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Factors associated with the initiation of biologic disease modifying antirheumatic drugs in Texas Medicaid patients with rheumatoid arthritis

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Factors associated with the initiation of biologic disease modifying antirheumatic drugs in Texas Medicaid patients with rheumatoid arthritis

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Dedication

I dedicate my thesis to my best friend and husband, Mingey Lee, who gave me the best support that I could ever ask for throughout my studies. I also dedicate this thesis to my dear parents who have given me the opportunities to pursue my education and dream.

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Abstract

Factors associated with the initiation of biologic disease modifying antirheumatic drugs in Texas Medicaid patients with rheumatoid arthritis

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Rheumatoid arthritis (RA) is a progressive autoimmune disorder of joints that is associated with high health care costs and yet lacks guidance on how early to initiate biologic disease-modifying antirheumatic drugs (DMARDs), a class of medications that is the major cost driver in RA management. The main purpose of this study was to examine patient socio-demographics, medication use patterns, and clinical characteristics associated with initiation of biologic DMARDs.

This was a retrospective study using Texas Medicaid prescription and medical claims database during the study period of July 1, 2003 – December 31, 2010. Patients (18 – 63 years) with an RA diagnosis (ICD-9-CM code 714.xx), no non-biologic DMARD or biologic DMARD use during the pre-index period, and a minimum of 2

prescription claims for the same non-biologic DMARD during the post-index period were included in the study. The primary study outcomes were time to initiation of biologic DMARDs and likelihood of initiating biologic DMARDs.

There was a total of 2,714 subjects included in the study. The majority had claims for pain medications (92.4%), glucocorticoids (64.9%), and non-biologic DMARD monotherapy (86.4%); while 24.3% initiated on biologic DMARDs and 58.9% had a Charlson Comorbidity Index (CCI) score=1. Compared to time to initiation (days) of biologic DMARDs for methotrexate (539.7±276.9) users, it was longer for sulfasalazine (670.2±167.8) and hydroxychloroquine (680.2±158.7) users and similar to leflunomide users (541.6±286.5; $p<0.0001$). There were no significant differences in time to initiation between non-biologic DMARD mono vs. dual therapy. Younger age, glucocorticoid use, methotrexate user (vs. sulfasalazine, hydroxychloroquine users), and non-biologic DMARD monotherapy user (vs. dual therapy user) were significantly associated with higher likelihood to initiate biologic DMARDs.

In conclusion, age, glucocorticoid use, non-biologic DMARD type and therapy were significant factors associated with initiation of biologic DMARDs. Healthcare providers and Texas Medicaid should recognize these potential driving factors and take efforts to achieve optimal therapy for RA patients through thorough RA medication evaluation, well-structured RA monitoring programs, and patient education.

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Chapter 1: Introduction and Literature Review

1.1 PROBLEM STATEMENT

Note: Please see Appendix A for a list of abbreviations. Rheumatoid arthritis (RA) is a progressive autoimmune disorder that is characterized by chronic inflammation of multiple joints, and it is the second most common arthritis after osteoarthritis.[1-4] RA patients may experience a wide range of symptoms from joint stiffness, pain, swelling, and chronic joint deformities to extra-articular (i.e., 'outside of the joint') complications (e.g., rheumatoid nodules, vasculitis, pleural effusions, pulmonary fibrosis, pericarditis, bone marrow suppression).[5] RA affects approximately 1.3 million adults in the United States.[6,7] The prevalence of RA is approximately 0.3 – 1.0% among adults, and it is higher among older individuals (average age ~67), females, and those in developed countries.[6,8] The etiology of RA is not clear, but potential risk factors include being female, oral contraceptive or tobacco use, and genetic factors.[1,9,10] RA patients have lower quality of life as they often experience persistent pain as well as functional disability and psychological problems.[11] Patients with established RA are known to have an average of two or more comorbidities, with cardiovascular disorders and pulmonary disorders (primarily infections) being most common.[12] In addition, RA patients have a mortality rate 1.5 – 1.6 times higher than that of the general population.[13] RA is an economic burden on employers and society. A recent study reported that U.S. employees with RA (N = 2,705) had average annual direct costs (i.e., medical and prescription costs) of $7,445 ($4,687 higher than those without RA; $p < 0.0001$) and indirect costs (i.e., sick

leave, short- and long-term disability, workers' compensation absences) of $1,262 ($525 higher than those without RA; $p < 0.05$) per patient. Based on this study, the total annual economic burden of RA to employers consisted of $5.8 billion ($5.2 billion in direct costs and $579 million in indirect costs), and 4.0 million incremental work loss days.[14]

In RA management, medications are fundamental to treatment and can be divided into three categories:(1) symptomatic drugs (e.g., nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opioid analgesics) help alleviate pain; (2) disease-modifying anti-rheumatic drugs (DMARDs), which are classified into non-biologic and biologic, reduce inflammation and joint damage, and (3) glucocorticoids (GCs) have both anti-inflammatory and disease-modifying properties that help with symptom relief and mitigation of disease progression. The present study will focus primarily on non-biologic and biologic DMARDs.

Non-biologic DMARDs, also known as "conventional DMARDs," have been used to slow disease progression for decades. Examples of non-biologic DMARDs include methotrexate (MTX), sulfasalazine (SSZ), leflunomide (LEF), and hydroxychloroquine (HCQ).[15,16] Biologic DMARDs are relatively new agents that have a significant effect on disease activity, functional capacity, and structural damage.[17,18] Biologic DMARDs are subcategorized into anti-tumor necrosis factor agents (i.e., adalimumab, etanercept, infliximab, certolizumab, golimumab), and non-tumor necrosis factor agents (i.e., abatacept, rituximab, tocilizumab). One significant difference between non-biologic and biologic DMARDs is cost. Non-biologic DMARDs costs range from

$30 to $900 monthly, whereas biologic DMARDs costs range from $2,000 to $5,000 monthly.[19] Current RA treatment guidelines agree that non-biologic DMARDs should be the first line therapy and should be initiated immediately upon diagnosis.[15,18] MTX or LEF are usually the drugs of choice among non-biologic DMARDs. MTX has been a preferred drug because of its effectiveness and relatively low side effect profile with long-term use.[15,16] If targeted outcomes are not achieved with non-biologic DMARD monotherapy, non-biologic DMARD combination therapy is recommended before moving to advanced therapy, which may include an addition of or switch to a biologic DMARD agent.[15,16]

Few studies have explored prescription use patterns among RA patients using non-biologic DMARDs before advancing to biologic DMARDs. Adherence rates of non-biologic DMARDs may impact initiation of biologic DMARDs. For example, if a patient is not adherent with his or her non-biologic DMARD, he or she may start on a biologic DMARD earlier than a patient who was adherent. Adherence rates varied from 30 – 107% among several cross sectional and longitudinal studies. In general, adherence to MTX was higher than to other non-biologic DMARD monotherapy and MTX combination therapy. Several studies have shown that MTX users have longer medication persistence compared to other non-biologic DMARD users.[20-23] In addition to adherence and persistence, socio-demographic factors (age, income, ethnicity/race, and insurance type) and clinical factors (comorbidities, disability, RA severity, and previous therapy with steroids or non-biologic DMARDs) may be associated with the initiation of biologic DMARDs.[24-26]

1.2 STUDY AIM

This study aims to assess medication adherence and persistence of RA patients on non-biologic DMARD therapy, and to investigate the socio-demographic and clinical factors associated with initiation of biologic DMARD therapy.

1.3 STUDY RELEVANCE

This study may help clinicians and researchers better understand if specific non-biologic DMARDs are associated with longer initiation time to biologic DMARDs among RA patients. In addition, understanding what patient demographic and clinical characteristics are associated with shorter time to use of biologic DMARDs may lead to interventions that lengthen the time horizon. For example, interventions to improve non-biologic DMARD adherence and persistence may delay biologic DMARD use, which may lead to overall healthcare cost savings. Finally, the results from this study may be useful for future studies that address treatment protocols for patients with RA.

1.4 LITERATURE REVIEW

1.4.1 Definition, characteristics, and etiology of rheumatoid arthritis (RA)

Rheumatoid arthritis (RA) is a progressive autoimmune disorder that is characterized by flares of inflammation of multiple joints, progressive joint erosion, and presence of autoantibodies.[1-3] RA is the second most common arthritis after osteoarthritis.[4] RA patients usually present with joint stiffness and pain, swelling, and chronic joint deformities. At more advanced disease stages, patients may also experience

extra-articular complications (e.g., rheumatoid nodules, vasculitis, pleural effusions, pulmonary fibrosis, pericarditis, bone marrow suppression).[5] Eighty percent of patients have poor prognosis and are expected to be disabled within 20 years from being diagnosed with RA.[27] Patients are typically diagnosed with RA during their third to fifth decade of life, and RA affects approximately 1.3 million adults in the United States. While the exact cause of RA is unknown, potential risk factors include being female, oral contraceptive or tobacco use, and genetic factors.[1,9]

1.4.2 Prevalence and incidence of RA

RA prevalence is estimated at 0.3 – 1.0% of the adult population, with higher prevalence among older age groups, females, and in developed countries.[6] RA prevalence decreased from 1.1% in 1985 to 0.6% in 2007, which is equivalent to 1.5 million adults in the U.S.[6,28] From one study conducted in a Minnesota county, RA incidence and prevalence were shown to increase as age increased up to 74 years of age, and then it decreases afterwards. For prevalent RA, the average patient's age increased from 63.3 years in 1965 to 66.8 years in 1995.[6] Incidence and prevalence are higher for females than for males (see Table 1.1).[6] RA has been more prevalent among females throughout the years. Among men, prevalence was 0.41 per 100,000 in 2005; and among women, it was 0.98 per 100,000 in 2005.[28] In one study of the civilian, non-institutionalized U.S. population, the age- and sex-adjusted prevalence of arthritis and multiple rheumatic conditions, including RA, was significantly lower among Hispanics (11.2 ± 1.0%) when compared to that of non-Hispanic whites (15.5 ± 0.3%) or non-Hispanic blacks (15.4 ±

0.8%).[29] While China (0.3%), Japan (0.09 per 1000 persons years), northwest Greece (0.15 – 0.36 per 1000 persons), and rural African countries (0.4 – 0.68%) are known to have lower prevalence of RA, Native Americans (2.4 – 7.1%) are reported to have higher prevalence.[30-36] Furthermore, compared to the prevalence of RA in developed countries at 0.3 – 1%, that of RA in developing countries remains at the lower end of the range (i.e., closer to 0.3%).[6]

Table 1.1. Annual incidence ratesa of RA in Olmsted County, Minnesota residents, 1995 – 2007, by gender and age group

	Male		Female		Total	
Age group (years)	**Patients (N)**	**Rate**	**Patients (N)**	**Rate**	**Patients (N)**	**Rate**
18 – 34	7	3.6	27	13.8	34	8.7
35 – 44	26	19.1	73	55.0	99	36.2
45 – 54	30	26.9	72	62.4	102	44.9
55 – 64	36	51.7	55	74.2	91	63.3
65 – 74	31	72.4	51	104.4	82	89.4
75 – 84	13	52.3	30	81.1	43	69.5
≥ 85	2	26.1	13	63.7	15	53.5
Total (95% CI)	145	27.7 (23.1, 32.2)[b]	321	53.1 (47.3, 58.9)[b]	466	40.9 (37.2, 44.7)[c]

[a] Values are the annual incidence rates (95% confidence interval [95% CI] per 100,000 population)
[b] Age-adjusted to the 2000 U.S. white population
[c] Age- and sex-adjusted to the 2000 U.S. white population

Source: Adapted from Myasoedova E, Crowson CS, Kremers HM et al. Is the incidence of rheumatoid arthritis rising?: Results from Olmsted County, Minnesota, 1955-2007. *Arthritis Rheum* 2010; *62*(6); 1576-1582.

1.4.3 Morbidity, mortality and costs

RA has a significant impact on individuals and society. Many RA patients have significant morbidities, such as persistent pain, functional disability, and psychological problems that impact multiple domains of their daily lives[37,38] and that are associated with lower quality of life.[11] The symptoms of RA may vary daily and are oftentimes unpredictable.[39] Nearly 70% of RA patients have irreversible joint damage within a year of disease onset.[3] Furthermore, the autoimmune nature of RA can lead to extra-articular complications (e.g., rheumatoid nodules, vasculitis, pleural effusions, pulmonary fibrosis, pericarditis, bone marrow suppression).[9]

Established RA patients are known to have an average of two or more comorbidities. RA patients' functional status is related to the number of comorbidities, in addition to RA itself. Using data from the US National Data Bank for Rheumatic Diseases, Table 1.2 below shows the top five comorbidities associated with mortality, hospitalization, disability and medical costs among those with RA. Pulmonary disorders, cardiovascular diseases, and liver problems had the highest association with mortality, hospitalization and medical costs. Pulmonary disorders in RA may occur due to impaired immunity as well as drug toxicity from non-biologic DMARDs (i.e., SSZ, MTX, LEF) or biologic DMARDs (e.g, etanercept, infliximab, abatacept). Epidemiological studies have highlighted that RA may contribute to cardiovascular diseases (i.e., myocardial infarction, stroke) through systemic inflammation along with other classic cardiovascular risk factors (i.e., hypertension, dyslipidemia, insulin resistance).[12] Liver problems may be caused by medication hepatotoxicity or in rare cases, via RA's extra-articular manifestations.[40] In addition, RA medications such as glucocorticoids (GCs) and anti-TNF therapy are also known to contribute to increased risk of infections, particularly in the lungs, because of their immunosuppressive properties.[12] RA patients, especially those in active and severe states, are more susceptible to bacterial, tubercular, fungal, opportunistic and viral infections. Depression had the highest association with all three types of disability (i.e. social security, work, Health Assessment Questionnaire (HAQ)). Other significant comorbidities include fracture (due to bone erosion) and GI disorders (due to increased use of GCs and NSAIDs).[12]

The number of comorbidities is an important factor in determining prognosis. As shown in Table 1.3, various comorbidity scoring systems are used to assess disease severity, health status, mortality and morbidity. The scoring systems assign different weights to each disease state, which reflect that varying comorbidity weights result in varying prognoses.

Table 1.2. Ranked importance of comorbid conditions for specific outcomes in patients with RA

Outcome	Comorbid conditions (ranked importance)				
	1	**2**	**3**	**4**	**5**
Mortality	Lung[a]	MI	Fracture	Stroke	Diabetes
Hospitalization	MI	Lung	Other CVD	Hypertension	Depression
SS disability	Depression	Fracture	Lung	Diabetes	Ulcer
Work disability	Depression	Diabetes	Lung	Hypertension	Non-ulcer GI
HAQ disability	Depression	Fracture	Diabetes	Ulcer	Non-ulcer GI
Medical costs	Lung	Liver	Diabetes	Hypertension	Other CVD

CVD, cardiovascular disease; GI, gastrointestinal; HAQ, Health Assessment Questionnaire; MI, myocardial infarction; SS, US social security

[a]Pulmonary disorders

Source: Adapted from Michaud K, Wolfe F. Comorbidities in rheumatoid arthritis. *Best Pract Res Clin Rheumatol;* 2007; *21*(5); 885-906.

Table 1.3. Comorbidity indices and use

Index	Content	Use
Charlson Comorbidity Index (CCI)	19 weighted CCs at hospital admission	Mortality
Kaplan/Feinstein	Rated severity (0 – 3) of cogent CCs	Mortality
Chronic Disease Score (CDS)	Pharmacy data weighted for prescription medications	Disease severity, health status, mortality, hospitalization
Index of Co-Existent Disease (ICED)	Rated severity (0 – 4) of worst CC at hospital admission	Functional outcome, post-hospital complications
Cumulative Illness Rating Scale (CIRS)	Sum of 14-organ system reviews by severity (0 – 4)	Level of overall CCs
Functional Comorbidity Index (FCI)	Sum of 18 CCs	Physical function
Michaud/Wolfe (unpublished data)	11 weighted CCs from patient report	Mortality, hospitalization, work and functional disability, medical costs

CC, comorbid condition

Source: Adapted from Michaud K, Wolfe F. Comorbidities in rheumatoid arthritis. *Best Pract Res Clin Rheumatol;* 2007; *21*(5); 885-906.

