AN EXAMINATION OF BIOLOGIC TREATMENT GROUPS OF PSORIASIS PATIENTS IN A COHORT OF THE NEWFOUNDLAND AND LABRADOR POPULATION

ANDREA MORRISSEY

AN EXAMINATION OF BIOLOGIC TREATMENT GROUPS OF PSORIASIS PATIENTS IN A COHORT OF THE NEWFOUNDLAND AND LABRADOR POPULATION

by

© Andrea Morrissey

A thesis submitted to the

School of Graduate Studies

In partial fulfillment of the

Requirements for the degree of

Master of Science

Division of Clinical Epidemiology

Faculty of Medicine

Memorial University of Newfoundland

St. John's, NL

June, 2012

ABSTRACT

Objective:

To examine psoriasis patients receiving biologic treatment by biologic treatment type, demographic factors and various prognostic factors. Also, to examine health service utilization and comorbid conditions among biologic patients. In addition, to determine the risk of developing specified comorbidities based on treatment type received. Finally, to examine whether or not biologic treatment is associated with an increased Charlson Comorbidity Index (CCI) score.

Methods:

In this cross-sectional study, psoriasis demographic, clinical and treatment data were linked to physician claims, hospital and mortality data to investigate health service utilization of psoriasis patients between 1995/96 and 2007/08.

Results:

Findings indicate that the majority of patients receiving biologic treatment had moderate/severe psoriasis. Among biologic patients, 63.7% had at least one hospital separation, and 96.3% had at least one physician visit. Female biologic patients had a higher number of mean comorbidities compared to males (9.53±2.77 versus 8.20±2.78, respectively, $p<0.01$), as well as a higher mean CCI score (2.37±1.54 versus 1.93±1.32, respectively, $p=0.04$). The odds of having a 'skin and sub-cutaneous disorder' diagnosis

was found to be 10 times greater if the psoriasis patient is taking biologics versus not taking biologics [10.49 (confidence interval 1.41-78.18), p=0.02].

Conclusions:

Biologic patients are likely to have moderate/severe psoriasis, and to utilize health services (both physician and hospital), more so than non-biologic patients. Female biologic patients appear to be at a greater risk of developing comorbid conditions than male biologic patients; therefore, different comorbidity and treatment monitoring may be necessary for males and females. Biologic patients are more likely to develop skin and sub-cutaneous disorders than non-biologic patients.

ACKNOWLEDGEMENTS

I would like to take this opportunity to thank a few people without whom this work could not have been completed. First and foremost, I would like to thank my supervisor Dr. Marshall Godwin for his commitment to this work and especially his advice and guidance along the way. I would also like to thank the other members of my advisory committee, Dr. Don MacDonald, Dr. Kayla Collins and Dr. Wayne Gulliver, for their time and valuable feedback.

In addition, I would like to extend a special thank you to my friend and colleague Neil Gladney. From his friendly, easygoing and approachable nature, to his expertise in data linkage, to his vast knowledge on everything psoriasis-related, he was indispensable to my completing this project. I am also very grateful to the support of the Newfoundland and Labrador Centre for Health Information, in particular the Research and Evaluation Department, whose employees are always eager to help.

I would also like to thank my husband and best friend, Andy, who rightfully deserves a portion of the credit for this accomplishment. He sat through many practice presentations and read through countless versions of papers and offered suggestions and feedback, all the while providing advice, coffee, comic relief, back rubs and unconditional love!

Lastly, I would like to send out a special acknowledgement to my Natalie, the light of my life. She is a wonderful surprise who came along halfway through the thesis. She may have delayed its completion, but becoming her mommy changed my life for the better.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

CHAPTER 1: INTRODUCTION

1.1 Background of Study

Psoriasis is a chronic, genetic-based, inflammatory skin disease that affects the body's immune system[1] and negatively impacts quality of life[2]. Skin cells in the affected area reproduce every three to six days, instead of twenty-eight, resulting in the raised, scaly, red plaques characteristic of the disease[3]. Plaque-type psoriasis is the most common form, accounting for about 90% of all cases[4]. Such plaques typically affect the scalp, trunk, elbows, knees and genital areas, but can manifest in any part of the body, even the nails[5]. Psoriasis lesions can be painful and very itchy[6] but are non-contagious[7]

Psoriasis is a complex disease with varying levels of severity that can occur equally in men and women, of any age[1, 5, 8]. Life expectancy is 3.5 years shorter in men and 4.4 years shorter in women with severe psoriasis[9] The disease tends to come and go with time; psoriasis may slip into remission for long periods of time, and/or may manifest in response to specific triggers such as stress, infection, injury, certain drugs, etc.[1]. It is also classified as an immune-mediated (or autoimmune) disease, meaning the immune system attacks the body's own tissue[1, 10]. Psoriasis affects an estimated 2-3% of the world's population[11].

Many treatment options exist for psoriasis patients – these include topical therapies, phototherapy and systemic therapies, the aim of which are to reduce the number, size and

severity of psoriasis lesions. Often, psoriasis patients will require a combination of treatments. Ultraviolet phototherapy and systemic therapy can be quite time-consuming and can have toxic effects[12, 13] resulting in end-organ damage that can limit their long term use[14, 15] This often leads to low treatment-related satisfaction and poor adherence[16]. Non-adherence to treatment results in treatment failure or resistance, disease progression, increased health system use due to preventable hospitalizations, as well as unnecessary medical costs[16]. Unfortunately, none of the existing traditional psoriasis therapy options will "cure" the disease.

The recent introduction of biologics as treatment for psoriasis patients has brought with it the promise of an effective and safe therapy over topical, phototherapy and systemic therapy[17, 18]. A new generation of naturally occurring molecules, biologics are defined by their mode of action[19] and are designed to target the activity of the immune system, thus inhibiting the activation and trafficking of T-cells and cytokines that are responsible for inducing psoriasis[20]. Biologic agents provide optimum efficacy with minimum side effects, making them a likely treatment alternative for patients suffering from moderate to severe psoriasis[17, 21, 22]. They have also demonstrated a convenient dosing schedule[18]. However, most data on biologics is limited to shorter-term trials[18].

To date, very little research has been done to assess which comorbidities may develop in psoriasis patients using biologics. In a recent review of psoriasis treatments and risks of malignancy, Patel et. al. concluded that the risk of malignancy with biologic treatment is

unclear, although it is thought that TNF-α inhibitors may cause a slight increase in risk of cancer, including both melanoma skin cancer and hematologic malignancies[23]. In another recent study, Naldi et al. concluded that an increased risk of cancer is of concern with newly introduced biologics[21]. Alwawi et al. emphasized the need for long-term efficacy trials of biologics to properly assess possible risks associated with this treatment[18]. Since biologics are relatively new (most have been introduced to the market during the past ten years), they have not been in circulation long enough to assess their long-term outcomes.

This cross-sectional study examined treatments, health service utilization and comorbidities among a cohort of confirmed cases of psoriasis patients, with a focus on psoriasis patients receiving biologic treatment. Such patients attended a private dermatology clinic in St. John's (NewLab Clinical Research Inc.) between 1999 and 2009 with the confirmed diagnosis of psoriasis by a dermatologist. This study will help our understanding of the different biologic treatments and associated comorbidities among a sample of psoriasis patients in the Newfoundland and Labrador population.

1.2 Rationale

As comorbidities are increasingly being recognized as contributing to a patient's overall health and quality of life, monitoring of comorbid conditions is of particular importance in achieving the best medical management of the patient. The results of this study will provide important prognostic information for potentially predicting an effective treatment regimen and the comorbidities which could arise with a particular treatment modality, to

enable a more informed approach to comorbidity monitoring and treatment. Information gained from this study will help in our understanding of the different biologic treatments and their impact on health status among a sample of psoriasis patients in the Newfoundland and Labrador population. Although the prevalence of psoriasis is estimated at 2-3% of the Newfoundland and Labrador population[24], limited information on treatment effects, in particular those specific to biologics, is available. Since the provincial prevalence is higher than the Canadian average (2-3% versus 1.7%[25], respectively), Newfoundland and Labrador is an ideal setting for a study of this scope.

1.3 Objectives

The objectives of the present study are as follows:

1. to describe the distribution of psoriasis patients by biologic treatment type, demographic factors and the prognostic factors disease severity, age of onset and genotype status;
2. to describe health service utilization (hospital and physician visits) of biologic patients by treatment type (between 1995/96 and 2007/08);
3. to describe the distribution of comorbidities among psoriasis patients by biologic treatment type, demographic factors and the prognostic factors disease severity, age of onset and genotype status;
4. to determine the risk of developing specified comorbid conditions based on treatment type received (i.e., biologic versus non-biologic); and
5. to examine whether or not biologic treatment is associated with a higher Charlson Comorbidity Index (CCI) score.

1.4 Outline

Chapter 2 summarizes current research regarding the history and burden of psoriasis, as well as a description of psoriasis types, psoriasis etiology, psoriasis pathogenesis, psoriasis and comorbidities and psoriasis treatment options. The different biologic types and classes are discussed as well in terms of their mechanism of action and their performance. Chapter 3 outlines the methodology used in conducting this research including descriptions of the study design, data sources, study population, data quality, data linkage, measures, data analysis and ethical considerations. Chapter 4 presents the results of the study, which include linkage results, mortality results, health care utilization and comorbidities among both biologic patients and non-biologic patients. The chapter concludes with a logistic and linear regression analysis. Chapter 5 follows with a discussion of the results including study strengths and limitations, while Chapter 6 concludes with a summary of findings, recommendations for future research and conclusions.

CHAPTER 2: LITERATURE REVIEW

The goals of this chapter are i) to summarize what psoriasis is (its history, burden, etiology, pathogenesis, etc.), ii) to report on a review of research assessing which comorbidities are present among psoriasis patients, iii) to report on a review and summary of the literature concerning specific biologic drugs (alefacept, efalizumab, adalimumab, etanercept, infliximab, onercept, ustekinumab and peptide t); and iv) to report on a review of what available research says concerning comorbidities and/or adverse outcomes among psoriasis patients receiving biologics.

A comprehensive literature review was carried out to obtain a general overview of psoriasis and then to identify articles associated with each particular biologic. Then, a search to identify those articles concerning comorbidities found among psoriasis patients receiving biologic treatment was initiated. Article search and retrieval included a broad review process whereby relevant studies were identified based on search terms such as the generic drug name and/or the brand name in combination (e.g., "alefacept and/or amevive"). An academic librarian was consulted and assisted with creation of search terms and strategies. Medical Subject Headings (MeSH) were used in the PubMed searches; these were exploded to include all related items. Examples of MeSH headings used include "psoriasis", "biological products", "adverse effects", "drug effects", and "comorbidity". MeSH terms used in PubMed were also used in Embase and The Cochrane Library as part of the search strategy. Grey literature was assessed through many sources including ClinicalTrials.gov, Google Scholar, The Scholarly Publishing &

Academic Resources Coalition, Government of Canada Publications, National Academies Press, Library and Archives Canada, National ETD Portal (South African theses and dissertations), Australasian Digital Theses Program, Centre for Research Libraries, Global Resources Network, Worldcat, Canadian Agency for Drugs and Technologies in Health: Grey Matters, Health Canada website, Public Health Agency of Canada website, and several association pages (The Psoriasis Association, The National Psoriasis Foundation and the Psoriasis Society of Canada). Finally, any additional literature was identified by reviewing references of articles previously found.

2.1 History of Psoriasis

According to an article written in 1955[26], it is now believed that Biblical leprosy (known as Zaraath) included many more diseases than true leprosy. For example, any scaly or ulcerated condition of the skin that presented an unpleasant sight was called Zaraath. The Old Testament details an example of this through Naaman, captain of the hosts of King Syria. He bathed seven times in the Jordan River to rid himself of Zaraath. Many now believe Naaman was suffering from psoriasis.

Among ancient Greek writers, cutaneous diseases were classified as either psora (meaning itch), lepra (meaning scaly) or leichen (meaning tuberculosis). Psoriasis was most likely known to the Greeks as a form of lepra[26].

Robert Willan was a dermatologist who made the first accurate description of psoriasis. He called it "lepra" and coined a scaly condition of the eyebrows and scrotum as

"psoriasis". Eventually, others criticized Willan because his lepra and psoriasis were likely one and the same disease. Over time, the term psoriasis "stuck" while lepra gradually faded out of textbooks[26].

2.2 Burden of Psoriasis

Psoriasis is an immune-mediated, genetic disease of the skin which affects people in different ways, from small numbers of small plaques to scaly lesions covering large body surface areas[27]. It affects an estimated 2-3% of the world's population[11], 2% of the US population[28], 1.7% of the Canadian population[25], and 2-3% of the Newfoundland and Labrador population[24]. The prevalence is approximately 1.5% in the Caucasian population[29], while in other ethnic groups, such as the Japanese, the prevalence is much lower[30].

Psoriasis is a chronic and currently incurable skin disease that requires a lifetime of therapy[31]. It negatively affects the physical, mental, social, sexual and financial aspects of patients' well-being[32-36] in addition to their quality of life[2, 37]. It is rarely life-threatening but is life-ruining to many of the estimated 14 million sufferers worldwide; in fact, an estimated 25% of psoriasis patients have contemplated suicide[38] These patients also have an increased incidence of anxiety, depression and low self-esteem[39, 40].

Psoriasis also presents direct costs to the patient and health care system in terms of treatment, and indirect costs in terms of time lost from work and difficulties with

employment in general[41]. The total direct and indirect health care costs associated with psoriasis are quite significant – calculated at 11.25 billion American dollars annually, with work loss accounting for forty percent of this burden[7], including a $3.5 billion drug market[41, 42]. This disease represents a significant economic burden to patients and the health care system alike, due to frequent outpatient visits, hospitalization, the high cost of necessary medications and other indirect costs[43].

2.3 Psoriasis and Comorbidities

Substantial comorbidity is associated with psoriasis[10, 44], most likely due to dysregulated immunity and ensuing inflammation[43], although some speculate whether or not such comorbidities are due to behaviors (e.g., smoking and alcohol abuse). Nonetheless, psoriasis patients have been shown to have a higher rate of comorbidities compared with patients without psoriasis[45]. Psoriasis is associated with several inflammatory-type conditions such as arthritis[46], inflammatory bowel disease[43], diabetes[5, 47-51], cardiovascular disease[5, 45, 47, 51-53], the metabolic syndrome[43], Crohn's disease[54], and irritable bowel syndrome[55]. Other conditions associated with psoriasis include chronic obstructive pulmonary disease[56], myocardial infarction[57], lymphoma[23, 57-59], cancer[28, 58], obesity[5, 47], hypertension[5, 49], dyslipidaemia[49] and depression[5, 39, 40]. About a quarter of patients also develop pain, stiffness and swelling in their joints, known as psoriatic arthritis[5, 54]. A greater risk of mortality has also been associated with psoriasis[9]. In a recent study in Newfoundland and Labrador, it was found that mental disorder, skin and sub-cutaneous

disorder, neoplasm, digestive system disease and circulatory system disease were leading comorbidities among psoriasis patients[60].

A specific and detailed immune response is thought to be involved in the pathogenesis of psoriasis-associated comorbidities[37].

2.4 Types of Psoriasis

Psoriasis patients typically present with only one type of psoriasis at a time. The following descriptions of each type are taken from the National Psoriasis Foundation[7].

Plaque psoriasis (psoriasis vulgaris) is the most prevalent form of psoriasis, accounting for about 80% of all psoriasis patients. It presents as raised, inflamed, red lesions covered by a silvery-white scale. It is commonly found on the elbows, knees, scalp and lower back. Cytokines released from T-cells and keratinocytes are thought to play a role in the formation of such plaques[61], which can be painful and very itchy[6]

Guttate psoriasis typically begins in childhood or young adulthood, and presents as small, red, individual spots on the skin. Such lesions usually appear on the trunk and limbs, and aren't as thick as plaque lesions. Guttate psoriasis onset is fast; upper respiratory infections, streptococcal throat infections, tonsillitis, stress, injury to the skin and certain drugs (antimalarials and beta-blockers) have been known to trigger this type of psoriasis.

Inverse psoriasis appears as smooth and shiny bright red lesions. Typically found in the armpits, groin, under the breasts and in other skin folds around the genitals and buttocks, this type of psoriasis is prone to irritation from rubbing and sweating. It can be problematic for overweight individuals and those with deep skin folds.

Pustular psoriasis is characterized by white blisters of noninfectious pus (consisting of white blood cells) surrounded by red skin. There are three types of pustular psoriasis (Von Zumbusch, Palmoplantar pustulosis and Acropustulosis), all of which are primarily seen in adults. Onset begins with reddening of the skin, followed by formation of pustules and scaling. Pustular psoriasis can be triggered by internal medications, irritating topical agents, overexposure to UV light, pregnancy, systemic steroids, infections, stress and sudden withdrawal of systemic medications or potent topical steroids.

Erythrodermic psoriasis manifests as periodic, widespread, fiery redness of the skin and the shedding of scales in sheets, as opposed to small flakes. The reddening and shedding of the skin are often accompanied by severe itching and pain, increases in heart rate, and fluctuating core temperatures. This type of psoriasis causes protein and fluid loss that can lead to severe illness, infection, pneumonia and/or congestive heart failure. Triggers include the abrupt withdrawal of a systemic psoriasis treatment, allergic reactions to drugs, sunburns, infection and medication such as lithium, anti-malarial drugs, etc.

2.5 Psoriasis Etiology/Triggers

It is thought that at least ten percent of the general population inherits one or more of the genes that result in a predisposition to psoriasis. However, only two to three percent of the population actually develops the disease. This is because in order for a person to develop psoriasis, s/he must have a combination of the genes that cause psoriasis and be exposed to specific triggers[7]. Several family studies have presented compelling evidence of a genetic predisposition to psoriasis, although the pattern of inheritance is still unclear[62]. A tendency has been shown for a child with one parent with psoriasis to have a 1 in 4 chance of developing the condition[1].

Using genome-wide linkage studies, researchers have attempted to identify specific loci responsible for psoriasis onset and/or progression. One particular locus (named psoriasis susceptibility 1: PSORS1) in the major histocompatibility-complex (MHC) region on chromosome 6 has been shown to be associated with psoriasis in several studies (as cited by Schon, 2005[62]). Susceptibility alleles include HLA-Cw6, HCR*WWCC and the HLA-associated S gene[63]. Early-onset of the disease has been associated with the presence of HLA-Cw6[64]. The environment also plays an important role in the etiology of psoriasis[18, 65].

