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# Associated risk factors and rate of relapse of plaque psoriasis following withdrawal of biologics

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BOSTON UNIVERSITY

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Thesis

**ASSOCIATED RISK FACTORS AND RATE OF RELAPSE OF PLAQUE  
PSORIASIS FOLLOWING WITHDRAWAL OF BIOLOGICS**

by

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**ABSTRACT**

Psoriasis is a chronic skin disease treated by a host of options. The most efficient treatments available are the biologic agents, that once initiated are often continued until further notice as discontinuation will likely lead to relapse. Many patients face withdrawal from these agents, reasons being multifactorial, and the risk of relapse often continues to increase the further one gets from withdrawal. There are a multitude of risk factors associated with faster times to relapse and protective factors, specifically lifestyle factors and serum levels of inflammatory cytokines. There are also small cohorts in nearly all studies of time to relapse that do not relapse at all. The goal of this proposal is to study both inflammatory cytokine levels and lifestyle habits in non-relapsers in real-world practice. This data may be used clinically to help prevent relapse in others or potentially highlight further evidence in the psoriasis pathway that may help with treatment advancement.

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## INTRODUCTION

### Background

Psoriasis is a chronic, immune-mediated, inflammatory disease of the skin, and generally characterized by well-demarcated, erythematous plaques with overlying, silvery, coarse scale. It affects between 2 and 3 percent of the world's population and often manifests itself on the scalp, arms, trunk, buttocks, knees and even nails.<sup>1</sup> It can be a disruptive disease depending on its severity, not only due to its ability to cause significant discomfort, but also in leading to dramatic changes in physical appearance. Effective treatment is crucial for maintaining quality of life in many who experience moderate to severe disease. Treatments range from topical agents to systemic immunosuppressive agents, and typically those affected by moderate to severe disease require more intense treatment.

Biologic therapy has become a mainstay of treatment, as many of the agents on the market are both safe and highly effective. They are often administered as subcutaneous injections or IV infusions and with varying dosing schedules; some are administered weekly, whereas some are given only a few times a year. Psoriasis is, however, incurable regardless of therapy, and a common concern of many patients offered a biologic agent is duration of therapy. However, there are no guidelines governing the length of a treatment course; the goal being to achieve a high percentage of skin clearance. Further patient concerns focus on discontinuation of a biologic agent, as most hope to withdraw at some point.

The focus of this review will be to determine what patients can expect after withdrawal, whether that be relapse or continued remission. Median times to relapse will be delineated, along with risk factors that may influence time to relapse. The review will also aim to reveal factors that protect against relapse.

### **Statement of the problem**

For many patients, withdrawal from a biologic leads to relapse of their psoriasis. The time to relapse, however, can vary drastically and may be affected by a multitude of factors. Additionally, there is a small percentage of individuals who do not experience relapse at all after withdrawal. Although not abundant, a fraction of participants within each trial or study evaluating time to relapse after medication withdrawal remain asymptomatic, a small population that is understudied.

Gordon *et al*<sup>22</sup> investigated this small subpopulation, and found that, following withdrawal from guselkumab, individuals who did not relapse had significantly lower serum levels of inflammatory cytokines directly related to the psoriasis pathway. If this phenomenon is generalizable to other medications and other groups, there may be more critical clinical data within the sera and lifestyles of those who do not experience relapse, that may in turn help others achieve long-term, medication-free clearance as well.

### **Hypothesis**

Non-relapsers and those who have much longer times to relapse following withdrawal from an IL-23 inhibitor (Guselkumab, Risankizumab, Tildrakizumab) will have lower serum levels of IL-23, Th17 cells, IL-17 and IL-22 inflammatory cytokines.

Furthermore, non-relapsers will have no or fewer lifestyle habits that contribute to physiologic inflammation or known risk factors for psoriasis relapse.

### **Objective and specific aims**

The goal of the proposed study is to explore the relationship between non-relapsers and physiologic levels of known inflammatory mediators of psoriasis. Gordon *et al*<sup>22</sup> has already investigated this relationship following withdrawal of guselkumab; however, this should be broadened to the entire class of IL-23 inhibitors used in the treatment of chronic plaque psoriasis. If suppressed levels of serum cytokines can be confirmed in other groups of non-relapsers, physiologic and/or lifestyle aspects of these individuals can be further studied to identify other potential protective factors against relapse. Although already delineated by multiple studies, surveying the non-relapsers regarding their lifestyle habits may help to elucidate more conclusive evidence between these habits and the risk for relapse. Specifically, this study aims to:

- Measure physiologic levels of IL-23, Th17 cells, IL-17 and IL-22 cytokines in non-relapsers.
- Survey the social habits and known associated risk factors for relapse of psoriasis.

## REVIEW OF THE LITERATURE

### Epidemiology of psoriasis

Psoriasis is a chronic, immune-mediated, inflammatory disease of the skin generally characterized by well-demarcated, erythematous plaques with overlying, silvery, coarse scale. It is considered to be an autoimmune condition however no specific self-antigen has been identified.<sup>1</sup> Worldwide, the prevalence of psoriasis ranges between 2 to 3%, with males and females affected equally. Children are less frequently affected, as the average age of onset occurs in two peaks, 20-30 and 50-60 years old, with the majority of onset before the age of 40 years old.<sup>1,4</sup> According to the National Psoriasis Foundation, an estimated 3.6% of Caucasians are affected, 1.9% of African Americans, and 1.6% of Hispanic populations are affected and Asian Americans even less.<sup>3</sup> There are multiple subtypes of psoriasis with chronic plaque psoriasis, the focus of this review, being the most common. Others include guttate psoriasis, erythrodermic psoriasis and pustular psoriasis. Severity of the disease varies with its natural course, ranging from mild to severe, however up to 70% of cases are considered mild-moderate. Psoriatic arthritis (PsA) is a common comorbidity associated with psoriasis, affecting up to 30% of psoriatic patients.<sup>1</sup> Most commonly it affects the distal interphalangeal joints (DIPs), but it can also act as an oligoarthritis in multiple small to medium sized joints, or affect the sacral spine. It is an important comorbidity to consider and screen for when making the diagnosis of psoriasis, as not all treatments are indicated for both diseases.

