COMPARATIVE PERSISTENCE OF TUMOUR NECROSIS FACTOR ALPHA ANTAGONISTS IN PATIENTS WITH RHEUMATOID ARTHRITIS

by

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ABSTRACT

Introduction: This thesis comprises three studies examining treatment persistence with tumour necrosis factor alpha (TNFα) antagonists in rheumatoid arthritis (RA) patients. Persistence, also commonly known as duration of treatment, has been suggested as an indirect measure that balances benefit and harm, and it is important for cost-effectiveness analysis and budget planning. Previous research has examined the effect of drug and patient characteristics on persistence with TNFα antagonists.

Objectives: 1) To estimate pairwise comparative persistence with TNFα antagonists infliximab, adalimumab and etanercept in RA patients; 2) To evaluate the impact of investigator factors (methods) and of prescriber factors (propensity for discontinuation and preference for prescribed drug) on comparative persistence estimates with TNFα antagonists in RA patients .

Methods: To address these objectives, three population-based studies of an RA cohort were conducted in British Columbia patients using survival analysis methodology. **Results**: 1) In RA patients similar persistence was observed with infliximab, adalimumab and etanercept, with median persistence equaling approximately 3.5 years; 2) The length of 'drug-free interval' used to ascertain drug discontinuation influences the observed magnitude and significance of comparative persistence estimates; 3) Physician factors (prescribing habits) are predictors and possible confounding factors in studies of persistence and comparative persistence.

Conclusions: This thesis provides evidence showing that researchers and physicians can influence estimated and actual comparative persistence on TNFα antagonists in RA patients. The role of researchers and physicians in affecting estimates of persistence may explain heterogeneity in these estimates across different studies. Improved methodology in conducting comparative persistence research is needed to establish a high quality body of evidence for the use of patients, clinicians, researchers and policy makers.

PREFACE

Sections of this thesis are multi-authored manuscripts intended for publication in peer-reviewed journals. Details of authors' contributions for Chapters 1 to 6 are as follows.

Chapter 1: Anat Fisher was responsible for design, literature search, collation and summary of papers, retrieval of articles, review of studies, and writing of Chapter 1. Colin Dormuth, James Wright and Ken Bassett provided critical review of Chapter 1.

Chapter 2: Anat Fisher was responsible for design, literature search, collation and summary of papers, retrieval of articles, review of studies, and writing of Chapter 2. Greg Carney contributed information to the section on the British Colimbia Ministry of Health Administrative Databases. Colin Dormuth provided critical review of Chapter 2.

Chapter 3: Anat Fisher was responsible for study concept and design, data management and statistical analyses, interpretation of results, writing Chapter 3, and revisions. Ken Bassett contributed to study concept, formation of research question, and critical review of Chapter 3. Colin Dormuth provided critical review of Chapter 3.

Chapter 4: Anat Fisher was responsible for study concept and design, data management and statistical analyses, interpretation of results, writing Chapter 4, and revisions. Colin Dormuth, James Wright, and Ken Bassett provided critical review of Chapter 4.

Chapter 5: Anat Fisher was responsible for study concept and design, data management and statistical analyses, interpretation of results, writing Chapter 5, and revisions. Colin Dormuth, James Wright, and Ken Bassett provided critical review of Chapter 5.

Chapter 6: Anat Fisher was responsible for integration of research results and formation of conclusions from aforementioned results. Colin Dormuth, James Wright, and Ken Bassett provided critical review of Chapter 6.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

$: Canadian dollars

µG: microgram(s)

ACR: American College of Rheumatology

ACR20: American College of Rheumatology 20% improvement

ACR50: American College of Rheumatology 50% improvement

ACR70: American College of Rheumatology 70% improvement

ANOVA: analysis of variance

ATTRACT (page 248): Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy

AUC (Table 20, page 239): area under the curve

$AUC_{0\text{-}72\,H}$ (Table 20, page 239): area under the curve between 0-72 hours after administration

BC: British Columbia

BIW (Table 20, page 239): twice a week

CCI (page 33): Correct Coding Initiative

CCP (page 33): Canadian Classification of Diagnostic, Therapeutic and Surgical

CI: confidence interval

CIHI (page 33): Canadian Institute of Health Information

C_{MAX} (Table 20, page 239): peak concentration

CORRONA: Consortium of Rheumatology Researchers of North America

COX-2 (page 151): cyclooxygenase-2

CRP: C-reactive protein

DAD: Discharge Abstract Databases

DAS: Disease Activity Score

DAS28: Disease Activity Score in 28 joints

DMARD: disease modifying antirheumatic drug

DNA: deoxyribonucleic acid

EOW (Table 20, page 239): every other week

ESR (page 242): erythrocyte sedimentation rate

EULAR: European League Against Rheumatism

F_{AB} (page 230): Fragment, antigen binding

F_C (page 229): Fragment, crystallizable

GM-CSF (page 226): Granulocyte-macrophage colony-stimulating factor

H: hour(s)

HACA (Table 19, page 237): human antichimeric antibodies

HAQ: Health Assessment Questionnaire

HAQ-DI (Table 22, page 253): Health Assessment Questionnaire Disability Index

HLA (page 226): human leukocyte antigen

ICBC (page 32): Insurance Corporation of British Columbia

ICD: International Statistical Classification of Diseases and Related Health Problems

ICD-10: International Statistical Classification of Diseases and Related Health Problems, version 10

ICD-10-CA (p. 271): International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canadian version

ICD-9: International Statistical Classification of Diseases and Related Health Problems, version 9

I_GG1 (page 229): immunoglobulin G type 1

IQR (page 17): interquartile ranges

ITT (page 118): intention to treat

KD (Table 19, page 237): antigen dissociation constant

KG: kilogram(s)

L: liter(s)

L_OE (Table 23, page 256): loss of efficacy

MD (Table 21, page 243) - means change scores from baseline of mTSS between active and control groups

MG: milligram(s)

ML: milliliter(s)

MSP: Medical Service Plan

MTSS (Table 21, page 243): modifications of Total Sharp scores

MTX: methotrexate

N: number of participants

N/A: not available

N/R: not reported

NF-KB (page 225): nuclear factor kappa B

NG: nanograms(s)

NR (Table 23, page 256): no response

NSAID: nonsteroidal anti-inflammatory drug

NSS: not statistically significant

P55 (page 225) : tumour necrosis factor alpha receptor type 1

P75 (page 225): tumour necrosis factor alpha receptor type 2

PPD: prescriber preference for the prescribed drug

PPV (page 35): positive predictive value

RA: rheumatoid arthritis

RABBIT (page 248): Rheumatoid Arthritis – Observation of Biologic Therapy (in German)

RCT: randomized clinical trial

RNA (page 220): ribonucleic acid

SAE (Table 21, page 243): serious adverse events

SAS: Statistical Analysis System

SD: standard deviation

SDAI (Table 22, page 253): Simple Disease Activity Index

TACE: tumour necrosis factor alpha converting enzyme

T_{MAX}: time to peak concentration

TNFα: tumour necrosis factor alpha

TNF-R1: tumour necrosis factor alpha receptor type 1

TNF-R2: tumour necrosis factor alpha receptor type 2

TRAF (page 225): tumour necrosis factor alpha receptor associated factor

U.S.: United States (of America)

VAS: visual analogue scale

VS.: versus

WDAE: withdrawals due to adverse events

WHO: World Health Organization

GLOSSARY

ACCURACY (of measurement): "The degree to which a measurement or an estimate based on measurements represents the true value of the attribute that is being measured" [1].

ADDITIVE RISK MODEL: A model in which the combined effects on the risks or rates of several factors is the sum of the effects that would be produced by each of these factors in the absence of others [1].

ADHERENCE: " Health-related behavior that adheres to the recommendations of a doctor, other health care provider, or investigator in a research project. The word adherence aims to avoid the authoritarian associations of compliance, formerly used to describe this behavior" [1]. In the context of this thesis, adherence describes the overall behavior, in terms of both compliance and persistence.

ALGORITHM: "A systematic process that consists of an ordered sequence of steps with each step depending on the outcome of the previous one" [1]. When the process is executed, it would lead for a definite number of output results. An example of algorithm used to identify disease cohort in this dissertation is presented in Figure 23, page 270. When this algorithm is executed on data of individual patient, the output is either 'patient is included in the cohort' or 'patient is not included in the cohort'.

ANKYLOSING SPONDYLITIS: "A chronic inflammatory disease of unknown origin, first affecting the spine and adjacent structures and commonly progressing to eventual fusion (ankylosis) of the involved joints … The disease primarily affects males under 30 years of age" [2].

ANTAGONIST: "Any agent, especially a drug or hormone, that reduces the action of another agent, the agonist" [3]. Antagonists work though several possible mechanisms: (a) combination with the substance being antagonized, (b) production of an opposite effect through a different receptor, (c) competition for the binding site of an intermediate that links receptor activation to the effect observed or (d) interference with other events that follow receptor activation [3].

BERNOULLI VARIABLE: "A variable having only two possible values (e.g. on or off, 0 or 1)" [1].

BIAS: "Systematic deviation of results of inferences from truth, or processes leading to such deviation" [1].

BIOLOGIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (BIOLOGICS): New antirheumatic drugs that target the dysfunctional immune system by using the body's own chemical mediators (manufactured by recombinant DNA technology) to reduce the immune mediated inflammatory response [4].

CENSORING (RIGHT): See RIGHT CENSORING.

CLINICAL SIGNIFICANCE: "Importance, relevance or meaning for the care of individuals, who may be – in clinical research – patients. A difference in the size effect that is considered to be important (e.g. , by a professional) in medical decisions, regardless of the degree of statistical significance" [1].

CLUSTERING (in analysis): A method of analysis of data, in which the observations are divided into groups using several possible scemes (e.g. hirarchial). The observation in each cluster (group) are more similar to each other than observations in different clusters.

COMBINATION THERAPY: "The simultaneous administration of more than one drug to treat a single disease" [5].

COMPARATIVE EFFECTIVENESS: "A type of health care research that compares the results of one approach for managing a disease to the results of other approaches. Comparative effectiveness usually compares two or more types of treatment, such as different drugs, for the same disease" [6].

COMPARATIVE PERSISTENCE: A relative measure used to compare the persistence (duration of treatment) between two groups of patients, usually treated with two different drugs from the same therapeutic group.

COMPLIANCE: "The extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen" [7]. Compliance reflects the intensity of executing the prescribing recommendations [1].

CONFOUNDER: A factor that may explain or produce all or part of the association observed between the exposure and the outcome. The three conditions for a factor to become a confounder are: (a) it is a risk factor for the outcome (among the unexposed); (b) it is associated with the exposure of interest among the population from which the cases are derived and (c) it is not an intermediate step in the causal pathway between the exposure and the outcone [8].

CONFOUNDING BY INDICATION: "A type of confounding bias that occurs when a symptom or sign of a disease is judged as an indication (or contraindication) for a given therapy and therefore is associated with both the intake of a drug or a medical procedure (or its avoidance) and with a higher probability of the outcome… Cofounding by indication stems from an initial lack of similarity in the prognostic expectations of treated and untreated subjects" [1].

CONFOUNDING BY SEVERITY: A type of confounding by indication bias that occurs when patients with the worst prognosis are assigned the most effective drug [8-12], and as a result, effectiveness is biased toward the null (no effect).

CONFOUNDING: "The distortion of a measure of the effect of an exposure on an outcome due to the association of the exposure with other factors [confounders] that influence the occurrence of the outcome" [1].

CONTAMINATION, TREATMENT: see TREATMENT CONTAMINATION

CROHN'S DISEASE: "A chronic inflammatory bowel disease of unknown origin, usually affecting the ileum, the colon, or another part of the gastrointestinal tract. Diseased segments may be separated by normal bowel segments, which give it the characteristic skip lesions" [2].

CYTOKINE: "Any of numerous small proteins released from a variety of cell types that affect cell behaviour. Cytokines can influence the cells releasing them or nearby cells; in some cases they can enter the bloodstream to influence distant cells. Cytokines are crucial to many aspects of cell proliferation, differentiation, migration, and function, and play a central role in immune responses and inflammation" [13].

DAYS-SUPPLY: "The number of days a prescription is intended to last. It is calculated by dividing the number of doses in the prescription by the number of doses per day" [14]. For the propose of this thesis 'days-supply' is defined as the number of days between the current dispensing and the expected next dispensing.

DIRECT MEDICAL COSTS (p. 217): "The cost of a defined intervention and all follow-up costs for other drug and health care interventions in ambulatory, inpatient, and nursing care" [15].

DRUG PERSISTENCE: Duration of treatment with a specific drug. Patients who discontinued this drug or switched to another drug within the same therapeutic group are no longer persistent [16]. See also TREATMENT PERSISTENCE.

DRUG: In this thesis the term drug refers to therapeutic drug which is any chemical substance used for medical treatment, cure or prevention of disease. Synonyms include medication and therapeutic regimen.

DRUG-FREE INTERVAL: In analysis of administrative data, a drug-free interval is a gap in the treatment continuum during which the patient is supposedly not exposed to the drug. It is usually defined from the time the dispensed days-supply was exhausted until a new dispensing occurs. Also called grace period or permissible gap [17,18].

EFFECTIVENESS: "A measure of the extent to which a specific intervention, procedure, regimen or service, when deploy in the field of the usual circumstances, does what it is intent to do for a specific population" [1].

EFFICACY: " The extent to which a specific intervention, procedure, regimen or service, produces a beneficial result under ideal conditions... Ideally, the determination of efficacy is based on the results of randomized controlled trial" [1].

FAIR PHARMACARE: A British Columbia drug reimbursement program, which started on May 2003. It covers the cost of most drugs for residents who are eligible based on net taxable family income criteria. See also PHARMACARE.

HAZARD: "A theoretical measure of the probability of occurrence of an event per unit time at risk; e.g., death or new disease, at a point in time, t, defined mathematically as the limit, as Δt approaches zero, of the probability that an individual well at time t will experience the event by $t + \Delta t$, divided by Δt" [1].

HETEROGENEITY: "(1) Used in a general sense to describe the variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies, or the variation in internal validity of those studies. (2) Used specifically, as statistical heterogeneity, to describe the degree of variation in the effect estimates from a set of studies. Also used to indicate the presence of variability among studies beyond the amount expected due solely to the play of chance" [19].

IMMUNOMODULATOR: "Any agent that alters the extent of the immune response to an antigen, by altering the antigenicity of the antigen (i.e. the capacity of an agent to stimulate the formation of specific antibodies to itself) or by altering in a nonspecific manner the specific reactivity or the nonspecific effector mechanisms of the host" [3].

IMMUNOSUPPRESSANTS, IMMUNOSUPPRESSANT DRUGS: "Drugs that suppress the activity of the immune system". These drugs are used in treatment of autoimmune diseases such, as rheumatoid arthritis [20].

INDEX DATE: A date that serves to guide, point out, or otherwise facilitate reference. In the context of the current research, the index date is defined as the date of the first dispensing of the of any TNFα antagonist drug.

INDIRECT MEDICAL COSTS (page 217): "All costs to the national economy of the society due to productivity loss. Indirect costs can be due to decreased efficiency, total absence from work through an illness, or premature death" [15].

INTERDOSE INTERVAL: The period (recommended or actual) between two administrations of the same drug.

INTERMITTENT DOSING SCHEDULE: The drug is administered less frequently than once a day [21].

I-SQUARE QUANTITY: "A measure used to quantify heterogeneity. It describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). A value greater than 50% may be considered to represent substantial heterogeneity" [19].

JUVENILE RHEUMATOID ARTHRITIS (JUVENILE IDIOPATHIC ARTHRITIS): "A disease affecting the larger joints of children less than 16 years of age and often accompanied by systemic manifestations. As bone growth in children is dependent on the epiphyseal plates of the distal epiphyses, skeletal development may be impaired if these structures are damaged" [2].

META-REGRESSION: "An extension of meta-analysis in which the relationship between the treatment effect and known confounders is modeled using weighted regression. In this way insight can be gained into how the outcome is related to the design and population studied" [22].

MISCLASSIFICATION: A type of error in obtaining the needed information; errors in the measurement of subjects. "For discrete variables (variables with only a countable number of possible values, such as indicators for sex), measurement error is usually called classification error or misclassification. Classification error that depends on the values of other variables is referred to as DIFFERENTIAL MISCLASSIFICATION. Classification error that does not depend on the values of other variables is referred to as NONDIFFERENTIAL MISCLASSIFICATION" (page 138 [23]).

MONOCLONAL ANTIBODY: "An antibody produced by genetic engineering techniques from a cell clone (i.e. numerous identical cells originally derived from a single parent cell) and therefore consisting of a single type of immunoglobulin" [20].

MONOTHERAPY: Treatment of a disease by a single drug.

NONSTEROIDAL ANTI-INFLAMMATORY DRUG (NSAIDs): "Any one of a large group of drugs used for pain relief, particularly in rheumatic disease associated with inflammation. NSAIDs act by inhibiting the enzymes controlling the formation of prostaglandins, which are important mediators of inflammation" [24].

OSTEOARTHRITIS (page 225): "A degenerative disease of joints resulting from wear of the articular cartilage, which may lead to secondary changes in the underlying bone. The joints are painful and stiff, with restricted movement. The condition may be primary or may result from abnormal load to the joint or damage to the cartilage from inflammation or trauma" [24].

PERMISSIBLE GAP: See DRUG-FREE INTERVAL.

PERSISTENCE: See TREATMENT PERSISTENCE, DRUG PERSISTENCE.

PHARMACARE (BRITISH COLUMBIA): The provincial Ministry of Health drug benefit program that pays for all or part of the cost of eligible prescription drugs and designated medical supplies through seven drug plans - the largest is the Fair PharmaCare plan, which is income-based [25]. See also FAIR PHARMACARE.

PHARMANET (BRITISH COLUMBIA): A province-wide database that links all pharmacies to a central set of data systems. Every prescription dispensed in the province is entered into the database. PharmaNet is administered by the Ministry of Health and the College of Pharmacists of British Columbia with the goals of supporting prescription claim processing and improve prescription safety [26].

PRIMARY INEFFICACY (p. 255): Lack of response, the drug never produced the desired effect. See also SECONDARY INEFFICACY.

PSORIASIS: "A common chronic skin disorder characterized by circumscribed red patches covered by thick, dry silvery adherent scales that are the result of excessive development of epithelial cells. Exacerbations and remissions are typical" [2].

PSORIATIC ARTHRITIS: "A form of arthritis associated with psoriatic lesions of the skin and nails, particularly at the distal interphalangeal joints of the fingers and toes" [2].

REGISTRY: "The file of data concerning all cases of a particular disease or other health-relevant condition in a defined population such that the cases can be related to a population base" If cases are regularly followed up, information on remissions, exacerbations, incidence, prevalence and survival can be obtained [1].

RELIABILITY: "The degree of stability exhibited when a measurement is repeated under identical conditions. Reliability refers to the degree to which the results obtained by a measurement procedure can be replicated. Lack of reliability may arise from divergences between observers or instruments of measurement or instability of the attribute being measured" [1].

REMISSION: "A lessening in the severity of symptoms or their temporary disappearance during the course of an illness" [24]. Remission may be spontaneous or the result of therapy.

RIGHT CENSORING: "Loss or attribution of subjects from a follow up study, the occurrence of the event of interest among such subjects after a specific time when it is known that the event of interest had not occur; it is not known, however if or when the event of interest occurred subsequently" [1] .

ROBUSTNESS: "A property of a statistical test or procedure that confers to it a certain degree of insensitiveness to departure from the assumptions from which it is derived" [1].

SECONDARY INEFFICACY (p. 255): Loss of efficacy in patients who previously responded to the treatment. See also PRIMARY INEFFICACY.

SELECTION, DRUG SELECTION: In this dissertation, drug selection is defined as either (a) the physician decision as to which of the available therapeutic classes to use, following the decision to initiate pharmacological treatment for the disease; or (b) the decision as to which of the available drugs to prescribe, following the decision to prescribe a specific therapeutic class.

SENSITIVITY ANALYSIS: "A method to determine the ROBUSTNESS of an assessment by examining the extent to which results are affected by changes in methods, models, value of unmeasured variables, or assumptions" [1].

SIGNIFICANCE, CLINICAL: See CLINICAL SIGNIFICANCE.

SIGNIFICANCE, STATISTICAL: See STATISTICAL SIGNIFICANCE.

SPECIAL AUTHORITY PROCEDURE (pAGE 269): The British Columbia PHARMACARE procedure to grant coverage for drugs from several categories (limited coverage drugs, alternatives to Reference Drugs, alternatives to Low Cost drugs, some psychiatric drug and drugs included in the Alzheimer's Drug Therapy Initiative). Requests for Special Authority coverage must be submitted by the health care practitioner through a special application process. Authorization has to be granted before the plan provides coverage for the drug. The actual coverage is based on PharmaCare rules, including any deductible requirement [27].

STATISTICAL SIGNIFICANCE: "A statistical property of an observation or an estimate that is unlikely to have occurred by chance alone" [1].

SWITCHING (treatment): In the context of this dissertation, switching is the dispensing of a different drug within the same therapeutic class that occurred any time during the study period or a specified time period after a dispensing of the drug of interest.

THERAPEUTIC CLASS: Therapeutic class is a term used to describe a collection of drugs that are used to treat the same disease and have similar pharmacological target. Multiple classification systems exists for drugs (e.g., the World Health Organization (WHO) system [28] and the American Society of Health-System Pharmacists' Pharmacologic-Therapeutic Classification [29]).

TREATMENT CONTAMINATION (in epidemiology) (p. 25): "The situation that exists when a population being studied for one condition or factor also possesses other conditions or factors that modify results of the study" [1].

TREATMENT PERSISTENCE: The duration of time in which the patient is treated with the drug(s). It is measured from initiation to discontinuation of the treatment [7]. Treatment persistence can be categorized as DRUG PERSISTENCE, regimen persistence (any change in dosing or adding on drugs is considered discontinuation) and therapy persistence (switching is not considered discontinuation) (Table 1, page 24) [30].

ULCERATIVE COLITIS: "A chronic, episodic, inflammatory disease of the large intestine and rectum. It is characterized by profuse watery diarrhea containing varying amounts of blood, mucus, and pus" [2].

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This thesis is dedicated to my late mother, Nurit, whose love and care has continued to motivate and inspire me. You taught me to never to quit and never to lose hope.

CHAPTER 1: INTRODUCTION

This thesis explores comparative persistence of different tumour necrosis factor alpha (TNFα) antagonist drugs in patients with rheumatoid arthritis (RA). The thesis focuses on methodological aspects of measuring persistence in these patients, as well as the influence of various characteristics of physicians who provide them with medical care.

RHEUMATOID ARTHRITIS is a common chronic inflammatory disease that causes an approximately 1.5 fold relative increase in premature mortality and decreased life expectancy by 3 to 10 years compared with the general population [31], progressive morbidity and disability [32-36] and excessive economic burden [37,38]. Additional information on the disease is presented in **Appendix A**, Section A.1, page 215.

The TNFα ANTAGONISTS - infliximab, adalimumab and etanercept - are a novel therapeutic class indicated in a variety of inflammatory diseases, including RA. The TNFα antagonists were the first immunomodulating drug agents targeting cytokines, which are themselves modulators of inflammation. The drugs block the physiological action of the cytokine TNFα, which performs an important role in the pathogenesis of inflammation and of RA. Although the three individual TNFα antagonists are considered to belong to a single therapeutic class, the class is diverse in pharmacological and pharmacokinetic characteristics [39-43]. These differences may affect therapeutic benefits and harms. Additional information on the drugs is presented in **Appendix A**, Section A.2, page 223.

Treatment with TNFα antagonists does not cure patients [44], but rather treatment reduces symptoms, possibly induces remission, and prevents complications over the long term. TNFα

antagonists are considered by most physicians to benefit RA patients; however, the relative effectiveness of the three drugs is still unclear, mainly due to lack of head-to-head randomized controlled trials (RCTs) and a limited number of long-term observational studies. Additional information on TNFα antagonist treatment is presented in **Appendix A**, Section A.3, page 241.

TREATMENT PERSISTENCE is defined as the duration of time that elapses between the date that pharmaceutical treatment is initiated to the date it is discontinued [7]. As former American Surgeon General C. Everett Koop is often quoted "Drugs don't work in patients who don't take them", which means that therapeutic benefit depends on administration of the drug. Conversely, drug dispensing, as a measure of willingness to take a drug can be a measure of overall long-term harm-benefit balance of drug therapy, particularly in patients with alternative available therapies and chronic noncurable diseases [45]. Theoretically, patients will continue to adhere to a drug regimen as long as they experience or perceive a benefit to persisting and do not experience an unacceptable amount of harm. Drug persistence is defined as the duration a patients is exposed to a specific drug, as compared to COMPLIANCE, which defines the intensity of executing the prescribing recommendations (e.g., the proportion of doses taken as prescribed over a period of time).

Pharmacoepidemiology consists of four areas of research: (a) efficacy, the performance of the drug in ideal setting; (b) safety; (c) effectiveness, the performance of a drug in routine clinical setting and (d) drug utilization, which is "an eclectic discipline, integrating descriptive and analytical methods for the quantification, the understanding and the evaluation of the processes of prescribing, dispensing and consumption of medicines and for the testing of interventions to enhance the quality of these processes" [46]. Figure 1 presents the porpuse of estimating

treatment persistence within the framework of pharamcoepidemiological research. Treatment persistence research provides evidence of three of the areas of research: first, it is acceptable measure of drug utilization. In addition, it could generate signals on safety concerns, if persistence is diminished due to high risk of harm (adverse events). Lastly, since it is a measure that balances benefit and harm caused by the treatment, it can provides evidence on the overall effectiveness/risk of the drug .

COMPARATIVE PERSISTENCE is a relative measure estimated by comparing the average (or median) duration of treatment between different drugs, usually from the same therapeutic class. As a relative measure, comparative persistence minimizes the effect of systematic errors such as misclassification of discontinuation. That is, while different studies use different methods to ascertain drug discontinuation, individual studies usually use the same method for all drugs being compared.

Figure 1: Treatment persistence within the framework of pharmacoepidemiological research
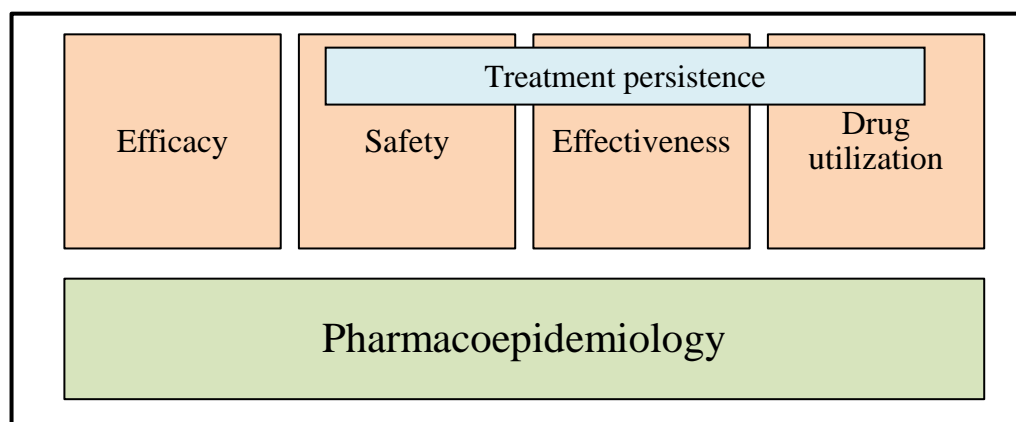
Comparative persistence is thought to mirror relative benefit-harm balance in chronic noncurable diseases, in that a drug with better persistence is considered more effective and/or safer. As such, comparative persistence estimates could be important to physicians and patients. Estimates of persistence and comparative persistence could also be important to policy makers and researchers. For policy makers persistence provides important information for cost-effectiveness estimates and for forecasting utilization. This could lead to restricted reimbursement policies, including sequence of treatment (e.g., a particular drug include as a benefit only as a second line). Comparative persistence is also important for conducting and interpreting effectiveness studies because differential persistence may bias the results.

1.1 Conceptual Framework and Previous Research

Theoretically, four classes of factors could influence persistence and/or persistence estimating, and therefore are regarded as predictors of persistence (Figure 2). The first class is drug properties that could be divided into two main subcategories: (a) properties that determine the drug's beneficial and harmful effects and (b) factors that influence persistence via treatment convenience and patient satisfaction. The drug pharmacological characteristics (structure, pharmacokinetics, mechanism of action, biological effects, immunogenicity, etc.) are a group of interlinking and relating properties that eventually determine the therapeutic effects and the benefit-harm balance of the drug treatment. A detailed description of these properties of the TNFα antagonists is presented in **Appendix A**, Section A.2.4, page 229. Other factor, such as

route of administration (**Appendix A**, Section A.3.6.1, page 262), cost and medications refill barriers could influence patient satisfaction and therefore could influence persistence.

The second group of factors that could influence persistence is patient characteristics. This group includes (a) demographics, (b) disease characteristics/clinical presentation (disease severity, comorbidities, and previous treatment) and (c) psychological factors. Drugs may have different effect in different patient population. For example, greater benefit is often observed in the more severely ill and increased risk of harmful effects may be expected in in patients with certain comorbidities. Furthermore, patients may perceive disease severity and drug effects (benefit and harm) differently, hence may response differently with regard to treatment persistence in the same clinical situation [47].

A third class of factors that have the potential to influence persistence is physician characteristics. In the same clinical situation, different physician may response differently – some of them would recommend discontinuing treatment while other would recommend continuing the treatment. These individual patterns may be associated with prescriber demographics, education, adherence to clinical guidelines and experience, but also with psychological factors such as physician preferences or susceptibility to marketing policy. Further discussion on the effect of physician characteristics is presented in **Chapter 5**, page 128.

Finally, investigator or study design factors may influence persistence estimates. Intuitively, persistence, defined as the period of time from treatment initiation until discontinuation, is influenced by methods used for ascertainment of treatment initiation and discontinuation. A detailed discussion on different study design factor is presented in **Chapter 2**, page 12.

Figure 2: Factors that influence treatment persistence (conceptual framework)
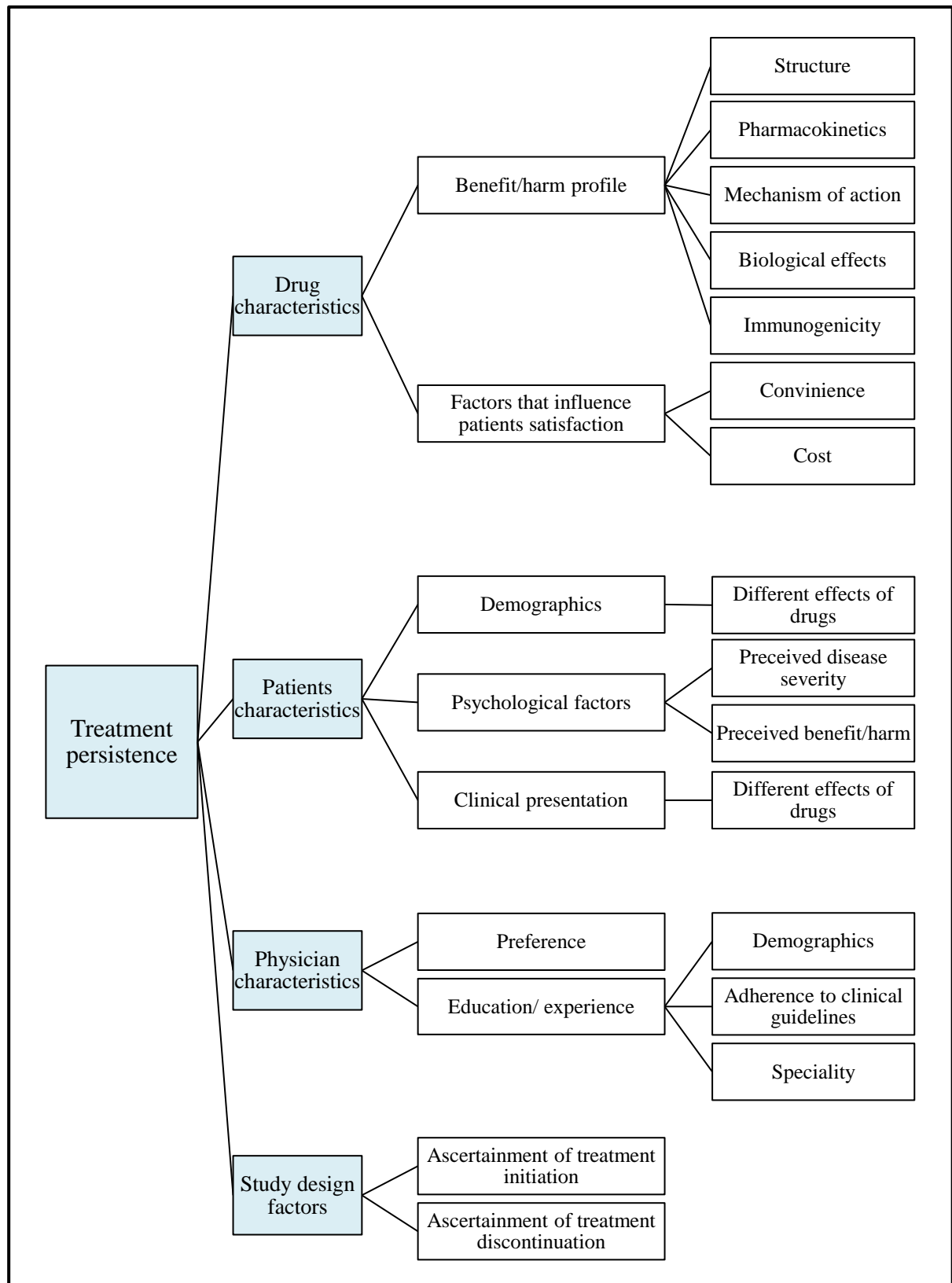
Similarily, comparative persistence, which could be regarded as the association between a drug (and its properties) and persistence could be influences by the remain third classes of factors: patient charateristics, physician characteristics and study design factors (Figure 3).

To date, drug persistence research has assumed that persistence is only determined by drug benefit-harm profile and patient characteristics. However, the consequences of different methods of measuring persistence, and the influence of different characteristics of the care-providing physicians, have not been studied except for one recently published study [48]. In that study, it was reported that significant clustering occurred around physicians of RA patients who discontinued TNFα antagonists due to lack of efficacy. This study is presented in detail in the Discussion Section of **Chapter 5** (Section 5.5.1.3, page 153).

Persistence and comparative persistence estimates for TNFα antagonists in RA vary in direction, significance and magnitude [49,50]. The reasons for these differences have not been previously studied. This thesis provides new knowledge of TNFα antagonist persistence and comparative persistence, as well as new and useful insights into the methodologies used to make these measurements and seek explanations for the observed differences in comparative persistence estimates.

Figure 3: Factors that influence comparative persistence (conceptual framework)
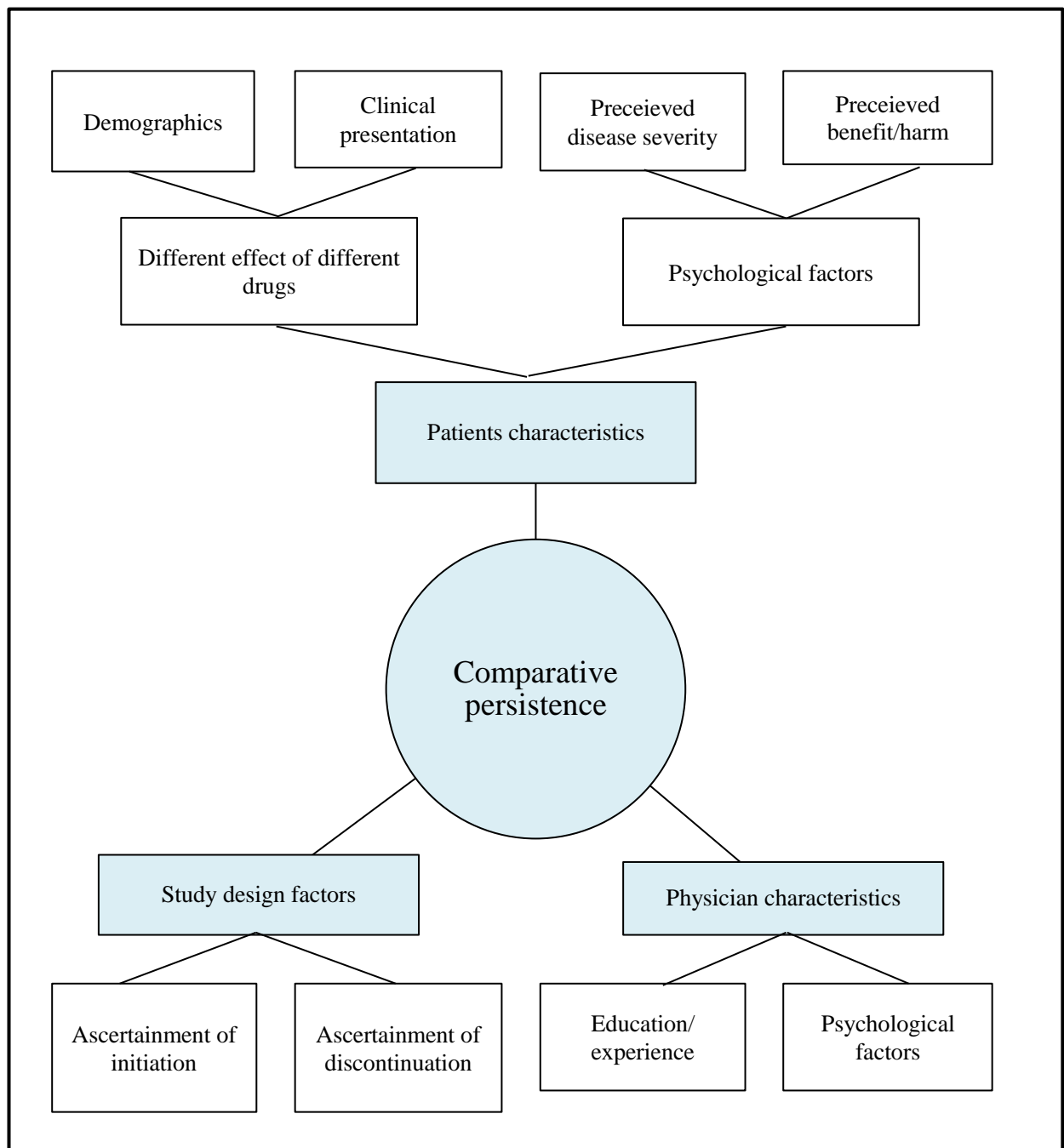
1.2 Thesis Goals

The main goal of this thesis is to compare persistence between three TNFα antagonists in RA patients: infliximab, adalimumab and etanercept. Additional goals are to 1) identify patient characteristics and physician prescribing habits that influence persistence, 2) identify confounding factors that bias estimates of comparative persistence, and 3) assess the impact of study design methodology on estimates of comparative persistence, specifically methodologies used to ascertain treatment discontinuation.

In **Chapter 3,** we identify patient characteristics and additional factors that predict persistence and confound comparative persistence estimates. The influence of study design methodology was studied primarily in **Chapter 4,** in which we present the consequence of increasing the length of drug-free interval used in discontinuation ascertainment on estimates of comparative persistence. In **Chapter 5** we study the effect of physician prescribing on persistence and comparative persistence.

Identifying predictors of persistence will help improve and standardize methodologies used in future research. It will also provide insights into pharmacoepidemiologic research using administrative health care data.

1.3 Overview of Thesis Chapters

The thesis consists of six chapters organized in a manuscript-based format. Versions of Chapters 3, 4, 5 are written for publication as separate manuscripts.

Chapter 2 summarizes essential background on the methodologies used in estimating comparative persistence. It consists of two parts. The first part introduces general challenges in measuring persistence and comparative persistence with drugs. It also summarizes the various methodological approaches used in previous studies. The second part of the chapter presents the rationale behind the methods used in this thesis to study comparative persistence with TNFα antagonist in RA patients using administrative health care databases.

Chapter 3 is a population-based study that estimates comparative persistence with TNFα antagonists RA patients in British Columbia. The effects of various patient and physician characteristics are explored.

Chapter 4 is a population-based study builds upon the work in **Chapter 3**, by critically examining the effect on comparative persistence estimates of using different algorithms to ascertain drug discontinuation. Specifically, it examines the effect of the length of the drug-free interval used in an algorithm, which is an exogenous factor chosen by the investigator, on the direction, significance and magnitude of hazard ratios for drug discontinuation. The study also describes patterns of reinitiating the same drug after a temporary interruption (30-180 days) in persistence.

Chapter 5 explores the extent to which persistence reflects prescriber rather than patient-characteristics. Specifically, **Chapter 5** estimates the effect of prescriber preference for a

prescribed drug, where the preference is estimated based on previous TNFα antagonist prescribing habits. The study also describes patterns of switching to a second drug. Supplementally, it explores possible confounder effects of prescriber preference for the prescribed drug on estimates of comparative persistence.

Chapter 6 is a concluding chapter that summarizes and organizes the main findings and relevance of the thesis. It also recommends specific topics for future research.

CHAPTER 2: METHODOLOGICAL ISSUES IN ESTIMATING PERSISTENCE

This chapter summarizes essential background on the methods used to estimate comparative persistence in general and in this thesis specifically. The first part provides general methodological considerations in estimating persistence and comparative persistence. We summarize and discuss the use of comparative persistence methods in the context of research conducted by other researchers, and in relation to the actual outcomes measured. The second part presents the methodological framework used in this thesis to study comparative persistence with TNFα antagonists in RA patients. Data from the British Columbia administrative health care databases are used. We introduce some of the major challenges in the analysis, discuss possible solutions, and present a selected methodological approach along with a rationale for our approach.

2.1 General Methodological Background

The general methodological background consists of a literature review that provides an overview of terminology and analytic issues. First, we present the terminology used (in the literature and in this thesis) to describe the degree to which patients follow prescribed dosing recommendations. Next, we introduce some of the major challenges in measuring treatment persistence, specifically ascertainment of treatment initiation, discontinuation and the date of discontinuation. We present these challenges in light of the data source used: (a) clinical data

from clinical registries or medical charts and (b) administrative health care databases that include data on prescription drug dispensing claims. Lastly, we summarize the essential background on the methods used to estimate comparative persistence.

2.1.1 Terminology

The degree to which patients follow prescribed dosing recommendations is an important determining factor of therapeutic outcomes. Not taking drugs as prescribed could lead to poor outcomes because the drug is not available in the optimal quantity to affect the patient's disease process [51-53]. Conversely, lack of therapeutic effect or the occurrence of side effects may interfere with adherence with dosing recommendations. Measures of the degree to which patients follow prescribed dosing recommendations reflect an association with final health outcomes rather than a straightforward causal relationship. The current medical literature is characterized by a lack of clarity on the use of the terms persistence, compliance and adherence, where often these words are used interchangeably [7].

PERSISTENCE reflects "the act of conforming to a recommendation of continuing treatment for the prescribed length of time" [7]. Persistence means that a patient continues to take a drug (or in an analysis of administrative data - refill the prescription) while DISCONTINUATION or nonpersistence means that the patient stopped the drug (or stopped refilling) at some point. Persistence can be documented as a continuous or a Bernoulli variable. Most commonly it is reported as a continuous variable and referred to as the duration of time from initiation to discontinuation of therapy. Basically persistence reflects the number of days, months or years

for which therapy was actually administered (Figure 4) [7] although some exceptions are applied. One exception occurs with the use of administrative data, since only dispensing claims are available to approximate actual drug administration. In an analysis of administrative data, therefore, persistence usually reflects the number of days the drug was available. In drugs with an intermittent dosing schedule (i.e., less than once daily) persistence is usually defined to reflect the number of days the patient was experiencing the therapeutic effect (e.g., until the first missed dose). Alternatively, persistence can be reported as a Bernoulli variable (i.e., whether or not a patient is persistent) at the end of prespecified period after the initiation of treatment [54]. For example, a patient is considered persistent at one year if the drug has not been discontinued by that time. Synonyms for treatment persistence used in

Figure 4: Persistence, adherence and compliance
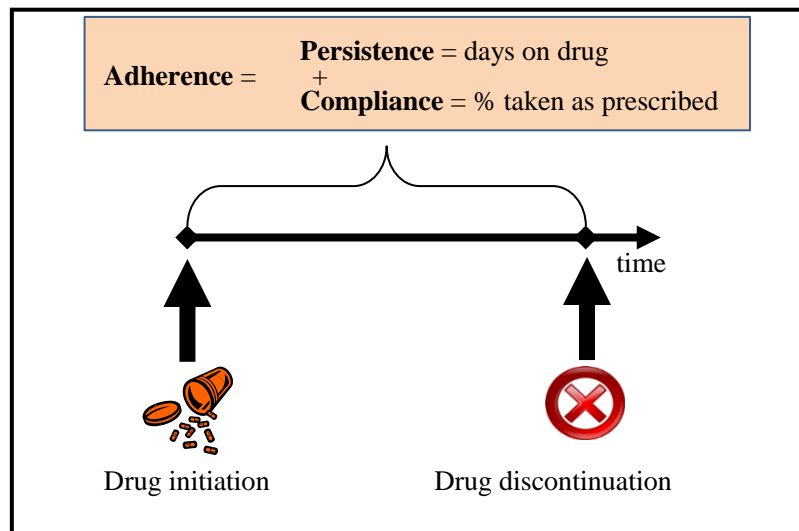
the scientific literature include 'duration of treatment', 'drug survival' (as imprinted by Wolfe [45]), 'treatment continuum', 'treatment continuation' (all for continuous presentation) and 'drug retention rate'[1] (for binomial presentation).

COMPLIANCE is defined as the extent to which a patient acts in accordance with a prescribed interval and dose [7]. It captures the intensity of the treatment compared to the recommended dosing while persisting. Noncompliance means that the patient is late to take a dose as scheduled or recommended and misses as least one day of therapy. Usually compliance is measured over a period of time and reported as a percentage of doses taken according to prescription (Figure 4).

Finally, in the literature the term ADHERENCE is often used interchangeably with the term compliance to describe the extent to which a patient acts in accordance with the prescribed interval and dose. However, the World Health Organization (WHO) emphasized that adherence also requires the patient's agreement to the recommendations [55]. In this thesis, ADHERENCE is used as a comprehensive term that includes three types of errors in dosing: nonacceptance, poor execution (compliance) and early discontinuation (persistence) (pp. 368-9 [56]). Our use of adherence encompasses both intensity (following the recommended interval and dose, compliance) and duration of time (persistence).

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[1] Drug retention time, on the other hand, is used to describe a pharmacokinetics property of drugs, which is closely related to bioavailability and is affected by the half-life of the drug. This term may be confusing, hence will not be used in this thesis.

2.1.2 Measuring Drug Persistence

Two types of studies characterize the literature on treatment persistence. The first type consists of original persistence studies conducted using various methodologies. The methods used varied according to the form of the persistence variable that was used (continuous or Bernoulli) and on the type of data source that was analyzed (clinical or administrative). The second type of academic publication does not report original persistence research but rather reviews methods used in persistence studies or suggests methodological guidelines on how to best conduct these studies [57-59]. In this section (Section 0) we discuss the methods most commonly used to estimate persistence as a continuous (Section 2.1.2.1) or a Bernoulli (Section 2.1.2.2) variable. We complete the discussion by presenting methodological and contextual issues in ascertaining the treatment initiation and discontinuation parameters that are required to estimate persistence.

2.1.2.1 Persistence as a Continuous Variable

Treatment persistence is commonly regarded as a continuous outcome variable that can be estimated using time-to-event data. Persistence is measured from the date on which the patient was first exposed to the drug (often defined as the index date, Section 2.1.2.3, page 19) until the date on which treatment is discontinued (Section 0, page 24). Patients are followed from the index date until they discontinue the drug or until the end of a prespecified follow-up period. Some patients are still on the treatment at the end of the prespecified follow-up period; hence, their data are considered to be (right) censored. Survival analysis methodology is used

to account for right censoring. This method allows maximum use of available data by accounting for patients who were censored and utilizing their known duration of treatment.

The main method used in studies of TNFα antagonists is Kaplan Meier product limit approach that allows direct estimation of persistence in one or more patient groups. Persistence is reported as a median value[2] with either a confidence interval or an interquartile range (IQR) provided to confer the degree of sampling variability. Kaplan Meier is considered to be a nonparametric approach, i.e., no assumptions on the distribution of persistence in the study population are made. Drug discontinuation[3] is considered 'failure' [57] and persistence is 'survival'.

The Kaplan Meier approach is based on several assumptions [60]. First, study patients are assumed to be drawn from a random sample of the target population. The second assumption is that the observations are independent of each other, meaning that choosing any one patient in the population does not affect the chance of choosing any other patient. Third, the index date (treatment initiation, cohort entry) and the treatment discontinuation date (failure) are both assumed to be defined and ascertained consistently during the study period. Fourth, average persistence is assumed to be constant during the course of the study. Finally, the time of

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[2] Uncommonly, treatment persistence is reported as mean, which is a biased estimate. Mean persistence is estimated as the area under the survival curve, and based upon the entire range of data. The mean is underestimated when the longest observation is censored [476,477]. In addition, since time-to-event data is right-skewed, median is a better measure of central tendency [478].

[3] Also called 'termination', 'withdrawal', 'ending' or 'stopping' the treatment

censoring is assumed to be unrelated to persistence, meaning that, on average, the persistence

of censored patients is identical to the persistence of noncensored patients. This last

assumption is especially critical to the validity of results when analyzing data in which many

patients are censored. This assumption can be assessed using information on patients who were

lost to follow-up. If the reason for leaving the study relates to persistence, then the estimated

persistence is biased.

2.1.2.2 Persistence as a Bernoulli Variable

Treatment persistence can also be analyzed using a Bernoulli outcome variable, depending

whether or not the patient was persistent at specific time points date (e.g., anniversaries). For

example, when estimating one-year persistence, patients who are considered persistent are

assigned the value 1 to the outcome variable, and patients who are not persistent are assigned a

value of 0.

There are multiple approaches used to ascertain persistence at specific time points [59]. The

most common approach is to consider patients as persistent until treatment discontinuation.

Using the same example, a patient is considered persistent (outcome variable=1) if

discontinuation was not observed during the first year of follow up, and nonpersistent (=0) if

discontinuation was observed during this year. Similar to the continuous variable approach

(Section 2.1.2.1, page 16) classifying the Bernoulli variable as 1 or 0 requires observation of

the index date and discontinuation date as described below (Sections 2.1.2.3 - 0, from page 19).

Alternatively, a Bernoulli persistence variable can be assigned as 1 or 0 using measures of

compliance (intensity of following the dosing recommendation) at a specific time interval [59].

A patient is persistent as long as the compliance measured is higher than a predefined threshold. For example, a threshold of three refills in the first year of treatment can be predefined as providing sufficient evidence of compliance. A patient who refills 0-2 prescriptions during the year is therefore considered nonpersistent and the outcome variable is assigned a value of 0. A patient who refills three or more prescription during the year is considered persistent and the outcome variable is assigned a value of 1.

2.1.2.3 Ascertainment of the Index Date

The index date is defined as the date of treatment initiation. Depending on the data source (clinical data or administrative data) and route of administration, the index date is defined as the date of the first prescription, dispensing or administration of the drug. In previous observational studies of TNFα antagonists in RA patients using administrative data [61-64], the index date was defined as the date of the first dispensing or the first insurance claim (usually but not always these dates are identical) in the study period. This definition assumes that the drug is administered immediately after the dispensing. In analyses of clinical data, the index date is often defined to be the date of first prescription. Examples include studies of TNFα antagonists in RA patients [65,66] and studies of other diseases using the United Kingdom General Practice Research Database [67]). Alternatively, when a drug is administered intravenously (e.g., infliximab) the index date can be defined as the first administration date [65,68,69].

A valid estimate of treatment persistence require new-user study design. In this design, patients A new-user design is restricted to patients with a minimum period of nonuse (washout or run-in) prior to treatment initiation [70], a period in which patients are not exposed to the drug

studied. In the absence of run-in period, the measured duration of treatment could be underestimated, since the patients might have been exposued to the drug before the initiation date.

Bias may be introduced as a consequence of the methods used to ascertain the index date. First, persistence may be overestimated in analysis of administrative data as the result of using dispensing data when there is a delay or failure in administering the drug. In practice, administration is assumed to occur immediately follow the prescription or dispensing and therefore this source of overestimation is viewed as minimal and insignificant. Second, differential misclassification may occur across study groups. This may occur, for example, when estimating persistence of several drugs from clinical data where different methods are used to ascertain the index date. Specifically, differential misclassification may have occurred in comparing infliximab to adalimumab or etanercept when the index date was ascertained from the first intravenous administration for infliximab and the date of prescribing for adalimumab or etanercept (self-administered) [65,71]. In this example, persistence with the latter drugs may have been overestimated compared to infliximab.