Specific established psoriasis triggers include stress, injury to the skin (known as the Koebner phenomenon) and certain medications. Some patients believe their allergies, their diet and the weather can trigger flare-ups of psoriasis[7]

2.6 Mechanism of Psoriasis/Pathogenesis

Pathogenesis of psoriasis is not entirely understood. There are two main hypotheses concerning the process of disease development. The first considers psoriasis as simply a disorder of excessive growth and reproduction of skin cells, a fault of the epidermis (the outermost layer of human skin) and its predominant cells, the keratinocytes. The second hypothesis considers psoriasis as an immune-mediated disorder, whereby the excessive reproduction of skin cells is secondary to factors produced by the immune system. T cells, which ordinarily help protect the body against infection, become active (although it is unclear why), migrate to the dermis, infiltrate the skin and trigger the release of cytokines (small cell-signaling protein molecules secreted by glial cells of the nervous system and by many cells of the immune system that are used in intercellular communication)[37]. Tumor necrosis factor-alpha (TNF-α) are among such released cytokines which cause inflammation along with the rapid production of skin cells. TNF-α is also produced by macrophages, keratinocytes and antigen-presenting cells and is a key factor in innate immune response[66]. In fact, studies have documented increased concentrations of TNF-α in both the lesion skin and the serum of psoriasis patients, with serum levels correlating with disease severity[67, 68]. Other cytokines of interest in the pathogenesis of psoriasis, whose release are triggered by T-cells, include interferon-γ, IL-17 and IL-22[69]. C-reactive protein is also present at increased levels in psoriasis patients[70]. The fact that immunosuppressant medications (such as biologic T-cell inhibitors and TNF-α inhibitors) have been shown to clear psoriasis plaques, as well as reduce circulating c-reactive protein levels, has led to support of the immune-mediated hypothesis of psoriasis

pathogenesis[71, 72]. Interestingly, similar reactions are hypothesized to contribute to the initiation and maintenance of other inflammatory diseases such as rheumatoid arthritis and Crohn's disease[15].

2.7 Treatment Efficacy: Psoriasis Area and Severity Index (PASI)

Efficacy of treatment is measured by the treating physician via the Physician Global Assessment (PGA) or the Psoriasis Area and Severity Index (PASI).

The PGA uses a 7-point scale: severe (very marked plaque elevation, scaling or erythema), moderate to severe (marked plaque elevation, scaling or erythema), moderate (moderate plaque elevation, scaling or erythema), mild to moderate (intermediate between moderate and mild), mild (slight plaque elevation, scaling or erythema), almost clear (intermediate between mild and clear) and clear (no signs of psoriasis)[73].

The PASI ranges from 0 (no psoriasis) to 72 (the most severe disease state) and combines the assessment of the lesion severity and the section of the body affected. The body is divided into four sections (head, arms, trunk and legs) and the percent area of skin involved is estimated and then transformed into a grade from 0-6 (where a grade of 0 implies 0% of involved area and a grade of 6 implies 90-100% of involved area). Severity of each area is measured on a scale of 0 (no severity) to 4 (maximum severity) and is estimated by three clinical features: erythema (redness), induration (thickness) and desquamation (scaling). The three severity measurements are then summed for each of

the 4 body sections, then multiplied by the percent area of skin score for that area and then multiplied by the weight of the respective body section (0.1 for head, 0.2 for arm, 0.3 for body and 0.4 for legs). These scores are entered into a formula to calculate the overall PASI number. A patient who experiences a 75% improvement in his/her PASI scores following treatment is said to have achieved PASI-75, which is generally the accepted gold standard for evaluating efficacy of treatment in moderate to severe psoriasis by physicians and patients alike. A PASI-75 improvement correlates well with a PGA of clear to almost clear[74].

2.8 Treatment Options

Due to the many different presentations of psoriasis, treatment approaches must be individualized and based on the nature and extent of disease, anatomical locations, quality-of-life concerns (self-esteem, social interactions, etc.) presence of other comorbidities, triggering factors (infections, medications, stress, obesity, excessive alcohol and tobacco consumption, etc.) as well as the patient's commitment to therapy[8, 14].

Treatment options for psoriasis include topical therapies such as corticosteroids, vitamin D derivatives (examples include calcitriol, tacalcitol and calcipotriol), a vitamin A derivative known as tazarotene, calcienurin inhibitors, dithranol (anthralin) and coal tar. Phototherapy is another treatment option and consists of ultraviolet radiation of differing wavelengths such as Ultraviolet A (UVA), Ultraviolet B (UVB) or psoralen + Ultraviolet A (PUVA). As well, systemic therapies are quite common; these include methotrexate, cyclosporine, soriatane (acitetrin) or tegison (etretinate). Many psoriasis patients require

ultraviolet phototherapy or systemic therapies; however, these processes are both time-consuming and may have toxic effects[12, 13] leading to end-organ damage that may limit their long-term use[14]. This can lead to low treatment-related satisfaction and poor adherence[16]. Non-adherence to treatment could result in treatment failure or resistance, disease progression, increased health system utilization due to preventable hospitalizations, as well as unnecessary medical costs[16]. To lessen the potential harm, rotational, sequential and intermittent forms of these treatments have been developed.

While none of the discussed traditional psoriasis therapy options are remedial, the recent introduction of biologics as an option for psoriasis patients brought with it the promise and hope of an effective and safe therapy over topical, phototherapy and systemic therapy[6, 17, 18]. A new generation of naturally occurring molecules, biologics are designed and engineered in the laboratory. They target the activity of the immune system (T-lymphocytes and cytokines, in particular) which cause the inflammation characteristic of psoriasis. These biologic agents are thought to be safer than most synthetic molecules, because they are processed by the same pathways as naturally occurring proteins in the body[17, 21, 22]. Examples include enbrel (etanercept), raptiva (efalizumab), humira (adalimumab), amevive (alefacept), remicade (infliximab), stelara (ustekinumab), onercept (r-h-TBP-1), or any combination of these. Biologics are divided into four classes: T-cell inhibitors, tumour necrosis factor-α inhibitors, interleukin-12/23 blockaders, and peptide T. Although biologic therapy is generally more expensive than traditional methods of psoriasis treatment[75], it is possible that these agents may contribute

to a decrease in health service utilization (thereby reducing the burden to the health care system in the long run) and an increase in productivity, along with significant improved patient outcomes and quality of life[76]. However, access to biologic therapy can be unfeasible for some patients due to the high cost (upwards to $1600.00 a month). It is important to note that many patients of the current study are clinical trial patients who receive biologic drugs at no cost for the duration of the trial, in addition to one year subsequent to trial completion. If the patient has no drug insurance plan, s/he may not be able to continue biologic treatment. As biologic treatment is an invasive and expensive procedure, it is more common among moderate/severe psoriasis patients than among mild.

2.9 Biologics: T-Cell Inhibitors

T-cells are a type of white blood cell present in the body to protect from infection. Psoriasis patients exhibit an increase in the amount of activated T cells and T-cell migration to the skin, leading to an increase in release of pro-inflammatory cytokines which are thought to be responsible for the rapid growth of skin cells and therefore development of psoriasis plaques. Alefacept and Efalizumab are FDA approved T-cell inhibitors for the treatment of moderate to severe plaque psoriasis[6].

2.9.1 Alefacept (Amevive)

In January 2003, alefacept became the first biological agent designed and marketed for the treatment of psoriasis[77]. Alefacept works by blocking T-cell activation, thus reducing

the number of activated T cells in the body. It is administered as a 15-mg intramuscular injection once a week for 12 weeks[78]. The primary concern with alefacept is the potential for it to deplete T-lymphocytes. Constant monitoring of CD4+ cells is required and treatment should cease if the CD4+ T-cell count drops below 250 μL[78].

In a double-blind, placebo-controlled multi-centre randomized trial designed to assess the efficacy of alefacept on patients with moderate to severe chronic plaque psoriasis, patients were randomly assigned to receive a placebo (group 1) or alefacept, at either a dose of 0.025 (group 2), 0.075 (group 3) or 1.50 (group 4) mg per kilogram of body weight (30-second injection) once a week for 12 weeks[79]. Clinical improvement was evident at two weeks. At 12 weeks, PASI-75 was achieved in 11% of group 1 and in 33%, 31% and 19% of group 2, 3 and 4, respectively. Likewise, a similar study which randomized patients to receive either 10 mg of alefacept (group 1), 15 mg of alefacept (group 2) or placebo (group 3) once weekly for 12 weeks concluded that intramuscular alefacept effectively and safely improves psoriasis and produces remissions without compromising normal immune function, and represents a convenient alternative to intravenous administration[80].

2.9.2 Efalizumab (Raptiva)

Efalizumab is a humanized monoclonal IgG1 antibody that targets the T-cell interactions thought to be responsible for the pathophysiology of psoriasis, marketed for psoriasis treatment in 2003[81]. It is an antibody against CD11a, the α-subunit of leukocyte function-

associated antigen 1 (LFA-1). By blocking the interaction of CD11a and intercellular adhesion-molecule-1 (ICAM-1), efalizumab acts at many levels[31], disrupting T-cell activation and decreasing T-cell migration into the inflamed skin[6]. Approved for treating patients with moderate to severe psoriasis, it is administered as a subcutaneous injection by the patient or physician/nurse. The first dose is 0.7 mg/kg, followed by a 1 mg/kg dose taken weekly on a continual basis[82]. The most common short-term effect experienced by efalizumab patients are flu-like symptoms that occur within the first two weeks of treatment. Rare occurrences of thrombocytopenia (a decrease of blood platelets) and hemolytic anemia (a form of anemia caused by hemolysis, the abnormal breakdown of red blood cells) have been noted; monitoring of platelet counts is therefore necessary[14].

In a randomized double-blind placebo-controlled multicentre trial of moderate to severe psoriasis patients, the efficacy and safety of efalizumab was assessed[83]. Results indicated that at the end of the 12-week treatment period, 27% of efalizumab patients attained PASI-75, compared to 4% in the placebo group. PASI-50 was achieved by 59% of efalizumab-treated patients versus 14% of placebo patients. Similar PASI results at week 12 were reported in two other studies[84, 85]. In each of these studies, the drug was well-tolerated and appeared to be efficacious and safe with no evidence of toxic effects. The safety, tolerability and efficacy of efalizumab was assessed in another longer-term study (3 years)[86]. The researchers concluded that efalizumab's safety profile was intact throughout 27 months of continuous treatment, as was its efficacy. However, in February 2009, Genentech Inc. (a biotechnology research-driven corporation) suspended sales of

efalizumab due to new safety concerns. An association between efalizumab and increased risk of developing progressive multifocal leukoencephalopathy, a disorder that damages the myelin that covers and protects nerves in the white matter of the brain, was the rationale behind this decision. This particular central nervous system disease is rare but fatal[87]; three cases were noted worldwide in patients receiving efalizumab[88].

2.10 Biologics: Tumor Necrosis Factor-α Inhibitors

A cytokine that causes an inflammatory response, TNF-α is produced by macrophages, keratinocytes, antigen-producing cells and lymphocytes. It fights off infection by signaling other cells to cause inflammation[67]. High levels of TNF-α can trigger inflammatory responses that lead to excessive keratinocyte proliferation and hence psoriasis plaques. Higher levels of TNF-α are found in psoriasis patients at affected sites and in serum. Adalimumab, etanercept, infliximab and onercept are approved TNF-α inhibitors that bind TNF-α to neutralize its pro-inflammatory effects. Clinicians and care-givers must exercise caution and pay heed to warnings when using these drugs as a number of side effects have been reported, such as tuberculosis, lupus, multiple sclerosis and heart failure[6].

2.10.1 Adalimumab (Humira)

Adalimumab is a human monoclonal immunoglobulin G1 antibody that acts by neutralizing TNF-α[11, 81]. It has been approved for use in moderate to severe psoriasis as well as psoriatic arthritis. In addition, it is used to treat Crohn's disease, ankylosing

spondylitis and adult/juvenile rheumatoid arthritis[6]. Administered as a subcutaneous injection, adalimumab patients receive an 80 mg dose the first week, followed by a 40 mg dose the second week and a 40 mg dose every second week thereafter[89].

Efficacy and safety of adalimumab was investigated in a double-blind, placebo-controlled multicentre trial where patients were randomized to receive either 80 mg of adalimumab at week 0 followed by 40 mg every second week beginning at week 1 (group 1), 80 mg of adalimumab at weeks 0 and 1 followed by 40 mg/week at week 2 (group 2) or placebo every week beginning at week 0 (group 3)[81]. At the end of the 12-week period, PASI-75 was achieved in 53% of group 1, 80% of group 2 and 4% of group 3. Similar conclusions that adalimumab is generally well-tolerated and efficacious were drawn in two other studies[11, 90].

2.10.2 Etanercept (Enbrel)

A fully human fusion protein that consists of a soluble tumor necrosis factor alpha (TNF-α,) receptor, etanercept binds to soluble and membrane-bound TNF-α molecules, thereby lowering the amount of TNF-α and inflammatory response characteristic of psoriasis[91, 92]. It is approved for use in moderate to severe psoriasis, psoriatic arthritis, adult/juvenile idiopathic arthritis and ankylosing spondylitis. Etanercept is administered as a subcutaneous injection twice weekly at a 50 mg dose for the initial 12 weeks of treatment, followed by continuous weekly 50 mg doses[6].

In a multicentre, double-blind, placebo controlled study, psoriasis patients were randomized to receive subcutaneously twice weekly (self-injected); 25 mg of etanercept or placebo for 24 weeks. At the end of the treatment period, PASI-75 was achieved by 56% of etanercept patients versus 5% of placebo patients. PASI-50 was achieved by 77% of etanercept patients versus 13% of placebo patients. Likewise, etanercept was deemed to be well-tolerated in other similar studies[93, 94]. Etanercept was also evaluated in a recent study[95] that assessed whether continuous or interrupted etanercept treatment made a difference. The researchers found that continuous etanercept treatment lead to greater improvements in patient-reported outcomes than interrupted therapy; however, they acknowledge that interrupting etanercept therapy (if needed) can be tolerated.

2.10.3 Infliximab (Remicade)

Infliximab is a part mouse, part human monoclonal antibody that blocks the effects of TNF-α by binding to soluble and membrane-bound TNF-α molecules. This inhibits the pro-inflammatory action of TNF-α and thereby reduces the symptoms of inflammation characteristic of psoriasis. This particular drug is approved for treating severe psoriasis, psoriatic arthritis, adult rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis and both adult and juvenile Crohn's disease[61]. It is administered as a 5 mg/kg intravenous infusion over a 2-3 hour period at a supervised infusion centre at weeks 1, 2, and 6, followed by every 8 weeks[6].

In a multicentre, double-blind, placebo-controlled trial, moderate to severe psoriasis patients were randomized to receive infliximab (group 1) or placebo (group 2)[61]. At week 24, PASI-75 was achieved by 82% of infliximab patients, as compared to 4% of placebo patients and PASI-90 was achieved by 58% of infliximab patients, as compared to 1% of placebo. This study showed that infliximab is effective in the treatment of psoriasis, with sustained effectiveness through 1 year of treatment. Another study of similar design assessed the effects of infliximab therapy on patients' quality of life, using the Dermatology Life Quality Index (10-item questionnaire administered to patients at baseline and again at week 10)[96]. Patients were randomized to receive either 3 mg/kg of infliximab (group 1), 5 mg/kg (group 2) or placebo (group 3). Therapy with infliximab resulted in substantial improvements of HRQOL at week 10; group 1 patients showed a median percentage improvement in DLQI scores of 84.0%, group 2=91.0% and placebo=0%. With respect to continuous versus intermittent treatment, a recent study concluded that continuous infliximab therapy worked better than intermittent infliximab therapy, as observed by the PASI scores at week 50[97].

2.10.4 Onercept (r-hTBP-1)

Onercept is a recombinant form of a natural human soluble tumor necrosis factor binding protein, developed by Merck Serono (a pharmaceutical company headquartered in Geneva, Switzerland) for the potential treatment of several disorders, including Crohn's disease, psoriasis and psoriatic arthritis[98, 99]. It is expected to form high-affinity complexes

with TNF-α, thereby neutralizing its effects. Onercept may be administered intravenously, intramuscularly or subcutaneously.

Rutgeerts et. al. (2003)[99] investigated the safety and efficacy of onercept in the treatment of patients with active Crohn's disease. Patients were randomly assigned to receive onercept subcutaneously at doses of 11.7 or 50 mg three times weekly for 2 weeks. At days 1, 8 and 15, and then monthly for up to 6 months after the end of treatment, patients were assessed. Efficacy was measured as a change in the Crohn's disease activity index. Results indicated that the Crohn's disease activity index decreased during treatment in both groups. This improvement was sustained for up to 4 months after stopping treatment. Onercept administration was well tolerated in this particular study.

Nikas & Drosos[98] discussed the results of a phase II, multicentre, double-blind, placebo-controlled 12-week study in which moderate to severe psoriasis patients were randomized to receive either placebo or onercept (administered subcutaneously at 150 mg three times a week or 100 mg seven times a week). The proportion of patients achieving PASI-75 was assessed. Results showed that 54% of patients receiving 150mg of onercept had a greater than 75% improvement in PASI scores compared with placebo. PASI-50 was achieved in 74% of onercept patients as compared to 26% in the placebo group.

It is worthwhile to mention that while patients of NewLab did receive onercept in certain clinical trials, this particular drug did not make it to market and thus its long-term treatment effects cannot be assessed.

2.11 Biologics: Interleukin-12/Interleukin-23 Blockaders

Interleukin-12 (IL-12) blockaders and Interleukin-23 (IL-23) blockaders are a relatively new class of biologics that work as inhibitors of the IL-12 and IL-23 cytokines that are involved in psoriasis plaque formation. IL-12 causes T-cells to differentiate into Th1 cells and production of IFN-γ. IL-23 is of interest because it causes differentiation into the Th17 T-cell subset that leads to maintained inflammation and severe autoimmunity[6]. IL-12 and IL-23 are each composed of a p40 subunit, which is over-expressed in psoriasis, leading to increased levels of these cytokines at psoriasis lesion sites. IL-12/IL-23 blockade drugs are injected antibodies that bind to the p40 subunit of IL-12 and IL-23 and thereby modulate levels of these cytokines[100].

2.11.1 CNTO 275 (Ustekinumab) (Stelara)

CNTO 275 is a human monoclonal antibody that targets the shared p40 subunit of IL-12 and IL-23 with high specificity and affinity. The drug is administered as a subcutaneous injection[101].

