The Effect of Biologic Therapies on the Risk of Suffering a Myocardial Infarction (MI) in Patients with Moderate to Severe Psoriasis

Shane A. Randell

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ABSTRACT

This case-control study aimed to test for significant difference between the risks of suffering a cardiovascular event between two groups of moderate to severe psoriasis (PSO) patients: those that had a biologic therapy (BT) and those that did not. The aim was to test for a protective factor in biologic therapies as patients with moderate to severe psoriasis have been reported to be at a higher risk of experiencing a cardiovascular event due to the chronic inflammatory nature of the disease. Cases were extracted from patient charts at Newlab Life Sciences, Inc. (NLS) and transferred to an electronic dataset, while controls were obtained from the Newfoundland and Labrador Centre for Health Information (NLCHI). The results of a logistic regression failed to show a statistically significant relationship between the outcome, myocardial infarction (MI), and the use of a biologic therapy however, there was a protective trend for those patients on a biologic therapy. There also appeared to be a relationship between age of onset and MI, as those patients diagnosed before the age of 25 saw a statistically significant greater risk of suffering an MI than those diagnosed after the age of 25. There were several limitations to this study including limited data and confounders, such as lifestyle factors and the change in price and availability of biologics to PSO patients over time. Based on the current literature limited evidence exists that supports the hypothesis that there is a significant protective factor associated with biologics in relation to cardiovascular events.

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ORGANIZATION OF THE DISSERTATION

This Master's thesis is presented in Chapters in order to keep the goals and objectives organized. Chapter 1 reveals the topic of interest as well as providing a summary of the goal of the thesis; Chapter 2 provides background information including the prevalence and pathophysiology of psoriasis, a literature review describing treatment options, biologic therapies (BT) over time and how they are used today, as well as background on the association of myocardial infarction (MI) with psoriatic arthritis (PSA); Chapter 3 describes the materials and methods used; Chapter 4 presents the results of the statistical analysis (logistic regression) and presents relevant tables and graphs; Chapter 5 is dedicated to the discussion of the results and how they relate to the literature available and concludes with a summary of the strengths and weaknesses of the study.

Conflicts to Consider:

None to declare. The student has no claims in any results within this manuscript. The student received graduate stipends from his academic advisor under full-time status which is governed by Memorial University's School of Graduate Studies. This study did not receive funding from any source.

LIST OF ABBREVIATIONS FOUND IN THIS DISSERTATION

AUC	Area Under the Curve
BSA	Body Surface Area
BT	Biologic Therapy
CDMS	Clinical Database Management System
CEC	Circulating Endothelial Cells
CI	Confidence Interval
CTCL	Cutaneous T-Cell Lymphoma
DLQI	Dermatology Life Quality Index
GP	General Practitioner
HCN	Health Care Number
HREA	Health Research Ethics Authority
HREB	Health Research Ethics Board
HRQoL	Health Related Quality of Life
ICD-9	International Classification of Disease, 9th Revision
ICD-10-CA	International Classification of Disease 10th Revision, Canadian Enhancement
ICD-10-CM	International Classification of Disease 10th Revision, Clinical Modification
IL	Interleukin
MACE	Major Adverse Cardiovascular Event
MCP	Medical Care Plan
MI	Myocardial Infarction
MTX	Methotrexate (systemic therapy)
MUN	Memorial University of Newfoundland
NBUV	Narrow-Band Ultra Violet
NL	Newfoundland and Labrador
NLCHI	Newfoundland and Labrador Centre for Health Information
NLS	Newlab Life Science, Inc.
PI	Principle Investigator
PRD	Psoriasis Research Database
PSA	Psoriatic Arthritis
PSO	Psoriasis
RCT	Randomized Controlled Trial
ROC	Receiver Operating Characteristic
SPSS	Statistical Package for the Social Sciences
UV	Ultra Violet
VWF	Von Willebrand Factor

CHAPTER ONE: INTRODUCTION

This section introduces the topic of this thesis including the research question, the problem presented, and the goals and outcomes to be considered.

Purpose

The purpose of this study was to assess whether or not biologic therapies (BT) have a protective factor with respect to cardiovascular events, specifically MI, in patients with moderate to severe psoriasis.

Objectives

- To test for statistically significant relationships between the binary primary outcome MI and predictive factors such as BT use, age, age of onset, gender and smoking status.
- To assess support for the continued use of BT in psoriasis patients.

Research Questions

- Does taking a BT play a role in the risk of experiencing an MI event?
- Are there potential confounders?
- Does PSO increase the overall risk of an MI event?
- Does age of onset (defined as before or after the age of 25) play a role in increasing the risk of an MI event?

The Research Problem and Rationale

Psoriasis is a relatively common auto-immune disorder associated with multiple co-morbidities and contributes to a significant economic burden (Gulliver et al., 2008). Co-morbidities include cardiovascular disease, psoriatic arthritis (PSA), ankylosing spondylitis, sacroiliitis, peripheral arthropathy, inflammatory bowel syndrome, dyslipidemia, type 2- diabetes (T2D), obesity, hypertension, metabolic syndrome and cutaneous t-cell lymphoma (CTCL) (Gulliver et al., 2011). Due to the incurable and chronic nature of PSO, and the potentially devastating effects from the condition and co-morbidities, a study like this is important as it may show a protective function of BTs. Given increasing evidence, BTs may become more readily prescribed and move towards more front-line status as a treatment option.

We are at an interesting position in time with respect to this study as BT as a treatment for PSO is relatively new. These drugs only began gaining momentum in the early 2000s and have only been studied for the past decade (Baker and Coleman, 2012). In recent years researchers have been able to begin assessing the moderate to long term effects of these treatments and to start weighing the pros and cons of delivering BTs to patients. Since BTs are becoming more accepted and their true effectiveness is gaining acceptance, insurance companies are more willing to provide coverage and the once hard to obtain BTs are becoming more accessible to PSO and PSA patients. By gathering and analyzing data from PSO patient charts we can test to see if these drugs may also decrease the risk of MI.

CHAPTER TWO: LITERATURE REVIEW

A literature search was conducted using PubMed and EMBASE databases in 2013 using the following search terms: psoriasis, psoriatic arthritis, biologic therapy, systemic therapy, methotrexate, cyclosporine, topical agent, UV therapy, cardiovascular disease, myocardial infarction and regression statistics. Using PubMed, the term 'psoriasis' was searched with filters to show only articles from the past ten years, for persons over the age of 18, full free articles, and from human species resulted in 1146 possible articles. After scanning titles and designs, 21 relevant articles were chosen for review. A second search using the same filters and the MeSH terms "psoriasis" and "biologic therapies" was conducted yielding 229 articles of which 9 were chosen based on a title scan. Finally, a third PubMed search was conducted using the MeSH terms "psoriasis" and "myocardial infarction" which returned 48 results. Of these, 41 were excluded based on title and/ or the abstract leaving 7. Therefore, PubMed provided 37 of the articles used in this dissertation.

Using the EMBASE database, a search for "psoriasis" and "therapies" with filters including the date range 2003-2013, article design, 18 years of age and over, human only and English language returned 3517 articles of which 215 were selected based on a scan of the titles. Of these 215 abstracts, 54 articles were chosen for full review resulting in the inclusion of 21 references for this study.

In addition to online databases, a hand search was conducted of 2 physical publications of dermatology journals resulting in 3 reference papers.

2.1 Inclusion/ Exclusion Criteria for Literature Review

Articles chosen for this study were selected based on relevance and date (title and published within the past ten years). To keep the focus of this review on the most current information, articles used to discuss the background/ pathology of psoriasis, therapies used, and psoriasis association with MI were from 2003 onwards. No RCTs were found for this paper.

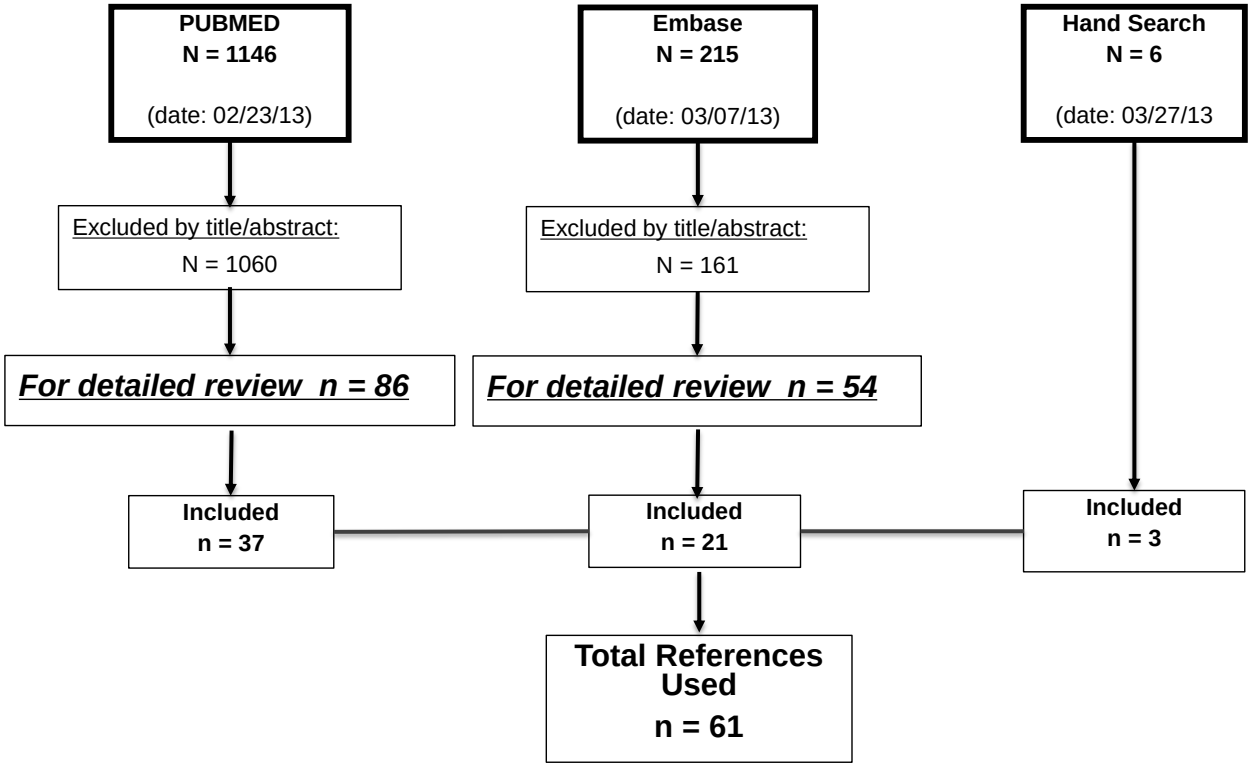

Figure 2.1: Overview of Systematic Literature Search

2.2 Psoriasis Overview

Psoriasis is a chronic inflammatory disease which presents itself as scaly lesions (or plaques) on the skin and can have spontaneous flare ups and remissions (Xu, 2012). Approximately 2-3% of the population or about 125 million people globally are afflicted by the condition, resulting in US$4.3 billion per year in health care costs (Gulliver, 2011). Although the etiology of the condition is not fully understood, evidence suggests that it has characteristics of an autoimmune disease with an inappropriate immune-mediated response. Psoriasis may also be dependent on a number of genetic and environmental factors. Psoriasis is a heritable disease and as such is 4-6 times more likely to develop in first-degree relatives of individuals with psoriasis (Girolomoni, 2012).