### **Genetics, etiology and pathogenesis of psoriasis**

The development of psoriasis is incited by a trigger in genetically predisposed individuals, genetic predisposition being necessary to establish the inflammatory response. Many (35-90%) patients with psoriasis report a family history of the disease.<sup>1</sup> A two-to-three-fold increase in the risk of development of the disease has been observed in monozygotic twins when compared to dizygotic twins, further supporting a significant genetic component.<sup>6</sup> Multiple alleles and gene loci have been implicated in the predisposition of psoriasis, specifically the PSORS1-9 loci and the HLA-Cw6 allele.<sup>1,5-6</sup> The presence of the HLA-Cw6 allele has been found to increase risk in Caucasians by 13-fold and 25-fold in those of Japanese descent and, additionally, has been linked specifically to the early onset of the disease (20-30 years old). It is considered the most accurate genetic marker in predicting risk of development of psoriasis.<sup>1</sup> The gene locus PSORS1 is located on chromosome 6 and contains the HLA-Cw6 allele.<sup>1,6</sup> It is estimated that 50% of the total risk of development is directly linked to the PSORS1 locus, however there are many other loci also thought to contribute to psoriasis development.<sup>6</sup> Genome-wide association studies have identified other genes linked with a predisposition for psoriasis, specifically those responsible for the development of certain cytokines and inflammatory cells involved in its pathogenesis, namely interleukin-23 (IL-23), interleukin-12 (IL-12), tumor necrosis factor (TNF-alpha), interferons (IFNs) and T helper 17 cells (Th17).<sup>1,6</sup> Other identified risk factors and/or potential triggers leading to development of the disease include obesity, cigarette smoking, alcohol consumption, certain medications, certain infections, and psychogenic stress. Specific medications

implicated as potential triggers are lithium, beta blockers, antimalarial drugs, and angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs).<sup>1,4-5</sup> Streptococcal infections have been directly linked as triggers of the onset of psoriasis, namely streptococcal pharyngitis.<sup>1,4</sup>

A general understanding of the pathogenesis of psoriasis is important, as this review will focus on many drugs that target certain areas of the pathways. Psoriasis, in any form, is a T-cell mediated disease, involving many cytokines and other immune cells found within the skin that together create a positive-feedback loop, leading to chronic activity of these pathways. As noted previously, the development of psoriasis requires a “perfect storm” - genetic susceptibility sparked by an environmental factor. Whether that trigger is an infection, a medication, stress, or a social habit, the exact trigger is often unclear. The environmental factor is believed to cause stress on keratinocytes (skin cells), which initiates the inflammatory psoriasis pathway. The keratinocytes react by releasing chemokines (immune cell attractants) and strands of DNA and RNA, which combine with LL-37, an antimicrobial peptide (AMP) found in the skin. LL-37 is known to be upregulated in early psoriatic skin.<sup>1,5-6</sup> Plasmacytoid dendritic cells, a type of antigen presenting cell within the skin, found in significantly higher numbers in the skin of psoriasis patients, are activated by this DNA-RNA-LL-37 complex.<sup>1</sup> The activated plasmacytoid dendritic cells begin releasing the cytokine, interferon alpha (IFN- $\alpha$ ), which, like most cytokines, plays a role in the activation of immune cells. IFN- $\alpha$  activates another type of dendritic cell, myeloid dendritic cells, within the dermis.<sup>1,6</sup> Myeloid dendritic cells are mainly focused on T cell recruitment and activation, which is done via

direct antigen presentation to T cells, and via cytokine and chemokine release. It is postulated that IFN- $\alpha$  also plays a role in this T cell activation process.<sup>6</sup> The cytokines released by activated dendritic cells, namely IL-23 and IL-12, act to differentiate and activate naïve CD4<sup>+</sup> T cells into Th17 and Th1 T helper cells, respectively.<sup>1,5</sup> Much of the pathogenesis of psoriasis is thought to be directly related to the Th17 pathway, with the Th1 pathway helping to contribute to the inflammatory response.<sup>1,4</sup> These T helper cells migrate to the areas of skin releasing chemokines and begin releasing the cytokines thought to be the main mediators of skin inflammation. Th1 cells release both IFN- $\gamma$  and TNF- $\alpha$ , which act on keratinocytes and dendritic cells to maintain their inflammatory states. Th17 cells release IL-17A, IL-22 and others, however, IL-17A is implicated as the primary cytokine mediating further keratinocyte activation, growth and proliferation that creates the characteristic psoriasis plaque.<sup>1,5-6</sup> Neutrophils and macrophages, attracted and activated by the chemokines and cytokines, also concentrate in these areas and contribute to this positive-feedback cycle by releasing additional IL-23, IL-17A and reactive oxygen species (ROS), leading to further tissue damage. Production of nitric oxide (NO), vascular endothelial growth factor (VEGF), and angiopoietin throughout the inflammatory process strongly promotes vasodilation and angiogenesis, creating leaky, tortuous vessels within psoriatic lesions.<sup>1</sup> The constitutive release of cytokines and chemokines from many of these implicated immune cells maintains their activation and leads to the chronicity of the disease. The inhibition of many of these molecules has a drastic effect on disease severity and is the forefront mechanism in treatment for this disease.