2.1.2.4 Ascertainment of Treatment Discontinuation

Ascertainment of treatment discontinuation from medical records, prospective clinical databases and patient surveys is relatively straightforward for TNFα drugs. Study researchers usually ascertain discontinuation based on records kept by the care-providing physician or from patient self-reports. However the exact method is usually poorly reported or not provided [49].

Ascertainment of treatment discontinuation presents a major challenge in analyses of administrative databases of dispensing claims. In these analyses, ascertainment of discontinuation is usually based on gaps in exposure (or availability) of the drug [17]. Typically, discontinuation is ascertained based on a DRUG-FREE INTERVAL (also termed permissible gap or grace period) of 7-180 days [17], often 30-60 days [18] after the dispensed quantity for each refill was exhausted. An algorithm is generally based on summing the dispensed days-supply of each refill and the predefined drug-free interval. If no additional dispensing claim is recorded during this period, the patient is considered to be a discontinuer, and any further dispensing events of the drug are censored (Figure 5). In studies of persistence with TNFα antagonists in RA patients using administrative data, drug-free intervals of 30 [61-63], 60 days [72] or 90 days [64] have been used.

The rationale of using a drug-free interval is to minimize underestimation of persistence. Several sources of bias are possible if discontinuation is assumed to occur when no refill occurs at the same date that the dispensed days-supply was exhausted. First of all, this zero-gap is very sensitive to compliance in that patients who experience even a temporary lack of compliance are defined as discontinuers in the analysis. Additional sources of bias include

Figure 5: Establishing discontinuation based on days-supply and drug-free interval
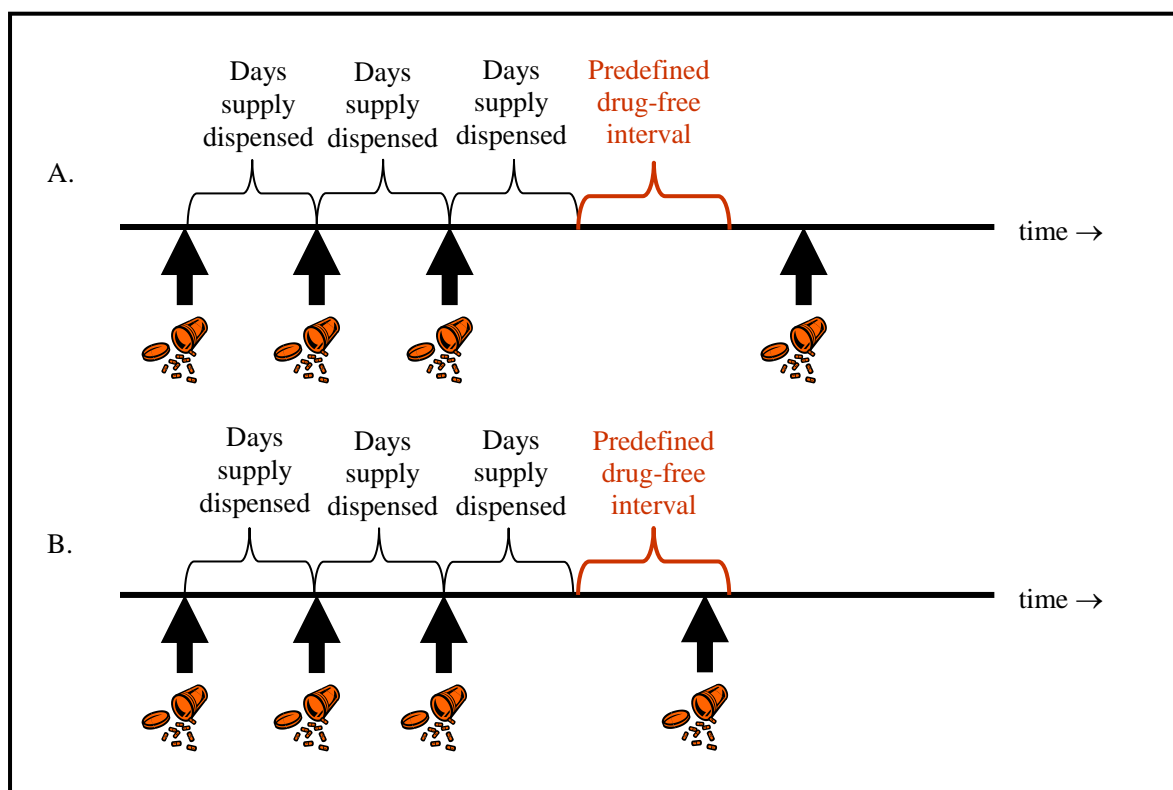
The figure presents two patients, who did not renew the drug once the dispensed days-supply of the third refill was exhausted. In patient A, the fourth dispensing event occurred after the predefined drug-free interval elapsed. Therefore, this patient is considered to be a discontinuer. In patient B, an additional dispensing event was recorded before the drug-free interval elapsed; hence, the patient is NOT considered to be a discontinuer.

errors in recorded quantity or days-supply dispensed, use of supplies that were previously dispensed and stockpiled, dose reduction and the use of samples or hospitalization [73,74].

Selection of a drug-free interval should be based on the pharmacology of the drug and the outcome of interest. However, the rationale for the length of a drug-free interval, if used, has only rarely been provided in published studies. The length of drug-free interval should be determined based on the pharmacologic properties of the drug and in the context of the treatment situation [7,59]. In studies of TNFα antagonists the duration of therapeutic effect has

been shown to significantly exceed the typical interdose interval in patients with RA. For example, the estimated median duration of effect on infliximab has been shown to be 16.5 weeks which is twice as long as the typical interdose interval of eight weeks [75]. The effect of adalimumab can be sustained in patients for four weeks to three months, which is many times longer than the typical interdose interval of two weeks [76]. This aspect of TNFα antagonist treatment is critically important because it suggests that using short drug-free intervals (e.g. 30 days) leads to underestimation of the duration of therapeutic response and patients may therefore be categorized as discontinuers even though they continue to benefit from the drug.

Second, the length of the drug-free interval used in a study substantially depends on whether the research is measuring persistence or adherence. In studies of persistence, discontinuation is the event of interest. The chance that discontinuers reinitiate treatment with the same drug is minimized by selecting a longer drug-free interval. In studies of adherence, the researcher may be interested in capturing also temporary interruptions in persistence, after which the patient reinitiates the treatment. In these studies the outcome integrates both duration and intensity of treatment, and the event of interest is nonpersistence [77] or nonadherence. It is more readily ascertained by using shorter drug-free intervals.

The selection of the length of the drug-free interval is often challenging and there is no consensus on the optimal way to choose an interval any given context. It has been previously suggested that examining the sensitivity of persistence estimates to a varying drug-free interval is appropriate [59,73] or as suggested by Caetano, it is appropriate "to examine a spectrum of persistence according to different levels of intensity" [59].

Additional methods to ascertaining discontinuation are found in the literature. For example, treatment discontinuation was also ascertained based on multiples of the days-supply dispensed [17] or a specified time period (in days) after each dispensing event (Refill-Sequence Model) [17,59]. The last method was used in a recent study of TNFα antagonists in RA for example [78].

Three additional changes in the prescribed regimen are of interest in studies of persistence: addition of another drug, dose adjustment and switching, defined as the dispensing of a different drug within the same therapeutic class that occurred any time during the study period or a specified time period after a dispensing [17]. Halpern et al 2006 [30] suggested that measures of treatment persistence could be categorized to (a) drug persistence, (b) regimen persistence and (c) therapy persistence (Table 1). The most common approach is DRUG

Table 1: Three approaches to treatment persistence (adapted from Halpern 2006 [30]**)**

Approach	Definition	Impact on persistence			
		Discontinuation of the drug	Addition of another drug	Dose adjustment	Switching to another drug
Drug persistence	Time on a specific drug	Yes	No	No	Yes
Regimen persistence	Time on a specific set of drugs without any change	Yes	Yes	No	Yes
Therapy persistence	Time on any drug for the disease	Depends whether the patients was switched or not. No impact if the patient was switched to another drug	No	No	No

PERSISTENCE (medication persistence), specifically patients who added-on drugs to initial therapy are usually considered to be persistent [16] and patients who switch away from their initial drug are considered by researchers nonpersistent (discontinuers) [16,61,62,64,79]. This is the approach used in this thesis, and therefore the term 'drug persistence' in used in the following text. Of importance is that switching or addition of new drug does not always indicate drug/treatment failure. If a new comorbidity has developed, for example, the patient may switch to or add a second drug that is indicated to both the disease of interest and the new comorbidity [30]. The Refill-Sequence Model that previously mentioned permits switching within the same therapeutic class or among drugs with shared indications and these patients are not considered to be discontinuers [59] and therefore is considered a therapy persistence approach. The approach to switchers depends on the study goal. When estimating comparative persistence, switchers should be considered discontinuers, to avoid cross-contamination by alternate drug exposures. However, if the interest is in comparing treatment approaches or clinical situations, then according to the 'intention to treat' approach switchers could be considered as to be persistent (i.e., therapy persistence approach, Table 1). Generally, dose adjustments (increase or decrease) do not reflect lack of compliance or persistence and therefore are not considered nonpersistence [30]. All the above methods require reliable and accurate recording of days-supply, which may be challenging especially in analysis of administrative data[59]. This issue is discussed in detail below (Section 2.2.4.1, page 47).

2.1.2.1 Ascertainment of the Date of Treatment Discontinuation

Once discontinuation is confirmed, how the <u>date</u> of discontinuation is ascertained varies depending on the data source. The date of discontinuation is the last date on which the patient has been exposed to the drug. Alternatively, in drugs with prolonged therapeutic effect such as

on which the patient has been exposed to the drug effect. When clinical data is used to estimate persistence with TNFα antagonists, the date of discontinuation can be defined as the date of the last administered dose, the date of the decision to discontinue or the first missed dose. Unfortunately, the method used is often poorly described in published studies.

In analysis of administrative data, ascertainment of the date of discontinuation is more challenging. In administrative databases with dispensing claims, there are generally fields for recording the dispensing date and the dispensed days-supply. When considering a drug which is administered at least once a day, the end of days-supply as recorded is often used as the date of drug discontinuation. Nevertheless, this may overestimate persistence, since patients may not use the entire quantity dispensed. Treatment with TNFα antagonists presents a more complicated situation due to the varied and prolonged interdose interval[4] (intermittent dosing schedule). The recorded days-supply may reflect the actual number of days until the next refill is expected or the number of days in which the drug is actually administrated (Section 2.2.4.1,

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[4] Recommended dosing schedules for the TNFα antagonists in patients with RA are presented in **Appendix A**, Table 20, page 3.

page 47). Several approaches that can be used to ascertain the date of discontinuation and their limitations are presented below.

1. The date of the last refill – Using this approach the persistence could be underestimated and the effect on persistence with the TNFα antagonists may vary by the interdose interval.

2. The date on which the days-supply was exhausted, also known as the date of the first missed refill – A major challenges is to validate the recorded days-supply or establish the actual days-supply. This method is based on the assumptions that all of the dispensed quantity was administered and that no effect of the drug continues once the days-supply runs out. The last assumption may not hold in treatment with TNFα antagonists in RA patients, as discussed previously (Section 2.1.2.4, page 21).

3. The date of the end of the therapeutic effect - This method is not used in practice because estimating the duration of the effect is demanding and there is large variability between patients.

When using a drug-free interval to ascertain discontinuation, the use of a date earlier than the end of the interval, such as the date on which the days-supply was exhausted, possess an additional complication. In this case, the investigator looks ahead in time and uses "future" data to ascertain an event that occurred in the past. This approach is unacceptable in research of therapeutic outcomes, mainly since in this case it is impossible to suggest a causal relation, For example, an uncertainty would be arisen whether treatment discontinuation caused the outcome, or whether the "outcome" caused treatment discontinuation. When estimating treatment persistence, setting the discontinuation date to the end of days supply would robustly

results in estimates shorter by the length of drug free interval compared to a situation in which the discontinuation date is set to the end of drug-free interval. When using fixed length of drug free interval in studies of comparative persistence, the comparison should not be significantly biased, because the difference in persistence using the two methods is fixed for both drugs.

2.1.3 Comparative Analysis of Persistence

Similar to persistence, estimating comparative persistence can be done using the Kaplan-Meier approach with a log-rank chi-square to test for differences between the persistence of any number of drugs. Alternatively, regression analysis can be used to investigate the comparative persistence of two or more individual drugs.

In general, comparative persistence can be estimated using an additive risk model, and be expressed as differences in risk for discontinuation or using a multiplicative risk model, expressed as a risk ratio. Risk differences are typically more informative than ratios; nevertheless, most published analyses of comparative persistence were conducted using the multiplicative scale and Cox proportional hazard regression.

2.1.3.1 Cox Regression

In Cox proportional hazard regression, results are reported as hazard ratios for drug discontinuation. Discontinuation has an inverse relationship to persistence: better persistence on a drug can also be expressed as a lower risk of discontinuation. However, the size of the ratio is not proportional: a hazard ratio of two means that the drug of interest is associated with

a two-fold increased hazard of drug discontinuation, but the persistence with this drug is not necessarily half the persistence of the comparator drug. The two-fold increased hazard is interpreted as following: patients treated with the drug of interest and who were still persistent at time t (i.e., did not discontinue) have twice the chance of discontinuing at time t compared to patients treated with the comparator drug.

The multiplicative approach is especially attractive because researchers can adjust and study the effect of covariates. It also allows the baseline hazard to be unspecified. In addition, interpretation of the estimated coefficients is simple. The main limitation of this approach is the difficulty in interpreting the hazard ratios and associating them to persistence. Hazard ratios should be regarded as a measure that allows hypothesis testing, but ideally it should be used in combination with a measure of duration (such as median persistence) to adequately describe the size of the effect.

2.1.3.2 Aalen's Additive Risk Model

Alternatively, the additive risk model suggested by Aalen [80,81] is useful when risk difference is the main interest as opposed to relative risk. The hazard at any time is a sum of an unknown baseline hazard and a linear combination of covariate values. Estimation of the risk coefficients is based on a least-squares method. The additive risk model allows covariate

effects to vary with time. The disadvantages of this model are its infrequent use and its

inappropriateness for use with some datasets[5], in contrast to the Cox model [82].

2.2 A Methodological Frame for Estimating Comparative Persistence Using British Columbian Ministry of Health Databases

This section presents the methodological framework we used to estimate comparative

persistence of selected TNFα antagonists using British Columbia Ministry of Health databases.

We introduce the data source and major methodological challenges that needed to be overcome

to conduct the research for this thesis. To use administrative data intended for financial and

management purpose to answer clinical questions presents major methodological challenges.

One strategy is to create algorithms - computerized step-by-step lists of simple instructions.

Algorithms were used to identify the study cohort, to calculate persistence of individual

patients and their censor status[6] and to assign values for the exposure and covariates.

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[5] The dataset requirements are described in details in Cao's dissertation [82] and are beyond the scope of this thesis.

[6] The concept of censoring and its significance are discussed in Section 2.1.2.1, page 3.

2.2.1 Data Source: The British Columbian Ministry of Health Databases

The British Columbia Ministry of Health databases are useful powerful resource for conducting population-based health research, particularly because patient-level information from multiple databases is available . For this thesis, data records were accessed from the original British Columbia Health Data Warehouse platform for this research [83]. The new platform, HealthIdeas data warehouse services was designed to enhance security and privacy, using tiered zone based architecture. It has been in operation from 2010 and was not used in this research.

For the purpose of our study, we used a dimensionalized database platform[7] that allowed a tailored access to various attributes of the following data, using a study-specific anonymized identification number:

1. **Registration data** (from January 1, 1986) - The dataset contains basic demographic data, such as age and sex, as well as data on registration in the provincial Medical Service Plan (MSP). First Nations and federal employee data were not accessible in the view of the dataset we obtained.

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[7] A dimensionalized database is a specialized data storage facility that stores summarized data for fast and easy access. The summary is available across different dimensions of data such as location, time and individual patient. Users can quickly view large amounts of data as a value at any cross-section of the dimensions of interest.

2. **MSP payment information data** (from April 1, 1985) - Data included all medically required services provided by fee-for-service practitioners (mainly physicians, but also some additional health providers such as nurse practitioners, chiropractors, massage therapist, physiotherapists) in British Columbia, for British Columbia residents covered by the provincial MSP. Data was also available for British Columbia residents who obtained services in Quebec, the United States (U.S.) and other countries that were paid by MSP as well as services provided by fee-for-service practitioners billed at the regular rates, but paid for by third parties such as the Insurance Corporation of British Columbia (ICBC)[8] and WorkSafe BC[9]. The dataset did not include services provided through alternative payment plans (salaried, sessional, and service agreement contracts), services for British Columbia residents who obtained medical services in other provinces and territories (except Quebec) and payments to physicians who perform WorkSafe BC expedited surgeries in public hospitals. Data on abortion (preganancy termination) procedures were also not included. The majority of billing records are submitted electronically by practitioners' offices to MSP. Diagnostic codes collected in the International Statistical Classification of Diseases and Related Health Problems version 9 (ICD-9) format (one to three codes per record) and considered accurate only to the 3rd digit level. MSP conducts routine audits/quality checks

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[8] ICBC is a provincial corporation that covers expenses, including medical expenses, cause by bodily injuries in motor accidents to BC motorists.

[9] WorkSafe BC (the Workers' Compensation Board of British Columbia) promotes workplace health and safety. In the event of work-related injuries or diseases, the board is responsible to health care benefits, compensation, return-to-work rehabilitation, and a range of other services [479].

on select fields. Diagnostic codes have been shown to be valid at the population level [84].

3. **Hospital separation data (Discharge Abstract Databases, DAD)** (from April 1, 1985) -
   Our access included information on the discharge, transfer and death of inpatients (and day
   surgery patients) from British Columbia acute care hospitals (British Columbia residents
   and non- British Columbia residents) as well as data on British Columbia residents who are
   admitted to a hospital in another province. Data on visits to emergency rooms/departments
   as well as outpatient services were not recorded in this file. Data on abortion procedures
   were not included as well. The format of the data changed significantly in 2001/02, as
   coding diagnoses switched from ICD-9 codes to ICD-10-CA[10] codes, and
   procedures/interventions coding from CCP[11] to CCI[12]. The centralized data processing of
   DAD records by the Canadian Institute of Health Information (CIHI) results in increased
   efficiency and standardization among the participating provinces. The CIHI performs an
   annual data quality study [85].

4. **PharmaNet Data** (from September 1995) - We obtained access to data on drugs dispensed
   in British Columbia pharmacies (prescription drugs only, excluding the prescriptions of
   hospital inpatients) and PharmaCare claims data.

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[10] The ICD-10-CA is an enhanced version of ICD-10 developed by the Canadian Institute of Health Information for morbidity classification in Canada.

[11] The Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures

[12] Canadian Classification of Health Interventions

Administrative health data, also known as claim data, are collected primarily for reimbursement, but usually contain some clinical data, such as diagnosis and procedures reimbursed [86]. Administrative data offer several advantages in research of therapeutic outcomes, especially in chronic disease. Data are collected in a systematic manner and usually are population based. Hence studies are quick, cheap and generalizable [87,88]. Administrative data provide estimates of effectiveness from a variety of clinical setting rather than efficacy and allow comparison of multiple alternative interventions beyond a placebo comparator as well as comparison of clinical strategies [86]. Large databases also allow research on rare and often delayed drug-related outcomes (benefit or harm) [86-88]. This type of data provides information on how the drug is dosed and applied in routine clinical practice [86]. In addition, administrative data is usually up-to-date and follow-up data is available before and after an event of interest. Finally, research using administrative health data prevents three types of bias that is present in other studies. First, since informed patient consent is not required studies are less prone to selection bias [89-91]. Second, information recorded in the pharmacies is usually more accurate than self-reported drug use that may introduce reporting bias (especially for elderly, ill or deceased) [89,92]. Finally, since the analyses are nonintrusive, the research and the researchers do not influence the outcomes [92,93]. Participants and providers in RCTs may change their behaviour (Hawthorne effect[13]), and this change may affect the magnitude of the

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[13] Hawthorne effect is "the effect (usually positive and beneficial) of being under study upon the person being studied; their knowledge of the study often influences their behavior" [1].

outcome for each group, and also may result in an inflated estimate of the effect size of the active comparator [94,95].

2.2.2 Creating the Study Cohort

The British Columbia physician services database is primarily used for payment purposes, and therefore the diagnostic coding in that database is often unreliable. As a consequence, the first challenge in this research was to identify patients with RA that would comprise the study cohort. Ideally, an algorithm with high specificity is used to identify a study cohort (i.e., all patients included in the cohort have RA). Specificity of potential algorithms can be conducted in validating studies in comparison to clinical data. Since we had no access to clinical data, we were dependent on previous validation studies.

The first step in developing an algorithm for our research was to design a disease algorithm in which patients diagnosed with RA could be identified. Prior to conducting the research and selecting the disease algorithm, we identify four different validation studies of different disease algorithms used on a variety of databases (Table 2). Two algorithms were identified that were based on a single recorded diagnosis of RA resulting in a sensitivity of 0.65-0.90 and positive predictive value (PPV) of 0.86-0.95.

Table 2: Published RA disease algorithms

Study	Setting	Algorithm examined	Compared to	Results
Katz et al 1997 [96]	8 rheumatologic clinics in 3 U.S. states	ICD-9 code of RA (714) used in Medicare Part B physician claim files	Criteria by the American College of Rheumatology	Sensitivity 0.90 (95% CI 0.85-0.95) (N=342) PPV 0.95 (95% CI 0.92-0.98) (N=307)
Losina et al 2003 [97]	THR recipients N=922	ICD-9 codes of Medicare physician claims	Hospital admission as recorded by physician	Sensitivity 0.65 (95% CI 0.49-0.80). PPV 0.86 (95% CI 0.73-0.99).
Singh et al 2004 [98]	Veterans hospital N=184	ICD code 714 for RA diagnosis in an administration hospital database	Chart documentation of RA diagnosis by a rheumatologist on at least 2 visits at least 6 weeks apart	Sensitivity 1.00 (95% CI n/a) PPV 0.66% (95% CI 0.59-0.73).
		ICD code 714 for RA diagnosis in an administration hospital database plus synthetic antirheumatic drug[14] prescription fill		Sensitivity 0.85 (95% CI 0.80-0.90) PPV 0.81 (95% CI 0.75-0.87)
Lix et al 2006 [99]	Manitoba	16 different algorithms were examined	Canadian Community Health Survey, cycle 1.1, collected between September 2000 and November 2001 [100]	Table 7 of the report presents the accuracy of different algorithm examined varied between 0.05-0.11 in different algorithms. PPV ranged

[14]The synthetic antirheumatic drugs are traditional short synthetic drugs from a variety of therapeutic classes used in treatment of RA. The term disease modifying antirheumatic drugs (DMARDs) or nonbiologic DMARDs have often been used in the literature to identify drugs from this heterogeneous group, regardless of lack of evidence that these drugs actually change the natural history of the disease. They include azathioprine, cyclosporine, hydroxychloroquine, leflunomide, methotrexate (MTX), penicillamine, sodium aurothiomalate, sulfasalazine and others.

Study	Setting	Algorithm examined	Compared to	Results
				between 0.63-0.81
				For example, algorithm requires 2 RA diagnosis in 1 year have sensitivity of 0.05 and PPV of 0.77

CI – confidence interval; **ICD** - International Classification of Diseases; **n/a** – not available; **PPV** – positive predictive value; **RA** – rheumatoid arthritis

For the purpose of evaluating the study hypothesis, we were interested in maximizing the PPV and minimizing the number patients with false RA diagnosis that were included in the cohort. Therefore we used similar, though not identical, a disease algorithm to that used in previous studies of RA patients in British Columbia [101-103]. RA patients were identified based on two outpatient visits with a diagnosis code of RA at least 60 days apart, or one hospitalization with a recorded discharge diagnosis of RA in three years prior to the index date. The list of ICD codes we used is presented in **Appendix B**, Table 28, page 271. We required two outpatient encounters with diagnosis of RA to increase the PPV and spaced at least 60 days apart to exclude transient joint disease or a diagnosis recorded as part of a diagnostic process in patients with other diseases. We regarded hospital diagnosis to be more accurate than outpatient diagnosis, since they are based on the discharge abstract, which is required for medical, and not payment, purposes.

In a second step, we designed an algorithm to exclude patients with diseases other than RA to increase the specificity of the study cohort. Treatment with TNFα antagonists is also indicated for Crohn's disease, ulcerative colitis, juvenile RA, ankylosing spondylitis, psoriasis and psoriatic arthritis. Previous persistence studies of RA patients using administrative data have similarly excluded patients with other diseases indicated for TNFα antagonists including juvenile RA (patients younger than 18 years at index) [61,64,72,104] and Crohn's disease [61,72].Our algorithm also excluded patients with either juvenile RA or Crohn's disease. In a preliminary analysis not presented in this dissertation, we found that crude persistence (based on Kaplan Meier curves and log-rank test) was significantly different between RA patients and Crohn's disease patients. Patients with both diseases presented persistence similar to patients with Crohn's disease. Therefore, we excluded patients with at least one recorded diagnosis of

Crohn's disease. We also routinely excluded young patients (under 18 years at index date), because they most probably had juvenile RA (also known as juvenile idiopathic arthritis) which is a similar, but not identical disease with different prognosis. In addition, patients with no data on the date of birth were excluded.

Patients with recorded diagnosis of other indications approved for TNFα antagonist treatment were not excluded, due to small number of patients. Ankylosing spondylitis was approved in middle of 2005 and psoriasis, psoriatic arthritis and ulcerative colitis were approved in the middle of 2006. Since the study cohort included patients who initiated TNFα antagonists until the end of 2008, we assume a small number of disease misclassifications occurred and did not check for these diagnoses.

2.2.3 The Exposure and Covariates

2.2.3.1 Ascertainment of TNFα Antagonist Drug Exposure

In analysis of administrative data, dispensing or claims data is used as proxies for drug use. Several possible sources of inaccuracy poses challenges in the analysis: (a) miscoding of the drug itself, strength and dose; (b) compromising for dose adjustment; (c) absent data on free samples and in-hospital drug; and (d) uncertainty that a filled prescription means the drug was actually administered. We discuss these challenges and design features taken to minimize bias in **Chapter 3**, Section 3.5.3.3, page 80.

2.2.3.2 Multiple and Mixed Exposures

A major concern when analyzing real life data is multiple and mixed exposure. Some patients experience a serial exposure to more than one drug (switchers), for example. In reviewing previous studies of TNFα antagonists, three approaches for dealing with this concern were identified. The most common approach was to analyze only the first course [79,105-110] (or only the second course [111,112]) of TNFα antagonists. Another approach includes grouping patients based on the first drug administered (the intention-to-treat approach) [63]. In these studies, switching to another drug is considered persistence. This approach is used in studies of therapy persistence (Section 2.1.2.4, page 21). The third approach involves analysis of all drug courses, and patients may be included more than once, depending on the number of courses administered [64, 113-117]. An additional approach, not used in studies of TNFα antagonists is censoring patients at the time of switching to another drug from within the same therapeutic class [118].

In the context of our study, we were interested in isolating patients treated with one drug only. Since previous studies showed differences in persistence between first course and second course, we chose to analyze only the first course of TNFα antagonists.

The second concern was the possible effect of cotreatment (as predictor or as a confounder), especially with regard to methotrexate (MTX). MTX has a role in preventing the formation of antidrug antibody [119-121]. Concomitant MTX therefore may decrease harm [122] and/or improved therapeutic benefit [122-124], however the available evidence is inconclusive. Concomitant MTX has been shown to improve persistence with TNFα antagonists

(unpublished data summarized in **Appendix A**, Section A.3.5, page 261). Consequently, we

adjusted the regression model for concomitant MTX.

2.2.3.3 Confounding and Confounding by Indication/Severity

One of the major threats to validly in observational studies is confounding, especially

confounding by indication (or disease severity). Confounding originates when drug allocation

is associated with factors that are also independent predictors the outcome. Confounding by

severity occurs when patients with the worst prognosis are assigned the most effective drug [8-

12], and as a result, effectiveness is biased toward the null (no effect). If, for example, drug X

is considered more efficacious than drug Y, patients with more severe disease may be treated

more frequently with drug X. Disease severity may also affect the outcome, as patients with

more severe disease may be less persistent. As a result, drug X that is actually more efficacious

is found to be associated with shorter persistence.

Limited or missing information on confounders in analyses of administrative data (such as

smoking, alcohol use, the age of menopause, disease severity and diagnostic results) may lead

to biased results. We could not evaluate the potential influence of factors relating to patients

beliefs, functional level and disease activity, though we used proxies in an attempt to adjust for

some of these factors. In addition, biased estimates of possible confounders should be

considered in analyses of administrative data. Disease duration, for example, is generally

underestimated, because the time of disease onset precedes the time of diagnosis. Several

methods have been advocated to minimize confounding, including use of multivariable

regression [125], propensity scores[15] [125-129] and instrumental variables[16] [130-132].

When comparing the effects of two drugs that are prescribed under the assumption of identical

effectiveness and safety, as the TNFα antagonists are, predictors of persistence can be

considered balanced and minimal bias is expected [133]. In this treatment situation no evidence

exists regarding the superiority of either drug (**Appendix A**, Section A.3.1, page 241) and

clinical guidelines recommend treatment with either TNFα antagonist interchangeably

(**Appendix A**, Section A.1.3, page 218). We applied a simple method to adjust for possible

confounding - multivariate regression. The main advantages of this approach are that it also

allows estimation of the effect of other possible predictors of outcomes, and testing for the

confounding effect of each variable separately. A disadvantage of this method is that it allows

adjustment only for measured variables.

The variables included in our regression models are presented in Table 3. We sought to adjust

for disease severity, accessibility of health services, socioeconomic status and concomitant

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[15] Propensity score is the "conditional probability of being treated given a certain set of measured covariates. It can be used to control confounding through matching, stratification, regression adjustment or combination of these methods and can be used along with other covariate adjustment" [1].

[16] Instrumental variable is a "method that, under certain assumptions, allows the estimation of causal inference even in the presence of unmeasured confounding for the exposure and effect of interest. An instrumental variable, or instrument, has to meet the following conditions: (1) it is associated with the exposure, (2) it affects the outcome only through the exposure, and (3) it does not share any (uncontrolled) common cause with the outcome" [1].

Table 3: The rationale for variables included in the regression model

Variable	Rationale
Demographics	
Sex	Females were shown to be less persistent with chronic therapies [134-136]. In addition, RA was shown to be more severe in females, and progress faster [137].
Age at index date	Older age was associated with improved persistence on chronic therapies [135,138,139]. In addition, age may affect the route of administration: younger patients (< 61 years old) were more confident about self-administering drug, and preferred subcutaneous route to intravenous administration [140].
Annual income level (based on MSP subsidy)	The covariate was used as a proxy to both socioeconomic status and out-of-pocket costs [141]. Some studies demonstrated that socioeconomic status influences adherence and persistence with drugs [142,143], but the effect is inconsistent. Out-of-pocket costs were shown to affect TNFα antagonists and other drugs persistence [63,144,145].
Patient's residence area	Residence area influences access to health care facilities and hence influences the selection of the individual TNFα antagonists. It was shown that residence area influenced persistence on chronic drugs [146].
Clinical status	
Physicians encounters in the year preceding the index date	The number of outpatient encounters was used as a proxy to (a) RA disease severity (b) presence of significant comorbidities, and (c) accessibility of health services.
Inpatients admissions in the year preceding the index date	The presence of hospital admission was used as a proxy to (a) RA disease severity (b) presence of significant comorbidities, and (c) accessibility of health services.
Extra-articular manifestation of RA[17]	A proxy measure of disease severity.
Comorbidities	The presence and severity of comorbidities may influence the selection of the specific drug. In addition comorbidities were shown to affect drug persistence [63,147,148].
Disease duration	Disease duration was shown to affect persistence with TNFα antagonists in some studies [114,149] but not other [113,150-152].
Drug therapies	
Concomitant MTX	Concomitant and previous use of MTX is strongly associated with improved persistence on TNFα antagonists in multiple studies [61,64,79,150,151,153-155].
Dispensing claims for NSAIDs	A proxy measure of disease activity (pain).

Variable	Rationale
Number of different antirheumatic drugs (synthetic drugs and corticosteroids) dispensed in the three years preceding the index date	The number of antirheumatic drugs was used as a proxy of disease severity. In addition, it was shown to be associated with persistence of TNFα antagonists [79,150,156].
Other	
Prescriber propensity for treatment discontinuation	We hypothesized that different likelihood to discontinuation was associated with different prescribers.
Calendar year at index date	Calendar year was included in the multivariable analysis to adjust for secular trends in clinical practice, such as initiating TNFα antagonists in patients with less severe disease and after exposure to a smaller number of antirheumatic drugs[157-160]. This variable also allowed adjustement for later availability of adalimumab, which was marketed since 2004.

MTX, all of which we consider possible confounders. Since we used administrative data, we did not have access to direct measures of disease severity; hence, we used several proxy variables: inpatient and outpatient encounters, disease duration, extra-articular manifestations[17], comorbidities, previous number of antirheumatic drugs and nonsteroidal anti-inflammatory drug (NSAID) use (as a proxy for pain). Adjustment for accessibility of health services were performed using geographical area of residence and inpatient and outpatient encounters. A proxy variable for socioeconomic status was the annual deductible level for Fair PharmaCare

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[17] Extra-articular (outside the joint) manifestations are caused by onvovemnet of tissues and organs outside the joints in the diseas. These include systemic or local manifestations such as weight loss, osteoporosis, lymphadenopathy (enlargments of the lymph nodes), vasculitis (inflammation of the blood vessels) and envolvement of the pleura and pericardium (lining surfaces of the lung and heart, respectively). The list of ICD codes used to identify patients with such manifestations is presented in **Appendix B**, Table 28, page 3.

reimbursement decisions, which is based on the family annual income. Age and sex could also be considered socioeconomic variables.

2.2.3.4 Prescriber-Specific Effects

We found that the impact of care-providing physician characteristics on persistence estimates was rarely studied. Generally, comparative persistence was estimated using Cox regression, which included a variety of patient's characteristics measured at baseline (and rarely were time dependent [150]). Some studies included patient's psychological factors [152] or adherence/compliance with the drugs [161] as predictors of TNFα antagonist persistence. Until recently, none of the TNFα antagonist studies included adjustment for the care-providing physician or his characteristics[18]. Rarely, persistence studies in other diseases adjusted for care-providing physician characteristics, such as age [135,162], gender [135,162], number of patients treated by this physician [135,162] or specialty [104,163-166].

We considered the care-providing physician (and specifically discontinuation habits) to be a source of confounding, and expressed this property as PRESCRIBER PROPENSITY FOR TREATMENT DISCONTINUATION. Since we used administrative data, we could not identify the care-providing physician. We used the prescriber recorded on the first dispensing claim for TNFα antagonist as a proxy of the care-providing physician, but we are aware that

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[18] A single recent study that examined the effect of the individual physician (prescriber propensity for treatment discontinuation) [48,289] is presented and discussed in **Chapter 5**, Section 5.5.1.3, page 3.

the prescriber may write a prescription based on the recommendation of another physician, with the other physician being the actual care-provider.

Generally, two approaches are used to adjust for the prescriber propensity for treatment discontinuation. The first is to include a series of individual Bernoulli variables for each prescriber, to allow an individualization (by prescriber) of the baseline likelihood for discontinuation (**Chapter 3**, **Chapter 4** and **Chapter 5**). The effect of other predictors in the model is assumed to be constant for all prescribers. The second approach is the use of marginal (**Chapter 5**) or mixed effect modeling [48] to allow adjustment for possible correlation between patients treated by the same prescriber. In this approach, patients who are treated by the same prescriber are considered more alike than patients treated by different prescribers. In this approach, the effect of the other predictors is averaged.

In our analysis, we included an adjustment for prescriber propensity for treatment discontinuation, using the methods described above. In the analysis described in **Chapter 5,** we added a new dimension to adjust for the effect of the care-providing physician - PRESCRIBER PREFERENCE FOR THE PRESCRIBED DRUG (one or other TNFα antagonist) as derived from their prescribing patterns. In this analysis, two groups of treatment courses according to the preference level were compared. We assigned value to the preference variable based on previous courses initiated by the same physician in the study cohort (**Chapter 5**, section 5.3.2, page 132). Additional discussion on modeling of prescribing habits is presented in **Chapter 5**, Section 5.5.2, page 156.

2.2.4 Outcome Variables

2.2.4.1 Ascertainment of Days-Supply

An accurate measure of the days-supply for each dispensing is required for ascertainment of the discontinuation date, as discussed in Section 0, page 15 [59]. The British Columbia dispensing data, recorded in pharmacies, as part of the dispensing process, include data on the drug and its strength, the date of dispensing, the quantity dispensed and the number of days-supply. We required an accurate measure of days-supply, which we defined as days until the next dispensing.

Due to the intermittent and complex dosing schedule for TNFα antagonists, we suspected that the recording of days-supply would be inaccurate. We also suspected that inconsistencies could exist in the record of quantity dispensed – weight (in milligrams), volume (in milliliters) or number of vials. Similar concerns were discussed by Wilensky et al in estimating persistence with ophthalmic solutions [167] and by Grymonpre et al regarding nondiscrete dosing forms (such as liquids, creams and ointment) [168]. Initially, we used descriptive statistics to familiarize ourselves with the data. As hypothesized, data on days-supply was problematic and reflected either number of days of administration (for example one day for one dose of infliximab), the number of days until the next dispensing (for example 14 days after the first administration of infliximab) or was set to 30 days based on PharmaCare reimbursement policy [169]. Next, we attempted to calculate the number of days until the next dispensing based on the quantity dispensed. Finally, if required, we used the recorded total cost as the most accurate and reliable field, since this field serves for claim and payment processing.

For infliximab (Figure 6, page 49), we based our calculation of days-supply on recorded total cost because both days-supply and dispensed quantity were found to be unreliable. The dispensed quantity was found to have been recorded in a large range (1-1000), with possible overlapping ranges between data recorded as weight, as volume or as number of vials (e.g., quantity of 9 could reflect number of vials or weight). To calculate the days-supply first we estimated the average annual cost per vial, based on dispensing records in which the quantity recorded was unquestionably vials. We expected secular trends in cost and some variation between pharmacies so we averaged the cost per vial in a time-dependent manner: that is estimates depended on the dispensing date. Then we used the annual average cost per vial to roughly estimate the number of vials dispensed in all the records in our data. Next, we calculated days-supply, defined as the number of days until the next expected dispensing event, based on the number of the estimated number of vials dispensed. For patients treated with infliximab, the administered dose is based on body weight. Because we had no access to this data, we used a simple algorithm to approximate the number of days-supply (presented in Figure 6). Finally, to ensure that we did not underestimate the days-supply, the longest period (largest number of days-supply) based on the calculated or the recorded days-supply was selected to be used in the analysis.

Figure 6: Algorithm used to establish the number of days-supply for patients treated with infliximab

Map average annual cost per vial, using dispensing records with (a) cost>100 and (b) quantity between 1 and 9

(Inconsistency was observed in recorded quantity, which was sometime recorded as mg and not vials)

For each record in which dispensed quantity is 0 or at least 10, calculate number of vials based on date of dispensing and average cost on dispensing date

Calculate number of doses based on the number of vials that was calculated in the previous step

Vials	Doses
0-2	1
3-5	2
>5	3

Calculate order of the dispensing (first, second or ≥3rd)

Calculate days-supply

Order of the dispensing	Number of doses previously dispensed	Calculated number of dose dispensed	Calculated days-supply
First	0	1	14
First	0	2	48
First	0	3	104
Second	1	1	28
Second	1	2	84
Second	1	3	140
Second	2	Any	Doses*56 days
3rd and above	Any	Any	Doses*56 days

Select the largest number of days-supply (recorded or calculated)

The recorded dispensed quantity for adalimumab was found to be consistent with the number of vials, hence was not manipulated (**Error! Not a valid bookmark self-reference.**, page 51). We used this quantity to calculate the days-supply. For etanercept, the recorded quantity supplied was either vials or weight (in milligrams), hence for large quantities (>99), the number of vials were calculated based on drug strength (25 or 50 mg per vial) (Figure 8, page 52). Again, we used this quantity to calculate the days-supply.

Figure 7: Algorithm used to establish the number of days-supply for patients treated with adalimumab

(Recorded quantity was found to be reliable; hence it was used to calculated days-supply)

↓

Calculate days-supply: dispensed quantity * 14

↓

Select the largest number of days-supply (recorded or calculated, minimum 14 days)
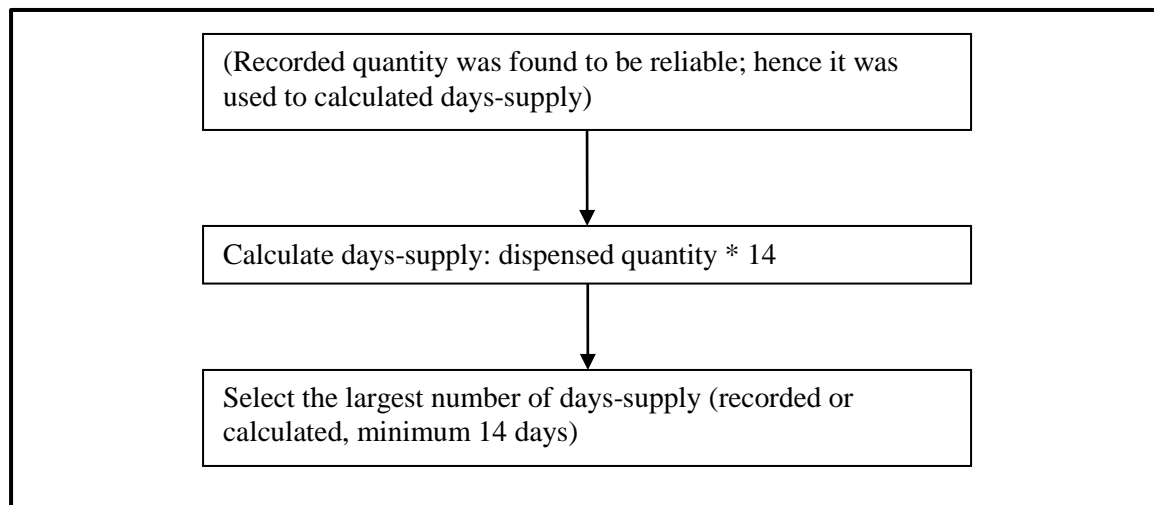
Figure 8: Algorithm used to establish the number of days-supply for patients treated with etanercept

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┌─────────────────────────────────────────────────────────────────┐
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│        ┌──────────────────────────────────────────────┐          │
│        │ (Inconsistency was observed in recorded       │          │
│        │ quantity, which was sometime recorded as mg    │          │
│        │ and not vials)                                 │          │
│        └──────────────────────────────────────────────┘          │
│                             │                                     │
│                             ▼                                     │
│        ┌──────────────────────────────────────────────┐          │
│        │ For dispensing records where quantity was      │          │
│        │ >99, calculate number of vials (=recorded      │          │
│        │ quantity/drug strength).                        │          │
│        │ For other records treated recorded quantity    │          │
│        │ as number of vials                              │          │
│        └──────────────────────────────────────────────┘          │
│                             │                                     │
│                             ▼                                     │
│        ┌──────────────────────────────────────────────┐          │
│        │ Calculate days-supply:                          │          │
│        │ number of vials * drug strength / 50 * 7 days   │          │
│        └──────────────────────────────────────────────┘          │
│                             │                                     │
│                             ▼                                     │
│        ┌──────────────────────────────────────────────┐          │
│        │ Select the largest number of days-supply       │          │
│        │ (recorded or calculated)                        │          │
│        └──────────────────────────────────────────────┘          │
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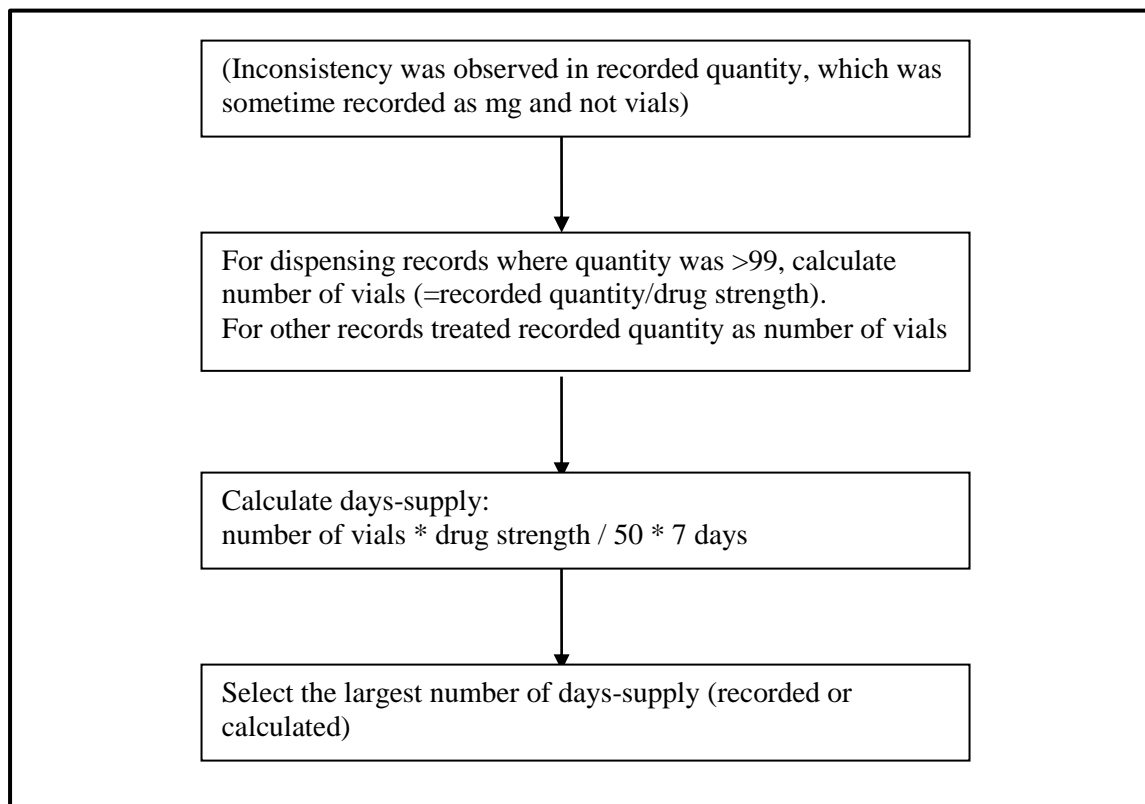
2.2.4.2 Dose Adjustment

Dose adjustment, mainly dose escalation, is frequent with the TNFα antagonists as a class and even more frequent in RA patients treated with infliximab (**Appendix A**, Section A.3.6.2, page 265). In analyses of dispensing claim data, days-supply may be overestimated by calculating dispensed days-supply based on dispensed quantity because dispensed quantity does not reflect that dose escalation is occurring when it occurs. For example, when the actual dose is twice the recommended dose, the patient is dispensed double quantity for a fixed time period (t). To calculate the days-supply, we use the standard recommended dose and do not take into account

the multiplier which represents the dose escalation. Dividing the actual dispensed quantity by the recommended dose produces a value which is twice larger than the actual days-supply (2*t). This value is used in ascertainment of discontinuation and date of discontinuation, and therefore the persistence is overestimated. Since dose escalation is more frequent in infliximab-treated patients then overestimated days-supply are more common with infliximab, causing differential bias.

Figure 9: Calculating days-supply in dose escalation may result in persistence overestimation
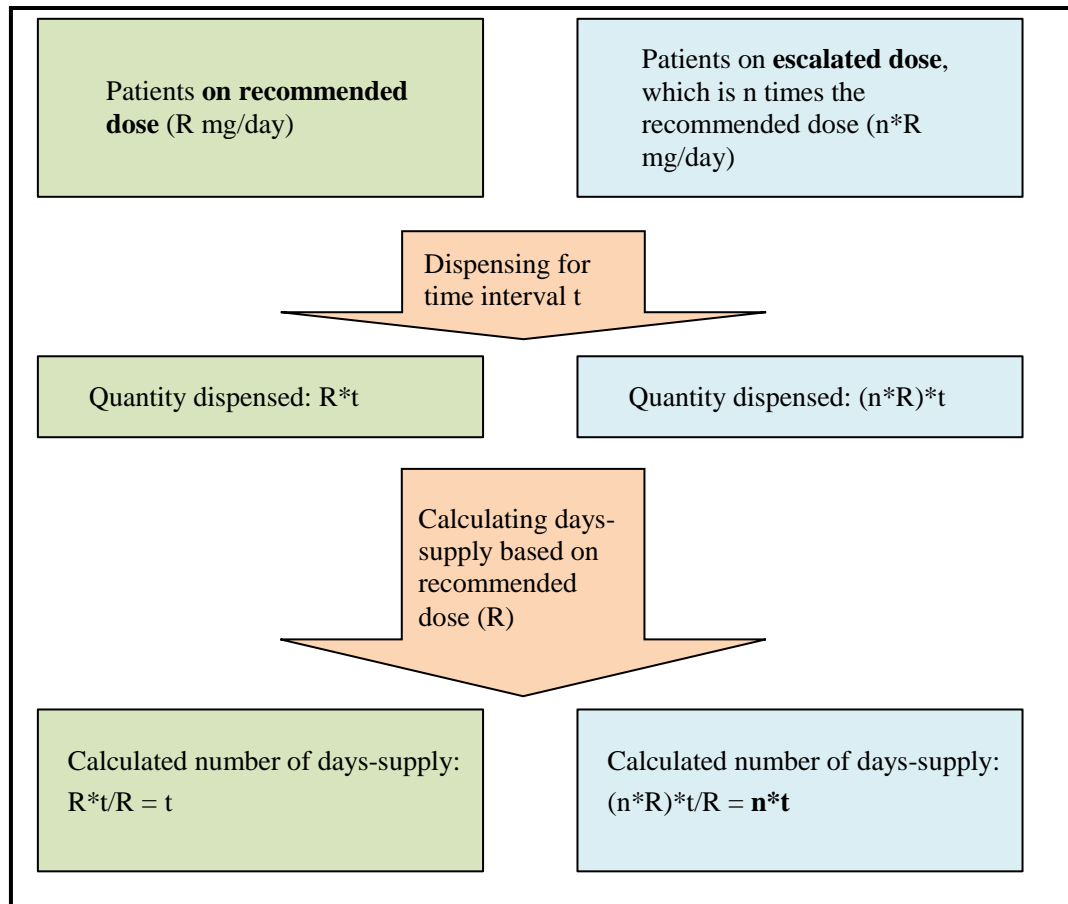
Two previous analyses of administrative databases [62,72] evaluated the frequency of dose escalation in RA patients treated with TNFα antagonist. However, in these studies days-supply recordings were assumed to be accurate and were not manipulated as in our analysis. Due to the limitation of our data on dispensed days-supply (Section 2.2.4.1, page 47), it was not possible to identify dose adjustment.

2.2.5 Analytic Approach

In the population-based analyses presented in this thesis, comparative persistence is estimated using a multiplicative approach (Cox proportional hazard regression) (Section 2.1.3.1, page 28). This approach is consistent with published research that has also adjusted comparative persistence of TNFα antagonists in RA using the Cox proportional hazard approach [61,110,113,150,151,161,170,171]. Cox regression analyses were also used to compare exposure to other factors, such as age [116,172], concomitant leflunomide [114] or MTX [64,150] and out-of pocket costs [63].

There are two major limitations of this approach in our study. First, it is uncertain whether the proportional hazards assumption holds in studies of pairwise comparative persistence of TNFα antagonists in RA patients. Only one study has reported assessing the proportional hazards assumption [61]. This study demonstrated comparable persistence of adalimumab and etanercept. Nevertheless, Cox regression is ubiquitously used and considered to be a relatively robust modeling approach [173]. A second disadvantage is that we estimate the risk ratio, not

the risk difference; hence, statistical significance may not imply clinical significance. Without presenting the absolute difference in persistence, the clinical significance of the results is uncertain.

CHAPTER 3: ESTIMATING COMPARATIVE PERSISTENCE OF TNFα ANTAGONISTS – A POPULATION-BASED STUDY

3.1 Introduction

Rheumatoid arthritis (RA) is a relatively common systemic inflammatory disease that causes significant mortality, progressive morbidity and disability and an excessive economic burden. Tumour necrosis factor alpha (TNFα) is a cytokine with an important role in the pathogenesis of this disease [174]. It is bound and inactivated by the TNFα antagonists - infliximab, adalimumab and etanercept. Treatment with a TNFα antagonist is not a cure [44] but rather reduces the symptoms of inflammation, possibly induces remission and possible prevents long-term complications. The individual TNFα antagonists have different pharmacological properties which may lead to substantive differences in therapeutic benefits and harms (**Appendix A**, Section A.2.4, page 229, [39-43]); however, their relative benefit-harm balance is not well studied and there are no randomized clinical trials (RCTs) that directly compare therapeutic outcomes of all three or pairs of the drugs. Knowledge about relative benefit-harm balance is important to patients, clinicians, policy makers and researchers to optimize clinical and policy decisions and to test the validity of studies.