When RA patients are left untreated, they can experience severe disability and premature mortality.[41] Sokka et al. showed that the mortality rates among those with RA were 1.5 – 1.6 times higher than the general population. While the overall mortality rates of the general population have improved over the last 4 years, one study reported that this does not hold true for RA patients.[13] Furthermore, RA is estimated to account for 22% of all deaths from arthritis and other rheumatic conditions.[42]

There is significant work productivity loss associated with RA. Approximately 80% of working-age RA adult patients have disabling pain, stiffness and declined functional ability, in addition to restricted ability to perform social roles.[3] A review demonstrated that a median of 66% (range 36% – 84%) of employed RA patients had

work loss because of RA in the previous 12 months, for a median time period of 39 days (range 7 – 84 days). For 50% of RA patients, work loss occurred between 4.5 – 22 years after diagnosis.[43] RA patients with more severe disease experienced higher work productivity loss.[44] The risk of future productivity loss was predicted by lower education level (< 10 years of education) [Reference group: ≥ 14 years of education, Odds Ratio (OR) = 2.40, 95% CI = 1.18 – 4.88], higher patient's global assessments of RA severity (severe RA ≥ 50 out of 100) [Reference group: score of < 50, OR = 1.77, 95% CI = 1.00 – 3.16], and higher self-reported disability Health Assessment Questionnaire score (higher disability ≥ 1.0 out of 3.0) [Reference group: score of < 1.0, OR = 1.85, 95% CI = 1.03 – 3.32].[45] A recent study reported that the U.S. employees with RA (N = 2,705) had average annual direct costs (i.e., medical and prescription costs) of $7,445 ($4,687 higher than those without RA; $p < 0.0001$) and indirect costs (i.e., sick leave, short- and long-term disability, workers' compensation absences) of $1,262 ($525 higher than those without RA; $p < 0.05$) per patient. Based on this study, the total annual economic burden of RA consists of $5.8 billion ($5.2 billion in direct costs and $579 million in indirect costs), and 4.0 million incremental work loss days.[14] As RA progresses to more severe stages, indirect costs increase, which leads to increased likelihood of unemployment.[46,47]

1.4.4 Disease progression and classification of RA

Next, RA progression and classification will be discussed as they are important in determining treatment strategies. RA is an autoimmune disorder in which progression is driven by autoimmunity and the inflammatory process.[41] This disorder is defined by three interrelated factors: disease activity, joint damage, and disability.[17] As shown in Table 1.4, several different scales are available to measure disease activity, which is a composite score of factors (e.g., joint tenderness or swelling, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)). Each scale categorizes the disease progression into four stages: *remission, low activity, moderate activity, and high activity*.[15,17] One study demonstrated that disease activity level and duration of remission influenced subsequent joint damage. Even after a period of remission, a carry-over effect from the previous inflammation remains, thus possibly leading to further progression of the disease and resulting in joint damage. The shorter the duration of remission, the more RA progression is likely to occur.[48] While disease activity is reversible, joint damage is irreversible and manifests the destructive nature of RA. Disability reflects the overall RA state characterized by physical function and quality of life.[17]

Table 1.4. Scales to measure RA disease activity levels[15]

Scales	Disease Activity Levels
Patient Activity Scale or PAS-II[49] (range 0 – 10)	Remission: 0 to 0.25 Low activity: > 0.25 to 3.7 Moderate activity: > 3.7 to < 8.0 High activity: ≥ 8.0
Routine Assessment of Patient Index Data 3[50] (range 0 – 10)	Remission: 0 to 1.0 Low activity: > 1.0 to 2.0 Moderate activity: > 2.0 to 4.0 High activity: >4.0 to 10
Clinical Disease Activity Index[51] (range 0 – 76.0)	Remission: ≤ 2.8 Low activity: > 2.8 to 10.0 Moderate activity: > 10.0 to 22.0 High activity: > 22.0
Disease Activity Score in 28 joints[52] (range 0-9.4)	Remission: < 2.6 Low activity: 2.6 ≤ to < 3.2 Moderate activity: ≥ 3.2 to ≤ 5.1 High activity: >5.1
Simplified Disease Activity Index[51] (range 0 – 86.0)	Remission: ≤ 3.3 Low activity: > 3.3 to ≤ 11.0 Moderate activity: > 11.0 to ≤ 26 High activity: >26

As with many other disease states, RA has classification criteria to monitor and treat the disease appropriately. The 1987 American College of Rheumatology (ACR) classification criteria (not shown in Table 1.4) mainly focused on clinical symptoms and laboratory test results to identify patients with RA.[53] While it was a useful tool to screen for RA, it was limited in classifying patients during the early stages of RA. In 2010, a joint working group comprised of the ACR and European League Against Rheumatism (EULAR) introduced new criteria to both identify *and* classify RA. The 2010 ACR-EULAR classification criteria highlight the importance of the "window of opportunity," which aims to identify RA earlier and to initiate treatment earlier for better outcomes (see Table 1.5).[41] One study demonstrated that the updated 2010 classification criteria

classified more patients earlier than the 1987 ACR criteria.[54] Subsequently, the ACR – EULAR classification criteria was used as a foundation when establishing the updated 2012 RA treatment guidelines in which RA is classified into early and established stages. The early and established stages are defined as having disease duration of less than 6 months and 6 months and longer, respectively.[15]

Table 1.5. The 2010 ACR-EULAR classification criteria for RA[a,b]

Criteria	Score
1. Joint involvement[c]	
1) 1 large joint[d]	0
2) 2-10 large joints	1
3) 1-3 small joints (with or without involvement of large joints)[e]	2
4) 4-10 small joints (with or without involvement of large joints)	3
5) > 10 joints (at least 1 small joint)[f]	5
2. Serology (at least 1 test result is needed for classification)[g]	
1) Negative RF and negative ACPA	0
2) Low-positive RF or low-positive ACPA	2
3) High-positive RF or high-positive ACPA	3
3. Acute-phase reactants (at least 1 test result is needed for classification)[h]	0
1) Normal CRP and normal ESR	1
2) Abnormal CRP or abnormal ESR	
4. Duration of symptoms[i]	
1) < 6 weeks	0
2) ≥ 6 weeks	1

ACPA = anti-citrullinated protein antibody; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor

Note: Patients who have at least 1 joint with definite clinical synovitis and/or with the synovitis not better explained by another disease should be tested for RA.[a] A patient is classified as having definite RA if their score is ≥ 6 (out of 10)[b]

[a] Differential diagnoses vary among patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted.

[b] Although patients with a score of <6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time.

[c] Joint involvement refers to any *swollen* or *tender* joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are *excluded from assessment*. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.

[d] "Large joints" refers to shoulders, elbows, hips, knees, and ankles.

[e] "Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

[f] In this category, at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g., temporomandibular, acromioclavicular, sternoclavicular, etc.).

[g] Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay. Where RF information is only available as positive or negative, a positive result should be scored as low-positive for RF.

[h] Normal/abnormal is determined by local laboratory standards.

[i] Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

Source: Adapted from https://ww2.rheumatology.org/practice/clinical/classification/ra/ra_2010.asp

1.4.5 RA treatment

1.4.5.1 Pharmacologic therapy

Regarding RA therapy, medications are considered fundamental to treatment (see Table 1.6). Pharmacologic therapy can be divided into three categories: (1) symptomatic medications (e.g., nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opioid analgesics), (2) disease-modifying anti-rheumatic drugs (non-biologic and biologic DMARDs), and (3) glucocorticoids (GCs). This section will provide a brief overview of each category.

Symptomatic medications

Symptomatic medications can be classified into two subgroups: non-opioid analgesics and opioid analgesics. Among non-opioid analgesics, NSAIDs, which are cyclooxygenase (COX) (i.e., nonspecific COX or COX-2) inhibitors, have antipyretic, analgesic, and anti-inflammatory properties. They are usually indicated to relieve mild to moderate pain, and administered orally or rectally. Common side effects include gastrointestinal (GI) effects (e.g., heartburn, nausea, vomiting) and dizziness. Acetaminophen is another non-opioid analgesic that has analgesic and antipyretic properties, but not anti-inflammatory effects. The drug is proposed to inhibit COX-3 in the central nervous system. It can be administered orally, rectally, or intravenously, and

its side effects are nausea and vomiting. Opioid analgesics, which interact with opioid receptors, are approved for moderate to severe pain, and administered orally, transdermally, rectally, vaginally, topically, and intravenously. Common side effects include constipation, nausea, vomiting, and dizziness. Unlike the non-opioid medications, opioid analgesics can produce tolerance and physical dependence.[55,56]

Disease-modifying antirheumatic drugs (DMARDs)

DMARDs are classified into non-biologic and biologic. Non-biologic DMARDs, which have been available for decades, help alleviate RA symptoms, reduce joint damage, and help with disease remission.[17] Among non-biologic DMARDs, MTX, an antimetabolite that interferes with cellular replication, is usually the drug of choice as monotherapy in the early stage or as part of combination therapy in advanced stages because of its effectiveness and relatively low side effect profile with long-term use. The drug is usually given orally once weekly. Common side effects include liver alopecia, oral ulcers, cytopenias, nausea, and vomiting.[15,16] According to the Treatment of Early Rheumatoid Arthritis (TEAR) trial, 30% of RA patients with early, poor prognosis were shown to respond well to MTX monotherapy and had comparable results to step up combination therapy (i.e., MTX + etanercept or MTX + SSZ + HCQ) at 2 years.[57] Other non-biologic DMARDs include LEF, HCQ, and SSZ. LEF is an immunomodulatory, antiproliferative, and anti-inflammatory agent that is given orally once daily, and its side effects include rash, diarrhea, respiratory tract infection, and agranulocytosis.[19] HCQ, an antimalarial with unknown mechanism of action for RA, is given orally once daily. Its

side effects include disorder of the cornea, torsades de pointes, neuromyopathy, and hearing loss.[19] SSZ also has an unknown mechanism of action and is given orally once daily as an initial dose followed by twice daily as a maintenance dose. Some common side effects include rash, abdominal pain, loss of appetite, headache, and hepatotoxicity.[19]

Biologic DMARDs are relatively new agents that are known to have a significant effect on disease activity, functional capacity, and structural damage.[17,18] Biologic DMARDs can be categorized into anti-tumor necrosis factor (TNF) and non-TNF agents. The following are anti-TNF agents: etanercept, infliximab, adalimumab, certolizumab, and golimumab. Anti-TNF agents prevent part of the cascade that leads to RA by blocking TNF-α's binding to its receptor. Common adverse events include injection-site or infusion reactions, infections, and malignancy. Regarding non-TNF agents (i.e., anakinra, tocilizumab, abatacept, and rituximab), each has a different mechanism of action such as Interleukin (IL)-1 and IL-6 inhibition, T-cell costimulation blockade and B-cell target. Even though anti-TNF and non-TNF agents have different mechanism of actions, their adverse effects are similar. Also, both have relatively long half-lives (4 – 19 days). While abatacept, a non-TNF agent, was approved as a first-line biologic DMARD in the U.S., some patients do not respond as rapidly as with anti-TNF agents. As shown in Table 1.6 below, there are more anti-TNF agents available than non-TNF agents. The latter agents are reserved for use in patients with established RA and high disease activity.[58] Note: Adalimumab, etanercept, and infliximab were approved by the FDA between 1998-2002, which was prior to the present study's timeframe, while other agents

(i.e., certolizumab, golimumab, abatacept, rituximab, tocilizumab) were approved between 2005-2010, which was during the present study's timeframe.

Biologic DMARDs are shown to have greater efficacy when combined with MTX or other non-biologic DMARDs.[16] Because of high costs, biologic DMARDs are usually reserved for advanced stage RA after other options have been utilized. Non-biologic DMARD costs range from $30 to $900 monthly, whereas biologic DMARD costs range from $2,000 to $5,000 monthly.[19]

Glucocorticoids (GCs)

GCs have both anti-inflammatory and disease-modifying properties. GCs, which can be administered orally, intra-articularly or intramuscularly, are usually given in combination with non-biologic DMARDs to slow down the progression of bone erosion. Low dose (5 – 10 mg/day) GCs are usually added to DMARDs (typically for up to 2 years), but higher doses are used for faster improvement and they are typically tapered within 6 to 8 months.[16,59] Low to medium dose of oral GCs, high dose of intramuscular GCs, or intravenous bolus GCs are usually used when patients wait for a non-biologic DMARD to take effect.[60,61] Intra-articular GC therapy is standard for patients with polyarticular disease activity.[62] Because of its long-term adverse effects (e.g., cardiovascular risk), GCs are recommended for short-term use, and the dosage needs to be determined after weighing the benefits and risks.[16,63]

Table 1.6. Pharmacological therapeutic options for RA by drug class[5,15]

Symptomatic Medications	
Non-opioid analgesics	**Nonselective nonsteroidal anti-inflammatory drugs (NSAIDs):** Aspirin, celecoxib, diclofenac, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, meclofenamate, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, sulindac, tolmetin **Acetaminophen**
Opioid analgesics	Codeine, hydrocodone, oxycodone, fentanyl, hydromorphone, meperidine, methadone, morphine, propoxyphene, tramadol
Disease Modifying Anti-Rheumatic Drugs (DMARDs)	
Non-biologic DMARDs	Methotrexate (MTX), sulfasalazine (SSZ), leflunomide (LEF), hydroxychloroquine (HCQ)
Biologic DMARDs[a]	**Anti-TNF:** Adalimumab, certolizumab, etanercept, infliximab, golimumab **Non-TNF:** Abatacept, rituximab, tocilizumab
Glucocorticoids (GCs)	
	Prednisone, prednisolone, methylprednisolone

[a] Approval dates: adalimumab (12/2002); certolizumab (5/2009); etanercept (11/1998); infliximab (11/1999); golimumab (4/2009); abatacept (12/2005); rituximab (3/2006); tocilizumab (1/2010)
TNF, necrosis factor

1.4.5.2 Non-pharmacologic therapy

Conventional therapies and surgical procedures are also used to treat RA. Examples of conventional therapies include: physical therapy, occupational therapy, comprehensive rehabilitation, self-management programs including cognitive behavioral approaches, and assistive devices such as wrist and finger splints and foot orthotics. In addition, many RA patients depend on a wide range of complementary and alternative medicine (e.g. herbs, vitamins, yoga, homeopathy, acupuncture).[39,64] In cases of significant functional impairment and pain, reconstructive surgery may be considered for

selected RA patients.[65] Among RA patients, 17% will have an orthopedic intervention in 5 years of RA diagnosis, and over 33% will undergo a major joint replacement.[27]

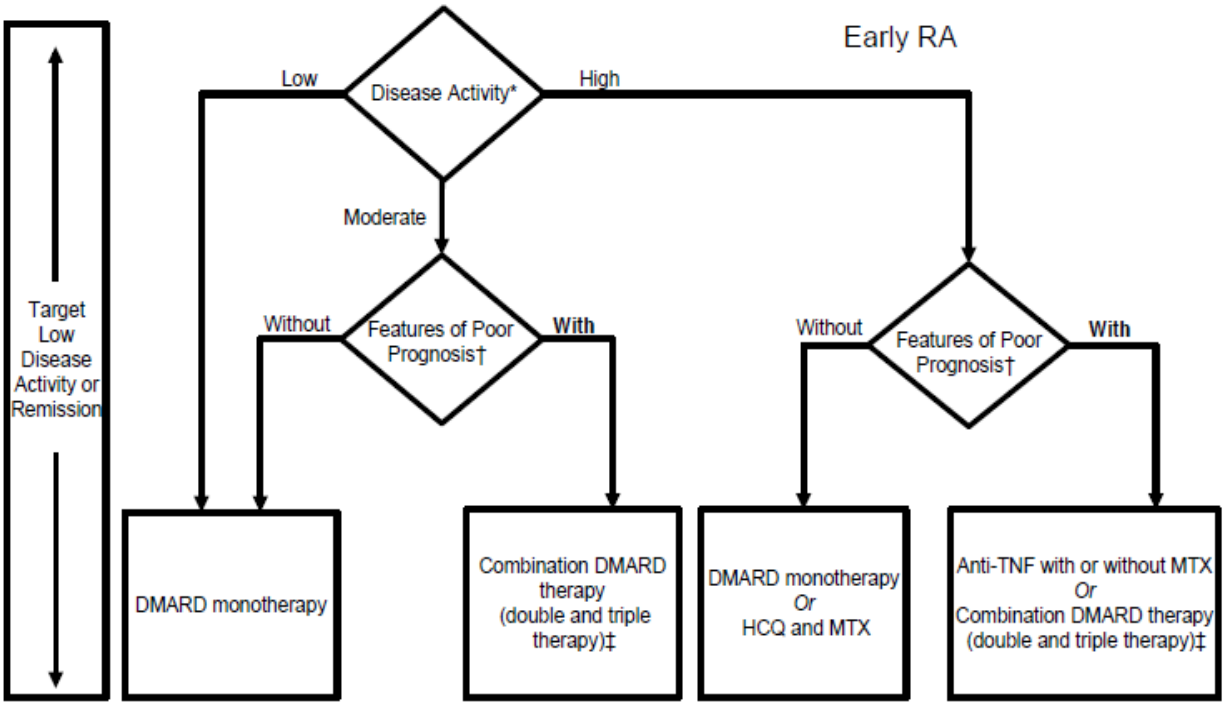
1.4.6 Overview of current RA treatment guidelines

Among several different sets of clinical guidelines available for managing RA, the ACR and the EULAR RA therapy management guidelines are the most utilized. This section will focus on the overarching principles of each set of guidelines and recommendations regarding transitioning from non-biologic DMARDs to biologic DMARDs.