## **Clinical course and management**

Following activation of the immune response, the clinical manifestations of the disease become apparent. The different subtypes of psoriasis are accompanied by distinct variations in clinical presentation. Only the presentation of chronic plaque psoriasis will be reviewed here, as it is the most common subtype and the focus of the research in this review. The classic presentation of chronic plaque psoriasis includes multiple, oval-shaped, well-demarcated, erythematous, lichenified plaques with thick, silvery scale. The plaques are most commonly located on extensor surfaces, the scalp, the trunk (especially the lumbosacral region and umbilicus) and the hands and feet. Sensitive anatomic areas that may be affected include the genitalia, ears, fingernails and intertriginous areas.<sup>1,4</sup> The plaques range in size from less than 1 cm to greater than 20 cm in diameter.<sup>1</sup> They often occur symmetrically if not in a midline location and the total body surface area (BSA) affected varies with clinical course, which helps physicians grade disease severity. The plaques may be asymptomatic, but pruritus and sensitization are common symptoms. Plaques may persist in the same location for years at a time or may resolve with treatment and reoccur in another area. The clinical course of plaque psoriasis is unpredictable. It is a chronic, life-long disease with periods of remission and relapse, but predicting when those periods will occur is difficult.<sup>1,4</sup> For many patients, the disease is more emotionally disruptive than physically; it can be disfiguring to exposed skin, which can lead to mental health illness.<sup>4</sup> Chronic plaque psoriasis also puts individuals at greater risk of cardiometabolic comorbidities, providing patients and clinicians with two consequential reasons to ensure disease control.<sup>5</sup> There is no cure for the disease, however the various

forms of treatment, which are reviewed below, can help maintain long-term remission and disease control.

Psoriasis is a clinical diagnosis; there are no definitive markers of this disease for which to test. Biopsy of the skin, while an option, is typically not recommended as it can exacerbate the immune activity.<sup>1</sup> A physical exam performed by an experienced clinician revealing the above-mentioned clinical manifestations alone is often enough to make a diagnosis. The presence of other autoimmune diseases, family history of autoimmunity, and risk factors are also helpful in making the diagnosis.<sup>5</sup> Two hallmark, but not technically diagnostic, signs of psoriasis include the Koebner phenomenon and the Auspitz sign. The Koebner phenomenon refers to psoriasis lesions occurring within a few weeks of trauma to that area of the skin, and is observed in up to 25% of patients.<sup>1</sup> The Auspitz sign refers to pinpoint bleeding within psoriasis plaques following removal of the overlying scale.<sup>4</sup> Both of these may be useful in supporting the diagnosis.

Fortunately for psoriatic patients, there are many options for treatment, ranging from topical products to light therapy to systemic or biologic agents that are taken orally, infused or injected. Treatments are chosen based on disease severity, patient preference, comorbidities, potential adverse effects, and drug accessibility. Mild disease is defined as  $\leq 5\%$  BSA involvement, moderate disease is 5-10% BSA, and  $> 10\%$  is considered severe disease.<sup>5</sup> Topical treatments are typically reserved for mild to moderate cases, where the disease is local enough to easily apply a topical agent. First-line and second-line options include topical corticosteroids, Vitamin D analogs, and retinoids. Potent topical steroids can produce rapid results via their anti-inflammatory and anti-

proliferative effects. However, they are contraindicated for use longer than a few weeks at a time as they increase the risk of skin atrophy.<sup>1,4-5</sup> Vitamin D analogs, such as calcipotriene, exert their effects via inhibition of epidermal proliferation and inducing normal keratinocyte differentiation.<sup>1</sup> They are much more effective when used in combination with a topical steroid - one in the morning and one at night. They are safe for regular, long-term use.<sup>1,4</sup> Tazarotene is a topical retinoid approved for the treatment of plaque psoriasis based on its ability to break down psoriatic scaling, however it tends to be very irritating and deters patients from its use.<sup>1,4,5</sup> Treatment of moderate to severe cases of psoriasis often requires more aggressive forms of therapy, such as phototherapy and systemic agents, as typically there is a much higher BSA involved. Phototherapy comes in many forms, including narrowband UVB, broadband UVB, and psoralen with ultraviolet A (PUVA). UV radiation also has antiproliferative and anti-inflammatory effects and is dosed at controlled wavelengths and intervals effective for the treatment of psoriasis.<sup>1,4</sup> Treatment with phototherapy can be a burden, as it is typically delivered multiple days a week and often requires visits to an office. Small molecule or systemic therapies include medications like methotrexate and cyclosporine, which exert strong immunosuppressive effects on T cells, or apremilast, a phosphodiesterase 4 inhibitor. Albeit effective, methotrexate and cyclosporine carry significant side effect profiles and require serum monitoring that may dissuade patients against their use. They have also been found to be less effective than biologic agents.<sup>1,4-6</sup> Apremilast, which does not require monitoring, is taken orally and has a less severe side effect profile. While less effective than biologic therapy, it may be a more comfortable starting point for some

patients.<sup>4-6</sup> Given the limited efficacy, short-term use, inconvenience, and high risk of adverse effects of these treatment options, biologic therapy has become the preferred option by both patients and clinicians.

