Systemic agent use and mental health outcomes among patients with psoriasis

by

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To my parents

Abstract

Psoriasis is a chronic immune-mediated skin condition affecting 2.5% of the Canadian population. Moderate-to-severe psoriasis is associated with high risks of depression and anxiety. In randomized controlled trials, biologic agents had better efficacy for skin clearance and anxio-depressive symptom reduction than conventional systemic agents (CSA) in patients with moderate-to-severe psoriasis. However, because of their high acquisition costs, biologic agents are covered by the Quebec public drug plan only if CSA treatment fails or is contraindicated. The goal of my thesis was to assess patterns of CSA and biologic agents (tumor necrosis factor inhibitors and ustekinumab [TNFi/UST]) use and their association with mental health outcomes and costs among patients with psoriasis.

In my four manuscripts, I used data from the province of Quebec health administrative databases (1997-2015) and conducted retrospective cohort studies of patients with psoriasis initiating a CSA.

In manuscripts 1 and 2, I used the same cohort to describe patterns of CSA and TNFi/UST use and assess sex disparities in factors associated with treatment switch and discontinuation. My cohort included 1,644 patients. In manuscript 1, I examined the CSA as a class. The rates of switch (or add) TNFi/UST and CSA discontinuation were 44.5 and 364.9 per 1,000 person-years, respectively, with no differences between sexes. Older age was associated with a reduced risk of switch in both sexes. Obesity and longer psoriasis duration in males and NSAID use, and adjustment, somatoform and dissociative disorders in females were associated with increased risks of switch, while rheumatoid arthritis was associated with a reduced risk in females. Patients at lower risks of CSA discontinuation were those followed by a rheumatologist and those with an all-cause hospitalization in the previous year among males; and those with rheumatoid arthritis, those receiving hypoglycemic and lipid-lowering agents and those initiated on methotrexate (versus any other CSA) among females. In manuscript 2, I studied each CSA, separately. During follow-up, 312 patients switched to a different systemic agent, with 82.7% receiving another CSA and 17.3% a TNFi/UST.

In manuscript 3, I described the trajectories of CSA and TNFi/UST use over a 2-year period and compared depression and anxiety-related health care costs between trajectory clusters. My cohort included 781 patients with no history of anxio-depressive disorders. Using sequence and hierarchical cluster analyses, I identified eight treatment trajectory clusters. The overall predicted mean annual cost per-patient was CAN$ 60. Compared to the cluster *persistent methotrexate users*, the clusters *adding a TNFi/UST* (cost ratio 3.63, 95% confidence interval, CI 1.47-5.97) and *CSA discontinuation then restart on acitretin or multiple switches between CSA* (cost ratio 13.30, 95% CI 5.76-22.47) had higher predicted mean costs. Female (versus male) patients had higher predicted mean costs (cost ratio 1.89, 95% CI 1.11-2.69). Results remained unchanged when adjustment disorder-related costs were also considered.

In manuscript 4, I assessed the risk of mental health disorders (depression, anxiety and adjustment disorder) in patients initiated on a CSA who subsequently switched/added TNFi/UST (TNFi/UST users) versus (vs) those who did not (TNFi/UST non-users). TNFi/UST users were included in the cohort at the date of TNFi/UST initiation and TNFi/UST non-users were included at a matched date. I separated the TNFi/UST non-user group into those who were currently using a CSA (current CSA users) and those who were not (previous CSA users). My cohort included 183 TNFi/UST users, 625 current CSA users and 525 previous CSA users. Using marginal structural models, TNFi/UST (vs. previous CSA) users were at lower risk for mental health disorders (Hazard Ratio, HR 0.48, 95% CI 0.28-0.94). The result for TNFi/UST vs current CSA users pointed to a non-significant lower risk (HR 0.60, 95% CI 0.31-1.20).

Findings of this thesis support the importance of considering certain subgroups of patients in the reimbursement process of biologic agents for the treatment of moderate-to-severe psoriasis. Improving access to biologic agents may save patients from the burden of going through a treatment failure experience with CSA and help improve their psoriasis and mental health outcomes faster.

Résumé

Le psoriasis est une affection cutanée chronique qui touche 2,5 % de la population canadienne. Le psoriasis modéré à sévère est associé à des risques élevés de dépression et d'anxiété. Dans les essais contrôlés randomisés, les agents biologiques se sont révélés plus efficaces pour la clairance de la peau et la réduction des symptômes anxio-dépressifs lorsque comparés au placebo et aux agents systémiques classiques (CSA) chez les patients atteints de psoriasis modéré à sévère. Cependant, en raison de leurs coûts d'acquisition élevés, les agents biologiques ne sont couverts par le régime public d'assurance-médicaments du Québec que si le traitement par CSA échoue ou est contre-indiqué. L'objectif de ma thèse était d'évaluer les schémas d'utilisation des CSA et des agents biologiques (inhibiteurs du facteur de nécrose tumorale et ustekinumab [TNFi/UST]) ainsi que le risque de problèmes de santé mentale et leurs coûts associés chez les patients atteints de psoriasis.

Dans mes quatre manuscrits, j'ai utilisé des données provenant des bases de données administratives sur la santé de la province de Québec (1997-2015) et j'ai mené des études de cohorte rétrospectives incluant des patients atteints de psoriasis ayant initié un CSA.

Dans les deux premiers manuscrits, j'ai utilisé la même cohorte pour décrire les schémas d'utilisation des CSA et des TNFi/UST et évaluer la présence de disparités entre les sexes dans les facteurs associés au changement de thérapie et à l'arrêt du traitement. Ma cohorte comprenait 1 644 patients. Dans le premier manuscrit, j'ai examiné les CSA en tant que classe. Les taux de changement (ou d'ajout) de TNFi/UST et d'arrêt du CSA étaient respectivement de 44,5 et 364,9 par 1000 personnes-année, sans différence significative entre les sexes. L'âge avancé était associé à un risque réduit de changement de traitement dans les deux sexes. L'obésité et la durée prolongée du psoriasis chez les hommes et les troubles de l'adaptation, somatoformes et dissociatifs chez les femmes étaient associés à un risque accru de changement de traitement, tandis que la présence de polyarthrite rhumatoïde était associée à un risque réduit chez les femmes. Les patients présentant un risque plus faible d'arrêt de CSA étaient les hommes suivis par un rhumatologue et ceux ayant déjà été hospitalisés dans l’année précédente pour toute cause, et les femmes atteintes de polyarthrite rhumatoïde, celles recevant des hypoglycémiants et des hypolipidémiants et celles initiées au méthotrexate (par rapport à tout autre CSA). Dans le deuxième manuscrit, j'ai étudié

chaque CSA séparément. Au cours du suivi, 312 patients ont changé d'agent systémique, parmi eux 82,7 % ont reçu un autre CSA et 17,3 % un TNFi/UST.

Dans le troisième manuscrit, j'ai décrit les trajectoires d'utilisation des CSA et TNFi/UST sur une période de 2 ans et j'ai comparé les coûts des soins de santé liés à la dépression et à l'anxiété entre les groupes de trajectoires. Ma cohorte comprenait 781 patients sans antécédents de troubles anxio-dépressifs. En utilisant des analyses de séquence et de partition hiérarchique, j'ai identifié huit groupes de trajectoires de traitement. Le coût annuel moyen prédit par patient était de 60 dollars canadiens. Par rapport au groupe des utilisateurs *persistants au méthotrexate*, les groupes *ajoutant un TNFi/UST* (ratio des coûts 3,63, intervalle de confiance à 95 %, IC 95% 1,47-5,97) et *l'arrêt de d'un CSA puis la reprise de traitement avec acitrétine ou changements multiples entre CSA* (rapport de coûts 13,30, IC 95 % 5,76-22,47) avaient des coûts moyens prédits plus élevés. Les coûts moyens prédits étaient plus élevés chez les femmes par rapport aux hommes (rapport de coûts 1.89, 95% CI 1.11-2.69). Les résultats sont restés inchangés lorsque les coûts associés aux soins du trouble de l'adaptation étaient également pris en compte.

Dans le quatrième manuscrit, j'ai évalué le risque de troubles de santé mentale (dépression, d'anxiété et de trouble de l'adaptation) chez les patients ayant initié un CSA et qui ont ensuite changé/ajouté un TNFi/UST (utilisateurs de TNFi/UST) par rapport à ceux qui n'ont pas reçu un TNFi/UST (non-utilisateurs de TNFi/UST). J'ai inclus les utilisateurs de TNFi/UST à la date de dispensation de leur premier TNFi/UST et les non-utilisateurs de TNFi/UST à une date matchée. J'ai séparé les non-utilisateurs de TNFi/UST en 'utilisateurs actuels de CSA' et 'anciens utilisateurs de CSA'. Ma cohorte comprenait 183 utilisateurs de TNFi/UST, 625 utilisateurs actuels de CSA et 525 anciens utilisateurs de CSA. En utilisant des modèles structurels marginaux, les utilisateurs de TNFi/UST (par rapport aux anciens utilisateurs de CSA) présentaient un risque plus faible pour les troubles de santé mentale (ratio de hazards, RH 0,48, IC 95% 0,28-0,94). Les résultats pour les utilisateurs de TNFi/UST par rapport aux utilisateurs actuels de CSA indiquaient un risque inférieur non significatif (RH 0,60, IC 95 % 0,31-1,20).

Les résultats de cette thèse soutiennent l'importance de considérer certains sous-groupes de patients dans le processus de remboursement des agents biologiques pour le traitement du psoriasis

modéré à sévère. Améliorer l'accès aux agents biologiques pourrait épargner aux patients le fardeau de vivre un échec thérapeutique avec un CSA et à améliorer plus rapidement leur psoriasis et leur santé mentale.

