significantly higher TNF inhibitor therapy cost while controlling for other variables in the model.

H_{10}: *TNF medication cost is significantly lower for ETN patients compared to patients on ADA and IFX while controlling for covariates*. (**Rejected**)

Table 4.19: Generalized Linear Regression Analysis Comparing TNF Inhibitor Therapy Cost among TNF Inhibitors (N = 822)

	Estimate	95% CI		Z	p-value
Medication Type†					
Adalimumab	0.1960	0.0885	0.3035	3.57	0.0004*
Infliximab	-0.2491	-0.3658	-0.1325	-4.19	<.0001*
Covariates					
Age	0.0001	-0.0055	0.0057	0.04	0.9661
Male†	0.1744	0.0590	0.2897	2.96	0.0031*
Non-Whites†	-0.0600	-0.1670	0.0471	-1.10	0.2722
Pre-index DMARD non-use	-0.2380	-0.3679	-0.1081	-3.59	0.0003*
Pre-index pain medications non-use	-0.1294	-0.2707	0.0120	-1.79	0.0728
Pre-index glucocorticoids non-use	-0.0756	-0.1870	0.0357	-1.33	0.1832
Pre-index RA related visits	0.0263	0.0113	0.0413	3.43	0.0006*
Pre-index non-RA related visits	-0.0115	-0.0537	0.0308	-0.53	0.5949
Total number of non-study RA-related medications	-0.0072	-0.0595	0.0451	-0.27	0.7876
Pre-index total utilization cost	0.0000	-0.0000	0.0000	0.67	0.5024
Charlson Comorbidity Index	-0.0786	-0.1794	0.0223	-1.53	0.1268

RA = rheumatoid arthritis; **TNF**= tumor necrosis factor

†Reference categories: Etanercept, females, whites, DMARD users, glucocorticoid users and pain medication users. Note: Race was dichotomized into two groups (Whites and others) due to small cell sizes.

*significant at $p < 0.05$

4.4.8 Relationship Between RA-related Healthcare Utilization Cost and Medication Adherence and Persistence

Objective 7 was to determine if RA-related healthcare utilization cost was associated with adherence and persistence to TNF inhibitors (ETN, ADA or IFX) while controlling for covariates. A generalized linear model (GLM), which was estimated using a generalized estimating equation (GEE), was used. The dependent variable was RA-related healthcare utilization cost and the independent variables were adherence and persistence to TNF inhibitor therapy. The same covariates used in the previous analyses were used in the GLM.

4.4.8.1 Relationship Between RA-related Healthcare Utilization Cost and Medication Adherence (GLM-GEE Model)

A gamma distribution and a log link was specified for the model as the normality assumption was rejected based on the significance of the KS test ($p < 0.01$). Table 4.20 shows the detailed results of the GLM model estimated using a GEE. The GEE parameter estimate results showed that adherence to TNF inhibitor therapy was positively and significantly ($p < 0.0001$) associated RA-related healthcare utilization cost while controlling for other variables in the model. Regarding the covariates, age ($p = 0.0034$), pre-index RA-related visits ($p = 0.0030$), total number of non-study RA-related medications ($p = 0.0340$) and pre-index total utilization cost ($p = 0.0308$) were significantly related to RA-related healthcare cost in the post-index period. An

increase in pre-index RA-related visits, total number of non-study RA-related medications or pre-index total utilization cost was significantly associated with an increase in RA-related healthcare cost in the post-index period while controlling for other variables in the model. Older age was associated with a significant decrease in RA-related healthcare cost in the post-index period while controlling for other variables in the model.

H_{11}: *RA-related healthcare utilization cost is significantly and positively related to TNF medication adherence while controlling for covariates*. (**Not Rejected**)

Table 4.20: Generalized Linear Regression Analysis Comparing Relationship Between RA-related Healthcare Utilization Cost and Medication Adherence (N = 822)

	Estimate	95% CI		Z	p-value
Adherence (MPR)	0.0132	0.0116	0.0147	16.60	<.0001*
Covariates					
Age	-0.0069	-0.0115	-0.0023	-2.93	0.0034*
Male†	0.0227	-0.0811	0.1265	0.43	0.6687
Non-Whites†	-0.0191	-0.1086	0.0703	-0.42	0.6753
Pre-index DMARD non-use	-0.0391	-0.1415	0.0634	-0.75	0.4550
Pre-index pain medications non-use	-0.0246	-0.1293	0.0800	-0.46	0.6445
Pre-index glucocorticoids non-use	0.0265	-0.0555	0.1085	0.63	0.5265
Pre-index RA related visits	0.0179	0.0061	0.0297	2.97	0.0030*
Pre-index non-RA related visits	-0.0132	-0.0441	0.0176	-0.84	0.4011
Total number of non-study RA-related medications	0.0441	0.0033	0.0848	2.12	0.0340*
Pre-index total utilization cost	0.0000	0.0000	0.0001	2.16	0.0308*
Charlson Comorbidity Index	-0.0511	-0.1175	0.0154	-1.51	0.1319

MPR = medication possession ratio; **RA** = rheumatoid arthritis; **TNF** = tumor necrosis factor
†Reference categories: Etanercept, females, whites, DMARD users, glucocorticoid users and pain medication users. Note: Race was dichotomized into two groups (Whites and others) due to small cell sizes.
*significant at $p < 0.05$