In patients with psoriasis, keratinocytes (the predominant epidermal cell) hyper-proliferate due to faulty signaling from the immune system. This hyper-proliferation is driven by t-cell produced cytokines and chemokines such as inferon-ϒ, tumor necrosis factor α (TNF-α) and Interleukin 17A and 22 (IL-17A and IL-22) among others. The over production of these cytokines amplifies the inflammatory response (as seen in psoriasis plaques) by causing the recruitment, retention and activation of immune cells in the skin (Girolomoni, 2012). An increase in angiogenesis is also seen in psoriatic patients as a four-fold increase of the endothelial microvascular bed in psoriasis skin has been observed (Liew 2012). This can present clinically as the "Auspitz's sign" where psoriatic plaques bleed in a predicted manner when excoriated.

The disease can present itself with variable severity which can be effectively grouped into low, moderate or severe psoriasis based on the body surface area (BSA) affected. Low severity corresponds to ≤ 3% BSA coverage, moderate corresponds to 3-10% BSA

coverage and severe corresponds to a BSA coverage of ≥10%. BSA is incorporated into the more rigorous Psoriasis Area and Severity Index (PASI) in order to generate a score reflecting severity, which is often used to monitor improvement of the condition over time under the effect of various treatment options. Most patients with PSO experience varying degrees of discomfort depending on severity (Langley, 2004). Since the mid-1990s, the dermatology life quality index (DLQI) is often used with the PASI score for the assessment of disease effect on day-to-day life for patients with psoriasis as well as other dermatological conditions (Finlay and Khan, 1994). Generally, a treatment is deemed moderately successful if a reduction of 50-74% in PASI score is seen (referred to as PASI 50), and a treatment is considered successful if the reduction in PASI score is 75% or more (referred to as PASI 75) (Banqueri 2012). Severity increase has been positively correlated with a 2-3 fold likelihood of mortality in severe psoriatic patients, with many reporting (>40%) that the condition adversely effects their daily routines (Gulliver, 2008). While lower health related quality of life (HRQoL) is valuable when studying the emotional effects of the disease on patients, it should not be used to diagnose severity due to the subjective nature of the measure (Girolomoni, 2012). The HRQoL tracks how an individual's well-being is impacted by a condition over time by a disease and is often used in the form of a self-reported questionnaire (Reich 2012).

Numerous co-morbidities are associated with psoriasis including psoriatic arthritis in 5-40% of patients (Weger, 2010) and depression (21-53% of patients) (Mrowitz, 2011; Fleming et al., 2014). It has been debated whether or not psoriasis is linked to an increased risk of myocardial infarction (MI) given the hypothesis that the inflammatory nature of the disease would, over time, cause deterioration on the cardiovascular system due to long term xposure to inflammation. It has also been shown that psoriasis patients have a higher prevalence of other

traditional cardiac risk factors such as obesity, hypertension, diabetes, smoking, and metabolic syndrome all of which may act as confounding variables (Ahlehoff, Skov et al, 2012). Several hospital-based studies have found evidence supporting the hypothesis that psoriasis is an independent risk factor for incident MI with higher risk in younger patients with higher severity psoriasis (Reich, 2011). It is hypothesized that this can be attributed to the fact that patients whom are diagnosed earlier (under the age of 40) will have more time exposure to systemic inflammation and thus have a higher likelihood of suffering the adverse effects of the disease (Gelfand, 2006).

There are presently multiple treatment options available for psoriasis. Traditionally milder psoriasis are treated with lower risk therapies such as phototherapy or topical corticosteroid (Akasaka, 2013). More severe psoriasis may be treated with systemic therapies such as cyclosporine and methotrexate (Dogra, 2013). Over the last decade biologic therapies (BTs) have gained momentum as a therapy of choice for PSO patients. These agents are designed to target specific mediators in the immune response. For example, Ustekinumab acts as an antagonist to IL-12 and IL-23 with the hopes of decreasing inflammation (Banqueri, 2012).

It is hypothesized that these biologic therapies may also decrease the risk of major adverse cardiac events (MACE) such as MI, acute coronary syndrome and acute MI by decreasing the heightened pro-inflammatory response seen in psoriatic disease. Because these therapies are relatively new, studies are needed to determine the long term effects. Cohort studies and meta-analyses examining the effect of biologic therapies on MI risk were studied with no consensus yet reached (Abuabara et al, 2011; Ryan et al, 2011). Due to the chronic long term nature of psoriasis, the potential cardio-protective benefits of biologic therapies may lead to a decrease in incident MI (Ahlehoff, 2012). Given the complexity and the chronic nature of the

disease, long term, individualized treatment regimens taking MI risk factors into consideration should be implemented in psoriatic patients (Mrowietz, 2012).

2.2.1 Mechanics of Psoriasis

Psoriasis (PSO) can manifest in a number of forms including plaque psoriasis, which accounts for 80% of diagnosed PSO, making it the most common type and is characterized by scaly, erythematous plaques and has a relapsing and remitting course (Xu, 2012). Other types of psoriasis include pustular; a rare, particularly inflammatory erythrodermic form which can effect most of the body surface including the scalp. Nail psoriasis is also commonly seen in psoriatic patients (Akasaka, 2013).

Once believed to be limited to the skin, more recent evidence indicates that PSO is a complex immune-mediated disorder. Due to erroneous immune signaling, keratinocytes in the skin hyper proliferate as a result of an overexpression of multiple chemokines, cytokines, and a reduction in t-cell regulation (Ahlehoff, 2011). Cytokines are signaling molecules which can induce an inflammatory response in the skin whereas chemokines are a special subtype of cytokine with chemotaxic properties and recruit immune cells to the site of the inflammation (Xu, 2012). For example, the cytokine interleukin-17A (IL-17A), helps to protect the body against invading extracellular bacteria and fungi (Girolomoni 2012). Neutrophils, mast cells, T-helper 17 and Tc-17 cells produce IL-17A, all of which are found in psoriatic lesions (Duan et al, 2001). IL-17A will induce the production of antimicrobial peptides and pro-inflammatory cytokines which can lead to the hyper-proliferation of keratinocytes resulting is psoriatic plaques (Harper, 2009).

Another factor which is seen to be over expressed in psoriatic patients is the single stranded, non-coding micro RNA-31 (MiR-31). MiR-31 regulates a protein complex which controls DNA transcription known as nuclear factor kappa-light-chain-enhancer of activated B cells (Xu, 2012) which basically regulates the function and production of inflammatory mediators in the immune system.

2.2.2 Tumor Necrosis Factor Alpha (TNF-α)

Tumor Necrosis Factor Alpha (TNF-α) is a cytokine associated with systemic inflammation and is mainly produced by macrophages. It is believed to be a key moderator in psoriasis flare ups and may be caused by polymorphisms in the TNF-α gene leading to an over production of the cytokine (Prieto-Perez et al, 2013). Upon activation, the macrophages release TNF-α at an altered rate in psoriatic patients causing an erroneous signal, resulting in an inflammatory response presenting as epidermal lesions. In recent years anti-TNF-α therapies have been used alone or in combination with other systemic therapies, such as methotrexate, or topical creams, such as dovobet, as a way of repressing the over production of TNF-α with the hopes of decreasing symptoms and system inflammation (Thorlund et al, 2012). These biologic therapies have proven to be effective although long term effects of TNF-α blockers are still under investigation. Certain cancers, as well as adverse skin conditions in the form of dermatitis and dermatosis, have been in seen in 10-60% of patients (Machado et al, 2013). A study from Japan (Nakayama, 2013) suggests that anti-TNF-α therapies may contribute to autoimmune hepatitis but that study was a single case-study report.

2.2.3 Association with Myocardial Infarction (MI)

PSO has long been understood to carry associations with numerous co-morbidities including diabetes mellitus, hypertension and dyslipidemia (Gulliver, 2008; Papp, 2013; Ahlehoff et al., 2011). Patients with PSO have also shown higher prevalence of traditional risk factors for MI including obesity, stress, depression and smoking (Gelfand, 2006). Recent studies now indicate that there is a measurable correlation between moderate to severe psoriasis and the risk of suffering an adverse cardiovascular event, although reports are still conflicting (Ahlehoff, 2011). Lin and associates conducted an analysis which suggests that some studies fail to find a correlation between psoriasis and an increased risk of MI but have failed to adjust for potential confounders and/or did not exclude patients with a previous history of MI. The majority of these studies focused on western societies which could be a limiting factor when trying to apply the results to a broader population (Lin, 2011). The most commonly reported results indicate that a patient with PSO will have approximately a 2-fold increase in risk of suffering a MI when adjusted for traditional risk factors, suggesting that psoriasis is an independent risk factor for atherothrombotic disease, coronary artery disease and cardiovascular mortality (Papp, 2013; Xiao, 2009). As previously noted, studies pertaining to this topic have varying results with odds ratios (OR) of suffering a MI being reported as low as 1.13 (95% CI: 1.08-1.18) and as high as 6.48 (95% CI: 3.12-13.44) (Papp, 2013). It is now widely hypothesized that this inherent increase in MI risk in PSO patients may be due to the general inflammatory nature of TNF-α mediated diseases like psoriatic and rheumatoid arthritis (Gelfand, 2006). Some suggest that treatments such as cyclosporin may also contribute to this elevated risk through higher blood pressure, hyercholesterolemia, triglyceridemia and low high-density lipo-protein cholesterol; all

traditional risk factors for MI (Xiao, 2009). Circulating endothelial cells (CEC) act as a marker of endothelial destruction in patients with atherosclerosis. Pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6 and IL-18, contribute to atherosclerosis by effecting pathophysiology of an inflammatory response. They cause the induction and maintenance of atherosclerosis factors such as hyperlipidaemia, insulin-resistance, adhesion of white cells to the endothelium, overexpression of some molecules, fatty streak formation and atherosclerotic plaque progression and rupture (Tam et al., 2013). An elevated number of CECs indicates a dysfunction in cardiovascular, hematological and/ or immune mediated inflammatory disorders (Batycka-Baron, 2012). As well, the Von Willebrand Factor (vWf), a multimeric glycoprotein in blood plasma, acts as a marker for endothelial destruction. Both CECs and vWf have been reported as elevated in psoriasis patients suggesting that damage to the circulatory system and the potential for suffering a MI is increased (Batycka-Baron, 2012).