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Contributions of authors

I developed the research questions and conceptualized the study designs with guidance from my supervisors Dr Elham Rahme and Dr Jacques LeLorier. I drafted the protocol and submitted it for approval to the Research Institute of the McGill University Health Centre Institutional Review Board (Appendix A). I was responsible for data management, cohorts' construction, definition and construction of the variables, data analysis, and drafting of the manuscripts. Dr Ivan V Litvinov provided clinical expertise regarding the management of psoriasis. Dr Marie-Josée Brouillette provided clinical expertise regrading mental health disorders. Dr Eric A Latimer provided expertise regarding the assessment and analyses of the cost data. Dr Anne Holbrook provided expertise regarding the overall clinical aspects of the studies. All co-authors were involved in reviewing the manuscripts for intellectual content and interpretation of the results and provided input during manuscript revisions.

Manuscript 1: Milan R, LeLorier J, Brouillette MJ, Holbrook A, Litvinov IV, Rahme E. *Sex differences in the patterns of systemic agent use among patients with psoriasis: A retrospective cohort study in Quebec, Canada*. Front Pharmacol. 2022 Feb 15;13:810309.

Manuscript 2: Milan R, LeLorier J, Brouillette MJ, Holbrook A, Litvinov IV, Rahme E. *Sex differences in factors associated with switch between systemic agents among individuals with psoriasis: A retrospective cohort study in Quebec, Canada*. JAAD Int. 2021 Jul 31;4:79-83.

Manuscript 3: Milan R, LeLorier J, Latimer EA, Brouillette MJ, Holbrook A, Litvinov IV, Rahme E. *Trajectories of systemic agent use and associated depression- and anxiety-related health care costs among patients with psoriasis.* JAAD Int. 2022 Jun 25;9:11-22.

Manuscript 4: Milan R, LeLorier J, Brouillette MJ, Holbrook A, Litvinov IV, Rahme E. *Depression, anxiety and adjustment disorders among patients with psoriasis receiving systemic agents: A retrospective cohort study in Quebec, Canada.* JEADV clin pract. 2022;1-14.

Statement of originality

The work presented in this thesis constitutes an original contribution to the evidence on (1) patterns of systemic agent use, including conventional systemic agents (CSA) and the biologic agents, tumor necrosis factor inhibitors and ustekinumab (TNFi/UST) in the real world; (2) sex differences in factors associated with these patterns; and (3) mental health outcomes and their associated costs among patients receiving TNFi/UST and CSA.

To date, there have been a handful of studies assessing patterns of CSA use among patients with psoriasis including treatment discontinuation and switch. However, to my knowledge, only two of these studies included first time CSA users and determined whether patients switched to a biologic agent or a different CSA. Additionally, no prior study has examined sex differences in factors associated with these patterns despite studies reporting differences in expectations and goals from systemic therapies between male and female patients with psoriasis. I have addressed these gaps in Manuscripts 1 and 2 by conducting two retrospective cohort studies among patients with psoriasis initiated on a CSA and performing separate analyses in male and female patients.

Studies have reported an incremental annual all-cause health care cost in association with psychiatric disorders among patients with psoriasis. However, no prior study has assessed mental health care-related costs in association with psoriasis treatment patterns. I have addressed this gap in knowledge in Manuscript 3 in a retrospective cohort study where I used sequence and cluster analyses to describe longitudinal trajectories of systemic agent use over two years. I subsequently assessed direct health care costs related to incident depression and anxiety by these treatment trajectories.

Lastly, randomized controlled trials (RCT) reported significant improvement in depressive and anxiety symptoms and quality of life among patients with psoriasis treated with biologic agents when compared to placebo and CSA. Nonetheless, several observational studies conducted on this topic have reported discordant results due to methodological limitations and heterogeneity in the study populations. In manuscript 4, I have addressed these limitations by comparing the incidence

of depression, anxiety and adjustment disorder among patients initiating a CSA who subsequently received a biologic agent as a switch or add-on versus patients who did not receive these agents.

Overall, this thesis provides an important addition to our knowledge regarding the use of systemic agents and related mental health outcomes among patients with psoriasis in Quebec.

I declare that I received guidance from my supervisors for my thesis objectives and input from my thesis committee members for the methodological and clinical aspects of my thesis. The conception, execution and drafting of the manuscripts and thesis were entirely my own.

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1. One stipend from the *Canadian Network for Observational Drug Effect Studies (CNODES).*
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3. Two dissemination awards from the *Réseau Québecois sur le Suicide, les troubles de l'Humeur et les troubles Asssociés* (RQSHA)
4. One travel award from the Division of Experimental Medicine
5. One travel award from the International Society for Pharmacoepidemiology.

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Table of contents

List of tables

Tables in manuscript 1

Tables in manuscript 2

Tables in manuscript 3

Tables in manuscript 4

List of figures

Figures in manuscript 2

Figures in manuscript 3

Figures in manuscript 4

List of acronyms and abbreviations

AHCA	Agglomerative hierarchical clustering analysis
APR-DRG	All patient refined diagnosis-related group
ASW	Average silhouette width
BIOBADADERM	Biological therapy in dermatological diseases (Spanish registry)
BMI	Body mass index
BSA	Body surface area
CHF	Congestive heart failure
CI	Confidence intervals
CSA or CST	Conventional systemic agents OR Conventional systemic therapies
CV	Cross validation
DENCOM	Drug common denominators
DIN	Drug information number
DLQI	Dermatology life quality index
DHM	Dynamic hamming measure
ED	Emergency department
GBTM	Group-based trajectory modeling
GMM	Growth mixture modeling
HADS-A	Hospital anxiety and depression scale – Anxiety
HADS-D	Hospital anxiety and depression scale – Depression
HBV	Hepatitis B virus
HCM	Histocompatibility complex
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HR	Hazard ratio
IBD	Inflammatory bowel diseases
ICD-9/10	International classification of diseases ninth and tenth editions
IL	Interleukin
ILi	Interleukin inhibitors
INF-α	Interferon alpha

IPTW	Inverse probability of treatment weights
IPCW	Inverse probability of censoring weights
IR	Incidence rates
IRR	Incidence rate ratios
LASSO	Least absolute and selection operator
MSM	Marginal structural models
NHANES	National health and nutritional examination survey
NIRRU	*Niveau d'intensité relative des ressources utilisées*
NSAIDS	Non-steroidal anti-inflammatory drugs
OHIP	Ontario health insurance plan
OR	Odds ratio
OTC	Over the counter
PASI	Psoriasis area and severity index
PL	Partial likelihood
PPV	Positive predictive value
PSORS	Psoriasis susceptibility regions
PUVA	Psoralen and ultraviolet light type A phototherapy
QoL	Quality of life
HRQoL	Health-related quality of life
RCT	Randomized controlled trials
RAMQ	*Régie de l'assurance maladie du Québec*
RR	Risk ratio
TNF-α	Tumor necrosis factor alpha
TNFi	Tumor necrosis factor inhibitors
TNFi/UST	Tumor necrosis factor inhibitors and ustekinumab
US	United-States
UV	Ultraviolet
UVB	Ultraviolet light type B phototherapy

Introduction

Psoriasis is a chronic immune-mediate skin condition affecting 2.5% of the Canadian population,[1] among whom 21.5% have moderate-to-severe disease.[2] This skin condition has a significant impact on patient's physical appearance, self-esteem, and quality of life (QoL), which in turn can increase the risk of mental health disorders such as depression, anxiety, and adjustment disorder, especially among those with moderate-to-severe forms of the disease and among female patients.[3-6] Previous studies reported that patients with psoriasis and mental health disorders had significantly higher annual all-cause health care costs per patient when compared to those without mental health disorders.[7-9] Because of the substantial clinical and economic burden on the patients and health care system, in 2014 the World Health Organization recognized psoriasis as a serious non-communicable disease.[10]

Systemic agents, including conventional systemic agents (CSA), such as methotrexate, acitretin, cyclosporine and apremilast, and the biologic agents tumor necrosis factor inhibitors (TNFi) and ustekinumab (TNFi/UST), are prescribed to manage moderate-to-severe psoriasis.[4] In randomized controlled trials (RCT), biologic agents were more effective than methotrexate and placebo in achieving skin clearance.[4] However, because of their high acquisition costs, the provincial drug plan in Quebec covers biologic agents only if treatment with CSA failed or is contraindicated.[11]

Population-based cohort studies report that patients with moderate-to-severe psoriasis tend to cycle through multiple systemic agents during their disease life course, which indicates failure of these agents to achieve treatment response or the emergence of agent-associated adverse events.[12-21] Failure to treatment can, in turn, increase the risk of psychiatric disorders.[22,23] In addition, population-based surveys report that female patients are more likely to have higher expectations and needs from systemic agents when compared to male patients.[24,25] However, no prior Canadian study has examined patterns of CSA use among patients with psoriasis in real-world settings and no prior study has assessed whether sex differences existed regarding factors associated with switching from a CSA to a TNFi/UST or those associated with CSA discontinuation.

In RCT, biologic agents were also more effective than CSA at improving anxio-depressive symptoms, QoL and fatigue.[26-33] However, observational studies comparing the risk of psychiatric disorders among patients receiving TNFi/UST versus CSA have reported discordant results due to methodological limitations and heterogeneity of the study populations.[34-40]

The overall purpose of my thesis was to address important gaps in knowledge regarding patterns of systemic agent use and associated mental health outcomes and costs among patients with psoriasis initiating a CSA. More specifically, I used the Quebec health administrative databases to address the following objectives:

1. Assess sex differences in patterns of CSA use and factors associated with
    a. switch to or add (switch/add) a TNFi/UST, switch/add any systemic agent and CSA discontinuation;
    b. switch/add any systemic agent (TNFi/UST or a different CSA, whichever occurred first),
2. Construct and describe clusters of longitudinal trajectories of systemic agent use and examine differences in depression- and anxiety-related health care costs between these trajectory clusters; and
3. Compare the risk of depression, anxiety, and adjustment disorder among patients with psoriasis initiating a CSA and who subsequently received a TNFi/UST versus those who did not receive these agents.