In a multicentre, placebo-controlled, double-blind study[101], moderate to severe psoriasis patients underwent randomization into 1 of 5 groups: one 45 mg subcutaneous dose of ustekinumab (group 1), one 90 mg subcutaneous dose of ustekinumab (group 2), 4 weekly 45 mg doses of ustekinumab (group 3), 4 weekly 90 mg doses of ustekinumab (group 4) or placebo (Group 5). At week 12, PASI-75 was achieved by 52% of group 1 patients, 59% of group 2 patients, 67% of group 3 patients, 81% of group 4 patients and

only 2% of placebo patients. Serious adverse events occurred in 4% of patients who received the drug as compared to 1% of placebo patients. Similar findings of safety and efficacy were noted in other studies[100, 102, 103].

2.12 Biologics: Peptide T

Peptide T is an octapeptide from the V2 region of gp120 of HIV that has been shown to resolve psoriasis lesions[104-107]. Its mechanism of action is not entirely understood, although the antichemotactic activities of peptide T are thought to be a possible explanation for its therapeutic efficacy in psoriasis[108]. It is worthwhile to mention that while patients of NewLab did receive peptide T in certain clinical trials, this particular drug did not make it to market and thus its long-term treatment effects cannot be assessed.

2.13 Biologics: A Comparison of Efficacy

A recent meta-analysis of biologic agents assessed the effects of alefacept, efalizumab, etanercept and infliximab on moderate to severe psoriasis patients using PASI[13]. Infliximab significantly increased the likelihood of achieving PASI 50, 75 and 90 compared with placebo. It also boasted the highest relative risk values compared to the other biological agents, meaning it was more likely than the other biologics to be more effective than placebo. The researchers also assessed improvements in health-related quality of life across the biologics. Alefacept treatment was associated with a significant improvement in health-related quality of life versus placebo. The same was true for efalizumab, etanercept and infliximab; however, the pooled rank order, in terms of which

treatment was most effective, was infliximab > etanercept > efalizumab > alefacept. The authors concluded that infliximab treatment over the first 10 weeks was significantly more likely than other biological treatments to reduce disease severity in patients with moderate-to-severe psoriasis. Interestingly, another meta-analysis published in the same year also assessed the efficacy of the same four biologics (alefacept, efalizumab, etanercept and infliximab) on moderate-to-severe psoriasis patients using PASI[77]. Pooled relative risks were also obtained; the decreasing rank order for pooled efficacy was infliximab > etanercept > efalizumab > alefacept. However, all studies included in the review by Reich et. al.[13] were also included in the study by Brimhall et. al.[77]; therefore it makes sense all the same conclusions would be drawn. However, in a separate meta-analysis that combined different studies, infliximab was actually found to be the most efficacious compared to other biologic and non-biologic systemic treatments (adalimumab, cyclosporine, efalizumab, etanercept, fumaric acid esters and methotrexate)[109].

In a retrospective cohort study, Inzinger et. al.[110] assessed the efficacy of PUVA therapy versus biologics in moderate-to-severe psoriasis patients, in terms of PASI reduction. Patients received either PUVA or biologic drugs (specifically, adalimumab, alefacept, efalizumab, etanercept, infliximab and ustekinumab) and were assessed for PASI-75 and PASI-90 at treatment completion for PUVA or at week 12 for biologics. PUVA was found to be superior to that of certain biologics (alefacept, efalizumab and etanercept;

$p<0.05$ for each), with the authors affirming the need for prospective, controlled head-to-head trials of PUVA and biologics.

Likewise, biologics were compared to a more traditional treatment regimen, Goeckerman therapy, in a retrospective analysis[111]. Goeckerman therapy includes dermal application of 2% crude coal tar three times a day and exposure to incremental doses of broad-band ultraviolet B radiation, 7 days a week. Researchers concluded that the risk-benefit ratio was more favorable for Goeckerman therapy compared with biologics. There were several limitations to this study; primarily, the researchers intended to compare biologics and Goeckerman therapy patients in terms of two outcomes: PASI reduction and remission maintenance. However, they only formulated one group (Goeckerman therapy patients) and did not create a comparison group (biologic patients). Rather, they based their conclusions on a former study[112]. Results of this particular study need to be interpreted with caution as study methodology/rigor is considered weak.

The efficacy of adalimumab, compared with methotrexate and placebo was assessed in a randomized controlled trial[90]. Moderate-to-severe psoriasis patients were randomized to receive either adalimumab (80 mg subcutaneously at week 0, then 40 mg every other week), methotrexate (7.5 mg orally, increased as needed/tolerated) or placebo for 16 weeks. The endpoint was the proportion of patients who achieved at least PASI-75. Results indicated that 79.6% of adalimumab-treated patients achieved PASI-75 compared with 35% for methotrexate and 18.9% for placebo. Likewise, significantly more

adalimumab-treated patients (16.7%) experienced complete clearance of the disease versus methotrexate-treated patients (7.3%) or placebo patients (1.9%). It was concluded that adalimumab demonstrated superior efficacy and more rapid improvements in psoriasis compared to methotrexate and/or placebo.

2.14 Biologics: Possible Associated Comorbidities

Adverse reactions during biological therapy are an obvious concern as previously discussed in the review of each individual biologic. In a recent study of adverse reactions occurring during biological therapy for psoriasis[113], researchers administered a survey concerning the clinical safety of four particular biologics (efalizumab, etanercept, infliximab and adalimumab) to 15 members of the Spanish Psoriasis Group (hospital dermatologists considered to be experts in the use of biologic drugs). Results indicated there was a particularly high proportion of reactions (34%) to infliximab infusions. Efalizumab was deemed to be different from other biologic drugs with regards to its side effects, such as higher frequency of headaches and influenza-like symptoms, higher rate of generalized inflammatory exacerbations and arthritis, more frequent rebounds following treatment, etc.

While cardiovascular disease has been shown to be associated with psoriasis patients in general[5, 45, 51-53], there has also been recent concern regarding biologics and their association with major cardiovascular events. In a recent meta-analysis of randomized controlled trials of ustekinumab, briankinumab, adalimumab, etanercept and infliximab, researchers investigated whether or not certain biologics (in particular, ustekinumab or

briankinumab) were associated with major adverse cardiovascular events[114]. Twenty-two randomized controlled trials met the predefined inclusion criteria. Trial results were combined using the Mantel-Haenszel fixed-effects method. They found no significant difference in the rate of major adverse cardiovascular events in those patients receiving any of the biologics investigated, compared with placebo.

A possible risk of lymphoma among biologic patients has been hypothesized. A systematic review[115] of case reports, case series, observational cohort studies, controlled clinical trials, open-label extension trials and meta-analyses has been conducted to investigate this association. It was concluded that current data are neither sufficient to rule out an increased risk of lymphoma associated with biologics, nor to establish a causal relationship between lymphoma and biologics. Short-term treatment (up to four years) appears to be safe with regards to lymphoma risk.

Malignancy is yet another concern among the newly introduced biologics, as these drugs mechanistically dampen the immune system against normally regressing cancers, thereby fostering malignant growth[23]. In a recent review, researchers summarized malignancy concerns with psoriasis treatments including phototherapy, methotrexate, cyclosporine and biologics (specifically, alefacept, efalizumab, etanercept, infliximab and adalimumab)[21]. Most trials in the review were limited to short-term effects, so it is difficult to assess the long-term risk of malignancy associated with biologics treatment. Similar conclusions were reached in another review[23] that assessed the risk of malignancy

associated with therapies for moderate-to-severe psoriasis, including phototherapy, systemic therapies and biologic therapies (specifically, alefacept, efalizumab, infliximab, etanercept, adalimumab and ustekinumab). The authors concluded that the risk of malignancy with biologic treatment is unclear, although it is thought that TNF-α inhibitors may cause a slight increase in risk of cancer, including both melanoma skin cancer and hematologic malignancies.

2.15 Knowledge Gaps

In general, the literature assessing comorbidities among psoriasis patients receiving biologics is limited, with many studies investigating the efficacy of biologic agents concluding that long-term trials are necessary. In a recent review, researchers attempted to focus on available long-term data on the efficacy of the biologic agents, in particular alefacept, efalizumab, etanercept, infliximab, adalimumab and ustekinumab. The researchers concluded there was a need for long-term efficacy trials of biologics to properly assess possible risks and comorbidities associated with this treatment[18]. Since biologics are relatively new, assessing their long-term outcomes becomes a challenge, hence the goal of the current study. However, grey literature searches revealed a long-term study (the Psoriasis Longitudinal Assessment and Registry - PSOLAR) that began in June 2007 and will end in January 2021; it is currently (2012) recruiting participants. This prospective cohort study will track the behavior of psoriasis patients in response to biologic drugs, evaluating clinical outcomes, quality of life, risks for patients, and clinical disease status. Another prospective study (Ustekinumab Safety and Surveillance Program Using the Ingenix NHI Database), not yet open for participant recruitment, will

investigate the incidence of serious outcomes and comorbidities among psoriasis patients receiving ustekinumab and other biologics, with an estimated study completion date of December 2018. Finally, Italian researchers have been following psoriasis patients treated with systemic drugs (cyclosporine, acitretin, PUVA, methotrexate, etanercept, efalizumab, infliximab and adalimumab) since 2005, with the intent to conduct epidemiological surveillance on such treatments and examine long-term effects[116].

As there are obvious gaps in the literature with respect to biologic treatment among psoriasis patients, in particular, comorbidities that might arise from biologic treatment, this study will contribute to the knowledge gap and aid in our understanding of the different biologic treatments and their impact on health status among psoriasis patients.

CHAPTER 3: MATERIALS AND METHODS

This chapter outlines the methodology used to address the research objectives, including a description of the study design, data sources, study population, data quality, data linkage, measures, data analysis and ethical considerations. The study was carried out with support from the Newfoundland and Labrador Centre for Health Information (the Centre).

3.1 Study Design

This study used a cross-sectional design that linked medical records of confirmed psoriasis patients who have received biologic treatment, to other clinical and administrative data sources in Newfoundland and Labrador. Medical records of patients with psoriasis who received biologic treatment obtained from a private dermatology clinic in St. John's (NewLab Clinical Research Inc.; hereafter referred to as "NewLab"), were linked to the NewLab Psoriasis Clinical Database (NPCD), the provincial hospital separation data, fee-for-service physician claims data and mortality data for the study period 1989 – 2009.

3.2 Data Sources

Data from the following sources were linked through a multi-step data linkage approach (see Appendix A), to create a comprehensive psoriasis biologic treatment database (NewLab Biologic Treatment Database): 1) NewLab biologic treatment data; 2) NewLab Psoriasis Clinical Database (NPCD); 3) the Clinical Database Management System (CDMS; hospital separation database); 4) the Newfoundland and Labrador Medical Care

Plan (MCP) Fee-For-Service Physician Claims Database; 5) the provincial Mortality System; and 6) Statistics Canada Annual Mortality Data Files.

3.2.1 NewLab Biologic Treatment data

The NewLab biologic treatment data, maintained by NewLab, includes treatment data on a sample of confirmed (by a dermatologist) psoriasis patients in Newfoundland and Labrador. At the time of this study, data was available from 1999 to 2009. The data was obtained from a clinical chart review (manual search by chart audit) of psoriasis patients attending the dermatology clinic at NewLab as well as the research clinic (as clinical trial patients) and was compiled internally by clinic staff. Extracted information included patients' name, MCP number (provincial health care number), date of birth, type of biologic taken, screening date of treatment, start date of treatment, end date of treatment, duration of treatment, PASI score before and after treatment and BSA (body surface area) score before and after treatment.

3.2.2 NewLab Psoriasis Clinical Database (NPCD)

The NewLab Psoriasis Clinical Database (NPCD), maintained by NewLab and housed at the Centre, includes demographic, clinical and genetic data on a sample of 3226 confirmed psoriasis patients in Newfoundland and Labrador. At the time of this study, data was available from 1989 to 2009. This data was obtained from a clinical chart review (manual search by chart audit) of psoriasis patients attending the dermatology clinic at NewLab and was compiled by clinic staff. Data extracted from this electronic database

included patient's MCP number, date of birth, sex, age-of-onset of psoriasis, age at first dermatologist visit, severity of disease, and HLA-Cw6 genotype status.

3.2.3 Clinical Database Management System (CDMS)

The Clinical Database Management System, maintained by the Centre, contains hospital separation data. At the time of study, data for fiscal years 1995/96 to 2007/08 was available. The CDMS captures demographic and clinical data for individuals receiving care in Newfoundland and Labrador on an inpatient or surgical day care basis. Information extracted for this study included care episode id (a unique number assigned to each admission), care episode type (acute care or surgical day care), admission and discharge dates, diagnosis codes and diagnosis type. Diagnosis codes correspond with the condition or conditions associated with the hospitalization and are based on the International Classification of Disease (ICD) versions nine (1995/96 to 2000/2001) and ten (2001/02 to 2007/08). Diagnosis type is related to the relevance of the diagnosis code within an episode of care; all diagnosis types (most responsible diagnosis, pre-admission comorbidity and post-admission comorbidity) were included.

3.2.4 Newfoundland Fee-for-Service (MCP) Physician Claims Database

The NL Fee-for-Service (MCP) Physician Claims Database captures demographic and clinical information on services provided to NL residents by physicians (specialists and general practitioners) on a fee-for-service basis between 1995/96 and 2007/08. Data extracted for this study included sex, age at time of service, date of service, diagnosis and procedure code. The physician claims database does not capture data relating to services

provided by salaried physicians (about one third of physicians in the province are salaried[117]). However, a high proportion of physicians (about eighty-five percent) in the St. John's region (the same region from which study patients were identified) are fee-for-service[117].

3.2.5 The Provincial Mortality System

The provincial Mortality System, maintained by the Centre, contains data extracted from provincial death notifications including demographics, health insurance number and data on the conditions surrounding each death; data at the time of study was available from 1991 to 2008. Conditions and/or diseases present at death are recorded but there is no indication of which of these conditions/diseases lead directly to death (i.e. the "Underlying Cause of Death").

3.2.6 Statistics Canada Annual Mortality Data Files

The Statistics Canada Annual Mortality Data Files is a compilation of data from provincial and territorial offices of vital statistics which are submitted annually to Statistics Canada and contain data on deaths in Canada. At the time of this study, data was available for 1993 to 2005. While data contained in the provincial mortality system is more current, the Statistics Canada Annual Mortality Data Files include the "Underlying Cause of Death". The underlying cause of death as reported in the Statistics Canada Annual Mortality Data Files represents the disease or injury that initiated the sequence of morbid events leading to an individual's death. The Statistics Canada Annual Mortality Data Files do not contain an individual's MCP number as a source of identification.

3.3 Study Population

The study population consisted of psoriasis patients who attended the NewLab clinic between 1989 and 2009 with a confirmed diagnosis of psoriasis by a dermatologist. The two study groups included:

Biologic Patients

This included confirmed psoriasis patients who presented to NewLab between 1999 and 2009 and received biologic treatment. Biologic treatment type and class was known for each patient.

Non-Biologic Patients

This included a random sample (generated by the software package SPSS) of confirmed psoriasis patients from the NCPD who presented to NewLab between 1989 and 2009. These patients did not receive biologic treatment, but may have received other type(s) of treatment (i.e., topical, systemic or phototherapy).

3.4 Data Quality

Quality assurance processes were carried out on the NewLab biologic treatment data to remove duplicate records and/or un-usable records and to correct invalid or missing data. A record was deemed un-usable if 1) its MCP number encompassed less than the standard twelve-digits, and 2) the record contained no date of birth. There were no data quality processes required for the other data sources as quality assurance is incorporated into the maintenance of the databases by the data custodians.

Three variables were used to identify potential duplicate records: patient name, date of birth and MCP number. Where all three variables matched for more than one record, the record was first checked to see if there was a legitimate reason for all three variables to match (as would be the case if the patient was taking more than one type of biologic drug). If there was not a legitimate reason for all three variables to match, the record was flagged as a duplicate and removed from the NewLab biologic treatment data. Where only two of the three variables matched for more than one record, the record was flagged as a potential duplicate and further investigated.

Where a record was missing name, MCP number and date of birth, the clinic was informed and the patient chart was reviewed again to provide updated data if available.

3.5 Data Linkage

The data linkage process will be described separately for biologic patients and non-biologic patients.

3.5.1 Biologic Patients

Using a multi-step data linkage approach (see Appendix A), the NewLab biologic treatment data was linked to other administrative and clinical data sources, as follows:

Step 1 – Linkage to NewLab Psoriasis Clinical Database: The NewLab biologic treatment data was linked to the NewLab Psoriasis Clinical Database first by MCP

number, and then by name and date of birth as a secondary link to capture variables such as age of onset, severity of disease, etc.

Step 2 – Linkage to Hospital Data: The data file was then linked to the CDMS via MCP number to identify patients who had at least one hospital separation between 1995/96 and 2007/08.

Step 3 – Linkage to Physician Data: The file was next linked to the Newfoundland Fee-for-Service Physician Claims Database via MCP number to capture data related to physician utilization between 1995/96 and 2007/08.

Step 4 – Linkage to the provincial Mortality System: The file was then linked to the provincial Mortality System via MCP number to capture those patients who had died, date of death, and conditions present at time of death between 1999 and 2008. A pseudo-id composed of 16 characters (first four letters of patient's last name, first four letters of patient's first name and date of birth of patient; where a first and/or last name did not have four letters, a blank space was inserted) was then created in the provincial Mortality System and in the linked file. This pseudo-id was used as a secondary linkage variable, for the purpose of identifying those patients who were not captured via MCP linkage.

Step 5 – Linkage to Statistics Canada Annual Mortality Data Files: Finally, the data file was linked to Statistics Canada Annual Mortality Data Files. This was done via a pseudo-id (described above), as the Statistics Canada Annual Mortality data files do not

include MCP numbers. Psoriasis patients identified as deceased in the provincial Mortality System (step 4) were linked to the Statistics Canada Annual Mortality Data Files to determine the underlying cause of death.

After linkage of the above data sources, the NewLab Biologic Treatment Database was complete. Following the completion of data quality processes and the linkage of all datasets, all direct personal identifiers were removed from the data file; only a study ID remained as a unique identifier in the linked data file. A study key was created and stored separate from the linked data set and was not accessible by the researcher.

3.5.2 Non-Biologic Patients

A similar data linkage approach to that outlined above was undertaken to create the Non-Biologic Psoriasis Database. A random sample of non-biologic patients was selected from the NPCD using SPSS. These cases were then linked to CDMS and the physician claims data, and the resultant database served as the Non-Biologic Psoriasis Database. Variables such as severity, age, age of onset, sex and genotype status were preserved for the non-biologic cases.

3.6 Measures

Age of onset of psoriasis, as defined by dermatologists of NewLab, included 1) early onset (type 1 psoriasis), defined as onset of psoriasis or before the age of 25 years; or 2) late onset (type 2 psoriasis), defined as onset of psoriasis at greater than 25 years of age.