1.4.6.1 American College of Rheumatology (ACR) treatment guidelines

In 2012, the ACR updated RA therapy management guidelines to address early stage RA (Figure 1.1) and established stage RA (Figure 1.2). The basic principles in the guidelines are to: a) reach low disease activity or remission as soon as possible; b) achieve tighter control of the disorder by frequent assessments every 1 – 3 months; and c) make therapy adjustments every 3 – 6 months.[15] According to the guideline, MTX or LEF (i.e., non-biologic DMARDs) are the first drugs of choice for most patients. After non-biologic DMARD monotherapy, patients are usually stepped up to non-biologic DMARD combination therapy before moving to advanced therapy, which may include an addition of or switch to a biologic DMARD agent.[15]

Figure 1.1. Treatment guidelines for early RA (disease duration < 6 months) from the 2012 American College of Rheumatology recommendations update



DMARD (disease-modifying antirheumatic drug) indicates non-biologic DMARD and includes hydroxychloroquine (HCQ), leflunomide (LEF), methotrexate (MTX), minocycline, and sulfasalazine

Anti-TNF (anti–tumor necrosis factor) indicates biologic DMARD and includes adalimumab, certolizumab, etanercept, infliximab, golimumab

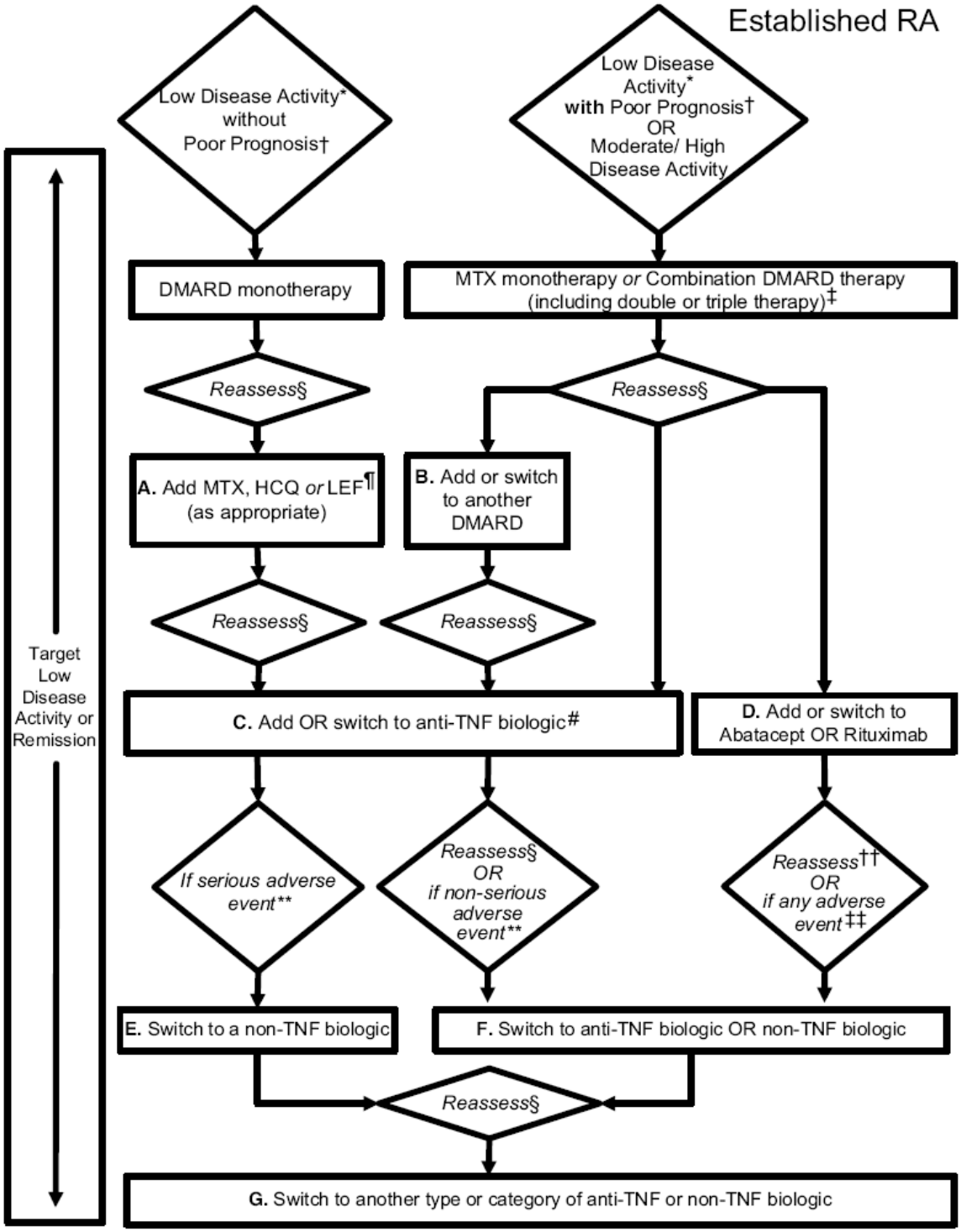
* Disease activity – categorized as low, moderate, and high according to validated scales (see Table 2)

† Patients were categorized based on the presence or absence of 1 or more of the following poor prognostic features: functional limitation, extraarticular disease, positive rheumatoid factor or anti– cyclic citrullinated peptide antibodies, and bony erosions by radiograph.

‡ Combination non-biologic DMARD therapy with 2 non-biologic DMARDs is most commonly MTX based.

Source: Adapted from 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 & Research* 2012; 64 (5): 625-639.

Figure 1.2. Treatment guidelines for established RA (disease duration ≥ 6 months) from the 2012 American College of Rheumatology recommendations update



In the diagram, DMARD refers to non-biologic DMARD

Non-biologic DMARD (disease-modifying antirheumatic drug) (includes hydroxychloroquine [HCQ], leflunomide [LEF], methotrexate [MTX], minocycline, and sulfasalazine); anti-TNF = anti–tumor necrosis factor.

* Disease activity – categorized as low, moderate, and high according to validated scales (see Table 2)

† Patients were categorized based on the presence or absence of 1 or more of the following poor prognostic features: functional limitation, extraarticular disease, positive rheumatoid factor or anti– cyclic citrullinated peptide antibodies, and bony erosions by radiograph.

§ 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 anticipated time for peak effect.

¶ LEF can be added in patients with low disease activity after 3–6 months of minocycline, HCQ, MTX, or sulfasalazine.

If after 3 months of intensified non-biologic DMARD combination therapy or after a second non-biologic DMARD has failed, the option is to add 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 experience associated with the use of a medical product in a patient. The FDA definition of serious adverse event includes death, life-threatening event, initial or prolonged hospitalization, disability, congenital anomaly, or an adverse event requiring intervention to prevent permanent impairment or damage.

Source: Adapted from 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 & Research* 2012; 64 (5): 625-639.

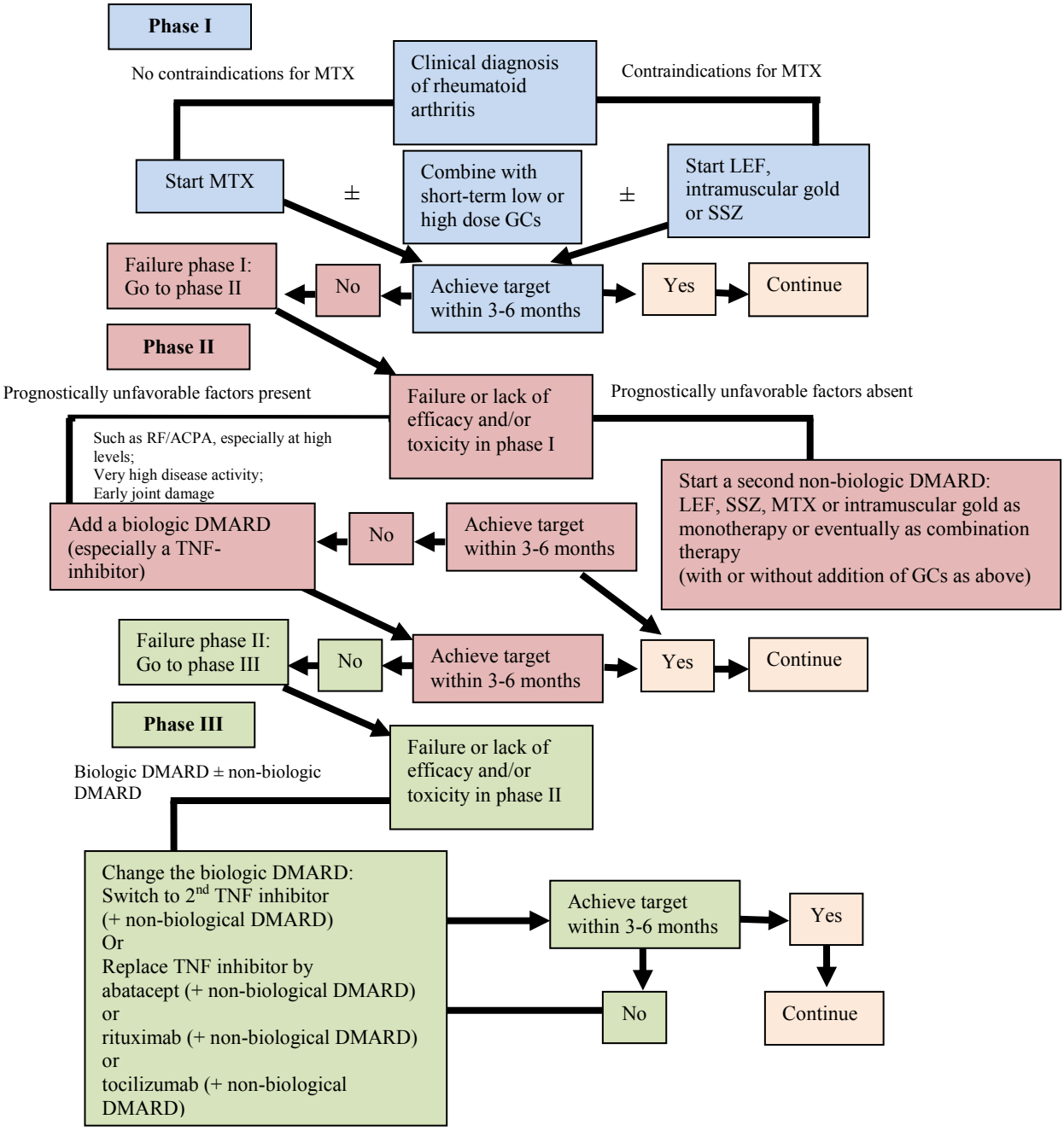
1.4.6.2 European League Against Rheumatism (EULAR) treatment guidelines

The 2010 EULAR guidelines have a set of recommendations (Figure 1.3) and a treatment algorithm (Table 1.7) regarding RA management including non-biologic and biologic DMARDs use. Non-biologic DMARDs are recommended to be initiated when RA is diagnosed. The following patients are recommended to consider a biologic DMARD: those who have poor prognostic factors and do not meet treatment targets with the first non-biologic DMARD, those who respond to MTX (with or without non-

biologic DMARDs) inadequately, and DMARD-naïve patients with poor prognostic factors. Furthermore, the guideline recommends that every patient be considered for intensive medication strategies. According to the EULAR guideline, even though GCs are advantageous with disease-modifying effects, they are recommended to be used for short-term (no specific time period mentioned) to avoid any long-term adverse effects. The guidelines do not explicitly recommend whether to use high or low dose GCs.[16]

While the two sets of guidelines have different treatment algorithms, both share a few key points. They hold the fundamental principle that for better outcomes: RA patients should be treated with non-biologic DMARDs as soon as they are diagnosed, and clinicians should aim for remission or low disease activity as soon as possible. When choosing a non-biologic DMARD, MTX is a preferred choice in both of the guidelines. Medications should be monitored and reassessed every 1 – 3 months. When adjusting therapy, patients are usually stepped up from non-biologic monotherapy to non-biologic DMARD combination therapy before adding or switching to a biologic DMARD.

Figure 1.3. Algorithm based on the EULAR recommendations



Source: Adapted from 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.

Table 1.7. Non-biologic DMARD-based monotherapy, dual therapy and triple therapy options based on the EULAR recommendations[16]

Monotherapy	**Medications**
Phase I	First line: MTX Second line: LEF, gold, or SSZ (if MTX is contraindicated)
Phase II	2nd non-biologic DMARD (when the 1st non-biologic DMARD failed)
Phase III	Biologic DMARD (change the biologic component)
Dual therapy	
Phase I	First line: MTX+ GC Second line: LEF, gold, or SSZ + GC
Phase II	Non-biologic DMARD combination (2 non-biologics)
Phase III	Biologic DMARD + non-biologic DMARD
Triple therapy	
Phase II	First line: non-biologic DMARD combination (2 non-biologics) + GC Second line: non-biologic DMARD combination (2 non-biologics) + biologic (TNF inhibitor)
Phase III	Non-biologic DMARD combination (2 non-biologics) + biologic (TNF inhibitor) + GC

Phase I is when clinical diagnosis of RA has initially been made

Phase II is when failure to, lack of efficacy of, or toxicity of Phase I therapy occurred

Phase III is when failure to, lack of efficacy of, or toxicity of Phase II therapy occurred

MTX, methotrexate; LEF, leflunomide; SSZ, sulfasalazine; DMARD, disease-modifying antirheumatic drug; GC, glucocorticoid; TNF, tumor-necrosis factor

1.4.7 RA medication use patterns

Medication adherence and persistence are critical in maintaining therapeutic benefit from medications and preventing adverse outcomes and higher costs of care associated with nonadherence. Especially with RA patients, early treatment and maintenance of therapy are important to avoid further disease progression and achieve remission or lower disease activity as soon as possible. Below is an overview of adherence and persistence in general, followed by adherence and persistence with non-biologic therapies among RA patients.

1.4.7.1 Overview of medication adherence and persistence

Medication adherence is defined as "active, voluntary, and collaborative involvement of the patient in a mutually acceptable course of behavior to produce a therapeutic result."[66] It measures the degree to which a patient follows his or her healthcare provider's recommendations in regards to prescribed timing, dose, and frequency. Medication persistence is defined as the act of resuming medications for the prescribed time period.[67] Studies show that 50% of the annual prescriptions dispensed are not taken as prescribed. Approximately 125,000 deaths and 33 – 69% of medication-related hospital admissions occur from medication nonadherence. In economic terms, nonadherence direct and indirect costs are between $100 billion and $300 billion annually. Patients with chronic diseases are reported to be adherent to their medications only 50 – 60% of the time.[68] Adherence rates in patients with acute conditions are usually higher than those with chronic conditions.[69] Regarding overall RA medication adherence,

greater self-efficacy, better patient-health care professional relationship, more social support, and older age have been shown to be associated with improved RA medication adherence.[70-74]

1.4.7.2 Non-biologic DMARD adherence and persistence in RA patients

Non-biologic DMARD adherence

Adherence to non-biologic DMARDs will be reviewed in this section. Patients who have little efficacy or increased adverse effects from non-biologic DMARDs are more likely to not adhere to therapy. Patients who are not adherent to non-biologic DMARDs may be more likely to initiate biologic DMARD therapy. Two review studies by Salt et al (2010) and van den Bemt et al (2012), respectively, revealed that rates of adherence to non-biologic DMARDs varied from 33 – 107% among four cross sectional and longitudinal studies. [73,78-80] Salt et al. examined 35 studies that were not limited to non-biologic DMARD adherence. Some studies assessed patients' beliefs about medication taking and persistence in biologic DMARDs. On the other hand, van den Bemt et al. examined 19 studies that evaluated medication adherence rates and factors associated with adherence. In both reviews, most studies did not specify DMARD type or investigated irrelevant medications (i.e., biologic DMARDs, D-penicillamine). There were only four studies that were relevant to non-biologic DMARD adherence.[70,75-77] The wide variation in adherence rates could be due to: study design, sample size differences,

heterogeneous patient populations, follow-up period variations, medications studied and varied adherence measurement methods.[78]

Because of similarities to the present study, which used Texas Medicaid, two retrospective database studies using Tennessee Medicaid will be reviewed in more detail below. Among Tennessee Medicaid enrollees (N=10,547) who had a new episode of non-biologic and/or biologic DMARD regimens between 1995 – 2004, mean adherence (MPR, Medication Possession Ratio) rates of non-biologic DMARDs (i.e., MTX, HCQ, SSZ, LEF, MTX + HCQ) were between 66% (SD not available) for MTX + HCQ and 85% (SD not available) for LEF, after one year follow-up. The study sample was mostly female (80%), white (72%), and aged 41 – 66.[75] A later (1995-2005) Tennessee Medicaid managed care study using a retrospective cohort of RA patients with a shorter follow-up period (180 days vs. 1 year) revealed lower median adherence rates, ranging from 33% to 69%, for MTX, HCQ, LEF, and SSZ. While SSZ had the lowest median adherence of 33%, LEF had the highest median adherence of 69%.[76] Note: adherence rates may have been lower in this study because the previous study reported means, while this study reported medians.

In another longitudinal study that included RA, polymyalgia rheumatica, or gout patients (N=127) at an outpatient rheumatology clinic in the Netherlands, adherence was assessed using Medication Event Monitoring Systems (MEMS). Of the total sample, 81 patients had RA and were taking NSAIDs and non-biologic DMARDs (i.e., SSZ, MTX). Three types of compliance were measured: "taking compliance", which was the

percentage of taking doses as prescribed during a study period, "correct dosing", which was the percentage of correct number of doses taken during a study period, and "timing compliance", which was the proportion of: the number of interdose-intervals (i.e., in-between dose interval ± 25%) of allowed period / the number of prescribed interdose-intervals. Patients on MTX (once-weekly dosing) had 107% (98 – 117%) taking, 81% (75 – 87%) correct dosing and 83% (76 – 90%) timing compliance, while patients on SSZ (twice-daily dosing) had 72% (60 – 84%) taking, 55% (44 – 67%) correct dosing and 25% (18 – 33%) timing compliance, respectively. SSZ adherence may have been lower because of a more frequent dosing schedule. The study subjects were mostly female (66%) and aged 60 ± 14 years.[70] In a randomized, controlled, assessor-blinded clinical trial, adherence was measured using pill counts. Brus et al. showed that adherence rates for SSZ were 82% and 91% for study periods 0 – 3 months and 3 – 6 months, respectively.[77]

Individual adherence comparisons were difficult with other studies because they did not specify non-biologic DMARD type or they reported combined NSAID and non-biologic DMARD adherence together. Interview-based studies reported adherence rates between 30% and 68% for non-biologic DMARDs and NSAIDs.[74,79-81] Overall, of the few studies conducted, there is a wide range of non-biologic DMARD adherence rates among RA patients regardless of measurement methods or medication type.