This thesis is manuscript based. Chapter 1 presents the background on psoriasis and comorbidities associated with this skin conditions. Chapter 2 presents the treatment options to manage moderate-to-severe psoriasis. Chapter 3 provides a literature review of previous observational studies conducted to 1) assess patterns of CSA use in psoriasis, 2) assess the incremental health care costs associated with having a psychiatric disorder among patients with psoriasis, and 3) compare the risk of mental health outcomes between patients with psoriasis receiving a CSA and those receiving biologic agents. Chapter 4 provides an overview of the data sources used in this thesis. Chapters 5 to 8 include the four manuscripts addressing the three objectives of this thesis. Chapter 9 summarizes findings from the four manuscripts and provides a discussion of the overall strengths and limitations and the implications of the findings. Chapter 10 provides a conclusion.

Chapter 1: Psoriasis

1.1 Clinical manifestation and diagnosis

Psoriasis is a chronic immune-mediated skin condition resulting from a genetic predisposition combined with environmental and behavioural triggers such as infections, smoking, medications and psychological stress.[4,41] Psoriasis exhibits substantial variability in morphology, distribution, and severity.[4,41] The disease can be chronic with stable lesions or may fluctuate between periods of substantial disease activity and remission.[4,41] There are four main phenotypes of psoriasis: Plaque, guttate, pustular and erythrodermic psoriasis.[4]

Plaque psoriasis is the most common form, affecting approximately 90% of patients with psoriasis.[4] Lesions have, in general, a symmetric distribution with scaly plaques. Common sites of involvement include the scalp, extensor elbows, knees, gluteal cleft and genitals. The extent of involvement can range from limited, localized disease to the majority of the body surface area. Involvement of intertriginous areas (inverse psoriasis), the ear canal, umbilicus, palms, soles, or nails may also be present. Pruritus is common in plaque psoriasis and involvement in the palm and sole areas of the body can include painful fissures.[4]

Guttate psoriasis is characterized by red, scaly, small, teardrop-shaped spots. Guttate psoriasis is more common in children and adolescent and is frequently preceded by an upper respiratory tract infection such as streptococcal infection. The trunk and proximal extremities are the primary sites of involvement. Guttate psoriasis typically occurs as an acute eruption in patients with no previous history of psoriasis. Less commonly, a guttate psoriasis flare occurs in a patient with pre-existing psoriasis.[4]

Pustular psoriasis is a rare and severe form of psoriasis characterized by the presence of superficial blisters filled with pus. Pustular psoriasis can be localized, on palms and soles (palmoplantar psoriasis), or generalized with widespread patches appearing randomly on any part of the body (general pustular psoriasis). Reported causes of pustular psoriasis flaring include pregnancy, infections, withdrawal of oral glucocorticoids and initiation of some TNFi.[4] Pustular psoriasis can lead to death, mostly due to septic shock and cardiorespiratory failure.

Erythrodermic psoriasis is characterized by extensive erythema and scaling involving most or all of the body surface area. The onset of erythrodermic psoriasis can be chronic or acute. Patients affected by erythrodermic psoriasis are at high risk for complications related to loss of adequate barrier protection, such as infection, sepsis and electrolyte abnormalities secondary to fluid loss. Causes include previous plaques in classic locations, characteristic nail changes, and central facial sparing.[4]

Psoriasis care is mostly delivered in outpatient settings by general practitioners or dermatologists. Nonetheless, severe psoriasis can still require hospitalization.[4] In clinical practice, assessment of psoriasis severity includes both an objective evaluation of the extent of involvement and a subjective evaluation of the impact of psoriasis on patient's life. There are four main standardized instruments to measure disease severity, extent of involvement and patient's quality of life (QoL).[4]

- Body surface area (BSA): measures the percentage of body surface affected by the disease. BSA uses the palm of the hand, as a reference, to estimate the extent of involvement of psoriasis. The palm of the hand represents 1% of the total body area. For example, if the size of the affected area is equal to three times the size of the palm, the patient has a BSA of 3%.
- Physician Global Assessment (PGA): a 5-point scoring system used to assess psoriasis severity. A score 0 (clear) indicates no signs of psoriasis, but post-inflammatory discoloration may be present; a score of 1 (almost clear) indicates a few scattered comedones and a few small papules; a score of 2 (mild) indicates slight plaque elevation, scaling, and erythema; a score of 3 (moderate) indicates moderate plaque elevation, scaling, and erythema; and a score of 4 (severe) indicates very marked plaque elevation, scaling, and erythema.
- Psoriasis Area and Severity Index (PASI): measures the severity (thickness, redness and scaling) and extent of body surface coverage of psoriasis. PASI assesses four body areas including head and neck, upper limbs, trunk and lower limbs. For each body area, the percentage of body involvement is computed with scores ranging from 1 (0%-9%) to 6 (90%-100%). Within each area, erythema, thickness/induration and scaling are assessed each on a five-point scale ranging from 0 (none) to 6 (very severe) and then multiplied by

the area score (neck/head = 0.1, upper limb = 0.2, trunk = 0.3 and lower limbs = 0.4). Lastly, the scores for all body areas are summed with a final score ranging from 0 (no disease) to 72 (maximal disease). PASI is often measured in randomized controlled trials (RCT) and improvement in PASI scores are used as primary and secondary endpoints. PASI-75 and PASI-100 indicate, respectively a 75% and 100% decrease or improvement in severity on the PASI scale.

- Dermatology Life Quality Index (DLQI): a self-reported questionnaire with 10 questions to assess itch, pain, feelings of embarrassment/self-consciousness, problems with treatment and interference of skin disease with the patients' daily activities, relationships, and sexual activities. Each question is scored on a scale of 0 to 3 (0: not all all/not relevant and 3: very much relevant). The sum of all the questions can range from 0 (no effect at all on patient's life) to 30 (extremely large effect on patient's life).

There is no consensus on how to clinically define the severity of psoriasis. In clinical practice, a BSA $\leq$ 3% or $\leq$ 5% is usually indicative of mild psoriasis, 3%-5% < BSA < 10% moderate psoriasis, and $\geq$ 10% severe psoriasis. Some even consider a BSA between 10% and 20% as moderate psoriasis and only $\geq$ 20% as severe psoriasis. In RCT, moderate-to-severe psoriasis is commonly defined as BSA $\geq$ 10 and PASI $\geq$ 12, or BSA $\geq$ 10% and PASI $\geq$ 10 and DLQI $\geq$ 10.[4]

A psoriasis clearance indicates the absence of psoriasis lesions after therapy, while satisfactory control indicates a satisfactory response to treatment without full clearance, usually defined as patients achieving at least PASI-70, BSA $\leq$ 3% or PGA between 1 and 2. Psoriasis exacerbation indicates worsening of psoriasis symptoms. Psoriasis flaring indicates an exacerbation while receiving a psoriasis treatment. Rebound indicates psoriasis exacerbation occurring within three months of treatment discontinuation due to clearance. Relapse indicates a loss of disease control in patients who previously achieved a satisfactory disease control.[4]

1.2 Incidence and prevalence

In a report by the World Health Organization summarizing the findings of 68 studies, the prevalence of psoriasis varied from 0.06% in the Republic of Tanzania (1994) to 11.4% in Norway (2009).[10] In these studies, psoriasis was either self-reported, identified using registry data, clinical

evaluation or a combination of these methods. Geographic latitude and ethnicity seemed to affect the prevalence of psoriasis which was more common in Western Europe and North America compared to other countries. In the US, the prevalence of psoriasis in population-based studies varied from 0.5% to 3.5%.[2,42] In the National Health and Nutritional Examination Survey (NHANES) (2011-2014), 3% of respondents reported having psoriasis with 21.5% of them having moderate-to-severe forms of the disease.[2] In this survey, higher psoriasis prevalence was reported among White people when compared to African American and Hispanic American people (3.6%, 1.5% and 1.9%, respectively).

In Canada, a 2007 online survey conducted across several provinces, including Quebec, reported a prevalence of psoriasis between 1.0% and 3.1% based on self-report.[43] One population-based study assessed the prevalence and incidence of psoriasis using the Ontario Health Insurance Plan (OHIP) claims databases.[1] The following algorithm was used to identify psoriasis cases: ≥1 diagnostic code (international classification of disease, ICD, 9th and 10th revision) in hospital records or ≥ 2 diagnostic codes assigned by any physician. A wash-out period of 10 years was considered for incident cases of psoriasis. This algorithm had a 52% sensitivity and a 62% positive predictive value (PPV). In this study, the overall prevalence was 2.5% and the overall incidence was 69.9 per 100,000 population. Age- and sex-standardized prevalence increased from 1.7% in 2000 to 2.3% in 2015, while the age and sex-standardized incidence decreased from 111.1 per 100,000 population to 68.7 per 100,000 populations in the same time period.[1] The prevalence of psoriasis was similar among male and female across all ages, with higher prevalence among patients ages 65 years and older.