Severity, as defined by dermatologists of NewLab, included 1) mild or 2) moderate/severe psoriasis. Mild psoriasis was defined as psoriasis affecting less than 5% of the body surface area and moderate/severe psoriasis was defined as psoriasis affecting greater than or equal to 5% of body surface area OR the face, palms, or genital area regardless of the percentage of body surface area affected.

Genotype status was defined as either negative or positive, depending on the absence or presence of the gene HLA-Cw6.

For the purposes of this study, comorbidity was defined as any condition that co-existed at the time of hospital admission (or physician visit) or developed during the hospitalization and significantly affected the treatment received by the patient[118]. Appendix B includes a list of comorbidities that were included and excluded when assessing health care utilization (hospital and physician visits) in this study. Comorbidity data presented in this study includes combined comorbidities due to hospitalizations and fee-for-service physician visits.

The Charlson Comorbidity Index (CCI) was assessed for psoriasis patients. The CCI predicts the one-year mortality for a patient who may have a range of comorbid conditions, including acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebral vascular disease, dementia, pulmonary disease, connective tissue disorder, peptic ulcer, liver disease, diabetes, diabetes complications, paraplegia, renal disease, metastatic cancer, severe liver disease and HIV. Each condition is assigned

a score of 1, 2, 3 or 6 depending on the risk of dying associated with each condition. For example, myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, ulcer, and chronic liver disease are all assigned a score of 1. Hemiplegia, moderate or severe kidney disease, diabetes, diabetes with complication, tumor, leukemia, and lymphoma are all assigned a score of 2. Malignant tumor, metastasis and AIDS are all assigned a score of 6. Scores are then summed and the patient is given a total score which predicts mortality. The higher the score, the greater the risk of mortality[119]. CCI score was assessed for psoriasis patients by analyzing who presented to the hospital with which CCI comorbid condition during the study period. Scores were assigned and then summed.

3.7 Data Analysis

Descriptive statistics were generated to describe the distribution of psoriasis patients who received each treatment type. Psoriasis patients were further described and analyzed according to which biologic treatment group they belonged, along with various prognostic factors (age of onset, severity of disease, HLA-Cw6 status). Chi-square tests were used to investigate whether there was an association between prognostic factors and treatment type. For continuous data (such as age), t-tests/ANOVA were used to investigate whether statistically significant differences existed between biologic treatment groups. The non-parametric median test was used to determine whether significant differences existed in the median number of hospitalizations or physician visits across biologic type and class, as hospitalization and physician visit variables were not normally distributed.

Five separate multivariate logistic regression analyses were performed to investigate associations between particular comorbid conditions ('mental disorder', 'skin and subcutaneous disorder', 'neoplasm', 'digestive system disease' and 'circulatory system disease') and biologic status (whether a patient takes biologics or not). Confounding variables such as age of onset, severity of disease, age and sex were controlled for in the logistic regression model. The above comorbid conditions were selected for assessment as they were leading comorbidities found among psoriasis patients who were either hospitalized or had died in a previous study[60]. The dependent variable was the comorbid condition, grouped as having the condition or not having the condition. Independent variables included age, sex, severity, age of onset, and whether or not the patient was receiving biologic treatment. Genotype status (HLA-Cw6) was not included in the model due to the low number of patients who had a genotype status recorded within the biologic and non-biologic groups (22.9% and 23.9%, respectively).

Linear regression analyses were performed to investigate the effect of biologic status (whether or not a patient received biologic treatment) on the Charlson Comorbidity Index (CCI) score. The dependent variable was CCI score. The independent variable of interest was biologic status (whether a patient takes biologics or not) and whether or not this was associated with CCI score. Other independent variables included age, sex, severity and age of onset. Genotype status (HLA-Cw6) was not included in the model for the same reasoning as above.

Two-sided p values of less than 0.05 were considered statistically significant. The Statistical Package for the Social Sciences (SPSS) version 15.0 and 17.0, as well as Statistical Analysis Software (SAS) version 9.2 were used for all analyses.

3.8 Ethical Consideration

The protocol for the study was approved by the Human Investigations Committee of Memorial University of Newfoundland (see Appendix D), as well as by the Secondary Uses Committee at the Newfoundland and Labrador Centre for Health Information. Members of the Secondary Uses Committee have expertise in privacy, security, research, data quality, standards and data extraction. The Committee conducts a full review of the study protocol to ensure best efforts are made to resolve or mitigate any risk to the privacy of study participants. Recommendations from the review of the request are then brought to the Centre's Chief Information Officer for final review and approval. All personal identifiers (name, date of birth, address, provincial health insurance number (MCP), etc.) were removed from the database prior to analysis. All study data was securely stored and accessed at the Centre.

CHAPTER 4: RESULTS

This chapter presents the main results of the study. Results pertaining to biologic patients are discussed first, followed by non-biologic patients and two separate regression analyses using biologic and non-biologic patients.

4.1 Biologic Patients (n=284)

4.1.1 Linkage Results

A total of 284 records for biologic patients were provided by NewLab. Table 1 describes the number of biologic patient records that linked to each of the data sets. Biologic patients presented to NewLab between 1999 and 2009; they may have linked to a hospitalization or fee-for-service physician visit prior to 1999, as hospitalization and physician data was available from 1995/96 – 2007/2008.

Table 1 Number of biologic patient records that linked to other data sources

Data Linkage Step	# Linked/Total
1) Linkage of biologic patient records to NPCD	284/284
2) Linkage of biologic patient treatment data to CDMS	183[a]/284
3) Linkage of biologic patient treatment data to FFS	275[a]/284
4) Linkage of biologic treatment data to the provincial Mortality System	2/284
5) Linkage of biologic treatment data to Statistics Canada Annual Mortality Files	2/284

[a] Numbers include only those people who had a hospitalization or a physician visit for a condition of interest. See Appendix B for a list of included and excluded conditions.

Table 2 presents a breakdown of the data availability in the NewLab Biologic Treatment Database. This database contained 284 records with sex available for 100% of the records, age for 96.8%, and disease severity for 93.3%. Type of biologic was available for 245 patients, thus any subsequent analysis related to biologic type or class will include these 245 patients only. Age of onset, genotype and PASI outcome were missing for a large proportion of cases.

Table 2 Data availability, NewLab Biologic Treatment Database

Variable	Missing values n (%)	Valid values n (%)
Sex	0 (0)	284 (100.0)
Age	9 (3.2)	275 (96.8)
Disease Severity	19 (6.7)	265 (93.3)
Age of Onset	158 (55.6)	126 (44.4)
Genotype	219 (77.1)	65 (22.9)
Type of Biologic	39 (13.7)	245 (86.3)
Start Date of Treatment	34 (12.0)	250 (88.0)
PASI Outcome	131 (46.1)	153 (53.9)

Table 3 presents data availability for those biologic patients with and without a hospitalization history. One hundred fifty six patients linked to the CDMS. Of these, sex was available for all patients, age for 96.2%, and disease severity for 92.3%. Eighty-nine records did not link to the CDMS (i.e., those patients did not have a hospitalization); of these, age was available for 96.6%, age of onset for 34.8%, and genotype for 12.4%.

Table 3 Data availability for biologic patients with and without hospitalizations, NewLab Biologic Treatment Database

Variable	With hospitalizations (n=156) n (%)	Without Hospitalizations (n=89) n (%)	Total (n=245)
Sex	156 (100.0)	89 (100.0)	245
Age	150 (96.2)	86 (96.6)	236
Disease Severity	144 (92.3)	82 (92.1)	226
Age of Onset	82 (52.6)	31 (34.8)	113
Genotype	42 (26.9)	11 (12.4)	53

Table 4 presents data availability for psoriasis biologic patients with and without a physician utilization history. Of the 236 patients that linked to physician visit data, sex was available for all patients, age for 97.0%, disease severity for 92.4%, age of onset for 47.9% and genotype for 22.5%. Nine records did not link to the MCP Fee-for-Service Physician Claims Database (i.e., those patients did not have a physician visit). Of those, sex was available for 100%, age for 77.8%, disease severity for 88.9%, age of onset for 0%, and genotype for 0%. The fact that 9 patients of NewLab did not link to the MCP Fee-for-Service Physician Claims Database, as would be expected given the dermatologist at NewLab is a fee-for-service physician, can be explained by the fact that some NewLab patients are research clinic (clinical trial) patients, and thus are never billed

through MCP. If such patients fare well on clinical trials and have no reason to see another doctor, they will not be captured in the MCP Fee-for-Service Physician Claims Database.

Table 4 Data availability for biologic patients with and without physician visits[1], NewLab Biologic Treatment Database

Variable	With physician visits (n=236) n (%)	Without physician visits (n=9) n (%)	Total (n=245)
Sex	236 (100.0)	9 (100.0)	245
Age	229 (97.0)	7 (77.8)	236
Disease Severity	218 (92.4)	8 (88.9)	226
Age of Onset	113 (47.9)	0 (0)	113
Genotype	53 (22.5)	0 (0)	53

[1] Includes visits to physicians paid by fee-for-service only

4.1.2 Mortality Results

As the number of individuals in the NewLab Biologic Treatment Database who died was very small (0.7% of the sample), a decision was made that further mortality analysis could not be conducted.

4.1.3 Distribution of Biologic Patients

Demographic and clinical characteristics of psoriasis biologic patients in the study population are presented in Table 5. The sex distribution included 174 males and 110 females (61.3% and 38.7%, respectively). Mean (±SD) age as of January 1, 2010 was 48.6 ±11.5 years. There was no significant difference (p=0.20) between mean age for males (49.3±11.1 years) and females (47.5±12.0 years). For the sub-sample of patients for which information on severity of disease was available (n=265), the majority (89.1%)

were identified as having moderate/severe psoriasis. No significant association was found between severity of disease and sex. Of the 126 patients for whom age of onset was available, 61.1% had an early age of onset. No association was found between age of onset and sex. Of the 65 psoriasis patients who were HLA-Cw6 genotype-tested, 66.2% tested positive for the HLA-Cw6 gene. No association was found between genotype and sex. The majority of patients (91.6%) were between the age of 25 and 64; 6.9% were 65 years or older and 1.5% were less than 25 years of age. Distribution of females and males were similar, although males accounted for a slightly higher proportion in all groups except the less than 25 years age group.

Table 5 Demographic and clinical characteristics of biologic patients, NewLab Biologic Treatment Database

Characteristic		Male (n=174) n (%)	Female (n=110) n (%)	Total (n=284) n (%)	p-value
Mean Age (± SD) (n=275)		49.3 (11.1)	47.5 (12.0)	48.6 (11.5)	p=0.20[a]
Severity (n=265)	Mild	18 (11.0)	11 (10.8)	29 (10.9)	p=1.00[b]
	Moderate/Severe	145 (89.0)	91 (89.2)	236 (89.1)	
Age of Onset (n=126)	≤ 25 years	42 (60.9)	35 (61.4)	77 (61.1)	p=1.00[b]
	> 25 years	27 (39.1)	22 (38.6)	49 (38.9)	
Genotype (n=65)	Positive	21 (65.6)	22 (66.7)	43 (66.2)	p=1.00[b]
	Negative	11 (34.4)	11 (33.3)	22 (33.8)	
Age Group (n=275)	< 25 years	2 (1.2)	2 (1.9)	4 (1.5)	p=0.94[b]
	25-64 years	154 (91.7)	98 (91.6)	252 (91.6)	
	≥ 65 years	12 (7.1)	7 (6.5)	19 (6.9)	

[a] p-value determined using independent samples t-test
[b] p-value determined using chi-square test for independence

The distribution of biologic treatment type by sex, severity, age of onset and genotype is shown in Table 6. Adalimumab was the most common biologic among the 245 study patients (whose biologic type was known), accounting for 25.3%; onercept was the least

common biologic, accounting for 2.4%. Adalimumab was the most common biologic among both males and females, whereas onercept was the least common biologic among males compared to etanercept for females. With respect to severity, very few biologic patients were classified as mild (11.9%); approximately 88% were classified as moderate/severe. A majority of the moderate/severe biologic patients received adalimumab (26.1%); few (3.0%) received onercept. Regarding age of onset, 61% of the study population was classified as early onset, while 39% was classified as late onset. The majority of patients classified as early onset received efalizumab as treatment (21.7%), while a majority classified as late onset received either adalimumab or infliximab (20.5% each). Based on available genotype information, the majority of biologic patients were HLA-Cw6 positive (36/53; 67.9%). Alefacept was the most common biologic prescribed to the genotype positive patients; adalimumab and alefacept were the most common biologics prescribed to genotype negative patients.

Table 6 Distribution of biologic type, sex, severity, age of onset and genotype

Characteristic		Adalimumab (n=62)	Alefacept (n=46)	CNTO-275 (n=31)	Efalizumab (n=30)	Etanercept (n=20)	Infliximab (n=37)	Onercept (n=6)	Peptide T (n=13)	Total (n=245)
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Sex (n=245)	Male	42 (27.6)	32 (21.1)	14 (9.2)	13 (8.6)	18 (11.8)	24 (15.8)	2 (1.3)	7 (4.6)	152 (100)
	Female	20 (21.5)	14 (15.1)	17 (18.3)	17 (18.3)	2 (2.2)	13 (14.0)	4 (4.3)	6 (6.5)	93 (100)
Severity (n=226)	Mild	7 (25.9)	5 (18.5)	7 (25.9)	1 (3.7)	2 (7.4)	5 (18.5)	0 (0)	0 (0)	27 (100)
	Moderate/ Severe	52 (26.1)	39 (19.6)	17 (8.5)	25 (12.6)	18 (9.0)	29 (14.6)	6 (3.0)	13 (6.5)	199 (100)
Age of Onset (n=113)	≤ 25 years	12 (17.4)	11 (15.9)	7 (10.1)	15 (21.7)	5 (7.2)	11 (15.9)	1 (1.4)	7 (10.1)	69 (100)
	> 25 years	9 (20.5)	7 (15.9)	4 (9.1)	5 (11.4)	7 (15.9)	9 (20.5)	0 (0)	3 (6.8)	44 (100)
Genotype (n=53)	Positive	8 (22.2)	9 (25.0)	2 (5.6)	6 (16.7)	1 (2.8)	5 (13.9)	2 (5.6)	3 (8.3)	36 (100)
	Negative	4 (23.5)	4 (23.5)	3 (17.6)	2 (11.8)	1 (5.9)	2 (11.8)	0 (0)	1 (5.9)	17 (100)

Note: age of onset information should be interpreted with caution, as data was only available for 46% (113/245) of the biologic patients. Likewise, genotype information was available only for a very small proportion of the sample (53/245; 21.6%).

The distribution of biologic treatment class by sex, severity, age of onset and genotype is shown in Table 7. TNF-α inhibitors accounted for just over half of the biologics prescribed (51.0%). With respect to sex, males and females showed similar distributions: TNF-α inhibitors were the most popular prescribed biologic class, followed by T-cell inhibitors, Interleukin 12/23 Blockaders and Peptide T. Regarding severity, the majority of mild patients (51.9%) and moderate/severe patients (52.8%) were found in the TNF-α Inhibitors class; the small number of mild psoriasis patients compared to moderate/severe psoriasis patients must be considered when interpreting these percentages. With respect to age on onset, the majority of early onset patients (42.0%) received TNF-α inhibitor drugs, as did the majority of late onset patients (56.8%). The majority of genotype positive patients (44.4%) received TNF-α inhibitor drugs, as did the majority of genotype negative patients (43.4%).

Table 7 Distribution of biologic class by sex, severity, age of onset and genotype

Characteristic		T-Cell Inhibitors (n=76)	TNF-α Inhibitors (n=125)	Interleukin 12/23 Blockaders (n=31)	Peptide T (n=13)	Total (n=245)
		n (%)	n (%)	n (%)	n (%)	n (%)
Sex (n=245)	Male	45 (29.6)	86 (56.6)	14 (9.2)	7 (4.6)	152 (100)
	Female	31 (33.3)	39 (41.9)	17 (18.3)	6 (6.5)	93 (100)
Severity (n=226)	Mild	6 (22.2)	14 (51.9)	7 (25.9)	0 (0)	27 (100)
	Moderate/Severe	64 (32.2)	105 (52.8)	17 (8.5)	13 (6.5)	199 (100)
Age of Onset (n=113)	≤ 25 years	26 (37.7)	29 (42.0)	7 (10.1)	7 (10.1)	69 (100)
	> 25 years	12 (27.3)	25 (56.8)	4 (9.1)	3 (6.8)	44 (100)
Genotype (n=53)	Positive	15 (41.7)	16 (44.4)	2 (5.6)	3 (8.3)	36 (100)
	Negative	6 (35.3)	7 (41.2)	3 (17.6)	1 (5.9)	17 (100)

4.1.4 Hospitalizations for Biologic Patients (1995/96 – 2007/08)

Of the 245 biologic patients whose biologic type was known, 156 (63.7%) had at least one acute hospital separation with a condition of interest (see Appendix B for list of included conditions) between 1995/96 – 2007/08. The median number of hospitalizations by biologic type and class is shown in Table 8. No significant difference for median number of hospitalizations across biologic type or biologic class was found.

Table 8 Median number of hospital separations per patient, by biologic type and class

Biologic Type (n=156)	Median Number Hospitalizations (± Range)	p-value[a]
Adalimumab (Humira) (n=35)	2.00 (1-14)	p=0.96
Alefacept (Amevive; LFA 3TIP) (n=28)	2.00 (1-10)	
CNTO 275 (Ustekinumab; Stelara) (n=20)	2.00 (1-10)	
Efalizumab (Raptiva; Anti-CD11a) (n=23)	2.00 (1-16)	
Etanercept (Enbrel) (n=13)	2.00 (1-14)	
Infliximab (Remicade) (n=23)	2.00 (1-13)	
Onercept (r-hTBP-1) (n=6)	2.00 (1-4)	
Peptide T (n=8)	2.50 (1-16)	
Total (n=156)	2.00 (1.00-4.75)[b]	

Biologic Class (n=156)	Median Number Hospitalizations (± Standard Deviation)	p-value[a]
T-cell Inhibitors (n=51)	2.00 (1-16)	p=0.78
TNF-α Inhibitors (n=77)	2.00 (1-14)	
Interleukin 12/23 Blockaders (n=20)	2.00 (1-10)	
Peptide T (n=8)	2.50 (1-16)	
Total (n=156)	2.00 (1.00-4.75)[b]	

[a] p-value determined using non-parametric median test
[b] range presented is interquartile range, equal to the difference between the upper and lower quartiles

4.1.5 Physician Visits for Biologic Patients (1995/96 – 2007/08)

Of the 245 biologic patients whose biologic type was known, 236 (96.3%) had at least one physician visit to a specialist or a general practitioner for a condition of interest (see Appendix B for list of included conditions) between 1995/96 and 2007/08. The median number of physician visits by biologic type and class is shown in Table 9. No significant difference was found in median number of physician visits across biologic type or class.

