Real-life Drug Survival of Tumour Necrosis Factor-α Antagonists in Inflammatory Arthritis

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Abstract

Introduction: Inflammatory arthritis is a spectrum of diseases arising from immune dysregulation in the body causing pain, stiffness, swelling, and tenderness in the joints. In severe cases, it can lead to permanent joint damage and even total joint destruction. Due to incomplete understanding of its pathogenesis, management has classically been directed at relieving symptoms in the short term, with little to no treatment capable of stemming the long-term progression of joint damage. Recently, tumor necrosis factor-α (TNF-α) antagonists (or simply, "anti-TNFs") have revolutionized inflammatory arthritis treatment because of their ability to act on the molecules driving joint inflammation. As a result, most inflammatory arthritis patients treated with these agents have significant reductions in disease activity. Although randomized controlled trials (RCTs) have been instrumental in demonstrating this effect, observational studies on the effectiveness and sustainability of anti-TNFs have been lacking. Such studies add value by ascertaining the long-term effects of an intervention in a highly generalizable population; in short, they are better at revealing real-life conditions.

Objectives: The two main objectives of this study were to compare the efficacy of a first course of anti-TNF therapy in three common forms of inflammatory arthritis [rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS)], and to compare the first-course efficacy of three widely used anti-TNFs (infliximab, etanercept, and adalimumab) within each of RA, PsA, and AS. Secondary objectives were to compare the efficacy of first and second courses of anti-TNF therapy in inflammatory arthritis patients overall, and to compare the efficacy of a second course of anti-TNF therapy by indication (RA, PsA, and AS) and by anti-TNF type (infliximab, etanercept, and adalimumab).

Methods: This study used a retrospective cohort study design. Efficacy was measured in all cases using the proven surrogate outcome of drug survival. Crude anti-TNF survival was compared using Kaplan-Meier curves with log rank testing, and anti-TNF survival adjusted for several potential confounders was

compared using Cox regression with hazard ratios (HRs) for treatment termination. First and second course anti-TNF survival was compared using a paired samples t-test.

Results: 332 patients were eligible for the first-course analysis (114 RA patients, 58 PsA patients, and 160 AS patients). Crude first-course anti-TNF survival was significantly greater in AS patients compared to RA ($p = 0.028$) or PsA ($p = 0.045$) patients. However, no significant differences were found between RA, PsA, and AS in the adjusted Cox regression. Both crude and adjusted first-course drug survival was greater in RA patients taking adalimumab vs. etanercept {$p = 0.010$ and HR = 0.34 [95% confidence interval (CI) 0.14-0.80]}. Male AS patients had superior first-course anti-TNF survival than did female AS patients [HR = 0.51 (95% CI 0.27-0.95)]. 98 patients were eligible for the second-course analysis. There was no significant difference in drug survival between first and second courses of anti-TNF therapy ($p = 0.443$). Both crude and adjusted second-course drug survival was greater in PsA patients than in RA patients [$p = 0.029$ and HR = 0.42 (95% CI 0.19-0.93)].

Conclusions: This study helps to validate two key findings observed in previous studies. These are the superior first-course anti-TNF survival in AS vs. PsA and RA patients and the superior first-course anti-TNF survival in male vs. female AS patients. However, it produced few significant findings which is most likely attributable to inadequate sample sizes. The greatest value of this study is in the novel questions it asked, such that the trends and findings identified here might be useful for generating hypotheses for future, sufficiently powered studies.

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List of Abbreviations

ACPA	Anti-citrullinated protein antibody
ACR	American College of Rheumatology
ANA	Anti-nuclear antibody
AS	Ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis international Society
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
CI	Confidence interval
CRP	C-reactive protein
DMARD	Disease-modifying antirheumatic drug
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
HLA	Human leukocyte antigen
HR	Hazard ratio
IFN	Interferon
IL	Interleukin
MHC	Major histocompatibility complex
MTX	Methotrexate
NLPDP	Newfoundland and Labrador Prescription Drug Program
NSAID	Non-steroidal anti-inflammatory drug
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
RCT	Randomized controlled trial
RF	Rheumatoid factor
SNP	Single nucleotide polymorphism
SpA	Spondyloarthritis
TNF	Tumor necrosis factor

Chapter 1 Introduction

1.1 Inflammatory Rheumatic Disease

Joint pain, or arthralgia, is a very common complaint in the practice of medicine. For the most part, arthralgia is caused by degenerative processes such as physical trauma or osteoarthritis. However, a small percentage of joint pain is inflammatory in nature and this is known as inflammatory arthritis. This inflammation, usually resulting from immune dysregulation in the body, can cause pain, stiffness, swelling, and tenderness in the joints. It can also lead to permanent joint damage, potentially rendering a joint completely unusable in severe cases. Unfortunately, due to incomplete understanding of its pathogenesis, the treatment of inflammatory arthritis has long been a challenge for clinicians. Management has classically relied on treating the symptoms of the inflammation, as well as non-specifically regulating the immune system. This approach, while perhaps capable of controlling pain and stiffness in the short term, is ultimately problematic because it only partially modifies disease progression and allows for joint damage to insidiously occur.

A fairly recent breakthrough in the field of arthritis research has been the development of drugs which can act on the very molecules driving joint inflammation. These drugs, known as biologic agents (or simply, "biologics"), have revolutionized inflammatory arthritis treatment because they are actually capable of significantly modifying disease progression and preventing joint damage in patients. This has led to many patients experiencing little to no symptoms of their disease while taking a biologic agent, a finding which is very well documented in the abundance of randomized controlled trials (RCTs) on the subject.

However, despite this documented efficacy, the findings of RCTs have not been generalizable due to their stringent exclusion criteria, short duration of operation, and unrealistically rigorous follow-

up procedures. Observational studies address each of these issues, allowing for a different perspective on the *real-life* effect of a biologic agent on disease outcomes. Moreover, in the RCTs performed on this subject so far, there is significant variability in response depending on the disease treated and biologic agent used; a study which compares arthritis patients' response to biologic agents both by disease and biologic type is absent in the literature. Thus, in this study, we will examine and compare the real-life efficacy of the three most widely used biologic agents (infliximab, etanercept, and adalimumab) in treating the three most common systemic forms of inflammatory arthritis [rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS)] using an observational study design. These diseases and drugs will be discussed in detail below.

1.1.1 Rheumatoid Arthritis

a) Classification

Rheumatoid arthritis is a chronic, systemic, inflammatory disorder which primarily involves the synovial joints (Venables, et al., 2010). In 1987, a set of classification criteria was developed by the American College of Rheumatology (ACR) which helps determine whether a patient has RA based on clinical features, radiographic imaging, and laboratory measures (Quilon, et al., 2010). It states that RA can be diagnosed if a patient meets four of the following criteria for at least 6 weeks: 1) morning stiffness of the joints, 2) arthritis of 3 or more joint areas, 3) arthritis of the hand joints, 4) symmetrical arthritis, 5) rheumatoid nodules, 6) elevated serum rheumatoid factor (RF), and 7) significant radiographic changes (e.g. periarticular erosion). Recently, an updated set of criteria has been released through collaboration of the ACR and the European League Against Rheumatism (EULAR; Table 1.1) (Aletaha, et al., 2010). The primary intent behind the new criteria is to help make an earlier diagnosis. For example, instead of including the radiographic damage criterion as in the previous set, the 2010 criteria include one for detection of the serological marker anti-citrullinated protein antibody (ACPA),

which can appear in RA patients before joint destruction even occurs (Aggarwal, et al., 2009). Other key features include a greater emphasis on small joint involvement and a criterion for the detection of C-reactive protein (CRP), an acute-phase reactant.

Table 1.1: The 2010 ACR/EULAR classification criteria for rheumatoid arthritis

	Score
Target Population (who should be tested?): Patients who 1) Have at least 1 joint with definite clinical synovitis (swelling) 2) With the synovitis not better explained by another disease	
Classification criteria for RA (score-based algorithm: add score of categories A-D; a score of ≥6/10 is needed for classification of a patient as having definite RA)	
A. Joint involvement	
1 large joint	0
2 – 10 large joints	1
1 – 3 small joints (with or without involvement of large joints)	2
4 – 10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed for classification)	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms	
<6 weeks	0
≥6 weeks	1

*ACPA, anti-citrullinated protein antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate

b) Epidemiology

RA has a worldwide prevalence of approximately 0.5 to 1%, with onset most frequently occurring between the ages of 20 and 60. Incidence and prevalence are both two to three times greater in women than in men (Uhlig, et al., 2005).

c) Etiopathogenesis

It is still not very clear what specifically causes RA but there is substantial evidence indicating it is a multifactorial disease involving genetic, immunological, and environmental determinants.

In terms of a genetic component, a recent study of 47,361 RA patients noted a standardized incidence ratio of 3.02 in offspring of affected parents, 4.64 in siblings, and 6.48 in twins (Hemminki, et al., 2009). Recent single nucleotide polymorphism (SNP)-based genetic studies have helped determine some of the specific genetic susceptibility loci which are responsible for this heritability. Although 46 regions of the genome have been definitively associated with RA, the strongest association has been found within the major histocompatibility complex (MHC) and its human leukocyte antigen (HLA) region, which is consistent with this region's major role in the regulation of immunity (Barton, 2010; Eyre, et al., 2012). HLA-DRB1 is the gene found to have an especially strong association with RA, and although several different alleles exist among RA patients of various ethnicities, most of these alleles produce a "shared epitope" in the gene product (Barton, 2010). This epitope (a 5-amino-acid sequence) causes a significant increase in the relative risk of RA among those who carry it. For example, among Caucasians, presence of the HLA-DRB1*0401 allele produces a relative risk of 5 to 11 (Barton, 2010). The HLA-DRB1*0405 allele, which also contains the shared epitope, has been found increasingly in Chinese and Japanese RA patients (Barton, 2010). In some populations, such as African-Americans and Greeks, the shared epitope is not present in the majority of RA patients' DRB1 genes (Barton, 2010). However, its

presence was still significantly higher in both groups' RA patients compared to their controls, indicating the epitope may still play a causative role here as well.

The pathogenesis of RA also involves alteration in the immunological pathways. The first of these changes is likely the pathologic activation of synovial T cells by one or more unknown antigens (Schur, 2010). An inflammatory response ensues, which involves the recruitment and activation of additional proinflammatory cells. This leads to pathologic changes in the synovium such as the generation of new blood vessels and the migration of leukocytes into the synovial tissue. This synovial proliferation is then sustained by a cascade of cytokine[1] activity among the synovial lining cells, lymphocytes, and various other leukocytes. Several cytokines are involved but tumor necrosis factor-α (TNF- α) is thought to be among the most important of these cytokines (Schur, 2010). It promotes synovitis by enhancing proliferation of T cells and B cells, enhancing synovial diapedesis of leukocytes, increasing expression of proteases involved in joint destruction, and indirectly inducing expression of HLA-DR molecules. Synovitis eventually leads to cartilage and bone destruction in the affected joints.

Environmental factors have been linked to RA as well. For example, both bacterial and viral infections have been studied intensely as possible etiologic factors. Epstein Barr virus (EBV) has been linked to RA in several studies. A 1981 study found that the antibody to an EBV nuclear antigen (termed RA-associated nuclear antigen) was present in 71% of RA patients versus only 6% of controls (Ferrell, et al., 1981). Furthermore, a 2003 study showed that EBV DNA load is increased almost 10-fold in the peripheral blood mononuclear cells of RA patients compared to that in controls (Balandraud, et al., 2003). Bacterial infection has not been linked to RA quite as well as viral infection. However, a hypothesis regarding Porphyromonas gingivalis is being investigated which states the bacterium may be able to induce RA in genetically susceptible individuals by stimulating citrullinated peptide antibody

[1] Cytokines are small proteins involved in intercellular signaling

production, a classic diagnostic marker for RA (Wegner, et al., 2010). Another prominently studied environmental etiologic factor is smoking. One study found that women who were pack-a-day smokers for 20 or more years were 39% more likely to develop RA than women who had never smoked (Karlson, et al., 1999). Another study finds that smoking and being homozygous for the HLA-DR shared epitope increases the risk of developing RA dramatically (21-fold) relative to that of non-smokers who do not carry the shared epitope (Klareskog, et al., 2006). This suggests that environmental and genetic causes of RA may act synergistically.

d) Clinical Features

The onset of RA is typically gradual and insidious, with the small joints of the hands, wrists, and feet being the most commonly affected. As the disease progresses inwardly and symmetrically from the periphery, larger joints such as the elbows, shoulders, and knees can also become affected. Symptoms include pain, stiffness, and swelling in many of the affected joints. Stiffness is usually particularly severe after waking and can last for several hours before returning to normal. RA also leads to cumulative structural damage of the joints, which is closely linked to the level of inflammation that causes the aforementioned symptoms.

RA can also have nonarticular manifestations which are particularly common among patients with more severe joint disease. For example, RA patients commonly experience symptoms related to lymphocytic infiltration (such as Sjögren's syndrome[2], hypothyroidism, interstitial lung disease, splenomegaly, and lymphoma) or vasculitis (such as rheumatoid nodules, scleritis[3], mononeuritis

[2] Sjögren's syndrome is an autoimmune disease involving destruction of the salivary and lacrimal glands, resulting in dryness of the eyes and mouth

[3] Scleritis is an inflammatory disease of the sclera, the outer coating of the eye

multiplex[4], and palpable purpura[5]) (Schur, et al., 2014). They are also at an increased risk of developing metabolic syndrome, with an especially increased incidence of cardiovascular disease.

e) Management

It is generally accepted that RA, as well as the other inflammatory arthritides, are managed most effectively if a few important principles are followed (Schur, et al., 2009). First is the importance of treating the disease as early as possible because untreated disease activity often leads to progressive, irreversible joint damage. Also, once initiated, a treatment protocol should achieve tight control of disease activity to keep symptoms and damage at bay. Thirdly, all three diseases benefit from general health promotion, especially physical exercise which can reduce pain, stiffness, and inflammation. Physical therapy, occupational therapy, adequate rest, and patient education all have significant therapeutic value as well (Schur, et al., 2010). The most important aspect of management, however, may be the use of pharmacologic therapy, which is of critical importance in slowing disease progression and achieving tight control of disease activity.

Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxen, and celecoxib are used for treating joint pain in RA patients (Schur, et al., 2009). Patients are also treated with a disease-modifying anti-rheumatic drug (DMARD) because these drugs help slow down disease progression. Methotrexate (MTX) is widely cited as the first line DMARD for treatment of RA. Others often used include hydroxychloroquine, sulfasalazine, azathioprine, and leflunomide. These drugs can also be used in combination for superior results. One such example is the "triple therapy" of MTX, hydroxychloroquine and sulfasalazine (Schur, et al., 2013). Prednisone, a corticosteroid, is also used to treat RA symptoms but is avoided whenever possible because of the serious side effects it can cause

[4] Mononeuritis multiplex is a disease in which there is damage to two or more nerves in separate parts of the body
[5] Palpable purpura are raised, non-blanching, subcutaneous hemorrhages

(e.g. osteoporosis, Cushing's syndrome, type II diabetes mellitus). If treatment with NSAIDs and multiple DMARDs does not adequately control the patient's disease, the next step is usually to treat with the newer biologic drugs (see Section 1.2). In RA, these drugs are often used in combination with MTX (Schur, et al., 2010).

1.1.2 Psoriatic Arthritis

a) Classification

Psoriatic arthritis is an inflammatory arthritis associated with psoriasis. A subtype of spondyloarthritis (SpA), PsA is recognized as a distinct form of arthritis and not the equivalent of, for example, RA with coincidental psoriasis (Gladman, et al., 2005). Traditionally, classification of PsA has been done using the 1973 criteria developed by Moll and Wright (Moll, et al., 1973). These state that a PsA patient must have an inflammatory arthritis, psoriasis, and a negative serology for RF. Meeting these three criteria, the PsA patient could then be assigned to one of five subgroups: 1) distal interphalangeal (DIP) involvement only, 2) asymmetric oligoarthritis, 3) symmetric polyarthritis, 4) spondylitis, or 5) arthritis mutilans[6]. These classification criteria have a high degree of sensitivity but their specificity has been criticized. For instance, one study concludes that some of the patients diagnosed using these criteria may have actually had seronegative RA with coincidental psoriasis (Helliwell, et al., 2005). Thus, a revised set of criteria favoring specificity has since been developed, the 2006 Classification criteria for Psoriatic Arthritis (CASPAR; Table 1.2) (Taylor, et al., 2006). CASPAR increases specificity by accounting for features such as dactylitis, nail dystrophy, and enthesitis.