Non-biologic DMARD persistence

Regarding persistence or discontinuation of non-biologic DMARDs, several studies have shown that MTX users have longer medication persistence compared to other non-biologic DMARD users.[20-23] Also, the majority of the studies did not report a gap period with persistence estimates. In a cross-sectional study that had a mean follow-up duration of 100.5 ± 69.4 months, Agarwal et al. showed that the median medication persistence periods (or retention rates), which were estimated by Kaplan-Meier survival analysis, for single or combination therapy were: MTX, 28 months; HCQ, 18 months; LEF, 15 months; SSZ, 12 months. The study revealed that MTX monotherapy had longer persistence than MTX combination therapy (28 months vs.19 months; $p = 0.001$).[20] Similarly, Aletaha et al., in a survival analysis study with 42 months follow-up, demonstrated that MTX users had longer persistence (28 ± 1 months) than SSZ users (23 ± 1 months) or LEF users (20 ± 1 months).[21] On the other hand, a Tennessee Medicaid prescription claims database study showed that using survival analysis, the overall persistence rates were similar among MTX, HCQ, LEF, and MTX + HCQ at 121-150 days; however, SSZ was much lower at only 53 days during the 10 year study period.[75] In another survival analysis, Grove et al. reported that <45% of MTX patients discontinued therapy at 96 months, while 50% of SSZ patients discontinued therapy at 34 months.[22] Furthermore, in a third survival analysis study with an average follow-up period of 13.6 ± 9.3 years, high dose therapy was associated with a longer time to discontinuation of therapy (high dose MTX – 73 months vs. low dose MTX – 39 months; high dose SSZ – 34 months vs. low dose SSZ – 7 months.[23] Folate added to MTX resulted in longer

persistence compared to MTX alone (61.7 vs. 30.3 months). This study also used survival analysis to estimate the persistence rates.[82] In a 10-year longitudinal prescription claims database study that investigated only MTX, of the total MTX index users (N=941), half of the patients had a treatment gap of over 90 days within 5 years of follow-up. On average, the patients experienced a 45 day treatment gap per year. The MTX treatment gap increased with older age, longer disease duration, low to moderate disease activity, and the presence of ulcer or mild liver disease.[83]

In summary, previous studies have reported a wide range of adherence among non-biologic DMARDs. Only a few studies investigated individual non-biologic DMARD adherence rates. While the literature is scarce, two studies suggest that more frequent dosing and combination therapy may be associated with lower adherence.[70,75] Furthermore, being MTX users, taking high doses of medications (i.e., MTX, SSZ), being younger, having shorter disease duration, severe disease activity, and absence of ulcer or mild liver disease may have an association with longer medication persistence.[20-23,83]

1.4.8 Initiation of biologic DMARDs

Previous studies have shown that early initiation of non-biologic DMARDs or biologic DMARDs leads to long-term benefits during the disease course.[26,84,85] Compared to non-biologic DMARDs, biologic DMARDs were shown to have better outcomes in radiographic structural joint damage, but not in disease activity.[86] Currently, there are no established rules in the clinical practice guidelines that show when to initiate biologic

DMARDs. This section will focus on the current practice patterns and factors associated with the initiation of biologic DMARDs.

1.4.8.1 Current practice patterns

Variations exist across countries and individual practitioners regarding when to initiate biologic DMARDs. From a prescriber's and patient's point of view, the initiation of biologic DMARDs may vary because of their perceptions of drug efficacy, tolerability, and long-term safety, as well as reimbursement factors.[87]

In a U.S. study that used commercial and Medicare databases, overall biologic DMARD use increased from 3% in 1999 to 26% in 2006. Among biologic DMARD initiators (N=8,218), 86% of patients received a non-biologic DMARD (66% were on MTX) 12 months prior, while 14% had no history of non-biologic DMARD use in the pre-period.[88] In a Swedish study, Soderlin et al. reported that over 40% of biologic DMARD-naïve patients starting on biologic DMARDs had disease duration of less than 5 years. Among these patients, those with disease duration of less than 2 years, the percentages of patients who initiated biologic DMARDs increased significantly from 3% in 1999 to 16% in 2006. As for the previous usage of non-biologic DMARD therapy, the percentages of biologic DMARD-naïve patients who previously used 1 or 2 consecutive non-biologic DMARDs increased, while those who used more than 2 consecutive non-biologic DMARDs decreased during the years 1999 – 2006 (see Table 1.8). In addition, there was no trend in the percentages of these patients who were on previous DMARD combination therapy (ranges 23 – 34%). Compared to the previous U.S. study, this study

indicated a higher percentage (> 90%) of patients who had received MTX prior to biologic DMARD initiation. Furthermore, patients with shorter RA duration and less disease severity were shown to be treated increasingly with biologic DMARDs.[89] In another Swedish study of RA patients, Zufferey et al. demonstrated that when biologic DMARDs were initiated earlier after RA diagnosis (5.5 years vs. other countries, 9 – 12 years), the outcomes improved. These patients used fewer non-biologic DMARDs and they improved in disease activity score (DAS) and remission rates.[26]

Table 1.8. Trend in the percentages of biologic DMARD-naïve patients starting on biologic DMARD who had previous non-biologic DMARD therapy[89]

Non-biologic DMARD use	1999	2006
1 previous	3%	27%
2 consecutive	10%	19%
>2 consecutive	56%	23%

1.4.8.2 Factors associated with initiation of biologic DMARDs

While there is currently no consensus regarding how early to start biologic DMARDs, there are various factors that may be associated with initiation of biologic DMARDs. As for socio-demographic factors, age, income, ethnicity/race, and insurance type may be related to initiation of biologic DMARDs, although there is no clinical reason for differential prescribing according to age or race/ethnicity.[24-26] DeWitt et al. demonstrated that older individuals (each 10 year increase in the age; odds ratio [OR] = 0.74, 95% CI = 0.66 – 0.82, $p < 0.01$) and lower annual income earners (each $10,000

reduction; OR = 0.95, 95% CI = 0.91 – 1.00, p = 0.04) were less likely to receive biologic DMARDs.[24] Another study by Dewitt et al. found that although those on public insurance have more severe RA (i.e., higher disease severity, worse disability, and longer disease duration), those on private insurance tended to initiate biologic DMARDs earlier than those on public insurance.[90] Furthermore, Pease et al. showed that there is variation among 13 countries in the initiation of anti-TNF agents, which may be because of different national reimbursement policies and different prescribing preferences. Five countries (i.e., Netherlands, Denmark, Norway, Sweden, U.S.), which have relatively less restrictive insurance policies for reimbursing biologic DMARDs, were shown to start biologic DMARDs at lower disease severity scores than others.[87]

DeWitt et al. found that among clinical factors, disability and previous treatment with steroids or non-biologic DMARDs may be associated with initiating biologic DMARDs. While gender, race, employment status, comorbidity, previous NSAID use, and treatment center were not significant factors, disability (each 1-unit increase in the Health Assessment Questionnaire score; OR = 1.45, 95% CI = 1.22 – 1.72, $p < 0.01$) and previous treatment with steroids (OR = 2.24, 95% CI = 1.71 – 3.46, $p < 0.01$) or non-biologic DMARDs (OR = 2.43, 95% CI = 1.71 – 3.46, $p < 0.01$) were significantly associated with initiation of biologic DMARDs.[24] Even though the previous study showed no significant association between comorbidity and initiation of biologic DMARDs, it is important to note that there are some disease states (e.g., congestive heart failure, sepsis, tuberculosis) that require pretreatment before using biologic DMARDs or are contraindicated in certain biologic DMARDs. Thus some groups of patients would

not be recommended to use biologic DMARDs.[24,87] Another factor that may predict initiation of biologic DMARDs is DAS. A review compared baseline characteristics of RA patients from twelve different countries' databases at the time of initiation of anti-TNF agents and noted that DAS ranged from 5.3 to 6.6 (high activity; see Table 1.3) at biologic DMARD initiation.[87,89,91] Although there is currently no minimal DAS score at which biologic DMARDs are to be initiated, this evidence may suggest that the higher the DAS score, the higher likelihood of initiating biologic DMARDs.

In summary, while there exist no established rules regarding when to initiate biologic DMARDs, previous studies showed that socio-demographic (age, income, ethnicity/race, and insurance type) and clinical (disability, RA severity, and previous therapy with steroids or non-biologic DMARDs) factors may be associated with the initiation of biologic DMARDs.[24-26]

1.4.9 Texas Medicaid and biologic DMARD utilization management

The Medicaid program is a jointly managed health care program by federal and state government that is intended to provide low-income Americans with access to health care. The Medicaid program was established in 1965 by Congress under Title XIX of the Social Security Act. The Texas Medicaid program began in September 1967. As years passed, Congress expanded the Medicaid eligible population to those with disabilities, children, pregnant women and older individuals. While the Social Security Act and federal regulations set the minimum requirements for health care coverage that state

Medicaid programs have to provide, each state develops its own health care program by including optional services and eligibility groups. Medicaid pays for acute health care as well as long-term care services. There are currently over 3.6 million Texas residents who are enrolled in Medicaid each month. As of the state fiscal year 2011, 55% of the Medicaid beneficiaries were female, and 77% were under 21 years old. Although the majority of recipients are non-disabled children (66%), they comprised only 33% of Texas Medicaid direct health care expenditures. Whereas, the elderly, blind, or disabled (25% of the Texas Medicaid population) comprised 58% of the expenditures.[92]

As Medicaid faces budget constraints, managing utilization of costly medications such as biologic DMARDs is a major concern. Fischer et al. showed that between 1999 and 2005, 32 states implemented or planned to implement prior authorization for Medicaid, with a wide variation of criteria, as a cost containment strategy. Texas had not implemented nor planned to implement the strategy. Despite the effort, biologic DMARD use was low only at the beginning of introducing prior authorization; total expenditures of state Medicaid programs on DMARDs increased dramatically from $200 million in 1999 to $567 million in 2005. Whereas $27.7 million (13.8% of expenditure on DMARDs) was spent on etanercept in 1999, $255 million (44.8%) was spent on etanercept and adalimumab. [93] As of 2013, Texas Medicaid has a preferred drug list of etanercept and adalimumab for the biologic DMARD class and prior authorization criteria is as follows: (1) treatment failure with preferred drugs within any subclass; (2) contraindication to preferred drugs; (3) allergic reaction to preferred drugs. [94]

1.4.10 Study purpose

Medication adherence and persistence are important for optimal RA management. From the payer's perspective, medication utilization patterns may be related to health care costs and outcomes. Because of their significant cost, it is important to understand more about initiation of biologic DMARDs, other RA medication utilization patterns, as well as factors associated with initiation of biologic DMARDs. Addressing this gap in the literature, this retrospective database study of Texas Medicaid recipients may be meaningful for the following reasons: (1) understanding drug utilization patterns and factors associated with the initiation of biologic DMARDs in an underserved and diverse population and (2) evaluating drug utilization and management of biologic DMARD use in patients with RA.

1.4.11 Study objectives and hypotheses

1. Describe patient socio-demographic (age, gender, race), medication use patterns [non-biologic DMARD type, non-biologic DMARD therapy (i.e., monotherapy, dual therapy), non-biologic DMARD adherence and persistence, pain medication use, glucocorticoid use], and clinical characteristics (i.e., comorbidities, and rheumatologist visit).

2. To determine whether adherence and persistence differ by non-biologic DMARD type.
   - **H_{2a}** Adherence to methotrexate is significantly higher than adherence to other non-biologic DMARD types.
   - **H_{2b}** Persistence to methotrexate is significantly higher than persistence to other non-biologic DMARD types.

3. To determine whether adherence and persistence differ by non-biologic DMARD therapy.
   - **H_{3a}** Adherence to non-biologic DMARD monotherapy is significantly higher than adherence to non-biologic DMARD dual therapy.
   - **H_{3b}** Persistence to non-biologic DMARD monotherapy is significantly higher than persistence to non-biologic DMARD dual therapy.

4. To determine whether time to initiation of biologic DMARDs differs by non-biologic DMARD type and therapy.
   - **H_{4a}** Time to initiation of biologic DMARDs does not differ significantly by non-biologic DMARD type.
   - **H_{4b}** Time to initiation of biologic DMARDs does not differ significantly by non-biologic DMARD therapy.

5. To determine if the likelihood of patients initiating biologic DMARDs differs by non-biologic DMARD type and therapy, while controlling for covariates: patient socio-demographics (age, gender, race), medication use patterns (non-biologic DMARD adherence and persistence, pain medication use, glucocorticoid use), and clinical characteristics (i.e., comorbidities, and rheumatologist visit).
   - **H_{5a}** The likelihood of methotrexate users initiating biologic DMARDs is significantly higher than that of methotrexate non-users, while controlling for covariates.
   - **H_{5b}** The likelihood of non-biologic DMARD dual therapy users initiating biologic DMARDs is significantly higher than that of non-biologic DMARD monotherapy users, while controlling for covariates.
   - **H_{5c}** With every year increase in age, the likelihood of patients initiating biologic DMARDs decreases significantly, while controlling for covariates.
   - **H_{5d}** Females are significantly more likely to initiate biologics compared to males, while controlling for covariates.
   - **H_{5e}** Caucasians are significantly more likely to initiate biologic DMARDs compared to non-Caucasians, while controlling for covariates.
   - **H_{5f}** Non-adherent (PDC < 70%) patients are significantly more likely to initiate biologic DMARDs compared to adherent patients, while controlling for covariates.
   - **H_{5g}** With every day decrease in persistence, the likelihood of initiating biologic DMARDs increases significantly, while controlling for covariates.
   - **H_{5h}** Pain medication users are significantly more likely to initiate biologic DMARDs compared to pain medication non-users, while controlling for covariates.
   - **H_{5i}** Glucocorticoid non-users are significantly more likely to initiate biologic DMARDs compared to glucocorticoid users, while controlling for covariates.

H_{5j} With every unit increase in the Charlson Comorbidity Index score, the likelihood of initiating biologic DMARDs increases, while controlling for covariates.

H_{5k} Patients seen by rheumatologists are significantly more likely to initiate biologic DMARDs compared to patients seen by non-rheumatologists, while controlling for covariates.

Chapter 2: Methodology

2.1 CHAPTER OVERVIEW

In this chapter, the study methods will be described in detail. The following will be presented: study design (e.g., inclusion and exclusion criteria, study periods), data source (e.g., data extraction method, study population). The operational definitions of each study variable and statistical analytical method will be described. In addition, sample sizes will be presented for study objectives.

2.2 INSTITUTIONAL REVIEW BOARD APPROVAL

The study was reviewed by the Institutional Review Board of The University of Texas at Austin. The Board determined that IRB oversight was not necessary because the data were de-identified; thus, the study did not meet requirements for human subjects research.

2.3 STUDY DESIGN AND DATA SOURCE

This is a retrospective study using Texas Medicaid prescription and medical claims data during the study period of July 1, 2003 – December 31, 2010. The study subjects were adult (18 – 63 years) patients diagnosed with RA. The following subsections will explain the inclusion and exclusion criteria, study periods, and methods for data collection.

2.3.1 Inclusion and exclusion criteria

Inclusion criteria:

Texas Medicaid recipients who meet the following criteria were included:

1) Between the ages 18 – 63 years at the index date;
2) Continuously enrolled for at least 6 months before and 24 months after the index date;
3) Diagnosed with RA during the pre-index period (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 714.xx);
4) No non-biologic DMARD used during the pre-index period;
5) No biologic DMARD used during the pre-index period;
6) At least 2 of the same non-biologic DMARDs in the post-index period.

Exclusion criteria:

Patients diagnosed with other types of arthritic or autoimmune disorders such as: psoriasis (ICD-9-CM 696.0x), psoriatic arthritis (ICD-9-CM 696.1x or 696.8x), ankylosing spondylitis (ICD-9-CM 720.0x), ulcerative colitis (ICD-9-CM 556.9), or Crohn's diseases (ICD-9-CM 555.0x, 555.1x, 555.2x, 555.9x, 565.1x, or 569.81) during the entire study period were excluded because biologic DMARDs are indicated for treatment with these disorders. In addition, patients with comorbid disorders such as leukemia (ICD-9-CM 208.x), non-Hodgkin's lymphoma (ICD-9-CM 202.8x), head, neck, lung, and breast cancers (ICD-9-CM 171.0, 162.9, 174.9), osteosarcoma (ICD-9-CM 170.9), mycosis fungoides (ICD-9-CM 202.1), gestational trophoblastic neoplasm (ICD-9-CM 181), lupus erythematosus (ICD-9-CM 710.0), malaria (ICD-9-CM 084.6), collagen disease (ICD-9-CM 710.9), exacerbation of multiple sclerosis (ICD-9-CM 340),

idiopathic thrombocytopenic purpura (ICD-9-CM 287.3), neoplastic disease (ICD-9-CM 239.9), nephritis disease/syndrome (ICD-9-CM 581), polymyositis (ICD-9-CM 710.4), renal transplant rejection (ICD-9-CM 996.81), transplantation of heart (ICD-9-CM V42.1), trichinosis (ICD-9-CM 124), tuberculosis meningitis (ICD-9-CM 013.0) during the study period were excluded because these disorders are also treated with non-biologic DMARDs or glucocorticoids.[19]

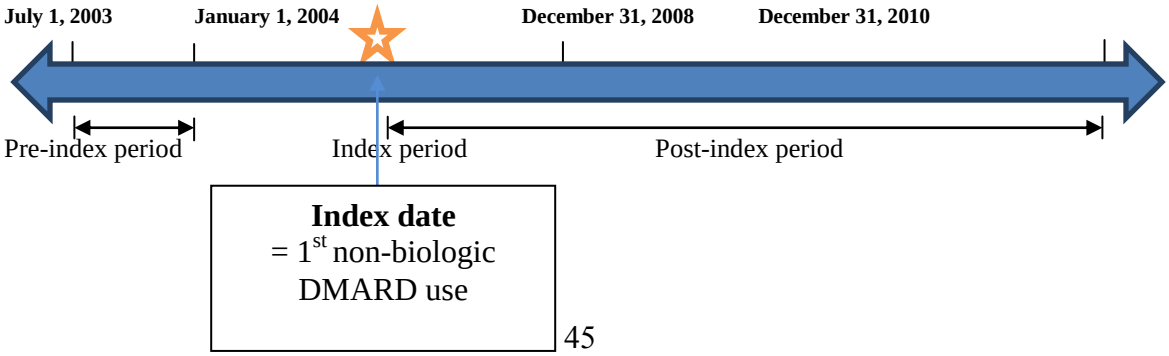
2.3.2 Index date

The index date was the date of the first prescription claim for a non-biologic DMARD agent.