Table 9 Median number of physician visits per patient by biologic type and class

Biologic Type (n=236)	Median Number Physician Visits (± Standard Deviation)	p-value[a]
Adalimumab (Humira) (n=58)	103.00 (20-446)	p=0.59
Alefacept (Amevive; LFA 3TIP) (n=45)	112.00 (29-442)	
CNTO 275 (Ustekinumab; Stelara) (n=31)	74.00 (16-385)	
Efalizumab (Raptiva; Anti-CD11a) (n=28)	112.00 (28-414)	
Etanercept (Enbrel) (n=19)	116.00 (45-292)	
Infliximab (Remicade) (n=36)	107.00 (1-580)	
Onercept (r-hTBP-1) (n=6)	147.50 (44-293)	
Peptide T (n=13)	135.00 (40-482)	
Total (n=236)	106.00 (70.00-179.75)[b]	
Biologic Class (n=236)	**Median Number Physician Visits (± Standard Deviation)**	**p-value[a]**
T-cell Inhibitors (n=73)	112.00 (28-442)	p=0.19
TNF-α Inhibitors (n=119)	107.00 (1-580)	
Interleukin 12/23 Blockaders (n=31)	74.00 (16-385)	
Peptide T (n=13)	135.00 (40-482)	
Total (n=236)	106.00 (70.00-179.75)[b]	

[a] p-value determined using non-parametric median test

[b] range presented is interquartile range, equal to the difference between the upper and lower quartiles

4.1.6 Comorbidities Among Biologic Patients

Table 10 presents the mean number of comorbidities per biologic patient by sex, disease severity, age of onset, and genotype status. The mean number of comorbidities was significantly higher for females compared to males (9.53±2.77 and 8.20±2.78, respectively). Median (data not shown) was similar. No significant differences were found in mean number of comorbidities across disease severity, age of onset or genotype status.

Table 10 Mean number of comorbidities per patient by prognostic factor

Prognostic Factor		Mean number Comorbidities (± Standard Deviation)	p-value[a]
Sex (n=284)	Male (n=174)	8.20 (2.78)	p=0.001*
	Female (n=110)	9.53 (2.77)	
	Total (n=284)	8.71 (2.84)	
Severity (n=265)	Mild (n=29)	8.31 (2.93)	p=0.37
	Moderate/Severe (n=236)	8.81 (2.80)	
	Total (n=265)	8.75 (2.81)	
Age of Onset (n=126)	≤ 25 years (n=77)	8.84 (2.56)	p=0.13
	> 25 years (n=49)	9.43 (1.76)	
	Total (126)	9.07 (2.29)	
Genotype (n=65)	Positive (n=43)	9.12 (2.33)	p=0.36
	Negative (n=22)	9.68 (2.28)	
	Total (n=65)	9.31 (2.31)	

*p<0.05

[a] p-value determined using one-way ANOVA

Table 11 presents the distribution of comorbidities by ICD Chapter for the 284 biologic patients who had at least one hospitalization or one physician visit during the study period. The most common comorbidity associated with health service utilization was 'symptoms, signs and ill-defined conditions' (see Appendix C for a list of conditions included in this ICD chapter) (96.8%), followed by 'skin and sub-cutaneous disease' (95.1%), followed by 'respiratory system disease' (85.6%) and 'musculoskeletal system/connective tissue disease' (84.9%). It is important to note that psoriasis falls under the 'skin and sub-cutaneous disease' ICD chapter. Therefore, interpretation of 'skin and sub-cutaneous disease' as a "comorbidity" among biologic patients might not be entirely accurate, as technically the diagnosis of psoriasis itself is captured in this ICD chapter.

Table 11 Comorbidities associated with hospitalization or physician visits for biologic patients

Comorbidity (ICD Chapter)	n (%)
Symptoms, Signs and Ill-Defined Conditions	275 (96.8)
Skin and Sub-Cutaneous Disease	270 (95.1)
Respiratory System Disease	243 (85.6)
Musculoskeletal System/Connective Tissue Disease	241 (84.9)
Nervous System/Sense Organs Disease	231 (81.3)
Genitourinary Disease	202 (71.1)
Circulatory System Disease	187 (65.8)
Digestive System Disease	182 (64.1)
Endocrine/Nutritional/Metabolic Disorder	169 (59.5)
Infectious Disease	159 (56.0)
Mental Disorder	145 (51.1)
Neoplasm	95 (33.5)
Blood Disease	60 (21.1)
Congenital Abnormalities	15 (5.3)

Note: percentages do not sum to 100% as a patient may have had multiple comorbidities associated with a single hospitalization and/or more than one hospitalization/physician visit for more than one condition.

Table 12 presents comorbidities associated with hospitalizations or physician visits, ranked. 'Symptoms, signs and ill-defined conditions' was the most common comorbidity across all biologic classes, followed by 'skin and sub-cutaneous disease', 'respiratory system disease', 'nervous system/sense organs disease' and 'musculoskeletal system/connective tissue disease'. For the same reasoning as mentioned above, interpretation of 'skin and sub-cutaneous disease' as a "comorbidity" must be done with caution.

Table 12 Comorbidities associated with hospitalizations or physician visits, ranked, by biologic class

ICD Chapter	Biologic Class									
	T-Cell Inhibitors (n=76)	Rank	TNF-α Inhibitors (n=125)	Rank	Interleukin 12/23 Blockaders (n=31)	Rank	Peptide T (n=13)	Rank	Total (n=245)	
	n (%)		n (%)		n (%)		n (%)		n (%)	
Infectious Disease	48 (63.2)	9	63 (50.4)	10	20 (64.5)	7	9 (69.2)	6	105 (57.1)	
Neoplasm	25 (32.9)	12	41 (32.8)	12	11 (35.5)	12	7 (53.8)	10	84 (34.3)	
Endocrine/Nutritional/ Metabolic Disorder	51 (67.1)	8	74 (59.2)	9	14 (45.2)	10	6 (46.2)	12	145 (59.2)	
Blood Disease	15 (19.7)	13	25 (20.0)	13	8 (25.8)	13	3 (23.1)	13	51 (20.8)	
Mental Disorder	42 (55.3)	11	59 (47.2)	11	13 (41.9)	11	8 (61.5)	7	122 (49.8)	
Nervous System/ Sense Organs Disease	65 (85.5)	5	97 (77.6)	5	29 (93.5)	3	13 (100.0)	1	204 (83.3)	
Circulatory System Disease	58 (76.3)	6	77 (61.6)	8	18 (58.1)	8	7 (53.8)	10	160 (65.3)	
Respiratory System Disease	67 (88.2)	3	107 (85.6)	3	25 (80.6)	5	11 (84.6)	5	210 (85.7)	
Digestive System Disease	46 (60.5)	10	82 (65.6)	7	17 (54.8)	9	9 (69.2)	6	154 (62.9)	
Genitourinary Disease	52 (68.4)	7	89 (71.2)	6	21 (67.7)	6	9 (69.2)	6	171 (69.8)	
Skin and Sub-Cutaneous Disease	73 (96.1)	1	115 (92.0)	2	30 (96.8)	2	13 (100.0)	1	231 (94.3)	
Musculoskeletal System/ Connective Tissue Disease	66 (86.8)	4	101 (80.8)	4	28 (90.3)	4	13 (100.0)	1	208 (84.9)	
Congenital Abnormalities	6 (7.9)	14	5 (4.0)	14	2 (6.5)	14	1 (7.7)	14	14 (5.7)	
Symptoms, Signs and Ill-defined Conditions	73 (96.1)	1	119 (95.2)	1	31 (100.0)	1	13 (100.0)	1	236 (96.3)	

Note: percentages do not sum to 100% as a patient may have had multiple comorbidities associated with a single hospitalization and/or more than one hospitalization/physician visit for more than one condition.

The number of comorbidities associated with hospitalization or physician visits by biologic class, per biologic patient, is presented in Table 13. Ten comorbidities was the most frequent number of comorbidities among biologic patients (i.e., 43 biologic patients out of 245 were found to have 10 comorbidities).

Table 13 Number of comorbidities associated with hospitalization or physician visits per biologic patient, by biologic class

Number of Comorbidities	Biologic Class				
	T-cell Inhibitors (n=76)	TNF-α Inhibitors (n=125)	Interleukin 12/23 Blockaders (n=31)	Peptide T (n=13)	Total (n=245)
	n (%)	n (%)	n (%)	n (%)	n (%)
0	3 (3.9)	6 (4.8)	0 (0)	0 (0)	9 (3.7)
1	0 (0)	1 (0.8)	0 (0)	0 (0)	1 (0.4)
3	0 (0	1 (0.8)	2 (6.5)	0 (0)	3 (1.2)
4	0 (0	4 (3.2)	1 (3.2)	0 (0)	5 (2.0)
5	4 (5.3)	6 (4.8)	0 (0)	0 (0)	10 (4.1)
6	3 (3.9)	10 (8.0)	3 (9.7)	2 (15.4)	18 (7.3)
7	5 (6.6)	10 (8.0)	4 (12.9)	1 (7.7)	20 (8.2)
8	9 (11.8)	20 (16.0)	3 (9.7)	2 (15.4)	34 (13.9)
9	17 (22.4)	13 (10.4)	5 (16.1)	1 (7.7)	36 (14.7)
10	15 (19.7)	18 (14.4)	7 (22.6)	3 (23.1)	43 (17.6)
11	6 (7.9)	19 (15.2)	2 (6.5)	1 (7.7)	28 (11.4)
12	9 (11.8)	13 (10.4)	3 (9.7)	2 (15.4)	27 (11.0)
13	5 (6.6)	4 (3.2)	0 (0)	1 (7.7)	10 (4.1)
14	0 (0)	0 (0)	1 (3.2)	0 (0)	1 (0.4)

The mean number of comorbidities per patient by biologic type and class is presented in Table 14. Median number of comorbidities was similar to the mean (data not shown). No significant differences were found among biologic type or class.

Table 14 Mean number of comorbidities per patient by biologic type and class

Biologic Type (n=245)	Mean Number Comorbidities (± Standard Deviation)	p-value[a]
Adalimumab (Humira) (n=62)	8.31 (3.14)	p=0.47
Alefacept (Amevive; LFA 3TIP) (n=46)	9.22 (2.72)	
CNTO 275 (Ustekinumab; Stelara) (n=31)	8.61 (2.61)	
Efalizumab (Raptiva; Anti-CD11a) (n=30)	8.77 (2.79)	
Etanercept (Enbrel) (n=20)	8.40 (2.80)	
Infliximab (Remicade) (n=37)	8.32 (3.15)	
Oncrcept (r-hTBP-1) (n=6)	10.50 (2.51)	
Peptide T (n=13)	9.38 (2.29)	
Total (n=245)	8.69 (2.88)	
Biologic Class (n=245)	**Mean Number Comorbidities**	**p-value**
T-cell Inhibitors (n=76)	9.04 (2.74)	p=0.41
TNF-α Inhibitors (n=125)	8.43 (3.07)	
Interleukin 12/23 Blockaders (n=31)	8.61 (2.62)	
Peptide T (n=13)	9.38 (2.29)	
Total (n=245)	8.69 (2.88)	

[a] p-value determined using one-way ANOVA

Table 15 presents mean Charlson Comorbidity Index (CCI) score per biologic patient by sex, disease severity, age of onset and genotype status. A significant difference between males and females in terms of mean CCI score was found, with females having a higher mean CCI score (2.37±1.54) compared to males (1.93±1.32), $p<0.05$. No significant differences were found in mean CCI score across disease severity, age of onset or genotype status.

Table 15 Mean CCI score per patient by prognostic factor

Prognostic Factor		Mean CCI Score (± Standard Deviation)	p-value[a]
Sex (n=182)	Male (n=111)	1.93 (1.32)	p=0.04*
	Female (n=71)	2.37 (1.54)	
	Total (n=182)	2.10 (1.42)	
Severity (n=173)	Mild (n=19)	1.89 (1.15)	p=0.55
	Moderate/Severe (n=154)	2.10 (1.46)	
	Total (n=173)	2.08 (1.42)	
Age of Onset (n=87)	≤ 25 years (n=50)	2.18 (1.67)	p=0.68
	> 25 years (n=37)	2.32 (1.55)	
	Total (n=87)	2.24 (1.61)	
Genotype (n=45)	Positive (n=28)	1.89 (1.17)	p=0.12
	Negative (n=17)	2.76 (2.02)	
	Total (n=45)	2.22 (1.58)	

*$p<0.05$

[a] p-value determined using one-way ANOVA

The mean CCI score per patient is presented by biologic type and class in Table 16. Median (data not shown) was similar. No significant differences were found in mean CCI score across biologic type or class.

Table 16 Mean CCI score per patient by biologic type

Biologic Type (n=159)	Mean CCI Score (± Standard Deviation)	p-value[a]
Adalimumab (Humira) (n=42)	2.00 (1.47)	p=0.66
Alefacept (Amevive; LFA 3TIP) (n=31)	2.23 (1.54)	
CNTO 275 (Ustekinumab; Stelara) (n=17)	2.06 (1.14)	
Efalizumab (Raptiva; Anti-CD11a) (n=20)	1.65 (0.99)	
Etanercept (Enbrel) (n=13)	2.54 (1.45)	
Infliximab (Remicade) (n=23)	2.30 (1.74)	
Onercept (r-hTBP-1) (n=5)	2.20 (0.84)	
Peptide T (n=8)	2.63 (1.85)	
Total (n=159)	2.13 (1.44)	
Biologic Class (n=159)	**Mean CCI Score**	**p-value**
T-cell Inhibitors (n=51)	2.00 (1.37)	p=0.69
TNF-α Inhibitors (n=83)	2.18 (1.51)	
Interleukin 12/23 Blockaders (n=17)	2.06 (1.14)	
Peptide T (n=8)	2.63 (1.85)	
Total (n=159)	2.13 (1.44)	

[a] p-value determined using one-way ANOVA

4.1.7 Psoriasis Area and Severity Index (PASI) Score Among Biologic Patients

Table 17 presents the frequency and percentage of patients who achieved PASI-50, PASI-75 and PASI-90, by biologic type and class. Overall, approximately half (50.4%) of the patients (whose before and after PASI scores were available; n=137) achieved PASI-50, 21.9% achieved PASI-75 and 13.1% achieved PASI-90. PASI-50 was attained in over half of the patients in four biologic groups (adalimumab=56.8%, alefacept=59.3%, efalizumab=56.5% and etanercept=66.7%). PASI-50 was attained in over half of the patients in two biologic classes (T-cell Inhibitors=58.0% and TNF-α Inhibitors=52.2%). Frequencies and percentages declined across biologic type and class as PASI level increased. The small sample sizes in the biologic groups needs to be considered in interpreting these results.

Table 17 PASI Outcome by biologic type and class

Biologic Type (n=137)	PASI Outcome		
	PASI-50	PASI-75	PASI-90
	n (%)	n (%)	n (%)
Adalimumab (Humira) (n=44)	25 (56.8)	10 (22.7)	6 (13.6)
Alefacept (Amevive; LFA 3TIP) (n=27)	16 (59.3)	4 (14.8)	2 (7.4)
CNTO 275 (Ustekinumab; Stelara) (n=8)	2 (25.0)	1 (12.5)	0 (0)
Efalizumab (Raptiva; Anti-CD11a) (n=23)	13 (56.5)	7 (30.4)	3 (13.0)
Etanercept (Enbrel) (n=3)	2 (66.7)	1 (33.3)	1 (33.3)
Infliximab (Remicade) (n=16)	7 (43.8)	5 (31.3)	4 (25.0)
Onercept (r-hTBP-1) (n=4)	1 (25.0)	1 (25.0)	1 (25.0)
Peptide T (n=12)	3 (25.0)	1 (8.3)	1 (8.3)
Total	69 (50.4)	30 (21.9)	18 (13.1)
Biologic Class (n=137)	**PASI Outcome**		
	PASI-50	**PASI-75**	**PASI-90**
	n (%)	**n (%)**	**n (%)**
T-cell Inhibitors (n=50)	29 (58.0)	11 (22.0)	5 (10.0)
TNF-α Inhibitors (n=67)	35 (52.2)	17 (25.4)	12 (17.9)
Interleukin 12/23 Blockaders (n=8)	2 (25.0)	1 (12.5)	0 (0)
Peptide T (n=12)	3 (25.0)	1 (8.3)	1 (8.3)
Total	69 (50.4)	30 (21.9)	18 (13.1)

4.2 Non-Biologic Patients (n=852)

4.2.1 Linkage Results

Table 18 presents data availability for the Non-Biologic Psoriasis Database. This database contained 852 records with sex and age available for 100% of the records and disease severity for 85.4%. Age of onset and genotype were missing a large proportion of data.

Table 18 Data availability, Non-Biologic Psoriasis Database

Variable	Missing values n (%)	Valid values n (%)
Sex	0 (0)	852 (100.0)
Age	0 (0)	852 (100.0)
Disease Severity	124 (14.6)	728 (85.4)
Age of Onset	310 (36.4)	542 (63.6)
Genotype	648 (76.1)	204 (23.9)

4.2.2 Distribution of Non-Biologic Patients

Demographic and clinical characteristics of psoriasis patients in the Non-Biologic Psoriasis Database are presented in Table 19. The sex distribution included 405 males and 447 females (47.5% and 52.5%, respectively). Mean (±SD) age as of January 1, 2010 was 52.9±17.2 years. No significant difference was found between mean age for males (53.7±16.3 years) and females (52.1±18.0) years). For the sub-sample of patients for which information on the severity of disease was available (n=728), about half were identified as having mild psoriasis (49.5%) and (50.5%) were moderate/severe psoriasis. No association was found between severity of disease and sex. Of the 542 patients whose information on age of onset was available, just over half (52.6%) had an early age of

onset (type 1 or ≤ 25 years). Early-onset psoriasis among the non-biologic psoriasis patients was more common in females (58.9%) compared to males (46.1%). Likewise, late-onset psoriasis was more common in males (53.9%) compared to females (41.1%). Thus, a significant association was found between age of onset of psoriasis and sex ($p<0.05$). Of the 99 psoriasis patients who were HLA-Cw6 genotype-tested, 56.9% tested positive for the gene. No association was found between genotype and sex. With respect to age distribution, the majority of patients (71.7%) were between the age of 25 and 64; 24.3% were 65 years or older and 4.0% were less than 25 years of age. Within each age group, the distribution of females and males was consistent, with females accounting for a slightly higher proportion per group. No association was found between age group and sex.