[6] Arthritis mutilans is a severe form of arthritis in which the affected joints are destroyed and deformed

Table 1.2: The 2006 CASPAR classification criteria for psoriatic arthritis

A patient is said to have PsA if inflammatory articular disease (joint, spine, or entheseal) is present, plus ≥3 total points from any of the 5 categories

Criterion	**Points**
1. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis - Evidence of current psoriasis on examination - Personal history - Family history	 2 1 1
2. Typical psoriatic nail dystrophy (onycholysis, pitting, hyperkeratosis) on examination	1
3. Negative test for rheumatoid factor	1
4. Dactylitis (inflammatory swelling of an entire finger or toe) - Current dactylitis on examination - Personal history	 1 1
5. Radiographic evidence of juxta-articular new bone formation on plain radiographs of hands or feet	1

b) Epidemiology

The prevalence of PsA is approximately 0.2% in the general population (Gladman, 2009). Its prevalence among psoriasis patients is quite variable (i.e. 6 to 42%) and this is attributable to differences in the definition of, and ascertainment strategies for identifying, inflammatory arthritis (Haddad, et al., 2012). However, the most recent study from general practice databases in the UK reports a 14% prevalence of inflammatory arthritis among psoriasis patients as defined by the CASPAR criteria (Ibrahim, et al., 2009). PsA affects men and women equally and the peak age of onset is between 30 and 50 years (Khan, 2002).

c) Etiopathogenesis

PsA exhibits a strong genetic component, with first-degree relatives of PsA patients being 30 to 55 times more likely to develop the disease than the general population (as reviewed by Rahman, et al., 2005). The most strongly associated genetic susceptibility loci have been identified within the HLA region. HLA-B27, for example, is commonly found in AS patients but is also found fairly frequently in PsA patients, particularly in those with spinal involvement (Gladman, et al., 1986). Other alleles, HLA-B38 and HLA-B39, are expressed more commonly in PsA patients with peripheral polyarthritis (Rahman, et al., 2005). Another MHC gene, HLA-Cw6, is associated with an earlier onset of psoriasis in PsA patients (Gladman, et al., 1999).

As in the proposed pathogenesis of RA, the products of these abnormal HLA genes are thought to be involved in pathologic T cell activation. This is supported by the observation of prominent T cell infiltration in PsA patients' skin and joint lesions (Veale, et al., 2002). Hyperplasia, angiogenesis, and the elevated production of pro-inflammatory cytokines such as TNF-α, IL-2, and interferon-gamma (IFN-γ) are other pathologic features seen in the joints and skin (Veale, et al., 2002). TNF-α in particular is thought to be heavily involved in the pathogenesis of PsA due to its role in activating synovial fibroblasts and osteoclasts, and in enhancing extravasation of leukocytes into the synovium (Choy, et al., 2001).

Physical trauma may be etiologically linked to PsA as well. The Koebner phenomenon, named for the 19th century dermatologist who discovered it, describes the development of psoriatic lesions on areas of skin subjected to mechanical, physical, or chemical trauma. This effect has since been substantiated by several case reports and controlled studies (Veale, et al., 2002). Joint inflammation in PsA patients may arise from physical trauma as well, with one study noting a higher incidence of PsA following trauma than either RA or AS (Punzi, et al., 1998).

d) Clinical Features

The onset of PsA typically begins with the development of psoriatic lesions, which can be found on both the skin and nails (Gladman, 2009). Skin lesions manifest mostly as inflamed areas covered with scaly white patches of skin called plaques. Nail lesions, which occur in 87% of PsA patients, mostly manifest as onycholysis (nail detachment) and as depressions in the nails called pits (Gladman, et al., 2005).

Although it can precede the onset of psoriasis in some PsA patients, joint disease in the majority of patients develops many years after psoriatic lesions have formed (Gladman, et al., 2005). Patterns of joint involvement among PsA patients can be very different. The most common patterns are symmetric polyarthritis and asymmetric oligoarthritis, but spondyloarthritis and DIP arthritis can also occur. These latter two subtypes of PsA usually occur with peripheral arthritis. Arthritis mutilans, a condition in which joints are deformed and destroyed, can occur in conjunction with any of these patterns. In terms of symptoms, PsA patients are similar to those with RA in that they experience pain and stiffness in their joints, both of which are particularly severe in the morning. However, tenderness of the joints tends to be less severe in PsA in comparison to other inflammatory arthritides (Buskila, et al., 1992). Apart from skin and joint involvement, PsA patients can also present with pitting edema in the hands and feet; anterior uveitis also occurs in some patients.

e) Management

The treatment strategy for PsA is guided heavily by the severity of the disease manifestations (Gladman, 2010). In 2009, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) published a set of evidence-based treatment recommendations for PsA (Table 1.3) (Ritchlin, et al., 2009). These guidelines give a separate algorithm for each of the 5 most common clinical

manifestations of PsA; the most severe manifestation dictates the treatment strategy. For example, if peripheral arthritis is the most severe feature of a patient's PsA, the algorithm states to first try treating with NSAIDs, then intra-articular steroids, then DMARDs, and finally biologic agents if all else fails. DMARDs used effectively for PsA include MTX, leflunomide, sulfasalazine, and cyclosporine. For PsA patients with severe psoriasis, treatment with psoralen and ultraviolet light A (PUVA) can be used in conjunction with a DMARD. Notably, following this treatment strategy often helps alleviate the arthritic and psoriatic symptoms of PsA patients.

Table 1.3: The GRAPPA treatment guidelines for psoriatic arthritis, categorized by disease characteristics and distinct organ involvement

	Treatment			
PsA manifestation	**1st line**	**2nd line**	**3rd line**	**4th line**
Peripheral arthritis	NSAID	IA steroids	DMARD (MTX, CsA, SSZ, LEF)	Biologics (anti-TNF)
Skin and nail diseases	Topicals	PUVA/UVB	Systemics (MTX, CsA, etc.)	Biologics (anti-TNF, etc.)
Axial disease	NSAID	PT	Biologics (anti-TNF)	_____
Dactylitis	NSAID	Injection	Biologics (anti-TNF)	_____
Enthesitis	NSAID	PT	Biologics (anti-TNF)	_____

***** CsA, cyclosporin A; IA, intra-articular; LEF, lefunomide; PT, physiotherapy; UVB, ultraviolet light B

1.1.3 Ankylosing Spondylitis

a) Classification

Ankylosing spondylitis is a chronic, inflammatory disease which primarily affects the axial joints. Until recently, the 1984 modified New York classification criteria had been widely used to diagnose AS (Quilon, et al., 2010). They state that an AS patient must have radiological evidence of sacroiliitis (either grade 2 to 4 bilaterally or grade 3 to 4 unilaterally) and meet one of the following criteria: 1) 3 or more months of low back pain that improves with exercise but not with rest, 2) restriction of lumbar spine movement in the sagittal and frontal planes, and 3) chest expansion decreased relative to normal values for age and sex.

These criteria have recently undergone major changes to help make an earlier diagnosis of arthritis. The idea here is to recognize the potential for developing AS before radiological evidence of sacroiliitis even occurs. This was done by incorporating newer diagnostic techniques (e.g. MRI) and including a test for the HLA-B27 allele, which has a very strong association with AS. Such changes reflect the evolving definition of spondyloarthritis (SpA), the family of arthritides affecting the vertebral column to which AS belongs. These newer criteria are called the Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axial spondyloarthritis (Table 1.4) (Sieper, et al., 2009). There are also classification criteria for peripheral SpA, another spondyloarthropathy with predominantly peripheral features such as dactylitis.

Table 1.4: The 2009 ASAS classification criteria for axial spondyloarthritis

In patients with ≥3 months of back pain and age of onset <45 years

Sacroiliitis on imaging* plus ≥1 SpA feature#	or	HLA-B27 plus ≥2 other SpA features*

*Sacroiliitis on imaging:	#SpA features
- Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA - Definite radiographic sacroiliitis according to modified NY criteria	- Inflammatory back pain - Arthritis - Enthesitis (heel) - Uveitis - Dactylitis - Psoriasis - Crohn's/colitis - Good response to NSAIDs - Family history for SpA - HLA-B27 - Elevated CRP

b) Epidemiology

AS is the most common form of spondyloarthritis with a prevalence of 1 to 3 out of every thousand in white populations (Brown, et al., 2003). It has a peak onset between 20 and 30 years and it affects more than twice as many men as women. Men generally develop AS at a younger age than women and their arthritis tends to be primarily axial, whereas women are more likely to have peripheral arthritis as well (Mori, et al., 2003). Men are also more likely than women to experience extra-articular manifestations of AS such as inflammatory bowel disease (Breban, et al., 2003).

c) Etiopathogenesis

AS has a very strong genetic component for a complex genetic disease. The recurrence risk ratio for siblings of probands with AS ranges from 50 to 80 and the heritability from twin studies is estimated to be over 90% (Brown, et al., 2002). Presently there are 27 genetic regions or genes reaching genome

wide significance for AS (Yu, 2011; International Genetics of Ankylosing Spondylitis Consortium, 2013). New genetic susceptibility loci have been identified for AS, including genes encoding two interleukin (IL) receptors and one encoding an anthrax toxin receptor, but the strongest association is again with a gene in the HLA region, HLA-B27 (Yu, 2011). This particular allele of the HLA-B gene is present in about 95% of AS patients in the US, China, and Europe, compared to a presence of less than 10% in each of those nations' general populations (Feltkamp, et al., 2001). HLA-B27 has many known subtypes and the most common subtype among Caucasians, B*2705, is highly associated with AS. This susceptibility is thought to be induced by substitutions in important amino acid residues of the HLA-B27 molecule, causing it to present abnormally conformed antigenic peptides to the T cells it normally interacts with (Yu, 2011).

The first immunological event leading to the onset of AS is thought to be the pathologic activation of CD8+ T cells by the peptide-presenting HLA-B27 protein. The host is normally tolerant of self-peptides presented by HLA-B, but autoimmunity can arise if these peptides bind in an alternative conformation so as to mimic microbial peptides. Following this pathologic T cell activation, an inflammatory response similar to that in RA occurs where cytokine activity is increased and then maintained, which eventually leads to proteolytic destruction of the joints. As in RA, TNF-α is thought to be an important factor in the disease process of AS (Yu, 2011). Studies have shown it to be more highly expressed in AS patients than in healthy controls (Bal, et al., 2007; Gratacos, et al., 1994).

Infection has also been heavily studied as an etiologic factor for AS. Although there is no definitive evidence for the role of microbial pathogenesis in human patients, experimentation with animal models has shown that bacterial agents may be involved. For example, one study found that HLA-B27—transgenic rats do not develop symptoms of AS in a germ-free environment but rats of the same litter will develop the disease in a normal environment (Taurog, et al., 1994). Of the several bacteria investigated as potential triggers of AS, Klebsiella pneumoniae has received the most attention

because of the homology existing between some of its proteins and HLA-B27 (Shamji, et al., 2008). Thus antibodies produced against these homologous Klebsiella proteins would be cross-reactive with HLA-B27. It has been shown that anti-Klebsiella antibodies bind more significantly to the synovial tissues of HLA-B27(+) AS patients than to those of healthy controls (Rashid, et al., 2007). Furthermore, experimental evidence suggests that anti-Klebsiella antibodies are significantly elevated in AS patients relative to healthy controls (Tani, et al., 1997; Sahly, et al., 1998).

d) Clinical Features

The effects of AS are felt mostly in the spinal and sacroiliac joints, with a slightly lesser degree of involvement in the sternum, ribs, hips and shoulders (Yu, 2010). Inflammation of peripheral, distal joints may occur in some cases but it typically manifests as acute, non-deforming monoarthritis. Enthesitis, inflammation of the area of ligament or tendon insertion into bone, is a characteristic feature of AS.

The first symptom of AS in 75% of patients is low back pain. This inflammatory spinal pain is distinct from mechanical back pain in that it actually improves with exercise and worsens with rest. As the disease progresses, postural abnormalities, and reduced spinal mobility and chest expansion may also become apparent. At its most advanced stage, AS can result in the fusion of the entire spine and complete loss of spinal mobility (Mori, et al., 2003). Also, pain and stiffness commonly develop in other joints like the sacroiliac joints, hips, knees, and shoulders.

AS patients can experience several extra-articular manifestations as well. The most common complication is acute anterior uveitis, which causes unilateral eye pain, photophobia, and blurred vision. AS can also cause respiratory issues by mechanically restricting the upper airways; patients can experience a decrease in chest expansion and therefore lung capacity. Inflammatory bowel disease also occurs in AS patients, and the risk for aortic insufficiency is significantly greater in these patients as well.

e) Management

The management of AS ranges from very conservative to intense pharmacologic treatment. For instance, occasionally there are cases where no significant intervention is required to control symptoms. This usually occurs in patients who are well oriented to their disease, have minimal symptoms, good posture, and are physically active. A larger subset of patients benefits from formal physiotherapy. Therapy might include postural training, range of motion stretching, recreational activities, and hydrotherapy (Yu, 2010a).

In terms of pharmacologic therapy, NSAIDs may be quite effective in AS patients whereas most DMARDs are not effective in treating the axial symptoms of spondylitis (Yu, 2010a). The only DMARD that is normally prescribed in the event of NSAID failure is sulfasalazine, which is only useful for treating peripheral symptoms (e.g. oligoarthritis of the knees and/or ankles). Intra-articular corticosteroid injections can also be used to relieve symptoms but long-term use is not recommended. If the patient's disease remains active despite trying at least two to three different NSAIDs (and at least one DMARD if their disease is predominantly peripheral), the patient is considered a candidate for biologic therapy (Yu, 2011; see Section 1.2). Table 1.5 shows a treatment strategy for AS developed through collaboration of ASAS and EULAR (Zochling, et al., 2006).

Table 1.5: The ASAS/EULAR recommendations for the management of AS

Non-pharmacological treatment (education, exercise, PT, rehabilitation, patient associations, self-help groups) plus:

	Treatment			
AS manifestation	**1st line**	**2nd line**	**3rd line**	**4th line**
Axial disease	NSAIDs	_____	_____	TNF-α antagonists
Peripheral disease	NSAIDs	SSZ	Local corticosteroids	TNF-α antagonists
Refractory disease (either)	Analgesics			
	----------	Surgery		

*SSZ, sulfasalazine; PT, physiotherapy

1.2 Biologic Therapy

1.2.1 Inflammatory Rheumatic Disease and Cytokine Activity

The traditional treatment strategies for each of the three arthritides, mainly involving NSAIDs and DMARDs, work well for many patients but do not adequately control disease activity for many others (Schur, et al., 2013; Yu, et al., 2013; Kyle, et al., 2004). Research into more effective and yet relatively safe treatment options for inflammatory rheumatic disease is therefore ongoing.

As was previously discussed, the precise pathogeneses of RA, AS, and PsA have not been clearly identified but numerous observations made over decades of research suggest that genetic, immunological, and environmental factors are all involved (Cassell, et al., 2005; Perl, 1999). Perhaps one of the most important breakthroughs in the last 20 years or so has been in the realm of immunological research with the discovery of pro-inflammatory cytokines. Cytokines, small proteins involved in intercellular signaling, are thought to play an important role in mediating the inflammatory process of all three arthritides (Choy, et al., 2001). While it is possible this process may be initiated much farther upstream by some genetic or environmental abnormality, the modification of cytokine activity is proven to have a significant effect on joint inflammation and damage (Choy, et al., 2001). Thus, specific inhibition of the cytokines responsible would represent the next innovation in drug therapy for inflammatory arthritis.

Tumor necrosis factor-α (TNF-α) is probably the most important of these cytokines (Choy, et al., 2001). It stimulates its own production and that of other inflammatory cytokines such as IL-1 and IL-6. It also stimulates the production of adhesion molecules by fibroblasts, which ultimately leads to the transportation of leukocytes to joint areas. Furthermore, it increases the expression of several proteases involved in joint destruction such as the matrix metalloproteinases of osteoclasts (McInnes, 2010).

Research into TNF-α inhibition has been intense, resulting in the creation of four medications[7] approved for use in RA, PsA, and AS: infliximab, etanercept, adalimumab, and golimumab.

1.2.2 Tumor Necrosis Factor-α Antagonists

Drugs designed to inhibit TNF-α, known as TNF-α antagonists (or "anti-TNFs"), are an example of a relatively new class of drugs called biologic agents. These agents are so named because they are synthesized biologically using human, animal, or bacterial cell cultures. This is significant because it allows for the production of compounds which are very similar to those naturally occurring in the body's immune system. Biological synthesis is a considerable departure from the chemical synthesis used to produce NSAIDs and DMARDs, which are relatively small molecules with virtually no likeness to any compounds produced endogenously. The products of biological synthesis, on the other hand, are usually large molecules such as proteins or nucleic acids designed with very specific functions. In the case of TNF-α inhibition, these molecules are either anti-TNF-α monoclonal antibodies or soluble TNF-α receptors.

a) Infliximab

Infliximab is a synthetic, monoclonal antibody that binds specifically to both soluble and membrane-bound TNF-α. The antibody is chimeric, incorporating murine variable regions with a human constant region. Infliximab works by binding TNF-α and neutralizing its activity by preventing it from binding its receptors.

[7] A fifth TNF-α antagonist, certolizumab, has recently been approved for use in RA, PsA, and AS but was not in use at the time our research was performed

The first randomized, placebo-controlled trial (RCT) testing the efficacy and safety of infliximab treatment in inflammatory rheumatic disease was a 1994 study involving 73 RA patients (Elliott, et al., 1994). Separated into three groups, the patients were given a single intravenous infusion of 1 mg/kg infliximab, 10 mg/kg infliximab, or placebo. After 4 weeks, 8% of the placebo group, 44% of the low-dose group, and 79% of the high-dose group had a 20% Paulus response[8] or better. Also, only 2 of 73 patients experienced severe adverse events during the study. Another study done in 1999 demonstrated the therapeutic potential of infliximab when combined with MTX. It was found that among RA patients who were not previously responding to MTX alone, the addition of infliximab significantly improved their symptoms according to ACR criteria (Figure 1.1A) (Maini, et al., 1999). In response to these findings, infliximab in combination with MTX therapy was approved by the US Food and Drug Administration (FDA) for treatment of RA in 1999. The requirement for concomitant MTX therapy is due to infliximab's chimeric nature, which results in the development of anti-infliximab antibodies and reduced efficacy in some patients. Concomitant MTX has been shown to decrease levels of these antibodies in RA patients (Maini, et al., 1999).