Drug persistence is considered an indirect simple approach that balances overall long-term benefit (effectiveness) and harm (safety, adverse events) of drug therapy, particularly in patients with chronic noncurable diseases [45]. Beside benefit and harm, it integrates the

effects of factors not primarily related to drug use, such as cost. Comparative persistence, which is a relative measure, is intuitively considered more accurate than absolute measurement (persistence with a drug) since the effect of systematic errors (e.g., exposure and outcome classification biases) is diminished. We have estimated comparative persistence with the TNFα antagonists in RA patients in the Canadian province of British Columbia.

3.2 Objectives and Hypothesis

The goal of the current study was to estimate pairwise comparative persistence with TNFα antagonists infliximab, adalimumab and etanercept in RA patients. The study hypothesis was that variations in pharmacological characteristics of the individual TNFα antagonist drugs caused statistically and clinically significant differences in persistence.

3.3 Patients and Methods

3.3.1 Data Source and Study Cohort

We analyzed a cohort of British Columbia residents who received a first course of a TNFα antagonist between March 2001 and December 2008, and had also been diagnosed with RA. Follow-up data were available until December 31, 2009. Patients were identified using four British Columbia Ministry of Health administrative databases: PharmaNet (prescription

dispensing data), Medical service Plan (MSP) registration information (demographic data), MSP Payment Information (fee-for-service payments to physicians and alternative providers), and the Discharge Abstract Database (hospital separations). The databases were linked using a study-unique anonymized identifier. The study protocol was approved by the Clinical Research Ethics Board of the University of British Columbia.

The study cohort was identified based on the algorithm presented in **Appendix B**, Figure 23, page 270. Patients were included based on one or more recorded dispensing claims for infliximab, adalimumab or etanercept between March 2001 and December 31, 2008. The index date was defined as the date of the first dispensing of a TNFα antagonist after a run-in period of at least 36 months of follow up without TNFα antagonist dispensing. RA patients were selected using similar, though not identical, criteria to previous studies in British Columbia RA patients [101-103]. RA patients were identified based on two outpatient visits with a diagnosis code of RA at least 60 days apart, or one hospitalization with a recorded discharge diagnosis of RA in three years prior to the index date. A list of International Classification of Diseases (ICD) codes that were used in the study is presented in **Appendix B**, Table 28, page 271. Diagnostic codes were recorded in the databases for billing purposes and were based on clinical judgment of the care-providing physician. Additionally, patients were required to have continuous provincial MSP coverage three years before the index date. A gap shorter than 30 days was not considered to be an interruption. Patients were excluded if they were previously treated with anakinra, rituximab or abatacept, if sex or date of birth were missing, if they had a concurrent diagnosis of Crohn's disease (based on at least one outpatient or inpatient diagnosis code in the three years preceding the index date), or if they were younger than 18 years old at the index date (to remove patients with juvenile RA).

3.3.2 Exposure and Covariates

The initial TNFα antagonist exposure was identified for each patient based on their pharmacy dispensing records. We limited the analysis to a single exposure categorical variable for each patient.

The choice of a specific TNFα antagonist drug could be associated with disease severity or additional factors that influence drug persistence. Therefore, we also included demographic and clinical status variables in the model to adjust for possible confounding bias. The demographic variables included sex, age and a proxy variable for socio-economic status (the annual deductible for prescription cost, which was based on family annual income [141]). Clinical status variables included the number of inpatient and outpatient encounters in the year prior to initiating treatment, the duration of disease (defined as time from the first recording of diagnostic code of RA in the data to the index) and the presence and severity of comorbidities. We used Quan's ICD-9-CM and ICD-10 coding algorithm for administrative databases [175], excluding rheumatic diseases, to determine the Charlson comorbidity score [176] for each patient in the cohort during the year preceding the index date. We also included three variables for other RA drugs: concomitant methotrexate (MTX) based on at least one dispensing in the 200 days prior to index[19] (1=yes, 0=no) and dispensing of any nonsteroidal anti-inflammatory

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[19] The period was selected based on mean plus two standard deviations of between-dispensing intervals of MTX in the study cohort

drug (NSAID) in the year preceding the index date (1=yes, 0=no). The third variable, the number of previous antirheumatic drugs was based on the dispensing of the following nine drugs within three years prior to the index date: MTX, hydroxychloroquine, sulfasalazine , azathioprine , cyclosporine , minocycline, penicillamine, sodium aurothiomalate, prednisone and intra-articular triamcinolone/methylprednisolone acetate. We included a categorical variable for the calendar year of the index date, which allowed adjustment for possible secular trends in clinical practice [157-160] and late availability of adalimumab. Finally, we included several Bernoulli variables for the 12 highest volume prescribers (physicians who initiated > 70 courses in the study cohort), to adjust for the prescriber propensity for treatment discontinuation. The list of covariates included in the models and their forms are presented in Table 4. The rationale for considering the covariates is presented in **Chapter 2**, Section 2.2.3.3, page 41.

3.3.1 Outcomes

The two outcomes variables were (a) a continuous persistence variable and (b) a binary censor variable. Drug persistence in years was calculated as the difference between the date of drug discontinuation and the index date. Drug discontinuation was ascertained by either switching to another antirheumatic monoclonal antibody or immunosuppressant drug (infliximab, adalimumab, etanercept, anakinra, rituximab, abatacept, certolizumab and golimumab), or elapsing of a drug-free interval of 180 days. A drug-free interval was defined as a period without additional dispensing of the same pharmaceutical component after the days-supply of

Table 4: List of covariates included in the final models

Variable	Period considered in assigning the value of the variable	Description
Demographics		
Sex		Bernoulli, reference=female
Age	Index date	Four mutually exclusive categories: 18-29, 30-69 (reference), 70-79 and ≥F80 years old
Annual deductible for prescription cost	Index date	Six mutually exclusive categories: $0 (reference), 1-500, 501-2250, >2251, other plan, no plan
Clinical status		
The number of previous outpatient encounters	One year preceding the index date	Continuous
The number of previous hospital admissions	One year preceding the index date	Four mutually exclusive categories: none (reference), 1, 2, >2
The presence and severity of comorbidities	One year preceding the index date	Five mutually exclusive categories: Charlson comorbidity score of 0 (reference), 1, 2, 3, >3
RA disease duration	From the beginning of the data until the index date	Four mutually exclusive categories: 0-3 years (reference), 3-8, 8-12, >12
Drug therapies		
Concomitant MTX	200 days preceding the index date	Bernoulli, reference=no
NSAIDs use	One year preceding the index date	Bernoulli, reference=no
The number of previous antirheumatic drugs	Three years preceding the index date	Four mutually exclusive categories: none, 1-2, 3-6 (reference) , >6
Other		
Calendar year at index date	Index date	Eight yearly categories were included for the years 2001-2008 (reference = year 2001).
Prescriber propensity for treatment discontinuation	Index date	12 Bernoulli variables for individual prescribers, reference=low-volume prescribers (<70 courses in the study cohort)

the latest dispensing was exhausted (Chapter 2, Figure 5, page 22). The date of drug

discontinuation was set to the end of days-supply or the date of the first dispensing of a

different antirheumatic monoclonal antibody or immunosuppressant drug, whichever was

earliest. Patients were considered censored if they were continuously treated with the first

TNFα antagonist on December 31, 2009 (end of follow-up period) or if they discontinued the

drug during an interruption of more than six days in the provincial MSP coverage. Death and

emigration from the province are the most common causes of interruptions in the provincial

MSP coverage. For details on assigning the values of the outcome variables refer to Appendix

B, Figure 24, page 271.

Original data on the number of days-supply recorded in PharmaNet were unreliable (**Chapter
2**, Section 2.2.4.1, page 47); hence we also calculated the expected number of days-supply

based on estimated vials dispensed, which was imputed using the cost field in the dispensing

record (**Chapter 2**, Figure 6, Figure 7 and Figure 8, from page 49). We used the longest

duration of days-supply, recorded or calculated, to determine both the length of drug-free

interval and the date of drug discontinuation. For discussion on calculating the number of days-

supply refer to **Chapter 2**, Section 2.2.4.1, page 47.

3.3.2 Statistical Methods

Summary statistics of baseline characteristics were compiled across the three drug groups. We

assumed normality of the continuous variables compatible with large sample size (>2500) and

the central limit theorem. The significance of differences between the drug groups was

assessed with one-way analysis of variance (ANOVA) F-test for continuous variables and the Pearson's Chi-square test for categorical variables. All statistical tests were two-sided.

The product-limit method and the log rank test were used to estimate and compare levels of drug persistence. Pairwise comparisons between the three drug groups were planned *a priori* but were considered only when the overall comparison indicated a significant difference between TNFα antagonists (a two-tailed p-value < 0.05). The crude and adjusted hazard ratios for drug discontinuation were estimated using Cox proportional hazards regression. Three pairwise comparisons were presented: infliximab versus adalimumab, infliximab versus etanercept and adalimumab versus etanercept. Drug-sex and drug-age interactions were examined but were included in the final model only if the overall significance was < 0.1. The proportional hazards assumption was assessed by testing for the significance of interactions between the variables and time or the natural logarithm of time, as well as by plotting the scaled Schoenfeld residuals [177]. The validity of the linearity assumption of continuous variables was assessed by log likelihood tests comparing models that included either categorical variable or polynomial variables. If nonlinearity was detected, the variable was categorized.

We also presented the adjusted hazard ratios for all variables included in the model. In addition, the confounding effect was presented for covariates that increased or decreased the crude adjusted hazard ratios (or their 95% confidence limits) by at least five percentages. All calculations were performed using the SAS software package [178].

3.4 Results

Between March 2001 and December 2009, a total of 7,212 British Columbia residents were
treated with TNFα antagonists. The study cohort included 2,923 RA patients who initiated
TNFα antagonists by December 31, 2008 and met all selection criteria. Of those, 2104 (72%)
were females and age ranged from 18-92 years (mean± standard deviation [SD], 55.9±13.6
years). Patients treated with adalimumab were older and had more previous hospital
admissions and lower prevalence of concomitant MTX and dispensing claims of NSAIDs
compared to patients on infliximab and etanercept. The baseline characteristics across the three
drug groups are presented in Table 5.

3.4.1 Comparative Persistence With TNFα Antagonists

The Kaplan Meier curves for persistence are presented in Figure 10, page 67. The median
persistence with infliximab was 3.68 years (95% confidence interval (CI) 2.88-4.95), with
adalimumab – 3.33 (95% CI 2.63-4.10) and with etanercept 3.78 (3.31-4.32). Insignificant
differences in persistence were demonstrated between the three individual drugs (log rank test
p-value of 0.23). In the multivariable analysis, the estimated adjusted hazard ratios were
comparable for the three TNFα antagonists' contrasts (Table 6, page 68). Drug-sex or drug-age
interactions were not significant.

Table 5: Baseline characteristics

Variable	All patients (N=2923)	Infliximab (N=620, 21%)	Adalimumab (N=474, 16%)	Etanercept (N=1829, 63%)	P-value for comparison
Females, n (%)	2104 (72%)	438 (71%)	344 (73%)	1322 (72%)	NSS
Age at index (years) median (range)	56 (18-92)	56 (18-87)	58 (22-91)	56 (18-92)	0.002[20]
Annual deductible for prescription cost n (%)					
None	345 (12%)	49 (8%)	83 (18%)	213 (12%)	<0.0001
$1-500	252 (9%)	34 (5%)	56 (12%)	162 (9%)	0.001
$501-2250	570 (19%)	96 (15%)	118 (25%)	356 (19%)	0.0005
>$2250	255 (9%)	40 (6%)	46 (10%)	169 (9%)	NSS
The number of previous outpatient encounters median (range)	32 (2-158)	33 (3-158)	31 (2-112)	32 (3-136)	NSS
The number of previous hospital admissions median (range)	0 (0-8)	0 (0-6)	0 (0-5)	0 (0-8)	0.01[21]
The presence and severity of comorbidities (Charlson comorbidity score) median (range)	0 (0-8)	0 (0-6)	0 (0-8)	0 (0-7)	NSS

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[20] Infliximab versus adalimumab p=0.0007; adalimumab versus etanercept p=0.0023

[21] Infliximab versus adalimumab 0.0115; adalimumab versus etanercept 0.0025

Variable	All patients (N=2923)	Infliximab (N=620, 21%)	Adalimumab (N=474, 16%)	Etanercept (N=1829, 63%)	P-value for comparison
RA disease duration (years) median (range)	8.3 (0-17.9)	9.1 (0.1-17.9)	7.7 (0.3-17.9)	8.2 (0-17.8)	NSS
Concomitant MTX n (%)	1596 (55%)	417 (67%)	277 (59%)	902 (49%)	< 0.0001[22]
Dispensing claims of NSAIDs n (%)	1539 (53%)	332 (54%)	224 (47%)	983 (54%)	0.0367
The number of previous synthetic antirheumatic drugs median (range)	4 (0-9)	4 (0-8)	4 (0-8)	4 (0-9)	NSS
Calendar year at index date median (range)	2005 (2001-2008)	2003 (2001-2008)	2007 (2004-2008)	2005 (2001-2008)	< 0.0001[23]

%- percent; **$**-Canadian dollars; **MTX**-methotrexate; **N**- number of patients in this drug group; **n**-number of patients; **NSAID**- nonsteroidal anti-inflammatory drug; **NSS** – not statistically significant

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[22] Infliximab versus adalimumab p-value= 0.0027; infliximab versus etanercept <0.0001; adalimumab versus etanercept 0.0004

[23] Adalimumab versus etanercept p-value=0.01

Figure 10: Drug persistence curves

	No. of Subjects	Event	Censored	Median Survival(95% Ci)	
Adalimumab	474	46% (219)	54% (255)	3.33 (2.63	4.10)
Etanercept	1829	52% (960)	48% (869)	3.78 (3.31	4.32)
Infliximab	620	53% (328)	47% (292)	3.68 (2.88	4.95)
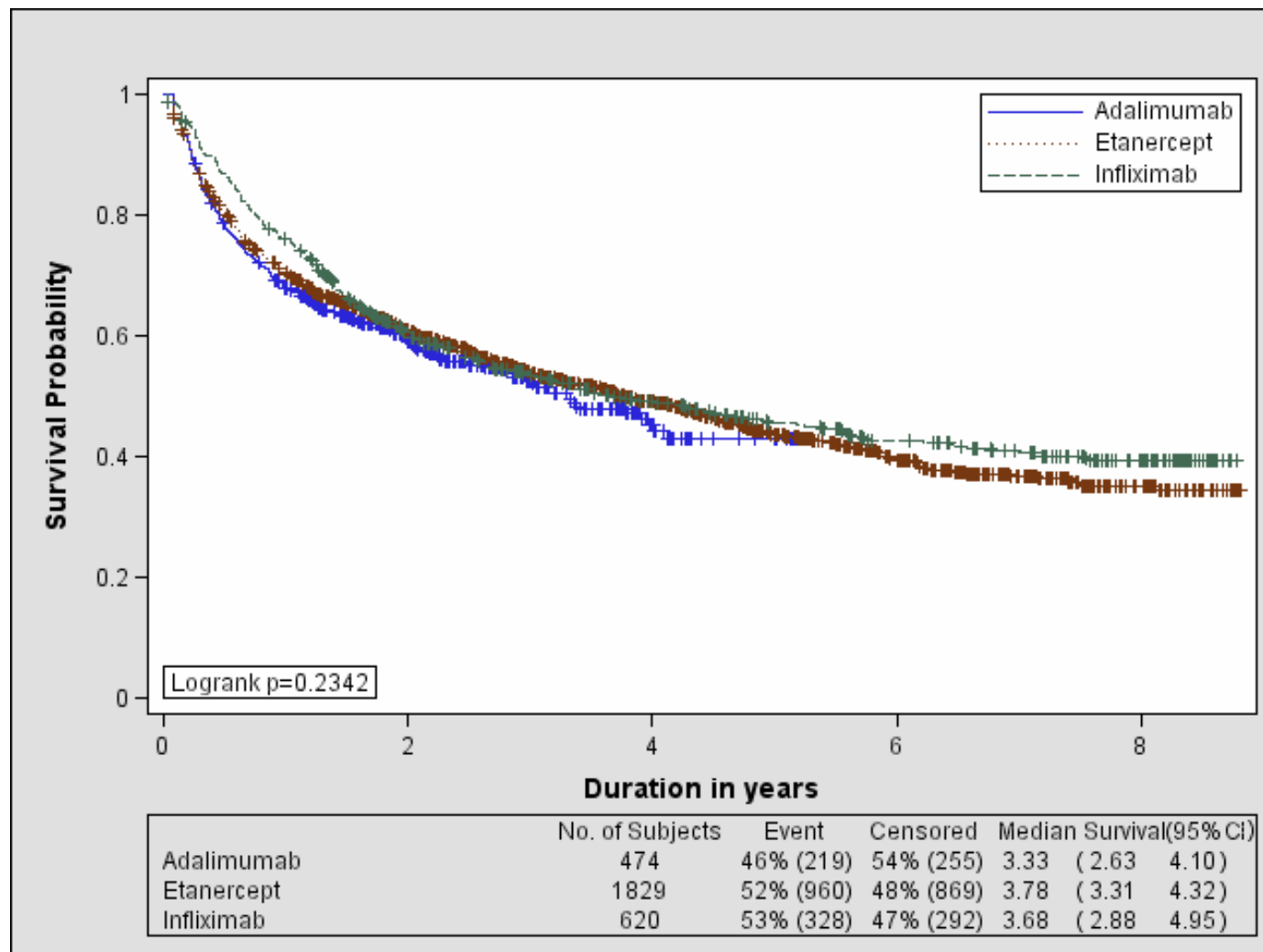
Table 6: Hazard ratios for discontinuing TNFα antagonists

	Crude hazard ratio (95% CI), p-value	Adjusted hazard ratio (95% CI), p-value
Infliximab versus etanercept	0.92 (0.81-1.04), p=0.19	0.98 (0.85-1.13), 0.76
Infliximab versus adalimumab	0.87 (0.73-1.03), p=0.10	0.95 (0.78-1.15), 0.57
Adalimumab versus etanercept	1.06 (0.92-1.23), p=0.42	1.04 (0.88-1.22), 0.68

CI – confidence interval

3.4.2 Predictors of Drug Discontinuation

Female sex and younger or older age (<30 years or > 70 years) were predictors of discontinuing the TNFα antagonists (Table 7), while the deductible cost had no effect on the risk for discontinuation. The hazard for discontinuation was increased in patients with admission to hospital in the year preceding the index date, but the number of outpatient encounters, comorbidity and disease duration had no effect. Concomitant MTX, dispensing claims of NSAIDs and smaller number of previous synthetic antirheumatic drugs (<7) were all associated with decreased hazard for discontinuation. Lastly, prescriber propensities to treatment discontinuation were significantly associated with the hazard for discontinuation.

Table 7: Statistical significance of covariates

Variable	P value (chi-square log likelihood test)[24]	Category	Hazard ratio (95% CI), p-value for type 3 Wald chi-square statistic
Sex (reference female)			0.76 (0.68-0.86), <0.0001
Age (reference 30-70 years)	<0.0001	18-29 years	1.53 (1.20-1.96), 0.0007
		70-79 years	1.32 (1.14-1.54), 0.0003
		≥80 years	1.83 (1.39- 2.41), <0.0001
Annual deductible for prescription cost (reference $0)	0.80	$1-500	0.94 (0.74-1.18)
		$501-2250	1.01 (0.83-1.23)
		>$2250	0.87 (0.67-1.12)
		No plan	1.00 (0.82-1.22)
		Other plan (not income-based)	1.02 (0.83-1.25)
The number of previous outpatient encounters		Increase of one encounter	1.003 (1.000-1.006), 0.051
The number of previous hospital admissions (reference 0)	0.006	1 admission	1.26 (1.09-1.47), 0.003
		2 admissions	1.10 (0.86-1.42)
		>2 admissions	1.51 (1.09-2.10), 0.02
The presence and severity of comorbidities (reference Charlson comorbidity score of 0)	0.23	Score of 1	1.01 (0.87-1.17)
		Score of 2	1.12 (0.89-1.42)
		Score of 3	1.24 (0.86-1.79)
		Score >3	0.62 (0.35-1.10)
RA disease duration (reference 8-12 years)	0.07	0-2 years	1.19 (0.997-1.43)
		2-4 years	1.08 (0.91-1.30)
		4-8 years	0.94 (0.81-1.10)
		>12 years	0.95 (0.80-1.11)

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[24] For categorical variables with more than two categories

Variable	P value (chi-square log likelihood test)[24]	Category	Hazard ratio (95% CI), p-value for type 3 Wald chi-square statistic
Concomitant MTX (reference no)		Yes	0.79 (0.71-0.88), <0.0001
Dispensing claims of NSAIDs (reference no)		Yes	0.89 (0.80-0.99), 0.03
The number previous synthetic antirheumatic drugs (reference 3-6 drugs)	0.03	None	1.38 (0.99-1.92)
		1-2 drugs	1.04 (0.90-1.20)
		7-9 drugs	1.40 (1.09-1.81), 0.009
Calendar year at index date (reference 2005)	0.08	2001	0.79 (0.63-0.997), 0.047
		2002	0.78 (0.62-0.97), 0.03
		2003	0.71 (0.57-0.88)
		2004	0.84 (0.70-1.02)
		2006	0.89 (0.73-1.08)
		2007	0.84 (0.69-1.03)
		2008	0.76 (0.60-0.96), 0.02
Prescriber propensity for treatment discontinuation[25] (reference prescribers with <70 courses)	<0.0001	Prescriber	0.57 (0.42-0.76) , 0.0001
		Prescriber	0.67 (0.47-0.98), 0.04
		Prescriber	1.38 (1.03-1.84), 0.03
		Prescriber	1.57 (1.26-1.96), <0.0001

$- Canadian dollars; **CI**- confidence interval; **MTX**- methotrexate; **NSAIDs**- nonsteroidal anti-inflammatory drugs; **RA**- rheumatoid arthritis

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[25] Only four prescribers with significant hazard ratios are presented

3.4.3 Confounding

Concomitant treatment with MTX had a confounding effect on the hazard ratio of infliximab versus etanercept. Confounding was defined as an increase or decrease of the crude hazard ratios (or their confidence intervals) by at least five percentage points. Prescriber propensity for treatment discontinuation had a confounding effect on hazard ratios of adalimumab (infliximab versus adalimumab and adalimumab versus etanercept). None of the remaining covariates had a large influence on the magnitudes of the estimated hazard ratios (Table 8).

Table 8: Confounding effects

Model	Hazard ratio (95% CI)		
	Infliximab versus etanercept	Infliximab versus adalimumab	Adalimumab versus etanercept
No adjustment	0.92 (0.81-1.04)	0.87 (0.73-1.03)	1.06 (0.92-1.23)
Adjustment for concomitant MTX	0.98 (0.86-1.11)		
Adjustment for prescribers		0.90 (0.76-1.08)	1.01 (0.87-1.17)

Data is presented for covariates that changed the magnitude of point estimate (or confidence limits) of the hazard ratios by at least 5% only

MTX- methotrexate

3.5 Discussion

3.5.1 Similar Persistence With Infliximab, Adalimumab and Etanercept

The hypothesis that different TNFα antagonists have different persistence in RA patients was not supported by the results of an analysis of British Columbia data. There are several explanations for the finding that treatment with infliximab, adalimumab and etanercept were associated with similar persistence in RA patients. One explanation is that drug persistence is not an accurate measure of benefit-harm balance, due to two reasons. First, while most RA patients discontinue TNFα antagonists for lack of benefit or perceived harm (**Appendix A**, Section 0, page 255), they also discontinue for a variety of other reasons such as remission [170,179], planned pregnancy [108,170,180], financial constraint [68] and patient or prescriber preference for subcutaneous administered drugs [181]. Imbalance between the drug groups with regard to any of these reasons could introduce bias. For example, discontinuation due to preference for subcutaneous administered drugs was applicable only for patients who were treated with infliximab. As a result, infliximab discontinuation in these patients was not associated with impaired benefit or increased harm. Second, the intravenous administration of infliximab requires regular physician follow-up that has been shown to encourage adherence and persistence to drug therapy in a variety of diseases [162,182-185]. As a result, persistence with infliximab may not reflect solitarily drug benfit-harm balance. Therefore, in studies comparing persistence with infliximab to the other drugs, persistence may not be a valid measure of differences in benfit-harm balance.

Assuming, however, that persistence is an indirect and valid measure that balances benefit and harm leads to an examination of alternate explanation for the findings. Comparable effectiveness amongst the three TNFα antagonists may result from conflicting effects of the pharmacological characteristics and the route of administration of the three drugs. We demonstrate the conflicting effects using the example of the characteristics of infliximab.

Several pharmacological characteristics of infliximab may decrease its effectiveness or increases its harmful effects compared to etanercept and adalimumab. Higher immunogenicity of infliximab compared to adalimumab and etanercept [186,187] may lead to increased risk of harm, mainly as infusion reaction. Additionally, the steady-state concentration-time profiles of infliximab is less smooth then with the other two drugs, with wide fluctuations in serum concentration [42,188]. This increases the risks of exceeding the maximum tolerated concentration leading to harm, or of reaching suboptimal concentrations leading to lack of therapeutic benefit. Lastly, interferon gamma production is inhibited by infliximab but not etanercept [189] and may result in excessive risk for tuberculosis.

On the other hand, several characteristics may be associated with improved effectiveness with infliximab compared to etanercept

t. First, infliximab can causes apoptosis (cell death) of activated T cells and circulating monocytes [189], which is a potentially desirable property in chronic inflammation. Additionally, etanercept is the only drug that binds to lymphotoxin alpha, with an affinity that is similar or even higher than to soluble TNFα. This may results in unneutralizing the soluble

TNFα [188]. Lymphotoxin alpha was suggested to attenuate the function of TNFα [190] and therefore blocking both lymphotoxin alpha and TNFα activity resulting in higher activity of residual TNFα and decreased benefit.

Comparable persistence with the three drugs was previously demonstrated in studies from Europe [108,113,171] and the United State [72]. Additional studies compared two of the drugs and found similar persistence of infliximab and etanercept [191] or adalimumab and etanercept [61,192]. On the other hand, multiple studies have demonstrated differences in persistence [62,106,110,150,151,161,170,193,194]. An in-depth exploration of the reasons for the differences between the studies was beyond the scope of this study.

Implications Accepting the assumption that drug persistence is a valid indirect measure that integrates both therapeutic benefit and harm, we can infer that the benefit-harm balance of the three TNFα antagonists is comparable. In this case, drug selection should be based on other factors such as patient preference for route of administration and cost. Policy of drug reimbursements plans should be recommended based on costs, availability etc.

Additional Research Discrepancies between published studies in the significance and direction of estimates of comparative persistence with the three TNFα antagonists require further research. Consequently, we conducted a systematic review and meta-analysis designed to pool the estimates and explore possible factors that contribute these discrepancies (unpublished study). In this study, we found substantial between-studies heterogeneity in three pairwise comparisons of persistence with TNFα antagonists. We demonstrated that in the

research published to date, heterogeneity arises mainly from the use of different types of data sources and suggested that it could also arise from the use of different methodological approaches to ascertain discontinuation.

Two main directions of **future research** are proposed. First, based on the abovementioned unpublished systematic review and meta-analysis ,we hypnothesize that the heterogeneity in comparative persistence estimates that was associated with type of data source could be caused by the different methods used in the ascertainment of discontinuation. This hypothesis was examined in **Chapter 4.** Specifically, since we only had access to administrative data, we applied several different algorithms to ascertain discontinuation, and then examined their influence on estimates of comparative persistence. Second, we suggest research to direct support of the association between therapeutic benefit and harm of TNFα antagonists, such as decrease in disease severity during treatment, and following discontinuation. Access to time-series clinical data on changes in disease activity and therapeutic harm would be required.

3.5.2 Possible Confounders

In this analysis of British Columbia data, we demonstrate that including variables for concomitant MTX and prescriber propensity for treatment discontinuation changed the magnitude of the crude hazard ratios (or their confidence interval) by at least five percentages. These factors should therefore be considered to be confounders and be included in future

studies of comparative persistence. The effect of prescriber propensity for treatment

discontinuation was consistently ignored in studies of persistence with TNFα antagonists in

RA and in other clinical situations[26].

We consider several explanations for differences in discontinuation risk in patients treated by

different physicians (prescriber propensity for discontinuation). First, differences in clinical

practice and prescribing habits because of differences in education or adherence to different

guidelines (**Appendix A**, Section A.3.2, page 251) may lead to differences in the likelihood of

discontinuing TNFα antagonists. Second, patients treated by the same prescriber are probably

more similar to each other than patients treated by different prescribers are (correlation). We

discuss analytic methods used to adjust for the risk differences (prescriber propensity for

discontinuation) in **Chapter 5**, Section 5.5.2, page 156.

Implication Studies of persistence with TNFα antagonists in RA patients should, in our

opinion, always include the following variables in the final model, regardless of the predictor

of interest: concomitant MTX and prescribers.

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[26] A recent study of TNFα antagonist discontinuation in RA patients (published after the completion of the thesis research) included clustering by physician to adjust for the possible effect of the individual physician (the degree to which the physician favors discontinuation) [48] . The study is discussed in **Chapter 5**, Section 5.5.1.3, page 3.

Future Research The ways that the prescriber could influence drug persistence require further exploration. Testing for possible correlation between patients treated by the same prescriber could be conducted by comparing the fit of models for clustered data, such as mixed effect or marginal model and models for noncorrelated data. In **Chapter 5**, we present a study conducted to test for the hypothesis that prescriber preference for the prescribed drug influences the persistence.

3.5.3 Strengths and Weaknesses of the Study

One of the main strengths of our population-based study our data source of provincial administrative claims for drugs and medical encounters. The universal nature of the Canadian health care system should have minimized selection bias thus increased the external validity of our results. Access to complete information on all dispensed prescription drugs and multiple sources of data (physician encounters, hospital separation and pharmacies) contributed to the usefulness of the data, and made the cohort an excellent resource for pharmacoepidemiologic research.

The study was characterized by large sample size (N=2923), which provided ample power as well as relatively long durations of follow up in our study patients (roughly nine years from the enrollment of the first patient). Furthermore, the British Columbia Ministry of Health uses a largely systematic and standardized approach to data collection, which ensures the better representativeness of real life treatment patterns and drug-taking behaviour [133] and therefore generalizability [93]. Selection bias should have been minimized because our population-based

cohort included all patients regardless of their disease severity, duration of disease, comorbidities or concomitant treatments [93]. Administrative data do not suffer from recall bias[27] [133]. Analysis of administrative data is also inexpensive, unobtrusive and quick. The results are often referred to as 'signals' that warrant further research using clinical data.

Measurements of drug utilization (persistence and compliance) using administrative data have been validated through patient surveys [168,195,196], medical charts [197], pill counting [168,195] electronic devices [196] and simulation [73]. However, each method has its limitations and a gold standard method to measure persistence and compliance does not exist [198].

This study was designed to minimize the effect of potential sources of bias caused by inaccuracies in data recordings (diagnosis and drug refills), possible confounding effects and possible limited generalizability – all are sources of bias that should be considered in an observational study.

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[27] Recall bias is a "systematic error due to differences in accuracy or completeness of recall to memory of past events or experiences" [1]

3.5.3.1 Inaccuracy of Diagnosis Recording

Disease diagnoses are coded and recorded in British Columbia databases for payment purpose; hence, accuracy might be compromised or biased. There are multiple opportunities for inaccuracies to arise, including misdiagnosis, miscoding of diagnosis[28] and undercoding (failure to record complete information), especially of secondary diagnoses - all these sources of bias may be random or systematic. In addition, differences in accuracy of codes between the care-providers (e.g., different physicians) and variation in coding precision in different diseases are to be expected. To minimize the effect of these sources of inaccuracy, we designed a disease algorithm requires at least two outpatient encounters with RA diagnosis (**Chapter 2**, Section 2.2.2, page 35).

3.5.3.2 Diagnostic Shift

 Diagnosis shift is a change in the frequency of the diagnosis coding without actual change in the disease frequency, and can be caused by change in clinical practice, payer guidelines or in coding systems. Coding shifts have been demonstrated in several diseases [199-206], but not in RA or other rheumatologic diseases and

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[28] The ICD-9 and ICD-10 coding systems do not provide diagnostic criteria to diseases, nor do these systems enforce the use of specific diagnostic criteria. Social, psychological and functional aspects of the health status are often not captured by the coding system [480]. In addition, in some clinical situation several codes may be appropriate and the coding may be motivated by preference of the payer [92]

therefore we did not consider it a possible source of bias. Additionally, we included a categorical variable to adjust for the calends year of treatment initiation, that could adjust for diagnostic shift, if exists.

3.5.3.3 Drug Exposure

In analysis of administrative data, dispensing or claim data is used as proxies to drug use. Several sources of inaccuracy should be considered.

1. **Miscoding** of the drug itself, strength, dose and dispensed days-supply would influence the ascertainment of drug exposure as well as the estimate of persistence.

2. **Inaccuracy in dispensed days-supply** - The number of days-supply recorded is used to ascertain drug use, as well as drug discontinuation. Generally, the number of days-supply reported by the pharmacists should be validated, especially when an intermittent dosing schedule is in use. Systematic errors in recording days-supply might be as a result of the refill policy of the drug-coverage plan, different interpretations of days-supply (**Chapter 2**, Section 2.2.4.1, page 47), dose titration, unknown actual use, and drugs used only as needed [93]. In this analysis using British Columbia data, we found that diverse approaches were used by pharmacists to record days-supply; hence calculation of actual days-supply was required (**Chapter 2**, Section 2.2.4.1, page 47). By using a conservative estimate of days-supply (the longest among several possible approaches to estimations), we might have underestimated the actual length of drug-free intervals and therefore underestimated the

number of patients defined as discontinuers. It is possible that inaccuracies in the calculated number of days-supply biased the ascertainment of

drug discontinuation. Nevertheless, since the data for the three drugs were treated similarly, we believe that the hazard ratios were not systematically biased in this regard.

We calculated the actual number of days-supply based on dispensing cost. We regarded cost the most accurate data, because it was necessary for billing and payment processes. Estimation of days-supply for patients treated with infliximab was especially challenging. Since infliximab dosing is based on weight [207] and the patient weight was inaccessible, we used an algorithm based on number of vials and assumption of weight < 70 Kg. This could lead to overestimation of days-supply in heavier patients. Consequently, the persistence with infliximab was potentially overestimated, which could bias the estimates of comparative persistence of infliximab versus adalimumab or etanercept.

3. **Dose adjustment** influences both the calculated number of days-supply and the date of drug discontinuation but may be challenging to ascertain. Two analyses of administrative databases [62,72] previously evaluated the frequency of dose escalation in RA patients treated with TNFα antagonist, but in these studies days-supply recordings were regarded as accurate and were not modified as in our analysis. Based on our data and the requirement to estimate days-supply based on cost, we could not identify patients with dose adjustment. Therefore, we may have overestimated the calculated days-supply for patients who experienced dose escalation (**Chapter 2**, Section 2.2.4.2, page 52). Dose escalating has been found to be more common in patients treated with infliximab (**Appendix A**, Section A.3.6.2, page 265), and therefore the estimated comparative persistence of infliximab

versus adalimumab or etanercept were possibly biased toward overestimated persistence with infliximab. Further discussion is presented in **Chapter 2**, Section 2.2.4.2, page 52.

4. **Absent data on free samples and in-hospital drugs** may cause selection bias, as not all patients treated are included, especially those with shorter persistence, and also lead to an underestimate of persistence in included patients.

5. Even if dispensing data is accurate, though filling a prescription is generally regarded as an indication of the patients willingness to persist, there is no certainty that a filled prescription means the drug was actually administered [208]. As a result, drug persistence may be overestimated.

3.5.3.4 Outcome Misclassification

We used a long drug-free interval to ascertain discontinuation; this design minimized outcome misclassification (i.e. persistent patients are considered discontinuers). A long drug-free interval minimized the number of patients considered discontinuers for a temporary interruption in persistence. We claim that temporary interruptions should be considered noncompliance, not discontinuation. By using short drug-free intervals, previous studies captured a complex measure of both persistence and compliance and therefore the end point in these studies should be considered nonpersistence and not discontinuation [77]. Further discussion is presented in **Chapter 2**, Section 2.1.2.4, page 21 and **Chapter 4**, Section 4.5.1, page109.

3.5.3.5 Confounding

We designed the study to address potential confounding, especially confounding by indication and/or severity – a major concern in a non-randomized observational study. To diminish possible confounding, a threat to internal validity, we used multivariable regression methods. To adjust to possible differences in disease activity, we used the following proxies in multivariable regression: (a) sex (RA is more severe in females [137]), (b) the number of previous outpatient encounters and the number of previous hospital admissions, (c) disease duration, (d) dispensing records of NSAIDs (as a proxy for pain) [29] and (e) number of previous synthetic antirheumatic drugs the patient was exposed to[29]. Further discussion on confounding is presented in **Chapter 2**, Section 2.2.3.3, page 41. In this study, we identified imbalances between the drug groups with regard to age distribution, annual deductible for prescription costs, the number of previous hospital admissions, concomitant MTX, dispensing claims for NSAIDs and calendar year at index. We found that age, the number of previous hospital admissions, concomitant MTX and dispensing claims for NSAIDs were also predictors of persistence and therefore were likely to confound the results.

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[29] Dispensing records of NSAID and number of previous antirheumatic drugs were identified in data fron the year preceding treatment initiation.

3.5.3.6 Absence of Clinical Data

The study was designed to compensate to the absence of access to clinical data by using proxy measures for drug exposure and clinical variables (discussed above). In addition, while persistence in years and the rate of discontinuation could be estimated, the reasons for discontinuations, specifically the contribution of decreased benefit or perceived harm cannot be determined using data from administrative databases. However, since most guidelines recommend at least three months of treatment with TNFα antagonists before ascertainment of lack of benefit, a reasonable assumption is that discontinuation within the first three months of treatment was caused by harmful events.

3.5.3.7 Generalizability

Threats to generalizability could potentially be caused by coverage exemptions - First Nation and federal employee data was absent from the British Columbia data available to us. In addition, patients who left the province would be lost to follow up and this could potentially affect the outcome estimate.

This study is characterized by population-based data and a study design that attempted to minimize the effect of multiple sources of bias. Therefore the estimates of comparative persistence are of high quality and be easily generalized.

3.6 Conclusions

☐ The study results indicate that persistence with infliximab, adalimumab and etanercept is similar in RA patients. Accepting the assumption that persistence accurately reflects the benfit-harm balance of the therpy, the drugs' benefit-harm balance could be considered equivalent. Accordingly, clinical and policy decisions for treatment with TNFα antagonist should be based on convenience and cost.

☐ The study was designed to minimize the effect of multiple possible sources of bias. Among other features, we used a disease algorithm with a high degree of specificity, ascertained discontinuation using a long drug-free interval, corrected recorded days-supply to minimize outcome misclassification; and adjusted for multiple possible confounders, including prescriber propensity for treatment discontinuation.

☐ Enforcement of an improved and uniform policy for recording days-supply in the British Columbia PharmaNet would improve the accuracy of measurements of drug persistence.

CHAPTER 4: SENSITIVITY OF COMPARATIVE PERSISTENCE ESTIMATES TO THE METHODS USED TO ASCERTAIN DISCONTINUATION

4.1 Background

We study comparative persistence with tumour necrosis factor alpha (TNFα) antagonists in patients with rheumatoid arthritis (RA). Comparative drug persistence was suggested as an indirect measure with which to compare overall benefit-harm balance of competing drugs in patients with noncurable diseases [45]. This measurement approach is based on the assumption that a drug is continued in these patients provided that it has therapeutic benefit and only mild harmful effects that the benefit overweights [45,209]. Knowledge on the relative benfit-harm balance of the three TNFα antagonists – infliximab, adalimumab and etanercept – is limited due to the absence of head-to-head RCTs and unrepresentativeness of RCT participants (**Appendix A**, Section A.3.1, page 241 [210-212]). Studies have shown that the therapeutic benefit of TNFα antagonists is exaggerated in RCTs compared to routine practice as a result of unrepresentativeness of RCT participants (**Appendix A**, Section A.3.1.2, page 246, [210-212]).

Drug persistence can be estimated using clinical data, administrative (claim) data or patient surveys; however, only data from the first two sources were utilized in studies of TNFα antagonists in RA (unpublished original systematic review and meta-analysis [49,50]. In an original unpublished systematic review and meta-analysis of comparative persistence of TNFα antagonists in RA patients, we found heterogeneity in the magnitude, significance and

direction of the results. We identified the type of data source as the main factor that contributes to the heterogeneity, though the type of data source did not explain all the heterogeneity. We suggested that some of the heterogeneity could be attributed to different methods used to ascertain drug discontinuation.

4.2 Study Goals

We theorized that the heterogeneity in reported comparative persistence of TNFα antagonists that we identified was a consequence of the diversity in methods used to ascertain drug discontinuation. To test this hypothesis, we applied a commonly used methical approach to estimate persistence [17,208]. We ascertained drug discontinuation based on an algorithm that included either switching or a drug-free interval (also known as permissible gap) between dispensing events. The study hypothesis is that increasing lengths of the drug-free interval are associated with a significant change in comparative persistence, which manifests as differences in the significance and/or the direction of these estimates. We also explored patterns of reinitiation of the index drug after a drug-free interval of at least 30 days.

4.3 Patients and Methods

4.3.1 Data Source and Study Cohort

We analyzed a cohort of British Columbia residents who received a first course of a TNFα

antagonist between March 2001 and December 2008, and had also been diagnosed with RA.

Follow-up data were available until December 31, 2009. Patients were identified using four

British Columbia Ministry of Health administrative databases: PharmaNet (prescription

dispensing data), Medical Service Plan (MSP) registration information (demographic data),

MSP Payment Information (fee-for-service payments to physicians and alternative providers),

and the Discharge Abstract Database (hospital separations). The databases were linked using a

study-unique anonymized identifier. The study protocol was approved by the Clinical Research

Ethics Board of the University of British Columbia.

The study cohort was identified based on the algorithm presented in **Appendix B**, Figure 23,

page 270. Patients were included based on one or more recorded dispensing claims for

infliximab, adalimumab or etanercept between March 2001 and December 31, 2008. The index

date was defined as the date of the first dispensing event of a TNFα antagonist after a run-in

period of at least 36 months of follow up without TNFα antagonist dispensing.. RA patients

were selected using similar, though not identical, criteria to those used in previous studies of

RA patients in British Columbia [101-103]. RA patients were identified based on two

outpatient visits with diagnosis of RA at least 60 days apart, or one hospitalization with a

recorded discharge diagnosis of RA in three years prior to the index date. A list of International

Classification of Diseases (ICD) codes that were used in the study is presented in **Appendix B**, Table 28, page 271. Diagnostic codes were recorded in the databases for billing purposes and were based on clinical judgment of the care-providing physician. Additionally, patients were required to have continuous provincial MSP coverage three years before the index date. A gap shorter than 30 days was not considered an interruption. Patients were excluded if they were previously treated with anakinra, rituximab or abatacept, if sex or date of birth were missing, if they had a concurrent diagnosis of Crohn's disease (based on at least one outpatient or inpatient diagnosis code in the three years preceding the index date), or if they were younger than 18 years old at the index date (to remove patients with juvenile RA).

4.3.2 Exposure and Covariates

The initial TNFα antagonist ('the index drug') was identified for each patient based on their pharmacy dispensing records. We limited the analysis to a single exposure categorical variable for each patient.

The choice of a specific TNFα antagonist drug could be associated with disease severity or additional factors that influence drug persistence. Therefore, we also included demographic and clinical status variables in the model to adjust for possible confounding bias. The covariate variables are presented in **Chapter 3**, Table 4, page 61. Demographic variables added to the model included sex, age and a proxy variable for socio-economic status (the annual deductible for prescription cost, which was based on family annual income [141]). Clinical status variables included the number of inpatient and outpatient encounters in the year prior to

initiating treatment, the duration of disease (defined as time from the first recording of diagnostic code of RA in the data to the index) and the presence and severity of comorbidities. We used Quan's ICD-9-CM and ICD-10 coding algorithm for administrative databases, excluding rheumatic diseases [175] to determine the Charlson comorbidity score [176] for each patient in the cohort during the year preceding the index date. We also included three variables for other RA drugs: concomitant methotrexate (MTX) based on at least one dispensing in the 200 days prior to index[30] (1=yes, 0=no) and dispensing claims of any nonsteroidal anti-inflammatory drug (NSAID) in the year preceding the index date (1=yes, 0=no). The third variable, the number of previous synthetic antirheumatic drugs and corticosteroids was based on the dispensing of the following nine drugs within three years prior to the index date: MTX, hydroxychloroquine, sulfasalazine, azathioprine, cyclosporine, minocycline, penicillamine, sodium aurothiomalate, prednisone and intra-articular triamcinolone/methylprednisolone acetate. We included a categorical variable for the calendar year of the index date, which allowed adjustment for possible secular trends in clinical practice [157-160] and late availability of adalimumab. Finally, we included several Bernoulli variables for the 12 highest volume prescribers (physicians who initiated > 70 courses in the study cohort), to adjust for prescriber propensity for treatment discontinuation. The rationale for considering the covariates is presented in **Chapter 2**, Section 2.2.3.3, page 41.

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[30] The period was selected based on mean plus two standard deviations of between-dispensing intervals of MTX in the study cohort.

4.3.3 Outcomes

The two outcomes variables were (a) a continuous drug persistence variable and (b) a binary censor variable. Drug persistence in years was calculated as the difference between the date of drug discontinuation and the index date. Drug discontinuation was ascertained by either switching to another antirheumatic monoclonal antibody or immunosuppressant drug (infliximab, adalimumab, etanercept, anakinra, rituximab, abatacept, certolizumab and golimumab), or elapsing of a drug-free interval. A drug-free interval was defined as a period without additional dispensing event of the same pharmaceutical component after the days-supply of the latest dispensing was exhausted (**Chapter 2,** Figure 5, page 22). The date of drug discontinuation was set to the end of days-supply or the date of the first dispensing of a different antirheumatic monoclonal antibody or immunosuppressant drug, whichever was earliest. Patients were considered censored if they were continuously treated with the first TNFα antagonist on December 31, 2009 (end of follow-up period) or when their date of drug discontinuation was during an interruption of more than six days in the provincial MSP coverage. Death and emigration from the province are the most common causes of interruptions in the provincial MSP coverage. For details on assigning the values of the outcome variables refer to **Appendix B**, Figure 24, page 271.

Original data on the number of days-supply recorded in PharmaNet were unreliable (**Chapter 2**, Section 2.2.4.1, page 47); hence, we also calculated the expected number of days-supply based on estimated vials dispensed, which was imputed using the cost field in the dispensing

record. We used the longest duration of days-supply, recorded or calculated, to determine both the length of drug-free interval and the date of drug discontinuation. For discussion on calculating the number of days-supply refer to **Chapter 2**, Section 2.2.4.1, page 47.

4.3.4 Sensitivity Analysis

In multiple analyses, four lengths of drug-free interval were used to ascertain drug discontinuation: 30, 60, 90 or 180 days after the days-supply was exhausted. Lengths of 30-90 days were commonly used to ascertain discontinuation in other studies of comparative persistence of TNFα antagonists in administrative health databases (30 days [61-63,213,214], 60 days [72,107,213,215,216], 90 days [64,213]). We also applied a length of 180 days, which we considered appropriate to identify patients who discontinued drug instead of only experiencing a temporary interruption in drug persistence. A temporary interruption in drug persistence should be interpreted as poor compliance (or nonpersistence) rather than discontinuation [77]. This length of drug-free interval (180 days) has also been used in estimations of comparative persistence using clinical data [113,114,170].

4.3.5 Statistical Methods

Summary statistics of baseline characteristics were compiled across the three drug groups. We assumed normality of the continuous variables compatible with large sample size (>2500) and the central limit theorem. The significance of differences between the drug groups was

assessed with one-way analysis of variance (ANOVA) F-test for continuous variables and the Pearson's Chi-square test for categorical variables. All statistical tests were two-sided.

The product-limit method and the log rank test were used to estimate and compare levels of drug persistence. The results were presented for increasing lengths of drug-free interval. Pairwise comparisons between the three drug groups were planned *a priori* but were considered only when the overall comparison indicated a significant difference (a two-tailed p-value < 0.05) between TNFα antagonists. The crude and adjusted hazard ratios for drug discontinuation were estimated using Cox proportional hazards regression. Three pairwise comparisons were presented: infliximab versus adalimumab, infliximab versus etanercept and adalimumab versus etanercept. Drug-sex and drug-age interactions were examined but were included in the final model only if the overall significance was < 0.1. The proportional hazards assumption was assessed by testing for the significance of interactions between the variables and time or the natural logarithm of time, as well as by plotting the scaled Schoenfeld residuals [177]. The validity of the linearity assumption of continuous variables was assessed by log likelihood tests in models that included either categorical variable or polynomial variables. If nonlinearity was detected, the variable was categorized. All calculations were performed using the SAS software package [178].

4.3.6 Analysis of Reinitiation

We explored patterns of reinitiating the index drug in discontinuers. In these patients, drug discontinuation was ascertained based on an algorithm that included a drug-free interval of 30

days or switching. Reinitiation was ascertained when discontinuers reinitiated the index drug

(before switching to another antirheumatic monoclonal antibody or immunosuppressant drug).

In discontinuers who were followed for at least 60, 90 or 180 days from the date of drug

discontinuation, we then estimated proportions of patients who reinitiated the index drug

within 31-60 days, 31-90 days or 31-180 days, respectively. Chi-square tests were used to

detect statistically significant differences. 'Added persistence' was defined as the time from the

date of discontinuation based on a drug-free interval length of 30 days or switching until the

date of discontinuation based algorithms that included intervals of 60, 90 or 180 days or

switching (Figure 11). The product-limit median quantity of 'added persistence' in patients

who reinitiated treatment was estimated for each drug group.

We considered that the results we obtained in analysis of reinitiation could have been biased in

patients treated with adalimumab because of shorter duration of follow-up attributable to being

the last of the three TNFα antagonists introduced to the Canadian market (about 3.5 years after

infliximab and etanercept). We therefore repeated the analyses of reinitiation in discontinuers,

limiting the analysis to patients with index date between January 2005 and December 2008. At

that time, all three drugs were available.