2.3.3 Data collection and study periods

The following data were obtained from the Texas Medicaid medical and prescription claims database: de-identified patient identification numbers, gender, age, race/ethnicity, enrollment dates, diagnostic codes (i.e., ICD-9-CM codes), National Drug Codes (NDCs), prescription fill date, outpatient procedure codes for injectables, days supply, and prescriber type.

Data collection period



2.4 STUDY VARIABLES

Table 2.1 below describes operational definitions of each study variable.

2.4.1 Dependent variables

The primary dependent variables for this study were time to initiation of biologic DMARDs and likelihood of initiating biologic DMARDs. The secondary dependent variables included medication adherence and persistence. Note: the secondary dependent variables also serve as covariates in objective 5.

2.4.2 Independent variables (and covariates)

The primary independent variables were non-biologic DMARD type and non-biologic DMARD therapy. The study covariates were: (1) clinical factors (adherence and persistence to non-biologic DMARDs, comorbid conditions, pain medication use, glucocorticoid use, rheumatologist visit); and (2) socio-demographic factors (age, gender, race).

Table 2.1. Operational definitions of study variables

Study variables	Operational definitions
Dependent variables	
Time to initiation of biologic DMARDs	The number of days between the index date and the first biologic DMARD (i.e., abatacept, rituximab, tocilizumab, adalimumab, etanercept, infliximab, certolizumab, golimumab) fill date [continuous variable]
Initiation of biologic DMARDs	1 = Yes, 0 = No [dichotomous variable]
Medication adherence	Measured using PDC (proportion of days covered) to non-biologic DMARDs during the post-index period. PDC=Number of days when drugs were available x 100 / number of days in the study period [continuous variable] 1 = ≥ 70% PDC, 0=<70% PDC [categorical] (Note: Covariate for Objective 5)
Medication persistence[a]	The number of days in which non-biologic DMARD was continuously used during the post-index period without a gap. Gap period: last days supply + 60 days (sensitivity analyses: last days supply + 45 days; last days supply + 90 days). [continuous variable] (Note: Covariate for Objective 5)
Independent variables	
Non-biologic DMARD type	1 = methotrexate, 2 = sulfasalazine, 3 = hydroxychloroquine, 4 = leflunomide [categorical variable]
Non-biologic DMARD therapy[b]	1 = monotherapy, 2 = dual therapy [categorical variable]

Table 2.1. Operational definitions of study variables, cont.

Covariates	
Clinical factors	
Comorbid conditions	Charlson Comorbidity Index score were derived from the sum of relevant weighted conditions. See Table 2.2 for algorithm 1 = score of 1, 2 = score of 2, 3 = score of ≥3 [ordinal variable]
Pain medication use	1 = Yes, 0 = No [categorical variable]
Glucocorticoid use during the post-index period	1 = Yes, 0 = No [categorical variable]
Rheumatologist visit	Rheumatologist visit during study period 1 = Yes, 0 = No [categorical variable]
Socio-demographic factors	
Age	Age of the subject at index date [continuous variable]
Gender	0 = Male, 1 = Female [categorical variable]
Race[c]	1 = Caucasian, 2 = African American, 3 = Hispanic, 4 = Others [categorical variable]

DMARD, disease-modifying antirheumatic drug; NSAID, nonselective nonsteroidal anti-inflammatory drugs

[a] Persistence gap period of last days supply + 60 days was selected because 2 months without treatment is a reasonable period to assume that the patient has discontinued therapy.

[b] Dual therapy was defined as the two non-biologic DMARDs filled with two overlapping periods of at least 15 days, with the first claim filled within 4 months of the index date.

[c] Others included American Indians, Asians, and unknown.

Table 2.2. Charlson comorbidity index scoring algorithm

Comorbid Conditions	Weights	Dartmouth-Manitoba codes
Myocardial infarction	1	410.xx, 412*
Congestive heart failure	1	402.01, 402.11, 402.91, 425.x, 428.x, 429.3, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93
Peripheral vascular disease	1	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)*
Cerebrovascular disease	1	362.34, 430-436, 437-437.1, 437.9, 438, 781.4, 784.3, 997.0, 38.12(P), 38.42(P)
Dementia	1	290.x*, 331-331.2*
Chronic pulmonary disease	1	415.0*, 416.8-416.9*, 491.x-494*, 496*
Connective tissue disease	1	710.x, 714.x
Ulcer disease	1	531.xx-534.xx
Mild liver disease	1	571.2*, 571.5-571.6*, 571.8-571.9*
Diabetes	1	250.0x-250.3x*
Diabetes with end organ damage		250.4x-250.9x*†
Hemiplegia	2	342.x, 344.x
Moderate or severe renal disease	2	585-586*, V42.0*, V45.1*, V56.x*, 39.27(P)*, 39.42(P)*, 39.93-39.95(P)*, 54.98(P)*
Any tumor	2	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)
Leukemia	2	
Lymphoma	2	
Moderate or severe liver disease	3	572.2-572.4*, 456.0-456.2x*, 39.1(P)*, 42.91(P)*†
Metastatic solid tumor	6	196.x-199.x*†
AIDS	6	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.

Source : Adapted from: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.

2.5 STATISTICAL ANALYSIS AND SAMPLE SIZE

In performing data analysis, SAS for Windows, Version 9.3 (SAS Institute, Cary, NC.) was used. For all statistical analyses, tests were two-tailed and the significance level was determined at probability (p) < 0.05. Data distributions were evaluated by performing frequencies, histograms, and box plots. To address study objective 1, descriptive statistics were performed. For objectives 2 and 3, data distributions were inspected for normality, and appropriate parametric (i.e., ANOVA, t-test) or non-parametric (i.e., Kruskal Wallis, Mann-Whitney U) tests were used accordingly. Statistical tests for each study hypothesis are shown in Table 2.3. Kaplan-Meier analysis and logistic regression analysis were used for objectives 4 and 5, respectively.

2.5.1 Statistical test assumptions and sample size calculations

This section will present the statistical test assumptions and sample size calculations for each study objective.

Analysis of Variance (ANOVA)

To address study objective 2, one-way ANOVA was employed because both of measurement variables (i.e., adherence, persistence) were normally distributed. In each ANOVA test, there was a set of one measurement variable and one nominal variable (i.e., non-biologic DMARD type). There were three basic assumptions: independent observations, normal distribution of data, and homogeneity of variances.

For ANOVA, the total sample size was calculated using G-Power software and resulted in 100 subjects (medium effect size (f) = 0.36, $\alpha = 0.05$, power = 0.8, number of groups = 5) for objective 2. The total sample size needed for objective 3 was 92 based on G-Power software (medium effect size (f) = 0.36, $\alpha = 0.05$, power = 0.8, number of groups = 4).

T-test and Mann-Whitney U test

To address study objective 3, t-tests were used because the measurement variables (e.g., adherence, persistence) were normally distributed. In t-test, two groups (i.e., non-biologic DMARD therapy) were compared. There were three assumptions: independent observations, normal distribution of data, and homogeneity of variances.

Chi-square test

For objectives 2 and 3, after performing ANOVA and t-test, a chi-square test was further performed to compare the proportions of adherence (PDC $\geq$ 70%) in each dichotomous variable (i.e., methotrexate users vs. non-methotrexate users; monotherapy users vs. dual therapy users) (see Tables 2.3 and 2.4). Because the literature lacks information on the proportions of adherence, the tables below show comparisons of various percentages representing possible proportions of adherence comparisons. Thus the needed sample size ranged between 80 and 137.

Table 2.3. Sample sizes needed for chi-square test depending on varying proportions of adherence in methotrexate users vs. non-methotrexate users

Proportion of adherence[a] in methotrexate users	Proportion of adherence[a] in non-methotrexate users	Sample Size
25%	10%	97
30%	15%	118
35%	20%	137
40%	20%	80

[a] Adherence is defined as proportion of days covered (PDC) ≥ 70%

Table 2.4. Sample sizes needed for chi-square test depending on varying proportions of adherence in non-biologic DMARD monotherapy users vs. non-biologic DMARD dual therapy users

Proportion of adherence[a] in non-biologic DMARD monotherapy users	Proportion of adherence[a] in non-biologic DMARD dual therapy users	Sample Size
80%	60%	80
70%	50%	92
60%	40%	97

[a] Adherence is defined as proportion of days covered (PDC) ≥ 70%

Kaplan-Meier analysis and log rank test

Kaplan-Meier analysis was used to estimate the fraction of study subjects reaching the study endpoint (i.e., time to initiation of biologic DMARDs) as addressed in objective 4. The time frame was from the time when subjects started on a non-biologic DMARD to the time when they started on a biologic DMARD. Survival function curves of time to initiation to biologic DMARD were plotted by the measurement variable (i.e.,

non-biologic DMARD type and therapy). Log rank test was used to further test whether there is a significant difference between the survival times of different treatment groups.

Logistic regression analysis

Logistic regression was performed to address objective 5. Logistic regression was used because the dependent variable (i.e., initiation of biologic DMARDs) is binary (i.e., yes or no). The following is the logistic regression model:

$\ln [\pi(x)/(1-\pi(x))] = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_5 x_5 + \beta_6 x_6 + \beta_7 x_7 + \beta_8 x_8 + \beta_9 x_9 + \beta_{10} x_{10} + \beta_{11} x_{11}$
$\pi(x)$ = probability of initiating biologic DMARDs
$1-\pi(x)$ = probability of not initiating biologic DMARDs
β_0 = constant = intercept of the logistic regression model
β_n = regression coefficient
x_1 = non-biologic DMARD type
x_2 = non-biologic DMARD therapy
x_3 = medication adherence
x_4 = medication persistence
x_5= Charlson comorbidity score
x_6= pain medication use
x_7= glucocorticoid use
x_8= age
x_9= gender
x_{10}= race
x_{11}= rheumatologist visit

As for sample size calculation, G-Power showed that a total of 1,138 patients would be needed to address this objective (odds ratio = 1.2, Pr (Y=1/X=1) H_0 = 0.3, α = 0.05, power = 0.8). Since this analysis requires the largest sample size for the study, 1,138 was selected to perform data analysis.

Table 2.5. Summary of study objectives/hypotheses, study variables, study measures, and statistical tests

Objectives/ hypotheses	Dependent variable	Measurement level	Independent variable	Measurement level	Statistical analysis
Objective 1: **Describe patient socio-demographic (age, gender, race), medication use patterns [non-biologic DMARD type, non-biologic DMARD therapy (i.e., monotherapy, dual therapy), non-biologic DMARD adherence and persistence, pain medication use, glucocorticoid use], and clinical characteristics (i.e., comorbidities and rheumatologist visit).**					
			Age	Continuous	Mean (SD)
			Gender	Categorical 0 = Male 1 = Female	Frequencies
			Race	Categorical 1 = Caucasian 2 = African American 3 = Hispanic 4 = Others	Frequencies
			Non-biologic DMARD type	Categorical 1 = methotrexate 2 = sulfasalazine 3 = hydroxychloroquine 4 = leflunomide	Frequencies
			Non-biologic DMARD therapy	Categorical 1 = monotherapy 2 = dual therapy	Frequencies
	Non-biologic DMARD adherence	Continuous Categorical 0 = nonadherent (<70% PDC) 1 = adherent (≥70% PDC)			Mean (SD) Frequencies
	Non-biologic DMARD persistence	Continuous			Mean (SD)
			pain medication use	Categorical 1 = yes 0 = no	Frequencies
			Glucocorticoid use	Categorical 1 = yes 0 = no	Frequencies
			Comorbidities	Ordinal 1= score of 1 2= score of 2 3= score of ≥3	Frequencies
			Rheumatologist visit	Categorical 1 = Yes 0 = No	Frequencies

Table 2.5. Summary of study objectives/hypotheses, study variables, study measures, and statistical tests, cont.

Objectives/ hypotheses	Dependent variable	Measurement level	Independent variable	Measurement level	Statistical analysis
Objective 2: **To determine whether adherence and persistence differ by non-biologic DMARD type.**					
H_{2a}: Adherence to methotrexate is significantly higher than adherence to other non-biologic DMARD types					
	Adherence	Continuous	Non-biologic DMARD type	Categorical 1 = methotrexate 2 = sulfasalazine 3 = hydroxychloroquine 4 = leflunomide	ANOVA or Kruskal Wallis
	Adherence	Categorical 0 = nonadherent (<70% PDC) 1 = adherent (≥70% PDC)	Non-biologic DMARD type	Categorical 1 = methotrexate 2 = sulfasalazine 3 = hydroxychloroquine 4 = leflunomide	Chi-square
H_{2b}: Persistence to methotrexate is significantly higher than persistence to other non-biologic DMARD types					
		Continuous	Non-biologic DMARD type	Categorical 1 = methotrexate 2 = sulfasalazine 3 = hydroxychloroquine 4 = leflunomide	ANOVA or Kruskal Wallis
Objective 3: **To determine whether adherence and persistence differ by non-biologic DMARD therapy.**					
H_{3a}: Adherence to non-biologic DMARD monotherapy is significantly higher than adherence to non-biologic DMARD dual therapy.					
	Adherence	Continuous	Non-biologic DMARD therapy	Categorical 1 = monotherapy 2 = dual therapy	t-test
	Adherence	Categorical 0 = nonadherent (<70% PDC) 1 = adherent (≥70% PDC)	Non-biologic DMARD therapy	Categorical 1 = monotherapy 2 = dual therapy	Chi-square
H_{3b}: Persistence to non-biologic DMARD monotherapy is significantly higher than persistence to non-biologic DMARD dual therapy.					
	Persistence	Continuous	Non-biologic DMARD therapy	Categorical 1 = monotherapy 2 = dual therapy	t-test

Table 2.5. Summary of study objectives/hypotheses, study variables, study measures, and statistical tests, cont.

Objectives/ hypotheses	Dependent variable	Measurement level	Independent variable	Measurement level	Statistical analysis
Objective 4: **To determine whether time to initiation of biologic DMARDs differs by non-biologic DMARD type and therapy.**					
H_{4a}: Time to initiation of biologic DMARDs does not differ significantly by non-biologic DMARD type.					
	Time to initiation of biologic DMARDs	Continuous	Non-biologic DMARD type	Categorical 1 = methotrexate 2 = sulfasalazine 3 = hydroxychloroquine 4 = leflunomide	Kaplan-Meier analysis Log-rank test
H_{4b}: Time to initiation of biologic DMARDs does not differ significantly by non-biologic DMARD therapy.					
	Time to initiation of biologic DMARDs	Continuous	Non-biologic DMARD therapy	Categorical 1 = monotherapy 2 = dual therapy	Kaplan-Meier analysis Log-rank test
Objective 5: **To determine if the likelihood of patients initiating biologic DMARDs differs by non-biologic DMARD type and therapy, while controlling for covariates: patient socio-demographics (age, gender, race), medication use patterns (i.e., non-biologic DMARD adherence and persistence, pain medication use, glucocorticoid use), and clinical characteristics (i.e., comorbidities, and rheumatologist visit).**					
H_{5a}: The likelihood of methotrexate users initiating biologic DMARDs is significantly higher than that of methotrexate non-users, while controlling for covariates.					
	Initiation of biologic DMARDs	Categorical 1 = yes 0 = no	Non-biologic DMARD type	Categorical 1 = methotrexate 2 = sulfasalazine 3 = hydroxychloroquine 4 = leflunomide	Logistic regression analysis
H_{5b}: The likelihood of non-biologic DMARD dual therapy users initiating biologic DMARDs is significantly higher than that of non-biologic DMARD monotherapy users, while controlling for covariates.					
	Initiation of biologic DMARDs	Categorical 1 = yes 0 = no	Non-biologic DMARD therapy	Categorical 1 = monotherapy 2 = dual therapy	Logistic regression analysis
H_{5c}: With every year increase in age, the likelihood of patients initiating biologic DMARDs decreases significantly, while controlling for covariates.					
	Initiation of biologic DMARDs	Categorical 1 = yes 0 = no	Age	Continuous	Logistic regression analysis
H_{5d}: Females are significantly more likely to initiate biologics compared to males, while controlling for covariates.					
	Initiation of biologic DMARDs	Categorical 1 = yes 0 = no	Gender	Categorical 0 = male 1 = female	Logistic regression analysis

Table 2.5. Summary of study objectives/hypotheses, study variables, study measures, and statistical tests, cont.