### **Biologic therapy in the treatment of psoriasis**

Biologic therapies for autoimmune conditions have been a game changer for treatment in the last 25 years as they are the most efficacious options available. There are a multitude of biologic agents available today, however this section will focus only on the specific agents named in the literature review to follow. There are four major classes, each targeting a different cytokine within the psoriasis pathway. Most biologics are monoclonal antibodies, others are receptor fusion proteins, and they are administered at intervals ranging from every week to every 12 weeks, making many of them attractive options for low-maintenance patients.<sup>6</sup> The classes include TNF- $\alpha$  inhibitors, dual IL-12/IL-23 inhibitors, IL-23 inhibitors and IL-17 inhibitors with each having their own set of contraindications of use and side effect profiles. All agents should be discontinued during any serious infection.<sup>5</sup> The most common side effects across all classes include injection site reactions, upper respiratory tract infections, nasopharyngitis, candidal infections, and headache.<sup>4-6</sup> TNF- $\alpha$  inhibitors are the oldest biologics available and include infliximab (Remicade), adalimumab (Humira), etanercept (Enbrel) and certolizumab pegol (Cimzia); all four are approved and effective for the treatment of plaque psoriasis. Infliximab requires an infusion given every 8 weeks after a loading dose, adalimumab and certolizumab are subcutaneous injections every 2 weeks after a loading dose, and etanercept another subcutaneous injection given every week after a

loading dose.<sup>1,4-5</sup> Network meta-analyses have found that, when compared to each other, Infliximab is the most effective in the treatment of plaque psoriasis, followed by adalimumab and certolizumab, and lastly etanercept.<sup>5</sup> This class of drug has higher infection rates than those of the IL-12/IL-23 class but long-term safety data has determined the rates of malignancy for those on this drug are no greater than the general population.<sup>5</sup> Infliximab and adalimumab can lead to the development of autoantibodies against the drug, which may decrease their efficacy.<sup>4</sup>

The only biologic agent that targets two cytokines, ustekinumab (Stelara), is a monoclonal antibody that targets a shared subunit of both IL-12 and IL-23, thereby interfering with both the Th1 and Th17 pathways. It is approved and effective for the treatment of plaque psoriasis; it is more effective than adalimumab and etanercept in RCTs and is administered subcutaneously every 12 weeks after a loading dose.<sup>4-5</sup> Ustekinumab has longer drug-survival, or average duration of treatment before discontinuation, when compared to the TNF-alpha inhibitors and no increased rates of serious infection or malignancy were found when compared to placebo.<sup>5,6</sup>

The IL-23 inhibitors, the newest class of biologics, only target IL-23 with no action against IL-12, interfering with only the Th17 pathway. They include guselkumab (Tremfya), tildrakizumab (Ilumya), and risankizumab (Skyrizi); all are approved and effective for the treatment of plaque psoriasis. Guselkumab is administered subcutaneously every 8 weeks after a loading dose and tildrakizumab and risankizumab subcutaneously every 12 weeks after a loading dose.<sup>4,5</sup> Of the classes of biologics, the IL-23 inhibitors are one of the most effective, having one of the greatest percentage of

patients reaching PASI 90 (a 90% reduction in disease severity from baseline) within 4 months of therapy, with IL-17 inhibitors showing similar efficacy.<sup>5-6</sup> Nearly 50% of patients receiving Risankizumab reached PASI 100 within 3 months of therapy.<sup>6</sup> Guselkumab and Risankizumab were shown to be superior to adalimumab in head-to-head trials, as well as guselkumab being superior to secukinumab, tildrakizumab superior to etanercept, and Risankizumab superior to Ustekinumab.<sup>5</sup> No increased rates of serious infection or malignancies have been identified.<sup>5</sup>

The final class, IL-17 inhibitors, target either the molecule itself or its receptor to inhibit the latter half of the IL-23/Th17 pathway. The agents in this group include secukinumab (Cosentyx), ixekizumab (Taltz) and brodalumab (Siliq); all three are approved and effective for the treatment of plaque psoriasis. Secukinumab and ixekizumab are administered subcutaneously every 4 weeks after a loading dose and brodalumab every 2 weeks after a loading dose.<sup>4,5</sup> This class has a more rapid onset, within the first 4 weeks of therapy, compared to other classes.<sup>4-6</sup> All three members of this class were superior to ustekinumab in head-to-head trials and secukinumab and ixekizumab were superior to etanercept.<sup>5</sup> Similar to other classes, no increased rates of serious infection or malignancies have been identified.<sup>5</sup>

### **Aftermath of biologic withdrawal**

Considering the chronicity of psoriasis, biologic agents are intended for continuous use after initiation. However, in real-world practice, discontinuation and withdrawal from these drugs is not uncommon. Common reasons for discontinuation of a biologic are disease remission, surgery, pregnancy, illness/development of a

contraindicated condition such as malignancy, inefficacy of drug, adverse effects, patient preference/personal reasons, long-term safety concerns of patient or provider, lost to follow up, drug unavailability/financial barriers, COVID concerns or COVID infection.<sup>7,9-10,14</sup> It is critical to understand the prognosis of withdrawal for a patient on a biologic given how common it is in real-world practice. For the majority of patients, withdrawal leads to relapse, however depending on multiple factors, the time to relapse varies. A major factor delineated in this review is the specific biologic being withdrawn from, as the time to relapse after withdrawal differs amongst the different classes. This idea becomes pertinent when choosing a biologic for a patient, as a longer relapse-free time-period after withdrawal may influence their decision.

Data on the time to relapse following withdrawal of each biologic will be reviewed. It is important to define “relapse”, and to understand that there are different definitions used by different studies. There are two separate scoring tools that are commonly used to determine the following during clinical trials: severity of disease at baseline, measure the amount of clinical improvement on therapy, and to define relapse. The Psoriasis Area and Severity Index (PASI) is the most commonly used criteria by clinical trials. The PASI score is based on the extent of a patient’s erythema, induration, scaling and body surface area (BSA) involved; it does not include any measures of quality of life from the patient.<sup>2</sup> The score ranges from 0-72 with anything above 10 considered severe disease.<sup>2</sup> Clinical improvement is evaluated by the *reduction* in PASI, with commonly used intervals of 50% reduction, 75% reduction and 90% reduction in disease severity from baseline - PASI 50, PASI 75 and PASI 90, respectively. PASI 100