Figure 11: Calculating "added persistence"

Index date

Date of discontinuation based on a drug-free interval of 30 days

Drug reinitiation

Date of discontinuation based on a drug-free interval of 60/90/180 days

Persistence based on a drug-free interval of 30 days

Duration of interruption

'Added persistence'
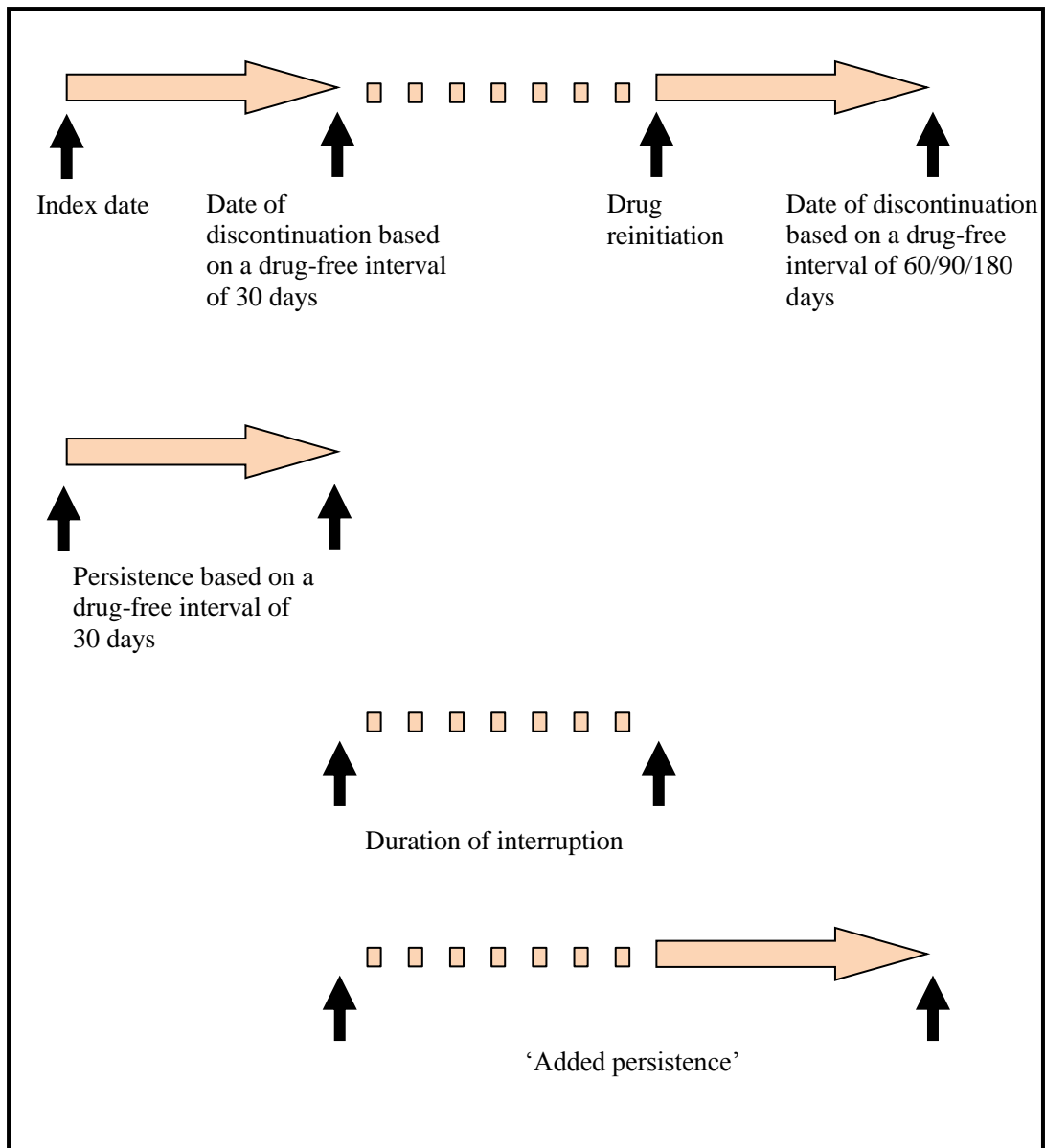
4.4 Results

4.4.1 The Study Cohort and Baseline Characteristics

Between March 2001 and December 2009, a total of 7,212 British Columbia residents were treated with TNFα antagonists. The study cohort included 2,923 RA patients who initiated TNFα antagonists by December 31, 2008 and met all selection criteria (**Chapter 3**, Table 5, page 65); 2,104 (72%) were females and age ranged from 18-92 years (mean±SD, 55.9±13.6 years). Patients treated with adalimumab were older and had more previous hospital admissions and lower frequency of concomitant MTX and dispensing claims of NSAIDs compared to patients on infliximab and etanercept. Baseline characteristics are presented in Table 5, page 65.

4.4.2 Effect of Increased Length of Drug-Free Interval

The product-limit persistence estimates for different discontinuation ascertainment algorithms are presented in Figure 12 and Table 9. As expected, a longer drug-free interval was associated with improved persistence within each TNFα antagonist and an increase in the overall median persistence from 1.13 years to 2.19, 2.87 and 3.70 years, when applying drug-free intervals of 30, 60, 90, and 180 days, respectively. This suggests that some patients had short interruptions in drug persistence after which they reinitiated the index drug. Applying a drug-free interval of 180 days, persistence on the three individual TNFα antagonists was similar. When applying

lengths of 30, 60 or 90 days, infliximab was associated with statistically significant improvements in persistence compared to the other two TNFα antagonists. The persistence curve of patients on adalimumab and etanercept became closer to those on infliximab with increasing of drug-free interval lengths (Figure 12), which suggests that interruptions in drug persistence were more common with adalimumab and etanercept, after which patients reinitiated the index drug.

Similarly, the results of univariate Cox regression demonstrated that the hazard ratios for discontinuation approached 1.0 (Table 10, crude hazard ratios) for longer drug-free intervals. For drug-free intervals of 30, 60 or 90 days, infliximab was associated with a statistically significant lower hazard for drug discontinuation compared to the etanercept and adalimumab, with hazard ratios of 0.66, 0.78 and 0.84 compared to etanercept and 0.71, 0.76 and 0.80 compared to adalimumab (for drug-free intervals of 30, 60 or 90 days, respectively). As with the Kaplan-Meier analysis, applying a drug-free interval of 180 days, the hazards for drug discontinuation with infliximab, adalimumab and etanercept were similar.

Figure 12: Persistence by algorithm to ascertain discontinuation

A. Switching or a drug-free interval of 30 days
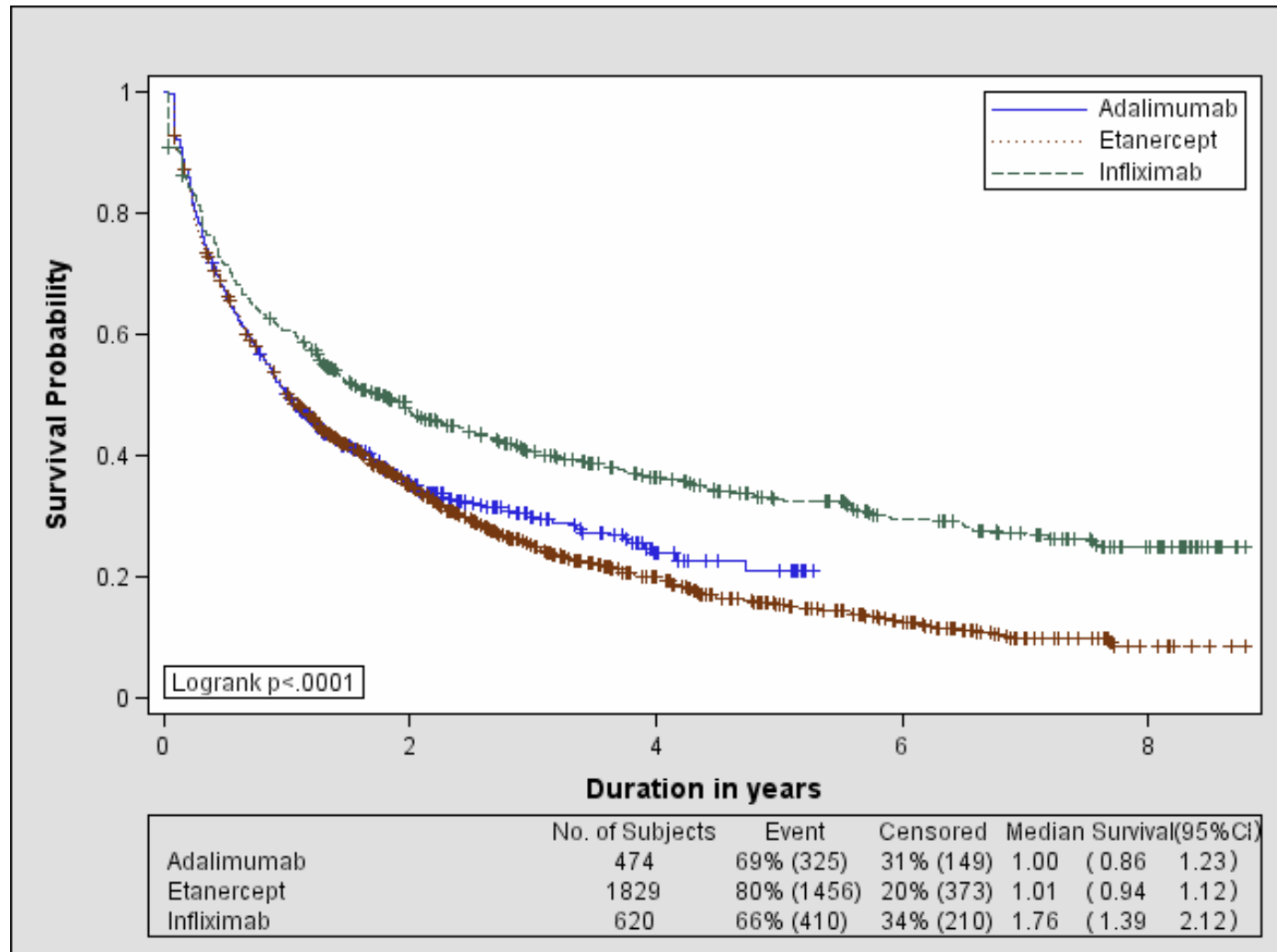
B. Switching or a drug-free interval of 60 days
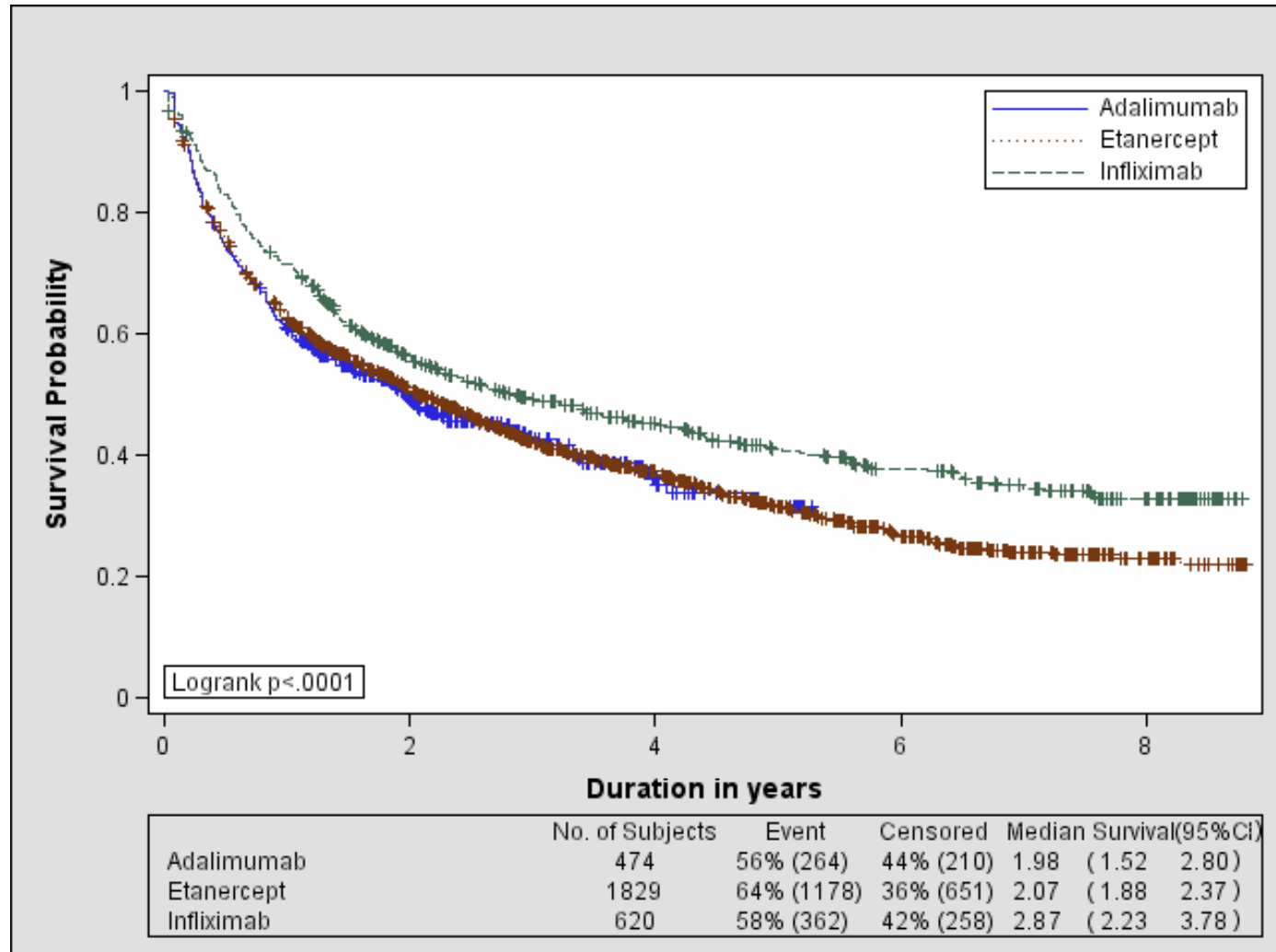
C. Switching or a drug-free interval 90 days

D. Switching or a drug-free interval of 180 days

	No. of Subjects	Event	Censored	Median Survival(95% CI)		
Adalimumab	474	46% (219)	54% (255)	3.33	(2.63	4.10)
Etanercept	1829	52% (960)	48% (869)	3.78	(3.31	4.32)
Infliximab	620	53% (328)	47% (292)	3.68	(2.88	4.95)
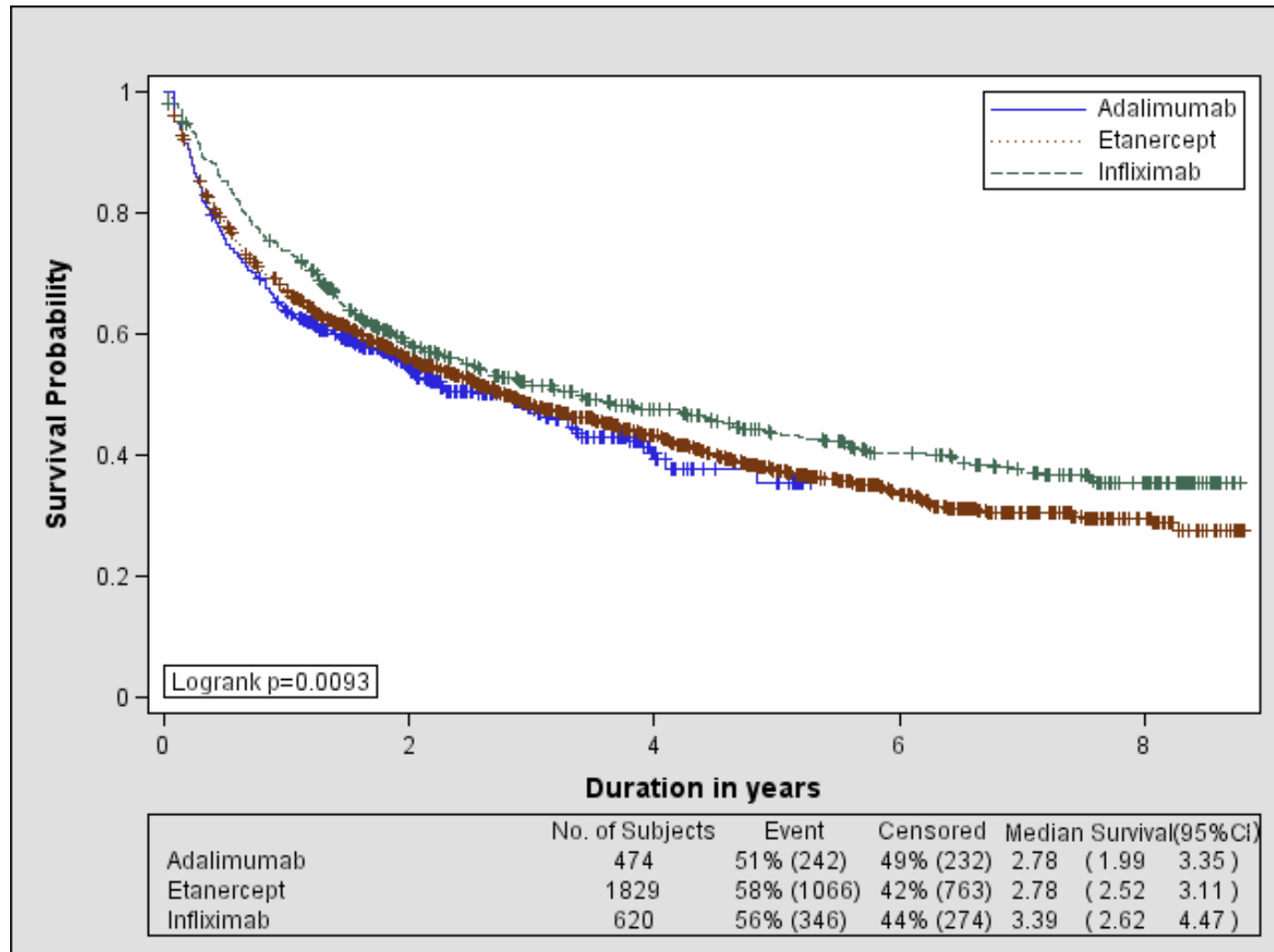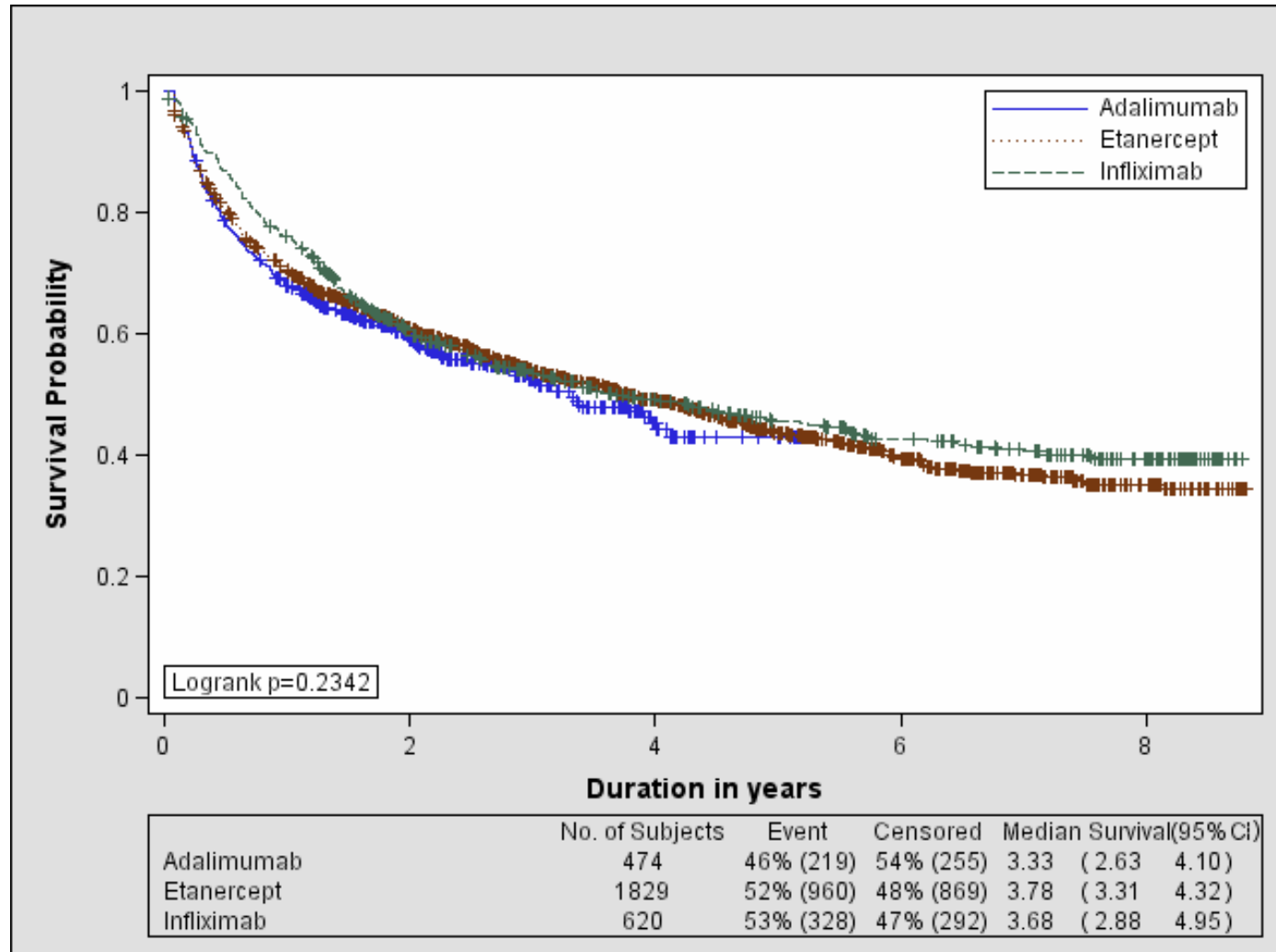
Table 9: Kaplan Meier estimates of persistence for increasing drug-free intervals

Drug	% censored	Median persistence (95% CI)	IQR	1 year	5 years
A drug-free interval of 30 days					
All three	25	1.13 (1.02-1.23)	0.32-3.78	52%	20%
Infliximab	34	1.76 (1.39-2.12)	0.42-7.61	61%	33%
Adalimumab	31	1.00 (0.86-1.23)	0.33-3.90	50%	n/a
Etanercept	20	1.01 (0.94-1.12)	0.31-3.01	50%	15%
Log rank test p-value<0.0001 (infliximab versus etanercept p-value<0.0001, infliximab versus adalimumab p-value=0.0001, adalimumab versus etanercept NSS)					
A drug-free interval of 60 days					
All three	38	2.19 (1.99-2.40)	0.56-n/a	64%	34%
Infliximab	41	2.87 (2.23-3.78)	0.78-n/a	71%	42%
Adalimumab	44	1.98 (1.52-2.80)	0.48-n/a	61%	n/a
Etanercept	36	2.07 (1.88-2.37)	0.52-n/a	63%	31%
Log rank test p-value<0.0001 (infliximab versus etanercept p-value<0.0001, infliximab versus adalimumab p-value=0.002, adalimumab versus etanercept NSS)					
A drug-free interval of 90 days					
All three	43	2.87 (2.57-3.17)	0.64-n/a	68%	39%
Infliximab	44	3.39 (2.62-4.47)	0.92-n/a	74%	43%
Adalimumab	49	2.78 (1.99-3.35)	0.51-n/a	64%	n/a
Etanercept	42	2.78 (2.52-3.11)	0.60-n/a	67%	37%
Log rank test p-value=0.009 (infliximab versus etanercept p-value=0.006, infliximab versus adalimumab p-value=0.01, adalimumab versus etanercept NSS)					
A drug-free interval of 180 days					
All three	48	3.70 (3.32-4.16)	0.76-n/a	71%	44%
Infliximab	47	3.68 (2.88-4.95)	1.06-n/a	76%	45%
Adalimumab	54	3.33 (2.63-4.10)	0.63-n/a	68%	n/a
Etanercept	47	3.78 (3.31-4.32)	0.70-n/a	70%	43%
Log rank test p-value NSS					

Infliximab (n=620), adalimumab (n=474), etanercept (n=1829)

% - percentage; **1-year** - Percentage still on drug one year after the index date; **5-year** - Percentage still on drug five years after the index date; **CI** - confidence interval; **IQR** - intra-quartile range, presented are the point estimates for the 25 and 75 percentiles of persistence; **n/a** - cannot be calculated from available data; **NSS** - not statistically significant (p-value≥0.05)

Adjusting for patient characteristics and other covariates had a significant effect on the estimated hazard ratios when applying a drug-free interval of 90 days. The hazard ratios for infliximab compared to the other TNFα antagonists became insignificant (Table 10). Otherwise, the addition of the other covariates was often associated with hazard ratios that approached the null without a change in the significance. A significant drug-sex interaction was present when comparing infliximab versus etanercept and applying a drug-free interval of 30 days, but not otherwise. No drug-age interaction was significant.

Table 10: Hazard ratios for increasing drug-free intervals

Comparison	Crude hazard ratios (95% CI)		Adjusted hazard ratios (95% CI)	
A drug-free interval of 30 days				
Infliximab versus etanercept	0.66 (0.59-0.74)	p<0.0001	Males 0.51 (0.41-0.64)	p<0.0001
			Females 0.74 (0.65-0.85)	p<0.0001
Infliximab versus adalimumab	0.71 (0.62-0.83)	p<0.0001	0.70 (0.60-0.83)	p<0.0001
Adalimumab versus etanercept	0.93 (0.82-1.05)	p=0.21	0.96 (0.84-1.10)	p=0.56
A drug-free interval of 60 days				
Infliximab versus etanercept	0.78 (0.69-0.87)	p<0.0001	0.82 (0.72-0.93)	p=0.003
Infliximab versus adalimumab	0.76 (0.65-0.90)	p=0.001	0.82 (0.69-0.98)	p=0.03
Adalimumab versus etanercept	1.02 (0.89-1.16)	p=0.83	0.99 (0.86-1.15)	p=0.92
A drug-free interval of 90 days				
Infliximab versus etanercept	0.84 (0.75-0.95)	p=0.006	0.89 (0.78-1.02)	p=0.09
Infliximab versus adalimumab	0.80 (0.68-0.94)	p=0.008	0.86 (0.72-1.04)	p=0.12
Adalimumab versus etanercept	1.06 (0.92-1.22)	p=0.45	1.03 (0.88-1.20)	p=0.70
A drug-free interval of 180 days				
Infliximab versus etanercept	0.92 (0.81-1.04)	p=0.19	0.98 (0.85-1.13)	p=0.76
Infliximab versus adalimumab	0.87 (0.73-1.03)	p=0.42	0.95 (0.78-1.15)	p=0.57
Adalimumab versus etanercept	1.06 (0.92-1.23)	p=0.10	1.04 (0.88-1.22)	p=0.68

CI- confidence interval; **p** – p-value (Cox regression)

4.4.3 Analysis of Reinitiation

There were 2,167 discontinuers who were followed for at least 60 days, including 2,153 for at least 90 days and 2,097 for at least 180 days from the date of discontinuation (Table **11**). A larger proportion of patients reinitiated etanercept within 60, 90 and 180 days after the beginning of an interruption of 30 days or longer in drug persistence compared to infliximab and adalimumab. This may suggest better compliance with infliximab, manifested as less short interruptions in drug treatment, compared to etanercept. The quantity of 'added persistence' was similar across the three drug groups, but it was proportionally smaller with infliximab, because infliximab was associated with longer persistence when applying the algorithm with a 30-day drug-free interval. No differences were observed in drug reinitiation patterns between infliximab and adalimumab.

Next, we established a sub-cohort of patients with index dates between January 2005 and December 2008. We first compared drug persistence using nonparametric survival analysis and found the comparative persistence sensitive to the length of drug-free interval (**Appendix C**, Figure 25, page 276). A significant difference in persistence between drugs was demonstrated when applying drug-free intervals of 30 and 60-day (log rank test p-value <0.0001 and 0.03 respectively) but not when applying 90 or 180-day lengths. This supports the robustness of the results presented in Section 4.4.2, page 96. We repeated the analyses to explore patterns of reinitiation. A significantly larger portion of adalimumab and etanercept discontinuers reinitiated the index drug compared to infliximab (Table 12). Again, no significant difference was observed with the quantity of 'added persistence', except when applying the 180 days interval in ascertainment of discontinuation.

Table 11: Analysis of patients reinitiating the same drug (treatment initiated 2001-2008)

Drug	N	Number of patients who reinitiated the index drug (%)	'Added persistence' median (95% CI)
Returned within 31-60 days after discontinuation			
Infliximab	404	108 (26.7)	2.91 (1.70-4.67)
Adalimumab	319	101 (31.7)	1.83 (1.52-3.01)
Etanercept	1446	605 (41.8)	2.35 (1.93-2.88)
Testing for homogeneity of the three drug groups		(Chi-square) three drugs p<0.0001; Infliximab vs. etanercept p<0.0001; Infliximab vs. adalimumab NSS; Adalimumab vs. etanercept p=0.0008	(log rank test) NSS
Returned within 31-90 days after discontinuation			
Infliximab	400	137 (34.3)	3.23 (2.19-4.67)
Adalimumab	315	119 (37.8)	2.64 (2.13-n/a)
Etanercept	1437	709 (49.3)	3.39 (2.79-4.01)
Testing for homogeneity of the three drug groups		3 drugs p<0.0001; Infliximab vs. etanercept p<0.0001; Infliximab vs. adalimumab NSS; Adalimumab vs. etanercept p=0.0002	NSS
Returned within 31-180 days after discontinuation			
Infliximab	390	146 (37.4)	1.30 (2.78-n/a)
Adalimumab	302	131 (43.4)	3.44 (2.34-n/a)
Etanercept	1405	771 (54.9)	5.23 (4.30-6.40)
Testing for homogeneity of the three drug groups		3 drugs p<0.0001; Infliximab vs. etanercept p<0.0001; Infliximab vs. adalimumab NSS; Adalimumab vs. etanercept p<0.0003	NSS

N - number of patients who discontinued the drug based on a drug-free interval of 30 days or switching; n/a – cannot be estimated from available data; NSS – not statistically significant (p-value ≤0.05); p – p-value; vs.- versus

Table 12: Analysis of patients reinitiating the same drug (treatment initiated 2005-2008)

Drug	N	Number of patients who reinitiated the index drug (%)	'Added persistence' median (95% CI)
Returned within 31-60 days after discontinuation			
Infliximab	125	25 (20.0)	1.79 (1.06-n/a)
Adalimumab	286	92 (32.2)	2.14 (1.72-n/a)
Etanercept	656	241 (36.7)	2.30 (1.74-n/a)
Testing for homogeneity of the three drug groups		(Chi-square) three drugs p=0.001; Infliximab vs. etanercept p=0.0003; Infliximab vs. adalimumab p=0.01; Adalimumab vs. etanercept NSS	(log rank test) NSS
Returned within 31-90 days after discontinuation			
Infliximab	121	34 (28.1)	1.79 (1.10-3.24)
Adalimumab	282	108 (38.3)	3.44 (2.14-n/a)
Etanercept	650	291 (44.8)	3.55 (2.65-n/a)
Testing for homogeneity of the three drug groups		3 drugs p=0.002; Infliximab vs. etanercept p=0.0005; Infliximab vs. adalimumab p=0.05; Adalimumab vs. etanercept NSS	NSS
Returned within 31-180 days after discontinuation			
Infliximab	115	34 (29.6)	1.99 (1.18-n/a)
Adalimumab	269	117 (43.5)	3.44 (2.16-n/a)
Etanercept	630	314 (49.9)	n/a (n/a)
Testing for homogeneity of the three drug groups		3 drugs p=0.0002; Infliximab vs. etanercept p<0.0001; Infliximab vs. adalimumab p=0.01; Adalimumab vs. etanercept NSS	0.03

%- percentage; **N** - number of patients who discontinued the drug based on a drug-free interval of 30 days or switching; **n/a** - cannot be estimated from available data; **NSS** - not statistically significant (p-value ≤0.05); **p** - p-value; **vs.**- versus

4.4.4 Effect of Covariates

Sex, age, the number of previous hospital admissions, prescriber propensity for treatment discontinuation and concomitant of MTX were all significantly associated with TNFα antagonist persistence. Females, the extremes of age range (<30 or >70 years old) and increased number of admissions were associated with increased risk of drug discontinuation. Concomitant MTX was associated with improved persistence. Comorbidities and disease duration had no effect on drug persistence in analyses of all four drug-free interval lengths. However, the significance of the association of the remaining variables with persistence (the calendar year of index date, the number of visits, the annual deductible level, dispensing claims for NSAIDs and the number of previous synthetic antirheumatic drugs and corticosteroids) was sensitive to the drug-free interval length.

4.5 Discussion

Our results support the study hypothesis that the heterogeneity in reported comparative persistence of TNFα antagonists was caused by the use of different algorithms to ascertain drug discontinuation. In this study, we evaluated the effect of a drug-free interval, which is a common end-point in algorithms to ascertain drug discontinuation in analyses of administrative data. The length of drug-free interval used in an algorithm, which is an exogenous factor chosen by the investigator, was an important factor affecting both the magnitude and the statistical significance of the hazard ratios for discontinuation of TNFα antagonists in patients with RA.

4.5.1 Ascertainment of Drug Discontinuation

Ascertainment of discontinuation is critical in studies measuring drug persistence, because persistence is measured as time to discontinuation of a given drug. Yet investigators using clinical data have typically not reported the method used in ascertainment of drug discontinuation in studies of persistence with TNFα antagonists in RA patients. Instead, ambiguous descriptions have been provided, such as "The date of drug discontinuation was recorded" , "Withdrawal from treatment was registered prospectively" [150], "All treatment terminations ...are recorded" [115]. Comparison between studies is not feasible without full disclosure of how drug discontinuation was ascertained and the date of discontinuation was defined.

In analyses of dispensing claim data, drug discontinuation was often ascertained based on two events: (a) elapsing of a drug-free interval ('permissible gap') after the exhaustion of the drug dispensed [17] or (b) switching to an alternative drug (either from the same therapeutic class or from a different class). The rationale for applying a drug-free interval in ascertainment of drug discontinuation, rather than the exhaustion of the dispensed days-supply, was to minimize underestimation of persistence because patients treated in clinical setting were expected to have variable times to refill after the dispensed quantity was exhausted [217,218]. This could have been caused by dosing or recording errors, dose adjustment, stockpiling, mild adverse events such as abnormal laboratory results, drug interactions, vacations, hospitalizations and so on. Ascertainment of discontinuation using a drug-free interval (sometimes also switching) allows investigators to assign persistence a continuous or Bernoulli value (**Chapter 2**, Section

0, page 15). Assigning continuous values to persistence permits survival analysis, which accounts for censored patients and reflects lengths of follow up for all patients.

Selecting the length of the drug-free interval presents a major challenge and as a result, different lengths were applied in different studies of the same treatment. In published analyses of administrative data, various lengths of drug-free interval were used to ascertain discontinuation of TNFα antagonists in RA patients: 30 days [61-63,213,214], 60 days [72,107,155,213,215,216] and 90 days [64,213]. Three principles should be considered in the decision on the lengths of drug-free interval.

First, the selection of the length of the drug-free interval should be based on the pharmacological properties of the drug and the clinical situation [7,59]. The rationale for selecting a specific interval was rarely discussed in studies of TNFα antagonists or other drugs, whereas the interval was often selected to match previous studies of the same drug. For example, a drug-free interval of 30 days was commonly used for daily drug [18,219] based on convention rather than pharmacological rationale. Ideally, the length of a drug-free interval should approximate the maximum period for which deprivation of the drug would not reduce therapeutic benefit (or increase harm) [220]. Unfortunately, this knowledge is limited for most treatments. In patients treated with infliximab at a dose of one milligram per kilogram body weight with concomitant MTX, more than 60% of the patients maintained the 20% Paulus

response criteria[31] for a median duration of 16.5 weeks and the 50% Paulus response criteria

for 12.6 weeks [75]. With adalimumab, response (based on the European League Against

Rheumatism (EULAR) [32] and American College of Rheumatology (ACR)[33]) was sustained four

weeks to three months [76]. However, large variation was observed between patients and the

applicability of the response criteria used to clinical outcome (such as pain, morbidity and

mortality) is not established. Using a short drug-free interval (30 days or less) in studies of

TNFα antagonists has therefore led to biased and underestimated duration of therapeutic effect.

Second, sensitivity analysis applied to various lengths of drug-free interval is recommended for

checking the robustness of persistence estimates [30,59,73]. Often the selection of the length of

drug-free interval to ascertain discontinuation was arbitrary because of limited knowledge. It is

intuitive that a longer drug-free interval is associated with improved persistence on an

individual drug, because some patients reinitiate the index drug after a short interruption and

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[31] Paulus criteria were developed based on data from multiple trials in RA patients, according to their ability
to differentiate between patients treated with DMARDs and patients treated with placebo. Response requires
fulfillment of at least four of the following criteria: 20% or 50% (a) improvement in morning stiffness, (b)
erythrocyte sedimentation rate (ESR), (c) joint tenderness score, (d) joint swelling score and (e)
improvement by at least two grades on a five-grade scale (or from grade two to grade one) for patient and
physician global assessments of current disease severity [481].

[32] EULAR response specifies response based on disease activity score in 28-joints (DAS28). Good
responders are patients with an improvement in DAS28 of >1.2 and a present score of ≤3.2. Moderate
responders are patients with an improvement of >0.6–≤1.2 and a present score of ≤5.1, or an improvement of
>1.2 and a present score of >3.2 and non-responders are patients with an improvement of ≤0.6, or patients
with an improvement between 0.6–1.2, and a present score of >5.1. DAS28-defined remission is a score of
<2.6 [439].

[33] The ACR response criteria are described in **Appendix A**, Section A.3.1, page 3.

this interruption is not considered to be a discontinuation. A longer drug-free interval was associated with improved persistence in our study and in studies of other drug [218,221-223]. When considering comparative persistence, the effect of increasing lengths of drug-free interval is not straightforward. If the effect is similar for both drugs, a change in the drug-free interval applied to ascertain discontinuation does not affect the estimates of comparative persistence. If, on the other hand, noncompliance and short interruptions are more frequent with one drug, then increased interval may be associated with differences in magnitude, significance and even direction of comparative persistence. Sensitivity analysis applying varied lengths of drug-free interval is helpful to disclose instability of the comparative estimates. Only a minority of studies estimating comparative persistence with different therapeutic classes performed sensitivity analysis.

Greevy et al 2011 [217], in their analysis of oral antidiabetic drugs, showed that increasing the length of drug-free interval from zero to 30 days reversed the direction of the hazard ratio for discontinuation of sulfonylurea versus metformin. More commonly, sensitivity analysis showed that estimates of comparative persistence were robust, in survival analysis (persistence as a continuous variable) or logistic regression (persistence as a Bernoulli variable) analyses. Increasing lengths of drug-free interval were associated with robust estimates of comparative persistence in patients treated with cholinesterase inhibitors for Alzheimer's disease [224], interferons and glatiramer acetate for multiple sclerosis [225] or with serotonin-specific reuptake inhibitor for psychiatric conditions [226]. Additionally, an increased drug-free interval did not affect the results of comparisons of six different therapeutic classes of drug used by patients with a variety of chronic diseases [147].

In investigations of RA patients treated with TNFα antagonists, only three studies reported

persistence estimates when increasing the length of drug-free interval (**Appendix C**, Table 29,

page 280). The first two studies examined percentage of discontinuers in the first anniversary

after the index date, using administrative data. Li et al 2010 [213] reported discontinuation in

patients treated with infliximab and etanercept. The investigator reported "comparable

discontinuation rates" of the two drugs (an unknown test for between group comparisons was

performed and the differences were insignificant for all lengths applied). Ogale et al 2011

[215] examined the proportion of discontinuers based on switching and a drug-free interval of

60 and 180 days. They demonstrated that longer drug-free intervals were associated with

decreased percentage of patients who experienced discontinuation, "but the relative pattern

remained the same". No statistical test was reported. The third study examined discontinuation

at the second anniversary after the index date. Schmeichel-Mueller et al [216] applied drug-

free intervals of 60 and 360 days in ascertainment of discontinuation using administrative data.

This study was reported as an abstract and comparisons between discontinuation proportions in

the three drug groups were not reported. Overall, the effect of increasing drug-free interval

lengths on estimates of comparative persistence remained unclear based on these studies.

The third principle in ascertainment of drug discontinuation pertains to the interpretation of the

outcome measure. Specifically, the length of the drug-free interval determines the implication

of the outcome measure estimated in the study. Prolonging the drug-free interval ensures a

lower frequency of reinitiating the same drug after ascertainment of discontinuation; therefore, the measure estimated is persistence. When the investigators apply a short drug-free interval of 60 days or less, the measure estimated encompasses both duration and intensity of dispensing events[34]. Therefore, the outcome measure estimated in these studies should be regarded as a mixed measure of compliance and persistence. Furthermore, the different methods used to measure the outcome 'persistence' in different studies could imply that investigators in fact measured different phenomena and therefore (a) heterogeneity in the results is expected, even between analyses of the same type of data source and (b) pooling the results from different studies is inappropriate.

4.5.2 Possible Superiority of Infliximab

We showed that the proportion of patients reinitiating the index drug after a temporary interruption probably played a role in the differential influence of the length of drug-free interval on the estimated persistence with different TNFα antagonists. As a result, the significance of comparative persistence estimates was sensitive to the length of the drug-free interval. We interpret interruptions in drug persistence followed by reinitiating the index drug

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[34] Caentano 2006 [59] was the first to distinct between duration and intensity in following the prescription recommendations.

as noncompliance, rather than nonpersistence[35]. The reasons for temporary interruptions in drug persistence were previously studied in RA patients who were treated with etanercept [227]. The main reasons identified were neutropenia, infection, abnormal liver function tests and thrombocytopenia.

We found that interruptions in drug persistence followed by reinitiating the index drug were less frequent on infliximab. Our results are supported by an abstract presented by Schmeichal-Mueller 2011 [216]. In an analysis of administrative data, a higher proportion of etanercept (62.1%) and adalimumab users (49.7%) reinitiated the index drug after an interruption of longer than 60 days compared to infliximab (12.8%). Flendrie et al 2009 [228] showed that temporary interruptions in persistence were more common with adalimumab (42.6%) compared to infliximab (19.3%) or etanercept (13.3% of the treated patients). The most common reason was adverse events (not further specified). Unfortunately, temporary interruption was not defined in the report. Better compliance with infliximab compared to etanercept was also reported by Harley 2003 [229] and Li 2010 [213], and compared to etanercept and adalimumab by Carter 2010 [230] and Schmeichel-Mueller 2011 [71].

There are several possible explanations for possible improved compliance with infliximab. First, adverse events were shown to predominate in infliximab discontinuation, compared to other TNFα antagonist drugs. In RCTs, withdrawals due to adverse events (WDAEs) were

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[35] For discussion on the definition of persistence and compliance, refer to **Chapter 2**, Section 2.1.1, page 3.

more common with infliximab compared to adalimumab [231]. Other studies showed that in routine clinical practice, a higher proportion of infliximab discontinuations were due to adverse events[36], especially acute systemic reactions [108,110,170]. It is unlikely therefore, that patients who discontinued a drug because of an adverse event, especially a serious one, reinitiated the same drug. Second, infliximab is an infusible agent and regular physician follow-up is required for administration. Regular encounters have been shown to encourage compliance and persistence of drug therapy [162,184,185], though this was not studied in patients treated with TNFα antagonists. Lastly, dose escalation is more frequent in patients treated with infliximab compared to the other drugs [62,72]. It is possible that the use of standard dosing to determine the number of days-supply led to an overestimation of this number and an underestimation of the length of actual drug-free intervals in patients who were treated with escalating doses of infliximab (**Chapter 2**, Section 2.2.4.2, page 52).

Our results suggest possible superior adherence with infliximab. Improved persistence with infliximab was observed also by Gomez-Reino et al [117], Tang et al [104], Yazici et al [62] and recently by Ogale et al 2011 [215]. This may be the result of more frequent dose

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[36] In meta-analysis of multiple studies examining reasons for discontinuing the TNFα antagonists in RA, similar proportion of patients discontinue infliximab due to adverse events, compared to adalimumab and etanercept (**Appendix A**, Table 24, page 3); nonetheless, the included studies were not identified using systematic review methodology.

escalation in patients on infliximab as an alternative to switching in patients with lack or loss of efficacy [62,72] (**Chapter 2**, Section 2.2.4.2, page 52), or, as mentioned before, due to frequent physician encounters.

4.5.3 Persistence as a Measure That Integrates Benfit and Harm

The assumption that drug persistence could be used as an indirect measure of therapeutic benefit-herm balance, first introduced by Wolfe in 1995 [45], has often been quoted in studies of rheumatologic diseases, especially RA [64,232-234]. Correspondingly, comparative persistence, a relative measure, was suggested as an indirect measure of the relative benefit and harm of individual drugs.

An advantage of using drug persistence is that benefit and harm are inherently accounted for together because the main reasons for discontinuations are reduced therapeutic benefit or perceived harm. On the other hand, benefit and harm are usually reported separately in clinical trials. This is important because clinical decisions have inherent tradeoffs between positive and negative drug effects; therefore, a measure that reflects both benefit and harm is easier to interpret and implement in clinical practice compared to separate measures of either benefit or harm [235]. In addition, persistence can be estimated easily and cheaply, using varying types of data source, including administrative data.

However, we advise caution when interpreting drug persistence as a measure of therapeutic benfit-harm balance. We mentioned before (**Chapter 3**, Section 3.5.1, page 72) the absence of direct evidence as to the validity of persistence as a measure of benefit and harm. Longitudinal studies estimating an association between a change in disease severity or an adverse event during treatment and subsequent hazard for drug discontinuation are needed. An alternative approach, relating therapeutic outcomes to persistence at a single time point could be biased due to the analytic methods used. Intention to treat analysis (ITT) with last observation carried forward (commonly used in RCTs) or per protocol analysis [156,236]) tend to inflate the proportion of patients who experienced therapeutic benefit. On the other hand, ITT analysis per se [156,237] tends to underestimate the therapeutic benefit, as observations later than the discontinuation date are included. Drug discontinuation represents cessation of the drug opportunity to impact therapeutic effect, and therefore patients who discontinue the drug are expected to experience worsening of disease activity, especially if the drug is effective.

A second limitation in interpreting persistence is that it is a summary measure, and as such it failed to express the diverse reasons that cause discontinuation and weight these causes accordingly. Discontinuations caused by insufficient therapeutic benefit are accounted for in a similar way as is discontinuation due to harm regardless of severity.

Drug persistence was suggested to indirectly estimate benfit-harm balance based on the assumption that drug is continued in these patients provided that it has therapeutic benefit and only mild harmful effects that the benefit overweights [45,209]. Theoretically, three conditions required to be fulfilled.

1. All patients who discontinue the drug did so as a result of either inadequate therapeutic benefit (real or perceived inefficacy) or drug-related harm (real or perceived). Based on previous studies, decreased benefit and perceived harm are the main reasons for discontinuing TNFα antagonists in RA (**Appendix A**, Section 0, page 255), however, other causes should be considered as well. A notable proportion of the patients (up to 23%) discontinued the drug due to other reasons, such as planned pregnancy [108,170,180] and financial constraint [68]. Drug persistence may be affected by nonmedical reasons including out-of-pocket costs, change in insurance coverage or formulary status, preference or aversion to different routes of drug administration and advertising or new products choice [235]. Most importantly, drug persistence does not account for discontinuation due to remission in disease activity [170,179]. Some guidelines suggest that in RA patients who achieve remission with TNFα antagonists, discontinuation of these drugs could be considered [238,239]; even though a high relapse rate is expected in patients who discontinue TNFα antagonists due to remission [240-242]. Discontinuation followed by relapse in disease activity and reinitiation of a drug leads to a temporary interruption in drug persistence.

   Comparative persistence, as a relative measure, could theoretically reflect relative benefit-harm balance accurately if discontinuation due to non-effectiveness-related reasons is distributed equally in the drug groups. One of the implications of using a relative measure, is that systematic errors in measuring the outcome (in this case non-effectiveness-related reasons for discontinuation) cancel each other out as long as they are equally distributed between the groups. Imbalances between drug groups in these types of nonmedical causes of discontinuation however, may bias the results. For example, of the three TNFα

119

antagonist drugs we studied, patient preference for a subcutaneous route of administration [181] would only be a reason for infliximab discontinuation and as a causal factor may have exerted a greater effect at the time when a new subcutaneous drug (adalimumab) was introduced. As a result, infliximab persistence may have fluctuated during the study period, and comparative persistence may therefore have underestimated the effectiveness of infliximab compared to the other two drugs.

2. All patients who experienced harm or inadequate benefit discontinue the drug. This is not true in treatment with TNFα antagonists. Not all RA Patients who experience inefficiency or harm discontinue the TNFα antagonists. Kievit et al 2009 [243], for example, showed that only 19% of the patients who were classified as nonresponders after three months of treatment with TNFα antagonists discontinued these drugs, in concordance with the Dutch guidelines. Alternative strategies to inadequate therapeutic benefit include increasing dose (especially of infliximab) [244], or adding-on or optimization of concomitant synthetic antirheumatic drugs [245,246]. In case of harm, the drug may be temporarily interrupted [227] or the dose reduced [247,248].

    Comparative persistence could reflect relative benefit-harm balance accurately if other strategies for lack of benefit or perceived harm are equally distributed between the drug groups. However, this is not the case with RA patients treated with TNFα antagonists. Previous studies demonstrated higher prevalence of dose adjustment in RA patients treated with infliximab compared to the other two TNFα antagonists (**Appendix A**, Section A.3.6.2, page 265). These patients persist with the TNFα antagonists despite ineffectiveness. Some patients may experience benefit (or decreased drug-related harm)

with the new dose schedule, but in other patients, these strategies may only delay discontinuation until the effect of the new dose schedule is clear. Consequently, persistence might overestimate effectiveness in patients treated with infliximab and comparative persistence of infliximab versus other drugs could be biased.

3. Only drug properties and patients characteristics determine persistence. We present evidence that this condition is not fulfilled. Prescriber propensity for treatment discontinuation was demonstrated to affect measures of persistence and comparative persistence (**Chapter 3**, Section 3.4, page 64). This is probably a result of discrepancies in clinical guideline regarding indication for TNFα antagonist discontinuation, especially the use of sometimes vague definitions of lack of efficacy or harmful events (**Appendix A**, Section A.3.2, page 251). More importantly, neither the Canadian nor the American guidelines defined inefficacy or harm [249-253], and therefore discrepancies in discontinuation decisions are expected amongst British Columbian prescribers who may follow one or other guideline. In **Chapter 3**, we showed that not only do individual prescribers presented significantly different rates of discontinuation compared to others (Table 7, page 69), but prescriber propensity for treatment discontinuation also confounded the estimates of comparative persistence (Table 8, page 71). Some prescribers had a different baseline tendency to recommend discontinuation compared to most prescribers. Similarly, Zhang et al showed the effect of the prescriber propensity for treatment discontinuation on TNFα antagonists' discontinuation related to decreased benefit in a recent study [48]. This study is discussed in **Chapter 5**, Section 5.5.1.3, page 153.

In this chapter (**Chapter 4),** we demonstrate an exogenous factor that influences estimates of persistence and comparative persistence – the investigator. The instability of persistence and comparative persistence estimates and the effect of methods on these estimates also limit their validity as measures of benefit-harm balance.

Briefly, persistence and comparative persistence have attracted interest as measures of benefit-harm balance, especially in rheumatic diseases. They are easy to estimate and express the effect of both therapeutic benefit and harm. We discussed multiple limitations of the measures, and showed that the interpretation of either persistence or comparative persistence as a measure of benefit-harm balance may be misleading and caution should be taken.

4.5.4 Strengths and Limitations of the Study

Please refer to **Chapter 3**, Section 3.5.3, page 77.

4.5.5 Clinical and Health Policy Implications

We showed that the estimates of comparative persistence with TNFα antagonists in RA were sensitive to the algorithm used to ascertain drug discontinuation. Previous studies were commonly conducted using a short drug free interval of 30 [61-63,213,214] or 60 days [72,107,213,215,216], and sensitivity analysis for the robustness of the etimates was not performed. Therefore, we regard published results of previous studies to be problematic.

Distinctions between these TNFα antagonists based on available evidence from persistence studies are not advised. Instead of using comparative persistence with TNFα antagonists as a measure of relative effectiveness estimates for clinical practice or health policy decision-making, we suggest postponing use until methodological issues are resolved and more reliable estimates are possible.

To improve the quality and applicability of research, we believe a consensus between clinicians, policy-makers and researchers on the algorithm to ascertain discontinuation is necessary. This consensus should also apply to studies measuring harm and other outcomes of TNFα antagonist treatment, since the risk is estimated until drug discontinuation or prespecified time after the discontinuation. We suggest considering the complex pharmacologic properties and the effect of the drugs before reaching a consensus on the most appropriate algorithm. The median duration of effect of infliximab in RA patients, for example, was 16.5 weeks (intra-quartile range 7 to >20 weeks) after administration [75] and the effect of adalimumab was shown to be sustained 4 weeks to 3 months [76]. Both estimates of effect duration exceeded drug exposure period based on the drug-free interval of 30 days, which is commonly used in observational studies.

4.5.6 Research Implications and Directions

We have suggested that sensitivity of persistence and comparative persistence estimates to the method used to of ascertain discontinuation has implication for interpretability of other therapeutic outcomes in RA patients treated with TNFα antagonists. Investigators defining

TNFα antagonist exposure based on dispensing data often consider the patients to be exposed based on the days-supply plus a drug-free interval. This method was used in studies examining serious infection [254], fatal infections [255], hospitalizations [256], congestive heart failure [257], malignancy [255] and other outcomes [258]. To examine the robustness of therapeutic outcomes, we suggest that sensitivity analysis using increasing lengths of drug-free interval should be applied in future comparisons between the TNFα antagonists and in studies of other treatments.

Generally, in the process of synthesizing and translating available knowledge, critical appraisal of the methodology of the studies is warranted. We have shown that that heterogeneity in comparative persistence estimates may be caused by the different methods used to ascertain drug discontinuation. Ascertainment of discontinuation and discontinuation date are especially important in studies of comparative persistence with the TNFα antagonists, because administration schedules vary from every three days (for etanercept 25 mg) to as much as 56 days (for infliximab, third dose and onwards). Using the last administered dose as the date of discontinuation, for example, biases the results toward inferior persistence on infliximab. We did not study the effect of ascertainment of discontinuation date on the direction, magnitude and significance of hazard ratios, and suggest that investigation of these additional hypotheses would yield useful results as well.