The heightened cytokine production in PSO patients increases the systemic inflammation (Reich, 2012). This can affect the migration of white blood cells to cause inflammation in both the skin and vasculature. Overall, it is reported that younger patients have a higher risk of suffering a MI because of the chronic nature of psoriasis (Xiao, 2009). Papp and associates suggests that a 30 year old with severe psoriasis may have a relative risk (RR) of suffering an MI of 3.10 (95% CI: 1.98 - 4.86) (Papp, 2013). Because of the conflicting results with respect to psoriasis as an independent risk factor for MIs, there is a need to better define ‘risk’ of cardiovascular disease to create a more standard practice as patients with psoriasis sometimes receive suboptimal cardio-protective care (Ahlehoff, 2011; Mrowietz, 2011).

2.2.4 Therapies

Psoriasis (PSO) has an array of therapies which differ greatly in composition, function, risk and effectiveness. As previously noted, for milder psoriasis a topical ointment, a corticosteroid ointment (sometimes with a vitamin D analog added) or UV phototherapy may be prescribed; for moderate to severe psoriasis UV therapy may also be prescribed or a stronger systemic therapy such as methotrexate (MTX) or cyclosporin (both given orally) are viable treatments. Both of these therapies generally result in PASI 50 reached within 4-6 weeks, however they tend to have a higher risk profile including an increased risk of skin cancer, renal toxicity and arterial hypertension if therapy continues beyond two years (Mrowietz, 2013). In the past decade, a handful of biologic therapies including Humira (adalimumab), Remicade (infliximab), Stelara (ustekinumab) and Enbrel (etanercept) have been approved for the treatment of moderate to severe psoriasis. These organically derived therapies have been shown to have high effectiveness as a therapy for PSO (Reich 2012). It is important to note that long term risk profiles for these newer therapies are not yet known. The severity of the condition as defined by PASI, BSA and HRQoL may guide the physician to choose which therapy is best suited for the individual patient and depending on the individual, a combination of therapies may also be utilized (Takahashi, 2013).

2.2.4.1 Topical Ointments and UV Therapy

Topical ointments have long been a standard therapy for PSO patients. They tend to have a low risk profile and are ideal for patients who cannot tolerate the adverse effects or afford the cost of systemic therapies. Mild cases of PSO can generally be effectively controlled with a combination of lower risk topical corticosteroids and vitamin D3 analogs (Akasaka, 2013). Although they have lower risk associated with them, topical ointments can still lead to skin atrophy, tachyphylaxis and suppression of adrenal function after prolonged use (Akasaka 2013).

Nail psoriasis is a relatively common form of the disease effecting approximately 80% of all PSO patients at some point in their lives and is characterized by sore, raised nail beds (Huang, 2013). Generally, systemic therapies are not recommended for nail psoriasis because the potential risks are not justified.

By destroying t-cells and antigen-presenting cells in the skin, UV phototherapy is an often called upon therapy for PSO which sees remission in approximately 10% of patients with marked improvement seen in 40% (Akasaka, 2013). Previously PUVA (psoralen plus UV) was the standard therapy; however increased efficacy has been shown in narrowband UV (NB-UV) therapy (Takahashi, 2013). Potential adverse effects of stronger therapies like biologics are not observed in phototherapy meaning that it has a comparatively low risk profile.

2.2.4.2 Systemic Therapies

Moderate to severe psoriasis may need a more rigorous therapy selection to control the disease (Reich, 2012). Systemic therapies such as cyclosporin and methotrexate may carry a greater risk of adverse effects, but have shown consistently higher efficacy over UV phototherapy and topical corticosteroid ointments. Cyclosporin, taken orally, generally generates quick improvement in erythema (Akasaka, 2013). Inhibiting t-cell function and pro-inflammatory mediator production (such as IL-2) interferes with the immune response and decreases the presentation of skin lesions. The standard initial dose of cyclosporin is 2.5-5mg/kg per day which generally sees clinically significant improvement after four weeks (Borhri, 2012). In approximately 20% of patients, nephrotoxicity is a potential adverse effect which is largely reversible upon therapy cessation (Sharma and Dogra, 2010). One study aimed to find evidence of toxicity transferred to a patient's offspring through breastfeeding. Although the transfer of cyclosporin was evident via the breastfeeding method, it was in very small amounts with no adverse effects on the child (Mazzuoccolo, 2012).

Methotrexate (MTX), another oral systemic therapy for moderate to severe psoriasis, is commonly used once per week and is considered to be the gold standard therapy (Dogra, 2012; Elango, 2012). Due to a higher risk profile, MTX use should be as limited as possible. Usually MTX is prescribed in a low dose and increased until significant improvement is recorded (Dogra, 2013). Its primary function is to inhibit t-cell mediated inflammation by inhibiting the growth of keratinocytes, much like biologic therapies. Interleukin-6 (IL-6) acts as a chemotactic factor for t-cells which stimulate migration to the epidermis as well as the growth and differentiation of dermal and epidermal cells (Elagno, 2012). IL-6 can then be a marker for pathological processes associated with psoriasis. Interestingly, one study showed that MTX may also decrease the risk

of experiencing a MI in PSO patients due to its suppression of the chronic inflammatory state (Prodanowich, 2005).

2.2.4.3 Biologic Therapies

Biologic therapies (BT) can be described as monoclonal antibodies made from organic materials such as recombinant therapeutic protein, somatic cells, tissues, viruses, blood components and allergenic materials. Their primary mode of action is as a systemic component blocker as well as an anti-inflammatory. Different agents or BTs play different roles in PSO and PSA patients. Adalimumab, for example, is a fully human monoclonal immunoglobulin G1 antibody that neutralizes TNF by blocking its interaction with p55 and p75 TNF receptors on the cell's surface, whereas Alefacept is a recombinant LFA-3-IgG1 fusion protein that binds to CD2 on t-cells and blocks a co-stimulatory signal for memory effector t-cell activation (Castelo-Soccio and Van Voorhees, 2009). Some may be used to treat PSO and psoriatic arthritis (PSA) simultaneously while others, such as Efalizumab, are deemed effective for PSO but failed to show effectiveness for PSA. To date there are only a handful of these biologic therapies approved for this indication and long term effects are still not completely understood. Because there has yet to be a study directly comparing all agents the comparative efficacy is deduced from individual agent studies which aid the physician in making the best choice for an individual patient (Reich et al., 2011). In one case four BTs were indirectly compared (Stelara, Humira, Remicade and Enbrel) using individual studies and no significant difference in efficacies were noted (Galvan-Banqueri et al., 2012). Some literature suggests that PSO patients receive suboptimal and disjointed care leading to a further diminution in QoL but with the addition of BT as a viable therapy option, a more individualized but standardized and efficacious algorithm

may be possible for patient care (Mrowietz et al., 2012). As previously stated, after a decade of testing the potential long term effects are not yet fully understood, however there has yet to be any evidence of cumulative organ specific toxicity seen in patients taking a BT (Leonardi et al., 2012). A study looking at the long term effects of Uztekinumab through 3 years of follow-up found that adverse effects were comparable between a placebo group (50.4%), a group receiving 45mg doses of the therapy (57.6%), and a group receiving 90 mg of the therapy (51.6%) with serious adverse effects remaining low across all groups (1.2-1.9%) (Lebwohl et al., 2011). Due to reasonably high efficacy and apparently low incidence of adverse effects (or at least low risks of them occurring), at this point in time the benefit-to-risk ratio is considered acceptable (Weger, 2010).

Biologic therapies are much more expensive than other regimes. A recent US based study using a commercial claims database from 2005-2009 describes health care costs of managing psoriasis on MTX and BT (Zhang and Hiscock, 2014). Analyzing 6,207 biologic patients they found that the average per annum health related costs for using a BT in psoriasis management was approximately $29,000.00 US. This is a steep price to pay for those without financial help (from insurance for example). A pharmacist at a local pharmacy in St. John's, NL was able to comment on the cost of four BTs to psoriasis patients and the results are presented in table 2.1 below.

Table 2.1: Cost of Four Commonly Prescribed Biologic Therapies in NL, Canada for One Year

Agent	**Doses/ Year**	**Cost of Dose**	**Cost/ Year**
Humira	~ 24	$803	$19272
Stellara	4	$5700	$22,800
Enbrel	52-100	$438	$22,776 - $43,800
*Remicade**	Highly Variable	$4000-$5000	~$29,000 - $39,000

*Remicade is so variable because dose is based on body mass which differs between individuals and can fluctuate over time and infusion rate can vary from every 4 weeks to every 8 weeks.

2.3 Literature on Biologic Therapies and Myocardial Infarction in PSO Patients

A relatively new hypothesis is that BTs may have a cardio-protective factor in PSO patients due to their anti-inflammatory nature, leading to reduced inflammation around the heart and an overall reduction in stress on the heart. As noted, those individuals diagnosed at an earlier age are seen to have a higher risk of suffering a myocardial infarction (MI) as the cumulative stress of PSO can play a destructive role on the cardiovascular system. The majority of the literature on this topic suggested no detectable protective factor for BT on MI in PSO patients; however two recent studies reported a significant cardio-protective effect (Ahlehoff et al, 2012; Wu et al, 2012).

2.4 Summary of the Literature Review

Psoriasis is a fairly common chronic autoimmune disorder with the most revealing symptom being scaly sore skin lesions. Previously, the most common therapies, including PUVA, UV therapy and topical non-steroidal and steroid containing agents, target just the skin lesions.. For more severe cases systemic therapies such as methotrexate and cyclosporine may be used. In recent years biologic therapies have become available and have proven to be effective with an acceptable benefit-to-risk ratio (although long term effects are still being studied). Due to the chronic inflammatory nature of PSO, it is credited with contributing to multiple co-morbidities including cardiovascular disease. An intriguing new hypothesis is that biologic therapies (BT) may provide protection against cardiovascular disease as they work systemically and have anti-inflammatory properties, although the current research has not been able to confirm that such a relationship exists.

CHAPTER THREE: MATERIALS AND METHODS

3.1 Study Design

This was an unpaired matched case-control study utilizing a mixture of physical patient charts and electronic hospitalization records to build a composite research dataset. Once ethics and secondary use approvals were granted (see appendices E and F) the data was combined into one Statistical Package for Social Sciences (SPSS) file for analysis. The cases were considered to be moderate to severe PSO patients (as determined by a dermatologist) taking a BT. The control group were individuals with moderate to severe psoriasis not taking (nor had ever taken) a BT.

3.2 Study Setting

The study was conducted in St. John's, Newfoundland and Labrador (NL) in Canada. Data came from two locations: Newlab Life Science, Inc. (NLS) and the Newfoundland and Labrador Centre for Health Information (NLCHI). The data from NLCHI came from a psoriasis research database as well as the clinical database management system (CDMS) which is a hospital discharge database. The CDMS database includes the variables MI (present or not present), number of MIs and date of admission to hospital for each event. Data for the control group came from randomly selected individuals from the psoriasis research database housed at NLCHI. This database includes about 3200 confirmed PSO patients in NL and includes date of birth, sex, age of onset, age of first dermatologic visit, severity of disease, and HLA-Cw6 genotype status.