Infliximab was approved for use in AS in 2004 and PsA in 2005 after RCTs had shown that the drug was effective against those diseases as well (Figure 1.1B,C) (van der Heijde, et al., 2005; Antoni, et al., 2005). Its efficacy as a treatment for each of the three arthritides has since been well documented. For instance, in RA, it has been shown to improve physical function and retard joint damage (Chen, et al., 2006); in AS, it has been effective at improving both axial and peripheral symptoms (Yu, 2010a); and in PsA, it has been shown to improve symptoms of both the skin and joint diseases, as well as inhibit radiographic progression (Gladman, 2005).

[8] The Paulus response is an endpoint which amalgamates improvement in the patient's joints, global assessment, and ESR

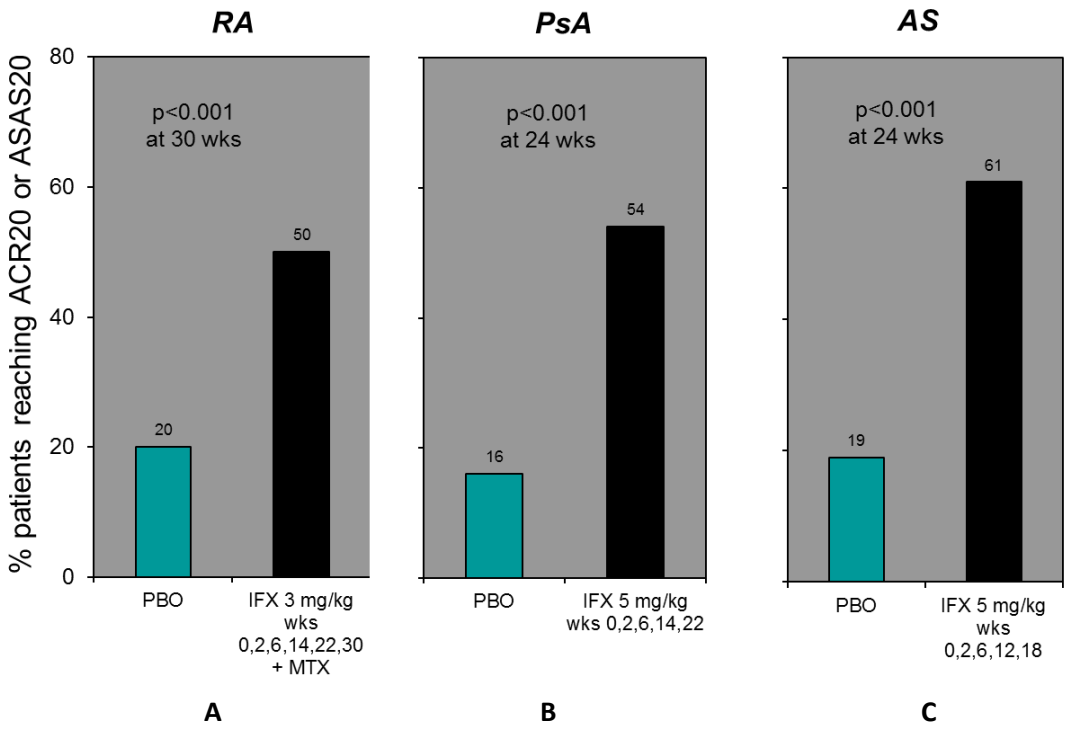

Figure 1.1: Percentages of patients that obtained an ACR20 or ASAS20 response in RCTs evaluating infliximab treatment in RA, PsA, and AS. PBO, placebo; IFX, infliximab.

b) Etanercept

Etanercept is a synthetic, soluble TNF-α receptor produced by the expression of recombinant DNA. It is a fusion protein that combines the human TNF-α receptor with the Fc component of human immunoglobulin G1 (IgG1). By acting as a decoy receptor for TNF-α, it essentially has the same effect as infliximab: neutralization of TNF-α activity.

An RCT investigating etanercept's use in RA patients was first conducted in 1997. 180 patients with active RA were randomized to placebo or one of three doses of etanercept twice weekly for three months (Moreland, et al., 1997). A dose-related effect was observed such that 75% of patients on the highest dose of etanercept obtained a 20% or better improvement in symptoms according to ACR criteria (ACR20 response); only 14% of placebo group patients obtained an ACR20 response (Figure

1.2A). This led to etanercept becoming the first TNF-α antagonist approved for use in RA by the FDA in 1998. Subsequent approval for use in PsA in 2002 and AS in 2003 also resulted from the promising findings of RCTs (Figure 1.2B,C) (Mease, et al., 2004; Davis, et al., 2003). For instance, treatment with etanercept produces at least an ASAS20 response[9] in a majority of patients with active AS (Davis, et al., 2003) and at least an ACR20 response in a majority of PsA patients (Mease, et al., 2000). The skin disease of PsA patients is also improved by treatment with etanercept (Mease, et al., 2004).

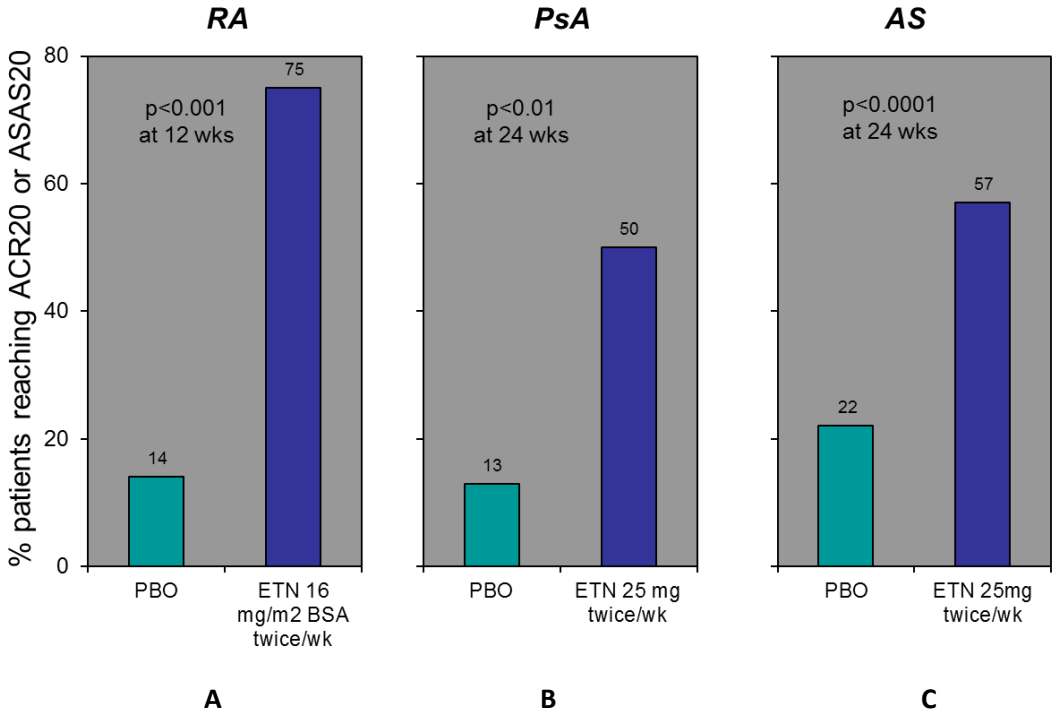

Figure 1.2: Percentages of patients that obtained an ACR20 or ASAS20 response in RCTs evaluating etanercept treatment in RA, PsA, and AS. ETN, etanercept; BSA, body surface area.

[9] An ASAS20 response is an endpoint signifying a 20% improvement in AS symptoms defined by the Assessment in Ankylosing Spondyltis criteria. The criteria include pain, function, inflammation, and global disease activity scores.

c) Adalimumab

Like infliximab, adalimumab is a monoclonal antibody that binds all forms of TNF-α and neutralizes its activity. However, adalimumab is a humanized monoclonal antibody (i.e. it has human constant and variable regions) whereas infliximab is a chimeric monoclonal antibody (i.e. it has human constant regions and murine variable regions). This difference is designed to make adalimumab less immunogenic for patients who use it.

The first prominent RCT to test the efficacy of adalimumab in RA patients was conducted in 1999. 283 patients with active disease were randomized to placebo or one of three weekly doses of the drug for 12 weeks (van de Putte, et al., 1999). At study's end, a dose-dependent improvement was observed as 56% of the high-dose group obtained an ACR20 response or better; only 10% of the placebo group achieved this outcome. Another study in 2001 assessed the efficacy of adalimumab in combination with MTX therapy in RA patients and found that this treatment was significantly better than MTX alone (Keystone, et al., 2001). Adalimumab was then approved by the FDA for treatment of RA in 2002 (Figure 1.3A) (van de Putte, et al., 2004). Co-therapy with MTX is considered optional since adalimumab is fully humanized and thus minimally immunogenic. Similar RCTs provided the empirical evidence needed to approve the drug for PsA in 2005 and AS in 2006 (Figure 1.3B,C) (Mease, et al., 2005; van der Heijde, et al., 2006). Since its approval, the drug has proven efficacious at improving joint pathology in RA (van de Putte, et al., 2004), AS (van der Heijde, et al., 2006), and both joint and skin pathology in PsA (Mease, et al., 2005) (Figure 1.4).

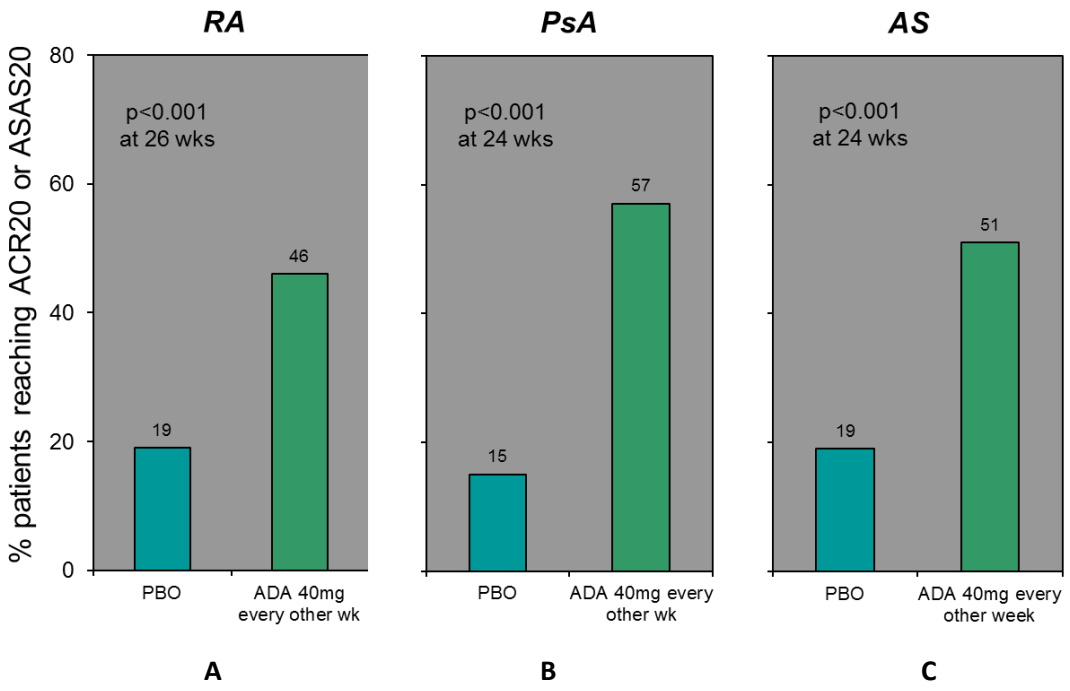

Figure 1.3: Percentages of patients that obtained an ACR20 or ASAS20 response in RCTs evaluating adalimumab treatment in RA, PsA, and AS. ADA, adalimumab.

d) Golimumab

Golimumab is a humanized monoclonal antibody which binds to both soluble and transmembrane forms of TNF-α and neutralizes its activity.

The first prominent, multicenter RCT testing the safety and efficacy of golimumab in RA patients was conducted very recently, in 2008 (Keystone, et al., 2009). The study randomized 444 patients to four experimental groups: placebo plus MTX, golimumab 100 mg plus placebo, golimumab 50 mg plus MTX, or golimumab 100 mg plus MTX. Injections of golimumab and its placebo were administered once every four weeks. After 24 weeks of therapy, the investigators found the combination of golimumab and MTX produced an ACR20 response which was significantly greater than that obtained with either golimumab

or MTX alone. Following the results of this and similar studies, golimumab was approved for treatment of RA in early 2009. An RCT has also been done to test the efficacy of golimumab monotherapy in each of PsA and AS; the positive results generated from both studies has led to approval of golimumab for PsA and AS in 2009 as well (Kavanaugh, et al., 2009; Inman, et al., 2008). Although it shows great promise as a biologic treatment for inflammatory arthritis, golimumab cannot yet be studied longitudinally due to its very recent approval. This limitation means it must be omitted from the present study.

1.2.3 Management of Inflammatory Arthritis with TNF-α Antagonists

Once a decision has been made to place a patient on anti-TNF therapy, the effectiveness of the treatment is monitored by routinely assessing disease activity (both clinically and using laboratory values), functional status, radiographic progression, and drug toxicity. The therapeutic target is tight control of all of these parameters, resulting in a state of remission or minimal disease activity. If this target is achieved with the first anti-TNF agent, treatment is continued indefinitely. If this target is not achieved within the first 6 months (i.e. the patient is a primary non-responder), switching to therapy with an alternative mechanism of action (i.e. not involving TNF-α inhibition) is indicated. If the patient begins to fail anti-TNF therapy after 6 months (i.e. a secondary non-responder), adjustments will be made to the type/dosage of DMARDs and/or the type of anti-TNF agent. If a severe adverse event secondary to anti-TNF therapy occurs (e.g. lymphoma or reactivated tuberculosis), the anti-TNF agent is stopped permanently or held and restarted at a later date at the discretion of the rheumatologist.

1.3 Rationale

Although they have all been approved for the treatment of RA, PsA, and AS in the last 17 years, TNF-α antagonists remain topical in medical research due to their ever-increasing use by arthritis patients. Several RCTs have been conducted to exhaustively determine the efficacy and safety of each anti-TNF as a treatment for each form of inflammatory arthritis (van de Putte, et al., 2004; Keystone, et al., 2004; van der Heijde, et al., 2005). The knowledge gleaned from these studies has been critical to guiding the treatment decisions of rheumatologists. However, despite their potential to produce internally valid, unbiased results, clinical trials often lack generalizability. Their patient populations are often homogeneous and free of significant comorbidities; monitored at an unrealistically high frequency; artificially motivated to remain on the study drug which is often free of charge for them; and followed for too short a duration to ascertain long-term drug effectiveness.

Observational studies can be used to address all of these issues. While its results are more vulnerable to bias than those of an RCT, an observational study's ability to assess the real-life effects of a drug on a population is unparalleled by most RCTs. For instance, generalizability can be increased by minimizing population exclusion criteria and by selecting the patient population from a typical clinical setting, where patients are assessed at a realistic frequency and without study-related incentives to remain on the study drug. Also, whereas an RCT incurs additional costs when its follow-up period is extended beyond what is initially planned, longitudinal follow-up in an observational study is far less costly; in fact, for a *retrospective* observational study, the cost might essentially be nothing. This makes it an acceptable method for studying the long-term effects of a remittive therapy such as an anti-TNF agent. Moreover, studying a treatment longitudinally allows for the assessment of drug survival, a proven surrogate marker for efficacy, as a primary outcome (Geborek, et al., 2002).

The validity of drug survival as a surrogate outcome for drug efficacy can be justified based on the criteria delineated by Haynes et al. First, a surrogate outcome must be prognostic for its hard outcome (Haynes, et al., 2006). It has been demonstrated in previous studies comparing RCT and observational study data that withdrawal from antirheumatic drug therapy is largely due to lack of efficacy (Maetzel, et al., 1999; Hawley, et al., 1991). Secondly, changes in a surrogate outcome must predict corresponding changes in its hard outcome and, thirdly, effects of treatment on the surrogate outcome should explain effects of treatment on the hard outcome (Haynes, et al., 2006). These have both been demonstrated in previous studies which measured drug survival and changes in patient quality of life (QOL) concurrently. In their study, Heiberg et al show that AS patients survive longer on anti-TNF therapy than do RA patients, and that AS patients on anti-TNF therapy also show greater improvements in physical QOL scores (i.e. bodily pain and physical limitations) than RA patients on these drugs (Heiberg, et al., 2008). QOL was measured in this study using a 36-item Short Form Health Survey (SF-36), which is used clinically to assess treatment efficacy (Schur, et al., 2014).

A few longitudinal, observational studies have been done recently which examine the survival of anti-TNF agents in patients with inflammatory arthritis. One study found that the three major anti-TNF agents (infliximab, etanercept, and adalimumab) had similar drug survival among a group of patients with various forms of inflammatory arthritis (Duclos, et al., 2006). They also found that overall anti-TNF agent survival was significantly better in SpA patients (PsA, AS, and other spondyloarthropathies) than in RA patients (Duclos, et al., 2006). Another study found that concomitant MTX use is associated with longer anti-TNF survival in patients with RA or PsA (Heiberg, et al., 2008).