4.4.8.2 Relationship Between RA-related Healthcare Utilization Cost and Medication Persistence (GLM-GEE Model)

Table 4.21 shows the detailed results of the GLM model which was estimated using a GEE. The GEE parameter estimate results showed that persistence to TNF inhibitor therapy was positively and significantly ($p < 0.0001$) associated RA-related healthcare utilization cost while controlling for other variables in the model. Regarding the covariates, age ($p = 0.0084$), pre-index RA-related visits ($p = 0.0021$), and pre-index total utilization cost ($p = 0.0436$) were significantly related to RA-related healthcare cost in the post-index period. An increase in pre-index RA-related visits or pre-index total utilization cost was associated with significant increase in RA-related healthcare cost in the post-index period while controlling for other variables in the model. Older age was associated with a significant decrease in RA-related healthcare cost in the post-index period while controlling for other variables in the model. Results were robust when sensitivity analyses were conducted using 90- and 120-day gap periods. When a 30- or 45-day gap period was specified, in addition to the variables above, total number of non-study RA-related medications was significantly and positively related to RA-related healthcare cost in the post-index period. With the 30-day gap period, CCI was also significantly but negatively related to RA-related healthcare cost in the post-index period.

H_{12}: *RA-related healthcare utilization cost is significantly and positively related to TNF medication persistence while controlling for covariates*. (**Not Rejected**)

Table 4.21: Generalized Linear Regression Analysis Comparing Relationship Between RA-related Healthcare Utilization Cost and Medication Persistence (N = 822)

	Estimate	95% CI		Z	p-value
Persistence‡	0.0025	0.0021	0.0028	14.83	<.0001*
Covariates					
Age	-0.0062	-0.0107	-0.0016	-2.64	0.0084*
Male†	0.0296	-0.0779	0.1371	0.54	0.5899
Non-Whites†	-0.0475	-0.1374	0.0423	-1.04	0.3001
Pre-index DMARD non-use	-0.0829	-0.1878	0.0220	-1.55	0.1213
Pre-index pain medications non-use	-0.0283	-0.1439	0.0872	-0.48	0.6308
Pre-index glucocorticoids non-use	0.0032	-0.0814	0.0878	0.07	0.9417
Pre-index RA related visits	0.0187	0.0068	0.0307	3.08	0.0021*
Pre-index non-RA related visits	-0.0142	-0.0459	0.0175	-0.88	0.3788
Total number of non-study RA-related medications	0.0291	-0.0122	0.0705	1.38	0.1671
Pre-index total utilization cost	0.0000	0.0000	0.0001	2.02	0.0436*
Charlson Comorbidity Index	-0.0578	-0.1260	0.0104	-1.66	0.0965

RA = rheumatoid arthritis; **TNF** = tumor necrosis factor
‡Based on a 60-day gap period
†Reference categories: Etanercept, females, whites, DMARD users, glucocorticoid users and pain medication users. Note: Race was dichotomized into two groups (Whites and others) due to small cell sizes.
*significant at $p < 0.05$

The results of all hypotheses tested in this study are summarized in Table 4.21.

Table 4.21 Results of Hypotheses Testing

Objectives/ Hypotheses	Statistical Analysis	Result
Objective 1: To describe and compare baseline socio-demographics and clinical characteristics of Texas Medicaid RA patients on etanercept (ETN), adalimumab (ADA) or infliximab (IFX)	Descriptive statistics	
Objective 2: To describe medication dosing patterns (initial or starting dose and dose category changes) among ETN, ADA and IFX users	Descriptive statistics	
Objective 3: To determine if the likelihood of having a dose escalation among ETN users differs significantly compared to ADA and IFX users while controlling for covariates†		
H_1: The likelihood of having a dose escalation is significantly lower among RA patients on ETN compared to patients on ADA and IFX while controlling for covariates	Conditional logistic regression	**Not Rejected**
Objective 4: To determine if medication use patterns (adherence, persistence, discontinuation and switching) among ETN users differ significantly compared to ADA and IFX users while controlling for covariates†		
H_{o2A}: There is no significant difference in medication adherence to ETN compared to ADA and IFX users while controlling for covariates	GLM model estimated with GEE	**Rejected**
H_{o2B}: The likelihood of being adherent (MPR≥80%) to ETN does not differ significantly compared to ADA and IFX while controlling for covariates	Conditional logistic regression	**Rejected**
H_{o3}: There is no significant difference in medication persistence to ETN compared to ADA and IFX users while controlling for covariates	GLM model estimated with GEE	**Not Rejected**
H_{o4}: The likelihood of discontinuing ETN does not differ significantly compared to ADA and IFX while controlling for covariates	Conditional logistic regression	**Not Rejected**
H_{o5}: There is no significant difference in duration of medication use prior to discontinuation of ETN compared to ADA and IFX while controlling for covariates	Cox proportional hazards regression	**Not Rejected**
H_{o6}: There is no significant difference in the likelihood of switching from index TNF inhibitor therapy to another biologic agent among ETN users compared to ADA and IFX users while controlling for covariates.	Conditional logistic regression	**Not Rejected**
H_{o7}: There is no significant difference in duration of medication use prior to switching from index TNF inhibitor among ETN users compared to ADA and IFX users while controlling for covariates	GLM model estimated with GEE	**Not Rejected**
Objective 5: To determine if total healthcare utilization cost for ETN users differs significantly compared to ADA and IFX users while controlling for covariates†		
H_8:Total healthcare utilization cost is significantly lower for ETN patients compared to patients on ADA and IFX while controlling for covariates	GLM model estimated with GEE	**Rejected**