Data recorded at NLS and NLCHI also included the Medical Care Plan (MCP) number which was removed during the de-identifying process. The MCP number is held by all residents of NL and is their health insurance number. NLCHI also houses the Newfoundland and Labrador Medical Care Plan fee-for-service physician claims database which collects demographic and clinical information on services provided by physicians to patients in NL. The MCP number is heavily used in the province to identify individuals at hospitals, physician clinics and other electronic databases that house personal health information.

3.3 Study Populations

All patients in this study were classified by a dermatologist as having moderate to severe psoriasis (PSO). Severity is determined by using the body surface area (BSA) – or the percent surface area of the body affected by the condition. The BSA is incorporated into the PASI score as discussed earlier. The body is then separated into four areas: the head, the trunk, the arms and the legs. Each section is observed and given a score between 0 and 4 based on erythema (redness), induration (thickness) and desquamation (scaling), as well as the BSA. The score from the three factors are summed and multiplied by the score from the BSA and then by the weighted value given to each area (0.1 for the head, 0.2 for the arms, 0.3 for the trunk and 0.4 for the legs). As seen in figure 3.1, the final score can be between 0 (no PSO detected) and 72 (full body coverage and the most red, thickest and most scaly lesions).

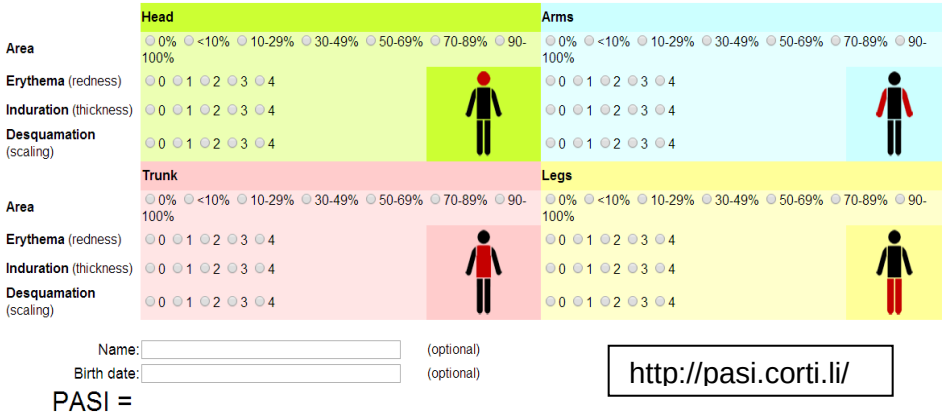

Figure 3.1: An example of an online PASI score calculator

3.3.1 Cases: Patients Actively Taking a BT

All patients selected at NLS were actively on a course of BT and were considered the case group. NLS is a medical and research clinic specializing in dermatology headed by Dr. Wayne P. Gulliver, MD, FRCPC. The case group included 178 patients taking or previously exposed to a BT. Inclusion criteria included having moderate to severe psoriasis as clinically diagnosed by a dermatologist, over the age of 18, and able to give legal consent for their information to be used for research. Since BTs are not prescribed to women who are pregnant (or goes into hiatus during pregnancy if a course of BT is already in progress) women who are pregnant were excluded from this study. Patients with mild PSO severity were excluded as these patients would not have an acceptable benefit-to-risk ratio for BTs. Since this study examines the protective factor of BTs in PSO patients, individuals in the case group having their myocardial infarction before the exposure to a BT were excluded from the final analysis. All patients included in this study (both cases and control) were from the province of NL. PSO patients in the case group were all exposed at some point to least one BT for at least 1 month, some of which had gone through two, three or four BTs due to therapy switching.

3.3.2 Controls: Patients Not Taking/ Have Not Previously Taken a BT

This group consisted of 561 patients who were not, or have never had a BT prescribed as a therapy. As with the case group, all patients included were at least 18 years of age and legally able to consent to their information being extracted and used for research. Because these patients were not on a BT, pregnancy was not considered, however it should be noted that patients on methotrexate (MTX) are generally not prescribed the drug if they are pregnant. All patients in this group, as with the cases group, were clinically diagnosed with moderate to severe psoriasis by a dermatologist again excluding mild cases. When the request for data was made to NLCHI, a filter of patients seen in 2000 onwards was applied. The rationale behind this was to try to get a time line closely related to the BT group since PSO patients taking a BT would generally have been seen in the last ten years. Using the same time frame would also decrease confounding effects which may have been brought on by varying general diagnostic procedures, lifestyles and non-BT treatments occurring over time.

3.4 Data Sources/ Data Linkage

3.4.1 Newlab Life Sciences

Data from NLS was extracted from physical patient charts and clinic letters through completion of a data collection sheet. Each patient file was filtered through and their age, date of birth, MCP number, age of onset, severity, BT type(s), duration on each BT (added together for total duration on BT) and smoking status (this variable was later excluded). The data was entered into a Microsoft Excel file and securely transferred to an employee of NLCHI for linking to the psoriasis research database (PRD) and hospital database (CDMS).

3.4.2 Newfoundland and Labrador Centre for Health Information

An employee of NLCHI extracted data from the both electronic databases (PRD and CDMS) for linkage to the NLS data. Ethics and Secondary Use Committees granted approval for the data to be used in the study (see sections below). Once approval was granted, the employee performing the data extraction and linkage was able to randomly select controls from the approximate 3200 confirmed psoriasis patients in the psoriasis research database. 561 controls were selected and matched to create a 3:1 ratio with respect to the cases (n=178) A 3:1 ratio was used to increase power since the primary outcome of MI was rare.

3.4.3 Clinical Database Management System (CDMS)

The CDMS is a provincial database collecting administrative, demographic and clinical data on patients' hospitalization in NL health care facilities. Data is collected by hospitals and forwarded to the Canadian Institute for Health Information (CIHI) which then populates the Discharge Abstract Database which is subsequently forwarded to NLCHI. The CIHI derives information such as expected length of stay and resource intensity weights. Individual patients are assigned a unique code once gender, health care number (HCN), province issuing HCN and date of birth are confirmed. The CDMS is where the variables "hospital admission date" and "MI event" came from and they had to be specially requested in an amendment to the original secondary use application. The CDMS has a comprehensive review and update cycle providing NLCHI with monthly cumulative updates and a year-end comprehensive file. NLCHI has had the responsibility of overseeing the CDMS for the Department of Health and Community Services since 1997.

3.4.4 International Classification of Disease Codes (ICD Codes)

The ICD are a set of codes used for the systematic identification of conditions and were used in the primary extraction of variables for this project. ICD-9 codes represent the ninth revision of ICD and are numeric, whereas the ICD-10 (tenth revision) are recoded into an alpha-numeric system. ICD is an international standard for reporting clinical diagnoses and was developed by the World Health Organization. This project used IDC-10-CA which was developed by the Canadian Institute for Health Information as a means of enhancing the system for Canadian research. These codes were used for CDMS data extraction as they identified various types of MI in PSO patients.

Table 3.1: ICD-9, ICD-10-CA Codes Used to Identify Myocardial Infarction Patients

	Code	**Description**
ICD- 9	410	Acute MI with stated duration of 8 weeks or less.
	412	Old MI: healed or prior MI diagnosed on ECG but currently presenting no symptoms.
	414.8	Chronic MI or with a stated duration of over 8 weeks (8 weeks or older and patient is still symptomatic).
ICD-10-CA	I21	Acute MI
	I22	Subsequent MI (within 4 weeks)
	I25.2	Old MI: healed or prior MI diagnosed on ECG but currently presenting no symptoms.

3.4.5 Data Retention

Destruction protocols will be adhering to Memorial University of Newfoundland's (MUN) policies on data storage (and access). Dr. Wayne P. Gulliver is the acting custodian of the Newlab Life Sciences dataset. The results will be stored for 5 years and destroyed following MUN policies for destruction which are available on the university's website.

3.4.6 Data Linkage

Data from NLS was sent to NLCHI via an encrypted secure file transfer and both sets were linked. An employee of NLCHI (not associated with the study) with clearance to access sensitive data randomly select patients from the psoriasis research database to include as controls. These patients were selected in a 3:1 (control: case) ratio and matched on age and gender to limit confounding effects. Variables collected from the PRD were age, gender and age of onset. Information on MI (hospitalization records), MI count and hospital admission dates for chronology of events were not recorded in the PRD at NLCHI but were recorded in the CDMS and was linked to the other two datasets forming the final dataset for this project. The variables case/control (to differentiate between cases, 1 and controls, 2) and ID were added. ID is a numeric value used as an individual identifier as the final data set was de-identified. The researcher did not have access to the names and MCP numbers of those individuals included in data from NLCHI. The final de-identified dataset was sent back to NLS using an encrypted file transfer and was stored on a secure desktop computer.

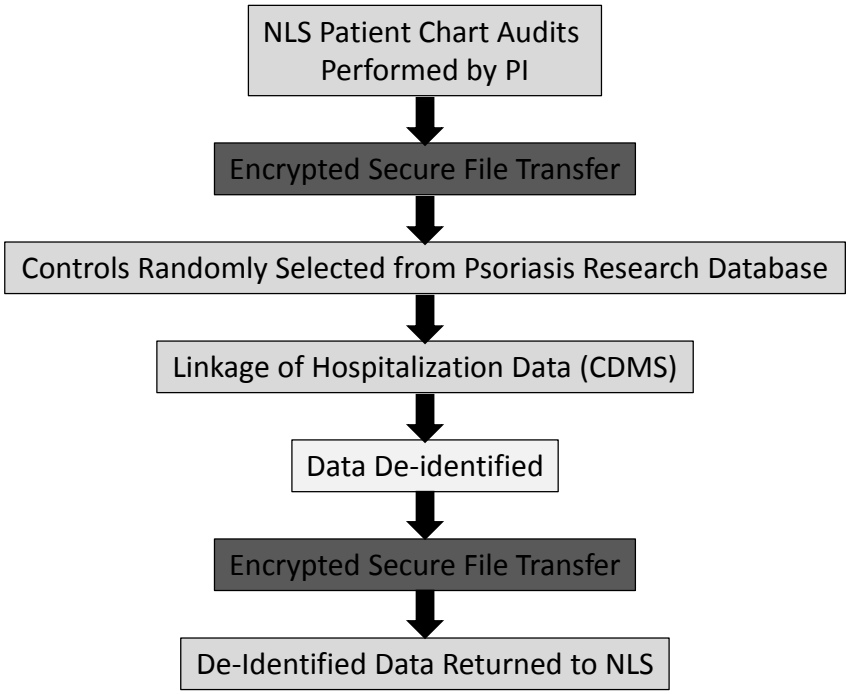

Figure 3.2: Pathway of Data between Centres

3.5 Statistical Analysis

All statistical analyses were conducted using IBM SPSS software (version 21, 2012) using a HP desktop computer using the Microsoft Windows XP operating system securely locked in a laboratory setting at NLS. Once all data were linked and put into an excel spreadsheet it was transferred to SPSS for analysis.