While the prevalence of psoriasis is similar between male and female patients,[1,44] several cross-sectional and prospective cohort studies using the BSA and PASI reported that male patients are more likely to suffer from moderate-to-severe psoriasis than female patients.[24,25,45,46]

1.3 Pathogenesis

It has been well established that plaque psoriatic lesions result from abnormal differentiation and growth of keratinocytes. Although the pathogenesis for this process is not completely understood, studies conducted in human and experimental psoriasis models demonstrated that it involves an

upregulation of the cellular immune system, dendritic cells, T cells, chemokines, and cytokines.[47-49] Additionally, psoriasis has a strong genetic component with environmental triggers.[50]

Psoriasis is thought to be triggered by the activation of plasmacytoid dendritic cells after being stimulated by complexes of host DNA and cathelicidin, an antimicrobial peptide, that are produced by keratinocytes after a minor injury.[47-49,51] In turn, the activated plasmacytoid dendritic cells and damaged keratinocytes produce interferon alpha (INF-α) and tumor necrosis Factor alpha (TNF-α).[47-49,51] The production of INF-α and TNF-α results in further production of TNF-α and interleukin (IL)-12 and IL-23 by plasmacytoids and recruited inflammatory dendritic cells. IL-12 promotes the differentiation of naïve $CD4^+$ T cells into IFN-α-producing T helper (Th) 1 cells. IL-23 is critically involved in the generation and activation of IL-17-producing effector cells.[47,48,51,52] These cells produce IL-17A and IL-22.[51,53,54] IL-17A binds to the IL-17 receptor (IL-17R), which is composed of IL-17RA and IL-17RC.[51,53-55] IL-17A upregulates the proliferation of keratinocytes and downregulates its differentiation.[51,56] The differentiation of keratinocytes is critical for the formation of the protective stratum corneum also known as outermost layer of the epidermis. In addition, IL-17A promotes the expression of TNF-α by keratinocytes, thus creating a vicious loop in the development of psoriasis lesions.[51,55]

1.4 Genetic factors

Forty percent of individuals with psoriasis have a family history of the disease and in studies among twins, psoriasis was more frequently concordant among monozygotic versus (vs) dizygotic twins.[57-60] Multiple susceptible loci for psoriasis have been identified, many of which are involved in the regulation of the immune system.[4]

At least 20 psoriasis susceptibility regions (PSORS) have been identified in different genetic regions.[4] PSORS-1 locus, identified within the major histocompatibility complex (HCM) on chromosome 6p1, is the most important genetic region and considered a major determinant of psoriasis.[61,62] The Human Leukocyte Antigens (HLA)-Cw6 located on chromosome 6 within the HCM in the most important allele for susceptibility of early-onset psoriasis.[63]

Multiple other genes involved in immune regulation were identified as susceptible loci for psoriasis. Some of these include the IL12B and IL23A genes that encode the shared subunits p40 and p19 of the receptor for IL-12 and IL-123 and TNIP1 and TNFAIP3 genes that are responsible for the downstream of TNF-α.[64-67]

1.5 Environmental and behavioural factors

While genetic factors are the largest contributors to the development and exacerbation of psoriasis, environmental and behavioral factors, such as geographic location, exposure to some pollutants, some medication use, lifestyle habits and stress have also been considered as psoriasis triggers or associated with disease onset.[68]

Geographic location has been associated with psoriasis onset with lower prevalence being reported in Africa and Latin America when compared to North America and Europe. In addition, exposure to environmental pollutants such as Cadmium (heavy metal found in soil, batteries, food and cigarette smoke) has been associated with psoriasis exacerbation, as higher level of this metal was found in blood samples of patients with psoriasis, especially those with higher disease severity when compared to non-psoriasis patients.[50]

Multiple medications have been associated with psoriasis exacerbation and flaring. The most common of which include lithium, beta blockers, chloroquine, hydroxychloroquine, quinidine and tetracycline.[4] In rare occasions, Selective Serotonin Reuptake Inhibitors and TNF inhibitors (TNFi), prescribed to manage moderate-to-severe plaque psoriasis, were associated with development of psoriasis-like eruption.[4,69-71]

Smoking is a risk factor for psoriasis onset and exacerbation. A pooled analysis of three prospective cohort studies in the US revealed that patients with a history of smoking (pooled Risk Ratio [RR] 1.39, 95% CI 1.27-1.52) and current smokers (pooled RR 1.94, 95% CI 1.64-2.28) were at increased risk of developing incident psoriasis by 1.39 and 1.94 folds.[72] In this study, increased risk of incident psoriasis was also reported with higher intensity and duration of smoking.[72] In a meta-analysis of 25 case-control and cross-sectional studies (2014), patients with psoriasis were 1.78 times more likely to be current smokers when compared to patients without

psoriasis (pooled odds ratio [OR] 1.78, 95% CI 1.52-2.06).[73] A similar result was observed among patients with moderate-to-severe psoriasis as assessed in 5 of these studies (pooled OR 1.72, 95% CI 1.33-2.22).

In a systematic review of 14 case-control and cross-sectional studies (2013), patients with psoriasis were more likely to consume alcohol, with ORs ranging from 2 to 3, when compared to the general population.[74] However, limited data was available to determine whether alcohol consumption was associated with an increased risk of incident psoriasis, as four of the five studies examining the incidence of psoriasis were case-control studies and may have suffered from recall and social desirability bias.[74] One prospective cohort study including only women from the US (1991) reported higher risk of confirmed new diagnosis of psoriasis among those consuming ≥ 2.3 drinks/week when compared to non-drinkers (RR 2.54, 95% CI 1.57-4.10).[75] Several observational studies reported that alcohol abuse exacerbated psoriasis and reduced the efficacy of psoriasis treatment.[76-81]

Overweight and obesity are strongly associated with psoriasis onset and exacerbation. In a meta-analysis of 16 cross-sectional and case-control studies (2012), patients with psoriasis were 1.66 times more likely to be overweight or obese when compared to the general population (pooled OR 1.66, 95% CI 1.46-1.89).[82] In studies reporting psoriasis severity, patients with moderate-to-severe psoriasis and those with mild psoriasis were both more likely to suffer from obesity when compared to the general population, with higher odds among those with increased psoriasis severity (pooled OR 1.46, 95% CI 1.17-1.82 and pooled OR 2.23, 95% CI 1.63-3.05, respectively).[82] Improving diet and physical activity among overweight and obese patients with psoriasis was significantly associated with improvement in psoriasis severity and QoL as shown in two RCT in which dietary intervention and/or physical activity were compared to informative counselling and placebo (no intervention) after 16 to 20 weeks of intervention.[83,84]

Psychological distress is often considered as an important contributing factor to psoriasis onset or psoriasis exacerbation. In a meta-analysis of 5 case-control studies conducted in Europe, US and Asia (2018), patients with psoriasis were 3.4 folds more likely to report having stressful events preceding disease onset when compared to patients with other dermatological disorders (pooled

OR 3.4, 95% CI 1.8-6.4).[85] However, an association between psoriasis exacerbation and stress could not be confirmed in this meta-analysis, because of conflicting results and the heterogeneity in the assessment of psychological stress, psoriasis exacerbation and the time-lag between stress and psoriasis exacerbation. In a prospective cohort study (2009) conducted among 62 patients with mild psoriasis, increased stress levels assessed by a dermatologist, was positively correlated with increased psoriasis severity (r = 0.28).[86]

1.6 Physical comorbidities

Patients with psoriasis are at increased risk of other immune-mediated conditions, metabolic syndrome and cardiovascular diseases. The presence of theses comorbidities is attributed to shared inflammatory pathways, genetic susceptibilities, and risk factors.[10,87]

Psoriasis can be associated with psoriatic arthritis, a spondyloarthropathy that involves inflammation of the joints and spine.[10,87] It is estimated that up to 35% of patients with psoriasis have also psoriatic arthritis, with greater risks among those with severe disease. Patients with psoriasis are also at higher risk of having rheumatoid arthritis, ankylosing spondylitis and inflammatory bowel diseases, particularly Crohn's disease.[10,87]

Metabolic syndrome includes type 2 diabetes, obesity, dyslipidemia, and hypertension. A meta-analysis of cross-sectional and case-control studies conducted in 2013 reported higher odds of metabolic syndrome (including all the conditions listed above) among patients with psoriasis vs the general population (pooled OR 2.26; 95% CI 1,70-3.01).[88] Female patients were more likely to have diabetes and dyslipidemia than male patients, while male patients were more likely to have higher BMI.[45,89-93] Metabolic syndrome is also associated with psoriasis incidence and vice versa. Patients with psoriasis are at higher risk of developing diabetes (pooled RR 1.27; 95% CI 1.16-1.40) when compared to the general population, most likely due to insulin resistance that is caused by inflammation.[94]

Several observational studies reported that patients with psoriasis, especially those with higher disease severity are at least at 25% increased risk of major cardiovascular adverse event, such as myocardial infarction and stroke when compared to the general population.[87]A population-based

study conducted in the UK found that the increase in risk of myocardial infarction associated with psoriasis appeared to be independent of traditional risk factors such as smoking and metabolic syndrome.[95]

1.7 Psychiatric comorbidities

Psoriasis can have a negative effect on patients' body image and self-confidence and has been associated with stigma, especially among female patients.[3-6] In addition, patients with moderate-to-severe psoriasis suffer from pain and pruritus, which can lead to disability, impaired QoL and self-isolation.[5,6,96]

Up to 34% of patients with psoriasis also suffer from depression.[97] In fact, studies consistently reported higher prevalence of depression among patients with psoriasis when compared to the general population and to patients with other dermatological conditions, with the exception of alopecia, dermatitis, ulcers and vitiligo that had comparable rates.[97] In a meta-analysis of 98 cross-sectional studies (2014), patients with psoriasis were 57% more likely to have depression (pooled OR 1.57; 95% CI 1.40-1.76) when compared to individuals without psoriasis.[98] Patients with psoriasis were also at 48% higher risk of incident depression when compared to those without psoriasis as reported in a recent meta-analysis (2020) of 17 retrospective cohort studies (pooled RR 1.48; 95% CI 1.16-1.89).[99] Additionally, both depression and psoriasis share similar pathological pathways mediated by inflammatory cytokine.[100] Depression also affects psoriasis treatment outcomes. Two prospective cohort studies conducted in China among patients with psoriasis receiving biologic agents reported worse psoriasis clinical outcomes when patients had sustained depressive symptoms after 6 months of therapy.[101,102]

Anxiety was also reported in up to 34% of patients with psoriasis,[97,103] with anxiety-level appearing to vary by disease site.[97,103] Patients with psoriasis were 2.9 folds more likely to have anxiety when compared to patients with other dermatological conditions (OR 2.91; 95% CI 2.01-4.21).[104,105] In a cross-sectional study conducted in China, patients with psoriasis involvement in the palms and face had a higher mean score on the Hospital Anxiety and Depression Scale – Anxiety (HADS-A) when compared to patients with involvement in other locations.[106]