Objectives/ Hypotheses	Statistical Analysis	Result
Objective 6: To determine if RA-related healthcare utilization cost for ETN users differs significantly compared to ADA and IFX users while controlling for covariates†		
H_9:Total RA-related healthcare utilization cost is significantly lower for ETN patients compared to patients on ADA and IFX while controlling for covariate	GLM model estimated with GEE	**Rejected**
H_{10}: TNF medication cost is significantly lower for ETN patients compared to patients on ADA and IFX while controlling for covariates	GLM model estimated with GEE	**Rejected**
Objective 7: To determine if RA-related healthcare utilization cost is associated with adherence/persistence to TNF inhibitors (ETN, ADA or IFX) while controlling for covariates†		
H_{11}: RA-related healthcare utilization cost is significantly and positively related to TNF medication adherence while controlling for covariates	GLM model estimated with GEE	**Not Rejected**
H_{12}: RA-related healthcare utilization cost is significantly and positively related to TNF medication persistence while controlling for covariates	GLM models estimated using GEE	**Not Rejected**

ADA= Adalimumab**; ETN=**Etanercept**; GEE**= Generalized estimating equation; **GLM**= Generalized linear model; **IFX**=Infliximab; **MPR**= Medication possession ratio; **RA**=Rheumatoid arthritis; **TNF**= Tumor necrosis factor

Covariates include age, gender, pre-index use of other RA-related medications, total number of other RA-related medications use at index, Charlson Comorbidity index, pre-index total RA-related visits, pre-index total non-RA related visits and pre-index RA-related healthcare utilization cost

CHAPTER 5: DISCUSSION AND CONCLUSION

5.1 CHAPTER OVERVIEW

This chapter provides a detailed discussion of the study results. The chapter begins with a brief review of the study purpose. This is followed by a discussion of the study results with possible explanations provided for study findings. The chapter concludes with a discussion regarding study uniqueness and limitations as well as suggestions for future research.

5.2 REVIEW OF STUDY PURPOSE

The aim of the present study was to evaluate medication use patterns (i.e., medication adherence, persistence, switching and dose escalation) of RA patients on etanercept (ETN), infliximab (IFX) or adalimumab (ADA) and the associated healthcare utilization costs using Texas Medicaid data (prescription and medical claims) from July 2003 to August 2011. While the majority of earlier studies were conducted using data from patients enrolled in private health plans or managed care organizations, the present study expands on findings using data from patients enrolled under Medicaid programs.

5.3 STUDY OBJECTIVES

Seven objectives and twelve hypotheses were addressed in this study. Results under each study objective are discussed and compared with findings from previous studies.

5.3.1 Objective 1

Objective 1 was to describe and compare baseline socio-demographics and clinical characteristics of Texas Medicaid RA patients on etanercept (ETN), adalimumab (ADA) or infliximab (IFX). At baseline, the three study groups presented with comparable socio-demographic characteristics (i.e., age, gender and race). However, the ETN and ADA groups differed in clinical characteristics from the IFX group necessitating the need for a matching procedure to be conducted. After matching using propensity scores, the three study groups were not significantly different from each other on any of the baseline characteristics. Demographic characteristics of the final matched sample (i.e., mean age [48.9±9.8 years] and gender [females accounted for 88.0 percent of study population]) were found to be within the range of values reported by earlier RA studies that were conducted using retrospective database analysis. The reported mean age by these studies ranged from 48.2±12.5 to 58.0 (SD not provided) years with female population ranging from 73.3-

88.4 percent.[2,4,21-28,30-33,212,213] However, in contrast to other studies[r] where the majority were White, the present study had a majority Hispanic population (53.7%).[23-25,33] This result was not surprising as Hispanics have been reported to account for a significant proportion (≈ 40%) of the Texas population.[214] Furthermore, having a majority Hispanic population makes the results of the present study a unique contribution to the literature as this population is under-represented in previous RA studies.

Regarding clinical characteristics, the pre-index use of other RA-related medications (i.e., DMARDs, glucocorticoids and pain medications) was consistent with what was expected for patients presenting with RA due to the nature of the disease condition.[2,22,25,26,212] Based on the RA treatment guidelines, patients were expected to have first initiated treatment on NSAIDs or short-term low-dose glucocorticoids and traditional DMARD therapy[s] before starting a TNF-inhibitor therapy since they are reserved for patients with suboptimal response to traditional DMARD therapy.[74] The mean Charlson Comorbidity Index score (CCI) obtained (1.2±0.5), mean pre-index RA-related visits (4.2±2.9) and mean all cause visits (5.5±3.4) were also within the range of values found in the literature. Earlier studies

[r] Those that explicitly reported information on race/ethnicity

[s] In cases of active disease

reported mean CCI values ranging from 0.3 (SD not provided) to 2.2 (SD not provided), mean RA-related visits ranging from 2.0 (SD not provided) to 3.4(±3.0) and mean all cause visits ranging from 5.0 (SD not provided) to 10.7 (SD not provided).[4,22,28-31,213] In summary, with the exception of race, the present study sample seemed similar to those of other studies regarding demographic and clinical characteristics.

5.3.2 Objectives 2 and 3

Objective 2 was to describe medication dosing patterns (initial dose and dose category changes) among ETN, ADA and IFX users. Objective 3 was to determine if the likelihood of having a dose escalation differs significantly among ETN, ADA and IFX users while controlling for covariates. As explained earlier under the results section, dosing patterns could not be assessed for patients on IFX due to absence of unit of service information in the medical claims needed to verify the quantity of vials administered (per Healthcare Common Procedure Coding System J-codes).