Descriptive statistics were prepared using the descriptive statistics toolbar and calculated gender and age distributions, case to control ratio, age of onset including missing values and duration of treatment.

Inferential statistics were run to test for significant relationships between variables using the binary MI (yes/no) as the primary outcome. Since this outcome is binary, a logistic regression was performed. Individual relationships between cofactors and the primary outcome

were first tested by running a univariate regression for each cofactor. The cases missing, omnibus test of model coefficients, model summary and final model tables are presented for each univariate regression. A p-value ≤ 0.05 was used to test for statistical significance and odds ratios were extracted for the final model table.

Once the univariate regressions were complete, a multivariate regression was completed presenting the same data as the univariate regressions and cofactors were tested for significance. To test for specificity and sensitivity of the model, a receiver operating curve (ROC) was produced and the area under the curve (AUC) was considered. Next, to test for confounding multivariate collinearity, diagnostics were run to check all variance inflation factors (VIFs) and tolerances. Finally, a case-control study sample size taking into account power and odds ratios was calculated using the program EpiInfo 7™ and a case/control relative risk was calculated by hand.

3.6 Ethical Considerations

In order to obtain data from NLCHI, approval from the Health Research Ethics Board (HREB) under the Health Research Ethics Authority (HREA) was obtained. HREA is the Newfoundland and Labrador ethics authority overseeing human research which aims to:

"… ensure that health research involving human subjects is conducted in an ethical manner. To be responsible for enhancing public awareness of the ethical dimension of health research involving human subjects".

Following HREB approval NLCHI required the completion of a secondary use application. This application was completed making requests for specific NLCHI data including the rationale behind why these variables were requested. Once this application was approved by the Secondary Use Committee, NLCHI data was released for research purposes.

CHAPTER FOUR: RESULTS

The results of the statistical analysis will be presented in two sections:

1. Descriptive Statistics: these statistics will include demographics such as age distribution and an MI summary, as well as biologic use patterns for the case group.
2. Inferential Statistics: a multivariate logistic regression testing for significant relationships between the binary primary outcome (MI event) and the cofactors.

4.1 Descriptive Statistics

This study contains 739 patients clinically diagnosed with moderate to severe psoriasis by a dermatologist; 463 males (62.7%) and 276 females (37.3%). These patients came from NLS and from NLCHI. Table 4.1 presents the baseline characteristics (age and gender) of patients from both NLS and NLCHI. Note, the cases and controls were matched based on age and gender.

Table 4.1: Gender and Age Characteristics

	Newlab Life Sciences		**Newfoundland and Labrador Centre for Health Information**	
	Male	***Female***	***Male***	***Female***
	N=109	N=69	N=354	N=207
	CASES		CONTROLS	
Range →	58	61	60	62
Minimum →	22	20	22	22
Maximum →	80	81	82	84
Mean →	52.6	49.6	52.9	50.0
SD →	11.0	12.3	10.9	12.4

The age of onset of psoriasis for both cases and controls were examined. This is a binary categorical cofactor describing the age at which patients were first diagnosed with their psoriasis.

Note that this is the age of clinical diagnosis as no data was available on whether or not patients self-reported earlier symptoms. In the literature there are discrepancies between what is considered “early onset”. Based on the numbers given, 25 years of age was chosen to be the threshold between early and late onset of psoriasis. Out of 739 patients, 121 (16.4%) were missing this data, all of which came from the control group leaving 440 controls with a known age of onset. 354 patients (85 cases and 269 controls) were considered to be early onset and 265 patients (94 cases and 171 controls) were considered to be late onset.

Table 4.2 is a contingency table of age of onset distribution in the case and control groups. Since our controls were matched based on gender and age it would be advantageous to have equal prevalence of early and late onset of disease within both groups. After a chi square test was applied a chi square value of 4.13 with a p-value of 0.042 was the result meaning that the prevalence of early versus late onset of disease was un-evenly distributed between cases and controls.

Table 4.2: Contingency Table Showing Early and Late Onset of Psoriasis in the Case and Control Groups

	Cases	Controls	Total
≤ 25	93	269	362
> 25	85	171	256
Total	178	440	**618**

*excluding the 121 missing values from the dataset

The number of biologics taken by patients varied with switching generally being the result of an adverse event, treatment failure or lack of efficacy. As well the duration on any biologic in (months) varied across patients. Since 32.6% of the patients were on the biologic for 60 months or longer, it seems that if a therapy is efficacious for an individual they are more likely to remain on that therapy for a longer time without switching. Of the 178 cases, 139 were exposed to just one biologic, 28 patients had switched once meaning these patients had been exposed to two different biologic therapies (BT), 7 patients had switched twice exposing them to three different BTs. Finally, 2 patients switched three times meaning exposure to four different BTs.

Table 4.3 below presents the 19 patients who have been admitted to hospital for an MI based on ICD-10-CA codes I21, I22 and I25.2 from the CDMS database. Of the 19 individuals presenting with an MI, only 1 was from the case group (5.3%) and 18 were from the control group (94.7%). The age range of those individuals suffering an MI in the control group was 51-74 with a mean of 61.7 for males (SD = 6.2) and 62.3 for females (SD = 7.1). The single patient in the case group had just one myocardial infarction which occurred after exposure to a BT. In the control group, 12/18 (66.7%) had one MI event, 5/18 (27.8%) had two events and 1/18 (5.6%) had five events.

Table 4.3: Characteristics of MI Patients

	Case (n=1)		Control (n=18)	
# of MI Events				
1	1		12	
2	0		5	
3	0		0	
5	0		1	
Gender	**M**	**F**	**M**	**F**
	1	0	14	4
Age				
Range	NA	-	23	15
Mean	NA	-	61.7	62.3
SD	NA	-	6.2	7.1

4.2 Inferential Statistics

4.2.1 SPSS Analysis

Table 4.4 presents the variables used in the following regression analyses. Before the multivariate regression was undertaken, each co-factor was tested for a significant effect via univariate regressions. Table 4.5 presents the omnibus model test and the pseudo R-square values for the univariate analyses. The omnibus model test explains whether or not the explained variance in the model is greater than the unexplained variance. The value of significance is the probability of obtaining the chi-square statistic if there is no effect of the independent variables, taken together, on the dependent variable used to determine if the overall model is statistically significant. The pseudo R-squares (Cox & Snell and Nagelkerke) are used in logistic regression as it does not have an equivalent to the R-squared that is found in ordinary least squares regression. It is a relaxed approach to explaining the proportion of variance explained by the predictors. Table 4.6 shows the results of these univariate analyses and the odds ratios with their respective significance. When tested individually, BT exposure did not show a significant relationship with MI outcome at the 0.05 level (p-value = 0.086) but was significant at the 0.10 level. Duration on BT also failed to show significance (p-value = 0.183). The co-factors that did show a significant relationship with MI were age, gender and age of onset with p-values of 0.000, 0.018 and 0.005, respectively. Males produced an odds ratio value of 3.6, meaning being a male increased the risk of suffering an MI by 3.6 times. Age produced an odds ratio of 1.1 suggesting that individuals are more likely to suffer an MI with each additional year of life added. The greatest increase in odds ratio was age of onset with early onset attributing to a nearly 9 fold increase in risk of suffering an MI. Of the two non-significant co-factors, BT exposure and duration, the univariate regression suggests that patients on a BT were 83% less

likely to suffer an MI than those not on a BT, which supports the alternative hypothesis that BT exposure would decrease the risk of an MI. The duration of therapy seemed to minimally decrease the risk of MI with an odds ratio of 0.976 for each additional month of therapy added.

Ho: Biologic therapies have no protective factor for MI events in PSO patients

Verses

Ha: Biologic therapies have a protective factor for MI events in PSO patients

Table 4.4: Variables to be tested in the Regression Analysis

Variable	**Type**	**Description**
MI	Binary (Dependent Variable)	Whether or not a patient suffered an MI
Age	Continuous	Age of patient in years
Gender	Binary	Male or female
Age of Onset	Binary	Diagnosis of PSA before or after the age of 25
Case/ Control	Binary	Have or have not taken a BT
Duration on Therapy	Continuous	Number of months on a BT in total

Table 4.5: Results of Univariate Regression Analyses (model tests and significance)

Co-factor	Omnibus Model Test		Pseudo R-Squared Values	
	Chi-Square	*Sig*	*Cox & Snell*	*Nagelkerke*
Age	14.858	0.000	0.020	0.072
Gender	7.348	0.007	0.010	0.036
Age of Onset	25.645	0.000	0.040	0.149
BT Exposure	5.029	0.025	0.002	0.008
BT Duration	0.942	0.332	0.001	0.005

Table 4.6: Results of Univariate Regression Analyses (Variable Significance and Odds Ratios)

Co-Factor	Odds Ratio	Significance
BT Exposure	0.170	0.086
Gender (male)	3.643	0.018
Age	1.072	0.000
Age of Onset (early)	8.852	0.005
Duration on BT	0.976	0.183

The Multivariate Regression was carried out adding variables at the same time with the "enter method". The results show that only age of onset maintained statistical significance and BT exposure and duration maintained a lack of significance, however the age and gender variables were not significant when tested in the multivariate model. Early age of onset maintained a higher risk of MI than late age of onset however the odds ratio decreased from 15.5 to 11.2. As seen in table 4.7, the multivariate model had an omnibus chi-square value of 24.9 and a significance of 0.000 meaning that the model appears to be better than no model at all since there is a <5% chance that a chi-square value that high would be from chance alone. The Cox and Snell R-square and the Nagelkerke R-Square values were reported as 0.04 and 0.2 respectively loosely interpreted as approximately 20% of variation in the model being predicted by the variables entered into the model. Table 4.8 outlines the final results of the multivariate

regression showing that only age of onset proved significant resulting in early onset contributing to about a 6.3 times increase in the likelihood of suffering an MI. Figure 4.2 presents a ROC Curve with an area under the curve (see figure 4.3) of 0.853 (95% CI: 0.0802 – 0.0903) suggesting that the model has high sensitivity (rate of true positive) and specificity (rate of true negative). Finally, to test for collinearity, diagnostics were run to check the tolerance and variance inflation factors (VIF) of each variable. As seen in table 4.9, all tolerances were over 0.10 and VIFs were under 5 indicating that collinearity was within an acceptable range.