Adjustment disorder, an emotional and behavioral reaction to a stressful event, is also prevalent among patients with psoriasis with rates between 13.3% to 62.5%.[107-110] Patients can have an adjustment disorder with depressive or anxiety symptoms which if not well managed, can lead to anxiety disorder, depressive disorder and suicidality.[111] Other psychiatric conditions that are prevalent among patients with psoriasis include substance and alcohol abuse, personality disorders, somatoform disorders, sexual dysfunction and sleep disorders.[3]

Sex differences in psychiatric comorbidity were also noted in patients with psoriasis, with female patients having higher risks for depression and anxiety than male patients and male patients reporting more alcohol and substance abuse than female patients.[3,6,45,96,112] In addition, while male patients tend to have a more severe psoriasis, female patients tend to have worse psoriasis- related QoL.[45]

Lastly, a risk of suicide was also observed among patients with psoriasis, although this association remains controversial. Suicide is not a psychiatric disorder; however, it is the most severe consequence of some mental health disorders such as depression and adjustment disorder. Suicidality is a composite outcome including suicidal ideations, non-fatal suicide attempt and fatal (complete) suicide, while suicidal behaviour includes only fatal and non-fatal suicide attempt. Two recent meta-analyses that compared the risk of suicide between individuals with psoriasis and the general population reported contradictive results.[113,114] The first meta-analysis (2017) included 11 cohort, cross-sectional and case-control studies and reported a two-fold increased risk of suicidal ideations and 23% increased risk of suicidal behaviour among individuals with psoriasis compared to those without this disease.[113] While the second meta-analysis (2017) included three cohort studies (two of which were also included in the first meta-analysis) and did not find an association between psoriasis and suicidality, fatal suicide or non-fatal suicide.[114] Investigations looking at the association between psoriasis severity and suicide risk have also yielded variable results, with inconsistencies attributed to differences in psoriasis severity definitions, suicide definitions and methodology used.[115-118]

Chapter 2: Management of psoriasis

Several pharmacological and non-pharmacological therapies are available to manage psoriasis and the choice of treatment varies according to the severity of the disease.[4] Topical agents are prescribed for patients with mild psoriasis. Phototherapy and systemic agents, including CSA and biologic agents, are recommended for patients with moderate-to-severe psoriasis.

2.1 Topical agents

Topical agents are the first-line treatment options for mild psoriasis. The main types of topical agents include corticosteroids, vitamin D3 analogs, retinoids, anthralin and over the counter products (OTC) such as coal tar and salicylic acid.[4,119] All topical agents can cause dermatitis, irritation, itching and erythema at the site of application.[4]

Corticosteroids are the most widely used topical agents for psoriasis and come in a variety of forms including ointments, creams, gels, lotions, spray and solutions. They also come in different strengths and the range varies from Class 1 – super potent to Class 7 – least potent.[119] Class 1 topical steroids are the most effective topical agents for psoriasis.[120] Rarely, long-term use of topical corticosteroids can increase the risk of hypothalamic-pituitary-adrenal axis suppression which can lead to Cushing's syndrome and hyperglycemia.

Calcipotriol, the only Vitamin D3 analog available in Canada, reduces inflammation and slows keratinocytes growth by inhibiting T lymphocytes activity. Calcipotriol is available as a lotion or spray. In a meta-analysis of RCT involving topical treatments for mild psoriasis, vitamin D3 analogs were as effective as all but the most potent (Class 1) corticosteroids.[120] However, vitamin D3 analogs are better tolerated when compared to corticosteroids. A combination of calcipotriol and betamethasone dipropionate (a potent steroid) is also available. According to several RCT lasting from 4 to 12 weeks, this combination, used concomitantly or sequentially, was more effective than calcipotriol or betamethasone alone.[4,119]

The topical retinoid, tazarotene, is a vitamin A analog that slows overactive skin growth by also modulating keratinocytes proliferation and differentiation. Tazarotene is available as a cream and gel with two different potencies and is often used to treat facial psoriasis. According to an RCT, tazarotene is as effective as class 2-potency topical corticosteroids.[121,122]

Anthralin also works by slowing skin cell growth. It is available as an ointment, cream, paste and shampoo. Anthralin is less effective than corticosteroids, vitamin B and A analogs.[4,119] Lastly, two topical agents, coal tar and salicylic acid are available OTC. They are often used as adjunct to other topical agents. Salicylic acid softens the plaques so that prescribed topical agents can better penetrate the skin, thus increasing their effectiveness. Coal tar slows skin cell growth, reduces inflammation, itching and scaling.[4,119]

2.2 Phototherapy and photochemotherapy

Ultraviolet radiation may act by slowing keratinization of the skin and by inducing T-cell apoptosis in psoriatic plaques. Two types of light therapy exist: phototherapy and photochemotherapy. Phototherapy includes narrowband and broadband ultraviolet B phototherapy (UVB). Narrowband UVB involves the delivery of 311 nm of UVB radiation and broadband UVB involve the delivery of 290 to 320 nm of UVB radiation. Narrowband is considered more effective than broadband UVB.[4,123] Photochemotherapy involves treatment with the photosensitizer psoralen (administered orally or bathing in a solution of psoralen) followed by ultraviolet A (PUVA) radiation at 320 to 400 nm.[4,123] UVB and PUVA are usually administered by a trained dermatologist in the clinic. There are also UVB phototherapy units that can be used at home for localized skin involvement.

UVB has a shorter wavelength, thus it only reaches the epidermis (the upper level of the skin). PUVA can also reach the dermis because of the longer wavelength and the use of psoralen. With both UVB and PUVA, the dose of ultraviolet light must be carefully titrated based initially on the patient's skin complexion and likeliness to burn or tan. Phototherapy can be administered two to four times per week during the treatment phase. When a satisfactory response is achieved, the frequency of treatments is tempered to the lowest frequency required to maintain improvement.[4,123]

RCT comparing the efficacy of narrowband UVB vs PUVA yielded inconsistent results, with some studies reporting that PUVA provided a faster and more sustained response.[4,123,124] However, narrowband UVB is generally preferred over PUVA because it does not require an administration of psoralen and it has less side effects. PUVA can lead to skin aging and freckling and has been associated with non-melanoma skin cancers, including squamous cell carcinoma and basal cell carcinoma.[4,123] To minimize the risk of cancer, lifetime exposure to PUVA should be capped at 200 sessions.[4,123]

2.3 Systemic agents

2.3.1 Conventional systemic agents (CSA)

In Canada, the CSA methotrexate, acitretin, cyclosporine and apremilast are approved for the managements of moderate-to-severe psoriasis. Dose regimens for these treatments are summarized in Table 2.1.

2.3.1.1 Methotrexate

Methotrexate is a competitive inhibitor of dihydrofolate reductase that decreases folate cofactors required for the synthesis of nucleic acids, thus impairing DNA replication of T cells.[4,125] Common side effects can occur directly after treatment initiation and include fatigue, nausea and stomatitis. Because methotrexate is an immunosuppressant, it can also increase the risk of infection and reactivation of latent tuberculosis, hepatitis and Epstein-Barr virus-associated B-cell lymphoma. Other adverse events include pneumonitis, myelosuppression, epidermal necrolysis and hepatotoxicity. In fact, methotrexate is not recommended for patients with one or more risk factors for hepatoxicity such as alcohol abuse, abnormal liver function test levels, history of liver disease, etc. Methotrexate is also contraindicated during pregnancies and contraception should be used when receiving this agent.[4,125]

2.3.1.2 Cyclosporine

Cyclosporine is a potent immunosuppressant that functions by inhibiting calcineurin, responsible of activating T cells, thus blocking pro-inflammatory signaling.[4,125] Continuous long-term use of cyclosporine can lead to cumulative renal toxicity and hypertension, which can lead to loss of renal

function, although this effect is usually reversible after treatment discontinuation. Because of its nephrotoxicity, patients should not be continuously treated with cyclosporine for more than two years. Discontinuation of cyclosporine can lead to psoriasis flaring unless other treatments are substituted. Concomitant use of cyclosporine and narrow-band UVB is contraindicated due to the increased risk of photocarcinogenesis. However, cyclosporine is not contraindicated during pregnancies. The choice to prescribe cyclosporine or methotrexate should be based on patient's clinical profile.[4,125]

2.3.1.3 Acitretin

Acitretin is an oral retinoid that modulates keratinocytes differentiation and proliferation with anti-inflammatory properties. Acitretin is the only CSA that is not immunosuppressive and can be prescribed for immunosuppressed patients. Compared to methotrexate and cyclosporine, acitretin is a slow-acting drug taking from 3 to 6 months for full treatment response.[4,125] Acitretin is also less effective than other CSA when treating plaque psoriasis and is often used in combination with topical calcipotriol and phototherapy (UVB or PUVA) to increase its efficacy. Although acitretin is generally more tolerated than methotrexate and cyclosporine, this medication is contraindicated in women with childbearing potential due to its teratogenic effect and during nursing. It is recommended that women wait at least three years before getting pregnant after completion of treatment. Acitretin does not affect fertility or teratogenicity in men. Other side effects, ranging from mild to severe, include xerosis, dryness of the eye, nasal and oral mucosa and burning of the skin. As with any systemic retinoid, acitretin also has a black box warning for mood changes including new onset or worsening of depressive symptoms and risk of self-harm. However, real-world data showed no evidence of increased psychiatric adverse events with acitretin.[126]

2.3.1.4 Apremilast

Apremilast is a phosphodiesterase 4 inhibitor that increases the level of intracellular cyclic adenosine monophosphate, which in turns, downregulates inflammatory responses involving lymphocytes T helper 1 and 17. During pivotal phase III RCT, apremilast was more effective than placebo after 16 weeks in achieving PASI-75 among patients with moderate-to-severe psoriasis. The most common adverse events of apremilast during RCT were diarrhea, nausea and upper

respiratory tract infections. Depression also occurred in 1% of the patients. Apremilast is often prescribed to patients who prefer to avoid frequent injections and laboratory monitoring.