These longitudinal studies do provide some insight into the use of TNF-α inhibition in inflammatory arthritis but more data are necessary. For instance, it would be helpful to know how each of the three major anti-TNF agents performs in each of RA, PsA, and AS. Head-to-head comparisons of

the anti-TNF agents, which are lacking in the current literature, are important for ascertaining differences in efficacy between monoclonal antibodies (i.e. infliximab and adalimumab) and synthetic receptors (i.e. etanercept), for example. Ascertaining the effects of potential confounding variables on anti-TNF performance (e.g. sex, age, and concomitant drug use) would also be very useful for guiding treatment decisions.

Another area lacking sufficient research is the etiology of drug failure. It has been shown that arthritis patients who fail a course of anti-TNF therapy prematurely (<6 months of therapy) present initially with less synovial TNF-α expression than patients who respond to therapy (Tak, 2012). Conversely, in patients who fail anti-TNF therapy later on (>6 months of therapy), it has been shown that endogenous anti-drug antibodies are partly responsible for failure (Wolbink, et al., 2006). Thus, for prognostic purposes, it would be useful to know if any particular patient characteristics (e.g. sex, age, or smoking status) correlate with either a premature or delayed mechanism of drug failure.

Finally, it would also be helpful to understand how well these drugs perform when given to patients who have already failed a course of anti-TNF treatment. There is evidence suggesting that the survival of the second course of anti-TNF treatment is significantly shorter than that of the first course for inflammatory arthritis patients (Duclos, et al., 2006). However, there are other sources which suggest that no significant difference exists between the survivals of the two courses (Heiberg, et al., 2008; Hyrich, et al., 2007). Resolution of this disagreement would require an examination of the survival of both courses for each of the three diseases. Stratifying this analysis by diagnosis is particularly important given that the majority of previous studies have either focused exclusively on RA patients or analyzed all 3 diseases together.

1.4 Questions and Hypotheses

The primary purpose of the present study is to address these deficits in the medical literature. Using a longitudinal, observational study design, the following two questions will be answered.

First, is real-life drug survival of the first course of anti-TNF therapy significantly different in patients with RA, PsA, or AS? Given the trends seen in existing studies, we hypothesize that anti-TNF survival will be significantly less among patients with RA than in patients with PsA or AS (Duclos, et al., 2006; Carmona, et al., 2006; Heiberg, et al., 2008).

Secondly, within each of these diagnoses, are there significant differences between the drug survivals of the first courses of infliximab, etanercept, and adalimumab? It is difficult to generate a hypothesis for this question due to a lack of data. However, there is evidence indicating that the three drugs have similar survivals among inflammatory arthritis patients in general (Duclos, et al., 2006).

Both of these questions will be answered with adjustments for the following known confounders of anti-TNF agent survival: sex, age, smoking status (Wendling, et al., 2013), concomitant use of MTX, and concomitant use of prednisone. Also, for each treatment group identified, the proportions of patients discontinuing anti-TNF therapy for reasons of either inefficacy or adverse event(s) will be assessed. This will help us determine how useful drug survival is as a surrogate outcome for drug efficacy, and whether the incidence of adverse events decreases its usefulness. Finally, in an attempt to elucidate potential reasons for premature vs. delayed anti-TNF failure, the baseline variables of these two groups will be compared for any significant differences.

A couple of secondary questions will be answered as well. First, in inflammatory arthritis patients overall, is there a significant difference between the drug survivals of the first and second courses of anti-TNF therapy? Since most of the evidence in the literature indicates either there is no

significant difference in survival between the two courses (Heiberg, et al., 2008; Hyrich, et al., 2007), or that the first course has a greater survival than the second (Greenberg, et al., 2012; Glintborg, et al., 2013; Duclos, et al., 2006), we hypothesize that anti-TNF survival will be significantly less among patients taking their second course of anti-TNF therapy than those taking their first.

Secondly, among patients taking a second course of anti-TNF therapy, is there a significant difference in drug survival among the 3 diagnoses and among the 3 different anti-TNF agents? This is another question which has not been adequately investigated in the literature to generate a meaningful hypothesis. Therefore, it is hypothesized that patterns of drug survival will be similar to what has been documented for patients taking a first course of anti-TNF therapy (i.e. decreased anti-TNF survival in RA vs. AS or PsA and similar survival among the 3 types of anti-TNF therapy). This question will be answered with adjustments for sex, age, smoking status, concomitant use of MTX, and concomitant use of prednisone.

Chapter 2 Methods

2.1 Study Design and Setting

This was a retrospective study using the medical records of patients with inflammatory arthritis from two clinics. A retrospective design was chosen for the following reasons. First, because we did not have access to an ongoing prospective database for anti-TNF therapy in the study setting, the study questions could only be answered by gathering data retrospectively. Secondly, this was an efficient design with respect to data collection and cost. Finally, a retrospective design is advantageous because it eliminates study-driven changes in patient behavior.

Patient data was gathered from two separate centers: one is the local rheumatology department at St. Clare's Mercy Hospital (SCMH) in St. John's, Newfoundland and Labrador (NL), Canada and the other is the rheumatology department at Toronto Western Hospital in Toronto. SCMH is the referral site for all rheumatology patients living in NL, serving a population of just over 500,000. Toronto Western Hospital is one of several hospitals serving rheumatology patients in the Toronto area, which has a population of over 5.1 million.

The primary setting for the study was the St. John's center. Five rheumatologists practiced in St. John's at the time of this study (four practiced at SCMH) and access was provided to the patient data belonging to three of them. All three rheumatologists practiced in a similar, university setting and no referral bias was observed in the types of patients seen by each rheumatologist. We were able to collect data from RA, PsA, and AS patients seen by these physicians.

All three major anti-TNF agents were available in NL at the time of this study but they were only covered by the provincial government since 2002 [via the NL Prescription Drug Plan (NLPDP)]. Furthermore, the NLPDP was initially biased towards covering etanercept due to cost. Thus, because

about 40% of patients on anti-TNF therapy in NL are covered by the NLPDP, we anticipated a larger quantity of St. John's center patients to be using etanercept than either infliximab or adalimumab.

The Toronto center was a secondary setting for this study and was only used to collect data from AS patients. All the data collected from this center belongs to one rheumatologist working in a university setting whose research and clinical practice focuses on AS.

2.2 Selection of Patients and Data Collection

Patients were eligible for the present study if they had been diagnosed with RA, PsA, or AS and treated with one or more of the three TNF-α antagonists (i.e. infliximab, etanercept and adalimumab). All RA patients included met the new ACR/EULAR classification criteria; all PsA patients included met the CASPAR criteria; and all AS patients included met the ASAS criteria. No additional criteria were used to determine study eligibility. Diagnostic codes were not used.

In the St. John's center, eligible patients were identified by exhaustively screening the files of patients seen by three out of the four rheumatologists practicing at SCMH. Once his/her eligibility was confirmed on screening, each patient was assigned a numerical code to ensure confidentiality. Since this screening was done over the summer of 2009, only patients who started their first anti-TNF prior to August 2009 were included in this study (i.e. patients starting any time prior to August 2009 (inclusive) were eligible).

Data collection for St. John's center patients was done by the principal investigator (SH) from February 2010 to August 2010 (thus February 2010 was the latest date for recorded follow-up). All the necessary demographic and treatment information was gathered using a form designed specifically for the present study (Appendix A). The demographic and clinical data collected for each patient included sex, year of birth, height, weight, smoking status, rheumatic diagnosis, disease duration, and previous

medications. These particular variables were chosen based on their effect on the outcomes of similar studies. Sex, age, body mass index (BMI), and smoking status have all been shown to significantly alter the effectiveness of anti-TNF agents in inflammatory arthritis patients (Heiberg, et al., 2008). For each course of anti-TNF treatment, the following data was collected: the ranking of the anti-TNF agent (first, second, or third), the type of anti-TNF agent, its initial prescription date, which concomitant DMARDs and/or corticosteroids were prescribed at the time the anti-TNF treatment was initiated, and the date of treatment termination or of most recent follow-up. Concomitant medications were recorded due to their known influence on anti-TNF agent performance (Heiberg, et al., 2008; Duclos, et al., 2006). Also, if anti-TNF treatment was terminated, the reason was noted; reasons were classified as inefficacy, adverse event, or other (e.g., planning a pregnancy, financial reasons, etc.). The reason for treatment termination was not known in some cases, owing to the fact that there was no pre-existing protocol for collection of this information; the retrospective nature of this study relied heavily on the routine documentation practices of the rheumatologists involved.

In the Toronto center, patient screening and data collection were done by a group not directly involved in the present study. Screening at this center took place at approximately the same time as it did at the St. John's center; data for patients who started their first anti-TNF after August 2009 were not included. All the required demographic and treatment information belonging to the Toronto center patients was electronically transferred to the study investigators and merged with the rest of the data set. One systematic issue with data collection here was missing concomitant DMARD and corticosteroid data for many of the Toronto AS patients (this is likely due to the reluctance to use DMARDs and prednisone in AS patients). This was addressed by adjusting the statistical analysis accordingly, as discussed below.

2.3 Statistical Analyses

The crude drug survival rates for each cohort were determined with Kaplan-Meier analyses, using the log rank test to test for significance between survival curves. For the first course of anti-TNF therapy, this was done to compare drug survival among the 3 diseases of interest, and to compare survival among the three anti-TNF s of interest within each disease. For the second course of anti-TNF therapy, this was done to compare drug survival among the 3 diseases, and to compare survival among the three anti-TNF s in the overall inflammatory arthritis population. Cox regression was then performed to assess the hazard ratios (HRs) for treatment termination for each cohort. This was done using adjustments for age, sex, smoking status, concomitant prednisone use, and concomitant MTX use; each of these variables was assigned as a covariate in the Cox regression model (except in the case of comparing anti-TNF survival exclusively in the AS patient population, where the concomitant prednisone and MTX covariates were omitted). The assumption of constant proportional hazards was assessed and held true for all covariates.

Among the patients who failed their first course of anti-TNF therapy, the baseline variables of those who failed in ≤6 months were compared with those who failed in >6 months. Apart from age, which was compared using an independent samples t-test, all variables (diagnosis, type of anti-TNF agent, sex, smoking status, concomitant prednisone use, and concomitant MTX use) were compared using Pearson's Chi-Square test.

In order to compare drug survival times of the first and second courses of anti-TNF therapy among the cohort of patients who received both, a paired samples t-test was used.[10]

[10] More robust forms of analysis such as Kaplan-Meier analysis and Cox regression could not be used in this instance as there were by definition no survivors in one of the groups being compared (i.e. the group taking their first course of therapy)

Using the data comparing first-course anti-TNF survival among the three diseases, the post hoc power of the study was evaluated. This was done using a log rank test statistic.

A significance level of 5% was used in all analyses. Statistical analyses were performed with SPSS software, version 17.0 (SPSS, Chicago, IL).

Chapter 3 Results

3.1 Patients

A total of 332 patients were eligible for the analysis (160 AS patients, 58 PsA patients, and 114 RA patients; Table 3.1). All patients were followed from the date they started their anti-TNF therapy to the date they stopped their therapy, or their date of most recent follow-up before February 2010. The earliest date of follow-up was June 1998. There was no loss to follow-up.

Table 3.1: Demographic and clinical characteristics of all patients at baseline

	RA (n=114, 34.3%)	PsA (n=58, 17.5%)	AS (n=160, 48.2%)	p-value*
Age, years ± SD	53.5 ± 11.1	45.9 ± 9.7	38.3 ± 12.0	0
Female, no. (% within Dx)	95 (83.3)	26 (44.8)	32 (20.0)	0
Smoker, no. (% within Dx)	20 (17.5)	8 (13.8)	49 (30.6)	0.006
Concomitant Pred, no. (% within Dx)	73 (64.0)	33 (56.9)	N/A	0
Concomitant MTX, no. (% within Dx)	68 (59.6)	16 (27.6)	N/A	0
Infliximab, no. (% within Dx)	22 (19.3)	5 (8.6)	78 (48.8)	0
Etanercept, no. (% within Dx)	61 (53.5)	34 (58.6)	52 (32.5)	0
Adalimumab, no. (% within Dx)	31 (27.2)	19 (32.8)	30 (18.8)	0

***p-values are for the overall comparison among the 3 groups**

As the p-values in Table 3.1 demonstrate, the three disease cohorts were significantly dissimilar with respect to every characteristic measured. RA patients were older on average than either PsA or AS patients and more RA patients were women whereas most PsA and AS patients were men. Etanercept was prescribed more heavily in RA and PsA patients whereas infliximab was the anti-TNF of choice in AS patients. Over half of the RA patients were taking either MTX or prednisone at the time they started their first anti-TNF. The same was true of PsA patients but for MTX only. Because this information was not available for a significant number of AS patients (namely those whose data came from the Toronto centre), it was not possible to assess how many of them were taking either prednisone or MTX.

However, the number of AS patients taking prednisone or MTX was estimated to be very low as neither is prescribed commonly for treating this disease.

3.2 Statistical Analysis

3.2.1 Survival of the First Course of anti-TNF Therapy

a) Overall Anti-TNF Survival in AS vs. PsA vs. RA

Kaplan-Meier analysis was used to assess the differences in crude drug survival among the three diseases. The estimated mean drug survival times were 53.5, 35.9, and 42.4 months for AS, PsA, and RA, respectively (Table 3.2). The log rank test showed that the differences in drug survival between AS and RA ($p = 0.028$ at 95% confidence) and between AS and PsA ($p = 0.045$) were both statistically significant, but the difference in drug survival between RA and PsA ($p = 0.712$) was not significant (Table 3.3, Figure 3.1).

Table 3.2: Estimated mean first-course anti-TNF agent survival times for AS, PsA, and RA patients

	Mean			
			95% Confidence Interval	
Dx	Estimate	Std. Error	Lower Bound	Upper Bound
AS	53.495	2.896	47.819	59.171
PsA	35.851	2.984	30.001	41.700
RA	42.382	3.286	35.942	48.821
Overall	47.702	2.013	43.757	51.647

Table 3.3: Pairwise comparisons of first-course anti-TNF survival among AS, PsA, and RA patients

		AS		PsA		RA	
	Dx	Chi-Square	Sig.	Chi-Square	Sig.	Chi-Square	Sig.
Log Rank (Mantel-Cox)	AS			4.036	.045	4.850	.028
	PsA	4.036	.045			.136	.712
	RA	4.850	.028	.136	.712		

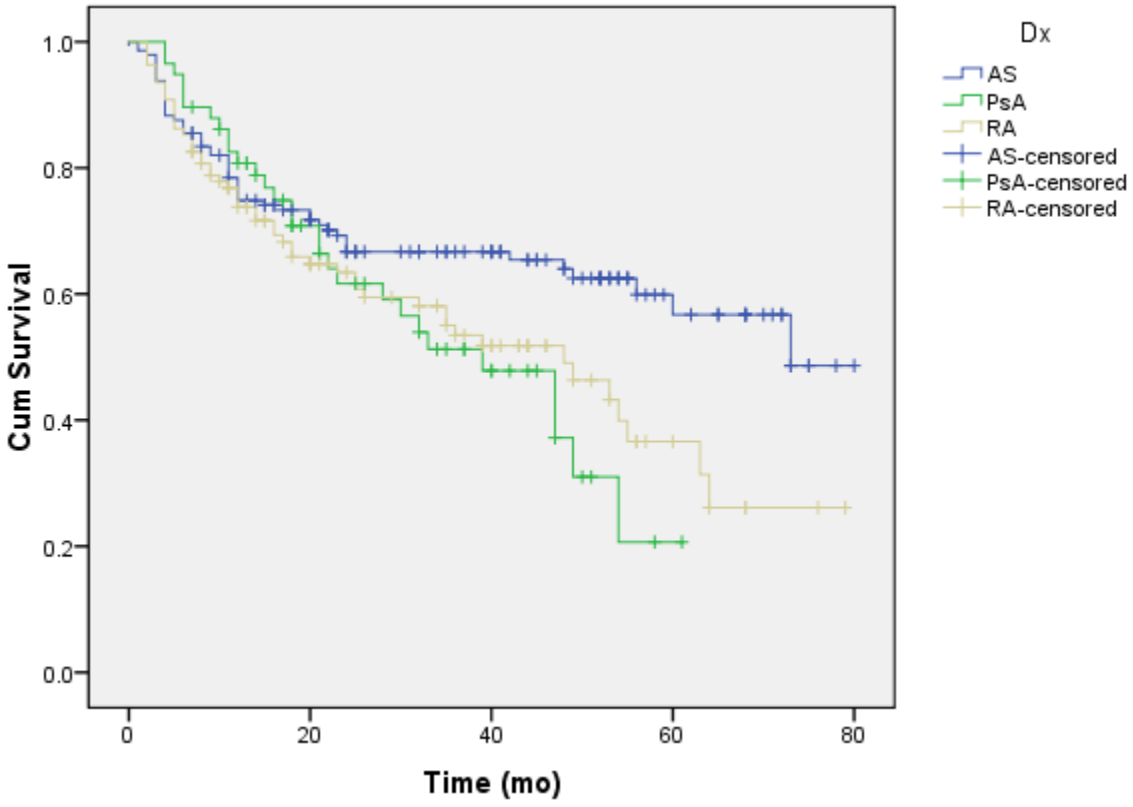

Figure 3.1: First-course anti-TNF agent survival among AS, PsA, and RA patients

Table 3.4A: Adjusted hazard ratios for discontinuing first-course anti-TNF agents among AS, PsA, and RA (RA reference)

	B	SE	Wald	df	Sig.	HR	95.0% CI for HR	
							Lower	Upper
RA (reference)			.916	2	.633			
AS	-.087	.235	.137	1	.711	.917	.579	1.453
PsA	.162	.234	.478	1	.489	1.176	.743	1.862

Table 3.4B: Adjusted hazard ratios for discontinuing first-course anti-TNF agents among AS, PsA, and RA (AS reference)

	B	SE	Wald	df	Sig.	HR	95.0% CI for HR	
							Lower	Upper
AS (reference)			.916	2	.633			
PsA	.249	.266	.877	1	.349	1.283	.762	2.160
RA	.087	.235	.137	1	.711	1.091	.688	1.728

After adjusting for age, sex, smoking status, anti-TNF agent type, concomitant MTX, and concomitant prednisone, the respective hazard ratios (HRs) and 95% confidence intervals (CIs) for treatment termination in AS and PsA patients versus RA patients were 0.92 (0.58-1.45) and 1.18 (0.74-1.86; Table 3.4A). The HR for treatment termination in PsA versus AS patients was 1.28 (0.76-2.16; Table 3.4B). The adjusted risk of anti-TNF treatment termination was not significantly different among the three arthritides. None of the covariates were found to be associated with treatment termination.

b) Etanercept vs. Adalimumab vs. Infliximab in AS patients

Kaplan-Meier analysis was done to assess the differences in crude drug survival among the three anti-TNF drugs within each diagnosis. In AS, the estimated mean drug survival times were 63.9, 54.2, and 80.0 months for etanercept, adalimumab, and infliximab, respectively (Table 3.5). The log rank test showed that the differences in crude drug survival between etanercept and adalimumab (p = 0.652), etanercept and infliximab (p = 0.333), and adalimumab and infliximab (p = 0.820) were not statistically significant (Table 3.6, Figure 3.2). After adjusting for age, sex, and smoking status the respective HRs and 95% CIs for treatment termination in AS patients taking etanercept and adalimumab versus those taking infliximab were 1.24 (0.66-2.33) and 1.14 (0.53-2.46; Table 3.7A). The HR and CI for treatment termination in AS patients taking adalimumab versus those taking etanercept was 0.92 (0.41-2.09; Table 3.7B). The adjusted risk of treatment termination in AS was not significantly different among the three anti-TNF drugs. Of the covariates tested, only sex was found to be associated with treatment termination: the HR and CI for termination in males versus females was 0.51 (0.27-0.95).