Table 19 Demographic and clinical characteristics of non-biologic patients, Non-Biologic Psoriasis Database

Characteristic		Male (n=405) n (%)	Female (n=447) n (%)	Total (n=852) n (%)	p-value
Mean Age (± SD) (n=852)		53.7 (16.3)	52.1 (18.0)	52.9 (17.2)	p=0.17[a]
Severity (n=728)	Mild	167 (47.9)	193 (50.9)	360 (49.5)	p=0.45[b]
	Moderate/Severe	182 (52.1)	186 (49.1)	368 (50.5)	
Age of Onset (n=542)	≤ 25 years	123 (46.1)	162 (58.9)	285 (52.6)	p=0.04*[b]
	> 25 years	144 (53.9)	113 (41.1)	257 (47.4)	
Genotype (n=204)	Positive	54 (54.5)	62 (59.0)	116 (56.9)	p=0.61[b]
	Negative	45 (45.5)	43 (41.0)	88 (43.1)	
Age Group (n=852)	< 25 years	14 (3.5)	20 (4.5)	34 (4.0)	p=0.61[b]
	25-64 years	296 (73.1)	315 (70.5)	611 (71.7)	
	≥ 65 years	95 (23.5)	112 (25.1)	207 (24.3)	

*$p<0.05$

[a] p-value determined using independent samples t-test

[b] p-value determined using chi-square test for independence

4.3 Logistic Regression

Table 20 presents the results of the multivariate logistic regression analyses that were used to investigate the effects of the independent variables on odds ratios (ORs) (and respective 95% confidence intervals [CIs]) for having a particular comorbidity or not. The results of the regression analysis show that whether or not a patient is receiving biologic treatment does not affect the occurrence of 'mental disorder', 'neoplasm', 'digestive system disease' or 'circulatory system disease' diagnosis. However, the odds of having a 'skin and sub-cutaneous disorder' diagnosis was found to be 10 times greater if the psoriasis patient is taking biologics versus not taking biologics ($p<0.05$), with a wide associated confidence interval.

Table 20 Adjusted odds rations for specified comorbid conditions

Variable	Receiving Biologic Treatment vs. not Receiving Biologic Treatment	
	OR[1] (95% CI)	p-value
Mental Disorder	1.32 (0.87-2.01)	0.19
Skin and Sub-Cutaneous Disorder	10.49 (1.41-78.18)	0.02*
Neoplasm	1.07 (0.67-1.69)	0.78
Digestive System Disease	0.97 (0.63-1.49)	0.88
Circulatory System Disease	1.53 (0.96-2.43)	0.07

* $p<0.05$

[1] controlled for age, sex, severity and age of onset

4.4 Linear Regression

Table 21 presents the results of a linear regression analysis that was used to investigate the effect of biologic status on the CCI score. The results show that whether or not a patient is receiving biologic treatment does not make a significant unique contribution to the prediction of CCI ($p>0.05$). However, sex and age do make a significant unique

contribution to the prediction of CCI ($p<0.05$): that is, being a female increases CCI score by 0.08 units, while every year of age increases CCI score by 0.5 units. In terms of the model fit, the R Square value indicates that the linear regression model explains 24.9% of the variance in CCI score. This model does reach statistical significance ($p<0.05$) according to the ANOVA summary below.

Table 21 Charlson Comorbidity Index (CCI) score prediction via linear regression

Variable	β Value	p-value
Constant	--	--
Biologic Status	.05	0.21
Sex	0.08	0.02*
Age	0.53	0.00*
Severity	-0.01	0.73
Age of Onset	-0.06	0.17

* $p<0.05$

Model Summary

Mode	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	0.505[a]	0.255	0.249	1.77648

[a] Predictors: (Constant), Age of Onset (Grouped), Severity, Sex, Biologic Status, Age

ANOVA[b]

Model	Sum of Squares	df	Mean Square	F	Sig.
Regression	695.587	5	139.117	44.082	.000[a]
Residual	2035.541	645	3.156		
Total	2731.127	650			

[a] Predictors: (Constant), Age of Onset (Grouped), Severity, Sex, Biologic Status, Age
[b] Dependent Variable: Charlson Comorbidity Index Score

CHAPTER 5: DISCUSSION

This chapter begins with a discussion of the main findings in relation to each objective, followed by a discussion of the study strengths and limitations. As this study was the first of its kind in some domains (i.e., describing biologic type and class by demographic and prognostic factors), the results will be discussed in relation to the literature where possible.

5.1 Discussion of Findings

Objective #1: To describe the distribution of psoriasis patients by biologic treatment type, demographic factors and the prognostic factors disease severity, age of onset and genotype status.

The distribution of biologic treatment type showed that adalimumab was the most common biologic among the 245 study patients, accounting for 25.3%, while onercept was the least common biologic, accounting for 2.4%. Biologic patients were analyzed according to sex, age, severity of disease, age of onset, and genotype status. No significant associations were found between mean age for males and females, between severity of disease and sex, between age of onset and sex nor between genotype and sex, according to chi-square tests of independence. In a similar cross-sectional study[60], researchers found no significant association between genotype and sex, but did find significant associations between mean age and sex, as well as between age of onset and sex. This discrepancy in findings can be explained by the fact that the current study had a sample size of 284 psoriasis patients (all of whom received biologic treatment), while the

Gulliver et. al. study had a sample of 3,226 psoriasis patients (whose treatment regimens varied). However, mean patient age was quite similar between the current study and the Gulliver et. al. study (48.6 years and 49.5 years, respectively).

Objective #2: To describe health service utilization (hospital and physician visits) of biologic patients by treatment type (between 1995/96 and 2007/08).

The results of this study showed that patients taking Peptide T had a higher mean number of hospitalizations that any other biologic type, although this was not statistically significant. As Peptide T also serves as its own biologic class, it also had a higher mean number of hospitalizations across biologic class. Peptide T patients also had a higher mean number of physician visits than any other biologic type or class. Peptide T has been shown to clear psoriasis lesions in clinical trials and is well-tolerated[103]. Examination of the most common comorbidities associated with health care utilization reveals that patients in the Peptide T group frequently presented with skin and sub-cutaneous disease, musculoskeletal system/connective tissue disease and/or nervous system/sense organs disease. It is possible that the presence of several comorbidities among each patient leads to more frequent health service utilization. This has been shown in previous literature; for example, health service utilization was shown to be increased in a sample of depressed patients who had other comorbidities as compared to depressed patients without reported concomitant diseases[120]. In a recent population-based study set in Newfoundland and Labrador, having two or more chronic conditions was associated with increased hospitalization compared to having no chronic illness, while having two chronic illnesses was associated with increased fee-for-service physician utilization relative to having no

chronic illness[121]. Likewise, a person's health care expenses (and therefore, utilization) have been shown to increase rapidly with increasing number of chronic conditions[122].

Objective #3: To describe the distribution of comorbidities among psoriasis biologic patients by biologic treatment type, demographic factors and the prognostic factors disease severity, age of onset and genotype status.

'Skin and sub-cutaneous disease' was the most common diagnosis at the ICD chapter level found across all biologic classes, followed by 'respiratory system disease', 'nervous system/sense organs disease' and 'musculoskeletal system/connective tissue disease'. With the exception of 'skin and sub-cutaneous diseases', this differed from the leading disorders found among psoriasis patients by Gulliver et. al.[60] Likewise, in a recent case-control study[113], psoriasis patients were found to have a higher risk of inflammatory arthritis, coronary heart disease, obesity, type 2 diabetes mellitus, hypertension, dyslipidemia and metabolic syndrome than the age and sex matched controls that did not have psoriasis. Given that these studies did not focus on psoriasis patients receiving biologic treatment, this might explain the discrepancies in the most common comorbidities found in these studies and the present study. Also interesting is that the risk of malignancy in biologic patients has been well-documented[53, 98, 114], however neoplasm was not one of the most common comorbidities found in the present study among biologic patients. In fact, the logistic regression neoplasm model further found that whether or not a patient received biologic treatment did not affect the occurrence of having a neoplasm.

Among biologic patients, females were found to have a higher mean number of comorbidities compared to males, as well as a higher mean CCI score. This finding is not unexpected as previous research has consistently found that, in general, women use outpatient medical services more frequently than men[112, 123], and perhaps because of this, women have higher rates of morbidity than men[111]. Previous research has also found that women have a tendency to report more symptoms because they tend to be more interested and have more knowledge about health than men and, as such, may be more likely to discuss symptoms and seek help[124]. Thus, different comorbidity and treatment monitoring may be necessary for males and females.

Although intuitively one might suspect mild psoriasis patients would have a lower mean number of comorbidities than moderate/severe patients, this study showed no significant difference in the mean number of comorbidities across disease severity, age of onset or genotype status. It appears mild psoriasis patients are as likely to develop other comorbid conditions as moderate/severe psoriasis patients in the current study. This is, in fact, supported by the literature, which states that psoriasis patients, irrespective of severity type, have been shown to have a higher rate of comorbidities compared to patients without psoriasis[45].

The present study showed that 95.1% of biologic patients had a "comorbidity" within the ICD chapter level of 'skin and sub-cutaneous disease'. This number should actually be 100%, as all patients included in this analysis have psoriasis. The fact that 4.9% of

NewLab's known psoriasis biologic patients are not coded within 'skin and sub-cutaneous disease' is puzzling. However, it is possible that these patients actually have very mild psoriasis and were also visiting NewLab with an inflammatory condition other than psoriasis (such as rheumatoid arthritis or ankylosing spondylitis) that required biologic use, i.e., psoriasis was not their "main diagnosis". If such was the case, they would likely get captured in either fee-for-service physician claims or hospitalization data with their "main diagnosis" (not psoriasis). Alternatively, some of NewLab's patients are research clinic (clinical trial) patients who are never billed through MCP. If such patients fare well on clinical trials and have no reason to see another doctor or visit the hospital, they will not show up under 'skin and sub-cutaneous disorder' unless they actually have another skin/sub-cutaneous condition (such as eczema, acne, etc.)

Objective #4: To determine the risk of developing specified comorbid conditions based on treatment type received (i.e., biologic versus non-biologic).

Of the five conditions assessed through logistic regression modeling, 'skin and sub-cutaneous disorder' was the only condition at the ICD Chapter level found to be significantly associated with biologic status; that is, in our study, a patient receiving biologics was more likely to have a 'skin and sub-cutaneous disorder' diagnosis than a patient not receiving biologics. As previously discussed, psoriasis falls under the category 'skin and sub-cutaneous disorder' as well as other skin and sub-cutaneous conditions. Therefore, it makes sense that the majority of psoriasis patients (biologic and non-biologic patients), by default, would be captured in the administrative health databases as having a 'skin and sub-cutaneous disorder' diagnosis. In future research, it would be

beneficial to remove psoriasis diagnoses from the ICD Chapter 'skin and cub-cutaneous disorder', so that only other skin conditions (like eczema, dermatitis, etc.), or true comorbid conditions, are being considered.

The fact that biologic patients are 10 times more likely than non-biologic patients to have a 'skin and sub-cutaneous disorder' diagnosis intuitively makes sense. As biologic therapy is a relatively new form of treatment, it seems appropriate that those patients who are taking biologics will present more often to the hospital/physician related to psoriasis. Follow-up is required once a patient begins biologic treatment, as well as prior to commencing biologic treatment. There are also many side effects associated with biologic treatment; perhaps the biologic patients were making more frequent visits to discuss side effects. In addition, some psoriasis patients, including non-biologic patients, would have received a diagnosis prior to 1995/96, the earliest year for which fee-for-service-physician data and hospitalization data is available. Such patients may have their psoriasis under control and, in recent years, have not been presenting to a fee-for-service physician and/or hospital related to psoriasis. Further, fee-for-service physicians in Newfoundland and Labrador are only permitted to code one reason for a patient visit, thus if such non-biologic patients present with flu, for example, this will be the diagnosis coded for that visit, even though there may be discussions related to 'psoriasis'. As such, there would be less of an opportunity to capture a 'skin and sub-cutaneous disorder' diagnosis among non-biologic patients compared to their biologic counterparts.

Objective #5: To examine whether or not biologic treatment is associated with a higher Charlson Comorbidity Index (CCI) score.

The linear regression model assessed whether or not taking biologics might predict a patient's CCI, with the hypothesis being that biologic patients may see a higher CCI score as compared to non-biologic patients. This rationale stems from the idea that the majority of biologic patients are also classified as moderate/severe. These patients (more-so than those classified as mild) may have a tendency to develop more comorbid conditions. However, the model indicated that whether or not a psoriasis patient received biologics did not significantly contribute to the prediction of CCI score. This discrepancy in hypothesis versus results may be explained by the fact that biologics are a relatively new class of drugs; biologic patients have not had as much of an "opportunity" as non-biologic patients to develop comorbidities. The linear regression model did, however, show that sex and age make a significant contribution to CCI prediction.

5.2 Strengths

There are several strengths associated with this study. First and foremost, the study contributes to the literature, as very little research has been previously undertaken/published with respect to the objectives of this study. For example, biologic and non-biologic patients were compared across many demographic and prognostic factors and comorbidities among specific biologic types and classes were investigated. Regression analyses were carried out to determine whether or not biologic status among psoriasis patients has an effect on development of certain comorbidities as well as to determine whether or not the use of biologics might predict a patient's CCI score.

Another strength is the fact that this study used existing data (i.e., administrative health databases such as CDMS and the NL Fee-for-Service (MCP) Physician Claims Database). Although the use of secondary data presents many challenges, it effectively eliminates researchers from having to design and conduct studies to enable data collection that would otherwise be quite labor-intensive.

5.3 Limitations

A number of limitations with respect to this study have been identified. One such limitation is the fact that the NewLab Psoriasis Clinical Database and the NewLab Biologic Treatment Database did not include all psoriasis patients in the province. Patient records for this study were from one private dermatology clinic in St. John's (NewLab Clinical Research Inc.) and thus results of the study cannot be generalized to the Newfoundland and Labrador population. As well, the use of previously collected data (i.e., administrative health databases) can be considered a limitation, as this type of data has been collected for purposes other than research and so the researcher has little to no control over data quality. With respect to hospitalization data, the coding classification system in the hospital separation database changed from ICD-9 to ICD-10 in April 2001. This presented challenges in describing/classifying the hospital utilization over time, given there is not a direct relationship between the two coding schemes. Another limitation is that approximately two-thirds of the province's physicians (general practitioners and specialists) are paid on a fee-for-service basis while the remainder are paid on a salary basis. Data on visits to salaried physicians are not captured, as salaried physicians are not required to submit medical claims for billing purposes. It is anticipated

that the majority of psoriasis patients are from the St. John's region because the clinic is in St. John's (i.e., a region with a high proportion of fee-for-service physicians [~85%][117]), however results related to fee-for-service physician visits should be carefully interpreted. In addition, records removed due to unavailable or missing data may have resulted in bias due to non-linkages, causing under-estimation.

The present study is also limited by its study design. A cross-sectional, descriptive design essentially takes a snapshot of a population at any given time; thus, temporal impacts are not considered. A conclusion that respiratory disease was one of the most common comorbidities found across all biologic classes must be interpreted with caution. It does not necessarily mean that the respiratory condition developed after taking biologic treatment, as the respiratory condition may have existed before biologic treatment began. A retrospective cohort design, in which biologic patients could be retrospectively followed, would be a stronger study design, but problems might still be encountered as currently there is a limited number of years of biologic treatment data available, as well as extensive missing data for start and end dates of biologic treatment. Also, because biologics are a relatively new class of drugs, patients receiving them have actually had less time to develop comorbidities compared to non-biologic patients who may have begun, for example, phototherapy treatment fifteen years ago. A biologic patient may have only begun treatment in 2005, for example, which affords them only a three-year window to develop a comorbid condition, many of which have long latency periods. It is therefore more likely that a psoriasis patient in the non-biologic database will present to a hospital/physician with more comorbidities than those patients in the biologic database.

This limitation is obvious when considering the logistic regression analyses, as these regressions attempt to explain the odds of developing a comorbid condition based on whether or not a patient is receiving biologic treatment. If non-biologic patients have an increased chance of developing comorbidities over biologic patients simply because of latency/timing, this bias will factor into the regressions. Analyses of these sort should be re-examined as more years of data become available for biologic patients.

The regression analyses included those biologic cases where comorbidities developed both before and after the start date of the biologic. Ideally, only those patients whose comorbidities developed after the start date of biologic treatment should have been included. However, very few cases exist in the current NewLab Biologic Treatment Database. As well, the issue of missing data becomes critical when performing this type of analysis. As previously noted, genotype status, a confounding factor to control for in the model, could not feasibly be included because of extensive missing data. In fact, the regression analyses can only be performed on those cases who have available data for all variables included in the regression (age, severity, sex, age of onset). The number of cases where data was available for all variables was quite small. Due to this large proportion of missing data, the regressions included only 55.2% of the regression sample, further heightening the possibility of bias.

Finally, there are gaps in the hospital and physician data for individuals whose onset of psoriasis came prior to the earliest years of hospital and physician data (1995/96). Comorbidities that developed or existed during that time frame are not known. For

example, hospital and physician data for a psoriasis patient who was diagnosed in 1989 is not known for the years 1989 – 1994.

CHAPTER 6: SUMMARY, RECOMMENDATIONS AND CONCLUSIONS

This chapter presents a summary of the study, followed by recommendations for future research and final conclusions.

6.1 Summary

This cross-sectional study focused on psoriasis (a chronic and currently incurable skin disease) treatments, in particular biologic treatment. Medical records of confirmed psoriasis patients who received biologic treatment were linked to other clinical and administrative data sources in Newfoundland and Labrador. This study assessed differences among biologic classes and types in terms of demographic factors, prognostic factors, numbers of comorbidities, presentations to hospitals and physicians, CCI scores and PASI scores, all of which have not been previously published in the literature, and have produced interesting findings.