Table 2.1. Dosage regimen of CSA

Systemic agent	FDA/HC approval for psoriasis	Mode of administration	Recommended dosing for plaque psoriasis
Methotrexate	1950/1950	Oral, intravenous, intramuscular or subcutaneous	7.5 mg to 25 mg weekly as a single dose or divided into 3 doses over 24 hours. Physician can prescribe a test dose of 2.5 mg to 5 mg that is followed by a complete blood count 5 to 7 days after the dose to examine whether patients are at risk of bone marrow suppression.
Cyclosporine	1997/1997	Oral and microemulsion	2.5 mg/kg/day to 3.0 mg/kg/day twice daily for 4 weeks before gradually increasing the dose by 0.5 mg/kg/day until adequate control is obtained
Acitretin	1997/1997	Oral	10 mg to 50 mg daily
Apremilast	2014/2015	Oral	30 mg twice daily. A titration schedule is required with an initial dose of 10 mg daily that is increased by up to 10 mg per day over the first 5 days

2.3.1.1 Other conventional systemic agents

Fumeric acids esters (fumerates) have immunomodulating, angiogenesis and antioxidant effect. They are approved for moderate-to-severe psoriasis only in Western Europe. Sulfasalazine is a disease-modifying anti-rheumatic drug prescribed for rheumatoid arthritis, psoriatic arthritis and Crohn's disease. Although sulfasalazine has not been approved for the management of psoriasis, it can be used when patients have a concomitant immune-mediated disorder for which this agent is prescribed or when other CSA are contraindicated. An RCT including 32 patients with moderate-to-severe psoriasis in Egypt reported that sulfasalazine was safer but less effective than methotrexate in achieving skin clearance among patients with moderate-to-severe psoriasis after 8 weeks of therapy.[127]

2.3.2 Biologic agents

2.3.2.1 Overview and efficacy of all biologic agents

Biologic agents have revolutionized the management of moderate-to-severe plaque psoriasis and other immune-mediated conditions such as rheumatoid arthritis, inflammatory bowel diseases, psoriatic arthritis and ankylosing spondylitis.[4,128] Most biologic agents are chimeric, humanized or fully human monoclonal antibodies, except for etanercept which is a recombinant human fusion

protein.[4,128] Biologic agents bind monospecifically to cytokines or receptors of cytokines involved in the pathogenesis of psoriasis, such as TNF-a, IL-12, IL-23, IL-17A or IL-17A receptor, and neutralize their activity. Biologic agents can be administered subcutaneously or as an intravenous infusion:

- TNF-a inhibitors include etanercept, infliximab, adalimumab and certolizumab pegol
- IL-12/23 inhibitor include ustekinumab
- IL-17A inhibitors include secukinumab, ixekizumab
- IL-17A receptor inhibitor include brodalumab
- IL-23 inhibitors include guselkumab, tildrakizumab and risankizumab

Table 2.2 summarizes the regimen dosing of each biologic agent. In all double-blind RCT, biologic agents were more effective than placebo and methotrexate in achieving a more rapid skin clearance (PASI-75, 90 and 100) within 10 to 16 weeks, and sustaining it over a longer period (up to 3 years) during the maintenance periods.[129,130]

In a recent Bayesian network meta-analysis of 60 phase II, III and IV RCT on the efficacy of all biologic agents for patients with moderate-to-severe psoriasis, risankizumab, ixekizumab, brodalumab and secukinumab had the higher PASI-75, 90 and 100 rates at the end of 10 to 16 weeks of treatments when compared to adalimumab, ustekinumab, certolizumab, etanercept and tildrakizumab, with etanercept having the lowest rates.[129] Similar results were observed during the maintenance period (44 to 60 weeks). Among all TNFi, infliximab achieved the highest PASI response when compared to placebo.[130]

Biologic agents may be combined with other psoriasis treatments, such as topicals, phototherapy or CSA to increase their efficacy. Some TNFi such as infliximab, etanercept and certolizumab are not human monoclonal antibodies and may be associated with immunogenicity.[128] Clinical guidelines recommend adding methotrexate to reduce the risk of losing response to these agents.[128]

Table 2.2. Dosage regimen of biologic agents

Biologic agent (Brand name)		FDA/HC approval for psoriasis	Mode of administration	Recommended dosing for plaque psoriasis
TNFi	**Etanercept (Enbrel)**	2004/2005	Subcutaneous injection	Loading/induction dose of 50 mg twice a week for the first 12 weeks (3-4 days apart) followed by a maintenance dose of 25 mg or 50 mg once a week
	Infliximab (Remicade)	2006/2006	Intravenous infusion	Loading/induction dose of 5 mg/kg at week 0, 2, 4 and 6 followed by a maintenance dose of 5 mg/kg every 8 weeks
	Adalimumab (Humira)	2008/2008	Subcutaneous injection	Loading dose of 80 mg followed by a weekly dose of 40 mg (or every other week).
	Certolizumab pegol (Cimzia)	2018/2019	Subcutaneous injection	Loading/induction dose of 400 mg at week 0, 2 and 4 followed by a dose of 200 mg every 2 weeks
IL-12/23 inhibitor	**Ustekinumab (Stelara)**	2009/2009	Subcutaneous injection	Patients ≤100kg: loading/induction dose of 45 mg at week 0 and 4 followed by maintenance dose of 45 mg every 12 weeks Patients >100kg: loading/induction dose of 90 mg at week 0 and 4 followed by maintenance dose of 90 mg every 12 weeks
IL-17A inhibitors	**Secukinumab (Cosentyx)**	2015/2015	Subcutaneous injection	Loading/induction dose of 300 mg at week 0, 1, 2, 3 and 4 followed by a maintenance dose of 300 mg every 4 weeks.
	Ixekizumab (Taltz)	2016/2016	Subcutaneous injection	Loading/induction dose of 160 mg at week 0 followed by 80 mg at week 2, 4, 6, 8 and 10 followed by a maintenance dose of 80 mg every 4 weeks.
IL-17A receptor inhibitor	**Brodalumab (Siliq)**	2017/2018	Subcutaneous injection	Loading/induction dose of 210 mg at week 0, 1 and 2 followed by a maintenance dose of 210 mg every 2 weeks
IL-23 inhibitors	**Guselkumab (Tremfya)**	2017/2017	Subcutaneous injection	Loading/induction dose of 100 mg at week 0 and 4 followed by a maintenance dose of 100 mg every 8 weeks
	Tildrakizumab (Ilumya)	2018/2021	Subcutaneous injection	Loading/induction dose of 100 mg at week 0 and 4 followed by a maintenance dose of 100 mg every 12 weeks
	Risankizumab (Skyrizi)	2019/2019	Subcutaneous injection	Loading/induction dose of 150 mg at week 0 and 4 followed by a maintenance dose of 150 mg every 12 weeks

FDA: Food and Drugs Administration; HC: Health Canada; IL: Interleukin; TNFi: Tumor necrosis factor inhibitors

2.3.2.2 Adverse events associated with biologic agents

Biologic agents are usually well tolerated. In rare instances, biologic agents were associated with an increased risk of serious infection such as abscess, sepsis and upper respiratory tract infection.[131] Patients should discontinue biologic agents during a serious infection until the infection resolves.[131] Biologic agents were also associated with reactivation of certain cancers, such as melanoma, basal cell carcinoma and squamous cell carcinoma.[131] TNFi also reactivate and worsen the prognosis of latent tuberculosis, hepatitis B virus, demyelinating diseases and advanced congestive heart failure (CHF).[131] Therefore, their use is either contraindicated or should be avoided in patients with these conditions. Etanercept is also contraindicated among patients with

HIV.[131] TNFi have also been associated with psoriasis-like eruptions and flaring among patients with psoriasis and other immune-mediated conditions. IL-17A and IL-17A receptor inhibitors are contraindicated in patients with a history or active IBD.

2.3.2.3 Access to biologic agents among patients with moderate-to-severe psoriasis covered by the province of Quebec drug plan

Although biologic agents are more effective than CSA in achieving skin clearance, access to these agents is limited in the province of Quebec because of their high acquisition costs. In Quebec, biologic agents are considered as "*médicaments d'exception*s" by the *Régie de l'Assurance Maladie du Québec* (RAMQ) drug plan.[11]

To be reimbursed for moderate-to-severe plaque psoriasis, the healthcare professional should submit a report to RAMQ on behalf of the patient attesting:

1. The presence of a score ≥15 on the PASI or the presence of large plaques on the face, palms or soles or in the genital area; **and**
2. The presence of a score ≥15 on the DQLI questionnaire; **and**
3. Phototherapy treatment of ≥30 sessions for three months has not made it possible to optimally control the disease **or** where a treatment of ≥12 sessions for one month has not provided significant improvement in the lesions. **Except** if phototherapy is contraindicated, not tolerated or not accessible; **and**
4. Treatment with two CSA (methotrexate, cyclosporine and acitretin), used concomitantly or not, each for at least three months, has not made it possible to optimally control the disease. **Except** in the case of a serious intolerance or a contraindication.

The initial request is authorized for a maximum of four months. When requesting continuation of treatment, the physician must provide information making it possible to establish the beneficial effects of the treatment, specifically:

1. An improvement of at least 75% in the PASI score compared to the base value; **or**
2. An improvement of at least 50% in the PASI score and a decrease of at least five points on the DQLI questionnaire compared to the base values; **or**

3. A significant improvement in lesions on the face, palms or soles or in the genital area compared to the pre-treatment assessment **and** a decrease of at least five points on the DQLI questionnaire compared to the base value.