Table 3.5: Estimated mean first-course anti-TNF agent survival times for AS patients using etanercept, adalimumab, or infliximab

	Mean			
			95% Confidence Interval	
Rx	Estimate	Std. Error	Lower Bound	Upper Bound
Etanercept	63.904	5.904	52.332	75.477
Adalimumab	54.216	5.760	42.926	65.506
Infliximab	80.003	5.708	68.815	91.191
Overall	77.820	4.262	69.467	86.173

Table 3.6: Pairwise comparisons of first-course anti-TNF survival among AS patients using etanercept, adalimumab, or infliximab

		Etanercept		Adalimumab		Infliximab	
	Rx	Chi-Square	Sig.	Chi-Square	Sig.	Chi-Square	Sig.
Log Rank (Mantel-Cox)	Etanercept			.203	.652	.939	.333
	Adalimumab	.203	.652			.052	.820
	Infliximab	.939	.333	.052	.820		

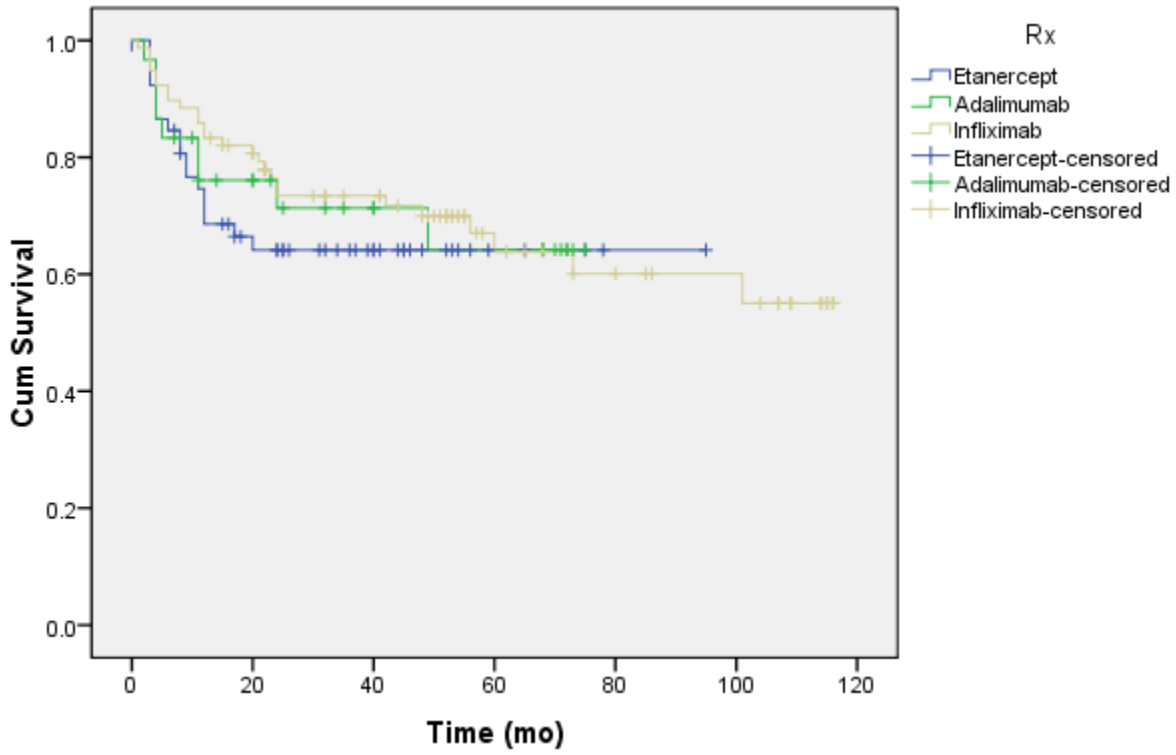

Figure 3.2: First-course anti-TNF agent survival among AS patients using etanercept, adalimumab, or infliximab

Table 3.7A: Adjusted hazard ratios for discontinuing first-course anti-TNF agents among AS patients (infliximab reference)

	B	SE	Wald	df	Sig.	HR	95.0% CI for HR	
							Lower	Upper
male	-.678	.319	4.508	1	.034	.508	.272	.949
Infliximab (ref)			.456	2	.796			
Etanercept	.214	.323	.440	1	.507	1.239	.658	2.332
Adalimumab	.133	.392	.115	1	.735	1.142	.529	2.464

Table 3.7B: Adjusted hazard ratios for discontinuing first-course anti-TNF agents among AS patients (etanercept reference)

	B	SE	Wald	df	Sig.	HR	95.0% CI for HR	
							Lower	Upper
male	-.678	.319	4.508	1	.034	.508	.272	.949
Etanercept (ref)			.456	2	.796			
Adalimumab	-.081	.418	.038	1	.846	.922	.407	2.092
Infliximab	-.214	.323	.440	1	.507	.807	.429	1.520

c) Etanercept vs. Adalimumab vs. Infliximab in PsA patients

In Kaplan-Meier analysis of PsA patients, the estimated mean drug survival times were 35.4, 36.5, and 25.0 months for etanercept, adalimumab, and infliximab, respectively (Table 3.8). The log rank test showed that the differences in crude drug survival between etanercept and adalimumab (p = 0.601), etanercept and infliximab (p = 0.685), and adalimumab and infliximab (p = 0.559) were not statistically significant (Table 3.9, Figure 3.3). After adjusting for age, sex, smoking status, concomitant MTX, and concomitant prednisone, the respective HRs and 95% CIs for treatment termination in PsA patients taking etanercept and adalimumab versus those taking infliximab were 0.77 (0.18-3.34) and 0.59 (0.12-2.94; Table

3.10A). The HR and CI for treatment termination in PsA patients taking adalimumab versus those taking etanercept was 0.77 (0.31-1.95; Table 3.10B). The adjusted risk of treatment termination in PsA was not significantly different among the three anti-TNF drugs. None of the covariates were found to be associated with treatment termination.

Table 3.8: Estimated mean first-course anti-TNF agent survival times for PsA patients using etanercept, adalimumab, or infliximab

	Mean			
			95% Confidence Interval	
Rx	Estimate	Std. Error	Lower Bound	Upper Bound
Etanercept	35.448	3.514	28.560	42.335
Adalimumab	36.454	4.736	27.171	45.738
Infliximab	25.000	6.627	12.011	37.989
Overall	35.851	2.984	30.001	41.700

Table 3.9: Pairwise comparisons of first-course anti-TNF survival among PsA patients using etanercept, adalimumab, or infliximab

		Etanercept		Adalimumab		Infliximab	
	Rx	Chi-Square	Sig.	Chi-Square	Sig.	Chi-Square	Sig.
Log Rank (Mantel-Cox)	Etanercept			.273	.601	.164	.685
	Adalimumab	.273	.601			.342	.559
	Infliximab	.164	.685	.342	.559		

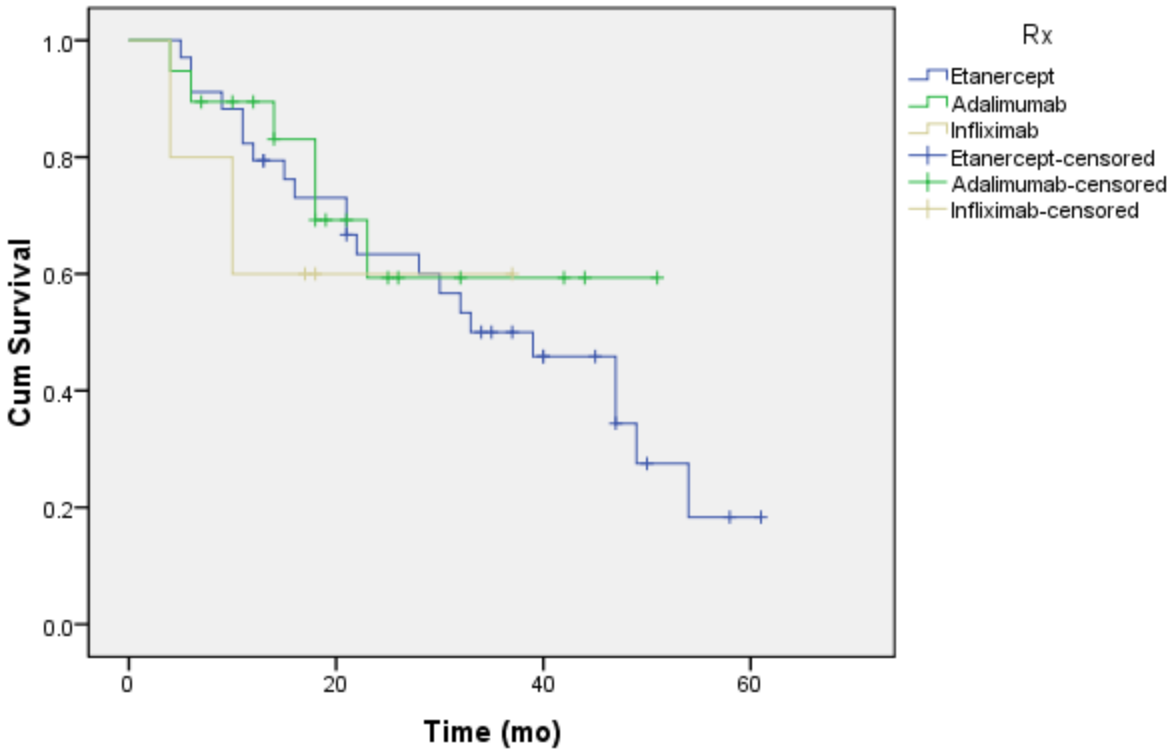

Figure 3.3: First-course anti-TNF agent survival among PsA patients using etanercept, adalimumab, or infliximab

Table 3.10A: Adjusted hazard ratios for discontinuing first-course anti-TNF agents among PsA patients (infliximab reference)

	B	SE	Wald	df	Sig.	HR	95.0% CI for HR	
							Lower	Upper
Infliximab (ref)			.505	2	.777			
Etanercept	-.268	.752	.127	1	.722	.765	.175	3.339
Adalimumab	-.526	.819	.413	1	.520	.591	.119	2.941

Table 3.10B: Adjusted hazard ratios for discontinuing first-course anti-TNF agents among PsA patients (etanercept reference)

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Etanercept (ref)			.505	2	.777			
Adalimumab	-.258	.472	.299	1	.584	.772	.306	1.949
Infliximab	.268	.752	.127	1	.722	1.307	.299	5.704

d) Etanercept vs. Adalimumab vs. Infliximab in RA patients

In Kaplan-Meier analysis of RA patients, the estimated mean drug survival times were 48.9, 54.0, and 63.3 months for etanercept, adalimumab, and infliximab, respectively (Table 3.11). The log rank test showed that the difference in crude drug survival between etanercept and adalimumab (p = 0.010) was statistically significant, but the differences in survival between etanercept and infliximab (p = 0.178), and adalimumab and infliximab (p = 0.227) were not statistically significant (Table 3.12, Figure 3.4). Initially, it may seem counterintuitive that adalimumab (mean survival = 54.0 months), and not infliximab (mean survival = 63.3 months), had a significantly greater survival than etanercept (mean survival = 48.9 months). However, the log rank test compares survival *distributions* and not survival *means*, allowing it to correct for drug survival data which may be deceptively inflated (i.e. in the case of infliximab, which has been prescribed for RA several years longer than adalimumab, allowing a greater mean survival for infliximab vs. adalimumab in the present study but not necessarily a superior survival distribution). After adjusting for age, sex, smoking status, concomitant MTX, and concomitant prednisone, the respective HRs and 95% CIs for treatment termination in RA patients taking etanercept and adalimumab versus those taking infliximab were 1.60 (0.79-3.23) and 0.54

(0.20-1.49; Table 3.13A). The HR and CI for treatment termination in RA patients taking adalimumab versus those taking etanercept was 0.34 (0.14-0.80; Table 3.13B). The adjusted risk of treatment termination was only significantly lower in RA patients taking adalimumab versus those taking etanercept. None of the covariates were found to be associated with treatment termination.

Table 3.11: Estimated mean first-course anti-TNF agent survival times for RA patients using etanercept, adalimumab, or infliximab

	Mean			
			95% Confidence Interval	
Rx	Estimate	Std. Error	Lower Bound	Upper Bound
Etanercept	48.896	7.333	34.523	63.269
Adalimumab	54.012	5.113	43.990	64.034
Infliximab	63.323	11.220	41.332	85.313
Overall	61.506	6.061	49.626	73.386

Table 3.12: Pairwise comparisons of first-course anti-TNF survival among RA patients using etanercept, adalimumab, or infliximab

		Etanercept		Adalimumab		Infliximab	
	Rx	Chi-Square	Sig.	Chi-Square	Sig.	Chi-Square	Sig.
Log Rank (Mantel-Cox)	Etanercept			6.714	.010	1.818	.178
	Adalimumab	6.714	.010			1.462	.227
	Infliximab	1.818	.178	1.462	.227		

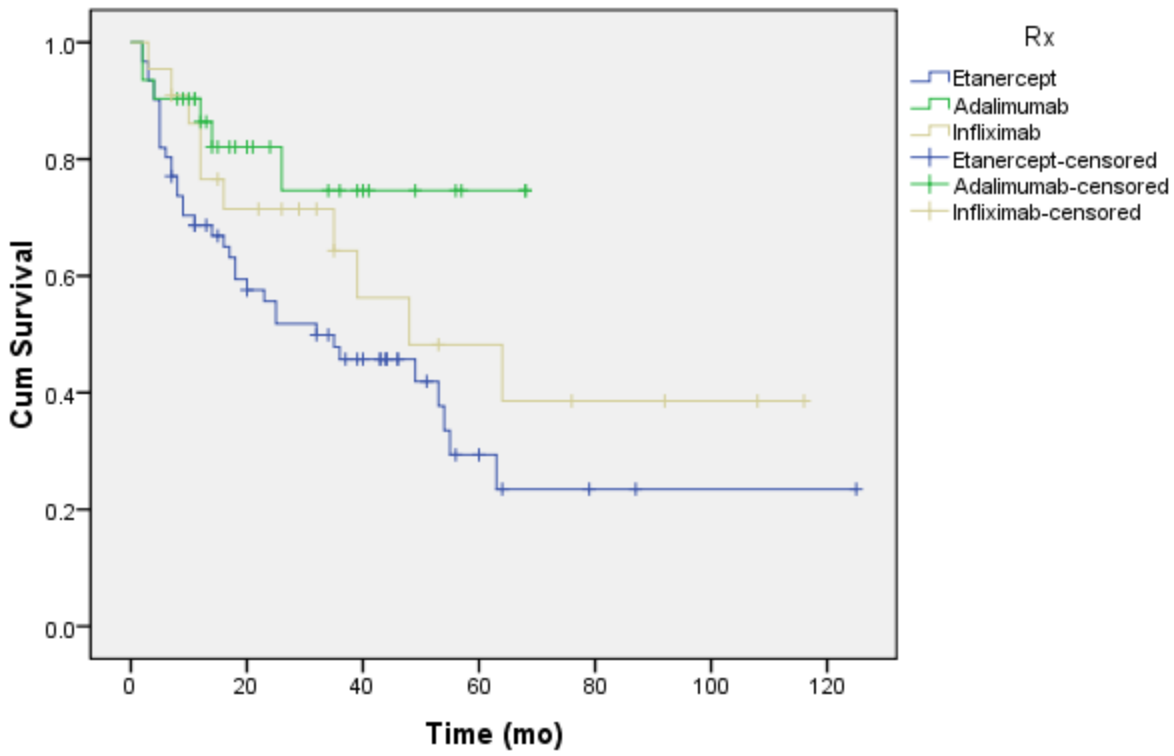

Figure 3.4: First-course anti-TNF agent survival among RA patients using etanercept, adalimumab, or infliximab

Table 3.13A: Adjusted hazard ratios for discontinuing first-course anti-TNF agents among RA patients (infliximab reference)

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Infliximab (ref)			6.841	2	.033			
Etanercept	.469	.359	1.699	1	.192	1.598	.790	3.232
Adalimumab	-.617	.518	1.418	1	.234	.539	.195	1.490

Table 3.13B: Adjusted hazard ratios for discontinuing first-course anti-TNF agents among RA patients (etanercept reference)

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Etanercept (ref)			6.841	2	.033			
Adalimumab	-1.086	.441	6.052	1	.014	.338	.142	.802
Infliximab	-.469	.359	1.699	1	.192	.626	.309	1.266

e) Inefficacy vs. Adverse Events in all patients

Table 3.14 shows the frequencies for the two chief reasons for first anti-TNF discontinuation among the disease and treatment groups identified. These reasons were lack of efficacy or one or more adverse events such as infection or malignancy. For some disease and treatment groups, the proportions discontinuing due to lack of efficacy or adverse events were similar. However, in the case of PsA patients, 21 stopped their anti-TNF due to lack of efficacy whereas only 3 stopped due to adverse events. Another imbalance is in the case of RA patients, with 32 quitting their anti-TNF due to lack of efficacy and 12 due to adverse events. Also, for all patients taking etanercept, 53 discontinued due to lack of efficacy and only 10 discontinued due to adverse events. Finally, an overall comparison of the two reasons for discontinuation in the entire first anti-TNF study population revealed that lack of efficacy was more of an issue than adverse events, with 74 quitting due to the former and 34 due to the latter. Notably, for 26 of the 134 total patients who discontinued their first course of anti-TNF therapy (i.e. 19%), there was no reason noted for anti-TNF discontinuation.