Objectives/ hypotheses	Dependent variable	Measurement level	Independent variable	Measurement level	Statistical analysis
H_{5e}: Caucasians are significantly more likely to initiate biologic DMARDs compared to non-Caucasians, while controlling for covariates.					
	Initiation of biologic DMARDs	Categorical 1 = yes 0 = no	Race	Categorical 1 = Caucasian 2 = African American 3 = Hispanic 4 = Others	Logistic regression analysis
H_{5f}: Non-adherent (PDC < 70%) patients are significantly more likely to initiate biologic DMARDs compared to adherent patients, while controlling for covariates.					
	Initiation of biologic DMARDs	Categorical 1 = yes 0 = no	Adherence	Categorical 0 = nonadherent (<70% PDC) 1 = adherent (≥70% PDC)	Logistic regression analysis
H_{5g}: With every day decrease in persistence, the likelihood of initiating biologic DMARDs increases significantly, while controlling for covariates.					
	Initiation of biologic DMARDs	Categorical 1 = yes 0 = no	Persistence	Continuous	Logistic regression analysis
H_{5h}: Pain medication users are significantly more likely to initiate biologic DMARDs compared to pain medication non-users, while controlling for covariates.					
	Initiation of biologic DMARDs	Categorical 1 = yes 0 = no	Pain medication use	Categorical 1 = yes 0 = no	Logistic regression analysis
H_{5i}: Glucocorticoid non-users are significantly more likely to initiate biologic DMARDs compared to glucocorticoid users, while controlling for covariates.					
	Initiation of biologic DMARDs	Categorical 1 = yes 0 = no	Glucocorticoid use	Categorical 1 = yes 0 = no	Logistic regression analysis
H_{5j}: With every unit increase in the Charlson Comorbidity Index score, the likelihood of initiating biologic DMARDs increases, while controlling for covariates.					
	Initiation of biologic DMARDs	Categorical 1 = yes 0 = no	Charlson Comorbidity Index score	Ordinal 1= score of 1 2= score of 2 3= score of ≥3	Logistic regression analysis
H_{5k}: Patients seen by rheumatologists will be significantly more likely to initiate biologic DMARDs compared to patients seen by non-rheumatologists, while controlling for covariates.					
	Initiation of biologic DMARDs	Categorical	Rheumatologist visit	Categorical 1 = Rheumatologist 2 = non-rheumatologist	Logistic regression analysis

Chapter 3: Results

3.1 CHAPTER OVERVIEW

This chapter describes the study results. First, the extraction process of eligible subjects from the database will be presented. Then patients' baseline demographic and clinical characteristics will follow. The rest of chapter will present the results of the study objectives.

3.2 FINAL SAMPLE

The initial population was comprised of 30,464 Texas Medicaid recipients with a diagnosis of RA during the study period. Of these, 20,521 subjects (67.4%) did not have any prescriptions for non-biologic DMARDs during the identification period, resulting in a sample size of 9,943 subjects. After applying the remaining criteria, 2,714 subjects comprised as the final study sample (Table 3.1).

Table 3.1. Attrition of study subjects in Texas Medicaid database

Criteria	Subjects Excluded		Subjects Remaining	
	N	%	N	%
Initial Sample			30,464	100.0
Had any non-biologic DMARD during the identification period[a]	20,521	67.4	9,943	32.6
Had at least 2 of the same index non-biologic DMARDs during the postindex period[b]	1,699	5.6	8,244	27.1
No use of non-biologic or biologic DMARD during the preindex period[c]	2,267	7.4	5,977	19.6
Age 18-63 years on index date	318	1.0	5,659	18.6
Had no disorders from the exclusion criteria during the study period[d]	838	2.7	4,821	15.8
Met the continuous eligibility criteria	2,090	6.9	2,731	9.0
Non-biologic monotherapy or dual therapy users only	17	0.0	2,714	8.9
Final sample			**2,714**	

DMARD = disease-modifying antirheumatic drug; **RA** = rheumatoid arthritis

[a] July 1, 2003 to December 31, 2008

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

[c] July 1, 2003 to December 31, 2003

[d] Other types of arthritic or autoimmune disorders such as: psoriasis (ICD-9-CM 696.0x), psoriatic arthritis (ICD-9-CM 696.1x or 696.8x), ankylosing spondylitis (ICD-9-CM 720.0x), ulcerative colitis (ICD-9-CM 556.9) or Crohn's diseases (ICD-9-CM 555.0x, 555.1x, 555.2x, 555.9x, 565.1x, or 569.81); leukemia (ICD-9-CM 208.x), non-Hodgkin's lymphoma (ICD-9-CM 202.8x), head, neck, lung, and breast cancers (ICD-9-CM 171.0, 162.9, 174.9), osteosarcoma (ICD-9-CM 170.9), mycosis fungoides (ICD-9-CM 202.1), gestational trophoblastic neoplasm (ICD-9-CM 181), lupus erythematosus (ICD-9-CM 710.0), malaria (ICD-9-CM 084.6), collagen disease (ICD-9-CM 710.9), exacerbation of multiple sclerosis (ICD-9-CM 340), idiopathic thrombocytopenic purpura (ICD-9-CM 287.3), neoplastic disease (ICD-9-CM 239.9), nephritis disease/syndrome (ICD-9-CM 581), polymyositis (ICD-9-CM 710.4), renal transplant rejection (ICD-9-CM 996.81), transplantation of heart (ICD-9-CM V42.1), trichinosis (ICD-9-CM 124), tuberculosis meningitis (ICD-9-CM 013.0)

3.3 STUDY OBJECTIVES

3.3.1 Objective 1: Description of baseline demographic and clinical characteristics

Objective 1 was to describe patient socio-demographic (age, gender, race), medication use patterns [i.e., non-biologic DMARD type, non-biologic DMARD therapy (i.e., monotherapy, dual therapy)], non-biologic DMARD adherence and persistence, pain medication use, glucocorticoid use, and clinical characteristics (i.e., comorbidities and rheumatologist visit). Baseline demographic and clinical characteristics of the final sample are shown in Table 3.2.

3.3.1.1 Demographic characteristics

The majority of the subjects were 45 – 63 years of age (68.8%) with mean(±SD) age of 48.1(±10.4) years. The subjects were predominantly female (89.1%) and Hispanic (55.3%).

3.3.1.2 Medication use and clinical characteristics

With respect to non-biologic DMARD type, almost 45 percent (44.8%) of subjects were prescribed MTX, followed by HCQ (25.1%). Over 10 percent (13.6%) were dual therapy users. The majority of subjects were monotherapy non-biologic DMARD users (86.4%). Mean PDC adherence for non-biologic DMARDs was 30.6%(±25.2%). Regarding dichotomous adherence, the initial cut-off value was 80%. However, it resulted in invalid tests because of small cell sizes. Thus, the PDC cut-off value was changed to 70%. The vast majority (89.9%) of subjects were non-adherent (PDC<70%) and their mean persistence was 190.2(±201.4) days. Regarding other medication use, most subjects shifted from glucocorticoid non-users (69.8%) in the pre-index period to glucocorticoid users (64.9%) in the post-index period. Over 90 percent (92.4%) of the sample were on pain medications in the post-index period. The majority of subjects had either a Charlson Comorbidity Index (CCI) score of 1 (58.9%) or 2 (28.9%). Finally, over 70 percent (73.9%) of subjects were prescribed a non-biologic DMARD by a non-rheumatologist. Note: Less than 5% (3.8%) of subjects were missing data on prescriber type.

Table 3.2. Baseline descriptive statistics

Demographic Characteristics	**N**	**%[a]**
Age groups		
18-34	334	12.3
35-44	512	18.9
45-54	939	34.6
55-63	929	34.2
Total	**2,714**	**100.0**
Mean(±SD)		48.1(±10.4)
Race/ethnicity[∞]		
Caucasians	630	23.2
African Americans	286	10.5
Hispanics	1,500	55.3
Others	298	11.0
Total	**2,714**	**100.0**
Gender		
Females	2,418	89.1
Males	296	10.9
Total	**2,714**	**100.0**
Medication Use and Clinical Characteristics	**N**	**%[a]**
Non-biologic DMARD type (index drug)		
MTX	1,216	44.8
SSZ	360	13.3
HCQ	682	25.1
LEF	86	3.2
Dual therapy (MTX+SSZ, MTX+HCQ, MTX+LEF)	370	13.6
Total	**2,714**	**100.0**
Non-biologic DMARD therapy		
Monotherapy	2,344	86.4
Dual therapy	370	13.6
Total	**2,714**	**100.0**
Adherence to non-biologic DMARDs		
Yes (PDC ≥ 70%)	275	10.1
No (PDC < 70%)	2,439	89.9
Total	**2,714**	**100.0**
Mean (±SD)		30.6(±25.2)
Persistence with nonbiologic DMARDs (days)		
Mean (±SD)		190.2(±201.4)
Pre-index glucocorticoid utilization[b]		
Yes	821	30.3
No	1,893	69.8
Total	**2,714**	**100.1**
Post-index glucocorticoid utilization[b]		
Yes	1,760	64.9
No	954	35.2
Total	**2,714**	**100.1**
Post-index pain medication utilization[c]		

Table 3.2. Baseline descriptive statistics, cont.

Yes	2,507	92.4
No	207	7.6
Total	**2,714**	**100.0**
Charlson Comorbidity Index score		
1	1,599	58.9
2	783	28.9
≥3	332	12.2
Total	**2,714**	**100.0**
Mean (±SD)		1.6(±0.93)
Rheumatologist		
Yes	605	22.3
No	2,005	73.9
Missing	104	3.8
Total	**2,714**	**100.0**

DMARD = disease modifying anti-rheumatic drugs; **HCQ**= hydroxychloroquine; **LEF** = leflunomide; **MTX** = methotrexate; **PDC** = proportion of days covered; **SSZ** = sulfasalazine

[a] Totals may not equal 100.0 due to rounding

[b] Glucocorticoids include both oral and injectables

[c] Pain medications include both NSAIDs and opioid analgesics

[∞] Others include American Indian, Asian, and unknown

3.3.1.3 Description and comparison of biologic DMARD starters and non-starters

Although not included in the original objectives, Table 3.3 shows the unadjusted bivariate comparison of biologic DMARD starters and non-starters. Biologic DMARD non-starters were (but not practically) older than starters (48.3(±10.3) vs. 47.3(±10.8) years, p=0.03) and there were significant differences in race/ethnicity, most notably with Caucasians and other categories (p=0.049). When compared to biologic DMARD non-starters, a higher proportion of biologic DMARD starters had claims for glucocorticoids during the pre-index period (28.2% vs. 36.3%, p<0.0001). Similar results were shown in the post-index period (60.1% vs. 78.7%, p<0.0001). Although both starter and non-starter groups had low comorbidities (median CCI=1), biologic DMARD starters had a higher mean CCI score than biologic DMARD non-starters (1.73(±0.99) vs. 1.56(±0.90),

p<0.0001). Regarding prescriber type, a larger proportion of biologic DMARD starters had a rheumatologist visit compared to biologic DMARD non-starters (26.6% vs. 24.1%, p=0.002). With respect to non-biologic DMARD type, there was a significant difference between the two groups (p<0.0001), but no differences regarding mono vs. dual therapy. Mean non-biologic DMARD adherence [(32.7%(±25.8%) vs. (17.2%(±14.7%)] and persistence [mean: 225.7(±220.1) vs. 178(±193.1) days ; median: 140.0 vs. 100.0 days)] were higher among starters than non-starters.

Table 3.3. Comparison of baseline characteristics by biologic DMARD initiation status

	Biologic DMARD starters (N=695)	**Biologic DMARD non-starters (N=2,019)**	**p-value**
Age, Mean (±SD)[a]	47.3 (±10.8)	48.3 (±10.3)	0.03
Females (%)[b]	622 (89.5)	1,796 (89.0)	0.69
Race/ethnicity (%)[b]			0.049
Caucasians	183 (26.3)	447 (22.1)	
African Americans	75 (10.8)	211 (10.5)	
Hispanics	375 (54.0)	1,125 (55.7)	
Others	62 (8.9)	236 (11.7)	
Preindex glucocorticoid utilization (%)[b]	252 (36.3)	569 (28.2)	<0.0001
Postindex glucocorticoid utilization (%)[b]	547 (78.7)	1,213 (60.1)	<0.0001
Postindex pain medication utilization (%)[b]	644 (92.7)	1,863 (92.3)	0.74
Charlson Comorbidity Index[c]			<0.0001
Median	1.0	1.0	
Mean(±SD)	1.73 (±0.99)	1.56 (±0.90)	
Rheumatologist visit[b]			0.002
Yes	185 (26.6)	486 (24.1)	
No	420 (60.4)	1,519 (75.2)	
Missing	90 (12.9)	14 (0.7)	
Non-biologic DMARD utilization (%)[b]			<0.0001
MTX	445 (64.0)	771 (38.2)	
SSZ	49 (7.1)	311 (15.4)	
HCQ	73 (10.5)	609 (30.2)	
LEF	30 (4.3)	56 (2.8)	
Dual therapy	98 (14.1)	272 (13.5)	

Table 3.3. Comparison of baseline characteristics by biologic DMARD initiation status, cont.

Non-biologic DMARD therapy[b]			0.68
Monotherapy (%)	597 (85.9)	1,747 (86.5)	
Dual therapy (%)	98 (14.1)	272 (13.5)	
Adherence to non-biologic DMARD[a]			<0.0001
Median	24.7	12.5	
Mean(±SD)	32.7(±25.8)	17.2(±14.7)	
Persistence to non-biologic DMARD[a]			<0.0001
Median	140.0	100.0	
Mean(±SD)	225.7(±220.1)	178.0(±193.1)	

[a] t-test
[b] Chi-square test
[c] Mann-Whitney U-test

3.3.2 Objective 2: Adherence and persistence by non-biologic DMARD type

Objective 2 was to determine whether adherence and persistence differ by non-biologic DMARD type (Table 3.4). LEF users had the highest mean adherence of 37.2%(±27.5%) and dual therapy users had the lowest mean adherence at 17.2%(±14.7%). ANOVA showed that there was a significant ($p<0.0001$) difference in adherence by non-biologic DMARD type. Duncan's multiple comparisons tests revealed that MTX users were significantly more adherent than SSZ and dual therapy users [(35.7%(±26.9%); 21.3%(±18.9%); 17.2%(±14.7%), respectively], while adherence to MTX did not differ from LEF (37.2%(±27.5%)) and HCQ users (32.6%(±25.2%)). Table 3.5 shows that there was a significant ($p<0.0001$) relationship between dichotomous adherence (PDC $\geq$ 70%) and non-biologic DMARD type. Therefore, the hypothesis below was rejected:

H_{2a}: Adherence to methotrexate is significantly higher than adherence to other non-biologic DMARD types. ***Rejected***

Persistence was calculated with a gap period of 60 days, with sensitivity analyses using 45 and 90 days. Overall mean persistence was 190.2(±201.4) days, which was slightly over six months. When grace periods of 45 and 90 days were applied, the overall mean persistence was 162.2(±182.5) and 231.5(±225.4) days, respectively. With the gap period of 60 days, persistence ranged from 110.0(±123.8) days (SSZ users) to 225.1(±230.0) days (LEF users). ANOVA showed that there was a significant ($p<0.0001$) difference among non-biologic DMARD type (see Table 3.4). Duncan's test showed that SSZ users (110.0(±123.8) days) had significantly lower persistence than all other users. LEF user persistence was the longest and significantly longer than SSZ and dual therapy users. MTX users had the second longest persistence, and had similar persistence compared to others except for SSZ users. Therefore, the hypothesis below was rejected:

> *H_{2b}: Persistence to methotrexate is significantly higher than persistence to other non-biologic DMARD types.* ***Rejected***

When a sensitive analysis with a 45-day gap period was performed, Duncan's test revealed that LEF users (203.4(±212.4) days) were more persistent than HCQ users (163.8(±187.9) days). All other group comparisons remained the same as in the 60-day gap analysis. On the other hand, with a longer gap period of 90 days, LEF users had

significantly higher persistence than all other users. All other pairwise group comparisons were the same as those in the 60-day gap analysis.