Findings suggest that the majority of patients receiving biologic treatment had moderate/severe psoriasis rather than mild. Also, 'symptoms, signs and ill-defined conditions', 'skin and sub-cutaneous disease', 'respiratory system disease', 'nervous system/sense organs disease' and 'musculoskeletal system/connective tissue disease' were some of the most common comorbidities found across all biologic classes. Among biologic patients, 63.7% had at least one unique hospital separation, and 96.3% had at least one physician visit between 1995/96 and 2007/08. Female biologic patients had a higher number of mean comorbidities and a higher mean Charlson Comorbidity Index

score compared to males. Of the biologic patients whose before and after Psoriasis Area and Severity Index (PASI) scores were available, approximately half (50.4%) achieved PASI-50, while 21.9% achieved PASI-75 and 13.1% achieved PASI-90. Although the finding that biologic treatment is associated with neoplasm was not supported by this study, several other comorbid conditions were found to be associated with biologic treatment including 'skin and sub-cutaneous disease', 'respiratory system disease', 'nervous system/sense organs disease' and 'musculoskeletal system/connective tissue disease'. After controlling for confounding variables, the odds of having a 'skin and sub-cutaneous disorder' was found to be ten times greater if the psoriasis patient was taking biologics versus not taking biologics; however, this finding should be interpreted with caution. Age and sex were shown to significantly contribute to prediction of the Charlson Comorbidity Index.

6.2 Recommendations

Given the limiting factors inherent in the study design, as well as missing data for certain variables and years, a stronger study design would be preferable (e.g., retrospective cohort). As more biologic data becomes available, future studies with stronger designs can be conducted to help gain a better understanding of which comorbidities are associated with which particular biologic types and classes.

6.3 Conclusions

Further investigation is required. However, findings of this study can assist in better understanding the distribution of psoriasis patients taking biologics with respect to a

number of demographic and prognostic factors in a cohort of the Newfoundland and Labrador population, and be the basis from which further investigation can be undertaken.

REFERENCES

1. [Internet]Toronto, ON: Jansseen-Ortho Inc. [cited 2011 08/23]. Available from: http://www.livingwellwithpsoriasis.com.

2. Feldman S. Advances in psoriasis treatment. Dermatol Online J 2000 Sep;6(1):4.

3. Langham S, Langham J, Goertz HP, Ratcliffe M. Large-scale, prospective, observational studies in patients with psoriasis and psoriatic arthritis: A systematic and critical review. BMC Med Res Methodol 2011 Mar 31;11:32.

4. Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. Lancet 2007 Jul 21;370(9583):263-71.

5. Torpy JM, Burke AE, Golub RM. JAMA patient page. psoriasis. JAMA 2011 Aug 24;306(8):896.

6. Gottlieb AB, Kardos M, Yee M. Current biologic treatments for psoriasis. Dermatol Nurs 2009 Sep-Oct;21(5):259,66, 272; quiz 267.

7. About Psoriasis - Statistics [Internet] [cited 2011 August 9]. Available from: http://www.psoriasis.org/netcommunity/learn_statistics.

8. Conway P, Currie CJ. Descriptive epidemiology of hospitalisation for psoriasis. Curr Med Res Opin 2008 Dec;24(12):3487-91.

9. Gelfand JM, Troxel AB, Lewis JD, Kurd SK, Shin DB, Wang X, Margolis DJ, Strom BL. The risk of mortality in patients with psoriasis: Results from a population-based study. Arch Dermatol 2007 Dec;143(12):1493-9.

10. Gulliver W. Long-term prognosis in patients with psoriasis. Br J Dermatol 2008 Aug;159 Suppl 2:2-9.

11. Menter A, Tyring SK, Gordon K, Kimball AB, Leonardi CL, Langley RG, Strober BE, Kaul M, Gu Y, Okun M, et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. J Am Acad Dermatol 2008 Jan;58(1):106-15.

12. Kurd SK, Smith N, VanVoorhees A, Troxel AB, Badmaev V, Seykora JT, Gelfand JM. Oral curcumin in the treatment of moderate to severe psoriasis vulgaris: A prospective clinical trial. J Am Acad Dermatol 2008 Apr;58(4):625-31.

13. Reich K, Sinclair R, Roberts G, Griffiths CE, Tabberer M, Barker J. Comparative effects of biological therapies on the severity of skin symptoms and health-related quality of life in patients with plaque-type psoriasis: A meta-analysis. Curr Med Res Opin 2008 May;24(5):1237-54.

14. Menter A, Griffiths CE. Current and future management of psoriasis. Lancet 2007 Jul 21;370(9583):272-84.

15. Sabat R, Philipp S, Hoflich C, Kreutzer S, Wallace E, Asadullah K, Volk HD, Sterry W, Wolk K. Immunopathogenesis of psoriasis. Exp Dermatol 2007 Oct;16(10):779-98.

16. Balkrishnan R. The importance of medication adherence in improving chronic-disease related outcomes: What we know and what we need to further know. Med Care 2005 Jun;43(6):517-20.

17. Ferrandiz C, Carrascosa JM, Boada A. A new era in the management of psoriasis? the biologics: Facts and controversies. Clin Dermatol 2010 Jan-Feb;28(1):81-7.

18. Alwawi EA, Krulig E, Gordon KB. Long-term efficacy of biologics in the treatment of psoriasis: What do we really know? Dermatol Ther 2009 Sep-Oct;22(5):431-40.

19. Weger W. Current status and new developments in the treatment of psoriasis and psoriatic arthritis with biological agents. Br J Pharmacol 2010 Jun;160(4):810-20.

20. Bhosle MJ, Feldman SR, Camacho FT, Timothy Whitmire J, Nahata MC, Balkrishnan R. Medication adherence and health care costs associated with biologics in medicaid-enrolled patients with psoriasis. J Dermatolog Treat 2006;17(5):294-301.

21. Naldi L. Malignancy concerns with psoriasis treatments using phototherapy, methotrexate, cyclosporin, and biologics: Facts and controversies. Clin Dermatol 2010 Jan-Feb;28(1):88-92.

22. Rozenblit M, Lebwohl M. New biologics for psoriasis and psoriatic arthritis. Dermatol Ther 2009 Jan-Feb;22(1):56-60.

23. Patel RV, Clark LN, Lebwohl M, Weinberg JM. Treatments for psoriasis and the risk of malignancy. J Am Acad Dermatol 2009 Jun;60(6):1001-17.

24. Nall L, Gulliver W, Charmley P, Farber EM. Search for the psoriasis susceptibility gene: The newfoundland study. Cutis 1999 Nov;64(5):323-9.

25. Canadian Psoraisis Guidelines Committee. Canadian guidelines for the management of plaque psoriasis. 1st edition. .

26. MEENAN FO. A note on the history of psoriasis. Ir J Med Sci 1955 Mar;(351)(351):141-2.

27. Driessen RJ, van de Kerkhof PC, de Jong EM. Etanercept combined with methotrexate for high-need psoriasis. Br J Dermatol 2008 Aug;159(2):460-3.

28. Stern RS, Nijsten T, Feldman SR, Margolis DJ, Rolstad T. Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. J Investig Dermatol Symp Proc 2004 Mar;9(2):136-9.

29. Nevitt GJ, Hutchinson PE. Psoriasis in the community: Prevalence, severity and patients' beliefs and attitudes towards the disease. Br J Dermatol 1996 Oct;135(4):533-7.

30. Langley RG, Krueger GG, Griffiths CE. Psoriasis: Epidemiology, clinical features, and quality of life. Ann Rheum Dis 2005 Mar;64 Suppl 2:ii18,23; discussion ii24-5.

31. Poulin Y, Papp KA, Carey W, Gulliver W, Gupta AK. A favourable benefit/risk ratio with efalizumab: A review of the clinical evidence. J Cutan Med Surg 2006;9 Suppl 1:10-7.

32. Crown WH, Bresnahan BW, Orsini LS, Kennedy S, Leonardi C. The burden of illness associated with psoriasis: Cost of treatment with systemic therapy and phototherapy in the US. Curr Med Res Opin 2004 Dec;20(12):1929-36.

33. Gelfand JM, Feldman SR, Stern RS, Thomas J, Rolstad T, Margolis DJ. Determinants of quality of life in patients with psoriasis: A study from the US population. J Am Acad Dermatol 2004 Nov;51(5):704-8.

34. Pariser DM, Bagel J, Gelfand JM, Korman NJ, Ritchlin CT, Strober BE, Van Voorhees AS, Young M, Rittenberg S, Lebwohl MG, et al. National psoriasis foundation clinical consensus on disease severity. Arch Dermatol 2007 Feb;143(2):239-42.

35. Schoffski O, Augustin M, Prinz J, Rauner K, Schubert E, Sohn S, Reich K. Costs and quality of life in patients with moderate to severe plaque-type psoriasis in germany: A multi-center study. J Dtsch Dermatol Ges 2007 Mar;5(3):209-18.

36. Wahl A, Loge JH, Wiklund I, Hanestad BR. The burden of psoriasis: A study concerning health-related quality of life among norwegian adult patients with psoriasis compared with general population norms. J Am Acad Dermatol 2000 Nov;43(5 Pt 1):803-8.

37. Brauchli YB, Jick SS, Miret M, Meier CR. Psoriasis and risk of incident cancer: An inception cohort study with a nested case-control analysis. J Invest Dermatol 2009 Nov;129(11):2604-12.

38. Kincaid L. Psoriasis: TNF-alpha inhibitors and beyond. Drug Discov Today 2005 Jul 1;10(13):884-6.

39. de Korte J, Sprangers MA, Mombers FM, Bos JD. Quality of life in patients with psoriasis: A systematic literature review. J Investig Dermatol Symp Proc 2004 Mar;9(2):140-7.

40. Nelson A, Pearce D, Fleisher AJ, Balkrishnan R, Feldman S. Infliximab for inpatient psoriasis management - is there a role? The Journal of Dermatological Treatment 2005;16(5-6):314.

41. Mukhtar R, Choi J, Koo JY. Quality-of-life issues in psoriasis. Dermatol Clin 2004 Oct;22(4):389,95, viii.

42. Lin HC, Lucas PT, Feldman SR, Balkrishnan R. Medication use and associated health care outcomes and costs for patients with psoriasis in the united states. J Dermatolog Treat 2011 Jan 22.

43. Vena GA, Vestita M, Cassano N. Can early treatment with biologicals modify the natural history of comorbidities? Dermatol Ther 2010 Mar-Apr;23(2):181-93.

44. Christophers E. Comorbidities in psoriasis. Clin Dermatol 2007 Nov-Dec;25(6):529-34.

45. Patel V, Horn EJ, Lobosco SJ, Fox KM, Stevens SR, Lebwohl M. Psoriasis treatment patterns: Results of a cross-sectional survey of dermatologists. J Am Acad Dermatol 2008 Jun;58(6):964-9.

46. Hemminki K, Li X, Sundquist J, Sundquist K. Familial associations of rheumatoid arthritis with autoimmune diseases and related conditions. Arthritis Rheum 2009 Mar;60(3):661-8.

47. Henseler T, Christophers E. Disease concomitance in psoriasis. J Am Acad Dermatol 1995 Jun;32(6):982-6.

48. Cohen AD, Dreiher J, Shapiro Y, Vidavsky L, Vardy DA, Davidovici B, Meyerovitch J. Psoriasis and diabetes: A population-based cross-sectional study. J Eur Acad Dermatol Venereol 2008 May;22(5):585-9.

49. Pearce DJ, Morrison AE, Higgins KB, Crane MM, Balkrishnan R, Fleischer AB,Jr, Feldman SR. The comorbid state of psoriasis patients in a university dermatology practice. J Dermatolog Treat 2005;16(5-6):319-23.

50. Shapiro J, Cohen AD, David M, Hodak E, Chodik G, Viner A, Kremer E, Heymann A. The association between psoriasis, diabetes mellitus, and atherosclerosis in israel: A case-control study. J Am Acad Dermatol 2007 Apr;56(4):629-34.

51. Sommer DM, Jenisch S, Suchan M, Christophers E, Weichenthal M. Increased prevalence of the metabolic syndrome in patients with moderate to severe psoriasis. Arch Dermatol Res 2006 Dec;298(7):321-8.

52. Mallbris L, Akre O, Granath F, Yin L, Lindelof B, Ekbom A, Stahle-Backdahl M. Increased risk for cardiovascular mortality in psoriasis inpatients but not in outpatients. Eur J Epidemiol 2004;19(3):225-30.

53. Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. J Am Acad Dermatol 2006 Nov;55(5):829-35.

54. Christophers E, Griffiths CE, Gaitanis G, van de Kerkhof P. The unmet treatment need for moderate to severe psoriasis: Results of a survey and chart review. J Eur Acad Dermatol Venereol 2006 Sep;20(8):921-5.

55. Bernstein CN, Wajda A, Blanchard JF. The clustering of other chronic inflammatory diseases in inflammatory bowel disease: A population-based study. Gastroenterology 2005 Sep;129(3):827-36.

56. Dreiher J, Weitzman D, Shapiro J, Davidovici B, Cohen AD. Psoriasis and chronic obstructive pulmonary disease: A case-control study. Br J Dermatol 2008 Sep;159(4):956-60.

57. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. JAMA 2006 Oct 11;296(14):1735-41.

58. Boffetta P, Gridley G, Lindelof B. Cancer risk in a population-based cohort of patients hospitalized for psoriasis in sweden. J Invest Dermatol 2001 Dec;117(6):1531-7.

59. Gelfand JM, Berlin J, Van Voorhees A, Margolis DJ. Lymphoma rates are low but increased in patients with psoriasis: Results from a population-based cohort study in the united kingdom. Arch Dermatol 2003 Nov;139(11):1425-9.

60. Gulliver WP, Macdonald D, Gladney N, Alaghehbandan R, Rahman P, Adam Baker K. Long-term prognosis and comorbidities associated with psoriasis in the Newfoundland and Labrador founder population. J Cutan Med Surg 2011 Jan-Feb;15(1):37-47.

61. Reich K, Nestle FO, Papp K, Ortonne JP, Evans R, Guzzo C, Li S, Dooley LT, Griffiths CE, EXPRESS study investigators. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: A phase III, multicentre, double-blind trial. Lancet 2005 Oct 15-21;366(9494):1367-74.

62. Schon MP, Boehncke WH. Psoriasis. N Engl J Med 2005 May 5;352(18):1899-912.

63. Mallon E, Bunce M, Wojnarowska F, Welsh K. HLA-CW*0602 is a susceptibility factor in type I psoriasis, and evidence ala-73 is increased in male type I psoriatics. J Invest Dermatol 1997 Aug;109(2):183-6.

64. Henseler T, Christophers E. Psoriasis of early and late onset: Characterization of two types of psoriasis vulgaris. J Am Acad Dermatol 1985 Sep;13(3):450-6.

65. Gottlieb AB, Dann F, Menter A. Psoriasis and the metabolic syndrome. J Drugs Dermatol 2008 Jun;7(6):563-72.

66. Vena GA, Vestita M, Cassano N. Can early treatment with biologicals modify the natural history of comorbidities? Dermatol Ther 2010 Mar-Apr;23(2):181-93.

67. Victor FC, Gottlieb AB, Menter A. Changing paradigms in dermatology: Tumor necrosis factor alpha (TNF-alpha) blockade in psoriasis and psoriatic arthritis. Clin Dermatol 2003 Sep-Oct;21(5):392-7.

68. Nickoloff BJ, Bonish BK, Marble DJ, Schriedel KA, DiPietro LA, Gordon KB, Lingen MW. Lessons learned from psoriatic plaques concerning mechanisms of tissue repair, remodeling, and inflammation. J Investig Dermatol Symp Proc 2006 Sep;11(1):16-29.

69. Davidovici BB, Sattar N, Prinz JC, Puig L, Emery P, Barker JN, van de Kerkhof P, Stahle M, Nestle FO, Girolomoni G, et al. Psoriasis and systemic inflammatory diseases: Potential mechanistic links between skin disease and co-morbid conditions. J Invest Dermatol 2010 Jul;130(7):1785-96.

70. Gisondi P, Girolomoni G. Psoriasis and atherothrombotic diseases: Disease-specific and non-disease-specific risk factors. Semin Thromb Hemost 2009 Apr;35(3):313-24.

71. Strober B, Teller C, Yamauchi P, Miller JL, Hooper M, Yang YC, Dann F. Effects of etanercept on C-reactive protein levels in psoriasis and psoriatic arthritis. Br J Dermatol 2008 Aug;159(2):322-30.

72. Sattar N, Crompton P, Cherry L, Kane D, Lowe G, McInnes IB. Effects of tumor necrosis factor blockade on cardiovascular risk factors in psoriatic arthritis: A double-blind, placebo-controlled study. Arthritis Rheum 2007 Mar;56(3):831-9.

73. Paolo Boffetta, Gloria Gridley, Bernt Lindelof. Cancer risk in a population-based cohort of patients hospitalized for psoriasis in sweden. The Journal of Investigative Dermatology 2001;117:1531.

74. Robert E. Kalb. Is the PASI system worthwhile and does it correlate with real-life psoriasis improvement? point understanding the value of the PASI system. Skin & Aging: Practical and Clinical Issues for Today's Dermatologist 2006;14(3).

75. Fonia A, Jackson K, Lereun C, Grant DM, Barker JN, Smith CH. A retrospective cohort study of the impact of biologic therapy initiation on medical resource use and costs in patients with moderate to severe psoriasis. Br J Dermatol 2010 Oct;163(4):807-16.

76. Raval K, Lofland JH, Waters H, Piech CT. Disease and treatment burden of psoriasis: Examining the impact of biologics. J Drugs Dermatol 2011 Feb;10(2):189-96.

77. Brimhall AK, King LN, Licciardone JC, Jacobe H, Menter A. Safety and efficacy of alefacept, efalizumab, etanercept and infliximab in treating moderate to severe plaque psoriasis: A meta-analysis of randomized controlled trials. Br J Dermatol 2008 Aug;159(2):274-85.

78. Chamian F, Lin SL, Lee E, Kikuchi T, Gilleaudeau P, Sullivan-Whalen M, Cardinale I, Khatcherian A, Novitskaya I, Wittkowski KM, et al. Alefacept (anti-CD2) causes a selective reduction in circulating effector memory T cells (tem) and relative preservation of central memory T cells (tcm) in psoriasis. J Transl Med 2007 Jun 7;5:27.

79. Ellis CN, Krueger GG, Alefacept Clinical Study Group. Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. N Engl J Med 2001 Jul 26;345(4):248-55.

80. Lebwohl M, Christophers E, Langley R, Ortonne JP, Roberts J, Griffiths CE, Alefacept Clinical Study Group. An international, randomized, double-blind, placebo-controlled phase 3 trial of intramuscular alefacept in patients with chronic plaque psoriasis. Arch Dermatol 2003 Jun;139(6):719-27.

81. Gordon KB, Langley RG, Leonardi C, Toth D, Menter MA, Kang S, Heffernan M, Miller B, Hamlin R, Lim L, et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: Double-blind, randomized controlled trial and open-label extension study. J Am Acad Dermatol 2006 Oct;55(4):598-606.