Table 4.7: Multivariate Omnibus Test of Model Coefficients and R-Squares

Chi-square	df	Sig.	Cox & Snell R Square	Nagelkerke R Square
24.9	5	.000	0.039	0.203

Table 4.8: Final Multivariate Logistic Regression Variable Significance and Odds Ratios

Variable	Odds Ratio	Significance
Sex (male)	3.952	0.078
BT Exposure	0.070	0.300
BT Duration	1.016	0.669
Age of Onset	6.252	0.023
Age	1.057	0.081

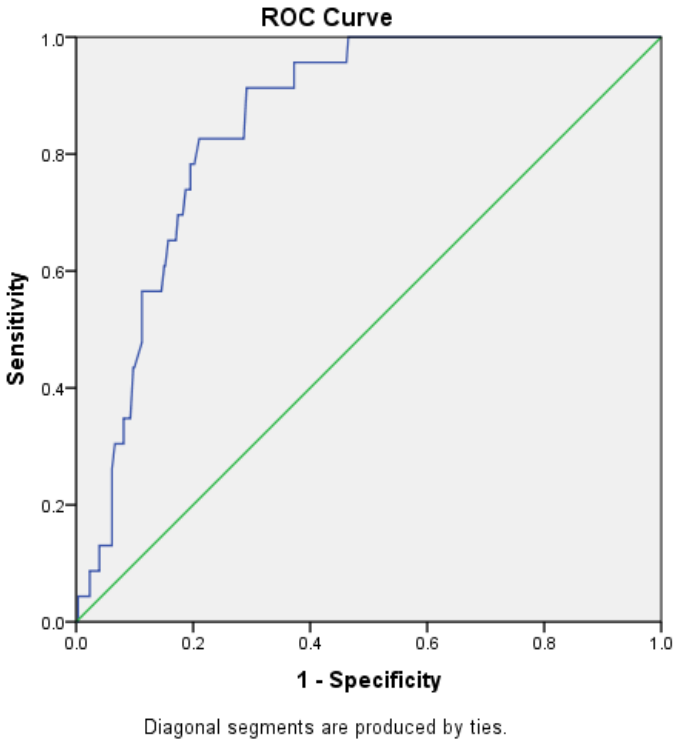

Figure 4.2: ROC Graph to test for Specificity and Sensitivity

Area Under the Curve

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.853	.026	.000	.802	.903

The test result variable(s): Predicted probability has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Figure 4.3: SPSS Output for AUC Analysis

Table 4.9: Tolerance and VIF Values to Test for Collinearity in the Multivariate Logistic Regression Model

Variable	Tolerance	VIF
BT Exposure	0.353	2.834
Gender	0.990	1.011
Age	0.808	1.237
Age of Onset	0.811	1.234
Duration on BT	0.355	2.813

This analysis showed no statistically significant relationship between risk of suffering an MI and being placed on a BT. Subsequently, the duration on the BT failed to show statistical significance.

4.2.2 Relative Risk Calculation and Sample Size Calculation

4.2.2.1 Relative Risk Calculation

The relative risk was calculated using the standard group exposure formula with subsequent confidence intervals and test statistic from the online software MedCalc (http://www.medcalc.org/calc/relative_risk.php). This calculation was performed in order to give a ratio of the probability of an MI event occurring between the case and control groups. According to this calculation, patients on a BT had a lower risk (RR=0.176) of experiencing a myocardial infarction than the patients not on a BT. This finding supports the hypothesis that BTs have a protective effect for MI.

$$RR = \frac{a/(a+b)}{c/(c+d)}$$

RR = [1/(1+177)] / [18/(18+543)]

RR = 0.176

Note: *a = number of MI in Case Group, b = number of non- MI case group, c = number of MI control group, d = number of non- MI control group*

The 95% CI is:

$$95\%\ \text{CI} = \exp\left(\ln(RR) - 1.96 \times \text{SE}\{\ln(RR)\} \right) \quad \text{to} \quad \exp\left(\ln(RR) + 1.96 \times \text{SE}\{\ln(RR)\} \right)$$

95% CI: (0.0198 to 1.0931), p = 0.0611

4.2.2.2 Sample Size Calculation

Using EpiInfo version 7.0™ a sample size was calculated based on the odds ratio given that this study was a case/control study. The final sample size with the Fleiss correction states 843 cases are needed as well as 2528 controls. The available data did not support that many cases.

CHAPTER FIVE: DISCUSSION

The discussion addresses four areas: 1) considers the results of this study and compares them to previous literature, 2) provides an overview of the strengths and weaknesses of this study, 3) suggests possible future study ideas that would better test the study hypotheses, and 4) summarizes the findings and conclusions.

5.1 Discussion

5.1.1 Comparing Results to the Literature

This study aimed to detect a significant decrease in risk of suffering an MI in patients with moderate to severe psoriasis when taking a biologic therapy. We looked at age, age of onset (defined as a PSO/PSA diagnosis before or after the age of 25 years), gender, whether or not the patient had been exposed to a BT at any point for at least 1 month, and the total duration of BT exposure. Other potential confounders such as smoking status and diabetes status were considered for analysis but unfortunately no data was available.

Psoriasis has long been studied, yet its aetiology is not fully understood. It has become more accepted that it is an auto-immune, systemic disorder rather than simply a skin oriented disease. There is an array of therapies approved for PSO and PSA including topical agents, UV therapy, systemic therapies and anti-inflammatory therapies, however in the past decade biologic agents have gained momentum as a second-line therapy (Sharma & Dogra, 2010). Studies such as this one may be used to move these BTs into a front-line therapy for PSO and PSA when severity warrants such a treatment. It may be likely that these therapies shall take on a front-line role as the positive effectiveness is becoming more documented, understood and supported (Choi et al., 2014). Even though biologic therapies show improved effectiveness there are noted trends

of treatment failure over time which results in BT switching (from etanercept to infliximab for example). This leads to difficulty in ascertaining and attributing long-term effects to specific biologic therapies (Simard et al., 2011). It is also important to remember that not all BTs work the same, as some act to block TNF-α while others inhibit IL-6, IL-12, IL-22 and/or IL-23 (and others). It may be difficult to choose the best BT for an individual patient (Mease, 2012), though anti-TNFs have a relatively safe profile thus far, even when other conditions are simultaneously occurring in a patient. Interestingly, a study by Tzellos et al (2013) found that those treated with IL-12/23 monoclonal antibodies, such as briakinumab, were at an elevated risk for MI but stated that mete-analysis on limited information may not be producing robust results. Senabra-Gallego et al (2013) studied etanercept and its long-term safety and efficacy outcomes finding that, after 5 years of collecting data on patients being treated for ankylosing spondylitis, there was a favorable risk-benefit ratio with no significant cumulative toxicity. Laurenti et al (2013) tested for the safety of an anti-TNF (looking at potential liver damage) in patients infected with the hepatitis B virus and found the same stable conditions as those seen in non-hepatitis B patients. In comparison, Nakayama (2013) reported that 20 cases of patients taking TNF-α blockers were diagnosed with auto-immune hepatitis within weeks of starting their therapy. Machado et al (2013) found an increase in anaphylactic-type adverse effects in skin lesions in females in advanced age when taking TNF-α blockers. Efficacy may be reported in a number of ways including the dermatology life quality index (DLQI), a simple questionnaire technique. Patients answer questions based on their daily lives over the past week and a final score is given to represent the impact of PSO on the patients' lives for that week. Scores range from 0 (no effect) to 30 (maximum impact) and over time can be used to track how well the patients are responding to any medication, or how the disease is progressing over time (Finlay & Khan, 1993).

Psoriasis is associated with multiple co-morbidities of which one of the more serious is cardiovascular disease. Previous studies have shown a significant increase in risk of suffering an MI in PSO patients and is most likely attributed to the overall chronic inflammatory nature of the disorder. Since BTs act as a systemic therapy (injectable or intravenous infusion) which decreases inflammation in skin lesions, it is hypothesized that there may be a protective factor for cardiovascular disease as the BT would decrease inflammation on the cardiovascular system. Table 5.1 summarizes 5 pertinent papers discussing the association with BT in PSO patients and MI outcome. Two of the papers failed to find a significant protective factor for MI in BTs. Two papers claimed a reduced risk of MI in BT patients and one paper suggested a possible increase in MI in BT patients.

Table 5.1: Summary of Studies Searching for an Association between BT and MI Outcome

Author(s) and Date	Study Type	Statistical Tests Conducted	Association Between BT and MI Significant?
Ryan *et al* (2011)	Meta-Analysis of RCTs	Absolute risk differences (two sided)	None Detected
Abuabara *et al* (2011)	Cohort Study	Proportional hazards model controlling for confounders	None Detected
Tzellos *et al* (2012)	Meta-Analysis of RCTs	Odds Ratio	Possible Higher Risk in BT Patients (IL12/23 blocker)
Ahlehoff *et al* (2012)	Retrospective Longitudinal Cohort Study	Chi-square and 2-sided t-tests for baseline characteristics, Cox regression model and sensitivity analysis	Reduced Risk in BT Patients
Jashin Wu *et al* (2012)	Retrospective Cohort Study	Chi-square and unpaired t-tests for baseline characteristics, Cox proportional hazards regression	Reduced Risk in BT Patients (TNF-α blocker)

5.1.1.1 Failed to Find a Statistically Significant Association

In the Ryan et al study, 22 RCTs comprised of over 10,000 patients were analyzed testing for absolute risk differences. The BTs under investigation included IL-12/23 blockers and TNF-α blockers. The primary outcome was the incident of MACE which encompasses MI, cerebrovascular accident and cardiovascular death. The meta-analysis performed was unable to find a significant difference in MACE risk between BT and placebo groups but the authors state

that the study may be under powered due to the quality levels in the original RCTs included in the meta-analysis.

The Abuabara et al study used administrative and pharmacy claims data provided by a large US insurer. It should be noted that Abuabara et al did not test BT specifically, but compared a placebo group to a group encompassing all systemic therapies (for example, BTs and methotrexate were combined). This limits the generalizability of the study, however results may still prove useful as an overall comparison. This study suggested a significant interaction for age, a known risk factor for MI. In the systemic group there were 25,554 patients and in the control group there were 4,220 patients receiving UV therapy, however there was a chance that a small proportion for the control group were exposed to a BT at some point during their disease. After an adjusted proportional hazards model was conducted, no significant difference in risk was detectable. In our study the logistic regression also was unable to detect any statistically significant differences between risks of MI in our cases versus the controls although a non-significant trend towards lower risk in the BT group was noted.

5.1.1.2 Possible Higher Risk in BT Patients

Even though the case/control groups did not differ significantly, there was a slight trend towards a decrease in risk of MI in the exposed to a biologic therapy group (Odds Ratio = 0.07, p = 0.300). Tzellos et al (2012) found a differing trend in their study which examined a control group compared to patients taking an IL-12/23. The final meta-analysis was carried out on 9 RCTs based on their inclusion/ exclusion criteria. The study makes a point to suggest that due to the ever increasing prevalence of BTs in the realm of PSO/PSA treatments, even the slightest statistical miscalculations may be amplified and adverse effects may be reported outside of the

clinical setting (meaning they may be missed in reports). Furthermore, it is stated that risk differences for rare events produce very conservative confidence intervals leading to poor statistical power. This is the case with this current study as well, given that out of the total 739 patients included (both cases and controls combined) there were only 19 patients (2.6%) who experienced an MI (data extended back to the mid-1990s).