The average weekly starting dose for ETN (50.1±6.2mg) obtained in the study was comparable to the manufacturer's recommended weekly dose of 50mg with the majority of the patients (98.2%) having a starting weekly dose that was less than or equal to 50mg. This was comparable with results in the literature. Previous studies reported average starting weekly doses which ranged from 46.5±7.0mg to 50.5 (SD not provided) with the proportion of patients having a starting dose that was less

than or equal to 50mg ranging from 85.0 to 100.0 percent.[26,28,30-32,212] The average weekly starting dose for ADA (22.6±7.8mg) was slightly higher than a weekly dose of 20mg equivalent to the manufacturer's recommended dose of 40mg every other week. However, it was comparable with the average starting weekly dose reported in the literature (21±4.8mg to 22.3mg [SD not provided]). [28,32,212] The proportion of patients (88.0%) on ADA with a starting weekly dose that was less than or equal to 20mg was also comparable with results (88.1% to 93.6%) reported in the literature.[26,28,30-32,212] Based on the starting weekly doses reported above for ETN and ADA, it can be inferred that the clinicians followed the manufacturer recommended starting doses for the majority of their RA patients.

Regarding dose escalation, a variety of definitions exist in the literature. In the present study, dose escalation was assumed to occur when the average weekly dose for all the subsequent prescriptions for the index TNF therapy exceeds the weekly dose of the index prescription by 150 percent. For IFX patients, dose escalation was calculated based on the ratio of the average of all J-code 1745 subsequent costs to the index J-code 1745 cost, with dose escalation identified if the ratio is greater than or equal to 1.5 (or 150%). Based on the study result, a significantly lower proportion of patients on ETN (2.2%) had a dose escalation compared to patients on ADA (9.9%; $p < 0.0001$) or IFX (8.4%; $p=0.0015$). Also ETN patients had a lower likelihood of having a dose escalation compared to patients on ADA ($p < 0.0004$) or IFX ($p=0.0031$). This result was not unexpected as dose escalation/increase is recommended for patients

on ADA or IFX in cases of suboptimal treatment response but has not been associated with significant improvement in treatment response rates in patients on ETN.[18-20,175-177,215] Dose escalation patterns obtained in the present study were similar to those reported across a number of dose escalation studies with the proportion of patients having a dose escalation being consistently and significantly lower for ETN compared to ADA and IFX.[26,28-33,212,216] Across all methods used to define dose escalation, the proportions ranged from 0.4 to 10.3 percent, 8.3 to 33.6 percent and 16.4 to 60 percent for ETN, ADA and IFX, respectively.[26,28-33,212,216] The proportion of ETN and ADA patients in the present study with a dose escalation were within the range found in the literature. However, for IFX, the proportion of those with a dose escalation was lower than the values reported in previous studies. Perhaps, compared to the previous studies, the IFX patients in the present study seemed to have a less severe form of RA.

A major implication of dose escalation in the management of RA actually lies in its impact on patient's cost of care.[174] Studies which compared cost of care between patients who had a dose escalation and those who did not reported a significant relationship between dose escalation and higher cost.[28,31,177] A similar trend was also observed in the present study with patients who did not dose escalate having significantly lower total healthcare cost ($p < 0.0001$), RA-related healthcare cost ($p < 0.0001$) and TNF inhibitor therapy cost ($p=0.0003$) compared to patients who dose escalated.

5.3.3 Objective 4

Objective 4 was to determine if medication use patterns (adherence, persistence, discontinuation and switching) differ significantly among ETN, ADA and IFX users while controlling for covariates.

5.3.3.1 Medication Adherence

Overall adherence (mean MPR±SD) and adherence rate (proportion of patients with MPR≥ 80%) to TNF inhibitor therapies in the study sample were low. Mean MPR was 52.5(±29.5) percent with 23.5 percent of the subjects adherent (MPR ≥ 80%) to the index TNF inhibitor therapy. Mean adherence, adherence rate and likelihood to adhere to index TNF inhibitor therapy were significantly higher for IFX patients compared to ETN patients, but were comparable between ETN and ADA patients. While results of indirect comparison showed that efficacy and safety were comparable among the three TNF inhibitor therapies, differences in adherence between IFX and ETN or ADA may be a function of the route and frequency of administration.[4] ETN and ADA are administered subcutaneously while IFX is administered intravenously (IV). ETN is given once weekly, ADA is given once every other week while IFX is given at week 0, 2 and 6, and every 8 weeks thereafter.[18-20] Of the three TNF inhibitor therapies, IFX is the only one administered at the physician's office since it is given via IV infusion. Perhaps, the patients on IFX adhered better due to the appoinment reminder messages that may have been sent by the clinic.

The reasons responsible for the low adherence values may be difficult to ascertain as other important information that impacts adherence (e.g., incidence of adverse events, lack of treatment response and increased disability) were lacking in the administrative claims data used for this analysis. Furthermore, adherence values obtained in the present study were lower compared to values obtained in previous adherence studies which also used administrative claims data (commercial or Medicaid).[2,22,23,25] This may be due to the presence of a high Hispanic population (53.7%) in the study sample since being of ethnic minority has been associated with poor medication adherence.[137] In addition, the study subjects were of low socioeconomic status (income and education) and subjects may lack adequate knowledge/understanding of the disease and its treatment. Other possible factors may include poor prior medication-taking behaviors and beliefs.[137] Clinicians caring for Medicaid patients need to be aware of these factors and should endeavor to work with each individual patient to identify patient-specific factors responsible for poor TNF-inhibitor therapy adherence.[217] Reducing the impact of these factors and improving adherence should be included as a major part of the treatment plan for each RA patient.