Table 3.14: Frequencies for reasons for discontinuation (D/C) by diagnosis and anti-TNF agent

	Reason for D/C	AS	PsA	RA	Total
Etanercept	**Adverse event(s)**	3	1	6	10
	Inefficacy	10	17	26	53
	Unknown	5	3	4	12
Adalimumab	**Adverse event(s)**	5	1	3	9
	Inefficacy	3	4	3	10
	Unknown	1	1	0	2
Infliximab	**Adverse event(s)**	11	1	3	15
	Inefficacy	8	0	3	11
	Unknown	7	1	4	12
Total	**AE,IE,UK**	19,21,13	3,21,5	12,32,8	134

***AE: adverse event(s), IE: inefficacy, UK: unknown**

f) Primary vs. Secondary Non-responders among all patients

To further explore the causes of premature anti-TNF discontinuation, the 134 patients who failed their first anti-TNF were split into primary non-responders (anti-TNF failure in ≤6 months) and secondary non-responders (anti-TNF failure in >6 months). These two groups were then compared on various baseline variables to see if any were significantly different (Table 3.15). Age was compared using an independent samples t-test. Diagnosis, anti-TNF type, sex, smoking status, concomitant MTX use, and concomitant prednisone use were compared using Pearson's Chi-Square test. No tested variables were found to be significantly different between the two groups.

Table 3.15: Comparison of baseline variables between primary non-responders and secondary non-responders to anti-TNF therapy

Baseline Variable (p-value)		Primary Non-Responder* (n=43)	Secondary Non-Responder* (n=91)
Age (p=0.528)		44.23	45.70
Dx (p=0.207)	AS	21	32
	PsA	6	23
	RA	16	36
Rx (p=0.226)	Etanercept	23	52
	Adalimumab	10	11
	Infliximab	10	28
Sex (p=0.969)	M	20	42
	F	23	49
Smoker (p=0.239)	N	31	73
	Y	12	17
MTX (p=0.308)	N	18	44
	Y	18	29
Prednisone (p=0.635)	N	17	38
	Y	19	35

***Primary non-responder: anti-TNF failure in ≤6 months, Secondary non-responder: anti-TNF failure in >6 months**

3.2.2 Survival of the Second Course of anti-TNF Therapy

a) First vs. Second Course of Anti-TNF Therapy in patients who tried both

In the 98 patients who failed their first anti-TNF agent and were placed on a second agent, crude drug survival was compared between the two courses using a paired samples t-test (Table 3.16). Mean drug survival for the first course was 18.1 months and that for the second course was 19.8 months (p = 0.443; Table 3.17). There was no significant difference in drug survival between first and second courses of anti-TNF therapy.

Table 3.16: Mean drug survival times for patients who took two courses of anti-TNF therapy

Anti-TNF Course	N	Mean Survival (months)	SD
1st Course	98	18.10	16.047
2nd Course	98	19.83	16.271

Table 3.17: Paired samples t-test comparing first vs second course of anti-TNF therapy

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	SD	Std. Error of Mean	95% CI of the difference Lower	Upper			
1st course – 2nd course	-1.724	22.184	2.241	-6.172	2.723	-0.770	97	0.443

b) Overall anti-TNF survival in AS vs. PsA vs. RA

Kaplan-Meier analysis was used to assess the differences in crude second-course anti-TNF survival among the three diseases. The estimated mean drug survival times were 37.0, 44.4, and 34.0 months for AS, PsA, and RA, respectively (Table 3.18). The log rank test showed that the difference in crude drug survival between PsA and RA (p = 0.029) was statistically significant, but the differences in survival between PsA and AS (p = 0.139), and AS and RA (p = 0.413) were not statistically significant (Table 3.19, Figure 3.5). After adjusting for age, sex, smoking status, anti-TNF agent type, concomitant MTX, and concomitant prednisone, the respective HRs and 95% CIs for treatment termination in AS and PsA patients versus RA patients were 0.62 (0.28-1.40) and 0.42 (0.19-0.93; Table 3.20A). The HR for treatment termination in PsA versus AS patients was 0.67 (0.25-1.81; Table 3.20B). The adjusted risk of treatment termination was only significantly lower in PsA patients versus RA patients. None of the covariates were found to be associated with treatment termination.

Table 3.18: Estimated mean second-course anti-TNF agent survival times for AS, PsA, and RA patients

	Mean			
			95% Confidence Interval	
Dx	Estimate	Std. Error	Lower Bound	Upper Bound
AS	36.952	5.596	25.984	47.921
PsA	44.352	5.429	33.710	54.994
RA	33.980	6.224	21.782	46.178
Overall	41.929	4.463	33.182	50.667

Table 3.19: Pairwise comparisons of second-course anti-TNF survival among AS, PsA, and RA patients

		AS		PsA		RA	
	Dx	Chi-Square	Sig.	Chi-Square	Sig.	Chi-Square	Sig.
Log Rank (Mantel-Cox)	AS			2.189	.139	.670	.413
	PsA	2.189	.139			4.766	.029
	RA	.670	.413	4.766	.029		

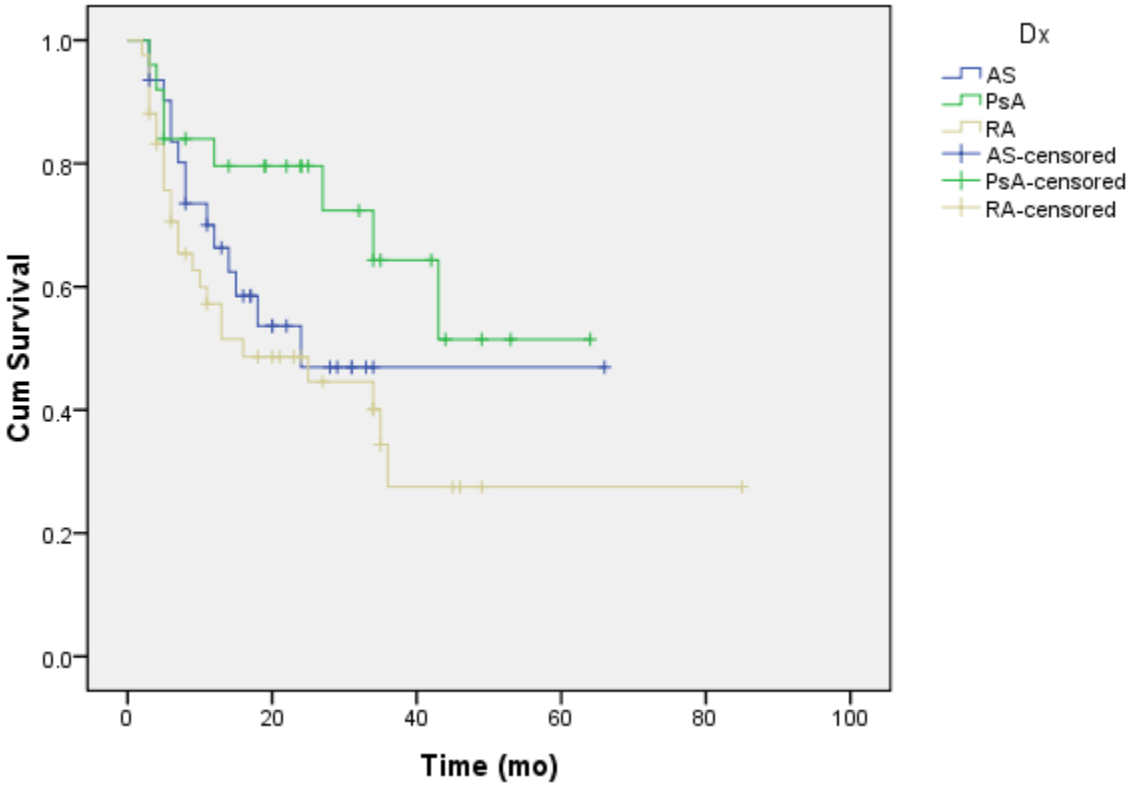

Figure 3.5: Second-course anti-TNF agent survival among AS, PsA, and RA patients

Table 3.20A: Adjusted hazard ratios for discontinuing second-course anti-TNF agents among AS, PsA, and RA (RA reference)

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
RA (reference)			4.956	2	.084			
AS	-.474	.412	1.326	1	.250	.622	.278	1.395
PsA	-.871	.410	4.524	1	.033	.418	.187	.934

Table 3.20B: Adjusted hazard ratios for discontinuing second-course anti-TNF agents among AS, PsA, and RA (AS reference)

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
AS (reference)			4.956	2	.084			
PsA	-.397	.506	.616	1	.433	.672	.249	1.812
RA	.474	.412	1.326	1	.250	1.607	.717	3.601

c) Etanercept vs. Adalimumab vs. Infliximab in all patients

Kaplan-Meier analysis was used to compare the crude second-course anti-TNF survival of the three anti-TNF agents in the entire inflammatory arthritis population. The estimated mean drug survival times were 35.2, 34.0, and 42.8 months for etanercept, adalimumab, and infliximab, respectively (Table 3.21). The log rank test showed that the differences in crude drug survival between etanercept and adalimumab (p = 0.67), etanercept and infliximab (p = 0.91), and adalimumab and infliximab (p = 0.74) were not statistically significant (Table 3.22, Figure 3.6). After adjusting for age, sex, smoking status, concomitant MTX, and concomitant prednisone, the respective HRs and 95% CIs for treatment termination in patients taking etanercept and adalimumab versus those taking infliximab were 0.83 (0.26-2.61) and 1.32 (0.51-3.41; Table 3.23A). The HR and CI for treatment termination in patients taking adalimumab versus those taking

etanercept was 1.59 (0.69-3.65; Table 3.23B). The adjusted risk of treatment termination in the entire inflammatory arthritis population was not significantly different among the three anti-TNF drugs. None of the covariates were found to be associated with treatment termination.

Table 3.21: Estimated mean second-course anti-TNF agent survival times for inflammatory arthritis patients using etanercept, adalimumab, or infliximab

	Mean			
			95% Confidence Interval	
Rx	Estimate	Std. Error	Lower Bound	Upper Bound
Etanercept	35.175	6.245	22.934	47.415
Adalimumab	34.001	3.964	26.232	41.770
Infliximab	42.845	10.589	22.090	63.600
Overall	41.929	4.463	33.182	50.677

Table 3.22: Pairwise comparisons of second-course anti-TNF survival among inflammatory arthritis patients using etanercept, adalimumab, or infliximab

		Etanercept		Adalimumab		Infliximab	
	Rx	Chi-Square	Sig.	Chi-Square	Sig.	Chi-Square	Sig.
Log Rank (Mantel-Cox)	Etanercept			.177	.674	.014	.905
	Adalimumab	.177	.674			.110	.740
	Infliximab	.014	.905	.110	.740		

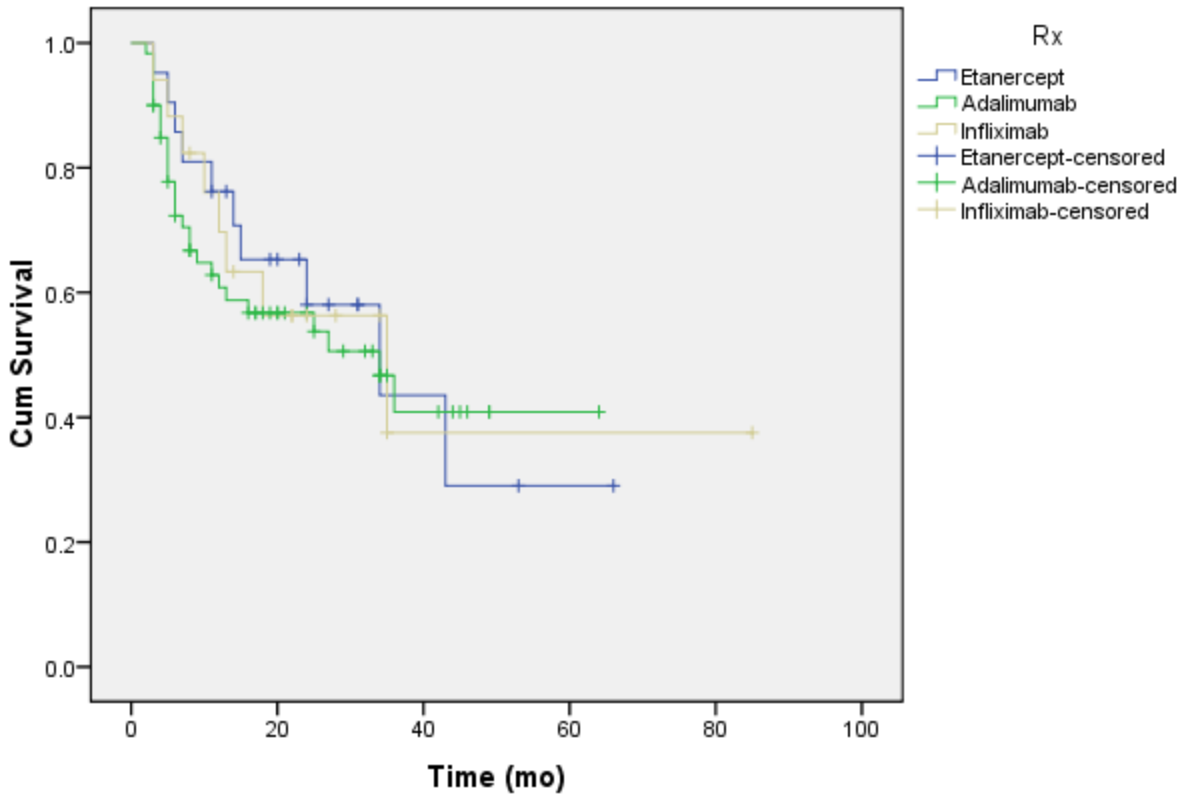

Figure 3.6: Second-course anti-TNF agent survival among inflammatory arthritis patients using etanercept, adalimumab, or infliximab

Table 3.23A: Adjusted hazard ratios for discontinuing second-course anti-TNF agents among inflammatory arthritis patients (infliximab reference)

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Infliximab (ref)			1.342	2	.511			
Etanercept	-.190	.586	.105	1	.746	.827	.262	2.610
Adalimumab	.274	.486	.317	1	.573	1.315	.507	3.411

Table 3.23B: Adjusted hazard ratios for discontinuing second-course anti-TNF agents among inflammatory arthritis patients (etanercept reference)

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Etanercept (ref)			1.342	2	.511			
Adalimumab	.464	.423	1.199	1	.273	1.590	.693	3.645
Infliximab	.190	.586	.105	1	.746	1.209	.383	3.815

3.2.3 Post Hoc Power Analysis

In order to assess the statistical power of the study, a post hoc power analysis was done using the data comparing overall first-course anti-TNF survival among the three diseases. The results show that only the comparison of anti-TNF survival between AS and PsA was adequately powered at 0.913 (Table 3.22). Since the statistical power of both the AS-RA and PsA-RA comparisons was less than 0.80 and thus underpowered, the results of these comparisons must be interpreted with caution.