We had no access to clinical data; therefore, we could not explore the effect of methods used to analyze this data type on the result obtained, nor could we compare methodologies used in analysis of administrative data to those used for clinical data. Further research using clinical data (clinical records or disease registry) is recommended to support our finding of the

significance of the method used to ascertain drug discontinuation in comparisons of persistence with TNFα antagonists. We speculate that discontinuation and the date of discontinuation were inconsistently ascertained in clinical studies, because they are based on physician recording of discontinuation and inconsistency in physician recording is possible. To obtain more robust estimates of comparative persistence for clinical and health policy decision making, it would be necessary to conduct a sensitivity analysis study using clinical data to more accurately establish the date of discontinuation, using date of last administered dose, date of end of drug coverage and date of physician visit to establish drug discontinuation. In addition, comparison of the clinical records to claim/pharmacy records would be required to provide further support for the hypothesis that distinct methods to establish date of drug discontinuation were used in studies using different types of data, and the diversity in methods led to heterogeneity in estimated of comparative persistence.

4.6 Conclusions

☐ Persistence with TNFα antagonists has shown promise as a valid tool to study relative benfit-harm balance in real life RA patients, because the main reasons to drug discontinuation were decreased benefit and perceived harm. However, persistence and comparative persistence should not be considered valid measures of the benfit-harm balance because of the following reasons:

- In previous observational studies, in about a quarter of the patients who discontinued TNFα antagonists non-effectiveness-related reasons were quoted, and these reasons were not evenly distributed between patients treated with different drugs

- Alternative clinical approaches were used in patients who experience lack of benefit or experience harmful events, and these approaches were not evenly distributed between patients treated with different drugs

- We showed that both the prescriber and more important – the investigator determine persistence and comparative persistence, and not only drug properties and patients characteristics

- We studied the significance of the length of 'drug-free interval' used to ascertain drug discontinuation and demonstrated its impact on hazard ratios for drug discontinuation. It would appear that the heterogeneity in the existing body of evidence on comparative persistence of TNFα in RA is largely a result of lack of standardization of this important design feature of comparative persistent studies. This problem is not easily resolved by one research group therefore a consensus in the field on this critical point would probably be necessary before persistence studies yield the useful findings anticipated. The consensus will allow researchers to conduct research that would contribute to clinical and policy meaningful knowledge to accumulate.

☐ Different methods to establish drug discontinuation (sensitivity analysis) should always be used to check the robustness of the results in studies comparing drug persistence. Similar approach (sensitivity analysis) is required in ascertainment of drug exposure in studies of other therapeutic outcomes, to ensure the robustness of the results, because we showed a differential influence of the method to ascertain drug discontinuation on the different drug.

☐ Patients treated with etanercept and adalimumab are more likely than patients treated with infliximab to experience temporary interruption in drug persistence, after which they reinitiate the same drug. This finding indicates better compliance with infliximab, probably due to more frequent encounters with health professionals (compared to patients treated with self-administered drug) and nonself administration of the drug. Consequently, programs to improve compliance with TNFα antagonists should focus on patients treated with etanercept and adalimumab. Additionally, poor compliance with etanercept and adalimumab should be accounted for in budget planning, cost effectiveness studies and so on.

CHAPTER 5: PRESCRIBER PREFERENCE FOR TUMOUR NECROSIS FACTOR ANTAGONISTS PREDICTS PERSISTENCE ON TREATEMNT IN RHEUMATOID ARTHRITIS

5.1 Background

Patient characteristics and therapeutic outcomes (both beneficial and harmful) have been established as major determinants of drug persistence in multiple chronic noncurable diseases, including rheumatoid arthritis (RA) [79,232,259,260]. We were interested in persistence with tumour necrosis factor alpha (TNFα) antagonists in patients with RA. A minority of TNFα antagonist persistence studies also assessed non-patient characteristics: prescriber specialty [104], payer type [62,104] and treatment center [110][37]. Potential roles of physician preference for the prescribed drug or prescribing habits as determinants of drug persistence have not previously been studied, in RA or other diseases.

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[37] Persistence studies of other treatments sometime included prescriber characteristics, such as age [135,162], gender [135,162], number of patients treated by this prescriber [135,162] or specialty [163-166] in the model.

We suspected that TNFα antagonist therapy in RA patients might be especially sensitive to drug preference of the prescribing physician for two main reasons. First, during the study period (2001-2008) there was limited clinical evidence on the comparative effectiveness of the drugs (**Appendix A**, Section A.3.1, page 241). Second, the published indications for discontinuation of TNFα antagonists were vague and confusing (**Appendix A**, Section A.3.2, page 251) and care-providing physicians could reasonably be expected to reach different clinical decisions given the same clinical situation (further discussion in this chapter, Section 5.5.1.3, page 153). Consequently, the decisions about which of the TNFα antagonists to initiate first (drug selection) and when to discontinue the drug are likely subject to the prescriber individual preference.

In **Chapter 3,** we demonstrate the importance of the prescriber propensity for treatment discontinuation both as a predictor of persistence and as a possible confounder of comparative persistence (Section 3.4, page 64). The prescriber recorded on the first dispensing claim for TNFα antagonist was used as a proxy of the care-providing physician. In this chapter, we extend our study of the prescriber's role in persistence and reveal the effect of prescriber preference for the prescribed drug (PPD) using data on previous prescribing habits.

5.2 Objectives and Hypothesis

The main study hypothesis was that increased PPD was associated with improved persistence. We also speculated that the PPD would not confound comparative persistence measures. Therefore, the goals of the study were (a) to estimate the effect of PPD on the TNFα antagonist

persistence in patients with RA, (b) to test whether PPD is a possible confounder of estimated

of comparative persistence estimates and (c) to characterize and compare levels of PPD in

patients who switched to a second TNFα antagonist.

5.3 Patients and Methods

5.3.1 Data Source and Study Cohort

We analyzed a cohort of British Columbia residents who received a first course of a TNFα

antagonist between March 2001 and December 2008, and had also been diagnosed with RA.

Follow-up data were available until December 31, 2009. Patients were identified using four

British Columbia Ministry of Health administrative databases: PharmaNet (prescription

dispensing data), Medical Service Plan (MSP) registration information (demographic data),

MSP Payment Information (fee-for-service payments to physicians and alternative providers),

and the Discharge Abstract Database (hospital separations). The databases were linked using a

study-unique anonymized identifier. The study protocol was approved by the Clinical Research

Ethics Board of the University of British Columbia.

The study cohort was identified based on the algorithm used for the studies in **Chapter 3** and

Chapter 4 and presented in details in **Appendix B**, Figure 23, page 270. Patients were

included based on one or more recorded dispensing claims for infliximab, adalimumab or

etanercept between March 2001 and December 31, 2008. We used the first dispensing claim

for a TNFα antagonist (index dispensing) after a run-in period of at least 36 months of follow up without TNFα antagonist dispensing to identify the index drug, index date and index prescriber for each patient in the cohort. RA patients were selected using similar, though not identical, criteria to those used in previous studies of RA patients in British Columbia [101-103]. RA patients were identified based on two outpatient visits with a diagnosis of RA at least 60 days apart, or one hospitalization with a recorded discharge diagnosis of RA within three years prior to the index date. A list of International Classification of Diseases (ICD) codes that were used in the study is presented in **Appendix B**, Table 28, page 271. Diagnostic codes were recorded in the Ministry of Health databases for billing purposes and were based on clinical judgment of the care-providing physician. Additionally, patients were required to have continuous provincial MSP coverage three years before the index date. A gap shorter than 30 days was not considered an interruption. Patients were excluded if they were previously treated with anakinra, rituximab or abatacept, if sex or date of birth were missing, if they had a concurrent diagnosis of Crohn's disease (based on at least one outpatient or inpatient diagnostic code in the three years preceding the index date), or if they were younger than 18 years old at the index date (to remove patients with juvenile RA). In the current study, we also excluded patients treated by an index prescriber who cumulatively initiated less than five courses in the RA cohort (a 'low volume' prescriber).

5.3.2 Exposure and Covariates

The PPD for a specific patient was determined at the index date and coded as a Bernoulli variable. For each patient, we identified courses of TNFα antagonists initiated by the index prescriber for all patients in the study cohort during the year preceding the index date (excluding the course of interest). From this one-year data, we calculated the proportion of patients with the same index drug divided by the total number of patients prescribed by the same prescriber (Figure 13). A PPD was assigned the value 'higher' when the calculated proportion was 60% or higher and the value 'lower' otherwise[38]. A threshold of 60% was selected to ensure that higher PPD meant the prescriber clearly favored this drug, even if only two TNFα antagonists were available (until October 2004) or prescribed. Assigning values based on the prior year allowed us to account for change in preference over time and for the later availability of adalimumab (at the end of 2004, while the other two drugs had been available since 2001). A sensitivity analysis was conducted to determine the robustness of results using thresholds of 70% or 80% for the level of PPD.

Multiple covariates, mainly patient characteristics that may influence drug selection and/or persistence, were included in the final models. A list of all covariates included in the multivariable analysis with description and format are presented in Table 13.

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[38] The value 'lower' was also assigned for patients when the index prescriber did not prescribed any course of TNFα antagonist in the cohort in the preceding year.

Figure 13: Calculating the proportion used to assign the value of PPD

For each patient, identify the index drug, index date and the index prescriber

Identify all courses initiated by the index prescriber in the year preceding the index date

Identify the drug initiated in these one-year courses

Calculate proportion from the one-year data: number of courses with index drug divided by the total number of courses

1 year

Course of interest

Courses initiated by the index prescriber

time

■ Infliximab

● Adalimumab

▲ Etanercept

n=2

n=1

n=6

Proportion of infliximab $= \dfrac{6}{6+2+1} = 66.6\%$

133

Table 13: List of covariates included in the final models

Variable	Description
Demographics	
Sex	Bernoulli variable, reference=female
Age at index date	Four mutually exclusive categories: 18-29 years, 30-69 (reference[39]), 70-79 and ≥80 years old
The annual deductible for prescription cost at index date	PharmaCare deductible level is based on annual income [141].
	Six mutually exclusive categories: annual deductible of 0 dollars (reference), deductible of 1-500, deductible of 501-2250, deductible of >2250, other PharmaCare programs (no deductible level available) and no PharmaCare program
Geographical area at index date	Geographical area was determined based on the first three letters/digits of the patient's postal code of residence.
	Five mutually exclusive categories based on: Greater Vancouver (reference), Greater Victoria, Vancouver Island (excluding Victoria), urban areas (excluding Vancouver and Vancouver Island) and rural areas (excluding Vancouver Island)
Clinical status	
Physicians encounters in the year preceding the index date	Continuous, one unit = one visit
Inpatients admissions in the year preceding the index date	Four mutually exclusive categories based on the number of admissions: no admission (reference), one admission, two admissions and at least three admissions
Comorbidities (presence and severity) during the three years preceding the index date	Charlson comorbidity score [176] was determined using Quan's ICD-9-CM and ICD-10 coding algorithm for administrative databases [175], excluding rheumatic diseases. At least two outpatient or one inpatient encounter with the diagnosis, were required.
	Four mutually exclusive categories: score of 0 (reference), score of 1, score of two and score above two
Disease duration	Continuous, one unit=one year, measured from the first diagnosis of RA (inpatient or outpatient) in the data.
The presence of extra-articular manifestation during the three years preceding the index date	Bernoulli, reference=no, based on recorded at least one diagnoses (inpatient or outpatient). A list of codes is presented in **Appendix B**, Table 28, page 271.

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[39] Patients within age range 30-70 years were found to have a similar hazard ratio in preliminary analysis.

Variable	Description
Drug therapies	
Concomitant MTX during 200 days[40] preceding the index date	Bernoulli, reference = no, based on dispensing claims
Dispensing claims for NSAIDs during the year preceding the index date	Bernoulli, reference = no
Number of different antirheumatic drugs dispensed in the three years preceding the index date	Dispensing claims of 10 drugs were included: MTX, hydroxychloroquine, sulfasalazine, leflunomide, azathioprine, minocycline, penicillamine, sodium aurothiomalate, prednisone, and intra-articular triamanolone or methylprednisolon. Four mutually exclusive categories: no drug, 1-2 different drugs (reference), 3-6 different drugs, >6 different drugs
Other	
Prescriber propensity for treatment discontinuation	An individual Bernoulli variable for the index prescriber (58 prescribers)
Calendar year at index date	The variable allowed controlling for secular trends in clinical practice [157-160] and availability of drugs[41]. Eight yearly categories were included for the years 2001-2008 (reference = year 2001).

ICD-10- International Classification of Diseases, 10th edition; **ICD-9-CM** - International Classification of Diseases, 9th edition, clinical modification; **MTX** – methotrexate; **NSAID** – nonsteroidal anti-inflammatory drug

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[40] The time interval (200 days) chosen was based on mean plus two standard deviations of between-dispensing intervals of MTX in the study cohort

[41] Adalimumab gain entry to the Canadian market at the end of 2004, while the infliximab and etanercept were available from 2001.

5.3.3 Outcome

The outcomes variables were defined and assigned values consistent with those used in the analysis presented in **Chapter 3** (Section 3.3.1, page 60). Specifically, the two outcomes variables were (a) a continuous persistence variable and (b) a binary censor variable. Drug persistence in years was calculated as the difference between the date of drug discontinuation and the index date. Drug discontinuation was ascertained by either switching to another antirheumatic monoclonal antibody or immunomodulator (infliximab, adalimumab, etanercept, anakinra, rituximab, abatacept, certolizumab and golimumab), or the elapsing of a drug-free interval of 180 days. A drug-free interval was defined as a period without additional dispensing claim of the same pharmaceutical component after the days-supply of the latest refill was exhausted (**Chapter 2**, Figure 5, page 22). The date of discontinuation was set to the end of the days-supply of the last refill before discontinuation or the date of the first dispensing of a different monoclonal antibody or immunomodulator, whichever was earliest. Patients were considered censored if they were continuously treated with the first TNFα antagonist up to December 31, 2009 (end of follow-up period) or when their date of discontinuation occurred during an interruption of more than six days in the provincial MSP coverage. Death and emigration from the province are the most common causes of interruptions in the provincial MSP coverage. For details on assigning the values of the outcome variables refer to **Appendix B**, Figure 24, page 271.

Original data on the number of days-supply recorded in PharmaNet were unreliable (**Chapter 2**, Section 2.2.4.1, page 47); hence, we also calculated the expected number of days-supply based on the estimated number of vials dispensed, which was imputed using the cost field in

the dispensing record. We used the longest duration of days-supply, recorded or calculated, to determine both the length of drug-free interval and the date of drug discontinuation. For further discussion on calculating the number of days-supply refer to **Chapter 2**, Section 2.2.4.1, page 47.

5.3.4 Statistical Analysis

Summary statistics of baseline characteristics were compiled across the three drug groups. We assumed normality of the continuous variables compatible with large sample size (>2500) and the central limit theorem. The significance of differences between the drug groups was assessed with one-way analysis of variance (ANOVA) F-test for continuous variables and the Pearson's Chi-square test for categorical variables. All statistical tests were two-sided. All calculations were performed using the SAS software package [178].

The product-limit method and the log rank test were used to estimate and compare persistence across drugs and levels of PPD. The crude and adjusted hazard ratios for drug discontinuation were estimated using two different approaches in a Cox proportional hazards regression. In the first approach, an analysis of nonclustered data, we ignored any possible correlation between patients who received a prescription for TNFα antagonist by the same prescriber. The model included an individual Bernoulli variable for each prescriber to allow individualization of the risk of discontinuation by prescriber (prescriber propensity for treatment discontinuation). In the second approach, a marginal model of clustered data, we adjusted for possible correlation between patients who received a prescription for TNFα antagonist by the same prescriber,

assuming that patients treated by the same prescriber were more similar to each other than to patients treated by other prescribers. We used Lee, Wei and Amato's approach to clustered survival data [261][42] using PHREG procedure in SAS [262,263]. The dependence structure between failure times was not specified in the model; however, possible correlation was accounted for in the variance-covariance matrix by the use of a robust sandwich estimator. We chose this method based on the assumption that PPD was not normally distributed, as was shown in a study examining physician preference to aggressive treatment by patient's age [264]. Under the circumstances of nonnormality of PPD, we could not specify a distribution for the random effect. The results were presented as hazard ratios for the effect of higher versus lower PPD, with 95% confidence intervals (CIs) and p-values. Two-tailed p-values smaller than 0.05 were considered to be statistically significant.

The proportional hazards assumption was assessed by testing for the significance of interactions between the variables and time or the natural logarithm of time, as well as by plotting the scaled Schoenfeld residuals [177]. The validity of the linearity assumption of continuous variables was assessed by log likelihood tests in models that included either categorical or polynomial variables. If nonlinearity was detected, the variable was categorized. Interaction between drug and PPD was planned *a priori*, but was included in the final models only if was statistically significant (a two-tailed p-value < 0.1).

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[42] Discussion of this method is beyond the scope of this dissertation, and can be found in the dissertation by Bo 2008 [482].

The possible confounding effect of PPD (using the three thresholds) on comparative persistence[43] was estimated. It was defined as increasing or decreasing the crude adjusted hazard ratios (or their 95% confidence limits) by at least five percentages (similar to the definition in the study presented in **Chapter 3**, Section 3.3.2, page 62).

5.3.5 *Analysis of Switchers*

We analyzed patients who switched to a second course of TNFα antagonists within 180 days after discontinuing a first course. Patients were divided into two groups, based on the level of PPD assigned to the TNFα antagonists prescribed as their in the first course. We compared the proportions of patients who were switched to a second drug with higher a PPD. The decision to select a second drug was conditional on failure of first drug; hence determining the value of PPD for the drug prescribed in a second course based on data pertaining to first courses prescribing only could not be considered valid. Accordingly, PPD for the second course was calculated using all courses of TNFα antagonists initiated by the prescriber to all RA patients

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[43] Comparative persistence was defined and estimated as presented in **Chapter 3**, Section 3.3.2, page 3 and **Chapter 4**, Section 4.3.5, page 3. We included three pairwise comparisons for hazard ratio of discontinuing (a) infliximab compared to etanercept, (b) infliximab compared to adalimumab and (c) adalimumab compared to etanercept.

in the study cohort[44] in the previous year. The threshold between assigned levels was set to 60%, consistent with analysis of the first course. We duplicated the analysis for switchers who were repeatedly treated by the same prescriber.

5.4 Results

5.4.1 Study Cohort and Baseline Characteristics

The study cohort included 2,742 RA patients treated by 58 prescribers who treated at least five patients[45] with infliximab (46 prescribers), adalimumab (49 prescribers) and/or etanercept (58 prescribers). Etanercept was the most frequently prescribed TNFα antagonist (1718 patients, 63%), versus infliximab (571 patients, 21%) versus adalimumab (453 patients, 16%). More patients on etanercept (70%) were treated by a drug with higher PPD, compared to infliximab (34%) or adalimumab (19%). Baseline characteristics are presented in Table 14. Patients

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[44] We examined courses for 2,923 RA patients who initiated TNFα antagonists by December 31, 2008 (the cohort presented in **Chapter 3**, Section 3.4, page 3). We did not exclude patients in which the first course was prescribed by 'low volume' prescriber, since the second course (or the third) could be initiated by prescriber included in the cohort analyzed in this chapter.

[45] A total of 2,923 patients that were included in RA cohort analyzed in **Chapter 3** (Section 3.4, page 3) and **Chapter 4** (Section 4.4.1, page 3). We excluded 181 patients that were prescribed by physician with initiated less than five courses in the RA cohort.

treated with adalimumab were significantly older and had a lower income (lower annual

deductible level for prescribing cost). They also had the lowest prevalence of dispensing claims

for nonsteroidal anti-inflammatory drugs (NSAIDs) and lowest rates of admission to hospital

in the year prior to initiating the study drugs. Residents of the Greater Vancouver area were

more commonly treated with infliximab. Patients who received infliximab also had the highest

prevalence of concomitant MTX therapy versus patients on etanercept with the lowest.

5.4.2 *Effect of Prescriber Preference on Persistence*

The product limit plots for the drug persistence are presented by specific TNFα antagonist

(Figure 14A' page 143) and by PPD level (Figure 14B, page 144). Similar persistence was

observed with the three TNFα antagonists (median persistence with infliximab 3.88 years [95%

CI 2.96-5.25], adalimumab 3.33 [2.63-4.10] and etanercept 3.87 [3.36-4.40], log rank test p-

value=0.15). These results are consistent with the analysis presented in **Chapter 3** (Section

3.4.1, page 64). Higher PPD was associated with improved persistence. The median persistence

of patients treated with a drug with higher PPD was 4.28 (95% CI 3.70-4.90) compared to

persistence with lower PPD of 3.27 years (95% CI 2.84-3.84), log rank test p-value=0.017.

The crude and adjusted hazard ratios for higher PPD, with and without accounting for

clustering by prescribers, are presented in Table 15 (page 24, column: PPD threshold 60%).

Higher PPD was associated with a significant decrease of 14-15% in the adjusted hazard for

Table 14: Baseline characteristics

Variable	Infliximab (n=571, 21%)	Adalimumab (n=453, 16%)	Etanercept (n=1718, 63%)	P-value for comparison
Courses with higher PPD n (precentages from courses of this drug)	193 (34%8)	84 (19%)	1198 (70%)	<0.0001
Demographics				
Females, n (%)	403 (71%)	326 (72%)	1239 (72%)	NSS
Age at index (years) median (range)	56 (18-87)	58 (22-91)	56 (18-92)	0.003
Annual deductible for prescription cost n (%)				
None	47 (8.3%)	80 (18%)	199 (12%)	<0.0001
$1-500	33 (5.8%)	53 (12%)	152 (8.9%)	0.004
$501-2250	92 (16%)	109 (24%)	315 (18%)	0.004
>$2250	35 (6.1%)	38 (8.4%)	143 (8.3%)	NSS
Residence in Greater Vancouver and Victoria n (%)	341 (60%)	224 (50%)	782 (46%)	<0.0001
Clinical status				
Physician visits median (range)	33 (3-158)	31 (2-112)	32 (3-136)	NSS
At least one admission to hospital n (%)	104 (18%)	63 (14%)	340 (20%)	0.01
Extra-articular manifestations n (%)	28 (4.9%)	14 (3.1%)	60 (3.5%)	NSS
Presence of comorbidity (Charlson comorbidity score > 0) n (%)	113 (20%)	95 (21%)	383 (22%)	NSS
RA disease duration (years) median (range)	9.2 (0.1-17.9)	7.7 (0.3-17.9)	8.0 (0-17.8)	NSS
RA drugs				
Concomitant MTX n (%)	388 (68%)	264 (58%)	856 (50%)	<0.0001
Dispensing claims for NSAIDs n (%)	307 (54%)	214 (47%)	923 (54%)	0.04
Number of different antirheumatic drugs median (range)	4 (0-8)	4 (0-8)	4 (0-9)	NSS

%- percent**; $**-Canadian dollars; **MTX**-methotrexate; **n**-number of patients; **NSAID**- nonsteroidal anti-inflammatory drug; **NSS** – not statistically significant; **PPD** – prescriber preference for the prescribed drug;

Figure 14: The product limit estimates of persistence

A. Drug persistence by drug

143
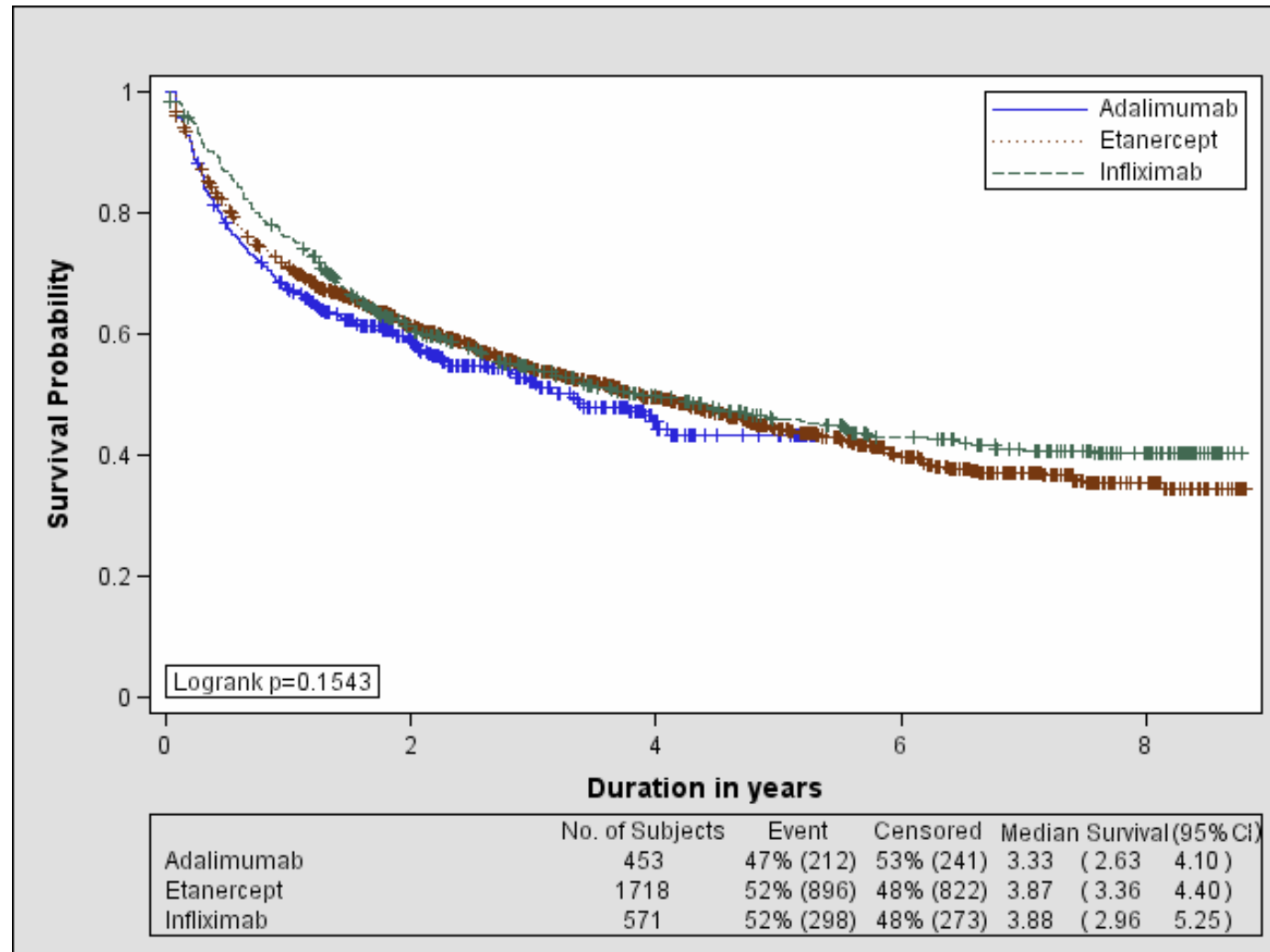
B. Drug persistence by PPD level

	No. of Subjects	Event	Censored	Median Survival (95% Ci)		
higher	1475	51% (745)	49% (730)	4.28	(3.70	4.90)
lower	1267	52% (661)	48% (606)	3.27	(2.85	3.84)
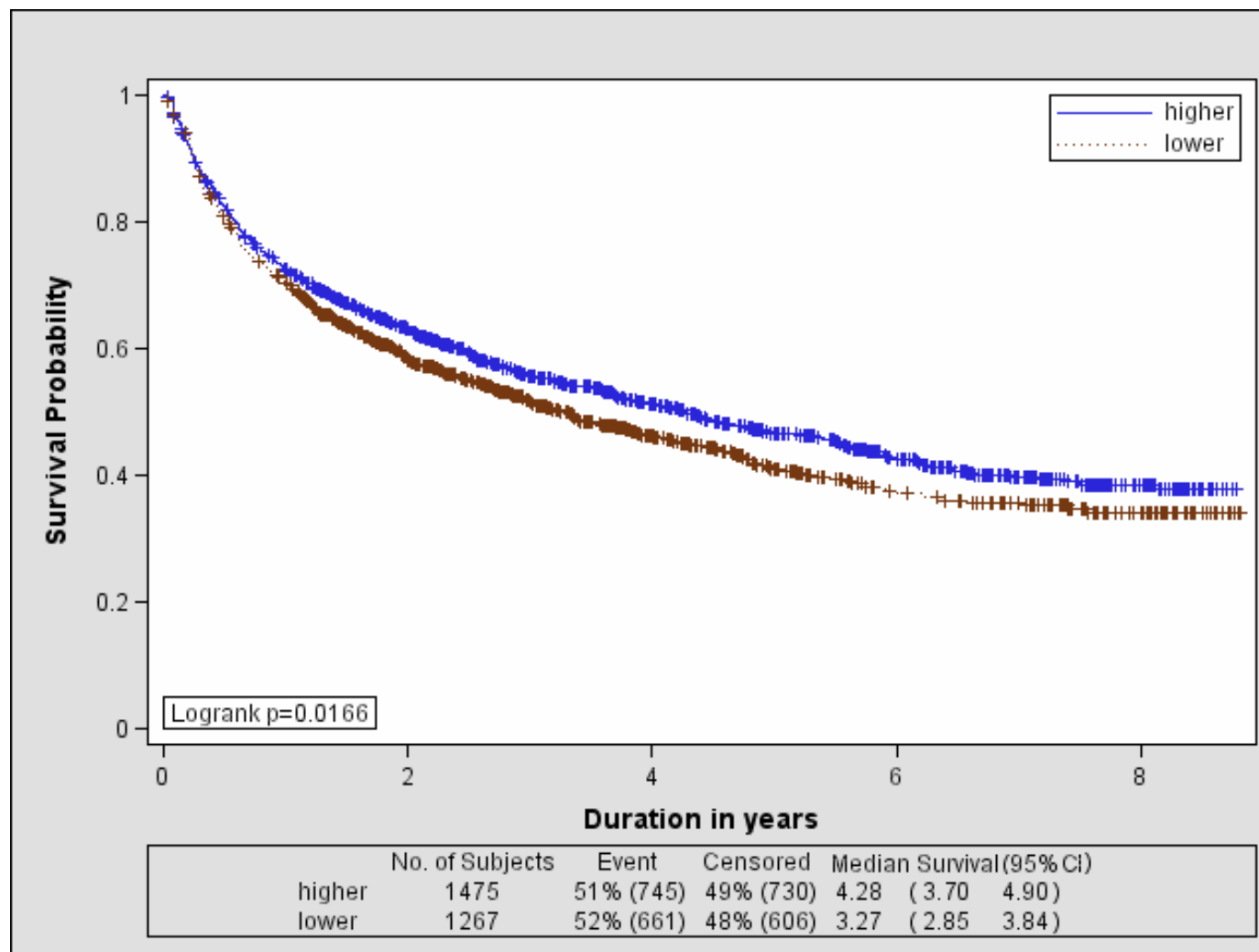
discontinuation compared to lower PPD. No significant interaction between the drug and PPD

was observed in either model. The results of analyses with thresholds of 60%, 70% and 80%

for PPD were robust (Table 15 and **Appendix D**, Figure 26, page 282). Higher PPD was

associated with a significantly decreased hazard for discontinuation by 12-15% in the three

multivariable models accounting for clustering (marginal models). The adjusted hazard ratio

Table 15: Hazard ratios for drug discontinuation, higher PPD versus lower PPD

Approach		Hazard ratio (95% CI), p-value		
		PPD threshold 60%	PPD threshold 70%	PPD threshold 80%
Patients with higher PPD (proportion)		0.52	0.45	0.36
Nonclustered data analysis	Crude	0.88 (0.79-0.98), 0.02	0.88 (0.80-0.99), 0.03	0.89 (0.80-1.00), 0.04
	Adjusted[46]	0.86 (0.76-0.98), 0.03	0.88 (0.77-1.00), 0.06	0.87 (0.75-1.00), 0.06
Marginal modeling of clustered data	Crude	0.88 (0.78-1.01), 0.05	0.88 (0.78-1.01), 0.07	0.89 (0.79-1.01), 0.06
	Adjusted[47]	0.85 (0.76-0.96), 0.01	0.87 (0.78-0.97), 0.01	0.88 (0.82-0.98), 0.02

CI – confidence interval; **PPD** – prescriber preference for the prescribed drug

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[46] Adjusted by drug, calendar year, patient's demographics and clinical status, and prescriber

[47] Adjusted by drug, calendar year and patient's demographics and clinical status

based on the nonclustered data analysis did not reach the significant level for thresholds of 70% and 80%, perhaps as a result of decreasing numbers of patients treated with a drug of higher PPD.

5.4.3 Effect of Prescriber Preference on Comparative Persistence

We estimated a possible confounder effect of PPD on comparative persistence by comparing estimates of hazard ratios for discontinuation using unadjusted modeling (crude estimated of hazard ratios, using nonclustered and clustered data approaches) and models that included one additional covariate – PPD. We used three thresholds to assign the value of PPD (as described in Section 5.3.2, page 132). The results are presented in Table 16. We found that PPD did have possible confounder effects on hazard ratios of infliximab compared to adalimumab in four of the six analyses, including all three models for clustered data. A possible confounder effect of PPD on hazard ratios comparing infliximab and etanercept was also demonstrated in one of the models of six analyses (threshold of 60% for the value of PPD, clustered data). No confounder effect was demonstrated for six analyses yielding hazard ratios for discontinuing adalimumab compared to etanercept.

Table 16: Possible confounder effect of PPD on comparative persistence

Model	Hazard ratio (95% CI)		
	Infliximab versus etanercept	Infliximab versus adalimumab	Adalimumab versus etanercept
Nonclustered data analysis			
No adjustment (crude estimate)	0.97 (0.84-1.13)	1.04 (0.88-1.22)	0.94 (0.77-1.15)
Adjustment for PPD (threshold=60%)		0.98 (0.83-1.17)	
Adjustment for PPD (threshold=70%)			
Adjustment for PPD (threshold=80%)			
Marginal modeling of clustered data			
No adjustment (crude estimate)	0.99 (0.82-1.18)	1.09 (0.92-1.29)	0.91 (0.71-1.17)
Adjustment for PPD (threshold=60%)	0.93 (0.78-1.11)	1.01 (0.85-1.21)	
Adjustment for PPD (threshold=70%)		1.03 (0.87-1.22)	
Adjustment for PPD (threshold=80%)		1.04 (0.89-1.22)	

Presented only for models in which PPD changed the magnitude of point estimate (or confidence limits) of the hazard ratios for discontinuation comparing different drugs by at least 5%

CI – confidence interval; **PPD** – prescriber preference for the prescribed drug

5.4.1 Analysis of Switchers

The proportions of patients who switched to a second drug with higher PPD are presented in Table 17. In patients who were repeatedly treated by the same physician (N=500), the likelihood of switching to second drug with higher PPD was increased when discontinuing a drug with lower PPD compared to discontinuing a drug with a higher PPD, 19.7% versus 11.1% (Chi-square test p-value = 0.008).

Table 17: Analysis of switchers

	Second course prescribed by any physician nN=603)		First and second course prescribed by the same physician (n=500)	
	n	Second course with higher PPD n (%)	n	Second course with higher PPD n (%)
Group 1: First course of a TNFα antagonist with lower PPD	282	62 (22.0)	239	47 (19.7)
Group 2: First course of a TNFα antagonist with higher PPD	321	51 (15.9)	261	29 (11.1)
Chi-square test comparing groups 1 and 2	NSS		p=0.008	

%- percent**; n**-number of patients in the category; **NSS** – not statistically significant; **PPD** – prescriber preference for the prescribed drug; **TNFα** – tumour necrosis factor alpha

5.5 Discussion

We investigated the possible effect of prescriber preference for a specific TNFα antagonist (PPD) on two prescribing situations: discontinuation of a first course and drug selection for a second course. In the first situation, that of discontinuing a first TNFα antagonist course, the results support our hypothesis that higher PPD is associated with improved TNFα antagonist persistence. We also demonstrated that PPD is a possible confounder of the hazard ratios for discontinuation. The second situation that we studied was drug selection[48] in patients who initiated a second course of TNFα antagonists (switchers). In switchers with continued

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[48] We use the term selection to describe the decision on which of the three available TNFα antagonists to use. This decision is conditional on the decision to prescribe a TNFα antagonist.

prescribing by the same prescriber, we demonstrate an increased likelihood of switching to a second TNFα antagonist with a higher PPD when patients discontinued a first course of TNFα antagonist with a lower PPD.

5.5.1 Prescribing Habits and Prescribing decisions

Prescribing decisions are complex processes influenced by multiple factors. Prescribing decisions can be divided into decisions on treatment initiation, adjustment and discontinuation. The effect of the prescribing habits was previously studied in RA treatment initiation and discontinuation.

5.5.1.1 Treatment Initiation

Treatment initiation can be described as a sequel of three decisions: (a) whether to initiate any treatment (default- no treatment), (b) the choice of a therapeutic class and (c) the selection of an individual drug from within the therapeutic class. Each of these decisions is conditional on the previous one. We do not discuss the decision to initiate RA treatment, because TNFα antagonists are rarely indicated as first line therapy (**Appendix A**, Section A.1.3, page 218); hence, the decision to treat the patient can be assumed to have already been made.

Patients who required treatment augmentation due to decreased benefit with a first line drug (synthetic antirheumatic drugs), could be treated with either synthetic antirheumatic drugs (a different drug or more commonly - combinations therapy) or a TNFα antagonist [265-267]. The decision whether to prescribe synthetic antirheumatic drugs or switch to a TNFα

antagonist is often motivated by disease activity and prognostic factors [267,268] but may also

be influenced by the cost of the drug [268-270]. Prescriber preference[49] was found to be the

most important determinant in initiating treatment with TNFα antagonists (compared to

prescribing synthetic antirheumatic drugs) in an on-line survey by Cush et al 2005 [271]. Of

1,023 United State (U.S.) rheumatologists, 48% selected provider preference versus patient

preference or payer guidelines (roughly 20% each).

The role of prescriber preference for the therapeutic class[50], based on previous TNFα

antagonist prescribing patterns, was also demonstrated by Curtis et al 2010 [272,273]. They

analyzed the demographic and clinical data of patients with RA enrolled in the Consortium of

Rheumatology Researchers of North America (CORRONA)[51] cohort study. Prescriber

preference for the therapeutic class was determined based on the proportion of initiators (or

prevalent users) of TNFα antagonists compared to all initiators (or prevalent users) of either

TNFα antagonists or synthetic antirheumatic drugs in patients populations treated by same

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[49] In the study by Cush et al [271], the term *prescriber preference* describes whether the physician favor initiating a TNFα antagonist over other treatment options, such as switching to or adding-on a synthetic antirheumatic drug. The use is similar to the term *prescriber preference for the prescribed drug* used in this thesis, except that is refers to the therapeutic class and not to a specific drug.

[50] In the study by Curtis et al [272,273], the term *prescriber preference* describes whether the physician favor initiating a TNFα antagonist over other treatment options, such as switching to or adding-on a synthetic antirheumatic drug. The use is similar to the term *prescriber preference for the prescribed drug* used in this thesis, except that is refers to the therapeutic class and not to a specific drug.

[51] The CORRONA is a longitudinal cohort that includes patients with RA, psoriatic arthritis, osteoarthritis, and osteoporosis treated by rheumatologists in 35 states in the U.S., founded in 2000. Clinical data is collected prospectively.

prescriber in the preceding year[52]. The analysis was conducted using generalized estimating

equations to account for the clustering of patients by prescriber. The results of the study

indicated that higher preference was associated with increased likelihood of initiating treatment

with a TNFα antagonist[53], especially in MTX naïve patients and in patients with low or

moderate disease activity. Nevertheless, the prescriber preference for the therapeutic class only

slightly improved the model's discrimination[54].

The role of prescriber preference for a therapeutic class was also studied in initiation of

selective inhibitors of cyclooxygenase-2 (COX-2) compared to nonselective NSAIDs in

patients with RA where it was demonstrated to be the most important factor in this decision[55]

[274-276]. Similar association was observed in the decision to prescribe either generic or

nongeneric serotonin reuptake inhibitors and serotonin- norepinephrine reuptake inhibitors

[277].

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[52] Preference was determined two ways: using data on initiators or data on prevalent users. The initiator proportion, for example, was calculated as (number of initiators of a TNFα antagonist)/(number of initiators of either a TNFα antagonist or a synthetic antirheumatic drug), data used in the numerator and denominator were on patients prescribed by the same prescriber in the previous year. For calculating the proportion of prevalent drug users, the researchers used data on all drug users, and not only initiators.

[53] The highest and middle tertiles of prescriber preference were associated with a 1.61-4.89 and 1.14-2.44 greater likelihood of initiating TNFα antagonists compared to the lowest tertile, respectively, after adjusting for demographic and clinical factors.

[54] The c-statistics increased from 0.79 in a model that included only demographic and clinical variable to 0.81 in a model that also included prescriber preference.

[55] Based on standard R-square as a measure of prediction [274,275], C-statistic [275] and Bayesian modeling [276]).

The next prescribing decision is the selection of a specific TNFα antagonist. It is accepted that selection of a specific TNFα antagonist depends on prescriber and/or patient preference, since the benefit and harm profiles of the three drugs are considered to be similar [278-280] despite limited relative effectiveness data. Prescriber and patient preferences for an individual TNFα antagonist are likely to be correlated for the following reasons. First, patient preference was found to be strongly correlated with prescriber preference in studies of NSAID treatment of RA patients [281,282], although this was not studied in patients treated with TNFα antagonists. Second, 67% of 77 Canadian rheumatologists surveyed reported concordance with the patient preference more than 80% of the time[56] [283].

Patient preference for route of administration of TNFα antagonist (**Appendix A**, Section A.3.6.1, page 262), dosing schedule [284,285] or the specific TNFα antagonists [140,286] has been studied. Patients reported preferring etanercept to methotrexate, gold and leflunomide[286] or adalimumab over infliximab and etanercept [140].

Physician preference for the individual TNFα antagonists was studied by Kamal et al 2006 [268]. In respond to mailed questionnaires, 68% of 428 U.S. rheumatologists who responded said they preferred etanercept over adalimumab (preferred by 28%) or infliximab (20%) and considered etanercept the most efficacious of the three drugs with less perceived harm [268].

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[56] Patients were not surveyed separately, but rather the results presented are from the rheumatologists reporting.

We are unfamiliar with any study examining the association between prescriber preference for a particular drug within a therapeutic class and drug selection, in RA patients or other diseases, although a correlation similar to the one observed regarding therapeutic class above could be reasonably expected.

5.5.1.2 Treatment Adjustment

Treatment adjustment consists of dose adjustment of the drug in use (**Appendix A**, Section A.3.6.2, page 265) as well as add-on therapies of additional drugs from the same or different therapeutic class or different class. In decision to adjust treatment in RA patients, physician have been found to be more influenced by objective factors, such as the disease activity score while patients are more influenced by subjective factors, including function, satisfaction with current treatment and motivation to get better [287,288]. The effect of prescribing habits on treatment adjustment strategy has not, to our knowledge, been studied.

5.5.1.3 Drug Discontinuation

Potentially, two aspects of prescribing habits could induce differences in discontinuation decisions: (a) between-physicians differences in response to similar clinical situations (prescriber propensity for treatment discontinuation) and (b) different response to similar clinical situations by the same physician, a response that could be corresponded to the prescriber preference for a particular drug (the rationale is presented in Section 0, page 159).

Between-physicians differences – The main reasons for discontinuing TNFα antagonists in patients with RA, as recorded by the care-providing physicians, are decreased benefit and perceived harm (**Appendix A**, Section 0, page 255). However, physicians may respond

differently to similar clinical situations, a pattern that can be described as prescriber propensity for treatment discontinuation. Differences in response to harm were reported by Cush et al 2005 [271]. American rheumatologists were asked in an on-line survey whether they would discontinue TNFα antagonists' treatment in response to a number of harmful effects. Higher agreement was observed in the events of severe infection (98% of the rheumatologists reported they would discontinue TNFα antagonist treatment in the event of septic arthritis, 97% in pneumonia and 91% in cellulitis) and worsening of congestive heart failure (91%) compared to other infections (50-80%) and following hospitalization (55%). Disagreement on the response to harmful events represents differences in prescriber propensities to treatment discontinuation.

Differences in prescriber response to decreased benefit with TNFα antagonists therapy was recently reported by Zhang et al 2011 [48,289]. Investigators examined the effect of prescriber propensity for treatment discontinuation (they used the term 'prescriber preference')[57] on TNFα antagonist discontinuation due to decreased benefit within the first year of treatment in the CORRONA RA patient cohort. Prescriber propensity for treatment discontinuation was modeled by clustering patients at prescriber level using mixed effect logistic regression model with a random intercept. The study demonstrated the importance of clustering by prescribers, even after adjustment for both baseline disease activity and improvement in disease activity.

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[57] In the study by Zhang et al [48,289], the term *prescriber preference* describes the degree to which the physician favors discontinuation of the TNFα antagonist treatment. In this dissertation, we used the term *prescriber propensity for treatment discontinuation* to describe this phenomenon.

The authors concluded: "We observed a significant clustering effect by physician associated with switching[58], consistent with the idea that there are individual physician-specific factors that affect treatment choices". These factors may include prescriber propensity for treatment discontinuation, the patient's insurance status (relevant to the U.S. health system), the formulary status of the particular TNFα antagonist or the prescriber's case mix of RA patients.

Differences in response of the same physician – Our study was the first to report an effect of PPD (prescriber preference for an individual TNFα antagonist, or any other drug) on discontinuation in RA patients (or any other treatment population). Our model included both a variable for PPD and adjustment for prescriber preference for discontinuation.

Generally, several approaches are appropriate model prescribing habits (preference for the prescribed drug/therapeutic class and propensity to discontinuation) in regression analysis, and they are described in

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[58] In the study by Zhang et al, the term switching included "either discontinuation of the anti-TNF agent and/or changing to a different agent for reasons other than safety/tolerability" [48].

5.5.2 Effect of Prescribing Preference

The effect of prescriber preference for the drug/therapeutic class and prescriber propensity for

treatment discontinuation on prescribing decisions had previously been studied using

administrative (claim) data, but not clinical data or physician survey. We identified two sets of

published analyses of administrative (claim) data that had modeled prescribing habits and their

effect on prescribing decisions. In the first set of studies, studies of treatment initiation,

prescriber preference for a particular drug/therapeutic class was modeled [272-277]. The

second set of studies modeled prescriber propensity for treatment discontinuation (describing

the degree to which the prescriber favored drug discontinuation over other alternatives) and

included a single study by Zhang et al 2011 [48,289]. Our study was the first to include both

types of prescriber variables (prescriber preference for the prescribed drug and prescriber

propensity for treatment discontinuation) in one model.

Analyses of administrative data for the effect of prescribing habits can be performed using

nonclustered or clustered data approaches. The difference in the outcome variable between the

abovementioned two sets of studies leads to discrepancies in interpretability of the results

between studies of treatment initiation versus studies of discontinuation (Figure 15 and Figure

16). Below, we present the methods and the interpretability of results of modeling the effect of

prescribing habits on drug discontinuation.

Figure 15: Adjusting for physician preference in studies of treatment initiation
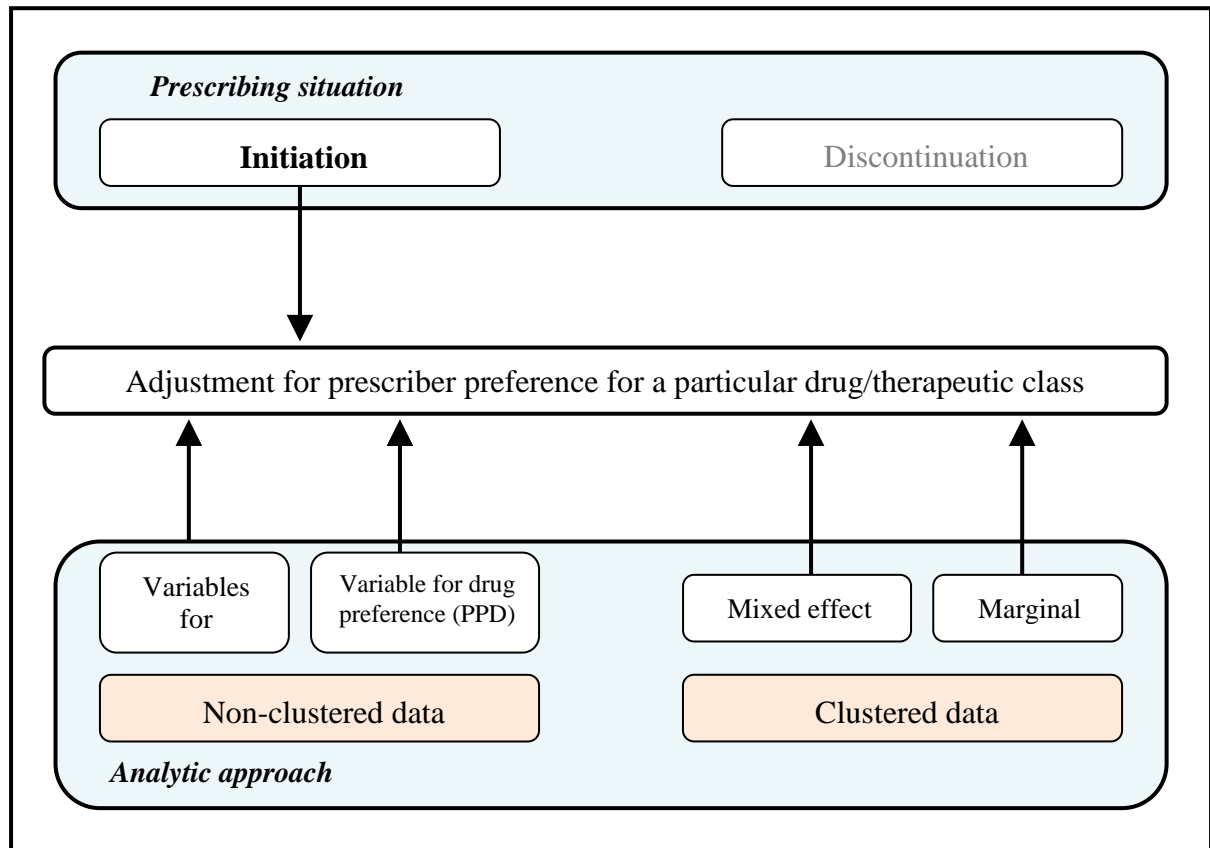
Figure 16: Adjusting for physician preference in studies of drug discontinuation
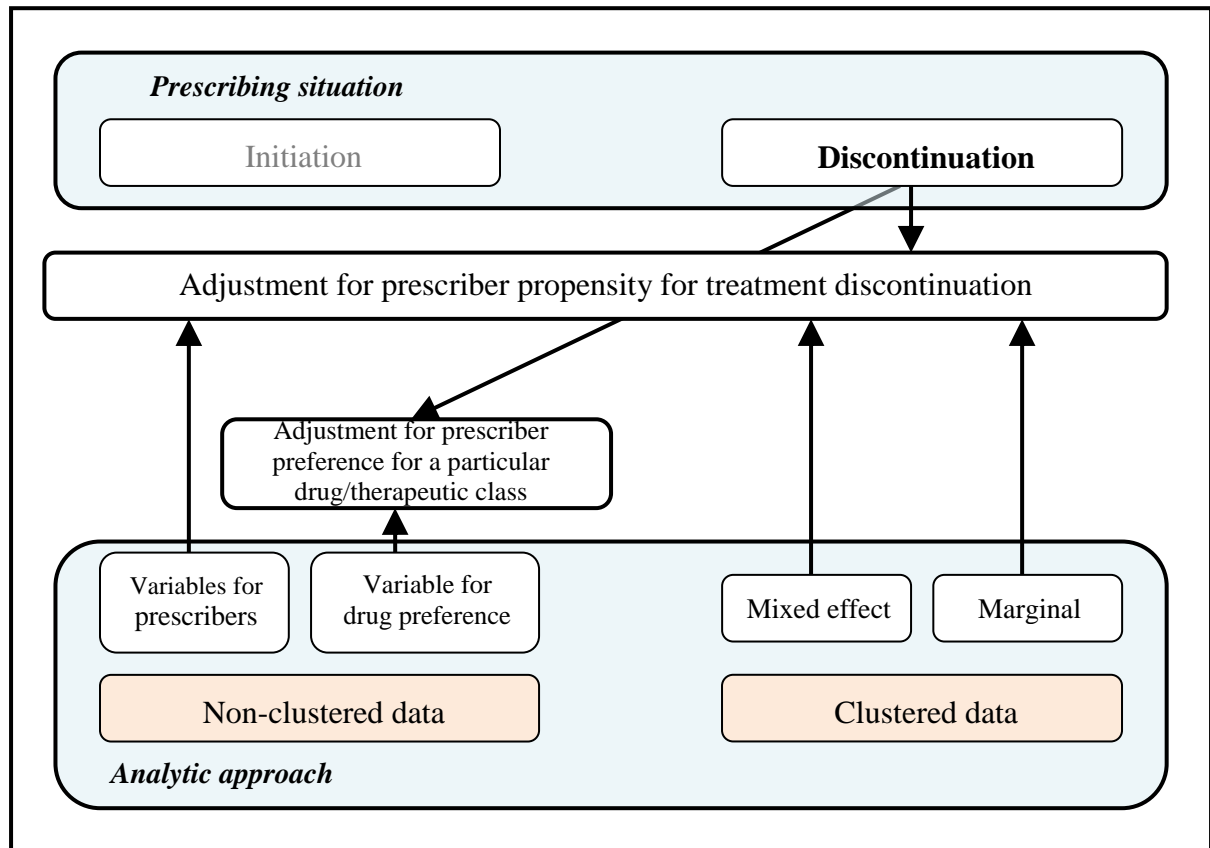
In analysis of nonclustered data, there are two acceptable approaches: (a) modeling the individual prescriber propensity for treatment discontinuation and (b) modeling prescriber preference for a particular drug/therapeutic class at treatment initiation (e.g., PPD). In the first approach, the analyst includes a Bernoulli variable for each individual prescriber (Chapter 3, Section 3.3.2, page 62 and Chapter 4, Section 4.3.5, page 92). This allows individualization of the likelihood of discontinuation (prescriber propensity for treatment discontinuation). Using this approach, we assume that the effect of all other predictors of discontinuation is uniform across all prescribers. The second approach for nonclustered data analysis is to include a variable that describes preference to initiate a particular therapeutic class or an individual drug (similar to the variable PPD used in this chapter, Section 5.3.2, page 132). Prescriber preference for the prescribed drug/therapeutic class is assigned based on previous prescribing habits of the prescriber, using either initiating data (this study and Curtis et al 2010 [272][59]), or all prescribing data (prevalent users [272,277][59,60]). The assumption that previous prescribing accurately describes prescriber preference for the prescribed drug was validated by Mark et al 2004 [290], who compared stated preference for various antialcoholism drugs measured using validated questionnaires with prescribing data based on actual prescribing decisions.