Despite the low adherence values, the direction of the study results were comparable with those of other studies. For studies that examined adherence to ETN over a 12-month period, mean adherence (mean MPR) ranged from 65.0 to 83.0 percent.[2,21,23] Similarly, mean MPR values ranged from 63.0 to 85.0 percent for ADA

and from 81.0 to 90.0 percent for IFX.[2,21,23] When mean proportion of covered days (PDC) was used, mean PDC values reported for IFX and ADA were 64.0 and 57.0 percent, respectively.[25] Overall, across these studies, mean adherence, adherent rate and likelihood to adhere were significantly higher for IFX compared to ETN but comparable between ETN and ADA patients.

Compared to the other two Medicaid studies[t], the study's adherence values were lower.[23,25] This may be a function of how the studies defined and calculated adherence as well as differences in patients' clinical and demographic characteristics even though they were all Medicaid patients. Differences in Medicaid requirements across the states may also be a contributory factor. The present study defined adherence (MPR) as the total days of drug supply divided by 365 with the maximum number of days of medication overlap restricted to 14 days and total number of days of drug supply not exceeding 365 days. Grijalva et al. defined adherence (MPR) as the aggregated number of days supply obtained during the episode divided by the length of the episode, excluding the last prescription fill.[23] Li et al. defined adherence as the number of days covered with the index biologic divided by 365 using the PDC approach.[25] The PDC method is expected to be more conservative than MPR in calculating adherence for cases of drug switches, therapeutic duplication, or multiple

[t] The previous studies used Medicaid data from the following states: Tennesse, California, New York and Florida.

drug use within the same therapeutic class, none of which was the case in the present study. Differences may also be a function of how days supply was adjusted/computed, especially for IFX, which was only documented in the medical claims data being administered in the physician's office, resulting in no documentation of days supply.

Covariates identified to be significantly associated with adherence were age, gender, pre-index RA-related visits and Charlson Comorbidity Index score (CCI). Age and RA-related visits were positively related with adherence while a negative relationship was observed between CCI and adherence. Male subjects were more adherent compared to female subjects. None of the previous studies reported any relationship between adherence and these covariates with the exception of age. Borah et al. reported a lower likelihood to being adherent with an increase in age.[2] Adherence studies in other chronic disease states (e.g., diabetes) have reported inconsistent results regarding the relationship between age, gender, CCI[u] and adherence.[218-223] Good patient-physician relationships have been found to improve adherence and as such it seems logical that increased pre-index RA-related visits was associated with an increase in adherence.[137] Also, having a negative relationship between CCI and adherence would be expected as an increase in CCI score is indicative of more comorbid disease conditions leading to an increase in treatments

[u] CCI was used as a proxy for disease severity. studies evaluating adherence in other chronic diseases have used different proxies but found inconsistent relationship with adherence

(drug therapies) which may negatively impact adherence. Since RA negatively affects mobility and productivity, male subjects may be more adherent in order to stay productive and continue working.

5.3.3.1 Medication Persistence, Discontinuation and Switching

Overall mean persistence (±SD) was low with a high proportion of patients discontinuing index medication. Mean persistence for the entire study sample was 203.9(±132.8) days with 64.8 percent of the subjects discontinuing index TNF inhibitor therapy. Mean persistence values (discontinuation rate) for the individual TNF inhibitor therapies were 196.7±134.0 days (66.8%), 199.0±130.5 days (65.7%) and 215.6±133.5 days (62.0%), respectively for ETN, ADA, and IFX patients. Mean persistence, proportion of patients who discontinued index therapy and likelihood to discontinue index therapy were comparable when patients on ETN were compared to patients on either IFX or ADA. Similarly, persistence prior to discontinuation was also found to be comparable when patients on ETN were compared to patients on either IFX or ADA.

Reasons responsible for low persistence values may be difficult to identify. However, factors proposed to have been responsible for low adherence values could also have accounted for the low persistence values. Compared to other studies which used administrative data claims to evaluate persistence and/or discontinuation, the mean persistence values obtained in the present study were lower and

discontinuation rates were higher. However, the overall direction of the study results was similar with results from four of the previous studies.[2,25,26,212] Across these studies, mean persistence ranged from 243 to 301 days (SD not provided), 231 to 284 days (SD not provided) and 281 to 298 days (SD not provided) for ETN, ADA and IFX patients, respectively.[4,28,31,212] Discontinuation rates ranged from 19.7 to 50.0 percent, 20.6 to 44.4 percent and 18.8 to 48.3 percent for ETN, ADA and IFX patients, respectively. [25,26,212]

Overall direction of study results was not consistent with results obtained from studies by Tang et al. and Harrison et al. Both studies found significant differences in mean persistence among the TNF-inhibitor therapies.[4,212] However, it is important to note that all the previous studies with the exception of Tang et al. and Harrison et al. used a definition of persistence/discontinuation similar to that used in the present study. Tang et al. and Harrison et al. defined persistence as the number of days between the first and last filled prescription/infusion without accounting for gaps between claims/infusion.