Requests for continuation of treatment are authorized for a maximum of 12 months. This policy is applied to all biologic agents approved by Health Canada and recommended by the *Institut National d'Excellence en Santé et en Services Sociaux* in Quebec. Similar policies of reimbursements are adopted by other Canadian provinces and other countries with universal drug plans.[132-135]

While Health Canada approved etanercept, the first biologic agent, in 2004 for the management of moderate-to-severe psoriasis, it was not included in the Quebec provincial drug formulary until June 2008 along side infliximab.[136,137] Before that date, biologic agents were covered by RAMQ for patients with psoriasis considered as exceptional patients "*patients d'exceptions*", i.e, treatments not included in the provincial drug formulary that can be reimbursed for patients under certain conditions.

Although apremilast is not a biologic agent, it is also covered by RAMQ as a *médicament d'exception*. Therefore, similar requirements as those listed above for biologic agents are requested by RAMQ for patients with moderate-to-severe psoriasis if they want to initiate apremilast.

2.3.2.4 Patient's needs and goals from systemic agent therapy

Several observational studies reported that adverse events were the main reasons of CSA discontinuation, while loss of efficacy was the main reason for biologic agent discontinuation.[12,138,139] Before initiating any psoriasis treatment, balance between having realistic expectations and patient needs and goals from therapy should be achieved to facilitate shared decision making with the healthcare professional and to find the optimal personalized treatment. However, few studies examined patient needs and goals from systemic therapies.[25,140]

A cross-sectional study conducted in Switzerland and Germany among 5,424 patients with psoriasis initiating a systemic agent (CSA or biologic agent) from 2008 and 2016 found that regain

control of the disease and be healed of all skin defects quickly were reported by more than 90% of study participants as the most important needs when initiating systemic agents.[25] The main goals after initiating systemic agents among patients younger than 65 years were to feel less depressed, lead a normal working life, be more comfortable showing themselves in public and improve their sexual life.[25] Among patients 65 years and older, lower risk for adverse events, improvement of sleep quality and lower number of medical visits were reported as the main treatment goals.[25] The authors also concluded that female patients, especially those with other immune-mediated conditions, had higher expectations from systemic agents' use than male patients and were more likely to report all treatment goals listed above.[25,140] The higher expectations of females from systemic agent therapy have been associated to their perceived psoriasis-related discrimination. Experiencing or perceiving discrimination may lead to self-isolation, impairment of self-confidence and lower QoL.[6,141] However, female patients with psoriasis tended to respond better to both CSA and biologic agents when compared to male patients.[24]

2.3.3 Improvement in health-related QoL (HRQoL), depressive and anxiety symptoms with biologic agents during RCT

RCT assessing the efficacy of TNFi/UST in patients with moderate-to-severe psoriasis also sought to determine the effect of these agents on HRQoL and anxiety/depressive symptoms as secondary efficacy endpoints.[26-33] These RCT consistently reported significant improvement in HRQoL and anxiety/depressive symptoms in patients treated with biologic agents when compared to placebo and methotrexate after 10 to 24 weeks of therapy, with most RCT examining the effect at 12 weeks. The beneficial effect of biologic agents on these secondary efficacy endpoints persisted during the extension periods, lasting up to three years after treatment initiation.[30,31,33] RCT comparing newer generation of biologic agents (IL-17 and IL-23 inhibitors) to older generations (TNFi and ustekinumab) reported significant improvement in depressive and anxiety symptoms and HRQoL with newer generation biologic agents.[142-150] In these RCT, the validated self-reported questionnaires, the Dermatology Quality Index (DLQI), the Short-Form 36 (SF-36) and the EuroQoL-5d (EQ-5D) were used to measure HRQoL.[26-33,142-150] Beck depressive inventory, Hospital Anxiety and Depression scale (HADS) and Hamilton rating scale (HAM-D) were used to assess self-reported improvement in depressive and anxiety symptoms. In one RCT, etanercept was also associated with improvement in fatigue symptoms using the Functional Assessment of Chronic Illness Therapy Fatigue scale (FACTIF-F).[26-33,142-150]

Chapter 3: Literature review

3.1 Patterns of systemic agent use among patients with psoriasis initiating CSA

In Canada, only one study described patterns of systemic agent use for moderate-to-severe psoriasis in 2007 using an online survey (N = 514).[151] Of all respondents, only 8% received CSA and 5% received biologic agents. Among participants from Quebec (N = 195), 10% and 7% received CSA and biologic agents, respectively.[151] Of note, this study was conducted before etanercept and infliximab, the first biologic agents indicated for psoriasis, were included on the Quebec drug formulary (June 2008). *It is likely that the use of CSA and biologic agent in psoriasis has changed since then.*

To date, 11 cohort studies (7 retrospective and 4 prospective) conducted in Europe, US and Asia have examined patterns of CSA and biologic agent use,[12-21] with three of these studies examining only CSA use (Table 3.1).[15,17,18] Patterns included treatment discontinuation, switch and (or) add-on. In some studies, these outcomes were combined to form one composite outcome labeled "treatment failure".[13,15,16,18,20] Studies that examined treatment failure, reported an increased risk over time, varying from 28.4% at one year to 90.0% at three years of therapy initiation.

The definition of treatment discontinuation varied between studies. In prospective cohort studies, CSA discontinuation was defined as either two consecutive missing doses[14] or self-reported discontinuation due to ineffectiveness, remission and/or side effects.[20,21] One study also considered treatment switch as discontinuation due to ineffectiveness and side effects.[20] In retrospective cohort studies, discontinuation was mostly defined as a gap of more than 30, 60 or 90 days between two consecutive prescription fills.[12,16,17,19] One study defined CSA discontinuation as treatment cessation due to a hospitalization related to psoriasis treatment,[18] and another study combined treatment cessation with treatment switch in their definition of discontinuation.[15] Due to this heterogeneity in the definitions, the reported percentage of CSA discontinuation at one year following initiation has varied from 3% to 85%.[12,14-17,19,152] In all studies comparing biologic agents to CSA use, the risk of discontinuation among CSA users was higher than that among biologic agent users.[12,14,16,19-21] Among CSA users, methotrexate was associated with lower risks

of discontinuation when compared to both acitretin and cyclosporine.[12,14,15,17,18] Four studies considered treatment cycles as the unit of analysis instead of individual patients.[12,14,16,21] In these studies, a treatment cycle was defined as the period from the start of a therapy until the last dose before discontinuation, and thus, some patients had multiple treatment cycles during the follow-up. *This exposure consideration may have introduced prevalent-user bias that varied over time. This bias occurs when previous experience with drug effectiveness and side effects affects the current choice of therapy.*[153] Only one study, conducted by Arnold and colleagues (2016) in Germany, performed a sensitivity analysis to examine the risk of treatment discontinuation separately among patients receiving a CSA as a first-line treatment (first cycle) vs those receiving it as ≥ second-line treatment (subsequent cycles).[12] In their main analyses, methotrexate, acitretin and cyclosporine were compared to fumarate acid esters (systemic agent not approved in North America) over all cycles. Acitretin (HR 2.13, 95% CI: 1.15-3.94) and cyclosporin users (HR 3.35, 95% CI: 1.48-7.58) were at higher risk of treatment discontinuation but not methotrexate users (HR 0.95, 95% CI: 0.63-1.43). The results remained consistent in the sensitivity analyses, although the point estimates were not reported in the manuscript.[12] In this study, patients using more than one systemic agent concomitantly were also included but discontinuation was examined for each of these agents separately.[12] A recent study conducted in France among 73,168 patients with psoriasis initiating a CSA reported that age over 40 years, male sex, psoriatic arthritis, IBD, hypertension, dyslipidemia, hepatic and kidney diseases, and cancer were associated with lower risks of CSA discontinuation.[17] Another study conducted among patients initiating methotrexate and acitretin in Israel found that among acitretin users, the presence of psoriatic arthritis was associated with an increased risk of treatment discontinuation (HR 1.98, 95% CI 1.59-2.46) and among the methotrexate group, patients with metabolic syndrome were at a lower risk of discontinuation (HR 0.87, 95% CI 0.76-0.99).[15]

Only four studies examined CSA and biologic treatment switch and add-on in patients with psoriasis.[16,18,19,154] In two studies, switch occurred if a patient received a fill for a different agent without refilling the initial one and an add-on occurred if they received a fill for a different agent and refilled the initial one.[16,18] Feldman and colleagues (2005) reported that after one year of initiating a CSA, 21.0% of cyclosporine users switched therapy compared to 19.7% of acitretin users and 10.2% of methotrexate users, while for treatment add-on, the proportions were 5.0% for

cyclosporine, 0.5% for acitretin and 1.6% for methotrexate users.[18] In this study, the authors did not report the type of treatment received after the switch/add. Svedbom and colleagues (2016) found that CSA users were more likely to switch and to receive a second psoriasis treatment as an add-on when compared to biologic agent users after 1 year of therapy.[16] However, the authors (1) did not differentiate between different agents within each treatment category; (2) did not report the type of treatment received after the switch; and (3) patients in that study were allowed to have multiple treatment cycles. Tabolli and colleagues (2015) also considered multiple treatment cycles per patient. They reported that 34% of patients receiving a CSA switched to a biologic agent and patients younger than 50 years (vs ≥ 50 years) were more likely to switch.[154] This study did not differentiate between switch and add-on.[154] Only one retrospective cohort study, conducted by Higa and colleagues (2019) in the US, reported the type of treatment received after a switch occurring within two years of treatment initiation.[19] In this study, systemic agents were separated into two treatment classes: oral and biologic with the CSA considered under the oral treatments, although methotrexate is also available by injection. A switch was defined as initiating a different class of treatment following the initial treatment discontinuation (gap > 30 days between two consecutive prescriptions), while restart of therapy was defined as receiving the same class of treatment following discontinuation.[19] Of the 3,044 patients initiating a CSA, 1,386 (45.5%) discontinued their initial treatment. From these, 157 (11.3%) switched to a biologic agent, 28 (2.0%) to apremilast, 8 (0.06%) to methotrexate and 834 (60.1%) restarted their initial treatment.[19] Use of a different systemic agent before CSA discontinuation was not considered a switch in this study. Therefore, the rate of those who added a second CSA or a biologic agent was not evaluated. In addition, some discrepancies were noted in the reported numbers of switches and restart of therapy. For example, it was not clear why the 36 occurrences of apremilast and methotrexate use following CSA discontinuation were reported in their flow-chart as switches and not restarts of therapy as per the authors' definition.