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[59] The studies cited assessed treatment initiating. No study assessing discontinuation adjusted for preference for the prescribed drug or therapeutic class.

[60] The study by Baser [277] modeled prescriber preference for a particular therapeutic class (selective serotonin reuptake inhibitors versus serotonin- norepinephrine reuptake inhibitors) and test for its strengths as an instrumental variable.

Alternatively, analysis of clustered data (by care-providing physician) can account for prescriber propensity for treatment discontinuation compared to other treatment alternatives. Investigators can use either mixed effect models [48,289] or marginal models (similar to the modeling presented in this chapter, Section 5.3.4, page 137) (Figure 16). Analysis of clustered data is based on the assumption that patients treated by the same prescriber were more similar to each other (and therefore had similar likelihood to discontinue) than to patients treated by other prescribers. One of the reasons for clustering effect is distinct prescriber propensity for treatment discontinuation, although other reasons are possible as well.

5.5.3 *Effect of Prescriber Preference for the Prescribed Drug on TNFα Antagonists Persistence*

We suggest three possible explanations for the finding of improved persistence with increased prescriber preference for the prescribed TNFα antagonist (PPD). First, the results could be explained in light of the theory of cognitive dissonance [291]. In line with this theory, treating with a drug believed to be inferior (lower PPD) induced dissonance[61]. In indefinite clinical situations, such as mild harmful effect, or questionable benefit, early drug discontinuation supports the physician's belief that the selected drug was inferior compared to the alternatives.

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[61] Dissonance is the uncomfortable feeling caused by holding conflicting ideas simultaneously.

On the other hand, in similar indefinite clinical situations, a drug with a higher PPD might be continued, to support a belief in its superiority. The interpretation of our results using the theory of cognitive dissonance is restricted by a lack of direct measurement of dissonance. Direct measures of cognitive dissonance are complicated and involve activities beyond the scope of the current study such as questioning the physician both at the time of treatment and initiation and discontinuation [292]. Database analyses are relatively inexpensive to perform, and in many cases, the results should be interpreted as signals of a possible association that justify further research. The indirect measure of dissonance we used, PPD, could also be influenced by factors unrelated to prescriber beliefs, such as limited availability of a drug or higher relative cost.

Secondly, the observed association between higher PPD and improved persistence might be the result of a correlation of both PPD and persistence with past experience with the drug, namely the total number of patients a prescriber has previously treated with the same drug. Increased experience with a specific drug may be associated with higher PPD as a result of the algorithm we used to define PPD, but also because of a tendency to continue doing what is familiar. Theoretically, increased experience with a specific drug should also be associated with improved persistence, due to improved patient selection which results in decreased risk of harmful effects or decreased benefit.

Lastly, a prescriber's stated preference for a particular drug has been shown to correlate with patient preference [281,282], although this correlation has not been studied in relation to TNFα antagonist therapy, nor has preference as estimated based on previous prescribing habits been correlated with patient preference in TNFα antagonists treatment or other treatment situations.

If this correlation is valid in the context in our analysis, then improved persistence may have been a result of higher patient rather than prescriber preference. The association between patient preference and persistence was discussed in **Appendix A**, Section A.3.6.1, page 262.

Implications We have demonstrated that care-provider characteristics, specifically prescribing habits, besides patient characteristics and an individual TNFα antagonist effect, also has an impact on persistence and this finding calls into question the validity of the assumption that persistence is a valid measure that balances benefit and harm. In addition to prescriber propensity for treatment discontinuation (**Chapter 3**, Section 3.4.2, page 68, [48,271,289]), we have demonstrated that prescriber preference for a particular TNFα antagonist also affects discontinuation. We therefore conclude that clinical and policy decisions based on the finding of persistence studies as a measure of effectiveness and harm may be unsound.

Awareness of the possible role of the cognitive dissonance in clinical decision-making based on beliefs unsupported by clinical evidence can contribute to the development of education programs for prescribers, as well as health policy development. We highlight a situation in which prescriber preference for a particular TNFα antagonist was not based on clinical evidence as confirmed by inconsistencies in treatment patterns amongst prescribers. Cognitive dissonance may also play a role in improving adherence to clinical or health policy guidelines in that insights gained about actual prescribing behaviour in the absence of rationale can be used to motivate rational prescribing. Most of this type of research is warranted to identify and explore similar situation for the purpose of developing evidence-based clinical guidelines and identifying effective policy implementation approaches.

Future research We suggest three alternative explanations for our findings, which could lead to further research in the corresponding direction of: (a) directly measuring cognitive dissonance, (b) analyzing the effect of prescriber experience on persistence and (c) measuring patient preference and its correlation with prescriber preference. In addition, we propose to directly measure prescriber preference for individual TNFα antagonist drugs, by using questionnaires at the time of treatment initiation and drug discontinuation. The correlation between preference and dissonance, preference and previous prescribing habits and preference and persistence could thereby be assessed. We also suggest extending the research to study the effect of prescriber preference in pharmacological treatments of chronic diseases, such as Alzheimer disease, chronic lung disease and other rheumatologic diseases, to test for the generalizability of our findings.

5.5.4 Effect of Prescriber Preference on Comparative Persistence with TNFα Antagonists

We demonstrate that comparative persistence was confounded by prescriber preference for a particular TNFα antagonist. This means that the effect of prescriber preference on persistence may be different for each TNFα antagonist. The effect is probably more pronounced in patients treated with infliximab as only hazard ratios comparing infliximab were affected. We propose that the close monitoring of patients treated with intravenous infliximab and regular communication between patients and physicians that must of necessity occur with intravenous administration is the root of this greater influence of PPD on persistence. In drugs administered subcutaneous, the effect is probably "diluted" by patient behaviour.

Implications Excluding PPD from analysis of comparative persistence may have been another factor that caused heterogeneity in previous estimated of comparative persistence with TNFα antagonists (an original unpublished systematic review and meta-anaysis). As a result, findings would appear to have been biased at least in some of the studies. This provides additional support for our conclusions about the limited validity of the current literature on comparative persistence with TNFα antagonists in RA. Therefore the available research to date on the comparative persistence of TNFα antagonists is an inappropriate basis for clinical and policy decisions.

Future research We suggest that adjusting for PPD is warranted in studies of comparative persistence of TNFα antagonists in RA patients because it may confound the results. We also suggest extending the research to study its possible confounding effect in comparative persistence studies of other pharmacological treatments of chronic diseases.

5.5.5 *Analysis of Switchers*

We suggest three possible explanations for the finding of an increased likelihood of switching to a second drug with higher PPD when patients discontinued the TNFα antagonist of lower PPD (in switchers with continuous prescribing by the same prescriber). First, this finding is also supported by the theory of cognitive dissonance because selecting a second drug believed to be superior would further decrease dissonance. Second, when a patient failed on a drug with a higher PPD, the second TNFα antagonist could be of higher PPD only if the prescriber preference had changed over time (between initiation of the first course and the second course).

This is probably not very common, especially with short persistence on the first and failed course. As a result, artificially low percentages of patients were treated with both first and second drug of higher PPD. Last, the results may be confounded by other factors that influence drug selection (for example age or accessibility to health services). We did not model the likelihood or adjusted for these other factors, but rather used crude proportions.

Future research While the effect of prescriber preference was often studied in the context of initiating treatment, we did not find studies examining the selection of a second drug i.e., studies of TNFα antagonist sequencing. Our attempt to study factors that influence drug sequencing failed due to insufficient sample size and this analysis is not presented in this dissertation. Therefore, this appears to be a useful area for further research.

5.5.6 Strengths and Limitations

In this population-based study, we used a large sample of patients with a prolonged duration of follow up. These features increased the power of the study to detect differences in persistence. We adjusted for multiple variables that might have influenced selection of a specific TNFα antagonist and/or drug persistence. Treatment with TNFα antagonists is especially suitable for studying effects of PPD, since the available evidence suggests that the drugs are indeed comparable (**Appendix A**, Section A.3.1.1, page 241). Published clinical guidelines recommend using either TNFα antagonist (interchangeably) based on assumed similar effectiveness of the three drugs (**Appendix A**, Section A.1.3, page 218). In addition, diverse indications for discontinuation are presented in these guidelines (**Appendix A**, Section A.3.2,

page 251), and it has been demonstrated that prescribers differ in the way they interpret and respond to decreased benefit [48,289] or perceived harm [271].

There are several limitations to ascertaining PPD based on TNFα antagonist initiation in the past. First, the PPD was not defined for all patients, for example, for the first patient treated by the prescriber, or if the physician did not prescribed this class of drugs in the preceding year. Second, we assumed that increased loyalty for a particular TNFα antagonist reflects preference, but we did not measure preference directly. As mentioned, stated preference and prescribing habits were shown to correlate in previous research [290].Third, we measured PPD at the time of treatment initiation and not at discontinuation, and prescriber preference might have changed over time. Finally, we assumed strong preference for one drug only and regarded situations in which the prescriber preferred two of the TNFα antagonist to be a situation of treatment with a drug of lower PPD.

5.6 Conclusions

☐ In RA patients treated with a first course of TNFα antagonists, higher PPD was associated with improved persistence.

☐ PPD was also found to confound estimates of comparative persistence. Consequently, our results provide additional explanations for the heterogeneity observed in previous studies of comparative persistence with TNFα antagonists in RA patients.

CHAPTER 6: CONCLUDING CHAPTER

This thesis sought evidence on methodological aspects of measuring persistence, as well as the influence of different characteristics of the care-providing physician in estimates of comparative persistence with TNFα antagonists in RA The main findings of the research, their context and their implications are presented below.

6.1 There Were Similar Persistence Levels Observed With Infliximab, Adalimumab and Etanercept but Improved Compliance Only With Infliximab in RA Patients

Our analysis of British Columbia administrative data showed similar persistence with infliximab, adalimumab and etanercept in patients with RA (median of roughly 3.5 years) (**Chapter 3**, Section 3.4.1, page 64). Discontinuation of TNFα antagonist therapy was based on either (a) a drug-free interval after a missed refill or (b) switching to another antirheumatic monoclonal antibody or immunosuppressant drug. Persistence was measured using a long drug-free interval of 180 days to ascertain discontinuation, in order to minimize the likelihood that the same drug was reinitiated after only temporary interruption.

Patients treated with etanercept and adalimumab were more likely than patients treated with infliximab to interrupt drug use (for 30 days or more) after which they reinitiated treatment with the same drug (**Chapter 4**, Section 4.4.3, page 105). About half of RA patients who had experienced an interruption of 30 days in persistence reinitiated the same drug within another

150 days. This result is compatible with findings in other chronic treatment situations, such as osteoporosis therapy [293] and treatment with statins [185]).Temporary interruptions in drug persistence are a possible signal of poor compliance. Therefore, our finding suggests compliance is best with infliximab, perhaps due to more frequent encounters with health professionals due to intravenous administration of this drug.

Clinical and policy implications Our results show that using short drug-free intervals can lead to invalid persistence estimates. Short drug-free intervals of 30-60 days have often been used to ascertain discontinuation in previous studies including those of TNFα antagonists. Approximately third of the patients included in our study reinitiated the same drug after interruptions of 30 days in persistence. Approximately half of the patients reinitiated the same drug within 150 days after such interruptions. Therefore, short drug-free intervals of 30-60 days should not be used to determine overall drug persistence, especially in drugs with intermittent dosing schedule, such as TNFα antagonists.

Improved compliance with a variety of treatments is associated with improved effectiveness and decreases in over-all direct medical costs. Our results showed that compliance among TNFα antagonists is best with infliximab. Therefore, any program developed to improve compliance with TNFα antagonists should specifically address why patients treated with etanercept and adalimumab are particularly less likely to comply. This approach will have the greatest impact in health outcomes and health care expenditures.

The effect of poor compliance on the effectiveness of TNFα antagonists has not been well studied. The prolonged therapeutic effect of TNFα antagonists may result in a weak association

between poor compliance and drug ineffectiveness. Consequently, the clinical significance of relatively poor compliance with adalimumab and etanercept compared to infliximab cannot be readily established.

Better compliance with infliximab should be addressed in cost effectiveness studies as well as in health budget planning. Decreased drug expenditures due to noncompliance may be offset by increases in other health care expenditures. Higher acquisition costs associated with intravenous administration of infliximab also need to be considered. Further research to assess the cost implications of our observed compliance estimates is also needed.

Research implications The use of a short drug-free interval of 60 days or less to ascertain TNFα antagonist discontinuation introduces a potential for poor compliance to distort estimates of persistence. This is because patients who experience a short interruption in treatment are likely to reinitiate the same drug and therefore falsely classified as discontinuers.

The use of a short drug-free interval of 60 days or less to ascertain TNFα antagonist exposure in studies of health outcomes may also lead to invalid treatment effect estimates due to exposure misclassification. Specifically, patients who are considered discontinuers using this method may actually reinitiate treatment and yet be analyzed as if they were unexposed. This may lead to misleading conclusions. For example, an increased risk of harm after discontinuation may be actually caused by reinitiating the drug and not by a rebound effect. Misclassification bias is also a concern when benefit is observed during exposure to the drug but is apparently diminished after the patient is wrongly considered to have discontinued the drug, a phenomenon that may actually be caused by 'tolerance' (i.e., diminished effect of the drug with longer exposure) in patients who continue to be exposed after reinitiating the drug.

169

6.2 Comparative Persistence with TNFα Antagonists was Sensitive to the Method Used to Ascertain Drug Discontinuation

We studied the effect that different pre-specified 'drug-free intervals' had on discontinuation of TNFα antagonists in patients with RA (**Chapter 4**, Section 4.4.2, page 96). A longer drug-free interval was associated with improved persistence with every TNFα antagonist. An increase in the overall median persistence from 1.13 years, to 2.19, 2.87 and 3.70 years was found after applying drug-free intervals of 30, 60, 90, and 180 days, respectively.

Similar persistence between the three drugs was demonstrated in multivariable-adjusted models by applying drug-free intervals of 30 and 60 days. Improved persistence was observed with infliximab compared to the other drugs after applying longer intervals of 90 and 180 day). Persistence with adalimumab and etanercept remained similar with the longer drug-free intervals.

Research Implications We provide evidence that heterogeneity in estimates of comparative persistence on TNFα antagonists in RA can be explained by a lack of consensus on the drug-free interval used to determine discontinuation. Achieving consensus on how to choose the drug-free interval is essential for establishing a chain of valid evidence whereby different studies can contribute data on a common and comparable measure of persistence on TNFα antagonists. This advice also applies more broadly, to persistence studies in other drug classes.

6.3 Physician Prescribing Preferences are Predictors and Possible Confounders in Comparative Persistence Studies

We examined how prescribing preference influenced persistence on TNFα antagonists. Specifically, we studied two aspects: prescriber preference for the prescribed drug (PPD) and physician's propensity to treatment discontinuation. The first habit, PPD, measures the frequency of prescribing the particular drug compared to other drugs within the same therapeutic class. Its value is unique for each course and is assigned to a patient based on the first prescriber and drug and the period during which it was measured. Not only was higher PPD was associated with improved persistence (median persistence of 4.28 compared to 3.27 years in courses with lower preference, **Chapter 5**, Section 5.4.2, page 141) but PPD was also found to confound estimates of comparative persistence (especially in comparisons of infliximab and adalimumab (**Chapter 5**, Section 0, page 146) .

The second habit is a physician's propensity for treatment discontinuation, i.e. an individual likelihood to recommend discontinuing a TNFα antagonist, with higher propensity associated with lower persistence of patients treated by this prescriber (**Chapter 3**, Section 3.4.2, page 68). These differences could reflect different "sensitivity" of the prescribers to benefit or harm or present difference in patients mix that were not adjusted for. Furthermore, a confounding influence on comparative persistence by a prescriber's propensity for discontinuation was demonstrated (a change of at least 5% in the magnitude of hazard ratios in comparisons of infliximab versus adalimumab and of adalimumab versus etanercept). Persistence remained similar (**Chapter 3**, Section 3.4.3, page 71).

Clinical and Policy Implications Our research is the first to demonstrate an effect of prescribing habits (drug preference and propensity for discontinuation) on treatment persistence with any drug. The effects of prescribing habits has not been well. Awareness of this effect should contribute to physician educational programs – a change in physician preference could prolong drug persistence. Restricting drug coverage policies without addressing drug preference probably would not achieve the same effect.

Research Implications Our results showed that confounding effects due to prescriber preference and propensity for discontinuation provide another possible reason for heterogeneity in comparative persistence estimates across different TNFα antagonist studies. We suspect that differences in drug preference and discontinuation propensity between different prescriber populations in different studies might have also led to different estimates. Ignoring this effect in future research studies of persistence likely limit the validity and interpretability of the results.

6.4 Confounding is a Threat to Validity in Estimating Comparative Persistence

Confounding is the main threat to validity of comparative persistence estimates. This source of bias should be considered in any interpretation and appraisal of comparative persistence research on TNFα antagonists in RA patients, and is a good advice for any disease where multiple treatments can be interchangeability used.

Three factors were found to confound estimates of comparative persistence with TNFα antagonists in RA patients: (a) concomitant use of MTX (**Chapter 3**, Section 3.4.3, page 71), (b) prescriber propensity for discontinuation (**Chapter 3**, Section 3.4.3, page 71) and (c) prescriber preference for a particular drug (**Chapter 5**, Section 0, page 146).

In addition, any predictor of persistence has the potential to confound estimates of comparative persistence if it is also associated with drug's selection. We demonstrate a number of patient characteristics that are predictors of shorter persistence and therefore have the potential to confound comparative persistence studies of TNFα antagonists in RA. These include: (a) female sex (**Chapter 3**, Section 3.4.2, page 68); (b) age under 30 or over 70 (**Chapter 3**, Section 3.4.2, page 68); (c) admission to hospital in the year preceding the index date (**Chapter 3**, Section 3.4.2, page 68); (d) absence of concomitant use of MTX (**Chapter 3**, Section 3.4.2, page 68 and **Appendix A**, Section A.3.5, page 261); (e) recent/current use of NSAIDs within the year preceding drug imitation (**Chapter 3**, Section 3.4.2, page 68) and (f) exposure to an increased number of synthetic antirheumatic drugs (**Chapter 3**, Section 3.4.2, page 68 and **Appendix A**, Section A.3.5, page 261). Additionally, we demonstrate that prescriber propensity for treatment discontinuation (**Chapter 3**, Section 3.4.2, page 68) and prescriber preference for the prescribed drug (**Chapter 5**, Section 5.4.2, page 141) influenced persistence.

Previous research has not shown that disease severity is a predictor of persistence (**Appendix A**, Section A.3.5, page 261). This is surprising, given that patients with more severe disease will presumably experience larger improvement in symptoms (regression to the mean[62]) and therefore be more likely to persist on their treatment. We could not confirm or refute this preassumption in our research because we lacked clinical data on disease severity.

Research Implications Failure to adjust a TNFα antagonist analysis for concomitant MTX, prescriber propensity for treatment discontinuation, and prescriber preference for the prescribed drug is a potential threat to study validity, since we have shown in our data that those variables are confounders. Therefore, future studies should include an adjustment for these factors in testing for hypothesis.

A second group of variables are predictors of drug persistence that have the potential to bias comparative persistence study results if unequally distributed between drug groups. Therefore, future studies could (a) test if these factors are confounders by testing for equal distribution of these factors between drug groups and adjusting for those factors if required; and (b) testing for an independent association between those factors and persistence.

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[62] Regression to the mean is "the tendency of an individual at the extreme to have values nearer to the mean on repeated measurement" [1].

Sex, age, hospital admissions, concomitant use of MTX, use of NSAIDs, number of previous synthetic antirheumatic drugs and prescriber preference for the prescribed drug are all predictors of persistence and therefore should be included in models predicting persistence. Adjustment for prescriber propensity for treatment discontinuation could be performed in these models using a marginal approach.

6.5 Interpretation of Persistence and Comparative Persistence as Measures of Benfit-Harm Balance or Relative Benfit-Harm Balance With TNFα Antagonists in RA Patients

Treatment persistence is often used as an indirect measure that integrates benefit and harm [45] in studies of RA patients. Accordingly, comparative persistence, a relative measure, has also been suggested as an indirect measure of the relative benefit-harm balance of individual drugs. In **Chapter 4** (Section 4.5.3, page 117), three arguments were put forward to challenge this assumption. First, when data from previous studies were pooled, we found that factors unrelated to drug benefit and harm were given as the reason for discontinuation for about one quarter of patients. Furthermore, these reasons were not evenly distributed between groups treated with different drugs which may result in differential influence of factors unrelated to drug effectiveness on persistence. Therefore, persistence would inaccurately reflect benefit-harm balance. Second, alternative clinical approaches have been used in patients who experienced either a lack of benefit or a harmful event. Pooled data from previous studies demonstrated that between-group differences in, for example, dose adjustment were more common in patients treated with infliximab compared to adalimumab or etanercept. Lastly, we

175

demonstrated that drug properties, such as therapeutic effect and harm, and patient characteristics were not the only factors that determine persistence. Persistence was also influenced by prescriber propensity for treatment discontinuation (**Chapter 3**, Section 3.4.2, page 68**),** prescriber preference for the prescribed drug (**Chapter 5**, Section 5.4.2, page 141) and investigator-related factors (methods, specifically ascertainment of drug discontinuation, **Chapter 4**, Section 4.4.2, page 96). These factors have differential effects between groups of patients treated with different drugs.

Clinical and policy implications Although comparative persistence is not a valid measure of the relative benefit-harm balance using currently available TNFα antagonists data, data on persistence and comparative persistence with the TNFα antagonists is useful in interpreting results of other studies, such as effectiveness studies (as described in Section 6.6, page 177).

Persistence on the drug, for whatever reason, is critical to determining cost associated with treatment and therefore information on persistence and comparative persistence with the TNFα antagonists is useful for cost-effectiveness analysis and budget planning.

Research implications The analysis herein as to whether or not persistence and comparative persistence are valid measures of benefit-harm balance is indirect. Definitive evidence is required from a study that directly tests for the correlation between persistence and effectiveness/adverse effects (using longitudinal data analysis). While all previous studies examined the effect of drug discontinuation on therapeutic benefit, testing for the influence of ineffectiveness on the likelihood to discontinue TNFα antagonists has been neglected. Patients should be followed to ascertain the benefit and harm they experience from the treatment, and determine the effect of lack of benefit or perceived harm on the likelihood of discontinuation.

This type of research is challenging and requires access to longitudinal data on therapeutic benefit, harmful events and TNFα antagonist administration dates, as well as techniques for complicated analysis.

6.6 Relevance to Studies of Therapeutic Outcomes

Accurate measurement of drug exposure is essential in pharmacoepidemiologic studies of therapeutic outcomes. Especially important are accurate descriptions of the exposed and unexposed populations, the timing of exposure, and the duration and intensity of exposure. We show that even when drugs within the same therapeutic group are compared, the relative duration of exposure to TNFα antagonists (comparative persistence) is sensitive to methodological issues and therefore the approach used may influence the estimated association between the drug and the study outcome. Sensitivity analysis using different methods to ascertain drug discontinuation is also essential in studies of therapeutic outcomes.

Studies of therapeutic outcomes seldom cluster patients by care-providers. It is intuitive that patients treated by the same physician are more similar than patients treated by other physicians, both because of the behaviour of the physician, but also as a result of the patient's reasons to approach a particular physician. The significance of clustering by care-providing physicians was demonstrated in drug initiating [274,275] and in drug discontinuation ([48], **Chapter 3**, Section 3.4.2, page 68). Therefore, it seems probable that the prescribing behaviour of physicians varies and therefore influences the length of exposure to the drug. Clustering by care-providing physician can also influence some of the outcomes by affecting time of

diagnosis or coding. We assume that ignoring clustering of patients by physician may bias

results of therapeutic outcome studies, due to differences in drug persistence (exposure), but

also awareness or sensitivity to therapeutic outcomes.

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APPENDICES

APPENDIX A: CLINICAL AND PHARMACOLOGICAL BACKGROUND (SUPPORTING MATERIAL)

This appendix presents in three parts the essential background about the triad being investigated in this thesis: the disease, the drugs and the treatment. The first part is about the disease of RA. RA is a common progressive disease that is costly in terms of impact on quality of life and health care resource use; hence, research is important to reduce these impacts. The second part presents the differences in the pharmacological characteristics of the TNFα antagonist drugs to support the hypothesis that different drugs have different magnitude of effectiveness. The third part describes several special features of TNFα antagonist treatment that are relevant to the thesis.

A.1. The Disease: Rheumatoid Arthritis

A.1.1 Clinical Manifestation and Diagnosis

RA is a common inflammatory systemic disease that causes progressive morbidity and disability, increased mortality and an excessive economic burden to individuals, their families and the health care system. The disease is characterized by inflammation of the lining surfaces of the joints (synovium), heart (pericardium) and lung (pleura) as well as by rheumatoid nodules and vasculitis. The characteristic manifestation is persistent symmetric polyarthritis

affecting mainly the small joints of the hands and feet. Diagnosing RA can be challenging

because there are no definitive test findings. A set of clinical and laboratory criteria developed

by the American College of Rheumatology (ACR) has therefore become the gold standard for

diagnosis [294]. At least four of the following criteria are required to confirm the diagnosis of

RA: (a) morning stiffness in and around joints lasting more than one hour, (b) arthritis of three

or more joint areas involved simultaneously, (c) arthritis of at least one area in a wrist,

metacarpal or proximal interphalangeal joint, (d) symmetrical arthritis involving the same joint

areas, (e) rheumatoid nodules, (f) positive serum rheumatoid factor, and (g) radiological

changes typical of RA in hand and wrist x-rays. RA is also associated with increased risk of

cardiovascular disease, infection, osteoporosis and depression, and may shorten life expectancy

by six to ten years [295].

A.1.2 Epidemiology and Economic Burden

The worldwide prevalence of RA is estimated to be 0.18-1.07% with an incidence of 10-50

new cases per 100,000 population annually [296]. In North America the estimated prevalence

is higher at 0.6-1.2% with an annual incidence of 40 per 100,000 [297,298]. In the Canadian

province of British Columbia, prevalence was roughly estimated to be between 0.71%[63] [299-301] and 0.90%[64] [301,302]. In general, a substantial decline in RA incidence was observed untl 1995[65] [296]; however, the incidence seems to be on the rise again in recent years [303,304]. RA is more common in women [305] and there is a secular trend toward a more elderly age of onset [296,306,307].

RA is associated with a significant economic burden since it cannot be cured and the ages of most frequent onset, the fourth or fifth decades of life, are relatively early in the life cycle. Estimates of direct and indirect medical costs of the disease vary greatly. This is due at least in part to methodological differences, such as the type of services included in those assessments. Nevertheless, all studies have concluded that costs of RA management are substantial and that a large portion of the overall cost is indirect (e.g., productivity loss, compensation for work disability and impact of mortality) [308]. The direct annual medical costs in Canada were estimated to be $5,100 per patient in the fiscal year May 1999 to May 2000 [309] increasing to $10,300 in the year 2002 [310]. The introduction of infliximab and etanercept to the Canadian market in 2001 was responsible for most of this difference, with a mean annual cost of $4,200

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[63] In 2000, 22,710 patients were identified with RA [299,300], census British Columbia population (2001) was 3,907,738 [301]; prevalence 0.71%

[64] In 2006 37,161 RA patients were identified [302], census British Columbia population was 4,113,487 [301]; prevalence 0.90%

[65] A decrease in the incidence rate of RA was observed in Rochester, Minnesota between 1955 and 1994 [483] and in Finland between the years 1980 and 1995 [484]

for antirheumatic monoclonal antibodies and immunomodulators [310]. When both direct and indirect costs of treatment are considered, the total annual cost increased from $9,300 in 1999/2000 to $25,000 in 2002.

A.1.3 Drug Therapy in Rheumatoid Arthritis

The antirheumatic drugs are a heterogeneous group of drugs from various therapeutic classes with a variety of mechanisms of action. Historically, drugs used in treatment of RA are divided into four categories: (a) nonsteroidal anti-inflammatory drugs (NSAIDs), (b) glucocorticosteroids (c) the 'old' or traditional antirheumatic drugs and (d) the 'new' antirheumatic drugs. The 'old' or traditional drugs are short synthetic drugs from a variety of therapeutic classes. The terms disease modifying antirheumatic drugs (DMARDs) or nonbiologic DMARDs have often been used in the literature to identify drugs from this heterogeneous group, regardless of lack of evidence that these drugs actually change the natural history of the disease. The 'new' drugs (sometimes termed biologics or biologic DMARDs) are a heterogeneous group of genetically engineered proteins that are either monoclonal antibodies or other immunomodulators. These drugs act to suppress inflammation by inhibiting various cytokines and cell function. We use the term synthetic antirheumatic drugs to describe 'older' drugs, including glucocorticosteroids and the term antirheumatic monoclonal antibodies and immunomodulators to describe the 'biologic drugs'. Table 18 presents the antirheumatic drugs marketed in Canada and approved for treatment of RA.

Table 18: Antirheumatic drugs in Canada

ATC, drug	ATC Level 1 ATC Level 3 ATC Level 4 [28]	Mechanism of action [28,311]
Synthetic antirheumatic drugs		
A07EC01 Sulfasalazine	Alimentary tract and metabolism Intestinal antinflammatory agents Aminosalicylic acid and similar agents	The mechanism of action of sulfasalazine in RA is not completely known. In vitro, sulfasalazine prevent the stimulation of T cells and the activation of nuclear transcription factor kappa B [312]. Additionally it may inhibit prostaglandin synthesis.
L04AD01 Cyclosporine (Ciclosporin)	Antineoplastic and immunomodulating agents Immunosuppressant Calcineurin inhibitors	Cyclosporine inhibits calcineurin, which is a calcium and calmodulin-dependent serine/threonine phosphatase. Presentation of antigen to T lymphocytes triggers an increase in intracellular calcium levels and activation of calcineurin. Calcineurin dephosphorylate the cytosolic nuclear factor of activated T cells, so it can translocate into the nucleus and stimulate production of cytokines [313].
L04AX01 Azathioprine L04AX03 Methotrexate	Antineoplastic and immunomodulating agents Immunosuppressant Other immunosuppressant	Azathioprine is a purine analog that is incorporated into replicating DNA and blokes de novo pathways of purine synthesis, an action which is probably specific to lymphocytes [314]. The mechanism of action of methotrexate in the treatment of RA is unknown but may be more anti-inflammatory than immunosuppressive: inhibition of interleukin-1 activity or other inflammatory cytokines (interleukin-6, TNFα) [315]
L04AA13 Leflunomide	Antineoplastic and immunomodulating agents Immunosuppressant Selective immunosuppressant	Leflunomide inhibits dihydroorotate dehydrogenase and tyrosine kinases, and therefore inhibits pyrimidine synthesis. Since activated lymphocytes expend their pyrimidine pool by about eight folds during proliferation, the drug arrests stimulated calls [316,317].

ATC, drug	ATC Level 1 ATC Level 3 ATC Level 4 [28]	Mechanism of action [28,311]
P01BA02 Hydroxychloroquine	Antiparasitic products, insecticide and repellents Antimalarial Quinolines	The drug rapidly enters the cell and the lysosomes and elevates the pH within the lysosome. This results in inactivation of acid proteases. The drug interferes with receptor function, inhibits intracellular processing and secretion of proteins, decreases lymphocyte proliferation and interferes with natural killer T-cell activity. It may interrupt activation of synovial fibroblasts [318] .
M01CB01 Sodium aurothiomalate M01CB03 Auranofin	Musculoskeletal system Specific antirheumatic agents Gold preparations	Azathioprine is an derivative of mercaptopurine that antagonizes purine metabolism and may inhibit synthesis of DNA, RNA, and proteins. It may also interfere with cellular metabolism and inhibit mitosis.
M01CC01 Penicillamine	Musculoskeletal system Specific antirheumatic agents Penicillamine and similar agents	The mechanism of action of penicillamine in RA is unknown. It produces no significant depression in absolute levels of serum immunoglobulins and depresses T-cell activity but not B-cell activity in vitro.
Antirheumatic monoclonal antibodies and immunomodulators		
L04AB01 Etanercept L04AB02 Infliximab L04AB04 Adalimumab L04AB05 Certolizumab pegol L04AB06 Golimumab	Antineoplastic and immunomodulating agents Immunosuppressants Tumour necrosis factor alpha inhibitors	Refer to Section A.2, page 223

ATC, drug	ATC Level 1 ATC Level 3 ATC Level 4 [28]	Mechanism of action [28,311]
L04AC03 Anakinra L04AC07 Tocilizumab	Antineoplastic and immunomodulating agents Immunosuppressants Interleukin inhibitors	Anakinra is antagonist of the interleukin-1 receptor. Endogenous interleukin-1 is induced by inflammatory stimuli and mediates a variety of immunological responses, including tissue (cartilage and bone) destruction [319] Tocilizumab is a recombinant humanized antihuman interleukin-6 receptor monoclonal antibody. IL-6 is a multifunctional cytokine, produced by a variety of cell types and involved in T-cell activation, induction of acute phase proteins, and stimulation of hematopoiesis. Elevated serum interleukin-6 levels have been reported in RA. Tocilizumab binds specifically to both soluble and membrane-bound interleukin-6 receptors and causes changes in neutrophils and platelet counts [320].
L01XC02 Rituximab	Antineoplastic and immunomodulating agents Other neoplastic agents Monoclonal antibodies	Rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B-lymphocytes. CD20 regulates cell cycle initiation; and, possibly, functions as a calcium channel. The mechanism of suppressing RA is not completely understood. Two alternative hypothesis were suggested: (a) elimination of B lymphocytes which are important players in inflammation or (b) the rituximab-B lymphocyte immune complexes bind effector cells and diminish their binding to other inflammation sites [321]by
L04AA24 abatacept	Antineoplastic and immunomodulating agents Immunosuppressants Selective immunosuppressants	Abatacept is a recombinant fusion protein comprising the extracellular domain of human cytotoxic T-lymphocyte antigen 4 and a fragment of the Fc domain of human IgG1. It acts by competing with CD28 (located on T lymphocytes) for binding to CD80 and CD86 on antigen presenting cells. The drug blocks the interaction between antigen presenting cells and T cells, which activates the T lymphocytes. As a result of the blocked activation, the production of the following immune response mediators is diminished: TNFα, interleukin-2, interferon gamma and granulocyte-macrophage colony-stimulating factor (GM-CSF) [322].

Improved understanding of the pathophysiology of RA has led to three key changes in the use of drug therapy [323]. First, early treatment is often recommended since treatment with synthetic antirheumatic drugs during the first five years after diagnosis has been found to minimize progression of radiographic damage [324-327]. Second, combining antirheumatic drugs has been found to be an effective strategy, especially in patients who have failed monotherapy [323]. Evidence from systematic reviews of methotrexate (MTX) monotherapy versus combination therapy [328], and synthetic antirheumatic drug monotherapy versus combination therapy [329] demonstrated superior therapeutic benefit with combination therapy in patients who failed monotherapy. Lastly, drugs targeting cytokines, such as TNFα or interleukin-1, have been developed and approved for marketing and so are newly available treatment options. The antirheumatic monoclonal antibodies and immunomodulators are mainly recommended for RA patients with inadequate response during combination or sequential therapy with synthetic antirheumatic drugs [253,330] .

First line therapy recommended by the ACR Guideline for all patients with RA regardless of disease duration or activity is MTX or leflunomide monotherapy [253,330]. For patients with poor prognostic features, alternative first line drugs include other synthetic antirheumatic drugs such as hydroxychloroquine, minocycline or sulfasalazine. TNFα antagonists (interchangeably [244]) in combination with MTX were recommended as first line therapy for a select group of patients characterized by early RA, high disease activity and features of a poor prognosis. TNFα antagonists were also recommended as second line therapy for two groups of patients: (a) those with an inadequate response to prior MTX and high disease activity and (b) those with an inadequate response to MTX combination therapy or sequential administration of other synthetic antirheumatic drugs.

A.2. The Drugs: TNFα Antagonists

In this thesis, we explore persistence (duration of treatment) of three drugs from a single therapeutic class: the TNFα antagonists, specifically infliximab, adalimumab and etanercept[66]. These drugs block the physiological action of the cytokine TNFα, which plays an important role in the pathogenesis of inflammation and RA (Section A.2.2, page 225). Treatment with TNFα antagonists does not cure patients [44], but rather reduces symptoms and possibly induces remission and prevents complications over the long term. TNFα antagonists were demonstrated to slow the radiographic progression of the disease in short-term RCTs [123,331]. These studies used continuous quantitative scale (radiographic scores) that are weaker predictors of clinical outcomes (mortality, costs and function) than patient function [332]. As well, the clinical outcomes are also questionable since some, but not all, long-term real life studies have demonstrated decreased mortality [333], especially from noninfectious causes [334], improved function, manifest as participation in the work force [335,336] and a decrease in hospital stays [337]. Evidence of harm from RCTs and postmarket experience is of major concern in patients treated with the drugs, especially serious and fatal infections [334,338], malignancy [338,339], neurologic and demyelinating events [340] and others. The

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[66] Two additional TNFα antagonists were recently approved for RA in Canada golimumab (April 2009) and certolizumab (September 2009). These medications were excluded from the analysis of British Columbia data because they were approved after the end of study identification period (31 December 2008).

three individual TNFα antagonists have different pharmacological properties, which may result in differences in therapeutic benefit and harm profiles (Section A.2.4, page 229).

A.2.1 The Cytokine TNFα

The cytokine TNFα primarily acts in the body as a proinflammation mediator by inducing apoptosis or cell death. High concentrations of TNFα released in response to bacterial endotoxins produce a shock-like syndrome, while chronic exposure to low concentration can cause a wasting syndrome in patients with cancer and other diseases [341-343]. Conversely, TNFα also has a role in regeneration and expansion of central or peripheral nerve cells [344,345] and skeletal muscles [346].

Mainly expressed by macrophages, TNFα is also released by a variety of other cells of the immune system, such as monocytes, neutrophils and lymphocytes in response to bacterial products. It is also expressed by a variety of nonimmune cell, including mast cells, endothelial cells, fibroblasts and neuronal tissue [347]. The TNFα cytokine is primarily produced as a transmembranous protein (homotrimer[67]) that was historically considered a precursor inactive form of the cytokine [348]. The transmembranous TNFα commonly undergoes proteolysis to

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[67] Homotrimer is a molecular structure, normally a protein, which consists of three identical subunits. The subunits are bonded to each other by a covalent bond (a chemical bond where the atoms are connected by sharing of at least two electrons).

its soluble homotrimeric form by the enzyme TACE (TNFα converting enzyme). The soluble

TNFα is considered the active form, although the transmembranous TNFα is also involved in

the inflammatory response. The soluble TNFα acts on sites remote from the producing cells,

while transmembranous TNFα requires cell-to-cell contact [349].

Both forms of TNFα (transmembranous and soluble) bind to one of two membranous

receptors: TNFα receptor type 1 (TNF-R1, p55) which is expressed in most tissues and TNFα

receptor type 2 (TNF-R2, p75) which is expressed in the cells of the immune system. The

receptor activation process is known to involve ligand-dependent trimerization of the receptor

but is not fully understood. Activation of TNF-R1 leads to apoptosis. Activation of both

receptors induces indirect recruiting of the TNFα receptor-associated factor (TRAF) family and

results in activation of nuclear factor kappa B (NF-kB) transcription factors [341-343]. The

protein NF-kB controls gene expression in animal cells, and is involved in immune response to

inflammation and infection [350].

A.2.2 TNFα in Rheumatoid Arthritis

TNFα is now considered an important mediator of many autoimmune and inflammatory

diseases, including RA. The possible role of this cytokine in the pathogenesis of RA was first

suggested in the 1980s, when it was demonstrated to have the potential to degrade cartilage and

bone in vitro [351,352]. In addition, RA synovial mononuclear cell cultures produce TNFα

and other cytokines [353]. In vivo studies have successfully detected TNFα in the synovial

fluid and serum of patients with RA but not in healthy volunteers or patients with osteoarthritis

[354-357]. Measured TNFα levels in the synovial fluid of the knee joints of RA patients were found to be higher in patients with bone erosions compared to those without erosions [357]. Additionally, a positive correlation between levels of TNFα and rheumatoid factor has been identified [355]. Finally, polymorphism in TNFα/b gene was shown to be an independent marker of RA susceptibility [358] and polymorphism in TNFα promoter -308 A/G was associated with susceptibility to develop severe RA in Latin American population [359,360].

Activated macrophages in inflamed synovial membranes tissue secrete TNFα. The TNFα cytokine has multiple roles in the pathogenesis of RA [361] including: (a) release of proinflammatory cytokines, such as interleukins 1, 6 and 23, as well as Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF); (b) leukocyte accumulation via release of chemokines, activation of endothelial cells and induction and/or maintenance of human leukocyte antigen (HLA) class II expression; (c) induction of angiogenesis[68]; (d) activation of chondrocytes[69] and osteoclasts[70] leading to cartilage and bone resorption; (e) prostaglandin E2 production and (f) induction of acute phase response by induction of hepcidin. The emerging knowledge on the physiologic role of TNFα and other cytokines and their importance in the pathogenesis of inflammatory diseases is potentially useful in developing therapeutic targets.

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[68] Angiogenesis is the process of forming new blood vessels from the existing vessels.

[69] Chondrocyte is a cartilage cell,

[70] Osteoclast is a large macrophage that erodes bone matrix and plays an important role in the remodeling of bone and the removal of dead bone [3].

A.2.3 From Drug Administration to Clinical Response

Administration of TNFα antagonist drugs produces a cascade of processes and events that lead to clinical response. A conceptual model developed by Nestorove 2005 uses four components to describe this sequence [362] (Figure 17).

Figure 17: Cascade of processes from administration of TNFα antagonists to clinical response
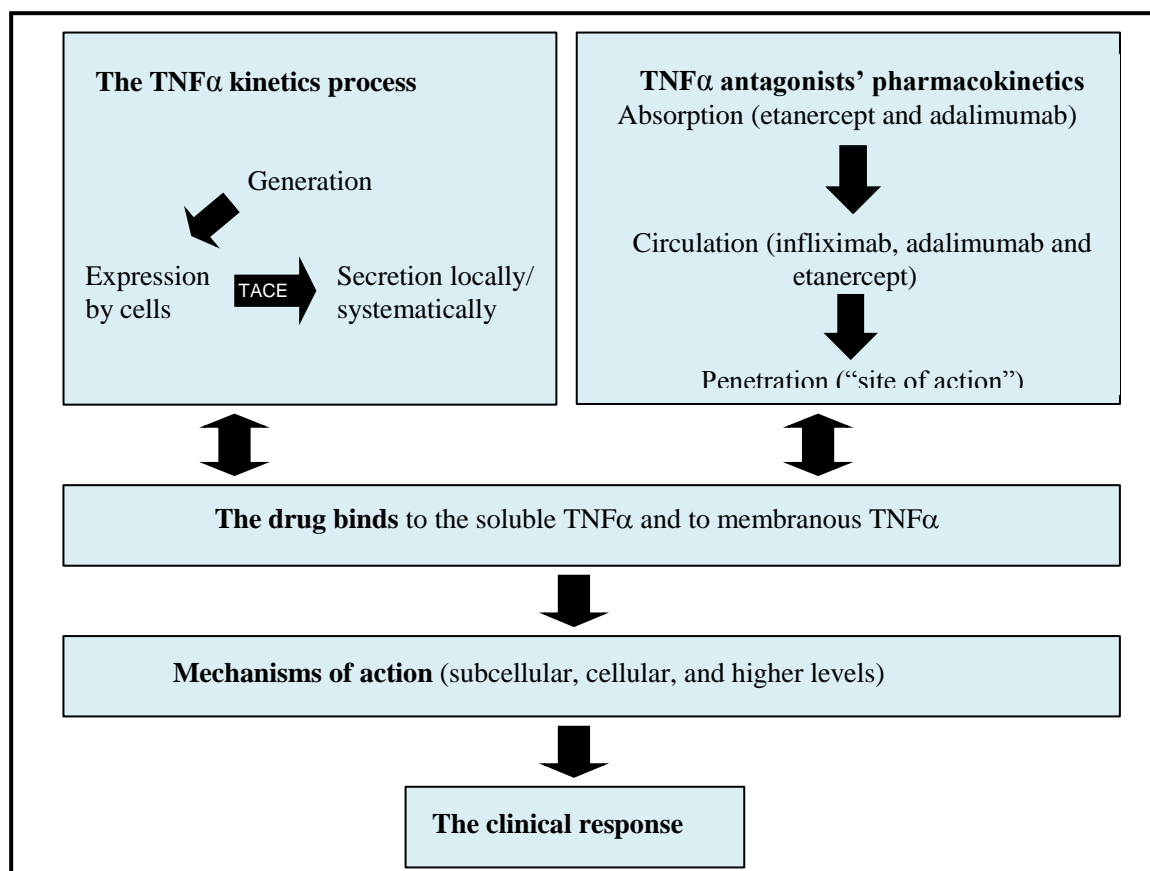
Adapted from Nestorov 2005 [360]

1. **TNFα kinetics** consists of TNFα production in response to bacterial products and its expression by immune (and other) cells. The transmembranous TNFα may undergo proteolysis by TACE that results in secretion of soluble TNFα, both systemically and in the tissues/fluids.

2. **TNFα antagonist pharmacokinetics** is represented by absorption of etanercept and adalimumab (administered subcutaneously) from the administration site to the circulation, probably via the lymphatic system [363]. The drugs are pulled by the flow of interstitial fluid into the highly permeable lymphatic capillaries; hence, time to reach maximum drug concentration in the blood (T_{max}) may take several days. Infliximab, on the other hand, is administered intravenously. From the blood, the three TNFα antagonists (infliximab, adalimumab and etanercept) penetrate various tissues and fluids.

3. **Binding** of the drug to the both soluble and transmembranous TNFα interferes with the existing equilibrium of the cytokine and leads to TNFα redistribution. The total TNFα level (both free and bound) increases [364], whereas the free (biologically active) TNFα decreases [362,364]. Certain concentrations of infliximab [365] and etanercept [366] reduce the rate of TNFα clearance and may prolong TNFα availability and further increase total TNFα level. Nestorove 2005 also suggests that the change in TNFα kinetics influences the pharmacokinetics of drugs [362], but this concept was not presented in details or nor supported by research.

4. Pharmacologic **mechanisms of action** at subcellular, cellular, and higher levels are triggered by the binding to soluble and transmembranous TNFα and result in **clinical**

response. The mechanisms of action of infliximab, adalimumab and etanercept are presented in Section A.2.4.3, page 233.

Knowledge of the pharmacokinetic properties of the TNFα antagonists is important in understanding differences in therapeutic benefit and harm between the drugs because absorption and distribution of drugs precede both pharmacodynamics action and clinical response.

A.2.4 Differences in Pharmacological Characteristics of the Individual TNFα Antagonists

Although the three individual TNFα antagonists are considered one therapeutic class, the class is diverse in pharmacological and pharmacokinetic characteristics (see Table 19, page 237 and Table 20, page 239). These differences may affect the therapeutic benefit and harm, as described below.

A.2.4.1 Structure

Infliximab and adalimumab are full-length immunoglobulin G type 1 (IgG1) monoclonal antibodies (Figure 18) with identical human derived fragment crystallizable (F_c) region. However, these two drugs have a different antigen-binding site. Infliximab is a chimeric protein, contains a mouse-derived antigen-binding site in addition to the human derived F_c region while adalimumab is fully human (Figure 19). Etanercept, on the other hand, is a fusion protein composed of a dimer of the extracellular portions of human tumour TNF-R2 fused to

the Fc region of human IgG1 (Figure 19) [188]. The Fc region of etanercept is different from

that of infliximab and adalimumab.

Figure 18: The structure of an antibody
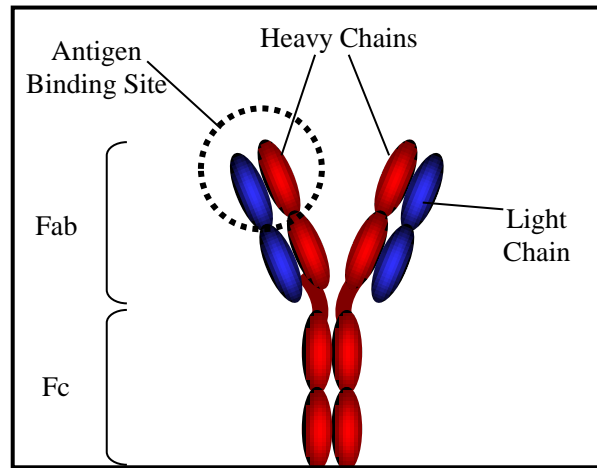
Immunoglobulin is a protein that contains two heavy (long) chains and two light (short) chains. The base is called the F_c region, and is composed of two heavy chains. This region binds to a specific class of receptors and other immune molecules to mediate the physiological effects. The antigen-binding fragment (F_{ab}) region is the site that can bind an antigen. The two F_{ab} regions are located on each of the two arms of the antigen molecule.