As with adherence, similar covariates were also significantly related to persistence. Age and pre-index RA-related visits were positively related to persistence, while a negative relationship was observed with CCI. An increase in CCI score was associated with an increased likelihood to discontinue index TNF inhibitor therapy, which was consistent with the association between CCI and adherence. As

with adherence, male subjects had better persistence compared to their female counterparts. Since adherence and persistence are related, the same reasons might hold for why these covariates were related to both. Previous studies found similar significant relationships between persistence/discontinuation and age[22], gender[2] and CCI.[4,22]

Regarding switching from index TNF inhibitor therapy to another biologic, 11.9 percent of the study sample switched at one point within the 12-month follow-up period. The proportion of patients on ETN (10.6%) who switched and likelihood to switch from index therapy were comparable with those of patients on either IFX (11.7%) or ADA (13.5%). These switch rates were comparable with those reported by Fisher et al. (ETN [12.2%]; ADA [9.1%] and IFX [10.4%]) but were higher than those reported by Li et al. (ETN [4%] and ADA [4%]). However, the overall study direction were similar as both studies reported no significant difference in proportion of patients that switched across the study TNF inhibitor therapies.[25,212]

Covariates associated with the likelihood to switch from index TNF inhibitor therapy include age, race, pre-index pain medication use, pre-index RA-related visits, pre-index non RA-related visits and total number of non-study RA-related medications. Increase in age, pre-index RA-related visits and pre-index non RA-related visits were associated with a higher likelihood to switch. Increase in total number of non-study RA-related medications was associated with a lower likelihood

to switch. Compared to those who were on pain medications, subjects who were not on pain medications in the pre-index period were more likely to switch while non-whites were less likely to switch compared to their White counterparts. Reasons responsible for these associations are unknown. However, with regard to pre-index RA-related and non RA-related visits, frequent visits to a physician may be indicative that the patient was not getting the desired anticipated relief from a prescribed medication which could increase the likelihood of switching. Furthermore, patients on pain medications in the pre-index period may be less likely to switch as they might have been advised by their clinicians to increase the dose of their pain medications when adequate relief was not achieved with the TNF-inhibitor therapy. A similar reason could account for why an increase in total number of non-study RA-related medications was associated with a lower likelihood to switch.

5.3.4 Objectives 5 and 6

Objectives 5 and 6 were to determine if total healthcare utilization costs (medical and medication costs) and RA-related healthcare utilization costs (medical and medication costs) differ significantly among ETN, ADA and IFX users while controlling for covariates. Overall, the median (mean±SD) total healthcare cost, RA-related healthcare cost and TNF inhibitor therapy costs incurred by the study subjects in the post-index period were $16,488 ($16,477±9,228), $13,921 ($13,713±8309) and $9,470 ($10,851±7,537), respectively. It is important to note that total

healthcare cost and RA-related healthcare cost were primarily driven by TNF inhibitor therapy cost. TNF inhibitor therapy cost accounted for 65.9 percent and 79.1 percent of total healthcare cost and RA-related healthcare cost, respectively.

Total healthcare costs, RA-related healthcare costs and TNF inhibitor therapy costs were significantly lower for ETN compared to ADA patients but significantly higher for ETN and ADA compared to IFX patients. When compared to results from previous retrospective database studies, the pattern of higher cost with ADA compared to ETN was consistent. However, previous studies reported higher costs with IFX compared to ETN. [2,28,29,31,183,224-226] The major difference between the present study and the previous cost studies lies in the type of study data. The present study analyzed Medicaid data while the other studies evaluated data from private health plans or managed care organizations. Differences in the level of rebates negotiated with pharmaceutical manufacturers by the private and Medicaid plans may contribute to the inconsistency.

Covariates significantly associated with the total healthcare cost include pre-index DMARD medication use, pre-index RA-related visits and pre-index cost. Covariates significantly associated with RA-related cost include gender, pre-index DMARD use, pre-index RA-related visits, pre-index total healthcare cost and CCI. Covariates significantly associated with TNF inhibitor therapy cost include gender, pre-index DMARD use and pre-index RA-related visits.

Increase in pre-index RA-related visits and pre-index total healthcare cost were associated with increase in cost while increase in CCI score was associated with a decrease in cost. Compared to those who were on DMARD medications, subjects who were not on DMARD medications in the pre-index period had lower cost while males had higher cost compared to their female counterparts. Increase in pre-index RA-related visits and pre-index total healthcare cost may be indicative of either a high level of disease severity or not achieving the desired treatment response which can lead to a higher cost. On the other hand, non-use of DMARDs in the pre-index period could also be indicative of a low level of disease severity which can be associated with lower cost. Tang et al. reported a positive relationship between pre-index total healthcare cost, CCI and total healthcare cost and lower total healthcare costs among female subjects compared to males. [4]

5.3.5 Objective 7

Objective 7 was to determine if RA-related healthcare utilization cost was associated with adherence/persistence to TNF inhibitors (ETN, ADA or IFX) while controlling for covariates. RA-related healthcare utilization cost was significantly and positively related to both adherence and persistence. Separate GLM-GEE models were used to test the relationship as adherence and persistence were highly and positively correlated ($r = 0.88513$; $p < 0.0001$) with each other. This positive relationship was expected and was comparable with results from previous studies.[2,4]

Borah et al. reported significantly higher total cost of care among adherent patients on either ETN or ADA.[2] Tang et al. also reported a positive relationship between persistence and total healthcare cost.[4] RA is a chronic disease condition and if remission does not occur, optimal adherence/persistence to prescribed medication serves as the major approach to improving patients' symptoms, physical functioning and quality of life while slowing the progression of the disease. Since TNF inhibitors account for a majority of both RA-related healthcare cost and total healthcare cost, increase in adherence/persistence means patients "take" their medication and therefore costs will also increase.

Covariates significantly associated with the RA-related healthcare cost include age, pre-index RA-related visits, pre-index total healthcare cost and total number of non-study RA related medications used at index. A positive relationship was observed between all these covariates (except age) and RA-related healthcare cost. As indicated in the previous section, increase in pre-index RA-related visits, pre-index total healthcare cost and and total number of non-study RA related medications used at index may be indicative of either a high level of disease severity or not achieving the desired treatment response which can lead to higher costs.