refers to complete remission while the benchmark efficacy in trials is often considered achieving PASI 75.<sup>2</sup> Similarly, the definition of relapse often varies in clinical trials and other studies, however the National Psoriasis Foundation Medication Advisory Board recommends using a *loss* of PASI 50 from baseline to define relapse.<sup>19</sup> Another tool, referred to as the Physician Global Assessment (PGA), is used less frequently to define disease severity and clinical improvement. It only considers a patient's levels of erythema, scaling and induration, and the final score ranges from 0-4: 0 being remission, 1 minimal disease, 2 mild disease, 3 moderate and 4 severe.<sup>2</sup> The FDA suggests defining relapse with this tool as a psoriasis recurrence scored as a 3 or greater ( $PGA \geq 3$ ).<sup>19</sup> It is difficult to compare results between the PASI and PGA scoring tools as they do not equate. The differing tools and definitions for relapse complicates the analysis of time to relapse for each biologic.

TNF-alpha inhibitors are associated with some of the fastest times to relapse; they do not maintain clinical improvement for long after discontinuation. Studies on etanercept found a loss of PASI 50 between 11 and 13 weeks after withdrawal at week 24 of dosing.<sup>8,13-14</sup> With relapse defined as a recurrence of  $PGA \geq 2$ , median time to relapse varied across studies from 5 weeks and 12 weeks after withdrawal at week 11 of dosing.<sup>8,11</sup> In the STOP study, etanercept had the shortest time to relapse when compared to infliximab and adalimumab.<sup>14</sup> With longer treatment times, defined as those who maintained a PASI 0/1 for 1 year on etanercept, median time to relapse was approximately 26 weeks, a clear indication that longer treatment times with sustained responses protect against short relapse times.<sup>13</sup> For adalimumab, the median time to

relapse, defined as loss of PASI 50, was 23 weeks for individuals who had achieved a PASI 75 and were withdrawn at week 32 of the trial.<sup>8</sup> With relapse defined as recurrence of PGA  $\geq$  3, median time to relapse was approximately 20 weeks in individuals who had achieved a PASI of 0/1 before withdrawal of treatment.<sup>13,25</sup> During the STOP study, the average length of treatment with adalimumab was nearly 21 months before withdrawal, and the average time to loss of PASI 50 was 16 weeks after discontinuation. Adalimumab was the most protective TNF-alpha inhibitor against time to relapse in the STOP study.<sup>14</sup> Data on infliximab was less available with a median time to loss of PASI 50 of 26 weeks after withdrawal at week 22.<sup>13</sup> However, in the STOP study, the average time to loss of PASI 50 was 10 weeks for individuals who had been on infliximab for an average of 34 months.<sup>14</sup>

Ustekinumab, the dual IL-12/IL-23 inhibitor, was superior in time to relapse compared to the TNF-alpha inhibitors.<sup>9</sup> With relapse defined as loss of PASI 50, the mean time to relapse after an average treatment duration of 16 months was 24 weeks. All individuals maintained a PASI 50 or better for at least 3 months on therapy prior to discontinuation.<sup>10</sup> In another trial defining relapse as loss of PASI 50, individuals withdrawn at week 28 experienced a median time to relapse of approximately 22 weeks for both 45 mg dosing and 90 mg dosing.<sup>21</sup> With relapse defined as recurrence of PGA  $\geq$  2, median time to relapse varied from 14 weeks to 22 weeks after withdrawal at week 12 with additional variation based on dose.<sup>8,11,13</sup>

The IL-23 inhibitors, guselkumab, tildrakizumab and sisankizumab exhibit the longest times to relapse. Guselkumab demonstrated a loss of PASI 75 after a median of

28 weeks from withdrawal; individuals were withdrawn at week 28 if they had achieved a PASI 90 response.<sup>15</sup> Loss of PASI 50 was not recorded in this trial, however one can deduce that loss of PASI 50 would not occur for quite a few weeks later than the median time to loss of PASI 75. In another trial where individuals were withdrawn from treatment at week 28, and only 50% of individuals had a loss of PASI 50 within 32 weeks of withdrawal.<sup>13,22</sup> The ECLIPSE study performed in Spain on guselkumab defined relapse as the point when a patient needed to restart a biologic agent. With this definition of relapse, the median time to relapse was approximately 40 weeks after discontinuation; individuals received an average of 48 weeks of treatment prior to discontinuation and had all achieved a PASI 90 response.<sup>13</sup> Tildrakizumab was evaluated in the reSURFACE trial for both median time to loss of PASI 50 and PASI 75. With withdrawal at week 28 after having achieved a minimum of PASI 75, the median time to loss of PASI 75 was approximately 23 weeks and to loss of PASI 50 was approximately 34 weeks.<sup>8,20</sup> Risankizumab was found to have one of the longest times to relapse. Relapse was defined as recurrence of PGA  $\geq 3$ , and participants were withdrawn at week 28. Only those who achieved a PGA of 0/1 were withdrawn, and median time to relapse was approximately 42 weeks. This was the longest time to relapse of any of the biologic agents studied thus far.<sup>17</sup>

While the efficacy of IL-17 inhibitors is similar to that of the IL-23 inhibitors, their time to relapse is less impressive. In one secukinumab study, the median time to loss of PASI 50 following withdrawal was 28 weeks among participants on therapy for 1 year at the 300 mg dose.<sup>13</sup> With relapse defined as loss of PASI 75 and discontinuation at

week 12 of secukinumab therapy, participants were withdrawn from either 100 mg dosing or 300 mg dosing. Median time to loss of PASI 50 for the 300 mg group was 24 weeks and 20 weeks for the 100 mg group.<sup>23</sup> In the ECLIPSE study, with relapse defined as restarting a biologic agent, after 48 weeks of 300 mg dosing of secukinumab, the median time to relapse was approximately 27 weeks.<sup>13</sup> For ixekizumab with withdrawal at week 12, multiple trials found that both recurrence of PGA  $\geq 3$  and loss of PASI 50 occurred within 20 weeks following discontinuation.<sup>8,13,16</sup> Lastly, analyses of brodalumab revealed a median of 8 weeks to recurrence of PGA 2 and 3 after withdrawal at week 12, the fastest time to relapse of the aforementioned biologic agents.<sup>8,24</sup>