Figure 19: The structure of the TNFα antagonists

A. Infliximab

Mouse variable region

TNFα homotrimer

Human IgG1
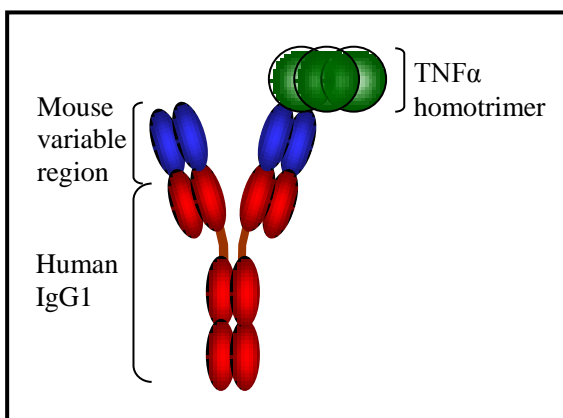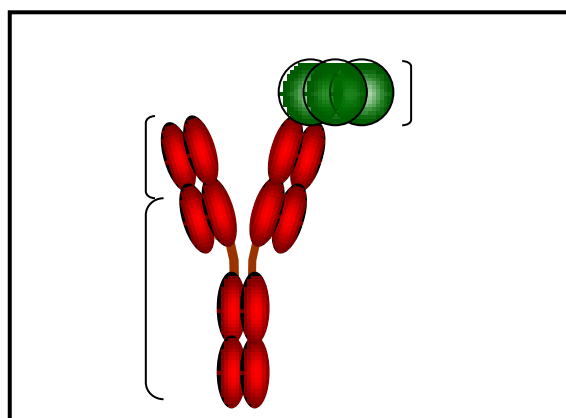
B. Adalimumab

C. Etanercept
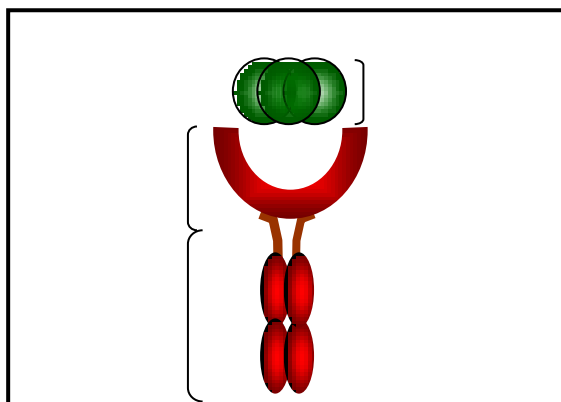
A.2.4.2 Pharmacokinetics

The steady-state concentration-time profiles of etanercept and adalimumab are smoother than infliximab, which may be a desirable quality (Figure 20) [42,188]. The profiles are a result of the route of administration and the serum half-life of the drugs (presented in Table 20, page 239). The wide fluctuations in serum concentrations of infliximab are due to administration in relatively large intravenous boluses. The maximum steady state concentrations of infliximab 3 mg/kg administered intravenously are about 40 times greater those of etanercept (administered

subcutaneously 25 mg twice a week) and roughly 13 times greater than whose of adalimumab (administered subcutaneously 40 mg every other week) [42]. Consequently, infliximab is associated with an increased risk of exceeding the maximum tolerated concentration at peak times (and concomitant increased risk for harm) or of reaching suboptimal concentrations at trough times (and impaired therapeutic benefit). In addition, the excessive inhibition of TNFα by infliximab may knock out macrophage function and result in improved therapeutic benefit and/or increased susceptibility to infection [189].

Figure 20: Steady-state concentration-time profiles of infliximab, adalimumab and etanercept
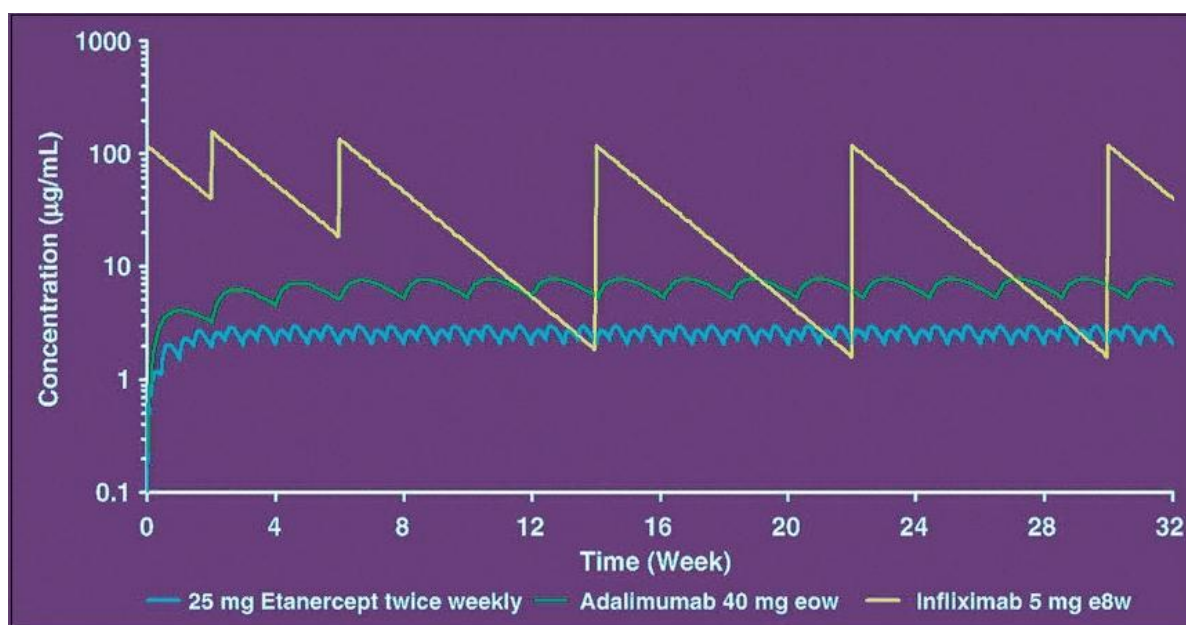
The figure represents the simulated steady-state serum concentrations of infliximab, etanercept and adalimumab based on a model developed using published pharmacokinetic parameters and dosing practice [188].

Reprinted from Pharmacology & Therapeutics 117(2), D. Tracey, L. Klareskog, E. H. Sasso, J. G. Salfeld, P. P. Tak Tumour necrosis factor antagonist mechanisms of action: A comprehensive review, Pages No 244-79., Copyright (2008), with permission from Elsevier (License Number: 2740470467986)

TNFα-Drug Complexes and Clearance TNFα-drug complexes, which are antigen-antibody complexes, are typically cleared by a combination of Fc receptor-dependent mechanisms (in the reticuloendothelial system, spleen and liver) and Fc-dependent mechanisms (intracellular degradation and renal filtration). The clearance rate of etanercept-TNFα complex is probably slower than that of infliximab or adalimumab complexes [188]. In addition, these complexes increase the level of circulating TNFα, in a dosage related manner [367-369]; however, the complexes lack bioactivity. TNFα-etanercept complexes are less stable compared to infliximab complexes [370]; hence, the TNFα may be redistributed from the inflamed tissues to other tissues.

A.2.4.3 Mechanism of Action

Two biological substances are the main targets for TNFα antagonists: TNFα and lymphotoxin alpha. In general, etanercept is distinctive in its faster binding to TNFα [188], inability to bind the monomer form of soluble TNFα [370] and binding to lymphotoxin alpha.

An ideal TNFα antagonist blocks the activity of both forms of TNFα (soluble and transmembranous) as both are involved in inflammation and the pathogenesis of the disease. Each infliximab or adalimumab molecule can bind up to two TNFα molecules (soluble or transmembranous) and a single TNFα homotrimer can bind up to three molecules of infliximab or adalimumab while etanercept binds in a 1:1 ratio [43,188,370,371] (Figure 21). At high, pathological concentrations of **soluble TNFα** (higher than 0.2 ng/ml), the three drugs have comparable potency to neutralize TNFα. However, at lower and nonpathological TNFα concentration (around 0.1 ng/ml), etanercept is 20 fold more potent [372]. Studies on binding to **transmembranous TNFα** are limited by the low level of transmembranous TNFα on

normal monocytes/macrophages and T cells, even after activation. This is mainly a result of

proteolysis of most of the transmembranous TNFα by the enzyme TACE (Section A.2.1, page

224). Consequently, the observed differences in binding to transmembranous TNFα may

reflect differences in the activity of TACE under varying experimental conditions and not real

differences between drugs [188].

Etanercept binds to **lymphotoxin alpha**, with an affinity that is similar or even higher than to

soluble TNFα. This may results in unneutralizing the soluble TNFα [188]. The clinical

significance of this is not clear; however some researchers proposed that manipulation of the

lymphotoxin pathway may result in less severe adverse effects [373], especially granulomatous

Figure 21: Binding of TNFα antagonists to TNFα
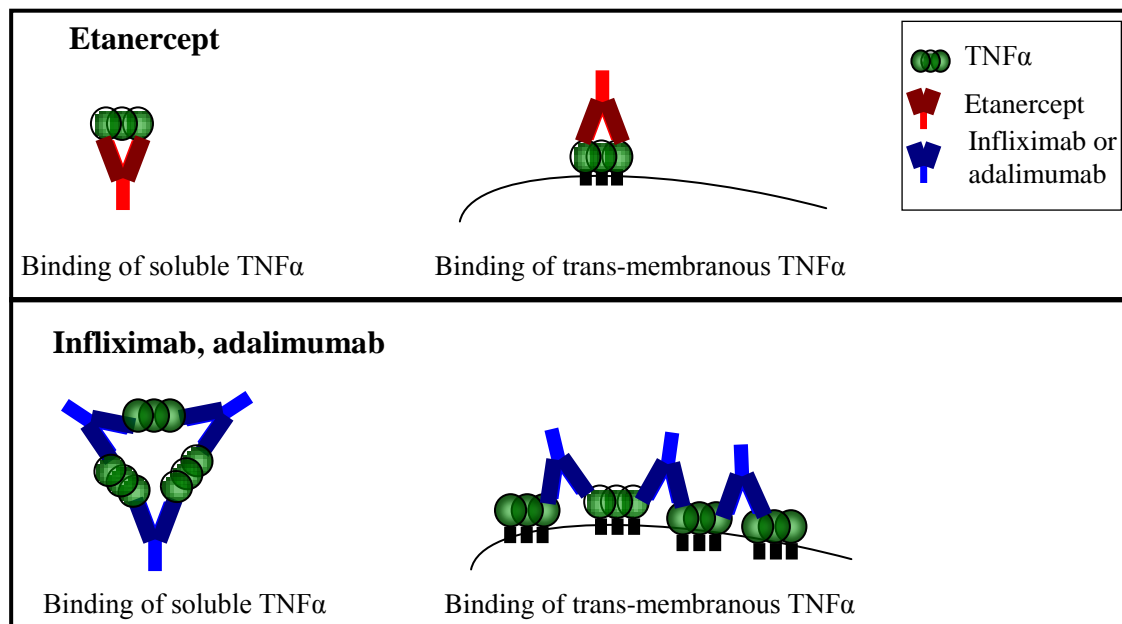
Each infliximab or adalimumab molecule can bind up to two TNFα (soluble or transmembranous)
homotrimers; a single TNFα homotrimer can bind up to three molecules of infliximab or adalimumab.
Etanercept binds in a 1:1 ratio. Adapted from Rigby 2007 [43]

infection [189]. Lymphotoxin alpha was hypothesized to attenuate the function of TNFα [190];

therefore, blocking both lymphotoxin alpha and TNFα activity could result in higher activity of

residual TNFα, compared to blockage of TNFα alone.

A.2.4.4 Biological Effects

Binding to TNFα produces a triad of biological effects: (a) complement-dependent or antibody-

dependent cellular toxicity that leads to cytolysis (cell outburst), (b) apoptosis (cell death) and

(c) inhibition of interferon gamma production. There are several differences between the TNFα

antagonist drugs with regard to these biologic effects.

Complement-dependent cytolysis is a process in which the complement binds to proteins on

the cell membrane and consequently pores are formed in the cell membrane. Pores allow water

to enter the cell and eventually the cell bursts. Infliximab and adalimumab are capable of

complement fixation resulting in complement-dependent cytolysis [43,188,189]. Additionally

these two drugs are capable of Fc-receptor binding [188] and induce antibody-dependent

cellular toxicity [43,189]. In this process, cells of the immune system act against other cells to

which antibodies are bound, and cause break down of the antibody-bound cells. The two

cytolysis processes are associated with monocytopenia (decrease in the amount of monocytes,

which are part of the immune system) that may increase susceptibility to granulomatous

infections, mainly tuberculosis. Etanercept, on the other hand, does not fix complement in vitro

[374] and does not bind to the Fc-receptors [40].

Infliximab and adalimumab can cause apoptosis of activated T cells and circulating monocytes

[189,375], which is a potentially desirable property in chronic inflammation. The mechanisms

suggested to explain this phenomenon include either binding to soluble TNFα and depriving cells of survival signals mediated by TNF-R1 signaling, or cross-linkage with transmembranous TNFα which induces a unique signal [43]. The capability of etanercept to induce apoptosis of human monocytes is questionable, as study results were inconsistent [375,376].

Interferon gamma production is inhibited by infliximab and adalimumab but not etanercept [189]. Interferon gamma is produced by T cells and is required for host defense against tuberculosis. The possible excessive risk for tuberculosis posed by infliximab may be a result of inhibition of both TNFα and interferon gamma.

A.2.4.5 Immunogenicity

Protein-based drugs such as TNFα antagonists may induce production of antidrug antibodies ('acquired drug resistance'). This in turn may reduce clinical efficacy due to inactivation and/or rapid clearance of the drug as well as increase the risk of harm, e.g.,. infusion or injection site reactions [188]. Chimeric proteins, which consist of both human and nonhuman parts, including infliximab, are more immunogenic compared to only-human proteins [39,377]. While increased doses of infliximab are associated with decreased immunogenicity [75], concomitant MTX reduces the immunogenicity of all drugs, probably due to its immunosuppressive effects [39,75,120].

Table 19: Pharmacological characteristic of the individual TNFα antagonists

Drug characteristics	Infliximab [186,207]	Adalimumab [186,378]	Etanercept [186,379]
Structure	A chimeric antibody that contains murine derived antigen binding variable region (25%) and human IgG1 constant region (75%)	A recombinant monoclonal antibody that contain two kappa light chain and two IgG1 heavy chain 1330 amino acids	A human fusion protein that contains two soluble domains of human TNF-R2 and Fc portion of human IgG1 934 amino acids
Weight (killodaltons)	149	148	150
Binding and affinity	Binds to soluble and transmembranous TNFα Affinity: KD 1.17 to $4.5*10^{-10}$ molar	Binds to soluble and transmembranous TNFα Affinity: KD $7.05 * 10^{-11}$ to $1.0 * 10^{-10}$ molar	Binds to soluble and transmembranous TNFα and lymphotoxin alpha Affinity: KD $2.35*10^{-11}$ to $1.15*10^{-9}$ molar
Production	Recombinant cell line cultured by continuous perfusion	Recombinant DNA techniques in mammalian cell expression system Purified by a process that includes specific viral inactivation and removal steps	Recombinant DNA techniques in Chinese hamster ovary mammalian cell expression system
Immunogenicity	Frequency of anti-infliximab antibodies (also known as human antichimeric antibodies (HACA)) 8-68%[186,187] The prevalence increases with prolonged persistence on infliximab [380] Lower doses of infliximab is associated with higher frequency of HACA [75,120,380-383] Concomitant MTX is associated with decreased incidence of antibody formation [75] The presence of HACA was associated	Frequency of anti-adalimumab antibodies in RA 1-87% [186,187]. After three-years of treatment, 28% of the patients developed anti-adalimumab antibodies [387] Concomitant MTX is probably associated with decreased prevalence of antibody formation [388,389] The effect on efficacy is controversial [389-391], while the effect on adverse events is not clear [391]	Incidence of anti-etanercept antibodies in clinical trials of RA 2-6% [186,187] with varying rate resulted from different assay No effect was demonstrated on efficacy or adverse events [392]

Drug characteristics	Infliximab [186,207]	Adalimumab [186,378]	Etanercept [186,379]
	with decreased efficacy [381,383,384]; however, the association with adverse events in RA patients is not well studied [385,386]		
Elimination	Not characterized [393]	Forms a number of immune complexes of varying weight with TNFα. A stable molecule (three alternating adalimumab and TNFα in a circular chain) is easily removed from the circulation.	The complex etanercept-TNFα is metabolized through peptide and amino acid pathways with either recycling of amino acids or elimination in bile and urine [394]

DNA - Deoxyribonucleic acid ; **IgG1** - Type 1 human immunoglobulin; **KD** - the antigen dissociation constant, smaller values reflect greater affinity; **MTX**-methotrexate; **RA**- rheumatoid arthritis; **TNFα** – tumour necrosis factor alpha

Table 20: Pharmacokinetics characteristics of individual TNFα antagonists

Drug characteristics	Infliximab [207,395,396]	Adalimumab [76,378,397,398]	Etanercept [379,394,399-401]
Route of administration	Intravenous over two hours	Subcutaneous	Subcutaneous
Recommended dose (adults patients with RA, product monograph)	3 mg/kg body weight, at week 0, 2, 6 and then every eight weeks. For patients with an incomplete response, the dose might be adjusted to 5 mg/kg every eight weeks or 3mg/kg every four weeks.	40 mg administered EOW. For patients with an incomplete response, the dose intensity may be increased to 40 mg every week	50 mg per week. Higher doses are not recommended.
C_{max}	RA patients, single dose of three mg/kg , no MTX 78.3±26.4 μg/ml (n=14) RA patients, ,multiple dosing of three mg/kg at week 54 25% < 0.001 μg/ml	Healthy subjects single dose 40 mg 4.7±1.6 μg/ml	RA patients, single dose of 25 mg 1.07 μg/ml (n=25) RA patients, multiple doses 25 mg BIW 2.4±0.99 μg/ml (n=23)
T_{max}	Not applicable (intravenous administration)	Healthy subjects single dose 40 mg 131±56 h	RA patients, single dose of 25 mg 69.2±33.8 h (n=25) RA patients, multiple doses 25 mg BIW 32.1±27.3 h (n=23)
AUC	RA patients, single dose of three mg/kg, no MTX 11765±4800 μg*h /ml (n=14)	RA patients, single intravenous dose of 0.5 mg/kg 2729±707 μg*h/ml	RA patients, single dose of 25 mg 201.7±94.3 μg*h/ml RA patients, multiple doses 25 mg BIW $AUC_{0-72 h}$ 143.6±57.2 μg*h/ml
Clearance	RA patients, single dose of 3 mg/kg, no MTX 18.1±5.8 ml/h (n=14)	RA patients 12 ml/h RA patients: MTX reduced clearance by 29% (single dose) to 44% (multiple dosing) Higher clearance in the presence of antibodies Lower clearance with increasing age	RA patients, single dose 25 mg (n=25) 160±80 ml/h

Drug characteristics	Infliximab [207,395,396]	Adalimumab [76,378,397,398]	Etanercept [379,394,399-401]
Volume of distribution	4.3±2.5 L (5 mg/kg intravenous)	4.7-6.0 L (0.25-10 mg/kg intravenous)	8.0 L (sum of central and peripheral compartments, 2-25 mg intravenous or subcutaneous, single dose or twice a week)
Half-life	RA patients, single dose of 3 mg/kg no MTX 218±126 h (n=14)	RA patients, single dose 40 mg mean 336 h (240-480 h in different studies)	RA patients, single dose of 25 mg 102.3±30.1 h (n=25) RA patients, multiple doses 25 mg BIW 93.7±18.6 h (n=23)
Average absolute bioavailability	Absolute bioavailability (administered intravenously)	RA patients, single dose 40 mg, 64%	RA patients, 63%
Steady state pharmacokinetics (Figure 20, page 232)	Data for the steady-state pharmacokinetic of infliximab are limited [41], no systemic accumulation of the drug was observed after repeated treatment with 3 mg/kg to 10 mg/kg at four or 8-week intervals When infliximab 3 mg/kg every 8 weeks (in RA patients) achieves steady state, the peak drug concentrations are at least 50-fold greater than the median trough concentrations, Trough concentrations were undetectable in 22% to 30% of patients [402]. Drug efficacy is probably compromised at low level of infliximab [120,402]	RA patients, 40 mg EOW: the mean steady state concentrations with MTX 8-9 μg/ml and without MTX - 5 μg/ml The steady state concentrations are greater than the clinically effective serum concentrations (0.8-1.4 μg/ml) [403]	Etanercept is absorbed slowly and reaches steady state plasma concentrations after 2-4 weeks [394]. Serum concentration profiles at steady state were comparable among patients with RA on 50 mg once weekly and 25 mg twice weekly. At steady state, the volume of distribution is comparable to with infliximab and adalimumab, which, assuming similar tissue distribution, implies greater tissue penetration for etanercept

μg –microgram; **AUC**- area under the curve; **AUC$_{0-72\,h}$**- area under the curve between 0-712 hours after administration; **BIW**- twice a week; **C$_{max}$** - peak concentration; **EOW**- every other week; **h**- hours; **mg**- milligram; **kg**- kilogram; **L**- liter; **MTX**- methotrexate; **RA**- rheumatoid arthritis; **T$_{max}$**- time to peak concentration

A.3. TNFα Antagonists Therapy in Rheumatoid Arthritis

A.3.1 The Efficacy and Safety of the Individual TNFα Antagonists

This section consists of two parts. The first part introduces a short summary of knowledge from RCTs on the relative benefit and harm of treatment with TNFα antagonists in RA patients. It focuses on comparisons between drugs rather than each drug compared to placebo. The second part includes a summary of the main limitations of available knowledge from RCTs of TNFα antagonists in RA patients. The latter justifies the necessity and importance of observational studies conducted using data from routine clinical practice, including research presented as part of this thesis.

A.3.1.1 Knowledge Based on Randomized Clinical Trials

RCTs are the gold standard research design for establishing causation between drug administration and therapeutic outcomes (benefit and harm). This is a reflection of design features, which ensure comparability of the control and intervention groups in all known and unknown prognostic factors, except the intervention of interest [404]. Most RA RCTs estimate the therapeutic benefit of TNFα antagonists using disease severity scores or response criteria. One of the most commonly used sets of criteria is the ACR response criteria [405]. These were determined by a consensus of clinicians and researchers to allow uniform measurement of improvement in disease activity to make comparison of RCT results possible. The ACR20 ACR50 and ACR70 response criteria require (a) 20, 50 or 70% reduction in the number of

swollen joints, (b) 20, 50, or 70% reduction in the number of tender joints, and (c) 20,50, or

70% reduction in three of the following measures: physician global assessment of disease,

patient global assessment of disease, patient assessment of pain, level of C-reactive protein

(CRP) or erythrocyte sedimentation rate (ESR), and degree of disability in Health Assessment

Questionnaire (HAQ) score [405]. ACR20 is measurable but of questionable clinical

significance while ACR50 or AR70 are considered clinically important [406].

Although there are no head-to-head RCTs comparing two (or more) individual TNFα

antagonists, multiple indirect comparisons have been conducted using different methodologies

to pool the data (Table 21). Most meta-analyses did not demonstrate any difference in

therapeutic benefit (ACR20, ACR50 and ACR70) between the drugs [231,407-410] while two

meta-analyses identified some differences in therapeutic benefit. **Wiens et al 2010** [411]

concluded that in short-term studies (6 months), treatment with etanercept and adalimumab had

greater benefit than infliximab, while in long-term studies (1-3 years) treatment with

adalimumab was the most efficacious of the three TNFα antagonists[71]. **Ingham et al 2010**

[412], in the only meta-analysis that focused on radiologic findings, concluded that infliximab

demonstrated twice the effect size of adalimumab. The difference in the mean change from

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[71] Estimates of therapeutic benefit were based on proportion of patients achieving the ACR response criteria. With short-term treatment (6 months), etanercept was associated with higher rates of reaching ACR20 and ACR50 and adalimumab of achieving ACR70. Over a long-term treatment course (1-3 years), adalimumab demonstrated the highest rate of achieving the three sets of criteria.

Table 21: Indirect comparisons of efficacy and safety of the individual TNFα antagonists in RA[72]

Reference	Number of studies included[73]	Outcome of Interest	Conclusions
Efficacy			

Hochberg 2006 [410]	4 (infliximab-1; adalimumab-2; etanercept-1)	ACR20, ACR50	The three TNFα antagonists have similar efficacy when added to methotrexate.
			Relative risk for achieving ACR50
			  infliximab versus etanercept 0.52 (95% CI 0.06-4.55),
			  adalimumab versus etanercept 038 (0.05-2.86),
			  adalimumab versus infliximab 0.74 (0.36-2.13)

Gartlehner 2006 [407]	14 (infliximab-4; adalimumab-5; etanercept-5)	ACR20, ACR50	Adjusted indirect comparisons indicated no significant differences in efficacy between TNFα antagonist drugs

Nixon 2007 [408]	10 (infliximab-2; adalimumab-4; etanercept-4)	ACR50	The effect of the individual TNFα antagonists was similar.
			Odds ratios of ACR50
			  infliximab versus etanercept 0.98 (95% CI 0.45-1.93);
			  adalimumab versus etanercept 0.94 (0.50-1.62),
			  adalimumab versus infliximab 0.96 (0.48-1.90))

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[72] The table presents only meta-analyses that were reported in full publications. Abstracts, conference proceeding and posters were not presented.

[73] For meta-analyses that included additional antirheumatic monoclonal antibodies and immunomodulators, the number of studies included presented in this table indicates studies with the three TNFα antagonists infliximab, adalimumab and etanercept.

Reference	Number of studies included[73]	Outcome of Interest	Conclusions
Alonso-Ruiz 2008 [409]	13 (infliximab-4; adalimumab-5; etanercept-5)	ACR20, ACR50, ACR70	No evidence that the relative effects of individual drugs differed
Singh 2009 [231]	16 (infliximab-4; adalimumab-8; etanercept-4)	ACR50	The absolute improvement was 22% with infliximab, 28% with adalimumab and 36% with etanercept. Differences were not statistically significant
Ingham 2010 [412]	3 (infliximab-1; adalimumab-1; etanercept-1)	Standardized mean differences (mTSS MD)	Infliximab demonstrated twice the effect size of adalimumab. Etanercept was not compared to either drug due to heterogeneity issues.
Wiens 2010 [411]	21 (infliximab-7; adalimumab-8; etanercept-6)	ACR20, ACR50, ACR70	In short-term therapy (6 months), etanercept and adalimumab demonstrated higher efficacy results. With long-term treatment (1-3 years), adalimumab was found to be the most effective of the three TNFα antagonists.
Devine 2011 [414]	10 (infliximab-2; adalimumab-4; etanercept-4)	ACR50	No significant difference between the individual drugs was observed
Safety			
Alonso-Ruiz 2008 [409]	13 (infliximab-4; adalimumab-5; etanercept-5)	WDAEs, SAEs and serious infections	In patients treated with infliximab and adalimumab, WDAEs were more frequent than in patients treated with etanercept. Treatment with infliximab was associated with a higher frequency of SAEs and serious infections

Singh 2010 [413]	16 (infliximab-4; adalimumab-8; etanercept-4)	SAEs	The effect of the individual TNFα antagonists was similar.
			
			Odds ratios for serious adverse events
			  adalimumab versus infliximab 0.76 (95% CI 0.52-1.12).,
			  adalimumab versus etanercept 0.80 (0.54-1.20),
			  etanercept versus infliximab 0.95 (0.66-1.37)

Reference	Number of studies included[73]	Outcome of Interest	Conclusions
		Serious infection	The effect of the individual TNFα antagonists was similar. Odds ratios for serious infection 　adalimumab versus infliximab 0.77 (0.47-1.27), 　adalimumab versus etanercept 1.06 (0.63-1.76), 　etanercept versus infliximab 0.73 (0.46-1.15)
		Total adverse events	The effect of the individual TNFα antagonists was similar. Odds ratios for total adverse events 　adalimumab versus infliximab 0.92 (0.73-1.16), 　adalimumab versus etanercept 1.05 (0.83-1.33), 　etanercept versus infliximab 0.87 (0.70-1.10)
		WDAEs	Infliximab was associated with more WDAEs. Odds ratios for WDAE 　adalimumab versus infliximab 0.50 (0.32-0.78), 　adalimumab versus etanercept 0.80 (0.51-1.25), 　etanercept versus infliximab 0.63 (0.41-0.95)

ACR20- American College of rheumatology 20% improvement; **ACR50**- American College of rheumatology 50% improvement; **ACR70**- American College of rheumatology 70% improvement; **CI**-confidence interval; **MD**- mean change scores from baseline of mTSS between active and control groups; **mTSS**- modifications of Total Sharp scores; **SAE** – serious adverse event; **TNFα** – tumour necrosis factor alpha; **WDAE**- withdrawal due to adverse event

baseline of modifications of total Sharp scores[74] between active and control groups was -6.8 (95% confidence interval [CI] -9.3 to -4.3) for infliximab compared to -2.6 (95% CI -3.8 to 1.4) for adalimumab.

With regard to harm, patients on infliximab experienced a higher rate of withdrawals due to adverse events (WDAE) compared to etanercept, however the risk compared to adalimumab varied across meta-analyses [409,413]. Higher risk of serious adverse events and serious infections with infliximab was observed in one meta-analysis [413] but not in another which observed a similar risk [409].

The interpretation and generalizability of these meta-analysis results are limited by the limitations of the individual RCTs (below)

A.3.1.2 The Limitation of Randomized Clinical Trials

RCTs in general are characterized by relatively small sample sizes and short durations of treatment. Consequently, they often fail to detect rare or delayed therapeutic effects or small or modest differences in major outcomes. Trial participants are often unrepresentative of all of the patients who actually take the drug, as was shown in several diseases [415-418]. Participants tend to be healthier with less comorbidities [419] and more compliant with treatment [420]

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[74] The Sharp score is a method used to score radiological changes in patients with RA. The scoring is based on erosions and joint space narrowing in radiographs of the hands, wrists and feet [332].

compared to real life patients. Additionally, the elderly, women, and minorities are all less

likely to be enrolled in RCTs [416,421-427]. The available RCTs of TNFα antagonists for

patients with RA need to be carefully appraised because of the potential for important

limitations, such as the aftermentioned, to affect the generalizability as well as the

interpretation of the results.

First, the duration of RCTs is considerably shorter than the lifetime of the disease (usually 1-2

years compared to several decades). This is particularly important in RA, a disease

characterized by a variation in disease activity and deterioration over time. The effects

observed in a short-term trial may not be significant in the long-term and a drug which had no

effect in short-term may prevent complications or progression of the disease over the long-term

[45,428].

Second, RCTs report benefit and harm separately, while in real life clinical decisions are based

on an integration of the positive and negative expected therapeutic effects and their relative

importance to a specific patient. Treatment persistence not only reflects the actual and

perceived benefit and harm of drugs, but also incorporates patient preference and non-

therapeutic effects (such as cost and drug coverage policy) that influence prescribing decisions.

Third, RA patients who participate in RCTs designed to assess therapeutic benefit and harm of

TNFα antagonists are not representative of actual RA populations [211] nor of patients treated

with TNFα antagonists in routine clinical settings [212]. Several studies demonstrated that

among patients treated with TNFα antagonists in routine clinical settings, only 5-79% were

eligible for RCTs based on inclusion and inclusion criteria [210-212,429]. Only about five

percentage of patients with advanced RA treated by a rheumatologist in Tennessee [211] were

eligible to participate in ATTRACT (Anti-TNF Trial in Rheumatoid Arthritis with

Concomitant Therapy)[75] [402]. Less than a third of patients treated with TNFα antagonists in

the German Biologics Register RABBIT [212] were eligible to participate in the major TNFα

antagonists RCTs[76]. Ineligible patients had lower baseline disease activity, more comorbidity,

and lower functional status. Among RA patients treated in 11 hospitals in the Netherland, 34-

79% fulfilled the inclusion criteria based on baseline disease activity required in the different

RCT [210]. Among RA patients treated by a single French physician, 42% met inclusion

criteria for RCTs [429]. Patients eligible to participate in RCTs had an improved response

compared to ineligible patients [210,212,429]. The relatively wide range observed in the

proportion of patients eligible to participate in RCTs probably reflects differences in treatment

policy or prescribing decisions, but also the use of different trials (with various eligibility

criteria) as a comparison. The above mentioned observations suggest that the current eligibility

criteria in RCTs may be too restrictive; hence, study findings do not apply to most patients

treated in clinical practice.

Fourth, mortality and long-term disability are clinically significant end-points, which

necessitate decades of follow-up. Instead, the main outcome criteria used in RCTs are the ACR

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[75] Patients were randomized to infliximab versus placebo, concomitant with methotrexate

[76] Eligibility were based on the inclusion and exclusion criteria of the following major RCT that led to the approval of the drugs for RA: the infliximab ATTRACT [485]; the etanercept study by Moreland et al 1999 [486] and TEMPO [123]; and the adalimumab ARMADA [388] and the study by van de Putte et al 2004 [390].

response criteria (presented in Section A.3.1.1, page 241), which include clinical and laboratory features. ACR response criteria have borderline significant association with the progression of joint destruction during a 48-week trial (p=0.03, [430]). Some studies examined the association of several components of the response criteria on mortality [431-434]. Nevertheless, no study measured the association between the response criteria (ACR50 or ACR70) and long-term mortality or disability; hence, the validity of these criteria as prognostic factors is suspect.

There are additional differences in the outcomes of interest between RCTs and the routine practice settings. In clinical trials, the main interest is change, while in clinical practice the main concern is health status [435]. Due to the life-long duration of chronic disease, treatment is prolonged, and the starting point (and change from the starting point) is less relevant as years pass and other clinical issues (such as complications or comorbidities) arise [435]. In addition, in RCTs the therapeutic effect is commonly presented relative to the placebo comparator, while in routine clinical setting the effect relies only on changes in the clinical presentation in the individual treated patient. In clinical setting patient measures, such as quality of life and function are considered of more relevance than physician and laboratory measures that are collected in RCTs, mainly because functional measures are predictive of mortality [434,436].

Last, the positive effect of TNFα antagonists in RA patients is likely to be overestimated in RCTs compared to effects observed in clinical settings. Both ACR20 and ACR50 response rates [210,212] and HAQ improvement [435] were less pronounced in patients in clinical settings compared to RCTs. There are several explanations for this observation. First, trial participants are not representative of those treated in routine clinical setting: their disease is

less severe (lower baseline DAS28, swollen joint count and tender joint count), their disease duration is longer, they experienced larger number of synthetic antirheumatic drugs and antirheumatic monoclonal antibodies and immunomodulators [212] and have a higher baseline HAQ [435]. The difference in estimated therapeutic effect between trial participants and routine practice population should be considered in the light of regression to the mean. The observed change depends on the baseline level of disease activity as well as treatment effect with a greater observed change with increasing disease activity. For example, when analyzing change in HAQ scores from visit to visit in clinical settings, Wolfe et al 2004 [435] showed the higher the HAQ score in the previous visit, the larger the change between the visits. The score change between visits increased by 0.24 (95% CI 0.18 to 0.28) for each one unit increase in baseline HAQ. The second explanation is that in clinical practice, the effect of the TNFα antagonists is added to prior treatments while RCTs represent a flare design in which patients must experience a flare prior to entering the trial, prior treatment is restricted and patients must be on stable synthetic antirheumatic drugs (including corticosteroids) prior to treatment [435]. This means that the change observed in RCTs is from a flare and not from a steady state. Lastly, participants in RCTs are more compliant with the treatment compared to routinely treated patients [420,437]. Therefore, greater exposure to the drug overestimates the benefit as compared to the clinical setting.

To conclude, studies of real life effectiveness remain important to determine the most useful role of each TNFα antagonist in clinical practice setting. This is due to the absence of real world head-to-head RCTs, and the limited generalizability of existing RCTs comparing TNFα antagonists to placebo. Multiple outcomes were used to estimate the effectiveness of TNFα antagonists in RA patients treated in routine practice settings. Most of them involved

estimation of disease activity using disease activity or response criteria similar to those used in RCTs, quality of life assessment and functional evaluation. Other effectiveness studies have evaluated harm including rates of infection, malignancy or neurologic complications. Measures encompassing both benefit and harm have rarely been used. Such measures include total hospitalizations (studies unavailable), total mortality [334,438,438] and treatment persistence.

A.3.2 Indications for Discontinuing TNFα Antagonists From Clinical Practice Guidelines

Multiple national and international guidelines, consensus statements and position papers on treatment for RA patients were published in the last decade; however, not all discussed and defined scenarios for discontinuing TNFα antagonists (Table 22, page 253). The indications for discontinuation of TNFα antagonists can be divided into three major groups:

1. **Lack of benefit/ inefficacy** (nonresponders, lack of efficacy or loss of efficacy) can be determined based two dimensions: disease activity and duration of exposure to the drug. Disease activity is commonly estimated using validated scores [439] such as the Disease Activity Scores (DAS)[77] [440] or the European League Against Rheumatism (EULAR)

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[77] DAS or DAS28 is calculated based on the number of tender joints, the number of swollen joints, the Erythrocyte Sedimentation Rate (ESR) or the level of C-reactive protein (CRP) and the patient global health measured on Visual Analogue Scale (VAS). A score larger than 5.1 means high disease activity whereas a

response criteria[78] [441]). Response is ascertained on a threshold level of disease activity achieved with treatment or minimal improvement with drug therapy. Patients who do not achieve these thresholds are considered nonresponders. The second dimension is a minimal period of continuous administration of the drug to ensure sufficient exposure to the drug. Unfortunately, differences in the criteria used to define both dimensions exist, and some of the guidelines define the dimensions vaguely (Table 22, page 253).

2. **Harm** (adverse events, adverse effects or intolerability) is considered an indication for discontinuation of the drug [238,239,442-444]. Only the minority of the guidelines discuss specific situations.

3. **Remission** is rarely discussed as an indication for discontinuation and even then is only considered among other treatment options, such as tapering off glucocorticosteroids, decreasing or discontinuing synthetic antirheumatic drugs or decreasing the dose of the TNFα antagonists.

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score lower than 3.2 indicates low disease activity. Remission is defined as a DAS28 score lower than 2.6 [430,440].

[78] EULAR response criteria are based on improvement from baseline of DAS28 and level of disease activity based on DAS28 during the follow up. For example, Good response is defined as improvement of more than 1.2 in DAS28 compared to baseline and a DAS28 follow up level of 2.4 or less. Non responders are defined based on either improvement of 0.6 or less in the score, or improvement of 1.2 or less and DAS28 of more than 3.7 at follow up [441].

Table 22: Summary of clinical guidelines - indications for discontinuing TNFα antagonists

Reference	Inefficacy	Safety	Remission	Other
The Canadian Agency for Drugs and Technologies in Health [249,250]	Disease activity: not defined Duration of treatment: 14-16 weeks	Not mentioned	"There was insufficient evidence for the panel to provide a recommendation on discontinuation of TNFα inhibitors in patients achieving remission"	
The Canadian Rheumatology Association [251,252,445]	"discontinued if meaningful improvement is not achieved'	Not mentioned	Not mentioned	
The American College of Rheumatology [253,330]	Not mentioned	Not mentioned	Not mentioned	
The National Institute for Health and Clinical Excellence[442]	Disease activity: response was defined as an improvement in DAS28≥1.2 Duration of treatment: six months	Not specified	Not mentioned	
The French Society for Rheumatology [238]	Disease activity: response was defined as either DAS28 <3 or DAS28 <5.1 with a an improvement ≥1.2 Duration of treatment: 12 weeks	Compromised safety was mentioned as an indication for discontinue the drug, and specific indications were further discussed by Club Rhumatismes et Inflammation [446]	The publication stated that "when a prolonged remission is obtained, a reduction in DMARDs and biotherapies can be considered." nevertheless, neither the definition of prolonged remission nor an optimal reduction schedule was agreed upon.	

Reference	Inefficacy	Safety	Remission	Other
Spanish Clinical Practice Guideline [239,447,448]	Disease activity: response was defined as DAS28<3.2 Duration of treatment: three months (Alternative therapeutic options are discussed as well)	Tumour , optic neuritis, cytopenia and active tuberculosis were mentioned as indications for discontinuation Toxicity was given as an indication for switching to abatacept or rituximab	TNFα antagonist discontinuation was mentioned as a treatment option in patients in remission (defined as DAS28<2.6 or SDAI <5)	Lactation
Recommendations in Italy [443]	Disease activity: no response was defined as either DAS >3.7 and DAS improvement ≤ 1.2; or DAS improvement < 0.6 Duration of treatment: 12 weeks	Discontinuation is recommended when serious infections and/or opportunistic infections occur, (septic arthritis, infected prostheses, acute abscess, osteomyelitis, sepsis, systemic fungal infections). Treatment should only be reinitiated if the infections have been treated adequately.	Not mentioned	
International consensus statement [444]	Disease activity: response was defined vaguely as "individually important responses, including patient oriented measures (for example, HAQ-DI, patients global VAS) or physical measures (for example, joint tenderness)" Duration of treatment: 8-12 weeks	The following are indications for discontinuation: Clinical evidence of a lupus-like Syndrome Serious infections, including septic arthritis, infected prostheses, acute abscess, osteomyelitis, sepsis, systemic fungal infections, Listeria etc. Treatment should only be reinitiated if the infections have been treated adequately. A demyelinating-like disorder or optic neuritis Pancytopenia and/or aplastic anemia	Not mentioned	Pregnancy

DAS28- Disease Activity Score in 28 joints; **DMARDs**- disease modifying antirheumatic drugs ; **EULAR**- the European league against rheumatism; **HAQ-DI**- Health Assessment Questionnaire Disability Index; **SDAI**- Simplified Disease Activity Index; **TNFα**- tumour necrosis factor alpha; **VAS**- (pain) visual analog scale

Published guidelines and consensus statements imply that persistence with TNFα antagonists in RA patients is affected mainly by the benefit and harm of the drug, because benefit and harm are the main considerations in drug discontinuation. Different and sometime vague definitions of inefficacy and harm are expected to lead to differences in prescribing habits of physicians. Different physicians in the same clinical situation may reach a different decision about discontinuing the TNFα.

A.3.3 Reasons for Discontinuing TNFα Antagonists

The two main reasons for discontinuing TNFα antagonists are inefficacy (decreased benefit) and harm. The term 'inefficacy' is often used broadly to include both primary inefficacy (lack of efficacy, patients who did not respond to the drug) and secondary inefficacy (loss of efficacy in patients who previously responded to the treatment). In a pooled analysis of studies reporting the reasons for discontinuation in patients treated with the three drugs, we found that 86% of patients discontinued TNFα antagonists due to either inefficacy or harm. The proportions of patients treated with infliximab, adalimumab or etanercept were 79%, 88% or 77%, respectively (Table 23, Figure 22 and Table 24). Only a small number of all discontinuations (<2%) were due to remission [151,179]. High rates of flares and drug reinitiation were observed in these patients: 0% in six months [242], 13-100% after one year of follow-up [240,241,449,450] and 22-71% after two or more years of follow-up [451,452]. Discontinuation due to remission and subsequent reflaring could cause a temporary interruption in treatment persistence followed by reinitiation of the same drug.

Persistence with the TNFα antagonists is likely a valid measure of benfit-harm balance in RA

patients because nearly all patients who discontinue these drugs do so as a result of inefficacy

or harm and only a small proportion (<2%) discontinue due to remission.

Table 23: Reasons for discontinuing TNFα antagonists

Reference	Drugs	Total number of patients treated	Total number of patients discontinue[79]	Percentage who discontinue due to inefficacy from all discontinuers[80]	Percentage who discontinue due to adverse events (safety)
Hyrich 2007 [453]	All	6739	2360	36%	43%
	INF	3037	1273	36%	41%
	ADA	876	265	41%	37%
	ETA	2826	405	34%	49%
Carmona 2006 [454]	INF, ADA, ETA	4006	1095	36%	49%
Hetland 2010 [110]	INF, ADA, ETA	2326	1089	67%	30%
Du Pan 2009[170]	All	2364 courses	803 (653) courses	50%	49%
	INF	595	(209)	43%	52%
	ADA	887	(213)	53%	43%
	ETA	882	(237)	53%	50%
Kievit 2011 [156]	INF, ADA, ETA	1560	694	41%	35%

[79] In parenthesis is the number of patients for whom reason was reported (if different from the total number of patients who discontinue.

[80] Includes both primary (no response) and secondary (loss of efficacy) inefficacy.

Reference	Drugs	Total number of patients treated	Total number of patients discontinue[79]	Percentage who discontinue due to inefficacy from all discontinuers[80]	Percentage who discontinue due to adverse events (safety)
Filippini 2010 [172] **and Marchesoni 2009** [151]	All	1064	659 (405)	44%	48%
	INF	519	226	46%	47%
	ADA	303	111	41%	54%
	ETA	242	68	45%	41%
Weinblatt 2009 [455]	ETA	772	573	24%	29%
Vander Cruyssen 2010 [456]	INF	507	298	35%	41%
Heiberg 2008 [115]	INF, ADA, ETA	847	293	39%	39%
Agarwal 2008 [79]	INF, ADA, ETA	503	210 (63)	60%	40%
Ornbjerg 2010 [179]	INF, ADA, ETA	522	210	46%	37%
Vander Cruyssen 2006 [181]	INF	479	196	33%	47%
Delabaye 2010 [457]	INF	504	158	26%	47%
Brocq 2007 [106]	All	441	147	59% (NR 27%, LoE 32%)	41%
	INF	113	69	71% (NR 20%, LoE 51%)	29%
	ADA	88	23	61% (NR 48%, LoE 13%)	39%
	ETA	210	55	42% (NR 27%, LoE 15%)	58%
Genevay 2007 [116]	INF, ADA, ETA	1561	128	58%	33%

Reference	Drugs	Total number of patients treated	Total number of patients discontinue[79]	Percentage who discontinue due to inefficacy from all discontinuers[80]	Percentage who discontinue due to adverse events (safety)
Filippini 2008 [458]	INF, ADA, ETA	295	114	37%	53%
Fernandez-Nebro 2007 [161]	INF, ADA, ETA	161	88	Not reported	58%
Mattey 2010 [152]	INF, ADA, ETA	162	79	53%	39%
Flendrie 2003[81] [108]	All	191	63	40%	59%
	INF	83	35	37%	71%
	ADA	94	24	46%	46%
	ETA	14	4	25%	25%
Braun-Moscovici 2008 [105]	INF	108	43	70%	30%
Figueiredo 2008 [459]	INF	152	40	35%	53%
Bertoli 2008 [68]	INF	77	33	12%	41%
Voulgari 2005 [155]	INF	84	25	36%	60%
Ducoulombier 2007 [69]	INF	50	15	47%	47%
Wendling 2005 [180]	INF	14	41	50% (NR 7%, LoE 43%)	29%
Conti 2009 [112]	INF, ADA, ETA	37 (second course)	12	92% (NR 59%, LoE 33%)	8%

ADA- adalimumab; **ETA**- etanercept; **INF**- infliximab; **LoE**- loss of efficacy in patients who responded; ; **NR**- no response;

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[81] Some patients discontinued due to more than one reason.

Figure 22: Forest plot for the risk of discontinuing TNFα antagonists due to inefficacy and safety (adverse event)

Study or Subgroup	Inefficacy Events	Total	Safety Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.1.1 All drugs							
Conti 2009	11	12	1	12	1.1%	11.00 [1.67, 72.40]	
Agarwal 2008	38	65	25	65	6.3%	1.52 [1.05, 2.20]	
Flendrie 2003	25	63	37	63	6.3%	0.68 [0.47, 0.98]	
Mattey 2010	42	79	31	79	6.4%	1.35 [0.96, 1.91]	
Filippini 2008	42	114	60	114	6.7%	0.70 [0.52, 0.94]	
Genevay 2007	74	128	42	128	6.7%	1.76 [1.32, 2.35]	
Brocq 2009	86	147	61	147	7.0%	1.41 [1.11, 1.78]	
Ornbjerg 2010	97	210	78	210	7.1%	1.24 [0.99, 1.56]	
Heiberg 2008	114	293	114	293	7.2%	1.00 [0.82, 1.22]	
Marchesoni 2009	180	405	194	405	7.4%	0.93 [0.80, 1.08]	
Kievit 2011	285	694	243	694	7.5%	1.17 [1.02, 1.34]	
Du Pan 2009	327	653	318	653	7.5%	1.03 [0.92, 1.15]	
Hetland 2010	727	1089	327	1089	7.6%	2.22 [2.01, 2.46]	
Carmona 2006	394	1095	537	1095	7.6%	0.73 [0.66, 0.81]	
Hyrich 2007	841	2360	1023	2360	7.6%	0.82 [0.77, 0.88]	
Subtotal (95% CI)		7407		7407	100.0%	1.14 [0.92, 1.41]	
Total events	3283		3091				
Heterogeneity: Tau² = 0.16; Chi² = 362.97, df = 14 (P < 0.00001); I² = 96%							
Test for overall effect: Z = 1.21 (P = 0.23)							
3.1.2 Infliximab							
Bertoli 2008	4	33	14	33	3.1%	0.29 [0.11, 0.78]	
Wendling 2005	7	14	4	14	3.2%	1.75 [0.66, 4.66]	
Ducoulombier 2007	7	15	7	15	4.5%	1.00 [0.47, 2.15]	
Voulgari 2005	9	25	16	25	5.9%	0.56 [0.31, 1.02]	
Braun-Moscovici 2008	31	108	13	108	6.0%	2.38 [1.32, 4.30]	
Figueiredo 2008	14	40	21	40	6.9%	0.67 [0.40, 1.12]	
Flendrie 2003	13	35	25	35	7.3%	0.52 [0.32, 0.84]	
Brocq 2009	49	69	20	69	8.4%	2.45 [1.64, 3.65]	
Delabaye 2010	41	158	75	158	9.6%	0.55 [0.40, 0.75]	
Vander Cruyssen 2010	104	298	121	298	11.0%	0.86 [0.70, 1.06]	
Du Pan 2009	90	209	108	209	11.0%	0.83 [0.68, 1.02]	
Marchesoni 2009	104	226	106	226	11.1%	0.98 [0.80, 1.20]	
Hyrich 2007	455	1273	520	1273	12.0%	0.88 [0.79, 0.97]	
Subtotal (95% CI)		2503		2503	100.0%	0.89 [0.73, 1.09]	
Total events	928		1050				
Heterogeneity: Tau² = 0.09; Chi² = 61.56, df = 12 (P < 0.00001); I² = 81%							
Test for overall effect: Z = 1.12 (P = 0.26)							
3.1.3 Adalimumab							
Flendrie 2003	11	24	11	24	9.3%	1.00 [0.54, 1.85]	
Brocq 2009	14	23	9	23	9.5%	1.56 [0.85, 2.85]	
Marchesoni 2009	45	111	60	111	23.4%	0.75 [0.57, 1.00]	
Hyrich 2007	109	265	98	265	28.4%	1.11 [0.90, 1.38]	
Du Pan 2009	112	213	92	213	29.4%	1.22 [1.00, 1.49]	
Subtotal (95% CI)		636		636	100.0%	1.06 [0.86, 1.32]	
Total events	291		270				
Heterogeneity: Tau² = 0.03; Chi² = 9.27, df = 4 (P = 0.05); I² = 57%							
Test for overall effect: Z = 0.57 (P = 0.57)							
3.1.4 Etanercept							
Flendrie 2003	1	4	1	4	0.7%	1.00 [0.09, 11.03]	
Marchesoni 2009	31	68	28	68	14.1%	1.11 [0.75, 1.63]	
Brocq 2009	23	55	32	55	14.2%	0.72 [0.49, 1.06]	
Weinblatt 2009	138	573	168	573	22.4%	0.82 [0.68, 1.00]	
Du Pan 2009	125	237	118	237	23.1%	1.06 [0.89, 1.26]	
Hyrich 2007	277	822	405	822	25.5%	0.68 [0.61, 0.77]	
Subtotal (95% CI)		1759		1759	100.0%	0.85 [0.69, 1.05]	
Total events	595		752				
Heterogeneity: Tau² = 0.04; Chi² = 19.77, df = 5 (P = 0.001); I² = 75%							
Test for overall effect: Z = 1.52 (P = 0.13)							

0.02 0.1   1   10   50
Safety   Inefficiency

Test for subgroup differences: Chi² = 5.12, df = 3 (P = 0.16), I² = 41.4%

Table 24: Discontinuing TNFα antagonists by reason[82]

Drug	Number of studies	Number of discontinuations	Percentage from all discontinuations			Risk ratio (95% CI) for discontinuing due to inefficacy versus discontinuing due to adverse events
			Inefficacy	Adverse events	Inefficacy and Adverse events	
All	14	7407	44%	42%	86%	1.14 (0.92-1.41)
Infliximab	13	2503	37%	42%	79%	0.89 (0.73-1.09)
Adalimumab	5	636	46%	42%	88%	1.06 (0.86-1.32)
Etanercept	6	1759	34%	43%	77%	0.85 (0.69-1.05)

CI- confidence interval; **n** – number of patients

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[82] Based on Table 23 and Figure 22.

A.3.4 Published Comparisons of Drug Persistence

Studies comparing persistence with the available TNFα antagonists in RA patients showed discrepant results. While some published studies reported comparable persistence on the three individual drugs [108,113,460], others demonstrated better persistence on infliximab [62,104] or etanercept [110,150,151,161]. To summarize the results and explore possible causes of heterogeneity, we performed a systematic review and meta-analysis of hazard ratios of discontinuing TNFα antagonists in RA patients (unpublished data). The main findings were: (a) We identified 51 studies in which RA patients were included, patients were treated with at least two TNFα antagonists and drug persistence was reported, but seven studies which report pairwise comparison were included in the main meta-analysis (b) substantial heterogeneity was observed in all comparisons; infliximab and adalimumab I-square quantity of 95% (95% CI 91-97%) (unpublished data), infliximab and etanercept 79% (95% CI 31-93%) (b) . (c) In the research published to date, heterogeneity arises mainly from the use of different types of data-sources and could be caused by the use of different methodological approaches to ascertain discontinuation from disparate sources.