5.4 STUDY LIMITATIONS

The present study is unique as it is the first study to the best of our knowledge to evaluate all medication use pattern parameters (medication adherence,

persistence, discontinuation, switching and dose escalation) and associated healthcare utilization costs across RA patients on etanercept, adalimumab and infliximab using Medicaid data. However, the study has limitations which needs to be considered when interpreting the study results.

The first study limitation lies with the use of administrative claims data. Administrative claims data are developed for the purpose of reimbursement rather than research. The presence of a claim for a TNF-inhibitor therapy (i.e., ETN or ADA) in the prescription claims data does not necessarily mean that the patient used the medication. However, for IFX, in the absence of fraudulent claims, the presence of a HCPCS[v] J-code 1745 in the medical claims data indicates that it was infused. Second, the non-randomized distribution of the study groups and presence of baseline differences in clinical characteristics could introduce bias (i.e., selection bias) in the study results. Although, propensity score (PS) matching and multivariate analyses were used to control for selection/channeling bias and confounding on known variables, there is the prossibility that the study groups may still differ in unknown or unmeasured parameters that were not available in the data set (e.g., disease activity and disability). These may have contributed to the differences observed in the study outcomes. In addition, the use of PS matching resulted in a significant

[v] Healthcare Common Procedure Coding System

decrease in the study sample size, causing a decrease in power. This may have be responsible for the inability to detect significant differences among study groups on some of the dependent variables.

Third, days supply information were computed based on manufacturer recommended infusion intervals for patients on IFX. This may not be consistent with the actual interval in days between infusions for the respective patient and may be responsible for the higher adherence values observed with IFX patients compared to those on ETN or ADA. In addition, due to the need to obtain IFX infusion at the physician's office and perphaps, receiving appointment reminder messages regarding these visits could have accounted for the higher adherence values among IFX patients.

Fourth, due to absence of unit of service information in the medical claims to determine the quantity of vials administered for patients on IFX, cost information associated with the HCPCS J-code 1745 was used as a proxy to determine dose esclation. This may have either overestimated or underestimated dose escalation rates in this study group.

Fifth, cost analyses were based on direct cost to the Texas Medicaid program and may not reflect the actual cost of therapy or service provided. While, the use of biologics have been shown to significantly impact productivity costs, these were not assessed in the cost analyses due to lack on data. Sixth, due to lack of information on clinical factors (e.g., incidence of adverse events, lack of response or presence of

suboptimal response) reasons for dose escalation, nonadherence, discontinuation and switching from index TNF inhibitor therapy could not be evaluated. Seventh, the present study only analyzed 12 months of post-index data for biologic-naïve patients. Study outcomes may differ if patients were followed for a longer time period as RA is a chronic disease condition. Finally, the study sample had an over-representation of women, minorities (Hispanics) and people of lower socioeconomic status compared to the general U.S. population and thus cannot be generalized.

5.5 CONCLUSIONS, RECOMMENDATIONS AND SUGGESTIONS FOR FUTURE RESEARCH

The main purpose of the present study was to evaluate medication use patterns (e.g., medication adherence, persistence, switching and dose escalation) of rheumatoid arthritis (RA) patients on etanercept (ETN), infliximab (IFX) or adalimumab (ADA) and the associated healthcare utilization costs using Texas Medicaid data. The study results suggest that ETN was associated with lower rates of dose escalation compared to ADA or IFX. However, adherence was better and associated healthcare costs were lower with the use of IFX.

In general, clinicians need to be aware of factors that impact RA patients' medication use behaviors. Clinicians caring for Medicaid patients with RA need to be aware that this group of patients present with poor medication use behaviors. Clinicians should endeavor to work with each individual patient to identify patient-specific factors responsible for poor medication use behaviors with TNF-inhibitor

therapies. Reducing the impact of these factors and improving medication use behaviors (especially adherence and persistence) should be included as a major part of the treatment plan for each RA patient. RA patients need to be adequately educated on the chronic nature of the disease as well as the importance of adhering and persisting to their TNF-inhibitor therapy as poor medication adherence/persistence negatively impacts the RA disease process. The Texas Health and Human Services Commission should invest in programs (e.g., patient education) aimed at improving RA patients' medication use behaviors. Such programs will go a long way in improving patients' disease condition, overall health related quality of life and productivity. In addition, in the long term, patients' risk of developing RA-related complications or comorbid conditions and their associated cost will be reduced.

Future research using Medicaid data can evaluate medication use patterns over a longer study period and can extend comparisons to include the new biologics. It will also be interesting to evaluate the relationship between medication use patterns and other clinical (e.g., disease activity) and humanistic parameters (i.e., HRQoL[w] and work productivity parameters).

[w] Health related quality of life

Appendices

Appendix A: Results of Unadjusted Analyses (McNemar's Test)

	Proportion of Patients with Dose Escalation‡			
	N	**%**	**Statistic (S)**	**P- value†**
ETN (N=274)	6	2.2		
ADA (N=274)	27	9.9	14.2258	< 0.0001*
IFX (N=274)	23	8.4	10.7037	0.0015*
Overall (N=822)	**56**	**6.8**		
	Proportion of Adherent Patients (MPR≥80%) ‡			
	N	**%**	**Statistic (S)**	**P- value†**
ETN (N=274)	58	21.2		
ADA (N=274)	45	16.4	2.1392	0.1766
IFX (N=274)	90	32.9	18.5780	< 0.0001*
Overall (N=822)	**193**	**23.5**		
	Proportion of Patients who Discontinued Index TNF-inhibitor Therapy‡			
	N	**%**	**Statistic (S)**	**P- value†**
ETN (N=274)	183	66.8		
ADA (N=274)	180	65.7	0.0720	0.8581
IFX (N=274)	170	62.0	1.4956	0.2589
Overall (N=822)	**533**	**64.8**		
	Proportion of Patients who Switched from Index TNF-inhibitor Therapy‡			
	N	**%**	**Statistic (S)**	**P- value†**
ETN (N=274)	29	10.6		
ADA (N=274)	37	13.5	1.0323	0.3742
IFX (N=274)	32	11.7	0.1636	0.7877
Overall (N=822)	**98**	**11.92**		