### **Limitations in the literature**

It is difficult to precisely compare the time to relapse for each of these agents from the above analyses for a multitude of reasons. First and foremost, many of the studies used separate definitions of relapse, making it impossible to standardize the definition and very likely affecting comparative outcomes. It is also clear that treatment length prior to withdrawal varied throughout, which has been found to directly affect time to relapse. However, it is important to note that in most trials no matter the agent, participants typically received a full loading dose and at least one maintenance dose; the dosing schedules just happen to vary dramatically between agents. Most of the above data is applicable only to individuals who achieved a significant clinical response to therapy; only those who had achieved a high level of response were withdrawn from treatment in most studies. This makes the data more difficult to generalize, as not everyone experiences such significant results prior to withdrawal in a real-life clinical setting,

which presumably would lead to an even shorter time to relapse. These studies also become difficult to compare with each other when it comes to the exact percentage of those who actually relapsed, as many of the studies limited their findings to only those who actually relapsed.

### **Non-relapsers**

Most analyses found a certain percentage of individuals who did not relapse at all during the study's timeframe, the most considerable proportion among individuals treated with IL-23 inhibitors. In the VOYAGE 2 trial for guselkumab, 36% of individuals withdrawn from treatment at week 28 still had not relapsed, defined as loss of PASI 50, 44 weeks later.<sup>22</sup> Nearly 24% of individuals withdrawn from either tildrakizumab 100 mg or 200 mg at week 28 in the reSURFACE 1 trial did not relapse, defined as loss of PASI 75, within the following 36 weeks.<sup>20</sup> With Risankizumab treatment, 61% of individuals who were withdrawn at week 28 still maintained a PGA 0/1 24 weeks after withdrawal and 7.1% maintained it 76 weeks after withdrawal.<sup>17</sup> There is also data on non-relapsers for ustekinumab, the dual IL-12/IL-23 inhibitor. In one trial, 27% of those withdrawn at week 12 were relapse free, defined as recurrence of PGA  $\geq$  2, one year later, however the study was limited by a small sample size (N=30).<sup>11</sup> For the IL-17 inhibitors, 17% of those withdrawn from ixekizumab at week 12 still had not relapsed, defined as recurrence of PGA  $\geq$  3, 48 weeks later.<sup>16</sup> And among the TNF-alpha inhibitors, after withdrawal from adalimumab at week 12 in one trial, 37% of participants did not relapse, defined as recurrence of PGA  $\geq$  3, within 40 weeks after discontinuation.<sup>25</sup> Thus, these specific

groups of non-relapsers is of clinical interest, as relapse does not seem to be dependent on the drug but rather specific protective factors.

### **Associated risk factors for and protective factors against relapse**

A recently appreciated factor that plays a role in the relapse of psoriasis is serum levels of both IL-17 and IL-22, the main mediators of the Th17/IL-23 pathway. In the VOYAGE 2 study, following withdrawal of guselkumab specifically, relapse was associated with loss of suppression of the IL-23 axis; serum levels of both IL-17 and IL-22 were found to increase.<sup>22</sup> On the contrary, individuals withdrawn from therapy that did not experience relapse had sustained, suppressed serum levels of the same cytokines.<sup>22</sup> Of note in this study, serum levels were found to increase *after* clinical worsening and/or relapse was appreciated clinically, supporting the theory that, after a trigger, the immune response initiates locally in the skin to cause relapse, and the increasing number of inflammatory cells then “leak” into the serum.<sup>22</sup> Elevated levels of cytokines in peripheral serum, therefore, did not appear to be the cause of relapse but an observation following relapse. Given such significant findings, it can be assumed that suppression or loss of suppression of this axis is largely related to relapse and further studies on individuals who are able to maintain suppression without continued therapy are warranted. Serum levels should also be analyzed after treatment with other agents. Another known source of psoriasis relapse involves tissue resident memory T cells, specifically CD4 and CD8 cells, that have been found to remain in skin that was previously affected by psoriasis, even after the lesion has healed.<sup>18,19</sup> These resident memory T cells retain the ability to secrete disease-perpetuating cytokines, the trigger for

which however is often unclear.<sup>18,19</sup> This, however, is contradictory to the findings suggestive of relapse being closely related to serum levels of cytokines; resident T cells negate the need for serum cytokines as they can be stimulated to produce their own locally. Hence, further research on non-relapsers is warranted.

Other than serum levels of cytokines, multiple other predictive factors of relapse have been identified. Risk factors that predicted a faster time to relapse according to many of the above studies include cigarette smoking, alcohol consumption, history of previous use of other biologic agents, having a family history of psoriasis, lack of clinically significant response to biologic agent, lack of rapid response to biologic agent, a high baseline PASI score prior to therapy, leukocytosis, shorter durations of therapy, longer durations of disease prior to biologic therapy, comorbid psoriatic arthritis or CKD, and having an elevated BMI.<sup>9-12,14,20</sup> Protective factors against time to relapse after withdrawal include no previous use of biologic therapy (biologic naivety), short duration of disease prior to initiation of biologic therapy (early biologic intervention), rapid and significant clinical response to therapy, lower baseline PASI score prior to therapy initiation, longer durations of therapy, lack of family history of psoriasis, and nonsmokers.<sup>10-11,13-14,20</sup> Modifiable factors that psoriasis patients should be aware of include cigarette smoking, alcohol consumption, BMI and early biologic intervention. Currently, biologic therapy is typically reserved as a last resort, however given the benefit of early biologic intervention, patients may prefer a more aggressive approach. If a patient is biologic naïve, knowing that using multiple different agents over time could affect their long-term outcome is also important in the original decision-making process.