A.3.5 Patient Characteristics Predict Persistence with TNFα Antagonists in Rheumatoid Arthritis

The effect of RA patient characteristics on persistence with TNFα antagonists has been explored in a number of studies. In a systematic review and meta-analyses of the effect of patient characteristics (unpublished data), we demonstrate the following:

1. Concomitant use of MTX was significantly associated with improved persistence, with pooled hazard ratio concomitant use compared to non-use 0.73 (95% CI 0.56-0.98, four studies, 4742 patients) and pooled hazard ratio for concomitant use compared to monotherapy 0.79 (95% CI 0.65-0.95, three studies and six drug subgroups, 12593 patients).

2. Exposure to an increase in the number of synthetic antirheumatic drugs was associated with statistically significant improved persistence with hazard ratio for one drug increase of 1.12 (95% CI 1.04-1.20, four studies, 5867 patients).

We demonstrate insignificant association between persistence and sex (seven studies, 4,925 patients), age (continuous variable, nine studies, 8,371 patients), disease duration (continuous variable, four studies, 2,547 patients), baseline DAS28 score (continuous variable, four studies, 4,097 patients) and baseline HAQ score (continuous variable, four studies, 4,249 patients).

A.3.6 Diversity in Drug Administration Patterns

Persistence with TNFα antagonists may be also influenced by characteristics of drug administration, such as route of administration and dose adjustments.

A.3.6.1 Route of Administration

Infliximab is the only drug administered intravenously. Intravenous drug administration requires use of a health facility and a longer administration time. Intravenous drug

administration therefore may be inconvenient or cause discomfort, which may encourage

discontinuation, and switching to a subcutaneous preparation. **Vander Cruyssen et al**

[181,456] reported that in the cohort of RA patients who were followed for seven years, the

third reason to discontinue infliximab (inferior only to inefficacy and harm) was a decision by

the care-providing physician or the patient to switch to a subcutaneous TNFα antagonist. On

the other hand, intravenous drug administration requires regular physician follow-up; a feature

of treatment that has been shown to encourage persistence and compliance to drug therapy in a

variety of diseases [162,182-185].

Patient preference to route of administration may have an effect on persistence. It is accepted

that patient preference influences persistence and compliance with drug therapy [461-464],

although the evidence for this acceptance is limited. Janevic et al 2003 [463] studied

compliance to an educational program for management of heart disease. Two formats of the

educational program were used: group or self-directed. The investigators compared compliance

of women who were randomized to the format of the program and women who chose program

format. They found no statistical difference between the compliance rates, although the

direction supported the theory that preferred program increases compliance. Decreased

adherence to antidepressants was observed in patients who preferred a different drug [465]. We

could not find additional studies that directly examined the relationship between patient

preference and compliance or persistence, in RA or other diseases.

RA patient preference to route of administration of TNFα antagonists was assessed in several

studies, in TNFα antagonist naïve and in patients with experience with these drugs. The results

of the studies are contradictory. A survey of 141 Canadian RA patients indicated that most

patients preferred intravenous to subcutaneous drug administration (63% versus 37%) [183].

On the other hand, two British studies demonstrated preference for subcutaneous drug

administration. In the first study, 164 of the 200 patients questioned were TNFα antagonist

naïve. Only half of them (109) responded to the mailed questionnaires. Most of the patients

preferred adalimumab - 47% versus infliximab 23%, etanercept 4% or no preference 27%

[140]. In a second study, 100 patients were questioned, half of them were treated with TNFα

antagonists [285]. Most of the patients who were not treated with TNFα antagonists preferred

the subcutaneous route (53%) to intravenous drug administration (18%). In patients treated

with TNFα antagonists, 41% preferred subcutaneous route and 35% - intravenous drug

administration. In an Italian survey of 43 RA patients who were treated first with infliximab

and then with etanercept, 63% preferred subcutaneous drug administration and 21% -

intravenous drug administration [466].

In summary, in this section we have examined the possible effect of the route of administration

of the TNFα antagonists on persistence. We suggest that patients may discontinue infliximab

because of preference of subcutaneous drug administration. However, the significance of this

causal factor is not established, because the percentage of patients who discontinue for this

reason is not reported in the literature. Next, we examined possible correlation between patient

preference to the route of administration and persistence. We found no evidence that patient

preference influences persistence (or compliance) to drug therapy, and there are contradictory

results as to which of the three TNFα antagonists is preferred by patients. We could not

determine whether the route of administration affected TNFα antagonist persistence.

A.3.6.2 Dose Adjustments

Escalation or reduction in dose may be an alternative for treatment discontinuation in patients with low therapeutic benefit or perceived harm. In patients with inadequate response to TNFα antagonists, higher doses at each administration or shorter interdose interval are sometimes considered an alternative to switching to another drug. In patients experiencing adverse events, lower dose or longer interdose interval may eliminate or minimize the harm.

Dose escalation - Dose escalation is a common practice in RA patients treated with TNFα antagonists, as reported in observational studies using routine clinical practice data (Table 25), even though this strategy is not recommended by most guidelines [239,250,442]. In a published systematic review [467], about 50% of patients treated with infliximab underwent dose escalation compared to 17% on etanercept. Dose escalation is commonly achieved by increasing the administered dose and not by shortening the interdose interval (Table 25). In more recent studies, 27-59% of the patients routinely treated with infliximab, 10-34% of the

Table 25: Dose escalation [467]

Drug	Number of patients with data available	Proportion of patients with dose escalation (95 CI %)			Days to dose escalation
		Dose increase and/or interval decreases	Dose increased	Interval decreased	
Infliximab	5862	0.53 (0.52-0.54)	0.44 (0.43-0.46)	0.08 (0.07-0.10)	128-254
Etanercept	2621	0.17 (0.16-0.19)	0.17 (0.16-0.19)	None	123

CI- confidence interval

patients treated with adalimumab and 0-10% of the patients treated with etanercept underwent

dose escalation (Table 26).

Table 26: Dose escalation (additional Studies, from 2006)

Reference	Duration of follow-up	Infliximab	Adalimumab	Etanercept
Kievit 2011 [156]	Mean 33 to 40 months (for the individual drugs) and a total of 174 patients had at least 5-year follow-up.	0.27	0.13	0.054
Huang 2010 [468]	Maximum two years			
Last dose versus first dose (index dose)		n/a	0.14	0.067
Average dose versus recommended dose		n/a	0.34	0.10
Kristensen 2009 [469]	24 months	minor[83] 0.42 major[84] 0.15	n/a	n/a
Yazici 2009 [62]	Up to three years	0.38	0.14	0.00
Figueiredo 2008[459]	Mean 13 months	0.39	n/a	n/a
Favalli 2008 [470]	12 months	0.59	n/a	n/a
Wu 2008 [72]	12 months	0.35	0.10	0.03
Fernandez-Nebro 7507 [161]	Up to six years, median 24 months	0.33	n/r	n/r

n/a- not available, patients treated with this drug were not included in the study; **n/r**- not reported

---

[83] Less than 100% increment

[84] more than 200% increment

The increase frequency of infliximab dose escalation in routine practice compared to etanercept and adalimumab has several implications for research on persistence. First, dosage escalating may artificially improve persistence, since it is considered an alternative to switching due to inefficacy. Patients persist longer on infliximab even if does escalation does not restore efficacy. Second, dose escalation may influence ascertainment of treatment discontinuation and the discontinuation date in studies using dispensing claims data (**Chapter 2**, Section 2.2.4.2, page 52).

Dose reduction Reducing the dose of TNFα antagonists, either by lowering the administered dose or lengthening the interdose interval, is not common in clinical practice but may be used as an alternative to treatment discontinuation is cases of mild adverse events [248] or remission. The proportion of patients experiencing dose reduction ranged from 2.8-24% in patients treated with infliximab, 0.6-23% with adalimumab and 0-56% with etanercept in observational studies (Table 27). In a manner parallel to dose escalation, when manipulating dispensing claim data to calculate days-supply dispensed, the strategy of dose reduction results in an underestimation of the days-supply. However, in all but one study [471] the frequency of dose reduction was very low for all drugs, hence the significance of dose reduction on estimates of treatment persistence is negligible.

Table 27: Dose reduction

Reference	Duration of follow-up	Infliximab	Adalimumab	Etanercept
Kievit 2011 [156]	Mean 33 to 40 months (for the individual drugs) and a total of 174 patients had at least 5-year follow-up.	0.028	0.006	0.014
Carter 2010 [471]	At least two year	n/a	0.23[85]	0.56[86]
Yazici 2009 [62]	Up to three years	0.24	0.10	0.00
Wu 2008 [72]	12 months	0.061	0.068	0.062
Fernandez-Nebro 7507 [161]	Up to six years, median 24 months	n/r	n/r	0.10

n/a- not available, patients treated with this drug were not included in the study; n/r- not reported

A.3.7 British Columbian Drug Coverage Plan

British Columbia PharmaCare is a province-wide drug benefit plan that subsidizes the cost of eligible prescription drugs and designated medical supplies. The Fair PharmaCare Program, which started on May 2003, covers the cost of most drugs for residents who are eligible based on net taxable family income criteria. Prior to Fair PharmaCare, full ingredient cost coverage for prescription drugs was publically subsidized for all resident senior citizens and those who received social income assistance [472].

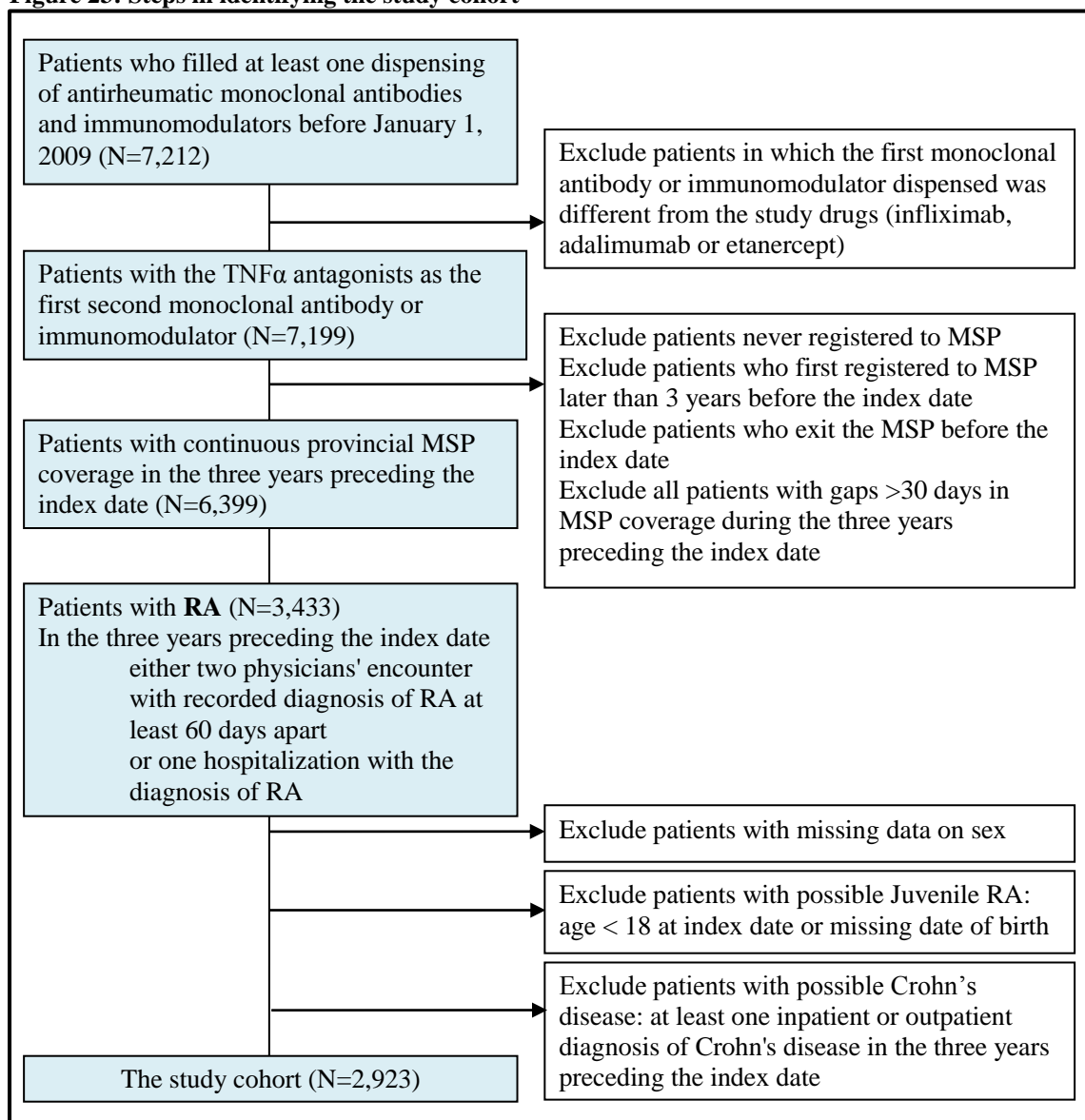[85] 10% below recommended

[86] 10% below recommended

Fair PharmaCare subsidizes the costs of TNFα antagonists under a limited coverage drug policy (called special authority) that requires RA patients to first try and fail treatment with 'first line' drugs such as MTX (combination or sequential) [473]. Patients who receive an exemption by special authority are eligible for one-year of coverage and can reapply annually for renewals.

Three TNFα antagonists were included among the top ten reimbursed drugs by cost during the fiscal year April 2009- March 2010. PharmaCare reimbursement expenses (for all indications) were $27.1 million for infliximab (third "most expensive" drug), $18.8 million for etanercept (seventh) and $17.7 million for adalimumab (eighth) [474]. In addition, TNFα antagonists were the fastest growing drug class in Canada between 2002 and 2008 [475].

Research on TNFα antagonist therapy is especially important to policy makers in British Columbia. First, TNFα antagonist therapy is associated with high (and increasing) cost and therefore has a major budget impact. Second, since treatment with TNFα antagonists requires special authority procedures, emerging evidence can potentially be translated into health policy modifications, which can then be quickly translated into practice.

Figure 23: Steps in identifying the study cohort

Patients who filled at least one dispensing of antirheumatic monoclonal antibodies and immunomodulators before January 1, 2009 (N=7,212)	Exclude patients in which the first monoclonal antibody or immunomodulator dispensed was different from the study drugs (infliximab, adalimumab or etanercept)
Patients with the TNFα antagonists as the first second monoclonal antibody or immunomodulator (N=7,199)	Exclude patients never registered to MSP. Exclude patients who first registered to MSP later than 3 years before the index date. Exclude patients who exit the MSP before the index date. Exclude all patients with gaps >30 days in MSP coverage during the three years preceding the index date
Patients with continuous provincial MSP coverage in the three years preceding the index date (N=6,399)	
Patients with **RA** (N=3,433). In the three years preceding the index date either two physicians' encounter with recorded diagnosis of RA at least 60 days apart or one hospitalization with the diagnosis of RA	Exclude patients with missing data on sex
	Exclude patients with possible Juvenile RA: age < 18 at index date or missing date of birth
The study cohort (N=2,923)	Exclude patients with possible Crohn's disease: at least one inpatient or outpatient diagnosis of Crohn's disease in the three years preceding the index date

Antirheumatic monoclonal antibodies and immunomodulators = infliximab, adalimumab, etanercept, anakinra, rituximab, abatacept, certolizumab and golimumab; MSP – medical Service Plan, RA – rheumatoid arthritis, TNFα – tumour necrosis factor alpha

Table 28: List of ICD-9 and ICD-10 codes used in the study

| Disease	ICD-9-CM Codes (hospital separations during 1998-2001 and community outpatient visits during 1998-2008)	ICD-10-CA Codes (hospital separations during 2002-2008)
Rheumatoid Arthritis	357.1, 359.6, 714, 714.0, 714.1, 714.2, 714.81, V82.1	G63.6, G73.7, I39, I41.8, J99.0, M05, M05.0, M05.1, M05.2, M05.3, M05.8, M05.9, M06.0, M06.2, M06.3, M06.8, M06.9
Crohn's disease	555, 5550, 5551, 5552, 5559	K50, K500, K501, K508, K509, M074, M091
Extraarticular Manifestations of Rheumatoid Arthritis	3571, 3596, 7141, 71481, 7142	G636, G737, I39, I418, J990, M050, M051, M052, M053

Figure 24: Assigning values for the outcome variables (five scenarios)

The symbols

|	
Index date	The index date of the first TNFα antagonist
	The last dispensing before discontinuation
	Date of discontinuation of the first TNFα antagonist
	The first dispensing of a second monoclonal antibody or immunomodulator drug
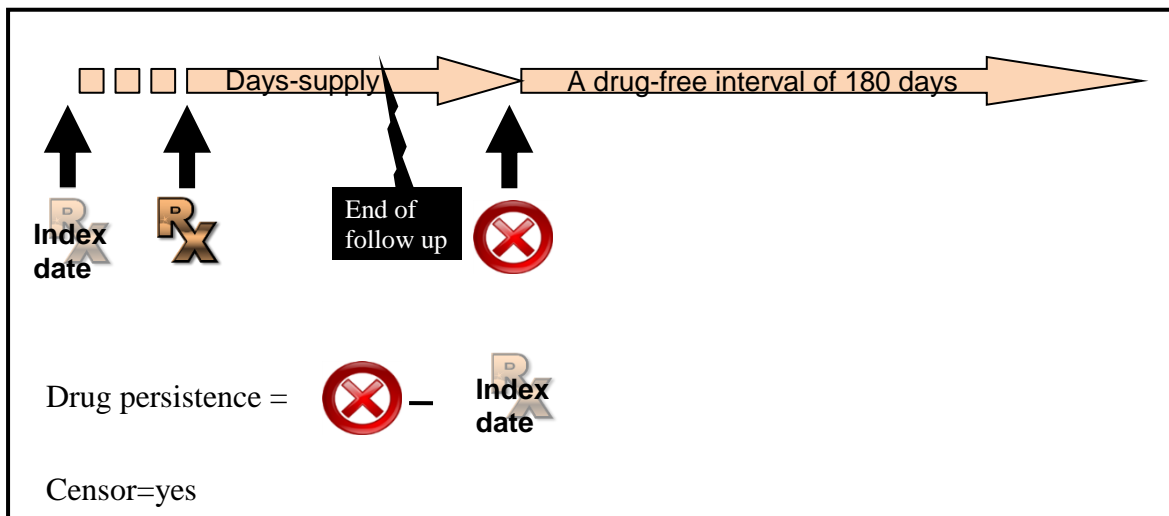
Scenario A: The patient was still on drug at the end of follow-up. Drug persistence is calculated from the index date to the date of end of days-supply. The patient is considered censored.
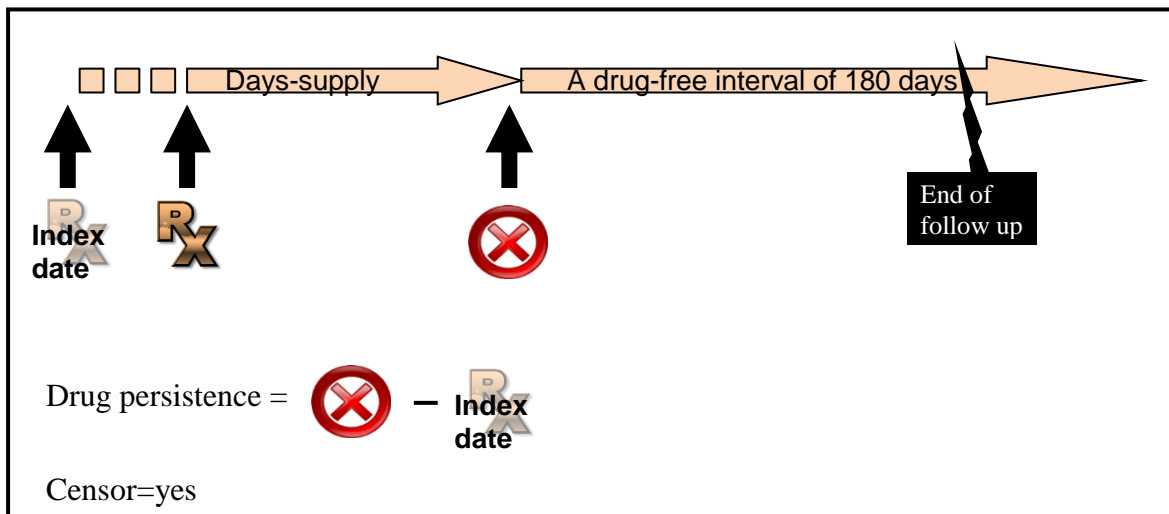

Scenario B: The patient was not on drug at the end of follow-up; however the predefined drug-free interval (180 days) did not elapse. Drug persistence is calculated from the index date to the date of end of days-supply. The patient is considered censored.
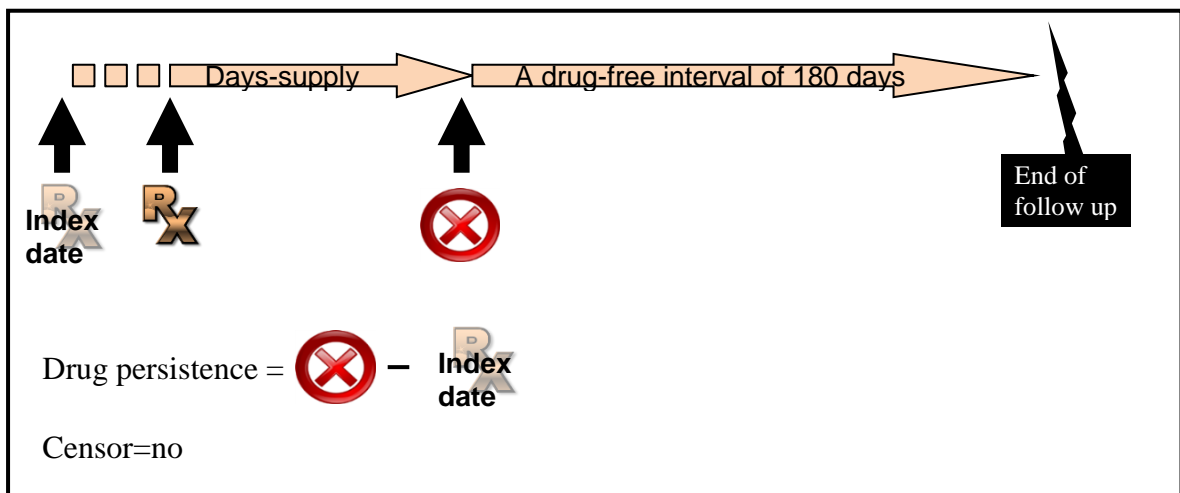
Scenario C: The patient was not on drug at the end of follow-up and the predefined 'drug-free interval' (180 days) already elapsed. Drug persistence is calculated from the index date to the date of end of days-supply. The patient is not considered censored.
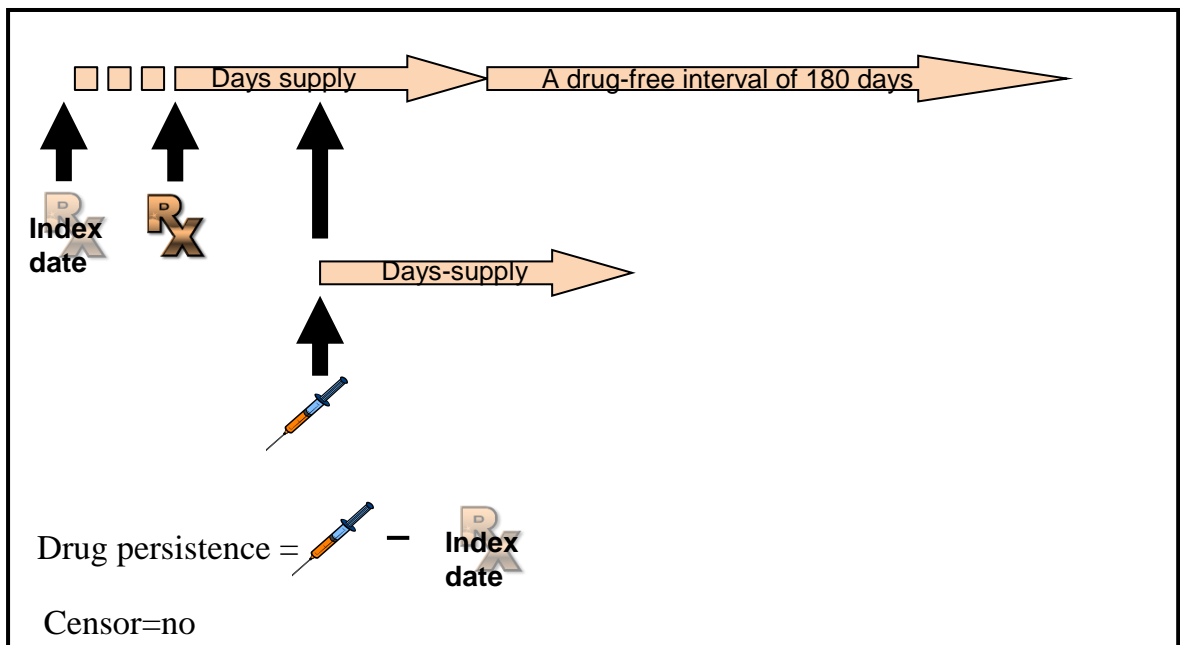
Scenario D: The patient switched to a second biologic drug anytime before the end of days-supply for the dispensing of the first TNFα antagonist. Treatment persistence is calculated from the index date to the date of the first dispensing of the second biologic drug. The patient is not considered censored.
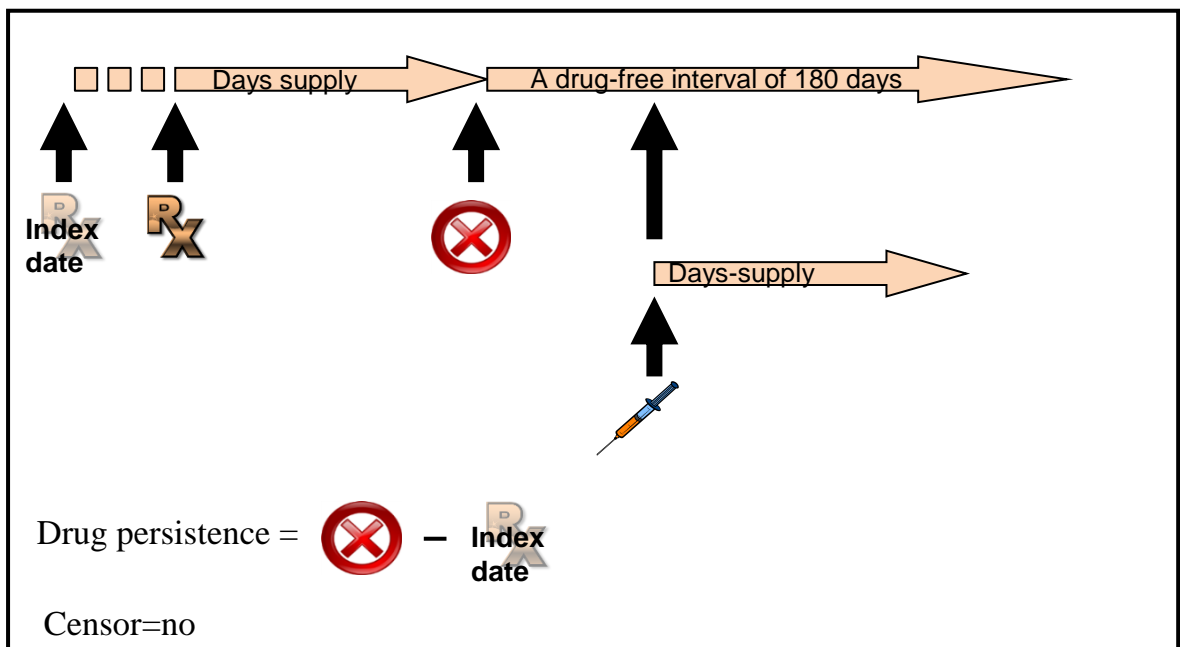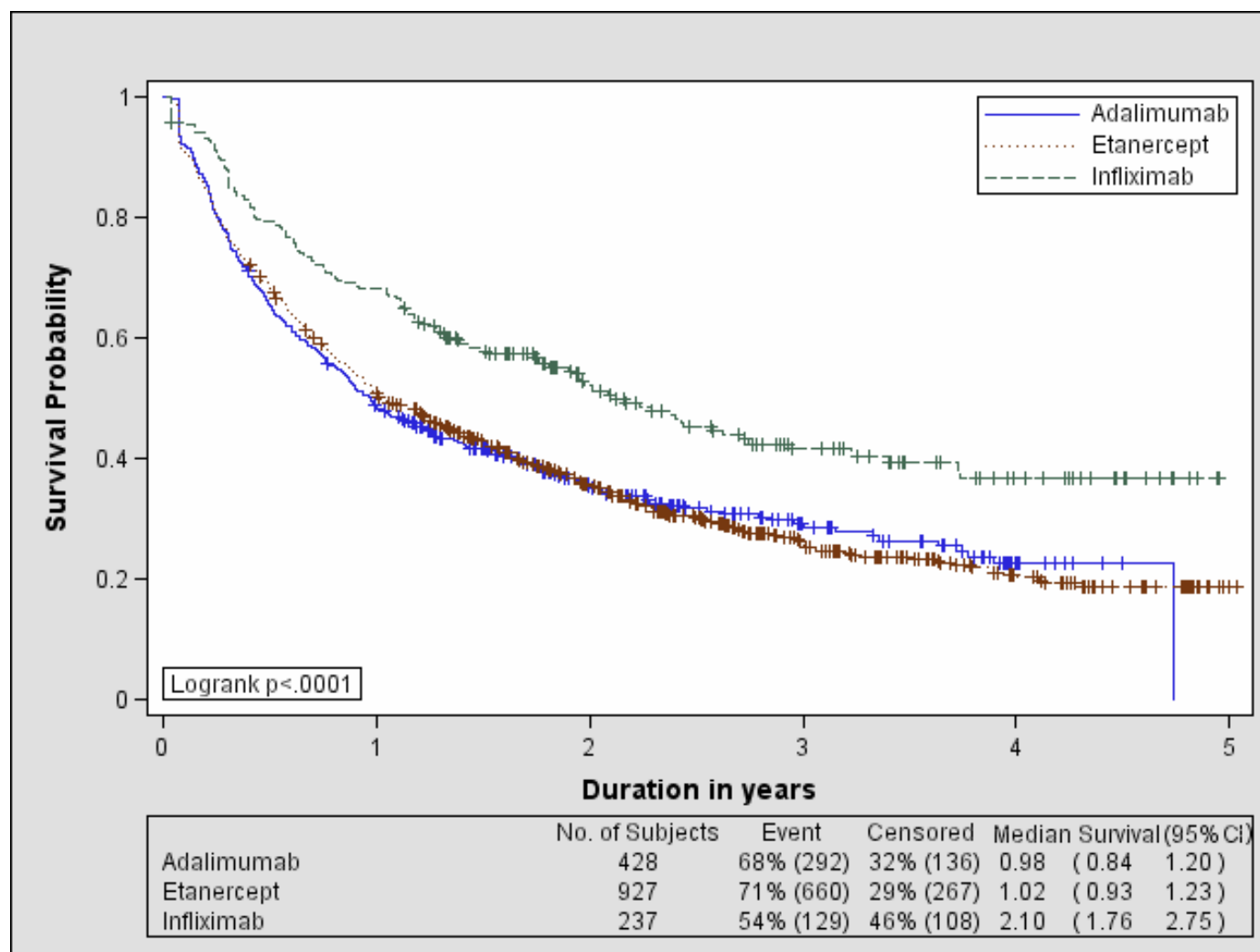
Scenario E: The patient switched to a second biologic drug anytime after the end of days supply for the dispensing of the first TNFα antagonists, but before the drug-free interval elapsed. Treatment persistence is calculated from the index date to the date of the end of days-supply of the last dispensing. The patient is not considered censored.
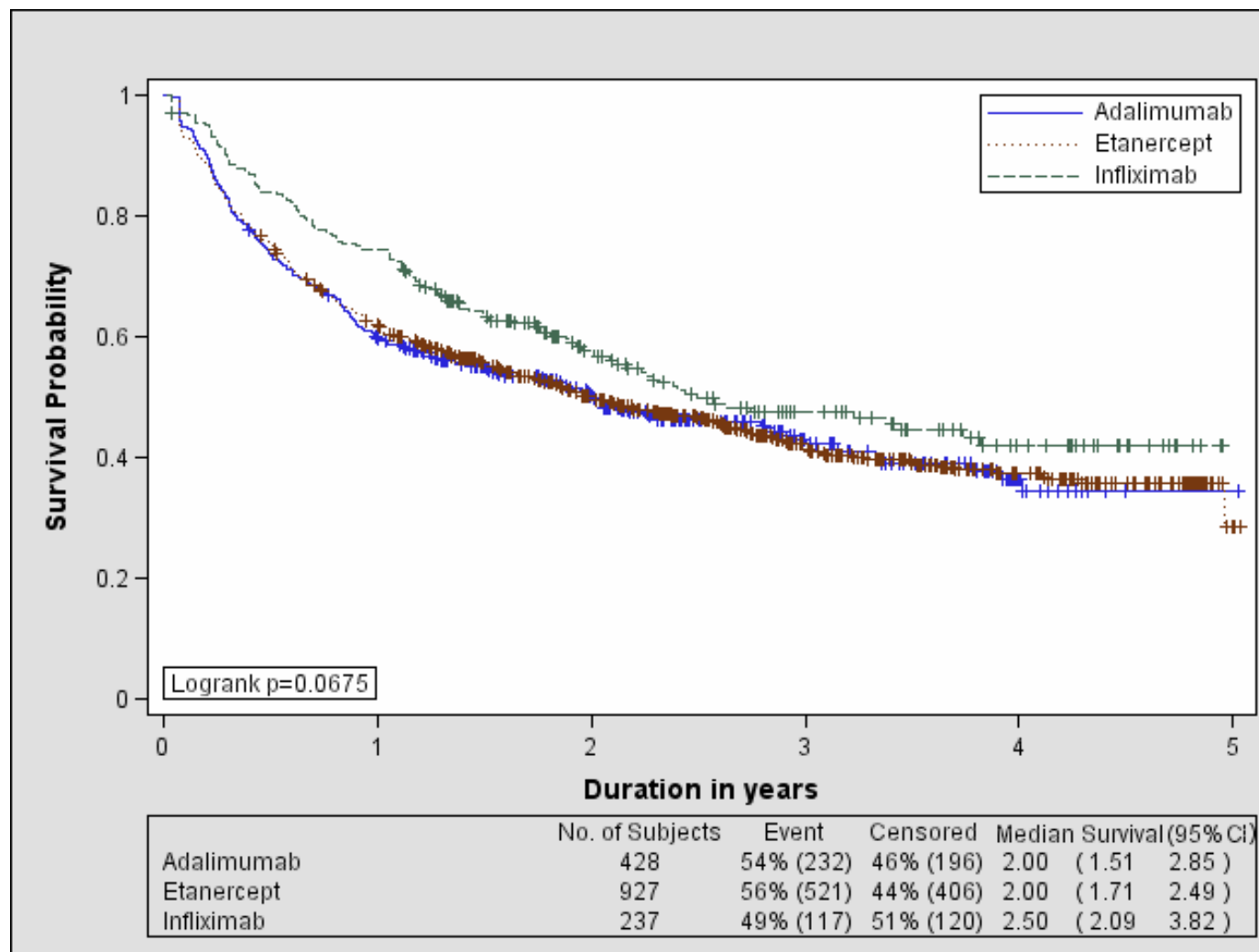
APPENDIX C: CHAPTER 4 (SUPPORTING MATERIAL)

Figure 25: Persistence by algorithm to ascertain discontinuation (index date 2005-2008)

A. Switching or a drug-free interval of 30 days

B. Switching or a drug-free interval of 60 days

	No. of Subjects	Event	Censored	Median Survival (95% CI)	
Adalimumab	428	54% (232)	46% (196)	2.00	(1.51 2.85)
Etanercept	927	56% (521)	44% (406)	2.00	(1.71 2.49)
Infliximab	237	49% (117)	51% (120)	2.50	(2.09 3.82)

C Switching or a drug-free interval of 90 days

	No. of Subjects	Event	Censored	Median Survival	(95% CI)
Adalimumab	428	49% (211)	51% (217)	2.82	(2.00 3.35)
Etanercept	927	51% (470)	49% (457)	2.73	(2.28 3.07)
Infliximab	237	47% (112)	53% (125)	3.23	(2.29 NA)

D. Switching or a drug-free interval of 180 days

	No. of Subjects	Event	Censored	Median Survival (95% CI)	
Adalimumab	428	45% (194)	55% (234)	3.16	(2.63 NA)
Etanercept	927	45% (420)	55% (507)	3.70	(3.00 NA)
Infliximab	237	46% (108)	54% (129)	3.38	(2.39 NA)

279
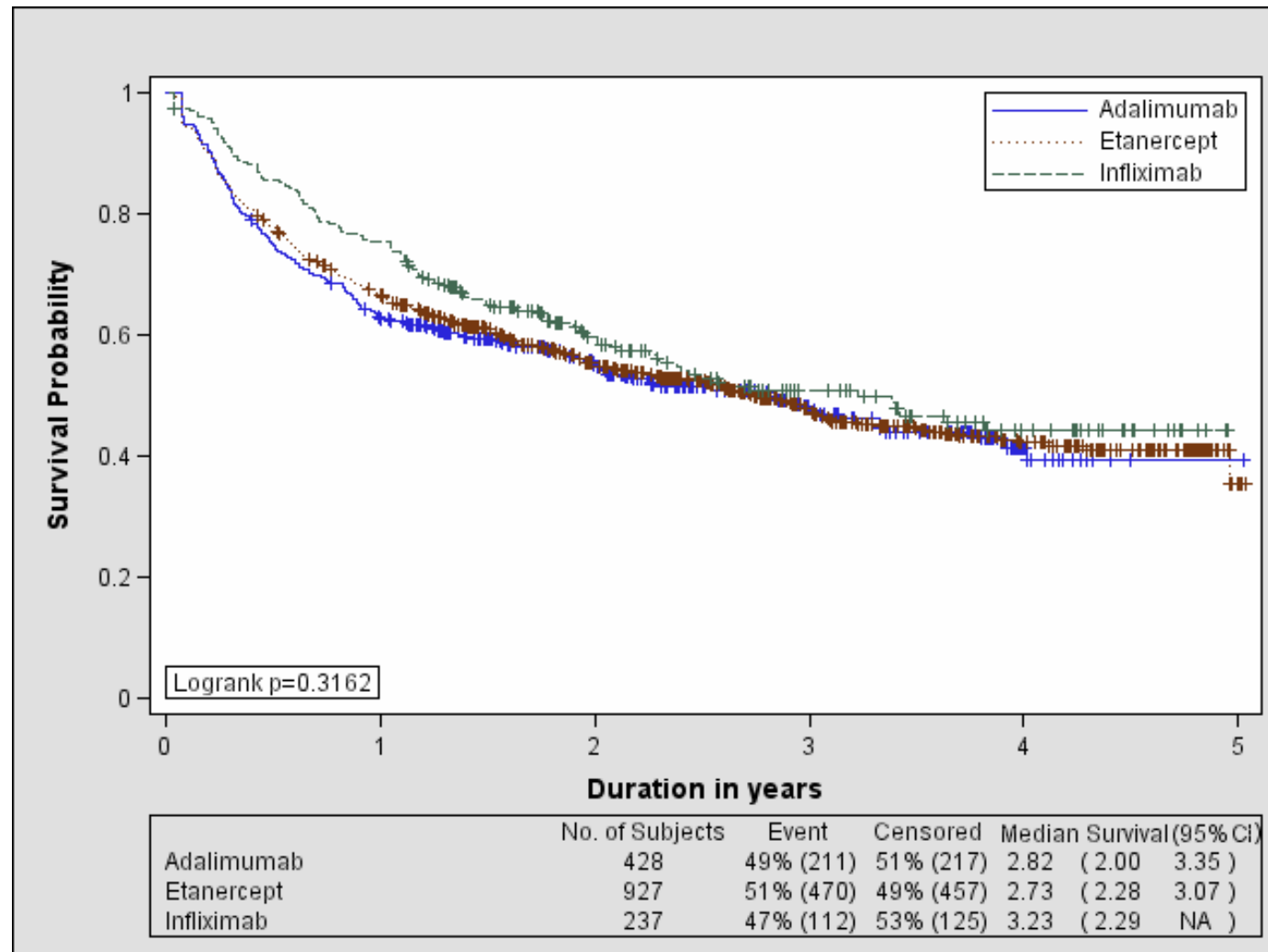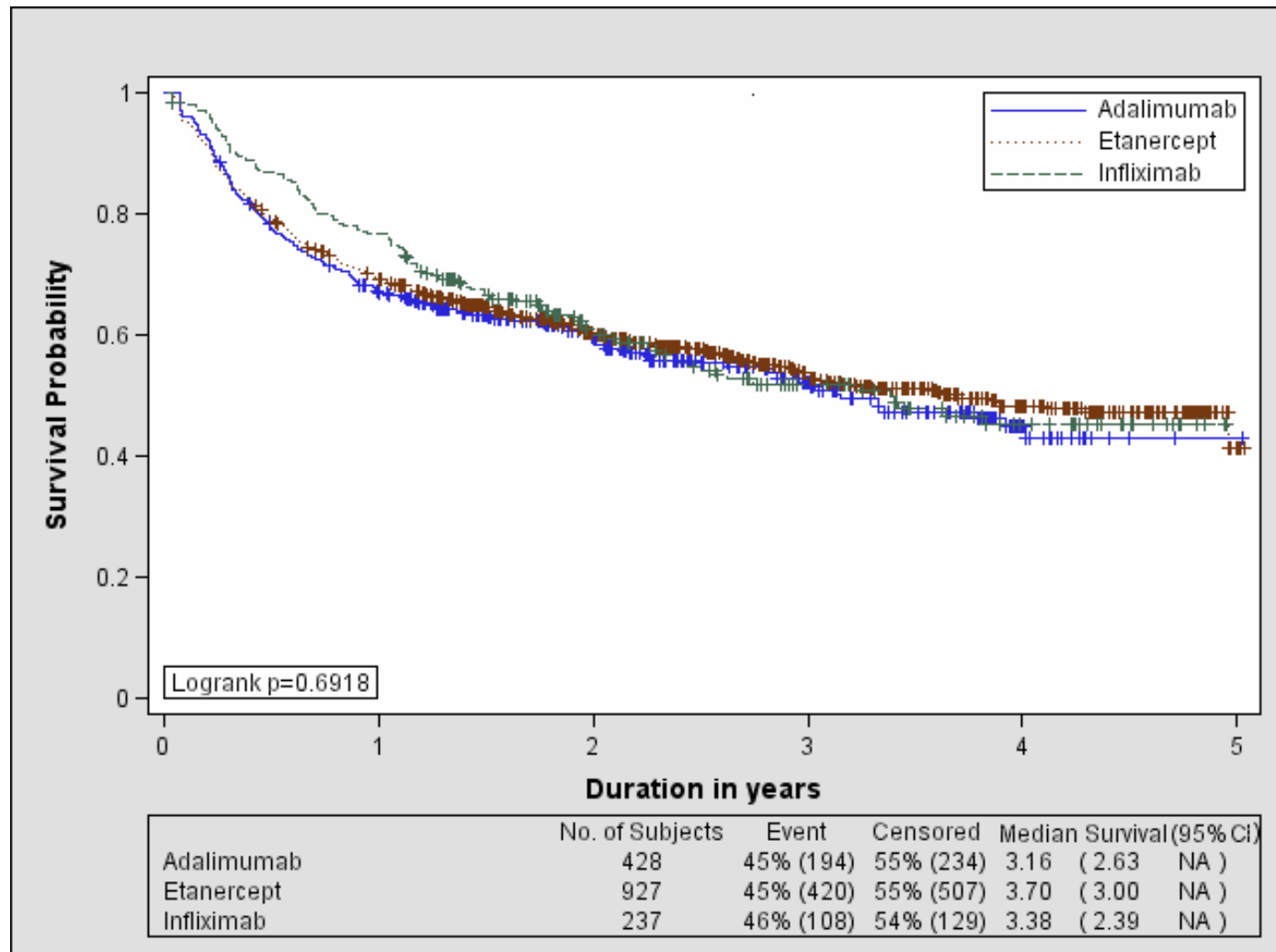
Table 29: Sensitivity analysis in studies of TNFα antagonists in rheumatoid arthritis

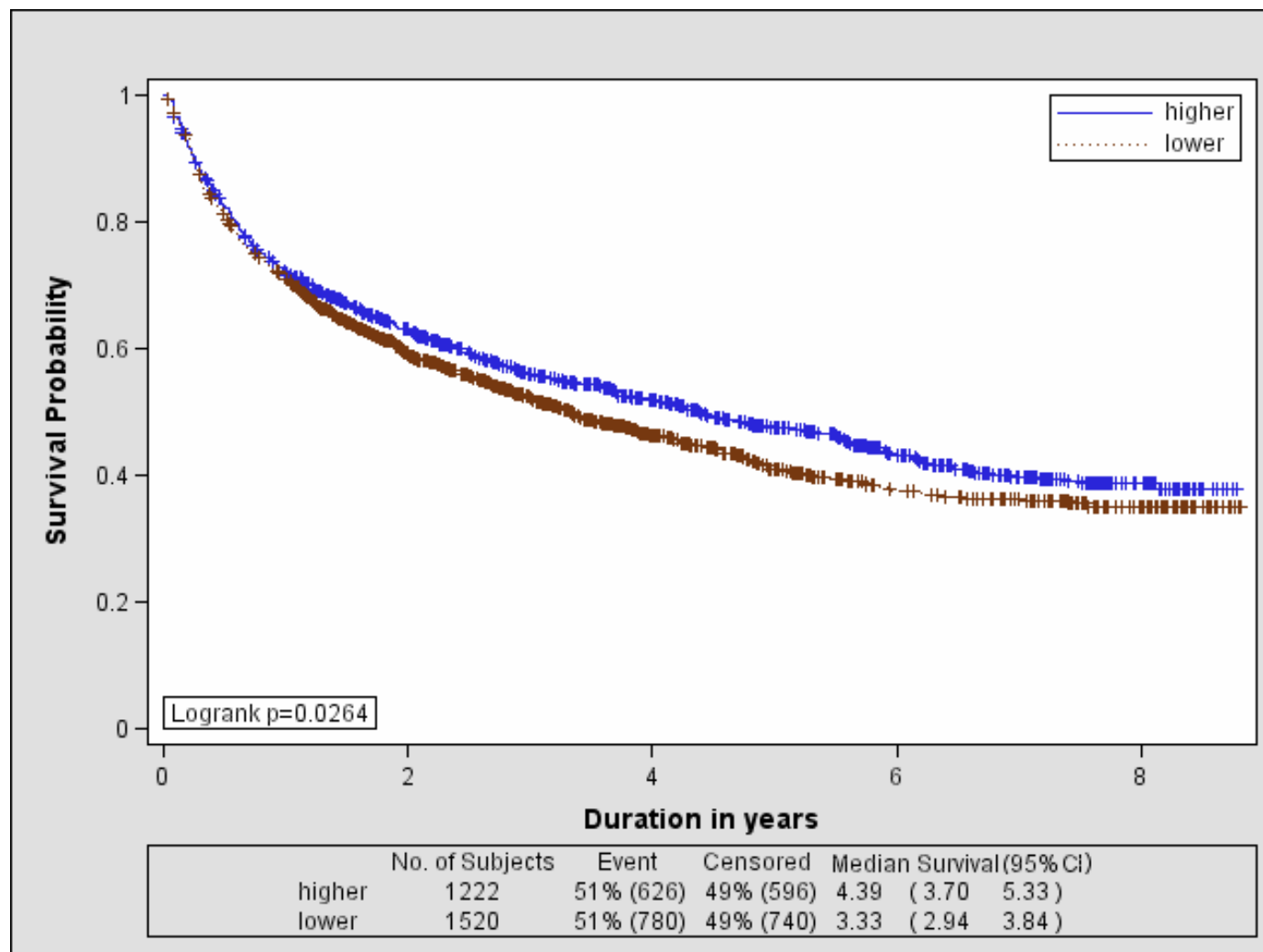| Reference	Duration of follow up	Drug-free interval	Percentage discontinuations		
			Infliximab	Adalimumab	Etanercept
Li 2010 [213] N=2371	1 year	30 days	65.3%	-	67.9%
		60 days	48.3%	-	50.0%
		90 days	40.9%	-	40.7%
		120 days	33.6%	-	34.5%
Ogale 2011 [215] (1st course of antirheumatic monoclonal antibodies and immunomodulators) N=3217	1 year	60 days	39.6%	52.9%	49.9%
		180 days	33.4%	42.6%	36.7%
Schmeichel-Mueller 2011[216] N=1780	2 years	60 days	37.6%	57.2%	57.5%
		360 days	18%	22.5%	17.3%

APPENDIX D: CHAPTER 5 (SUPPORTING MATERIAL)

Figure 26: Persistence with the first course of TNFα antagonists in rheumatoid arthritis patients, by PPD level

A. Threshold of 60%
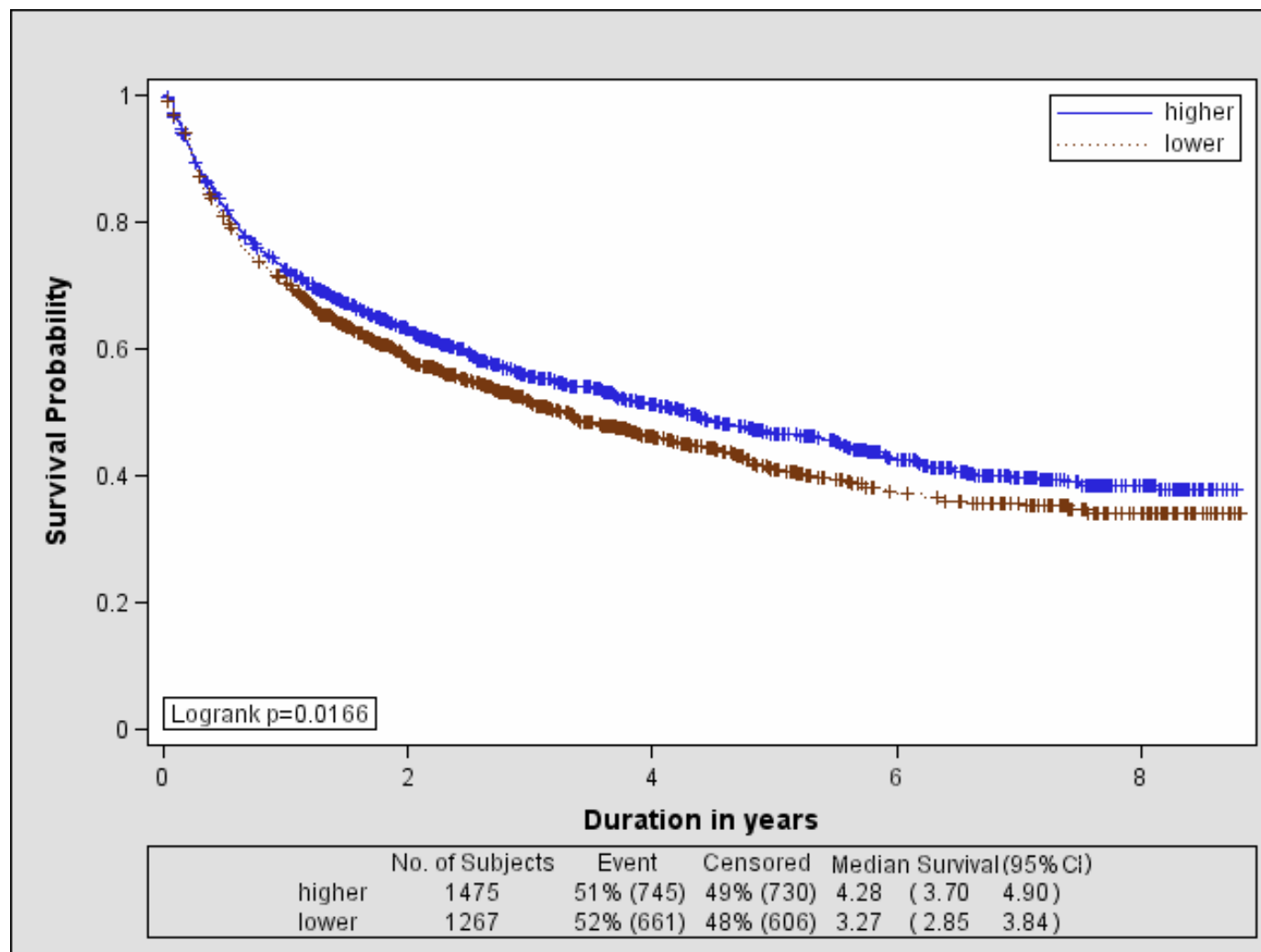
B. Threshold of 70%

C. Threshold of 80%