82. Wellington K, Perry CM. Efalizumab. Am J Clin Dermatol 2005;6(2):113,8: discussion 119-20.

83. Gordon KB, Papp KA, Hamilton TK, Walicke PA, Dummer W, Li N, Bresnahan BW, Menter A, Efalizumab Study Group. Efalizumab for patients with moderate to severe plaque psoriasis: A randomized controlled trial. JAMA 2003 Dec 17;290(23):3073-80.

84. Menter A, Gordon K, Carey W, Hamilton T, Glazer S, Caro I, Li N, Gulliver W. Efficacy and safety observed during 24 weeks of efalizumab therapy in patients with moderate to severe plaque psoriasis. Arch Dermatol 2005 Jan;141(1):31-8.

85. Dubertret L, Sterry W, Bos JD, Chimenti S, Shumack S, Larsen CG, Shear NH, Papp KA, CLEAR Multinational Study Group. CLinical experience acquired with the efalizumab (raptiva) (CLEAR) trial in patients with moderate-to-severe plaque psoriasis: Results from a phase III international randomized, placebo-controlled trial. Br J Dermatol 2006 Jul;155(1):170-81.

86. Gottlieb AB, Hamilton T, Caro I, Kwon P, Compton PG, Leonardi CL, Efalizumab Study Group. Long-term continuous efalizumab therapy in patients with moderate to severe chronic plaque psoriasis: Updated results from an ongoing trial. J Am Acad Dermatol 2006 Apr;54(4 Suppl 1):S154-63.

87. Genentech announces voluntary withdrawal of raptiva from the U.S. market

genentech newsroom: Press releases: News release april 8, 2009: Genentech announces voluntary withdrawal of raptiva from the U.S. market. ; 2009.

88. Warren RB, Griffiths CE. The future of biological therapies. Semin Cutan Med Surg 2010 Mar;29(1):63-6.

89. Patel T, Gordon KB. Adalimumab: Efficacy and safety in psoriasis and rheumatoid arthritis. Dermatol Ther 2004;17(5):427-31.

90. Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne JP, Unnebrink K, Kaul M, Camez A, CHAMPION Study Investigators. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br J Dermatol 2008 Mar;158(3):558-66.

91. Gottlieb AB, Matheson RT, Lowe N, Krueger GG, Kang S, Goffe BS, Gaspari AA, Ling M, Weinstein GD, Nayak A, et al. A randomized trial of etanercept as monotherapy for psoriasis. Arch Dermatol 2003 Dec;139(12):1627,32; discussion 1632.

92. Gordon KB, Gottlieb AB, Leonardi CL, Elewski BE, Wang A, Jahreis A, Zitnik R. Clinical response in psoriasis patients discontinued from and then reinitiated on etanercept therapy. J Dermatolog Treat 2006;17(1):9-17.

93. Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, Gottlieb AB, Etanercept Psoriasis Study Group. Etanercept as monotherapy in patients with psoriasis. N Engl J Med 2003 Nov 20;349(21):2014-22.

94. Papp KA, Tyring S, Lahfa M, Prinz J, Griffiths CE, Nakanishi AM, Zitnik R, van de Kerkhof PC, Melvin L, Etanercept Psoriasis Study Group. A global phase III randomized controlled trial of etanercept in psoriasis: Safety, efficacy, and effect of dose reduction. Br J Dermatol 2005 Jun;152(6):1304-12.

95. Gelfand JM, Kimball AB, Mostow EN, Chiou CF, Patel V, Xia HA, Freundlich B, Stevens SR. Patient-reported outcomes and health-care resource utilization in patients with psoriasis treated with etanercept: Continuous versus interrupted treatment. Value Health 2008 May-Jun;11(3):400-7.

96. Feldman SR, Gordon KB, Bala M, Evans R, Li S, Dooley LT, Guzzo C, Patel K, Menter A, Gottlieb AB. Infliximab treatment results in significant improvement in the quality of life of patients with severe psoriasis: A double-blind placebo-controlled trial. Br J Dermatol 2005 May;152(5):954-60.

97. Menter A, Feldman SR, Weinstein GD, Papp K, Evans R, Guzzo C, Li S, Dooley LT, Arnold C, Gottlieb AB. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. J Am Acad Dermatol 2007 Jan;56(1):31.e1,31.15.

98. Nikas SN, Drosos AA. Onercept. serono. Curr Opin Investig Drugs 2003 Nov;4(11):1369-76.

99. Rutgeerts P, Lemmens L, Van Assche G, Noman M, Borghini-Fuhrer I, Goedkoop R. Treatment of active crohn's disease with onercept (recombinant human soluble p55 tumour necrosis factor receptor): Results of a randomized, open-label, pilot study. Aliment Pharmacol Ther 2003 Jan;17(2):185-92.

100. Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, Guzzo C, Hsu MC, Wang Y, Li S, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results

from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet 2008 May 17;371(9625):1675-84.

101. Krueger GG, Langley RG, Leonardi C, Yeilding N, Guzzo C, Wang Y, Dooley LT, Lebwohl M, CNTO 1275 Psoriasis Study Group. A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. N Engl J Med 2007 Feb 8;356(6):580-92.

102. Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, Li S, Dooley LT, Gordon KB, PHOENIX 1 study investigators. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 2008 May 17;371(9625):1665-74.

103. Griffiths CE, Strober BE, van de Kerkhof P, Ho V, Fidelus-Gort R, Yeilding N, Guzzo C, Xia Y, Zhou B, Li S, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med 2010 Jan 14;362(2):118-28.

104. Marcusson JA, Lazega D, Pert CB, Ruff MR, Sundquist KG, Wetterberg L. Peptide T and psoriasis. Acta Derm Venereol Suppl (Stockh) 1989;146:117-21.

105. Marcusson JA, Wetterberg L. Peptide-T in the treatment of psoriasis and psoriatic arthritis. A case report. Acta Derm Venereol 1989;69(1):86-8.

106. Wetterberg L, Alexius B, Saaf J, Sonnerborg A, Britton S, Pert C. Peptide T in treatment of AIDS. Lancet 1987 Jan 17;1(8525):159.

107. Farber EM, Cohen EN, Trozak DJ, Wilkinson DI. Peptide T improves psoriasis when infused into lesions in nanogram amounts. J Am Acad Dermatol 1991 Oct;25(4):658-64.

108. Raychaudhuri SK, Raychaudhuri SP, Farber EM. Anti-chemotactic activities of peptide-T: A possible mechanism of actions for its therapeutic effects on psoriasis. Int J Immunopharmacol 1998 Nov;20(11):661-7.

109. Schmitt J, Zhang Z, Wozel G, Meurer M, Kirch W. Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis: Meta-analysis of randomized controlled trials. Br J Dermatol 2008 Sep;159(3):513-26.

110. Inzinger M, Heschl B, Weger W, Hofer A, Legat FJ, Gruber-Wackernagel A, Tilz H, Salmhofer W, Quehenberger F, Wolf P. Efficacy of psoralen plus ultraviolet A therapy vs. biologics in moderate to severe chronic plaque psoriasis: Retrospective data analysis of a patient registry. Br J Dermatol 2011 May 12.

111. de Miguel R, el-Azhary R. Efficacy, safety, and cost of goeckerman therapy compared with biologics in the treatment of moderate to severe psoriasis. Int J Dermatol 2009 Jun;48(6):653-8.

112. Leon A, Nguyen A, Letsinger J, Koo J. An attempt to formulate an evidence-based strategy in the management of moderate-to-severe psoriasis: A review of the efficacy and safety of biologics and prebiologic options. Expert Opin Pharmacother 2007 Apr;8(5):617-32.

113. Sanchez-Regana M, Dilme E, Puig L, Bordas X, Carrascosa JM, Ferran M, Herranz P, Garcia-Bustinduy M, Lopez Estebaranz JL, Alsina M, et al. Adverse reactions during biological therapy for psoriasis: Results of a survey of the spanish psoriasis group. Actas Dermosifiliogr 2010 Mar;101(2):156-63.

114. Ryan C, Leonardi CL, Krueger JG, Kimball AB, Strober BE, Gordon KB, Langley RG, de Lemos JA, Daoud Y, Blankenship D, et al. Association between biologic therapies for chronic plaque psoriasis and cardiovascular events: A meta-analysis of randomized controlled trials. JAMA 2011 Aug 24;306(8):864-71.

115. Dommasch E, Gelfand JM. Is there truly a risk of lymphoma from biologic therapies? Dermatol Ther 2009 Sep-Oct;22(5):418-30.

116. Prignano F, Pescitelli L, Ricceri F, Lotti T. Retrospective analysis of systemic treatments for psoriasis patients attending a psocare center in florence. relevance of biological drugs use and comorbidities. J Eur Acad Dermatol Venereol 2010 May;24(5):555-60.

117. Medical Care Plan (2009). Number of physicians active in practice (fee for service, APP & salaried position) by regional health authority, newfoundland and labrador. .

118. Canadian Coding Standards for ICD-10-CA and CCI for 2008 [Internet] [cited 2010 06/25]. Available from: http://secure.cihi.ca/cihiweb/products/canadian_coding_standards_2008_e.pdf.

119. McGregor JC, Kim PW, Perencevich EN, Bradham DD, Furuno JP, Kaye KS, Fink JC, Langenberg P, Roghmann MC, Harris AD. Utility of the chronic disease score and charlson comorbidity index as comorbidity measures for use in epidemiologic studies of antibiotic-resistant organisms. Am J Epidemiol 2005 Mar 1;161(5):483-93.

120. Lacruz ME, Emeny RT, Haefner S, Zimmermann AK, Linkohr B, Holle R, Ladwig KH. Relation between depressed mood, somatic comorbidities and health service utilisation in older adults: Results from the KORA-age study. Age Ageing 2012 Mar;41(2):183-90.

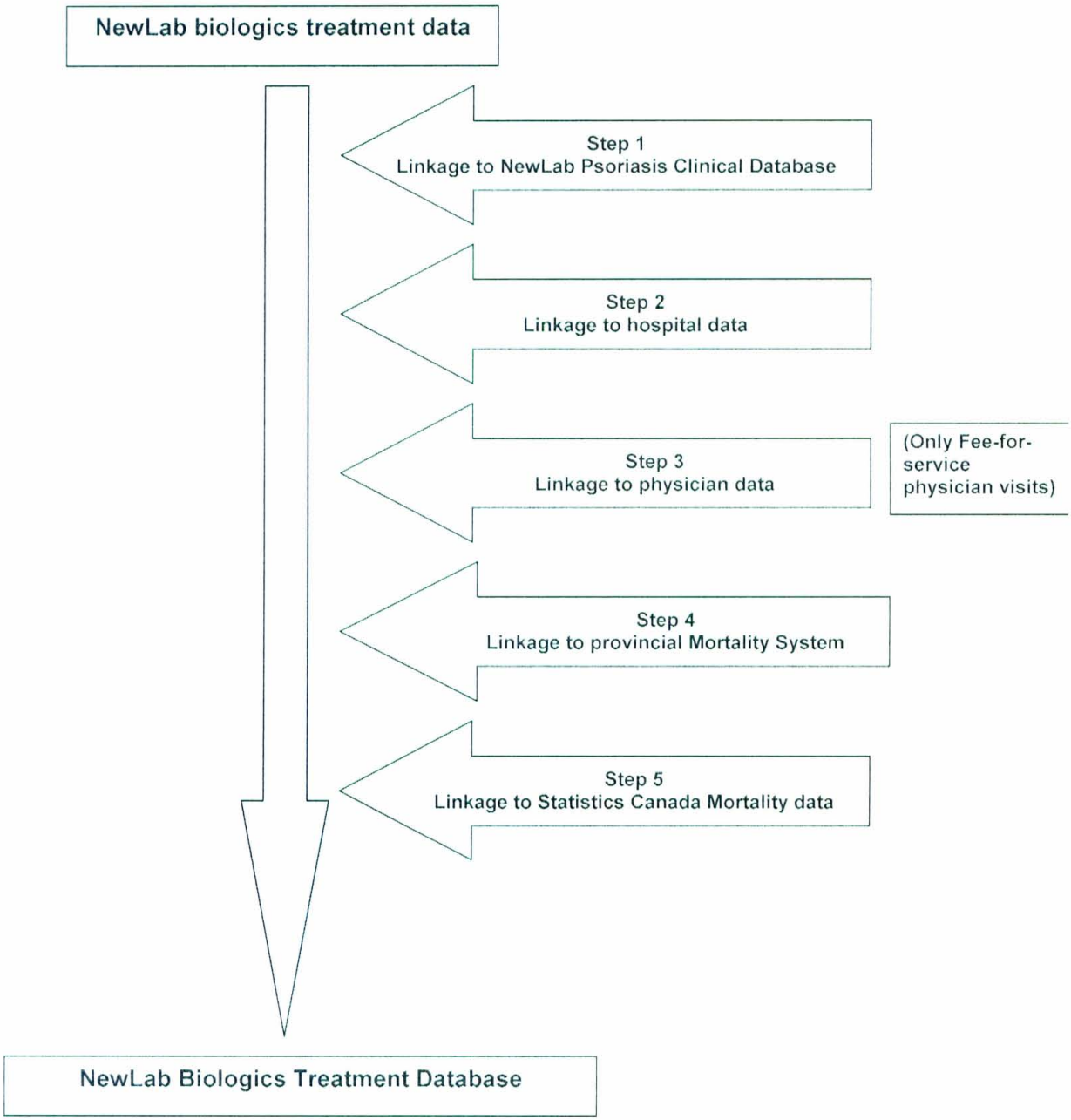
121. Knight JC. The association of continuity of family physician care with health care services utilization and costs in newfoundland and labrador. April 2011.

122. Friedman B, Jiang HJ, Elixhauser A, Segal A. Hospital inpatient costs for adults with multiple chronic conditions. Med Care Res Rev 2006 Jun;63(3):327-46.

123. Inzinger M, Heschl B, Weger W, Hofer A, Legat FJ, Gruber-Wackernagel A, Tilz H, Salmhofer W, Quehenberger F, Wolf P. Efficacy of psoralen plus ultraviolet A therapy vs. biologics in moderate to severe chronic plaque psoriasis: Retrospective data analysis of a patient registry. Br J Dermatol 2011 Sep;165(3):640-5.

124. Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne JP, Unnebrink K, Kaul M, Camez A, CHAMPION Study Investigators. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br J Dermatol 2008 Mar;158(3):558-66.

Appendix A Data Linkage Approach



Appendix B Conditions Included & Excluded When Assessing Health Care Utilization (either hospital or physician visits)

Conditions Included
Infectious Disease
Neoplasm
Endocrine/Nutritional/Metabolic Disorder
Blood Disease
Mental Disorder
Nervous System/Sense Organs Disease
Circulatory System Disease
Respiratory System Disease
Digestive System Disease
Genitourinary Disease
Skin and Sub-Cutaneous Disease
Musculoskeletal System/Connective Tissue Disease
Congenital Abnormalities
Symptoms, Signs and Ill-Defined Conditions
Conditions Excluded
Complications of Pregnancy/Childbirth and Puerperium
Conditions Originating in the Perinatal Period
Injury, Poisoning or other Certain Other External Cause of Death
Factors Influencing Health Status and Contact with Health Service
External Causes of Injury or Poisoning

Appendix C ICD Chapter 'Symptoms, signs and ill-defined conditions'

This Chapter is broken into blocks such as 'symptoms and signs involving the circulatory and respiratory systems', 'skin and sub-cutaneous tissue', etc. (moving through all body systems). For example, *Chest Pain, unspecified* is found under 'symptoms and signs involving the circulatory and respiratory system'.

This chapter also includes blocks on Abnormal Findings of blood tests, diagnostic imaging, urine tests, blood tests, etc. The last block in this chapter is 'ill-defined and unknown causes of mortality'. This block includes 'sudden infant death syndrome', 'other sudden death, cause unknown', 'unattended death' and 'other ill-defined and unspecified causes of mortality'.

For further information on ICD-9 codes, please refer to http://icd9cm.chrisendres.com/index.php?action=contents and for further information on ICD-10 codes, please refer to http://apps.who.int/classifications/icd10/browse/2010/en

Appendix D Human Investigation Committee approval letter

Faculty of Medicine

July 20, 2009

Reference #09.130

Ms. Andrea Snow
Newfoundland and Labrador Centre for Health Information
70 O'Leary Avenue
St. John's, NL
A1B 2C7

Dear Ms. Snow

RE: "A cross-section study comparing treatment groups of psoriatic patients in a cohort of the Newfoundland and Labrador population"

Your application received an expedited review by a Sub Committee of the Human Investigation Committee and **full approval** was granted effective July 20, 2009.

This approval will lapse on **July 20, 2010**. It is your responsibility to ensure that the Ethics Renewal form is forwarded to the HIC office prior to the renewal date. *The information provided in this form must be **current to the time of submission** and submitted to the HIC **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 HIC website http://www.med.mun.ca/hic/downloads/Annual%20Update%20Form.doc

The Human Investigation Committee advises THAT IF YOU DO NOT return the completed Ethics Renewal form prior to date of renewal:

- *Your ethics approval will lapse*
- *You will be required to stop research activity immediately*
- *You may not be permitted to restart the study until you reapply for and receive approval to undertake the study again*

Lapse in ethics approval may result in interruption or termination of funding.

For a hospital-based study, it is your responsibility to seek the necessary approval from Eastern Health and/or other hospital boards as appropriate.

Modifications of the protocol/consent are not permitted without prior approval from the Human Investigation Committee. Implementing changes in the protocol/consent without HIC approval may result in the approval of your research study being revoked, necessitating cessation of all related

research activity. Request for modification to the protocol/consent must be outlined on an amendment form (available on the HIC website) and submitted to the HIC for review.

This research ethics board (the HIC) has reviewed and approved the research protocol and documentation as noted above for the study which is to be conducted by you as the qualified investigator named above at the specified site. This approval and the views of this Research Ethics Board have been documented in writing. In addition, please be advised that the Human Investigation Committee currently operates according to *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* and applicable laws and regulations. The membership of this research ethics board is constituted in compliance with the membership requirements for research ethics boards as per these guidelines.

Notwithstanding the approval of the HIC, the primary responsibility for the ethical conduct of the investigation remains with you.

We wish you every success with your study.

Sincerely,

John D. Harnett, MD, FRCPC
Co-Chair
Human Investigation Committee

Fern Brunger, PhD
Co-Chair
Human Investigation Committee

C Dr. R. Gosine c/o Office of Research, MUN
Mr. W. Miller c/o Patient Research Centre, Eastern Health
HIC meeting date: July 23, 2009