Patients can also use previously determined clinical response times of each agent to aid in their decision, as a rapid, clinically significant response is protective against relapse, and certain therapies have faster responses than others.

Patients on biologic therapy may need to withdraw from their medication for many possible reasons. It is important that they are aware of the consequences of withdrawal so they not only may be able to prolong their relapse-free period but also to help ensure they choose the best possible option for their needs.

## METHODS

### **Project design**

This study will be a longitudinal cohort study, allowing collection of data that mirrors real-world practice as closely as possible. The study aims to determine the significance of serum cytokine levels and lifestyle habits in psoriasis patients after withdrawing from an IL-23 inhibitor. The outcomes include relapse after withdrawal. Participants will have been prescribed and initiate one of the three IL-23 inhibitors – guselkumab, tildrakizumab or Risankizumab. Participants will remain on therapy as long as they prefer, a specific duration will not be required as this model aims to observe real-world practice. Baseline serum levels of specific effector cytokines will be analyzed before, during and after treatment. Lifestyle habit surveys will be administered to all participants 6 months (24 weeks) after withdrawal, regardless of relapse status. For those who remain relapse free at 12 months, another survey will be administered. Each participant's dermatologist will be responsible for determining if a patient has relapsed, based on loss of PASI 75 response, and participants will have regularly scheduled follow ups with their clinician. The study will conclude when all participants have withdrawn and relapsed or one year after the last withdrawal without relapse, whichever happens first. Demographic data and potential confounding factors that will be collected and accounted for in the final analysis include history of biologic use, duration of treatment with IL-23 inhibitor, mean duration of psoriasis, family history of psoriasis, response rate to the IL-23 inhibitor, baseline PASI scores, presence or absence of psoriatic arthritis, and BMI.

**Project population and sampling**

The study population will be derived from dermatology clinics across the state of Massachusetts that are interested in participating. Clinics will be contacted via phone and/or email to offer participation. Inclusion criteria will consist of an age minimum of 18 years old, a diagnosis of moderate to severe plaque psoriasis defined as either Physician Global Assessment [PGA] score  $\geq 3$ , Psoriasis Area and Severity Index [PASI] score  $\geq 12$ , or body surface area involvement  $\geq 10\%$  and being naïve to treatment with IL-23 inhibitors. Exclusion criteria includes previous use of an IL-23 inhibitor, previous use of methotrexate, other biologic agent use in the last 6 months, cancer history (except for non-metastatic skin cancer), history of tuberculosis, and severe disease of any kind within the last 6 months. Participants that do not achieve at least a PASI 75 response prior to withdrawal will not be included in the final analysis. Sample size was calculated based on parameters from a previous study done by Gordon *et al.*<sup>22</sup> Alpha and beta values were chosen based on standard values, 0.05 and 0.2, respectively. The median level of serum cytokines across the entire sample population after conclusion of this study will provide the threshold between “high” and “low” levels, which we can assume will produce a q1 and q0 of 50%, or 0.5. The prevalence of relapse (loss of PASI 75) in the VOYAGE 2 study was approximately 60% 6 months after withdrawal and thus 0.6 was used for P in the calculation. Relative risk was estimated roughly at 4 (80:20), based on the fact that while mean cytokine levels were low in non-relapsers, and high in relapsers, there were variations in serum levels that did not correlate with clinical response in some individuals in the VOYAGE 2 study.<sup>22</sup> The calculated minimum sample size came out to 18, however

given a sample size of 72 in the VOYAGE 2 study, and the goal of assessing serum cytokine levels following withdrawal of three different drugs not just one, a sample size of 100 has been chosen. It should be feasible to find 100 eligible, interested participants in dermatology clinics across the state of Massachusetts.

### **Treatment, intervention or exposure groups**

Cytokine activity after withdrawal from an IL-23 inhibitor will be the exposure in this study with the groups split dichotomously as having elevated levels or low levels following withdrawal, based on the median cytokine level following conclusion of the study. The IL-23 inhibitor class was chosen based on its efficacy, not only in overall clearance of the disease but also in providing the longest times to relapse in previous studies. Comparing the three agents in this class will aid in expanding and supporting the data found by Gordon *et al*<sup>22</sup>, where only guselkumab was evaluated.

### **Project variables and measurement tools**

The outcome of relapse will be determined using the PASI scoring system, which will be the responsibility of each participant's dermatologist to determine clinically evaluate at each visit. Relapse will be defined as the loss of PASI 75, following withdrawal from an IL-23 inhibitor. Exposure, or cytokine levels within each participant's serum, will be measured via phlebotomy and measured in picograms per milliliter (pg/mL). Th17 cells require flow cytometry for measurement following blood draw. The lifestyle surveys that will be provided to all participants before and after treatment with an IL-23 inhibitor will focus on known factors and potential factors that can exacerbate psoriasis or cause an inflammatory response. These factors will include information on each participant's

alcohol intake, tobacco use, marijuana or other drug use, sleep schedules, general stress levels, recent illnesses (specifically viral or bacterial infections), specific diets (if any), amount of exercise, recent vaccines, and trauma to the skin. Questions will be formatted in a “in the last 6 months” format.

### **Recruitment**

Considering sample size, recruitment will start locally and expand across the state of Massachusetts as needed. To start, dermatology clinics in the Greater Boston area will be contacted via phone and/or email and offered participation in the study. If too few clinics agree to participate, the offer will be expanded to the North Shore and South Shore, extending to Worcester if necessary. Once a clinic has agreed to take part in the study, it will be the dermatologists’ responsibility to identify eligible candidates and offer to enroll them. Providers will then be responsible for sharing recruitment information with the study coordinators. Participating clinics will need to be willing to share EMR access for data collection.