5.1.1.3 Reduced Risk of MI in BT Patients

Ahlehoff et al (2012) carried out a retrospective longitudinal cohort study looking at PSO patients on systemic treatments versus not on systemic treatments. As with the Abuabara study, BTs and other systemic anti-inflammatories were combined and tested against patients using UV therapy and topical agents. Therefore the results can only be loosely compared to this current study because, as identified in the methods section, BT patients were unique and other systemic therapies were combined with non-systemic (non-BT) therapies. In the Ahlehoff study, 2,400 patients were identified as being on a systemic therapy and hazard ratios were calculated to compare the groups. The results showed a decrease in risk for systemic therapy patients after hazard ratios were adjusted for age, sex socio-economic status and co-morbities. Sensitivity analysis supported this decrease in risk after the exclusion of patients with a history of hospitalization due to MI or having been on cardiovascular therapies, both being probable confounders.

Dr. Wu (2012) and colleagues compared the risks of patients on and not on TNF-α blockers for MI events. Patient inclusion criteria included a diagnosis of PSO or PSA between the years 2004- 2010. It should be noted that during the univariate analysis, smoking status, methotrexate use, and obesity were not recorded as being statistically significant and were

dropped from the final analysis. Unfortunately there were no obesity or smoking data, and methotrexate use was absorbed in the "non-BT" group. Once Dr. Wu et al completed a Cox proportional hazards regression using all significant variables stratified for age, the team found a 54% reduction in hazard of incident MI.

The most significant and dramatic shift in OR for MI in this current study was seen in the "age of onset" variable. The literature states a number of "cut-off points" to distinguish between early and late onset, with 40 years of age being the standard cut-off point, however data at NLS used 25 years of age. This is because although psoriasis can begin at any age, most people are diagnosed between 15 and 30 years of age and by age 40, most people who will get psoriasis will already have it (Horreau et al, 2013). It is believed that earlier onset of disease is associated with a family history of disease, increased severity, a stronger correlation to genetic allele positivity (HLA-C*06 for example) and increased risk of co-morbities including MI (Queiro et al., 2013). In our study, after a multivariate logistic regression as well as collinearity diagnostics, age of onset was associated with an OR = 6.3 (p-value = 0.023).

5.1.2 Cost

Table 5.2: Summary of Cost Analysis Papers

Study and Date	Was the economic question properly posed?	Has the program's effectiveness been validated?	Measures for these costs and effects	Were comparisons properly adjusted for time?
Baojin Zhu *et al* (2013)	Yes – aimed to evaluate health care costs for PSA patients on BT	Yes - clinical support validating BT efficacy	Payment history for PSA patients in the emergency department as well as the pharmacy	Yes – PSA patient records from 2005-2009 used
Atsuyuki Igarashi *et al* (2013)	Yes – cost and efficacy comparison for PSO patients	BT efficacy supported	Cost of BT calculated on approved dosing schedule using National Health Insurance listed drug price	Yes – allowed for appropriate response times
Christine Ahn *et al* (2013)	Yes – Cost per patient achieving significant PSO improvement on BT	Yes – States BTs since 2003 with no measureable cumulative toxicity	Yes – based on 2010 wholesale price of BTs and included physician visits and laboratory costs	Yes – each patient was on BT for a t least 12 weeks
Laura Bojke *et al* (2011)	Yes – comparing costs of palliative care for PSA patients non-responsive to traditional therapies and those on BT	Yes – states efficacy of BTs as patients reach PASI 75	Quality-adjusted life years (QALY) to quantify cost and healthcare outcomes	Yes – cohort tracks 40 years of history in patients

Biologic therapies have traditionally been considered very expensive. The general trend appears to be that as effectiveness and adverse effects become better understood, the cost has decreased and insurance companies have been approving more coverage for these therapies. The

above table presents four cost-effectiveness studies on BT used by PSO and PSA patients and aims to evaluate the trends over time.

Zhu et al looked at the health care costs of PSA patients on BT using a cox proportional hazards model to evaluate time to discontinuation and logistic regression models were used to evaluate rate of BT switching. Costs were then compared between groups using propensity score adjusted bootstrapping methods. The study found that 67.7% of PSA patients used a BT as monotherapy while 32.3% used a BT in conjunction with other therapies such as topical agents. All-cause costs between BT monotherapy versus BT adjunctive therapy were not significantly different (approximately US$26,000 to $27,000 per year). They found that 67.4% of PSA-specific costs were accrued by pharmacy payments.

Igarashi et al compared cost-efficacy of BTs for PSO patients. The study examined three BTs (infliximab, adalimumab and ustekinumab) and drug costs were calculated using the National Health Insurance drug price list which included re-imbursements. Cost efficacy was compared by taking the annual drug acquisition cost divided by the mean probabilities of PASI response. PASI 75 weight-based efficacy was taken into consideration for validating the use of a BT. The lowest annual cost was for adalinumab in the first year at $23,995US (with second-best efficacy ratings) and the largest cost was for infliximab at $38,960US for the first year of therapy. This shows the potentially large expense of undergoing a BT as well as the significant differences in costs between specific BT agents.

Ahn et al looked at cost effectiveness of BT for PSO patients as well but focused specifically on plaque psoriasis. One year costs for patients reaching PASI 75 also seeing a significant improvement in their DLQI were calculated over a 12 week period and extrapolated

to get one year cost estimates. The study found infliximab to be the most cost effective and the most efficacious.

Finally, Laura Bojke et al composed a study looking at the cost-effectiveness of BTs for PSA patients. A probabilistic cohort model was used to track PSA patients over 40 years – some of which ended up on a BT and the others did not. Drug acquisition, application and monitoring costs were recorded based on pharmaceutical list prices. The results show a total lifetime cost of approximately $67,000US for those patients not on a BT, about $106,000US for those who have taken adalimumab, $115,000US for those on etanercept and about $142,000US for those on infliximab. It appears that the cost – effectiveness is still difficult to ascertain for BTs as the literature is inconclusive using differing methods and reporting results do not appear to be uniform.

Coleman et al suggest that it is "important to consider all relevant factors in drug utilization and cost analyses because these new agents redefine efficacy, safety, and mode of drug delivery". It is also suggested that BTs are playing a larger role in the treatment of PSO and PSA, so more rigid, uniform and standardized cost analyses should be considered in the future.

5.2 Strengths of this Study

This study involved a chart audit of available PSO patients on biologic therapies at Newlab Life Sciences, Inc. and controls from NLCHI to provide a 3:1 ratio in order to increase the power of this study as much as possible. Since this study was a case-control study, it is more robust than a cross-sectional or case report study. In order to limit confounding as much as possible the controls were matched to the cases based on age and gender increasing the chances of detecting differences between the case and control groups based on our primary co-factors; Exposure at some point to a biologic therapy and the duration of the exposure. Next, all patients were clinically diagnosed and followed by the same dermatologist. Finally, due to an increase in availability to the general public based on financial and insurance reasons, BTs have become more readily prescribed meaning there was access to more patient information than would have been possible in the past.

5.3 Limitations of this Study

Being a case-control study, this study cannot provide evidence for causation. A randomized controlled trial (RCT) would be very costly and time consuming to conduct given the nature of the therapy and outcomes. An RCT would more accurately measure longer term effects and potential cardiovascular – protective factors to the BTs but this goes beyond the scope of this M.Sc. thesis with limited time and no funding. It must also be taken into consideration that the NL population is believed to have a higher prevalence in of psoriasis, upwards of 6%, compared to the global average of 2-3% (Gulliver et al., 2011). Therefore results may not be generalizable outside the local community. As an extension of the previous

point, 100% of the patients in this study were of Caucasian descent limiting the extent that results could be generalized to other ethnicities.

In order to obtain **sufficient** power this study would have required approximately four times the number of available cases and controls. Unfortunately, those numbers were not obtainable based on available data. Next, one of the most significant variables, age of onset, was not recorded in patient charts for approximately 16% of the total sample size which lead to sample exclusion in the analysis. Additionally, the original methods planned for this study involved looking at diabetes and smoking status for these patients. Diabetes data was not obtainable and smoking status was extracted from NLS charts, however duration and amount of smoking as well as time since quitting (if the individuals had quit) was not available. Therefore smoking status was only recorded for a portion of the NLS cases with simply yes or no status and no smoking data was available from NLCHI. Another variable that was dropped was the severity of psoriasis (PSO). Initially the intention was to assess for MI outcomes based on mild, moderate or severe ratings of PSO. Once charts were audited it was realized that mild patients were not included in BT studies or regimes and moderate to severe was grouped together as an umbrella term without being clearly differentiated.

In order to obtain the most accurate results the case and control group were matched based on age and gender as we were interested in any change in risk of suffering an MI. Age of onset could not be matched but ideally would have equal prevalence of early and late onset of disease between the case and control groups. A simply chi square test showed that this distribution was significantly different with a p-value of 0.042.

Finally, it would have been beneficial to have other potential confounding data such as the presence of diabetes, weight/ obesity, diet, smoking and genetics to see whether or not these

variables had a significant impact on the outcome of MI events or were evenly distributed among cases and controls. With respect to the case group, there was no data on pre-existing MI conditions (through confirmed prescriptions for cardiovascular drugs or physician visits) other than hospitalization dates for the MI event itself.

5.4 Suggestions for Future Studies

If a similar study question were to be undertaken, a retrospective or prospective cohort could be examined. If multiple centres were recruited, the sample size could be significantly larger thus improving the likely of detecting differences if they truly existed. The PI could compose a standardized data extraction form(s) to ensure that personnel carrying out the chart audits would know what to record and how to record it to create seamless uploading to an electronic database. An RCT may be ideal, however when the disease may be associated with a major adverse event, ethics approval may prove challenging and the cost to run such a study may be substantial.

Since the BT exposure showed significance at the 0.10 level when run in a univariate analyses, a more robust study may reveal more accurately the true nature of the relationship that biologic therapies have with PSO and cardiovascular degradation. A higher powered study would require a larger sample size as well as detailed data on possible confounders such as smoking history, family history of MI, personal history of MI, genetic predisposition (like the presence or absence of certain genes), obesity, dietary intake and activity rates to name a few. Statistical tests to see if these variables are normally and randomly distributed among the cases and controls would make the results much more accurate with higher power.

5.5 Conclusions

This study had similar results to previous studies in relation to age of onset as a predictor of MI when a multivariate logistic regression was conducted. As was expected, males were much more likely to suffer an MI than female patients and an early age of onset (defined as before or after the age of 25 years) contributed to a higher risk of MI, presumably due to a lengthier exposure to a chronic inflammatory state. A significant relationship between age, BT exposure and duration of BT exposure was not detected, however a non-significant decrease in risk was seen in BT patients. The results of this study showed an odds ratio of 0.07 with respect to odds of suffering a myocardial infarction with a p-value of 0.300. Although non-significant, the results suggest that biologic therapies may have a protective effect in chronic plaque psoriasis patients who are considered to be at a higher risk for MI than the general population.