Table 3.4. ANOVA comparison of adherence and persistence (60-day gap period) by non-biologic DMARD type (N=2,714)

Non-biologic DMARD type	Adherence (%)[a] Mean(±SD)	Persistent days[b] Mean(±SD)
MTX	35.7%(±26.9%) [b, c]	212.2 (±223.0)[f, g]
SSZ	21.3%(±18.9%) [d]	110.0 (±123.8)[h]
HCQ	32.6%(±25.2%) [c]	195.1 (±205.4)[f, g]
LEF	37.2%(±27.5%) [b]	225.1 (±230.0)[f]
Dual therapy	17.2%(±14.7%) [d]	178.6 (±145.7)[g]
F, p-value	58.30, p<0.0001	19.47, p<0.0001

MTX=methotrexate; **SSZ**=sulfasalazine; **HCQ**=hydroxychloroquine; **LEF**= leflunomide
[a] ANOVA test showed a significant difference (F=58.30, p<0.0001)
[b,c,d] Like letters are not significantly different (Duncan's multiple range test)
[e] ANOVA test showed a significant difference (F=19.47, p<0.0001)
[f,g,h] Like letters are not significantly different (Duncan's multiple range test)

Table 3.5. Chi-square comparison of adherence by non-biologic DMARD type (N=2,714)

Non-biologic DMARD type	Adherent N (%)[a]
MTX (N=1,216)	176 (14.5%)
SSZ (N=360)	12 (3.3%)
HCQ (N=682)	70 (10.6%)
LEF (N=86)	13 (15.1%)
Dual therapy (N=370)	4 (1.1%)
X^2, p-value	79.1, p<0.0001

MTX=methotrexate; **SSZ**=sulfasalazine; **HCQ**=hydroxychloroquine;
LEF= leflunomide
[a]Adherence is defined as a PDC value of ≥70%

3.3.3 Objective 3: Adherence and persistence by non-biologic DMARD therapy

Objective 3 was to determine whether adherence and persistence (gap period of 60 days) differ by non-biologic DMARD therapy (see Table 3.6). Monotherapy users were significantly more adherent than dual therapy users (32.7%(±25.8) vs. 17.2%(±14.7)). Mann Whitney U analyses were conducted and showed similar results. Using a cut-off value of 70% for adherence, a higher proportion of monotherapy users were adherent

than dual therapy users (11.6% vs. 1.1%, chi-square=38.5, p<0.0001) (Table 3.7). Therefore, the hypothesis below was failed to reject:

> *H_{3a}: Adherence to non-biologic DMARD monotherapy is significantly higher than adherence to non-biologic DMARD dual therapy.* ***Failed to reject***

Persistence between monotherapy and dual therapy non-biologic DMARD users was not significantly different (192.0(±208.8) days vs. 178.6(±145.7) days). Mann Whitney U analyses were conducted and showed similar results. Therefore, the following hypothesis was rejected:

> *H_{3b}: Persistence to non-biologic DMARD monotherapy is significantly higher than persistence to non-biologic DMARD dual therapy.* ***Rejected***

Table 3.6. T-test comparison of adherence and persistence by non-biologic DMARD therapy (N=2,714)

Non-biologic DMARD therapy	Adherence (%)[a] Mean(±SD)	Persistent days[b] Mean(±SD)
Monotherapy (N=2,344)	32.7(±25.8)	192.0(±208.8)
Dual therapy (N=370)	17.2(±14.7)	178.6(±145.7)
t, p-value	16.56, p<0.0001	1.54, p=0.12

Table 3.7. Chi-square comparison of adherence by non-biologic DMARD therapy (N=2,714)

Non-biologic DMARD therapy	Adherent N (%)[a]
Monotherapy (N=2,344)	271 (11.6%)
Dual therapy (N=370)	4 (1.1%)
X^2, p-value	38.5, p<0.0001

[a]Adherence is defined as a PDC value of ≥70%

3.3.4 Objective 4: Time to initiation of biologic DMARDs by non-biologic DMARD type and therapy (or survival without biologic DMARDs)

Objective 4 was to determine whether time to initiation of biologic DMARDs differs by non-biologic DMARD type and therapy. Regarding non-biologic DMARD type, the overall mean time to initiation of biologic DMARDs was 601.3(±240.8) days. Time to biologic DMARD initiation differed by as much as 140 days. Table 3.8 and Figure 3.1 show that among monotherapy users, MTX users had the shortest time to initiation, while HCQ users had the longest [539.7(±276.9) days; 680.2(±158.7) days, respectively]. Log-rank group pairwise comparisons with MTX were performed using the Šidák adjustment method. Results showed that time to initiation for MTX was significantly shorter than SSZ, HCQ, and dual therapy users (539.7(±276.9) days; 670.2(±167.8) days; 680.2(±158.7) days; 605.0(±227.4) days, respectively). MTX and LEF users had similar mean times to initiation (539.7(±276.9) days; 541(±286.5) days, respectively). Therefore, the following hypothesis was rejected:

> *H_{4a}: Time to initiation of biologic DMARDs does not differ significantly by non-biologic DMARD type.* ***Rejected***

On the other hand, Log-rank test showed that monotherapy and dual therapy users did not differ significantly in time to initiation of biologics (see Table 3.9 and Figure 3.2). Therefore, the following hypothesis was failed to reject:

> *H_{4b}: Time to initiation of biologic DMARDs does not differ significantly by non-biologic DMARD therapy.* ***Failed to reject***

Table 3.8. Log-rank comparison of time to initiation of biologic DMARDs by non-biologic DMARD type (N=2,714)

Non-biologic DMARD type	Time to initiation (days)[a] Mean(±SD)
MTX (N=1,216)	539.7(±276.9)[b]
SSZ (N=360)	670.2(±167.8)[c]
HCQ (N=682)	680.2(±158.7)[d]
LEF (N=86)	541.6(±286.5)[b]
Dual therapy (N=370)	605.0(±227.4)[e]
F, p-value	58.30, p<0.0001

[a] Group pairwise comparisons with MTX were performed using the Šidák adjustment method
[b-e] Like letters are not significantly different (Log-rank test)
MTX=methotrexate; **SSZ**=sulfasalazine; **HCQ**=hydroxychloroquine; **LEF**= leflunomide

Table 3.9. Log-rank comparison of time to initiation of biologic DMARDs by non-biologic DMARD therapy (N=2,714)

Non-biologic DMARD therapy	Time to initiation (days)[a] Mean(±SD)
Monotherapy (N=2,344)	600.7(±242.9)
Dual therapy (N=370)	605.0(±227.4)
Chi-square, p-value	0.0387, p=0.8440

Figure 3.1. Time to initiation of biologic DMARDs by non-biologic DMARD type

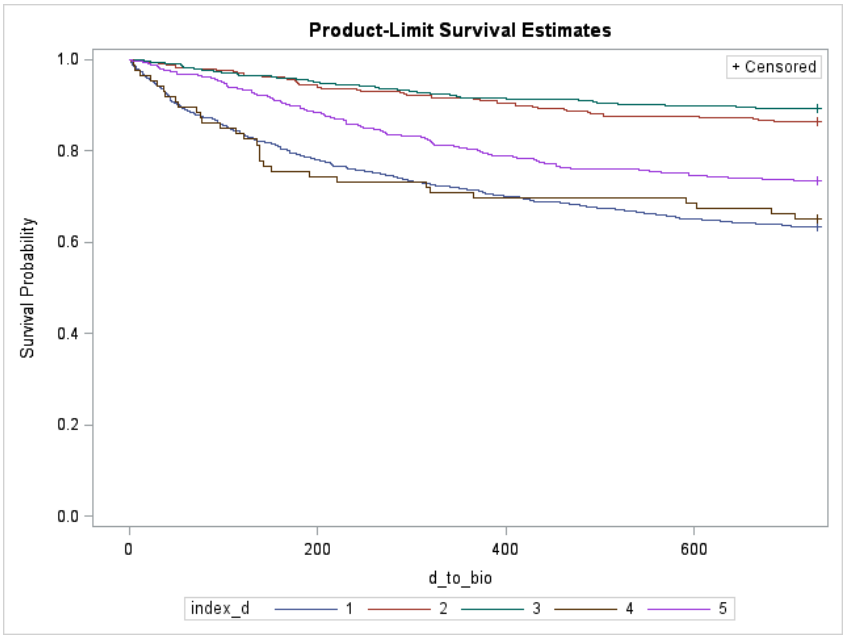
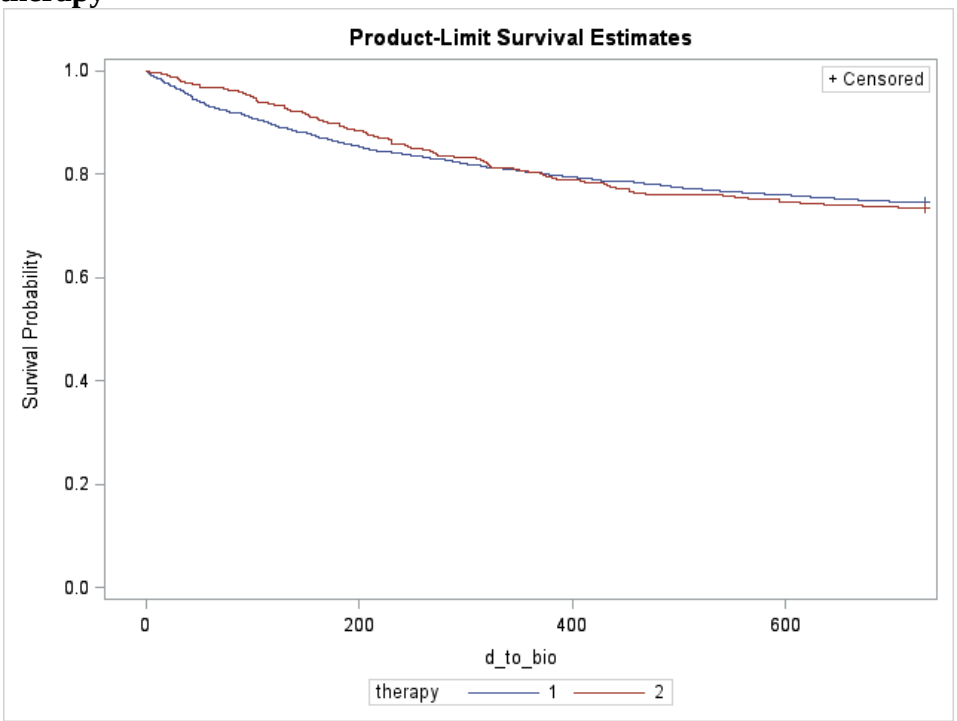


Figure 3.2. Time to initiation of biologic DMARDs by non-biologic DMARD therapy



3.3.5. Objective 5. Likelihood of initiation of biologic DMARDs by non-biologic DMARD type and therapy

Objective 5 was to determine if the likelihood of patients initiating biologic DMARDs differs by non-biologic DMARD type and therapy, while controlling for covariates: patient socio-demographics (age, gender, race), medication use patterns (i.e., non-biologic DMARD adherence and persistence, pain medication use, glucocorticoid use), and clinical characteristics (i.e., comorbidities, and rheumatologist visit). (Table 3.10). The likelihood of patients initiating biologic DMARDs was significantly associated with non-biologic type and therapy, age, glucocorticoid use, and persistence. With respect to non-biologic DMARD type, SSZ and HCQ users were less likely to initiate biologic DMARDs compared to MTX users by 69.0% (OR=0.310; 95% CI=0.221-0.434;p<0.0001) and 79.9% (OR=0.201; 95% CI=0.152-0.265;p<0.0001), respectively. Dual therapy users were 39.1% less likely to initiate biologic DMARDs compared to monotherapy users (OR=0.609; 95% CI=0.463-0.803;p=0.0004). Therefore, the following two hypotheses were rejected:

> *H_{5a}: The likelihood of methotrexate users initiating biologic DMARDs is significantly higher than that of non-methotrexate users, while controlling for covariates.* ***Rejected***
>
> *H_{5b}: The likelihood of non-biologic DMARD dual therapy users initiating biologic DMARDs is significantly higher than that of non-biologic DMARD monotherapy users, while controlling for covariates.* ***Rejected***

With 1 year increase in age, patients were 1.6% less likely to start biologic DMARDs (OR=0.984; 95% CI=0.975-0.993;p=0.0006). Therefore, the following hypothesis was failed to reject:

> *H_{5c}: With every year increase in age, the likelihood of patients initiating biologic DMARDs will decrease significantly, while controlling for covariates.* ***Failed to reject***

Glucocorticoid non-users were 53.8% less likely to start on biologic DMARDs than glucocorticoid users (OR=0.462; 95% CI=0.372-0.573;p<0.0001). Therefore, the following hypothesis was rejected:

> *H_{5i}: Glucocorticoid non-users are significantly more likely to initiate biologic DMARDs compared to glucocorticoid users, while controlling for covariates.* ***Rejected***

Patients with CCI score of ≥3 (not those with CCI score of 2) were approximately 1.6 times more likely to initiate biologic DMARDs than those with CCI score of 1 (OR=1.618; 95% CI=1.228-2.132;p=0.0006). Therefore, the following hypothesis was rejected:

> *H_{5j}: With every unit increase in the Charlson Comorbidity Index score, the likelihood of initiating biologic DMARDs increases, while controlling for covariates.* ***Rejected***

On the other hand, non-biologic DMARD type (LEF), gender, race, CCI (score of 2), adherence to non-biologic DMARDs, pain medication use, and rheumatologist visit

were not significantly related to the likelihood of patients starting on biologic DMARDs. Therefore, the following hypotheses were rejected:

> *H_{5d}: Females are significantly more likely to initiate biologics compared to males, while controlling for covariates.* ***Rejected***
> *H_{5e}: Caucasians are significantly more likely to initiate biologic DMARDs compared to non-Caucasians, while controlling for covariates.* ***Rejected***
> *H_{5f}: Non-adherent (PDC < 70%) patients are significantly more likely to initiate biologic DMARDs compared to adherent patients, while controlling for covariates.* ***Rejected***
> *H_{5g}: With every day decrease in persistence, the likelihood of initiating biologic DMARDs increases significantly, while controlling for covariates.* ***Rejected***
> *H_{5h}: Pain medication users are more likely to initiate biologic DMARDs compared to pain medication non-users, while controlling for covariates.* ***Rejected***
> *H_{5k}: Patients seen by rheumatologists are significantly more likely to initiate biologic DMARDs compared to patients seen by non-rheumatologists, while controlling for covariates.* ***Rejected***

Table 3.10. Logistic regression of initiation of biologic DMARDs by non-biologic DMARD type (N=2,714)

Non-biologic DMARD type	Odds ratio	95% CI	Wald X^2	p-value
Non-biologic DMARD type				
SSZ	0.310	0.221-0.434	46.3	<0.0001
HCQ	0.201	0.152-0.265	128.4	<0.0001
LEF	0.817	0.509-1.312	0.70	0.40
Non-biologic DMARD therapy				
Dual therapy	0.609	0.463-0.803	12.4	0.0004
Covariates				
Age	0.984	0.975-0.993	11.9	0.0006
Female	1.008	0.738-1.376	0.0023	0.96
Race/ethnicity				
African Americans	0.879	0.625-1.237	0.55	0.46
Hispanics	0.951	0.755-1.196	0.19	0.67
Others	0.646	0.455-0.918	5.94	0.015
Glucocorticoid non-user	0.462	0.372-0.573	48.99	<0.0001
Pain medication non-user	1.105	0.742-1.645	0.24	0.62
Charlson comorbidity index				
2	1.223	0.987-1.517	3.38	0.066
≥3	1.618	1.228-2.132	11.70	0.0006
Non-adherent to nonbiologic DMARDs (PDC<70%)	0.936	0.632-1.388	0.11	0.74
Persistence to nonbiologic DMARDs	1.001	1.000-1.001	4.5	0.034
Rheumatologist visit	1.174	0.946-1.459	2.12	0.15

Reference groups=MTX, monotherapy, male, Caucasians, glucocorticoid user, pain medication user, Charlson Comorbidity Index score=1, adherent to nonbiologic DMARD, non-rheumatologist visit

Table 3.11. Results of hypotheses testing

Objectives/ Hypotheses	Result
Objective 1: Describe patient socio-demographic (age, gender, race), medication use patterns [i.e., non-biologic DMARD type, non-biologic DMARD therapy (i.e., monotherapy, dual therapy)], non-biologic DMARD adherence and persistence, pain medication use, glucocorticoid use], and clinical characteristics (i.e., comorbidities and rheumatologist visit).	
Objective 2: To determine whether adherence and persistence differ by non-biologic DMARD type.	
H_{2a}: Adherence to methotrexate is significantly higher than adherence to other non-biologic DMARD types	**Rejected**
H_{2b}: Persistence to methotrexate is significantly higher than persistence to other non-biologic DMARD types	**Rejected**
Objective 3: To determine whether adherence and persistence differ by non-biologic DMARD therapy.	
H_{3a}: Adherence to non-biologic DMARD monotherapy is significantly higher than adherence to non-biologic DMARD dual therapy.	**Failed to reject**
H_{3b}: Persistence to non-biologic DMARD monotherapy is significantly higher than persistence to non-biologic DMARD dual therapy.	**Rejected**
Objective 4: To determine whether time to initiation of biologic DMARDs differs by non-biologic DMARD type and therapy.	
H_{4a}: Time to initiation of biologic DMARDs does not differ significantly by non-biologic DMARD type.	**Rejected**
H_{4b}: Time to initiation of biologic DMARDs does not differ significantly by non-biologic DMARD therapy.	**Failed to reject**
Objective 5: To determine if the likelihood of patients initiating biologic DMARDs differs by non-biologic DMARD type and therapy, while controlling for covariates: patient socio-demographics (age, gender, race), medication use patterns (i.e., non-biologic DMARD adherence and persistence, pain medication use, glucocorticoid use), and clinical characteristics (i.e., comorbidities, and rheumatologist visit).	
H_{5a}: The likelihood of methotrexate users initiating biologic DMARDs is significantly higher than that of non-methotrexate users, while controlling for covariates.	**Rejected**
H_{5b}: The likelihood of non-biologic DMARD dual therapy users initiating biologic DMARDs iswill be significantly higher than that of non-biologic DMARD monotherapy users, while controlling for covariates.	**Rejected**
H_{5c}: With every year increase in age, the likelihood of patients initiating biologic DMARDs will decrease significantly, while controlling for covariates.	**Failed to reject**
H_{5d}: Females are significantly more likely to initiate biologics compared to males, while controlling for covariates.	**Rejected**
H_{5e}: Caucasians are significantly more likely to initiate biologic DMARDs compared to non-Caucasians, while controlling for covariates.	**Rejected**
H_{5f}: Non-adherent (PDC < 70%) patients are significantly more likely to initiate biologic DMARDs compared to adherent patients, while controlling for covariates.	**Rejected**
H_{5g}: With every day decrease in persistence, the likelihood of initiating biologic DMARDs increases significantly, while controlling for covariates.	**Rejected**
H_{5h}: Pain medication users are more likely to initiate biologic DMARDs compared to pain medication non-users, while controlling for covariates.	**Rejected**
H_{5i}: Non-glucocorticoid users are significantly more likely to initiate biologic DMARDs compared to glucocorticoid users, while controlling for covariates.	**Rejected**
H_{5j}: With every unit increase in the Charlson Comorbidity Index score, the likelihood of initiating biologic DMARDs increases, while controlling for covariates.	**Rejected**

Table 3.11. Results of hypotheses testing, cont.

Objectives/ Hypotheses	Result
H_{5k}: Patients seen by rheumatologists are significantly more likely to initiate biologic DMARDs compared to patients seen by non-rheumatologists, while controlling for covariates.	**Rejected**

Chapter 4: Discussion and Conclusion

4.1 CHAPTER OVERVIEW

This chapter provides a discussion of the study results. The chapter covers a brief review of study purpose, followed by a discussion of the study results with possible explanations. The chapter will conclude with study limitations, conclusions, and future directions for research.