### **Data collection**

Participants will be logged by medical record number into RedCap, along with the IL-23 inhibitor they will be initiating, when they will initiate therapy, demographic data and potential confounding factors or known associated protective factors that each participant may carry. The duration of therapy with an IL-23 inhibitor will be followed in each patient’s chart once access has been granted by the clinic and entered into RedCap. Cytokine levels will also be noted in the EMR, and will be organized in RedCap by patient and date of blood draw. Lifestyle surveys will be sent electronically to each participant via

RedCap, where responses will be automatically uploaded for review by the coordinators. Psoriasis response and/or clinical status will also be followed in the EMR. RedCap will be used to follow and organize participant status' as relapse begins to occur.

### **Statistical analysis**

Data will be analyzed using the Chi-Square test to compare the proportions of individuals that relapse and do not relapse in relation to cytokine levels (high or low). The risk of relapse related to cytokine levels will be estimated with a risk ratio. Given the distinct possibility for participants to carry protective factors against relapse and/or associated factors with relapse, stratified analysis with the confounding factors listed in project design will be performed.

### **Timeline and resources**

The timeline for this study is hard to predict, as participants will have to decide how long they prefer to be on therapy, which may vary from months to years, followed by more time as the outcome and exposure require discontinuation of therapy first. A rough estimate is four years from approval to finalized data analysis. Serum cytokine levels will be evaluated prior to initiation, 3 months after initiation, and again repeated at the time of withdrawal. Following discontinuation, serum cytokine levels will be evaluated at relapse or every 6 months for non-relapsers to determine any potential patterns in their sera. The lifestyle surveys will be distributed upon entry into the study and repeated at relapse to determine any potential changes in habits around the time of relapse. Non-relapsers will re-complete the survey every 6 months following withdrawal to evaluate any patterns in behavior. Required personnel include the primary investigator, multiple coordinators, a

statistician and one clerical assistant and/or student volunteer. Computer access and Microsoft Office will be required. Participants can choose the most conveniently located laboratory for phlebotomy.

### **Institutional review board**

This project will be submitted to the Boston University Medical Center IRB, seeking approval for an exempt study. This study should be eligible for an expedited review of research under the category of collection of blood sample by venipuncture, as blood draws will not exceed 550 ml in an 8-week period and collection will not occur more than twice weekly. Considering this project has been designed to model real-world practice as closely as possible, the participants face the same risk in joining this study as they would starting this medication with their provider regardless of an involved study. All protected health information will be de-identified.

## CONCLUSION

### Discussion

The proposed study is designed to observe the natural changes that come with real-world practice; a large portion of the literature review were randomized control trials that predetermined duration of therapy for all participants. In the real-world, patients may not have a predetermined amount of time they would prefer to be on a new biologic; ideally, patients remain on the medication continuously, but they may also trial off when convenient or necessary. That is a strength of this study, as it will not restrict participants to a minimum or maximum amount of time on treatment. The definition of relapse in this study will be universal, as to eliminate the variability in definitions across the literature. The major strength of this study relates to its inclusion of both physiologic factors and social factors that affect the rate of relapse; Gordon *et al*<sup>22</sup> highlighted physiologic factors alone related to just one medication, while this study will explore the IL-23 inhibitors as a class and produce lifestyle data for comparison. Although there is a plethora of data on the use of many biologics in real-world practice, the IL-23 class is much newer and not thoroughly studied in a real-world setting, which also adds to the strength of this proposal.

While offering any of the biologic classes to participants in this proposal would provide the most generalized data, it would significantly limit the amount of data collected on each drug, as there would be more than 8 to choose from and only a limited number of participants. It is thus advisable to restrict participation to only those on IL-23 inhibitors, to gather a more robust amount of data on each drug. While biopsies of

relapse-free skin would likely give the most accurate data on the activity of the psoriasis pathway, the risk of causing a psoriasis flare due to the Koebner phenomenon is too great and may directly interfere with the study's main outcome. Biopsies of the skin could be considered in future studies.

A major anticipated obstacle of this proposal is insurance coverage/access to selected agents. As the IL-23 inhibitor class is newer to the market, these agents tend to be less readily covered than older agents; social determinants of health then may affect the overall composition of the population of this study and make it somewhat more difficult to generalize to larger populations. Otherwise, there are few exclusion criteria in the proposed study, which may speak to its generalizability.

### **Summary**

Psoriasis is a chronic condition that can not only be debilitating but may increase the risk of overall cardiovascular health and so it is crucial to have effective treatment options available. Many of these treatment options should be continued indefinitely, however there are a multitude of reasons to discontinue treatment that many patients encounter. Some of these patients may relapse, some may not. Some may relapse quickly, some may maintain a relapse-free state for many months. This review delineates the median amount of time that patients remain relapse free, the risk factors related to relapse, and the dearth of information individuals that do not relapse at all after withdrawal from a biologic. The results of the proposed project will help to further specify physiological and social differences of these non-relapsing populations that may be directly applicable to prevent relapse in other populations.

**Clinical and/or Public Health Significance**

Not only will this proposal strengthen and expand on the data found by Gordon *et al*<sup>22</sup>, it may highlight a physiologic finding that could be the impetus for a new method of treatment and precisely identify lifestyle habits that help prevent relapse from occurring. This information could be used in treatment development and given directly to patients during their healthcare visits to provide them their best chance at remaining relapse free following withdrawal. Decreasing relapse rates in general would help lessen the total disease burden on healthcare systems worldwide.

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**CURRICULUM VITAE**