Table 3.24: Post hoc power analysis of first anti-TNF agent survival among AS, PsA, and RA patients

Comparison	Statistical Power
AS vs. PsA	0.913
AS vs. RA	0.639
PsA vs. RA	0.248

Chapter 4 Discussion

4.1 Longitudinal, Observational Studies vs. RCTs for the study of anti-TNF Therapy in Inflammatory Arthritis

TNF-α antagonists represent the most advanced line of therapy for inflammatory rheumatic disease. Although they are relatively new and very expensive, they are still widely prescribed to arthritis patients; those with more severe disease are particularly reliant upon these drugs. For these reasons, the efficacy and safety profiles of these drugs are currently topical in medical research and have generated a great deal of studies. The majority of these studies have been RCTs. For example, a 2004 RCT investigated the efficacy and safety of adalimumab in RA patients over a six-month period (van de Putte, et al., 2004). Similar RCTs were done to examine etanercept in RA (Keystone, et al., 2004), infliximab in AS (van der Heijde, et al., 2005), adalimumab in PsA (Mease, et al., 2005), and every other possible TNF-α antagonist-inflammatory arthritis combination.

While these studies are useful for accurately measuring drug effects and minimizing study bias, they often have limited generalizability and thus do not account for many real-life patient experiences. For instance, RCTs often have strict inclusion criteria in order to generate a homogeneous study population. This helps the RCT to demonstrate a more uniform response to the intervention, but the external validity of the trial suffers as a result of this homogeneity. A common example of this problem among RCTs examining inflammatory arthritis is the tendency to include only those patients whose disease activity scores are very elevated. A 2003 study illustrated this by examining a 146-patient cohort with longstanding, active, routinely managed RA to determine which proportion met each of the disease activity score criteria most commonly used among RCTs conducted with RA patients (i.e. swollen joint count >6, tender joint count >6, erythrocyte sedimentation rate >28 mm/h, and morning stiffness >45 min). The study found that less than half of the cohort met each of the criteria and less than 10% met all

of them (Sokka, et al., 2003). Other characteristics commonly found in RCTs that reduce their external validity are the exclusion of patients with significant comorbidities (Keystone, et al., 2004), and a heightened frequency of patient assessment which is not feasible in a normal clinical setting. Another problem that predominates in these experimental studies is the recruitment of patients who cannot pay for their treatment and are thus particularly willing to take the study drug, which is often free of charge for them. Being especially incentivized to remain in the study, these patients may inflate the efficacy of the study drug.

There have been a few studies which address these issues (Heiberg, et al., 2008; Duclos, et al., 2006). These observational studies lack the often tight exclusion criteria of RCTs. Such studies might, for example, select all the arthritis patients who are treated with anti-TNF agents at a particular clinic in order to produce a highly generalizable study population. This population would likely consist of patients with a broad range of disease activity scores, a wide variety of comorbidities, and an overall realistic frequency of assessment. Also, since in an observational study the provision of treatment is outside the investigator's control, these patients would presumably only use an anti-TNF agent as long as it is effective. Thus the number of patients who cannot pay for and/or have limited access to alternative treatment would be minimized. Heiberg et al's 2008 study selected its patient population in just this fashion: they included all RA, PsA, and AS patients seen in five Norwegian rheumatology departments from 2000 onward who were treated with an anti-TNF agent (Heiberg, et al., 2008).

A further criticism of the RCT approach in studies of inflammatory arthritis is the length of the follow-up period: many of the prominent RCTs investigating anti-TNF agents in arthritis last no longer than 24 weeks (Antoni, et al., 2005; Mease, et al., 2004; van der Heijde, et al., 2006). While this may be sufficient time to assess the drugs' efficacy under optimal circumstances, it is not long enough to assess how the drugs perform under average circumstances, i.e. their effectiveness (Bombardier, et al., 1999).

The wide range of arthritis patients' disease activity, compliance, and comorbidities seen in real-life conditions makes assessing drug effectiveness using an RCT particularly challenging. Moreover, the very nature of anti-TNF agents as remittive therapies[11] for chronic, inflammatory arthritis makes studying them in the short term difficult. A longitudinal, observational study would therefore be better suited to this purpose. For example, in their observational study Heiberg et al observed their patients for an entire year, assessing patients' response to treatment at 3, 6 and 12 months (Heiberg, et al., 2008). However, instead of relying on a scoring system like the ACR20 to assess treatment efficacy, their longitudinal study design allowed them to assess the survival rates of anti-TNF agents in patients as their primary outcome.

Drug survival is not only an easily measured outcome, but also serves as a proven surrogate marker for a drug's efficacy (Geborek, et al., 2002). Several longitudinal studies have been done to examine the survival of anti-TNF drugs in inflammatory rheumatic disease. In their study of 770 patients with various forms of inflammatory arthritis, Duclos et al found that the three major anti-TNF agents had similar drug survival over a three-year period (Duclos, et al., 2006). They also found that overall anti-TNF agent survival was significantly better in SpA patients than in RA patients, and significantly better for patients on their first course of anti-TNF treatment than those on their second or third course (Duclos, et al., 2006). This finding was echoed in another study, which additionally concluded that a higher rate of adverse events in RA patients using anti-TNF agents is partially responsible for the reduced drug survival seen in that disease (Carmona, et al., 2006). Heiberg et al's one-year study generated similar results and also found that concomitant MTX is associated with significantly better anti-TNF agent survival in RA and PsA patients (Heiberg, et al., 2008).

[11] A remittive therapy is one which is designed to promote remission of a disease

4.2 Explanation of the Results

The present study used a longitudinal, observational design to assess and compare drug survival in several different groups of subjects. The subjects were categorized based on two principal variables: inflammatory arthritis type and anti-TNF drug type. This categorization, along with the inclusion of several confounding variables, allowed us to determine which diseases and drugs were associated with longer drug survival and thus greater efficacy. Thus, the key purpose of this study was to both build upon and deconstruct the findings of the aforementioned observational studies. Previous studies have typically compared *generalized* anti-TNF agent survival among the three arthritides or, conversely, compared survival of each anti-TNF agent in a *generalized* arthritis population. This study aimed to elucidate the effect that each drug and disease exerts on drug survival by comparing all combinations of these two variables.

4.2.1 Survival of the First Course of anti-TNF Therapy

a) Overall Anti-TNF Survival in AS vs. PsA vs. RA

When the study subjects were divided only by disease type and drug survival was compared, crude Kaplan-Meier analysis revealed the average first-course anti-TNF agent survival for AS patients was significantly longer than that of either RA patients or PsA patients. This finding is similar to those of other studies in the literature. For instance, Duclos et al found that the anti-TNF agent survival was significantly greater for SpA patients than it was for RA patients (HR of 1.60 for anti-TNF agent survival). While their study did not break down the SpA classification further for analysis purposes, it is suggested that the majority of their SpA patients may have had AS (166 had axial disease, 64 had peripheral disease, and 60 had PsA). Carmona et al had a similar result when comparing SpA to RA (HR of 0.66 for anti-TNF agent discontinuation) except their SpA cohort was approximately 50% AS patients and 50%

PsA patients. Heiberg et al's results also support this finding to a degree. Although their patients are only followed for a year, AS patients were found be at a significantly lesser risk of discontinuing their anti-TNF therapy than RA patients (HR of 0.66 for anti-TNF discontinuation). No such difference was found in that study between AS patients and PsA patients.

The superiority of drug survival in AS patients observed in the crude analysis was not observed once adjustments were made for several covariates (i.e. no significant HRs were found). Furthermore, no covariate contributed significantly to treatment termination. This has not been the case in other similar studies. Duclos et al found that concomitant DMARD (including MTX) decreased drug survival (HR of 0.70 for anti-TNF agent survival). In contrast, Heiberg et al found that concomitant MTX increased drug survival (HR of 0.53 for anti-TNF agent discontinuation). Also, Heiberg et al and Carmona et al both found that female patients were more likely than their male counterparts to discontinue an anti-TNF agent (HRs of 1.51 and 1.27 respectively for anti-TNF agent discontinuation).

Although we were not able to demonstrate a significant effect in the Cox regression analysis, it is clear from the Kaplan-Meier analysis and corroborated by other studies that AS patients tend to have superior anti-TNF drug survival. This may be due to increased efficacy of anti-TNF therapy in these patients but other potential reasons need to be considered. For example, it has been shown that once AS patients with axial disease have failed to respond to therapy with NSAIDs, the only effective treatment for them is anti-TNF therapy (Zochling, et al., 2006). This is in contrast to PsA and RA patients, who have several DMARDs available to them should NSAID therapy fail. Thus the increased drug survival observed in AS patients may be confounded by those patients' lack of effective treatment alternatives.

b) Etanercept vs. Adalimumab vs. Infliximab in AS patients

When AS patients were analyzed separately and survival of the 3 types of anti-TNF therapy were compared, both crude Kaplan-Meier analysis and Cox proportional hazards modeling found no significant differences between the survivals of each drug. This result correlates well with the findings of pre-existing RCTs. For instance, in their systematic review of 9 RCTs comparing various anti-TNF agents (2 studies with adalimumab, 2 with infliximab, and 5 with etanercept) against placebo in 1611 AS patients, McLeod et al were unable to distinguish between the efficacies of the 3 agents (McLeod, et al., 2007). A comparison of 3 more RCTs evaluating the efficacy of each of the 3 anti-TNF agents in AS patients somewhat corroborates this finding, with perhaps a slight trend towards an increased efficacy for infliximab and a decreased efficacy for adalimumab, i.e. one RCT found that 61% of AS patients treated with infliximab reached an ASAS20 after 24 weeks (van der Heijde, et al., 2005), another found that 57% treated with etanercept achieved this goal (Davis, et al., 2003), and another found that 51% treated with adalimumab achieved it (van der Heijde, et al., 2006). This trend is also observable in the results of the present study, with AS patients taking infliximab surviving for 80.0 months, those taking etanercept surviving for 63.9 months, and those taking adalimumab surviving for 54.2 months. It should be noted, however, that cross study comparisons are inherently difficult to interpret and vulnerable to considerable confounding. Thus these comparisons should be interpreted with caution.

One significant finding in the analysis of the AS subpopulation was that males were 50.8% as likely as females to discontinue anti-TNF therapy. This is consistent with the findings of Heiberg et al and Carmona et al, who found that being female predisposed to treatment termination in a generalized inflammatory arthritis population (Carmona, et al., 2006; Heiberg, et al., 2008). Glintborg et al had a similar finding when they examined AS patients in the Danish DANBIO registry, which includes >90% of adults in that country treated with biologics due to rheumatic disease in routine care (Glintborg, et al.,

2013). This 1436-patient cohort (25% female) was then subdivided into patients who had only been treated with one biologic agent ("non-switchers") and those who had received 2 or more courses of biologic therapy ("switchers"). They reported that women constituted only 22% of non-switchers but 33% of switchers, a statistically significant finding. Furthermore, once switchers had switched to a second biologic agent, male gender was a significant predictor of longer drug survival (HR of 1.76).

c) Etanercept vs. Adalimumab vs. Infliximab in PsA patients

In the separate analysis of PsA patients, Kaplan-Meier analysis and Cox proportional hazards modeling revealed no significant differences between the survivals of each of the 3 anti-TNF agents. This is also reflected in similar studies found in the literature: an RCT examining PsA patients treated with infliximab found that 54% reached an ACR20 after 24 weeks (Antoni, et al., 2005), another RCT found that 50% of PsA patients treated with etanercept reached an ACR 20 after 24 weeks (Mease, et al., 2004), and a third RCT found that 57% of PsA patients treated with adalimumab reached an ACR20 after 24 weeks (Mease, et al., 2005). A meta-analysis which indirectly compared the findings of 6 RCTs examining anti-TNF therapy in PsA patients (2 examining etanercept, 2 examining adalimumab, and 2 examining infliximab) also corroborates this finding of equivalence (Thorlund, et al., 2012). Their outcomes, relative risk (RR) of therapeutic response based on PsA Response Criteria (PsARC) and mean change in baseline health assessment questionnaire (HAQ) score, were not significantly different among the 3 anti-TNF agents (Thorlund, et al., 2012). They also compared the 3 agents on the outcome of mean change in baseline psoriasis area and severity index (PASI) score. All 3 agents were statistically equivalent for this outcome as well (Thorlund, et al., 2012).

In the Cox model of anti-TNF agent survival in PsA patients no covariates were found to contribute significantly to treatment termination. In contrast, Glintborg et al have demonstrated that anti-TNF agent survival is significantly reduced in female PsA patients (HR of 1.42 for anti-TNF

discontinuation) and in PsA patients not taking concomitant MTX (HR of 1.37) (Glintborg, et al., 2011). The latter finding is echoed in another study comparing anti-TNF monotherapy with anti-TNF plus MTX therapy in PsA patients (Heiberg, et al., 2008).

d) Etanercept vs. Adalimumab vs. Infliximab in RA patients

When RA patients were analyzed separately, both Kaplan-Meier crude drug survival analysis and Cox proportional hazards modeling showed that drug survival was superior in RA patients taking adalimumab compared to those taking etanercept. However, an indirect comparison of 3 RCTs examining anti-TNF therapy in RA patients gave markedly different results: one study found that 50% of RA patients treated with infliximab plus MTX reached an ACR20 after 30 weeks (Maini, et al., 1999), another study found that 75% of RA patients treated with etanercept reached an ACR20 after 12 weeks (Moreland, et al., 1997), and a third study found that only 46% of RA patients treated with adalimumab reached an ACR20 after 26 weeks (van de Putte, et al., 2004). A review of 3 more RCTs found altogether different results as well: the percentages of RA patients reaching ACR20 at 6 months were 92%, 63%, and 78% with infliximab, adalimumab, and etanercept, respectively (Jin, et al., 2010). Finally, there have also been studies which conclude there are no significant differences in effectiveness between etanercept, adalimumab, and infliximab for the treatment of RA (Mendoza, et al., 2010; Markenson, et al., 2011; Greenberg, et al., 2012). One was a retrospective study of a large, 5-year observational registry of RA patients. Investigators used one-year drug survival as their primary outcome and found that all 3 anti-TNF agents performed very similarly (persistence rates of 51% for etanercept, 48% for adalimumab, and 51% for infliximab) (Markenson, et al., 2011).

The present study found that none of the covariates tested (i.e. age, sex, smoking status, concomitant MTX/prednisone) had a significant effect on anti-TNF agent survival in RA patients. This has not been the case in several other studies in the literature, however. The addition of MTX to anti-TNF

therapy has previously been found to significantly increase drug survival in RA patients (Heiberg, et al., 2008; Hyrich, et al., 2006), whereas older age and concomitant prednisone have been shown to decrease drug survival (Hetland, et al., 2010). Smoking has also been reported to decrease efficacy and drug survival in RA patients taking infliximab (Hyrich, et al., 2006).

e) Inefficacy vs. Adverse Events in all patients

In order to further elucidate how each disease and drug affects anti-TNF survival in arthritis patients, and to assess the validity of drug survival as a marker for drug efficacy, a brief analysis was done to compare the different reasons for first anti-TNF discontinuation among all the main study groups. The reasons for discontinuation were assigned to two broad categories: drug inefficacy or adverse events, e.g. malignancy or infection. The results indicated that, in the overall study population, inefficacy was cited more than twice as often as intolerance as the reason for anti-TNF discontinuation. This result was echoed in a similar study which found that after 36 months of observation, 53.5% of a large population of inflammatory arthritis patients taking anti-TNF therapy had discontinued treatment due to inefficacy; only 16% of the population had discontinued due to intolerance after 36 months (Duclos, et al., 2006). When the results of the present study are broken down by drug and disease, the findings are similar to the overall result: lack of efficacy explains more of treatment discontinuation than do adverse events. For example, among patients in the study whose first discontinued anti-TNF was etanercept, there were more than five times as many failures due to lack of efficacy than there were due to adverse events. Thus, there appears to be some evidence in this study and elsewhere in the literature that inflammatory arthritis patients who fail anti-TNF therapy tend to do so because the drug is not efficacious for them, a finding which validates the use of drug survival as a marker for drug efficacy. However, it must be noted that a considerable number of patients in the present study (19% of

all first anti-TNF terminations) had no reason reported for treatment termination, a finding which casts some uncertainty on the use of the drug survival outcome.

f) Primary vs. Secondary Non-responders among all patients

An additional analysis was done to assess whether any of the patients' baseline variables were associated with a dichotomous drug survival outcome: anti-TNF failure before or after 6 months. This outcome denotes the difference between primary and secondary non-responders to anti-TNF treatment. The rationale for this distinction stems from research indicating that patients who respond 12-16 weeks after treatment initiation (i.e. primary responders) tend to present initially with increased synovial TNF expression, increased synovial lymphoid aggregates, as well as increases in other inflammatory biomarkers, when compared with those who do not respond in this timeframe (i.e. primary non-responders) (Tak, 2012). Secondary non-responders, on the other hand, are thought to fail treatment via an entirely different mechanism. These are patients who improve initially as primary responders do but after 6 months or more of treatment begin to become unresponsive to it, marked by a substantial loss of efficacy. It has been shown that this type of failure is at least partly precipitated by the development of anti-drug antibodies (Wolbink, et al., 2006).