4.2 REVIEW OF STUDY PURPOSE

The purpose of this study was to evaluate medication adherence and persistence of RA patients on non-biologic DMARD therapy, and to examine the socio-demographic and clinical factors associated with initiation of biologic DMARD therapy among Texas Medicaid recipients with RA. There are currently four studies that have examined non-biologic DMARD utilization patterns among RA patients.[70,75-77] Only two of them are large retrospective database-studies that examined Medicaid recipients.[75,76] These two studies will primarily be used to compare with the present study results. Moreover, several other studies and two RA treatment guidelines will be referred to when comparing and explaining the findings for each of the study objectives.[12,15,16,20-22,87,89-91,95,96]

4.3 STUDY OBJECTIVES

4.3.1 Objective 1

Objective 1 was to describe patient socio-demographic, medication use patterns and clinical characteristics. The majority of subjects were female (89.1%) and mean(±SD) age of 48.1(±10.4). This was expected as being female is one of the risk factors for RA. While the literature suggests a higher mean age of 67,[6] the above mean age was lower due to this study's inclusion criteria which limited subjects to ≤63 to avoid inclusion of dual eligible patients. The mean age was lower compared to that in the Tennessee (TN) Medicaid study in which the mean age ranged from 51 to 58 by DMARD regimen type.[75] Thus, the present study is one of the few studies that have examined non-elderly. As would be expected in Texas, over half of the study sample was Hispanic (55.3%). This differed from the previous TN Medicaid studies where over 70% of subjects were Caucasian. Otherwise, gender was similar between the TN and TX Medicaid studies.

As for the non-biologic DMARD use, the plurality of subjects (44.8%) was on MTX, followed by HCQ (25.1%). The order of prevalence was nearly identical in the TN Medicaid studies in which MTX was most commonly used (37%), followed by HCQ (30%).[75] The prevalent use of MTX was expected as it is the drug of choice recommended by both ACR and EULAR treatment guidelines.[15,16] Adherence to non-biologic DMARDs was low, with 10.1% of subjects who were adherent (PDC≥70%) to their therapy. The mean(±SD) adherence rate was 30.6±25.2%, and was in the lower

range of 33 – 107% adherence rates in previous studies.[70,75-77] The present study observed a lower adherence rate compared to previous studies for the following potential reasons: differences in adherence measurement methods (PDC vs. MPR, MEMS, pill counts), study medication regimens, and follow-up periods (2 years vs. 42 months – 10 years). PDC is one of the more conservative methods for measuring adherence. In addition, longer follow-up periods typically lead to higher discontinuation and lower adherence to therapies compared to shorter follow-up periods. The mean(±SD) persistence with non-biologic DMARDs was slightly over six months [190.2(±201.4) days] during the 2-year follow-up period. This suggests that subjects were either switching to other non-biologic DMARD regimens or initiating biologics. Persistence was not comparable to previous studies because they had longer follow-up periods than the current study.[20,22,23,75]

Regarding other non-DMARD use, GC use more than doubled from pre-index (30.3%) to post-index (64.9%) period. This was likely as GCs are usually given in combination with non-biologic DMARDs to slow down RA progression. GC use was reported in the TN Medicaid study, which ranged from 26 to 48% depending on DMARD regimen type, and was similar to the present study's pre-index GC use. The majority of subjects (92.4%) used pain medication while taking non-biologic DMARDs; nearly 30% of subjects (32.5%) were on opioid pain medications while 59.9% were on non-opioid pain medications (including both NSAIDs and acetaminophen). The high percentage of pain medication use was also expected since most RA patients are in need of pain relief. Pain medication utilization, although defined differently, seemed to be within the range of the TN Medicaid subjects where 35 – 59% of them were prescribed opioid pain

medications, and, 32 – 44% were prescribed NSAIDs.[75] The current study's comorbidity measure (i.e., CCI) was similar (nearly 90% had CCI score equal to 1 or 2), to what was previously reported (≥2 comorbid conditions).[12] Lastly, most subjects were seen by non-rheumatologists (73.9%), which suggests that the majority of RA patients initially seek medical assistance from general practitioners. This was not consistent with the recommendation by the EULAR that states that RA patients should primarily be cared by rheumatologists for early diagnosis, optimal therapy management, and better outcomes.[16] Previous literature shows conflicting reports on the difference in RA outcomes between rheumatologists and general practitioners. While Singh et al. suggested that RA care by rheumatology nurses and general practitioners are as effective as care by rheumatologist, van der Linden MP et al. showed that RA patients' earlier assessments by a rheumatologist are more likely to achieve better disease outcomes.[24,97-99]

When an unadjusted bivariate comparison was made between biologic DMARD starters and non-starters, biologic DMARD non-starters were older. This was anticipated because older patients are more likely to be vulnerable to immunosuppressant properties of biologic DMARDs, thus less likely to initiate biologic DMARDs. A study by Dewitt et al. also showed that older age was associated with a lower likelihood to initiate biologic DMARDs.[100] Among the TN Medicaid population, however, new users of biologic DMARDs were observed to be older (>55 years) than new users of non-biologic DMARDs. Although not addressed in the study, this may suggest another view that because older but non-elderly patients tend to have higher RA severity than younger patients, they may require more aggressive biologic therapies. While both biologic

DMARD starters and non-starters were predominantly females in similar proportions, they were different in terms of race. The similar prevalence of females was expected as suggested by the study by Dewitt et al.[100] In terms of race, Caucasians comprised a slightly higher proportion in the biologic DMARD starter group than the non-starter group (26.3% vs. 22.1%). In the largest category of race, Hispanics, the percentage of biologic DMARD starters was slightly lower than non-starters (54.0% vs. 55.7%). Because of the unique race/ethnicity distribution of Texas Medicaid and our specific study groups, the results cannot be compared to other studies. Regarding non-DMARD use, biologic DMARD starters were higher in GC use during both preindex and postindex periods. This was a predictable trend as GCs are commonly used in combination with biologic DMARDs as noted by the EULAR recommendations.[16] In addition, higher GC use in preindex period among biologic DMARD starters may indicate that the group had more severe RA at baseline compared to the non-starter group. There was no difference in pain medication use between the two groups. Biologic DMARD starters had a higher CCI score than non-starters (1.73(±0.99) vs. 1.56(±0.90)); however, this may not present a clinically significant difference. A higher proportion of biologic DMARD starters was seen by a rheumatologist compared to biologic DMARD non-starters (30.6% vs. 24.2%), which may suggest that rheumatologists are more aggressive in treating RA patients.

As for non-biologic DMARD utilization, there were significant differences among the five medication types; a higher proportion of biologic DMARD starters used MTX, LEF, and dual therapy, while a lower proportion used SSZ and HCQ compared to non-starters. Such a different trend by starter and non-starter groups was not anticipated. The

expectation was that there would be no particular utilization differences between the two groups with regards to medication type. This may be explained by different prescribing patterns by RA severity. In both starter and non-starter groups, the majority of subjects were non-biologic DMARD monotherapy users in similar percentages. Regarding adherence and persistence to non-biologic DMARDs, biologic DMARD starters were more adherent and persistent (to their non-biologic DMARD) than non-starters. Biologic DMARD starters may have been more aggressive in treating RA compared to non-starters. Overall, biologic DMARD starters tended to be younger in age, more likely to be Caucasian, more likely to take MTX or LEF, more adherent and persistent to their non-biologic DMARD, more likely to take glucocorticoids, higher in CCI, and likely to visit a rheumatologist when compared to biologic DMARD non-starters. Although not examined, RA severity may also play a role in the likelihood of starting a biologic DMARD. Furthermore, this study is unique in that it examined a younger population and one with a higher percentage of Hispanics compared to other studies.

4.3.2 Objective 2

Objective 2 was to determine whether adherence and persistence differed by non-biologic DMARD type. Overall, mean adherence was low across the non-biologic DMARD users, ranging from 17.2%(±14.7) to 37.2%(±27.5). Adherence was highest in the LEF user group, followed by MTX, HCQ, SSZ, and dual therapy user groups. The adherence comparison was similar to what was shown in previous studies conducted in TN Medicaid population: LEF and MTX with higher adherence with similar rates and

SSZ with lower adherence than others.[1,2] This trend was expected as MTX is usually the drug of choice because it has a low side effect profile with long-term use. LEF is another preferred drug after MTX as suggested by a study that showed similar effectiveness between LEF and MTX.[97] On the other hand, dual therapy users had the lowest adherence. This can be explained by the fact that taking more than one medication takes more effort, especially if the medications have different dosing schedules. SSZ users had the second lowest adherence, which was also observed in a previous study.[76] SSZ users may be less adherent than other medication users because it is taken twice daily as opposed to an easier once-daily dosing schedule. Another study by de Klerk et al. also demonstrated that MTX had higher adherence and SSZ had lower adherence.[70] Regarding persistence, LEF users had the longest persistence, followed by MTX, HCQ, dual therapy, and SSZ users, which was in a similar order as adherence. During the 2-year follow up period, LEF and MTX users similarly had an average persistence of over 7 months, and SSZ with the shortest persistence of a little over 3 months. In previous studies, MTX had the highest persistence and SSZ with the lowest persistence.[20-23,95,96] One study reported a different result that while MTX users had the highest persistence, LEF users had lower persistence than SSZ users.[21] With a low side effect profile, it is expected that MTX users would have higher persistence than others. A meta analysis revealed that HCQ and SSZ were discontinued mostly due to inefficacy.[95] Furthermore, Aletaha et al. showed that higher dose therapy was associated with longer persistence among MTX and SSZ users. This suggests that a higher dose, which results in higher effectiveness, leads to better persistence with therapy. This association could not be

confirmed with the present study as dose was not measured. It will be worthwhile to further explore the relationship in the future.

4.3.3 Objective 3

Objective 3 was to determine whether adherence and persistence differ by non-biologic DMARD therapy. Non-biologic DMARD monotherapy users were significantly more adherent than dual therapy users. This was consistently observed whether adherence was measured continuously or dichotomously. While the study by Grijalva et al. had different dual therapy regimens consisting of a non-biologic and a biologic DMARD, the study results revealed a similar pattern of having low mean adherence among dual non-biologic DMARD therapy users compared to monotherapy users. This shows that regardless of the medication type, taking two medications affects patients' medication taking behavior. When comparing persistence with non-biologic DMARD therapy, monotherapy users had longer days of persistence than dual therapy users but the results were not significantly different (192.0(±208.8) vs. 178.6(±145.7) days; p=0.12), which was consistent with previous studies.[20,75] This may imply that persistence is not associated with therapy (e.g., mono vs. dual) whereas adherence was in this study. Instead, as shown in objective 2, individual medication type affects persistence. Additionally, wide variations (i.e. large standard deviations) associated with persistence may have impacted significance tests (i.e. power).

4.3.4 Objective 4

Objective 4 was to determine whether time to initiation of biologic DMARDs differs by non-biologic DMARD type and therapy. When stratified by non-biologic DMARD type, MTX users had the shortest time to initiation, followed by LEF, dual therapy, SSZ, and HCQ users who had the longest time to initiation. There was a mean difference of 140 days for time to initiation between MTX and HCQ groups. Interestingly, there was an inverse relationship between non-biologic DMARD persistence and time to initiation of biologic DMARDs. MTX and LEF users had similar longer persistence and shortest time to initiation; SSZ users had the shortest persistence and second longest time to initiation in the study. This may indicate that those with higher persistence were more active in treating their disorder, which may have indicated more morbidity associated with their RA, and thus faster to initiate biologic DMARDs. By contrast, those who had shorter persistence may not have been as severe and, thus, time to initiate biologic DMARDs was longer. However, there may be other factors that could have affected time to initiation of biologic DMARDs. For instance, clinical parameters were not available to control for disease severity, which could confound the relationship. Clinical factors should be taken into consideration to re-examine this association in future studies. In terms of non-biologic DMARD therapy, there was no difference between time to initiation of biologic DMARDs between non-biologic DMARD monotherapy and dual therapy users. This suggests that time to initiation to biologic DMARDs is affected by individual medication type rather than medication therapy category.

4.3.5 Objective 5

Objective 5 was to determine if the likelihood of patients initiating biologic DMARDs differs by non-biologic DMARD type and therapy, while controlling for covariates: patient socio-demographics (age, gender, race), medication use patterns (i.e., non-biologic DMARD adherence and persistence, pain medication use, glucocorticoid use), and clinical characteristics (i.e., comorbidities, and rheumatologist visit). SSZ and HCQ users were less likely to initiate biologic DMARDs compared to MTX users. As shown in objectives 2 and 4, MTX users had relatively higher adherence and persistence to non-biologic DMARDs than others; this may signify that the MTX user group may have had more severe RA and thus were motivated to adhere and seek additional treatment. Unexpectedly, non-biologic DMARD dual therapy users were less likely to start on biologic DMARDs when compared to monotherapy users. This relationship requires further investigation, but it may be likely that the use of two therapies was effective enough to delay biologic DMARD initiation. The associations between younger age and GC use, and higher likelihood of initiating biologic DMARDs was consistent with another study result by Dewitt et al.[100] While higher CCI (i.e., CCI $\geq$3)was associated with higher likelihood of starting biologic DMARDs, Dewitt et al. did not find any significant association with comorbidity, which was defined differently as reported comorbidities. Certain comorbid disorders (e.g., congestive heart failure, sepsis, tuberculosis) are known to delay or prevent patients from starting biologic DMARDs. However, we did not control for these individual conditions. This study's finding suggests that having high comorbid levels may increase the likelihood of initiating

biologic DMARDs because of more pain and extra-articular complications. In addition, previous studies demonstrated that higher disability and DAS scores were associated with a higher likelihood of starting biologic DMARDs.[87,89,91,100]

4.4 STUDY LIMITATIONS

Several study limitations that may affect the study results are discussed next. First, the study utilized PDC as a proxy for measuring medication adherence. PDC does not reflect an actual adherence as subjects may have not taken the filled prescriptions as assumed in the study. Second, for those who were switching and/or stepping up and down from non-biologic DMARD therapy, they were estimated to be either monotherapy or dual therapy users as defined in the study. There were several assumptions in defining non-biologic DMARD monotherapy and dual therapy. Dual therapy was defined as having two non-biologic DMARDs filled with two overlapping periods of at least 15 days, with the first claim filled within 4 months of the index date. There may have been subjects categorized as monotherapy users instead of dual therapy users because of the stringent definition. Third, using the retrospective claims database precluded access to other relevant information such as clinical data (e.g., RA disease activity level, pain assessment). Including such clinical variables would make the analyses more robust because RA severity could be controlled. Furthermore, because there was no data on the days supply for MTX injectables in the database, dosing intervals were assumed depending on the dose in data analysis. Finally, the study findings are only generalizable to the Texas Medicaid population.

4.5 CONCLUSIONS AND SUGGESTIONS FOR FUTURE RESEARCH

The main purpose of this study was to examine the factors associated with initiation of biologic DMARDs. The study results showed that younger age, GC use, MTX user (vs. SSZ, HCQ users) and non-biologic DMARD monotherapy user (vs. dual therapy user) were significantly associated with initiation of biologic DMARDs. Unlike the expectation, adherence and persistence to non-biologic DMARDs were not shown to be predictors of initiation of biologic DMARDs. In addition, regarding the time to initiation of biologic DMARDs, MTX users took the shortest time and HCQ users took the longest time to initiate biologic DMARDs among the five types of non-biologic DMARD therapy users. To further investigate these associations, other pertinent factors, such as patients' attitudes/behaviors toward their medications and disorder and disease severity, should also be taken into account in future studies.

The secondary purpose of the study was to evaluate adherence and persistence of non-biologic DMARD therapy users. The overall adherence rate was low with only 10.1% of subjects being adherent (PDC≥70%) to non-biologic DMARDs. LEF and MTX users had similarly the highest mean adherence and persistence, while non-biologic DMARD dual therapy users had the lowest adherence and SSZ with the lowest persistence. For future research, it would be worthwhile to further examine the associations between adherence and/or persistence and health outcomes (i.e., clinical and economic outcomes).

Both clinicians and the Texas Health and Human Services Commission should recognize the potential driving factors of initiation of biologic DMARDs in this population with RA. Clinicians should take efforts to monitor for effective pain medication and GC use to better control for RA symptoms (e.g., using long-acting formulations of NSAIDs or delayed release formulation of GCs). They should thoroughly evaluate current non-biologic DMARD therapy users and consider dual therapy before stepping up to biologic DMARDs. This study showed that those more likely to initiate biologic DMARDs had the following characteristics: female, younger age, MTX user, non-biologic DMARD monotherapy user, and GC user. Providers may want to focus on this group specifically to identify needs and provide treatment and education that will lead to optimal RA therapy. Medicaid should promote well-structured RA monitoring programs for patients to effectively receive optimal therapy and to ensure appropriate use of expensive biologic DMARD therapies. In addition, they should also invest in patient education programs to enhance medication adherence and persistence to RA medications.

Appendix A. List of Abbreviations

ACR: AMERICAN COLLEGE OF RHEUMATOLOGY

DMARD: DISEASE-MODIFYING ANTIRHEUMATIC DRUG

EULAR: EUROPEAN LEAGUE AGAINST RHEUMATISM

GC: GLUCOCORTICOID

HCQ: HYDROXYCHLOROQUINE

LEF: LEFLUNOMIDE

MTX: METHOTREXATE

PDC: PROPORTIONS OF DAYS COVERED

SSZ: SULFASALAZINE

TNF: TUMOR NECROSIS FACTOR

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