The power of this study was a weakness and inability to detect statistically significantly differences may have been a result of the too small sample. Missing data and the absence of expected explanatory variables information were additional problems associated with the study. It is also important to take note that biologic therapies are becoming more available over time as effectiveness and safety are becoming better understood. This leads to a higher prevalence of use and insurance coverage making it possible for more patients to have access to these therapies and the longer term therapeutic and adverse effects for PSO patients, including MI outcomes, may become easier to study.

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APPENDICIES

Appendix A: Data Dictionary

Variable Name	Variable Type	Variable Description	Values/format
ID	Numeric	Randomly generated Record ID	
Case_Control_Group	Numeric	Variable to differentiate between Case and Control Group	1 = Case 2 = Control
SEX	String	Sex of Patient	F = Female M = Male
Age	Numeric	Age of patient as of April 2014	
SEVERITY	String	Psoriasis severity	
Age_of_Onset_STR	String	Age of onset (String Variable)	
Age_of_Onset_Num	Numeric	Age of onset (Numeric Variable)	1 = <= 25 2 = > 25
Biologic.1	String	Name of first Biologic treatment	
Start_Date.1	Date	Start date of first Biologic treatment	mm/dd/yyyy
End_Date.1	Date	End date of first Biologic treatment	mm/dd/yyyy
Duration_on_Treatment_.1	Numeric	Duration of first Biologics treatment	
Biologic.2	String	Name of second Biologic treatment	
Start_Date.2	Date	Start date of second Biologic treatment	mm/dd/yyyy
End_Date.2	Date	End date of second Biologic treatment	mm/dd/yyyy
Duration_on_Treatment_.2	Numeric	Duration of second Biologics treatment	
Biologic.3	String	Name of third Biologic treatment	
Start_Date.3	Date	Start date of third Biologic treatment	mm/dd/yyyy
End_Date.3	Date	End date of third Biologic treatment	mm/dd/yyyy
Duration_on_Treatment_.3	Numeric	Duration of third Biologics treatment	
Biologic.4	String	Name of fourth Biologic treatment	
Start_Date.4	Date	Start date of fourth Biologic treatment	mm/dd/yyyy
End_Date.4	Date	End date of fourth Biologic treatment	mm/dd/yyyy
Duration_on_Treatment_.4	Numeric	Duration of fourth Biologics treatment	
MI	Numeric	MI Event (Y/N)	0 = No 1 = Yes
ADMIT_SERV_DTE.1	Date	Admission date of first MACE event	mm/dd/yyyy
ADMIT_SERV_DTE.2	Date	Admission date of second MACE event	mm/dd/yyyy
ADMIT_SERV_DTE.3	Date	Admission date of third MACE event	mm/dd/yyyy

Appendix B: Original Variable Request Table

Case Group (Patient on Biologic Therapies)

Name of Requested Database	Variable(s) Requested	Rationale	Years Requested
Clinical database management system	Primary diagnosis of myocardial infarction (MI)	To determine if patients were diagnosed with an MI to ultimately define relative risks on biologics compared to control group	2000- 2013
Clinical database management system	Hospital admission date	In addition to knowing whether or not a patient has suffered an MI, I need to know when as it will be important to differentiate whether or not the MI occurred before or after treatment start date.	2000-2013
Clinical database management system	Hospital discharge date	To see the outcome of the hospitalization (did the patient die or leave the hospital?)	2000- 2013
Newlab psoriasis database	Board certified classification of psoriasis severity	Biologics are only prescribed to patients with a moderate or above severity of disease.	2000-2013
Clinical database management system	De-identified code	Case indicator	2000-2013
Clinical database management system	Sex	Test for significance of gender on risk of primary diagnosis of MI	2000-2013
Clinical database management system	Age	Test for significance of age on risk of primary diagnosis of MI	2000-2013
Clinical database management system	Age of onset	Test for significance of length of disease presentation on risk of primary diagnosis of MI	2000-2013
Clinical database management system	Treatment start date	Serve as an indicator for hospitalized patients to tell if they suffered an MI before or after start of biologic therapy	2000-2013
Clinical database management system	Treatment end date		

Control Group (Patients not on Biologic Therapies)

Name of Requested Database	Variable(s) Requested	Rationale	Years Requested
Clinical database management system	Primary diagnosis of myocardial infarction (MI)	To determine if patients were diagnosed with an MI to ultimately define relative risks on biologics compared to control group	2000- 2013
Clinical database management system	Hospital admission date	In addition to knowing whether or not a patient has suffered an MI, I need to know when as it will be important to differentiate whether or not the MI occurred before or after treatment start date.	2000-2013
Clinical database management system	Hospital discharge date	To see the outcome of the hospitalization (did the patient die or leave the hospital?)	2000- 2013
Newlab psoriasis database	Board certified classification of psoriasis severity	To ensure that a comparable control group is sampled to compare to the patients on biologic therapies.	2000-2013
Clinical database management system	De-identified code	Case indicator	2000-2013
Clinical database management system	Sex	Test for significance of gender on risk of primary diagnosis of MI	2000-2013
Clinical database management system	Age	Test for significance of age on risk of primary diagnosis of MI	2000-2013
Clinical database management system	Age of onset	Test for significance of length of disease presentation on risk of primary diagnosis of MI	2000-2013
Clinical database management system	Treatment Type	See trend in non-biologic therapies for moderate to severe psoriasis patients	2000-2013

ICD-9 and ICD-10-CA Codes
Myocardial Infarction

ICD-10-CA

I21 Acute myocardial infarction

I22 Subsequent myocardial infarction
Note: For morbidity coding, this category should be assigned for infarction of any myocardial site, occurring within 4 weeks (28 days) from onset of a previous infarction

I25.2 Old myocardial infarction
Healed myocardial infarction
Past myocardial infarction diagnosed by ECG or other special investigation, but currently presenting no symptoms.
Note: I25.2 would apply if a myocardial infarction when the MI occurred more than 4 weeks ago and the patient is not currently receiving treatment, observation or evaluation for the previous myocardial infarction.

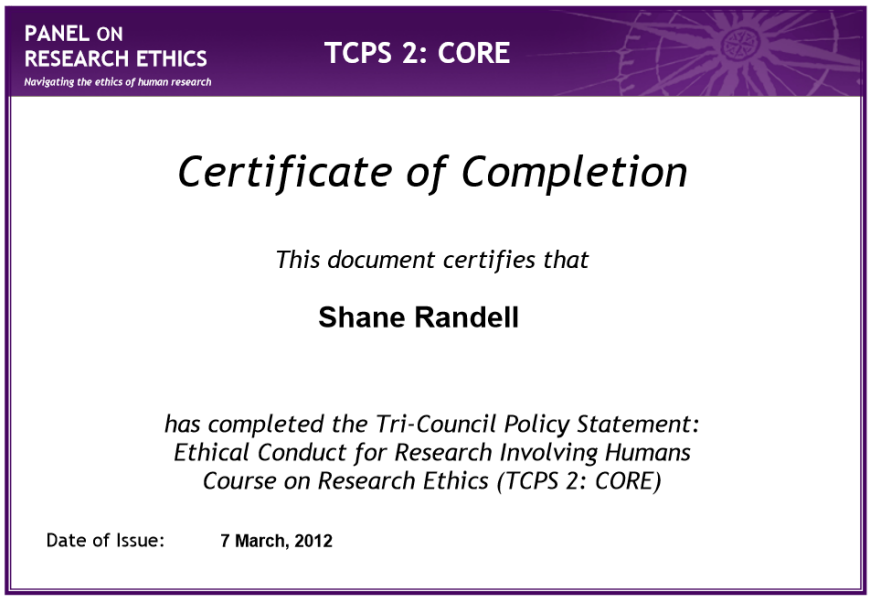
ICD-9

410 Acute myocardial infarction
- with a stated duration of 8 weeks or less

412 Old myocardial infarction
- healed myocardial infarction
- past myocardial infarction diagnosed on ECG or other special investigation, but currently presenting no symptoms

414.8 Chronic or with a stated duration of over 8 weeks
- this includes myocardial infarctions that are over 8 weeks old when the patient is still symptomatic; it also includes coronary insufficiency specified as chronic and myocardial ischemia not specified as acute

Appendix D: TCPA 2: CORE Certificate



PANEL ON RESEARCH ETHICS
Navigating the ethics of human research

TCPS 2: CORE

Certificate of Completion

This document certifies that

Shane Randell

has completed the Tri-Council Policy Statement:
Ethical Conduct for Research Involving Humans
Course on Research Ethics (TCPS 2: CORE)

Date of Issue: **7 March, 2012**

Appendix E: Full HREB Ethics Approval

Health Research Ethics Authority

Ethics Office
Suite 200, Eastern Trust Building
95 Bonaventure Avenue
St. John's, NL
A1B 2X5

March 13, 2013

Mr. Shane Randell
49 Otter Drive, ST. John's, NL
A1A 0B5

Dear Mr. Randell

Reference #13.046

Re: A decreased rate of cardiovascular events in patients with moderate to severe psoriasis treated with biologics

Your application received an expedited review by a Sub-Committee of the Health Research Ethics Board and **full approval** was granted effective **March 12, 2013.**

This approval will lapse on **March 11, 2014**. It is your responsibility to ensure that the Ethics Renewal form is forwarded to the HREB office prior to the renewal date. *The information provided in this form must be* ***current to the time of submission*** *and submitted to the HREB* ***not less than 30 nor more than 45 days*** *of the anniversary of your approval date.* The Ethics Renewal form can be downloaded from the HREB website http://www.hrea.ca.

This is to confirm that the following documents have been reviewed and approved or acknowledged (as indicated):

Appendix F: NLCHI Secondary Use Approval for Data Release

November 20, 2013

Shane Randell
49 Otter Drive
St. John's, NL
A1A 0B5

Re: Record level information request, IM00049452

Dear Shane:

This letter is to advise you that the Secondary Uses Committee of the Centre for Health Information reviewed your information request application on November 6, 2013 for the study **"Decreased Risk of Cardiovascular Events in Patients with Moderate to Severe Psoriasis treated with Biologic Therapies"**. Having consulted with the Secondary Uses Committee, I authorize the release of information for your project.

The use of the NewLab Psoriasis Clinical Database is conditional upon the following:

- The Centre is provided evidence of ongoing ethics approval from the Health Research Ethics Authority during the lifetime of the study.
- Another employee of the Centre who is not a member of the project team links and de-identifies the information.
- Members of the project team accessing the released information must not attempt to re-identify the subjects of the released information.
- Members of the project team must comply with Memorial University of Newfoundland's policy and procedures for storing data.
- The data must remain on a Memorial University of Newfoundland asset; it cannot be placed on the researcher's personal asset.
- The released information must be encrypted while held and stored.
- The dataset will be released under the supervision of Dr. Wayne Gulliver, the applicants Academic Advisor.
- Any new uses or disclosures of the released data must receive approval from the Secondary Uses Committee of the Centre for Health Information.