ADA= Adalimumab; **ETN**=Etanercept; **IFX**=Infliximab; **MPR**=Medication possession ratio;
‡ADA and IFX were individually compared to ETN.
†Bonferroni correction was used to control for type 1 error due to multiple comparisons with a prior p value set at 0.025 (0.05/n , where n=2 which is the number of comparisons)
*significant at $p < 0.025$

Appendix B: Results of Unadjusted Analyses (Paired T-Test)

	Medication Adherence (MPR)‡			
	Mean (±SD)	**95% CI**	**Statistic (T)**	**P-value†**
ETN (N=274)	48.8 (±28.7)	45.4 - 52.3		
ADA (N=274)	53.0 (±27.3)	49.8 - 56.3	1.77	0.0779
IFX (N=274)	55.7 (±31.9)	51.9 - 59.5	2.87	0.0045*
Overall (N=822)	**52.5 (±29.5)**	**50.5 - 54.5**		
	Medication Persistence (60-day gap period)‡			
	Mean (±SD)	**95% CI**	**Statistic (T)**	**P-value†**
ETN (N=274)	196.7 (±134.0)	180.8 - 212.7		
ADA (N=274)	199.4 (±130.5)	183.8 - 214.9	0.24	0.8132
IFX (N=274)	215.5 (±133.5)	199.7 – 231.4	1.80	0.0730
Overall (N=822)	**203.9 (±132.8)**	**194.8 – 213.0**		
	Time to Discontinuation (60-day gap period)§			
	Mean (±SD)	**95% CI**		
ETN (N=183)	116.5 (±85.5)	104.1 – 129.0		
ADA (N=180)	117.7 (±78.9)	106.1 – 129.3		
IFX (N=170)	127.5 (±90.1)	113.9 – 141.2		
Overall (N=533)	**120.4 (±84.9)**	**113.2 – 127.6**		
	Time to Medication Switch§			
	Mean (±SD)	**95% CI**		
ETN (N=29)	138.7 (±90.4)	104.3 – 173.1		
ADA (N=37)	139.6 (±89.5)	109.8 – 169.5		
IFX (N=32)	142.5 (±103.9)	105.1 – 180.0		
Overall (N=98)	**140.3 (±93.7)**	**121.5 – 159.1**		

ADA= Adalimumab; **ETN**=Etanercept; **IFX**=Infliximab; **MPR**=Medication possession ratio;
‡ADA and IFX were individually compared to ETN.
†Bonferroni correction was used to control for type 1 error due to multiple comparisons with a prior p value set at 0.025 (0.05/n , where n=2 which is the number of comparisons)
§Paired analysis could not be conducted due to presence of un-paired groups
*significant at $p < 0.025$

Appendix C: Results of Unadjusted Analyses (Signed- Rank-Test)

	Total Healthcare Utilization Cost‡				
	Median	**Mean (±SD)**	**95% CI**	**Statistic (S)**	**P-value†**
ETN (N=274)	$16,575	$16,325 (±8,469)	$15,317 - $17,331		
ADA (N=274)	$18,670	$18,299 (±9,074)	$17,220 - $19,378	3122.5	0.0171*
IFX (N=274)	$13,171	$14,808 (±9,792)	$13,643 - $15,972	3110.5	0.0175*
Overall (N=822)	**$16,488**	**$16,477 (±9,228)**	**$15,845 - $17,109**		
	RA-related Healthcare Utilization Cost‡				
	Median	**Mean (±SD)**	**95% CI**	**Statistic (S)**	**P-value†**
ETN (N=274)	$13,894	$13,391 (±7,421)	$12,508 - $14,273		
ADA (N=274)	$15,987	$15,777 (±8,005)	$14,825 - $16,729	4291.5	0.0010*
IFX (N=274)	$10,283	$11,972 (±9,002)	$10,902 - $13,043	3302.5	0.0116*
Overall (N=822)	**$13,921**	**$13,713 (±8,309)**	**$13,145 - $14,282**		
	TNF-Inhibitor Therapy Costs‡				
	Median	**Mean (±SD)**	**95% CI**	**Statistic (S)**	**P-value†**
ETN (N=274)	$10,209	$10,647 (±6,714)	$9,848 - $11,445		
ADA (N=274)	$13,190	$12,999 (±7,517)	$12,105 - $13,893	4740.5	0.0003*
IFX (N=274)	$6,279	$8,992 (±7,834)	$8,061 - $9,924	4531.5	0.0005*
Overall (N=822)	**$9,512**	**$10,879 (±7,543)**	**$10,363 - $11,396**		

ADA= Adalimumab; **ETN**=Etanercept; **IFX**=Infliximab

‡ADA and IFX were individually compared to ETN.

†Bonferroni correction was used to control for type 1 error due to multiple comparisons with a prior p value set at 0.025 (0.05/n , where n=2 which is the number of comparisons)

*significant at $p < 0.025$

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Vita

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