Given the data in the present study it might be possible to correlate certain patient baseline variables with a primary or secondary mechanism of anti-TNF failure based on when that failure occurred. None of the baseline variables tested were found to be significant in this analysis. Furthermore, a literature review yields no studies with similar analyses for comparison. Instead of using clinical characteristics (e.g. age, sex, and diagnosis) as a means to predict treatment success with a first course of anti-TNF therapy, most researchers have apparently focused on the *outcome* of that first trial of therapy to guide subsequent treatment decisions. For instance, one author presents an algorithm positing that a primary non-responder, whose disease is relatively less TNF-dependent, will likely not

respond well to a second anti-TNF agent (Tak, 2012). However, a secondary non-responder, whose loss of response may only be due to the development of specific anti-drug antibodies, might respond well to a second course of anti-TNF therapy.

4.2.2 Survival of the Second Course of anti-TNF Therapy

a) First vs. Second Course of Anti-TNF Therapy in patients who tried both

The final stage of analysis attempted to determine if a positive response to a second course of anti-TNF therapy was indeed possible. A paired samples t-test was used to compare mean drug survival of first and second courses of anti-TNF therapy among the segment of the patient population who tried both. Overall, survival of the second course of therapy was no different from the first course (19.83 vs 18.10 months, $p = 0.443$). In contrast, similar studies in the literature have consistently found that anti-TNF therapy is more efficacious in biologically naïve patients than in those trying a second course. An example is a study which compared biologic survival and periodic ACR scores among RA patients who were biologically naïve, first-time switchers, or second-time switchers. The authors observed that the OR for an ACR20/50/70 response was consistently <0.6 for first-time switchers vs. biologically naïve patients, and that the latter group remained on their ant-TNF therapy significantly longer as well (Greenberg, et al., 2012). A study examining anti-TNF agent survival in 1436 AS patients found a similar result in that disease, observing that median drug survival for first, second, and third courses were 3.1, 1.6, and 1.8 years, respectively (Glintborg, et al., 2013). Finally, a study comparing different courses of treatment in a large, generalized inflammatory arthritis population found that patients were more than twice as likely to persist on a first course of anti-TNF therapy than on a second course (HR 2.17 for anti-

TNF survival) (Duclos, et al., 2006). This result was still significant when the analysis was done separately for interruption due to either inefficacy or intolerance.

b) All patients analyzed by Disease and by anti-TNF Agent

When the second course of anti-TNF therapy was analyzed separately and drug survival of the 3 diagnoses was compared, both crude Kaplan-Meier analysis and Cox proportional hazards modeling showed that the average drug survival for PsA patients was significantly longer than that for RA patients. Interestingly, this finding differs from what was found in the corresponding first-course analysis, where AS patients survived longest on anti-TNF therapy. However, it is still somewhat in keeping with the findings of previous studies comparing first course survival, which show superior anti-TNF survival in SpA patients vs. RA patients (Carmona, et al., 2006; Duclos, et al., 2006). Unfortunately, no similar studies were found in the literature which compared second-course anti-TNF survival by indication.

The comparison of second-course survival among the 3 different anti-TNF types in the entire inflammatory arthritis patient population revealed no significant differences between drugs. With the exception of the analysis done on RA patients, this is consistent with the findings generated in the first-course survival analysis. Again, there are no similar studies in the literature comparing second-course anti-TNF survival by anti-TNF agent. However, the findings here are similar to those obtained in previous studies comparing first-course anti-TNF survival, where the general consensus is that etanercept, adalimumab, and infliximab perform fairly similarly (McLeod, et al., 2007; Mendoza, et al., 2010; Thorlund, et al., 2012).

4.3 Limitations of the Study

Many of the limitations of the present study stem from its retrospective, observational design. Despite all the previously discussed advantages this type of study has to offer over an RCT with respect to observing real-life conditions, its internal validity is reduced due to the heterogeneous nature of its patients and its non-standardized intervention administration. Also, drug survival was found to be somewhat unreliable as a surrogate outcome for drug efficacy.

The most significant limitation with respect to population selection was the inability to generate a sample size large enough to power our study; according to our power analysis, only one comparison in the primary analysis was adequately powered (anti-TNF survival in AS vs. PsA). It is also evident by examining the 95% confidence intervals generated throughout the Results section that statistical power was lacking in most analyses (i.e. most confidence intervals were wide and overlapped HR=1 by a significant margin). Population selection was limited to whichever patients retrospectively met the study criteria at the 2 centers available to the investigators and, unfortunately, this produced a sample size which was not adequate to power the study. Such a small sample size not only impaired the power of analyses undertaken in the study but also prevented the undertaking of certain analyses which may have been insightful. For example, a comparison of drug survival between a first and second course of anti-TNF therapy could only be done on a general level, even though it would have been more relevant to compare courses for each of the 3 diagnoses.

Furthermore, while the use of non-restrictive exclusion criteria did help to increase the patient population size, this strategy was also problematic in that it created marked heterogeneity in the population. Heterogeneity can certainly be beneficial in increasing study validity if it is properly accounted for in the analysis with the use of additional variables and stratification. However, given the small sample sizes available in the present study such stratification could not be accommodated without

a significant loss in power. An example of this unchecked heterogeneity would be disease activity among the patients. Because this variable was deliberately not stratified, it is possible that a significant finding such as AS patients surviving longer on primary anti-TNF therapy than either PsA or RA patients may in fact be due to a much higher proportion of milder disease activity in the AS patients who were included in the study. Another example would be patients' disease antibody status [i.e. rheumatoid factor (RF), anti-nuclear antibody (ANA)] as well as their disease duration.

Another source of heterogeneity in the patient population which may have skewed survival outcomes was the use of two very different study settings, NL and Toronto. This issue would have affected any analyses involving AS patients, as they were the only group with patients drawn from both settings. In this study, a significant effort was made to standardize all of the data by controlling for several important covariates in each of the Cox regression models. However, it is certainly possible that one or more key differences between the NL and Toronto populations were *not* accounted for, resulting in some degree of confounding bias. For example, there was likely a disparity in average disease severity between the two populations, owing to the different methods of referral between the two settings: AS patients in the NL setting were referred to their rheumatologist by their family physician, whereas AS patients in the Toronto setting were referred to a single rheumatologist (an expert in AS specifically) by their previous rheumatologist. Therefore, although not assessed in this study, disease severity was likely greater in the Toronto AS population, which may have decreased its anti-TNF survival.

A lack of control with respect to intervention administration, while consistent with our intended observational design, also significantly limited the internal validity of this study. It was not inherently problematic that there were dissimilar proportions of patients taking each of the 3 anti-TNF agents within each diagnosis; in fact, this dissimilarity likely captures the reality of clinical practice, which was our intent. However, the preferential use of certain anti-TNF agents for patients who are predisposed to

poorer drug survival may have been an issue. For instance, one factor which may have limited the sample size *and* average drug survival for infliximab is that it tends to be prescribed mostly for patients with more severe disease. This is due to that drug's cumbersome, intravenous administration; etanercept and adalimumab are more conveniently administered subcutaneously. An additional administrative factor which may have *inflated* the average drug survival for infliximab is that its dose and/or frequency is commonly escalated mid-course in patients who are beginning to lose drug effect; this cannot typically be done with etanercept or adalimumab.

The use of MTX presents a similar problem in this study. Although recommended to be used in combination with an anti-TNF agent for the treatment of RA and many forms of PsA (Schur, et al., 2013; Gladman, 2010), it is not used as systematically as it could be. This is likely due to the wide variety of adverse events associated with its use, its teratogenicity, and some of the lifestyle changes required while taking it (e.g. abstaining from alcohol consumption). Thus, the reason why MTX did not have any significant effect on drug survival in RA and PsA patients may be that it simply was not used when it was indicated. This is likely another accurate reflection of clinical practice, but it detracts from the validity of any statement made in this study regarding the efficacy of concomitant MTX therapy.

A further limitation with respect to interventions was the inability to control the use of other medications which may have interacted with the study interventions. For example, apart from prednisone and MTX, the use of concomitant medications such as NSAIDs and DMARDs was not controlled for in this study. This is problematic since these drugs are capable of improving disease severity and thus may have altered the survival of anti-TNF therapy for some patients. Furthermore, even though prednisone and MTX use was accounted for here, the starting doses for these drugs, which vary considerably, were not. This variability may have the potential to alter anti-TNF survival, introducing additional bias.

A final limitation associated with intervention administration would be patient access. Unfortunately, because anti-TNF therapy is very expensive ($15,000-25,000 annually) (Bonafede, et al., 2012), there are some patients with inflammatory arthritis who cannot afford it. While the NLPDP does provide coverage for most patients who require it, the process of obtaining anti-TNF therapy is still much easier and faster for those who are privately insured. Whereas a privately insured patient can usually obtain anti-TNF coverage as soon as their rheumatologist deems this therapy is necessary, a patient covered by the NLPDP may need to meet several other criteria before they receive their anti-TNF agent. For example, according to the NLPDP's "Criteria for the coverage of special authorization drugs", an RA patient seeking NLPDP coverage for adalimumab must have previously failed an adequate trial of at least 3 traditional DMARDs in sequence (or a combination of at least 2 DMARDs) and have failed an adequate trial of leflunomide before coverage will be provided (Government of Newfoundland and Labrador, 2013). NLPDP requirements for the other inflammatory arthritides and anti-TNF agents are similarly stringent. The impact of this problem on the present study is that there is likely a hidden subset of patients in the population whose anti-TNF survival is significantly affected by the timeliness of their treatment; certain patients may be starting their anti-TNF therapy when it is in fact too late for these drugs to have much therapeutic effect, a finding which has been documented previously (Tillett, et al., 2013).

The outcomes of this study and how they were reported represent another source of limitation here. Despite its accepted reliability as an indicator of therapeutic efficacy in several observational studies, drug survival is ultimately a *surrogate* marker for efficacy and should thus be interpreted with some caution. As discussed earlier, drug discontinuation occurs for reasons other than inefficacy. This includes adverse events, which were measured in this study, but also includes several others which were not, such as financial difficulties, pregnancy, and patient choice. Additionally, in some cases there was no reason for drug discontinuation reported in a patient's file. Thus it cannot be concluded that anti-TNF

survival is longer in one cohort than in another solely because of anti-TNF efficacy. Drug survival, therefore, would be better defined as a non-specific marker which captures a variety of reasons for drug discontinuation; its utility here is in identifying when a conscious decision was made to end a therapy, which happens for many reasons other than lack of efficacy in the real world. However, if one were interested in assessing drug efficacy specifically, a superior outcome measure would have been an ACR score for RA and PsA or an ASAS score for AS. These scores more accurately assess disease severity and would thus more reliably determine the efficacy of an intervention such as anti-TNF therapy. Unfortunately, a prospective RCT would normally be necessary to avail of these outcome measures as physicians do not routinely calculate ACR/ASAS scores to monitor patients' progress on anti-TNF therapy. Furthermore, unlike drug survivals for different diseases, ACR scores and ASAS scores are not directly comparable with one another. Thus, the comparisons made in this study would not have been possible using these latter outcome measures.

A final source of limitation here would be the use of a paired samples t-test to compare first vs. second course drug survival. As was explained in the Results section, comparing survival *means* instead of survival *distributions* subjects the analysis to bias arising from temporal differences in drug availability. For example, infliximab has been available as a treatment for inflammatory arthritis longer than adalimumab, allowing for inflation of the mean survival for patients who took infliximab. Because they instead compare survival *distributions*, Kaplan-Meier analysis and Cox regression are not susceptible to this temporal bias and are ideal for analyzing survival data. However, these analyses were not usable in the unique case of a paired first vs. second course survival analysis due to the total absence of survivors in the first-course cohort. Therefore, although it was not ideal due to its temporal bias, we felt a paired samples t-test was the optimal method of performing a first vs. second course survival analysis in the present study.

Chapter 5 Conclusions

5.1 Significant outcomes

Although several drug survival outcomes were investigated in this study, there were relatively few significant findings. One was that patients with AS survive longer on first-course anti-TNF therapy than do patients with either PsA or RA (when no adjustments are made for covariates). Another was that, among patients with RA, adjusted drug survival is longer for patients taking adalimumab than for those taking etanercept. Also, among patients with AS it was found that males are significantly less likely than females to discontinue anti-TNF therapy. Finally, among patients taking a second course of anti-TNF therapy, PsA patients survive longer on their anti-TNF than do RA patients, both crudely and when adjusted for relevant covariates.

5.2 Clinical significance of results

Because this study generated few statistically significant findings and the outcome measure utilized is only a surrogate measure of efficacy, it may be inappropriate to translate any of the findings here directly to clinical practice. Interestingly, some of the findings here do help to validate trends observed in existing studies. For instance, the superiority of anti-TNF drug survival in AS vs. PsA and RA patients has been observed previously; the same is true of superior drug survival in male vs. female AS patients. However, the generation of immediately usable, clinically practical data was never the intended purpose of this study. Rather, the idea was to address some of the obvious gaps in the medical literature, namely the section containing observational studies of anti-TNF therapy for inflammatory arthritis. Past studies have mostly investigated the effect of generalized anti-TNF therapy on one form of inflammatory arthritis, or one form of anti-TNF therapy on generalized inflammatory arthritis; no study could be found that compares the three major anti-TNF agents in each of AS, PsA, and RA. Therefore, it

is the comprehensive nature of this study which makes it novel in the literature. The optimum use of its findings would be in generating hypotheses for future studies. For instance, would a real-life, longitudinal study using a more direct measure of efficacy such as disease scores produce findings similar to those seen in this study? It might also be useful to simply repeat the present real-life drug survival study except with appropriately powered sample sizes.

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Appendices

Appendix A: Data collection form (St. John's center patients only) for TNF-α antagonist survival analysis

Demographics:

Study ID:	Subject Initials:	DoB (yyyy):	Sex: M / F
Rheumatic Diagnosis: ☐ RA ☐ AS ☐ PsA ☐ Other _____			
Date of Onset (yyyy):		Date of Diagnosis (yyyy):	
Smoker ☐ No ☐ Yes # of Yrs _____ # of Cigarettes _____			
Height: _____ ☐ Cm ☐ In		Weight: _____ ☐ Kg ☐ Lb	

Previous Medications:

NSAIDs:	N / Y Type/Dose: _____
Prednisone:	N / Y Dose: _____
MTX:	N / Y Dose: _____
Plaquenil:	N / Y Dose: _____
Arava:	N / Y Dose: _____
Other DMARDs:	N / Y Type/Dose: _____

1st anti-TNF:

Anti-TNF ☐ Etanercept ☐ Adalimumab ☐ Infliximab ☐ Golimumab ☐ Abatacept ☐ Rituximab		
Start (dd/mm/yyyy):	Stop (dd/mm/yyyy):	
Reason for stop: ☐ Efficacy ☐ Adverse event(s) ☐ Other _____		
Medications:	At Start of 1st anti-TNF	At most recent visit on 1st anti-TNF
NSAIDs:	N / Y Type/Dose: _____	N / Y Type/Dose: _____
Prednisone:	N / Y Dose: _____	N / Y Dose: _____
MTX:	N / Y Dose: _____	N / Y Dose: _____
Plaquenil:	N / Y Dose: _____	N / Y Dose: _____
Arava:	N / Y Dose: _____	N / Y Dose: _____
Other DMARDs:	N / Y Type/Dose: _____	N / Y Type/Dose: _____

2nd anti-TNF:

Anti-TNF □ Etanercept □ Adalimumab □ Infliximab □ Golimumab □ Abatacept □ Rituximab		
Start (dd/mm/yyyy):	Stop (dd/mm/yyyy):	
Reason for stop: □ Efficacy □ Adverse event(s) □ Other _____		
Medications:	At Start of 2nd anti-TNF	At most recent visit on 2nd anti-TNF
NSAIDs:	N / Y Type/Dose: _____	N / Y Type/Dose: _____
Prednisone:	N / Y Dose: _____	N / Y Dose: _____
MTX:	N / Y Dose: _____	N / Y Dose: _____
Plaquenil:	N / Y Dose: _____	N / Y Dose: _____
Arava:	N / Y Dose: _____	N / Y Dose: _____
Other DMARDs:	N / Y Type/Dose: _____	N / Y Type/Dose: _____

3rd anti-TNF:

Anti-TNF □ Etanercept □ Adalimumab □ Infliximab □ Golimumab □ Abatacept □ Rituximab		
Start (dd/mm/yyyy):	Stop (dd/mm/yyyy):	
Reason for stop: □ Efficacy □ Adverse event(s) □ Other _____		
Medications:	At Start of 3rd anti-TNF	At most recent visit on 3rd anti-TNF
NSAIDs:	N / Y Type/Dose: _____	N / Y Type/Dose: _____
Prednisone:	N / Y Dose: _____	N / Y Dose: _____
MTX:	N / Y Dose: _____	N / Y Dose: _____
Plaquenil:	N / Y Dose: _____	N / Y Dose: _____
Arava:	N / Y Dose: _____	N / Y Dose: _____
Other DMARDs:	N / Y Type/Dose: _____	N / Y Type/Dose: _____

Disease Status
AS:

1st anti-TNF	BASDAI at start: _____	BASDAI at 6 mo: _____
2nd anti-TNF	BASDAI at start: _____	BASDAI at 6 mo: _____
3rd anti-TNF	BASDAI at start: _____	BASDAI at 6 mo: _____

RA/PsA:

1st anti-TNF	ACR at 6 mo: □ ACR<20 □ ACR20 □ ACR50 □ ACR70
2nd anti-TNF	ACR at 6 mo: □ ACR<20 □ ACR20 □ ACR50 □ ACR70
3rd anti-TNF	ACR at 6 mo: □ ACR<20 □ ACR20 □ ACR50 □ ACR70