Only one prospective cohort study conducted by Hernandez-Fernandez and colleagues (2021) examined sex differences in the risk of discontinuation among 2,881 patients with psoriasis receiving CSA and biologic agents (41.7% females).[21] In their study, patients were not necessarily first-time systemic agent users. Patients were allowed to have been previously treated with a systemic agent that was different from the agent received at cohort entry. In their study, female

patients were 33% more likely to receive a biologic agent when compared to male patients (OR 1.33; 95% CI 1.15-1.55). However, the risks of discontinuation due to ineffectiveness of therapy or remission were not higher in female patients when compared to male patients (subHazard ratio 1.17; 95% CI 1.00-1.38 and HR 1.00; 95% CI 0.83-1.20, respectively), although the former was borderline significant ($p = 0.055$).

In summary, few studies examined treatment discontinuation and switch among first-time CSA users. In addition, no prior study was conducted in Canadian settings to (1) examine patterns of systemic agent use among patients with psoriasis initiating a CSA; (2) determine factors associated with CSA discontinuation and switch; and (3) examine if sex differences existed in patterns of discontinuation and switch among patients initiating a CSA. It is important to assess sex disparities with regards to patterns of treatment use and their predictors to inform patient counseling in clinical practice. Sex disparities in treatment use may arise because of the higher expectations of female patients from systemic agent treatments and thus their higher risk for unmet expectations and disappointment that may lead to treatment discontinuation.

Table 3.1. Summary of studies examining patterns of systemic agent use among patients receiving CSA

Author, year of publication (Country)	Data source (Study design)	Study population	Exposures	Outcome	Findings
Feldman, 2005 (United-States)[18]	Large managed care insurer in north-eastern USA – years of follow-up was not provided (Retrospective cohort study)	Patients with psoriasis initiating on a CSA	MTX (N = 404) CYC (N = 101) ACI (N = 235)	Treatment failure at 1 year	Treatment failure for cyclosporin (28.2%), acitretin (28.4%) and methotrexate (17.5%)
Levin, 2014 (United-States)[13]	Patients' medical electronic records from the Department of Dermatology clinic in Boston from 2008 to 2012 (Retrospective cohort study)	Patients with psoriasis receiving CSA and biologic agents	159 patients with 284 treatment cycles CSA (N = 84) Biologic agents (N = 200)	Treatment failure defined as treatment discontinuation for any reason	48% of biologic agent users discontinued vs 75% of CSA after 242 days on average
Shalom 2015, (Israel)[15]	Medical database of Clalit Health Services from 2002 to 2013 (Retrospective cohort study)	Patients with psoriasis initiating a CSA	MTX (N = 2,632) vs ACI (N = 3,624)	Discontinuation	MTX vs ACI aHR=0.95, 95% CI: 0.88-1.02)
Svedbom, 2015 (Sweden)[16]	Swedish Health administrative databases from 2005 to 2011 (Retrospective cohort study)	Patients with psoriasis receiving topical agents, CSA or biologic agents	CSA group (N = 2,963)	Discontinuation Switch to or add-on a different treatment category	Discontinuation = 47.9% Switch=12.5% add-on=45.3%
Tabolli, 2015 (Italy)[154]	Institute of dermatology in dell'Immacolata (Prospective cohort study)	Patients with moderate-to-severe psoriasis receiving CSA or biologic agent	Multiple treatment cycles allowed: CSA (N = 130)	Switch from CSA to a biologic agent	34% of patients receiving a CSA switched to a biologic agent
Davila-Seijo, 2016 (Spain)[14]	Spain registry of systemic therapy in psoriasis (BIODADERM) - from 2008 to 2013 (Prospective cohort study)	Patients diagnosed with psoriasis who received a CSA or a biologic agent. Patients could have received a CSA prior to cohort entry, but not the index CSA at cohort entry	Multiple treatment cycles allowed: MTX (N = 638), ACI (N = 340), CYC (N = 356)	Drug survival at the first year	MTX: 50.3% (95% CI: 46.3%-54.2%) ACI: 42.3% (95% CI: 36.9%-47.6%) CYC: 23.3% (95% CI: 19.0-27.8%)
Arnold, 2016 (Germany)[12]	Medical records of all patients of a dermatology clinic from 2003 to 2014	Patients with psoriasis with at least one CSA or a biologic agent prescription fill	Multiple treatment cycles allowed FAE (N = 158) MTX (N = 174)	Discontinuation	Compared to FAE: ACI: aHR=2.13 (95% CI: 1.15-3.94)

	(Retrospective cohort study)		ACI (N = 63); CYC (N = 19)		CYC: aHR=3.35 (95% CI: 1.48-7.58) MTX: aHR=0.95 (95% CI: 0.63-1.43)
Higa, 2019 (United-States)[19]	MarketScan database from 2014 to 2016 (Retrospective cohort study)	Patients with psoriasis who initiated a CSA	APR (N = 1,403) MTX (N = 1,466) ACI (N = 104) CYC (N = 71)	Discontinuation Switch to a different systemic agent after discontinuation	45.5% discontinued their initial CSA 11.3% patients switched to a biologic 2.0% switched to apremilast 0.06% switched to methotrexate
Bergqvist, 2020 (France)[17]	French National Health Insurance Database from 2008 to 2016 (Retrospective cohort study)	Patients with psoriasis who initiated a CSA	MTX (N = 27,761) ACI (N = 43,216) CYC (N = 2,191)	Discontinuation	Compared to ACI: MTX: aHR=0.48 (95% CI: 0.49-0.50) CYC: aHR=0.79 (95% CI: 0.48-0.50).
Puig, 2020 (Spain)[20]	SAHARA Study from 2012 to 2014 (Prospective cohort study)	Patients with moderate-to-severe psoriasis initiating a CSA or a biologic agent	CSA (N = 181) Biologic agents (N = 371)	Treatment discontinuation at 2 years defined as treatment cessation switch to adverse events and ineffectiveness	CSA users were at higher risk of discontinuation vs biologic agent users (log rank p<0.001) MTX=37.1% CYC=58.3% ACI: 52.8%
Hernandez-Fernandez, 2021 (Spain)[21]	Spain registry of systemic therapy in psoriasis (BIODADERM) - from 2008 to 2018 (Prospective cohort study)	Patients with psoriasis who initiated a CSA or a biologic agent. Patients could have received a CSA prior to cohort entry, but not the index CSA at cohort entry	2881 patients (41.7% females)	Sex differences in systemic agent discontinuation, self-reported due to ineffectiveness and due to remission	Female vs male patients: discontinuation due to ineffectiveness: sHR=1.17 (95% CI 1.00-1.38) Discontinuation due to remission: sHR=1.00 (95% CI: 0.83-1.20

ACI: acitretin; APR: Apremilast; aHR: adjusted hazard ratios; CI: confidence intervals; FAE: Fumerate acid esters; MTX: methotrexate; PSa: psoriatic arthritis; IBD: Inflammatory Bowel diseases; SHR=sub-Hazard Ratio (used in competing risks regression models and are similarly interpreted to hazard ratios in Cox regression)

3.2 Burden of mental health disorders among patients with psoriasis

Thus far, three studies conducted in the US have assessed the incremental healthcare costs among patients with psoriasis with (vs without) mental health disorders (Table 3.2).[7-9] Two of these studies included only patients with moderate-to-severe psoriasis who received systemic agents[7,9] and two studies assessed both incremental direct all-cause health care costs and indirect costs related to short-term disability associated with having a comorbid psychiatric disorder with psoriasis.[8,9]

Han in colleagues (2011) conducted a retrospective cohort study using PharMetric healthcare claims databases to compare annual all-cause healthcare costs among patients with psoriasis with (vs without) a prevalent psychiatric disorder between 2003 and 2004.[7] Patients were considered to have moderate-to-severe psoriasis if they received a diagnosis of psoriasis and either phototherapy, CSA or a biologic agent during that time period. Prevalent psychiatric disorders included depression, anxiety, bipolar, delirium, dementia, and schizophrenia. Annual all-cause healthcare costs included costs for all outpatient, inpatient, and emergency department (ED) visits, and those for any medication prescription fill assessed during the study period. It is worth noting that the authors did not mention when the psychiatric disorders were assessed (e.g. before or after cohort entry) and did not provide the duration of the follow-up. Patients with (N = 1,103) vs without a psychiatric disorder (N = 6,868) had higher mean annual healthcare costs ($17,638 vs $10,363, $p < 0.001$). Mean annual cost for outpatient visits ($5,249 vs $2,298), inpatient visits ($4,999 vs $1,421), ED visits ($383 vs $122) and prescription fills ($6,760 vs $5,687) were also higher among patients with (vs without) a psychiatric disorder ($p < 0.001$ for all).

Feldman and colleagues (2017) conducted a retrospective cohort study to assess the incremental health care and indirect costs associated with having physical and psychiatric comorbidities among patients with psoriasis (N = 56,406) using the MarketScan and Medicare health administrative databases.[8] To be included in the study, patients were required to have at least two psoriasis diagnoses between January 2010 and December 2011, with the first one occurring in 2010. Comorbidities were assessed based on the 2010 data. Annual healthcare costs included those for inpatient, outpatient and ED visits, and pharmacy claims. Indirect costs included those related to short-term disabilities (absenteeism). Two-part models were used to estimate adjusted costs.

Patients with depression (N = 4,388) had higher annual all-cause and indirect costs (incremental mean annual cost of $6,765; 95% CI $1,188–$2,081 and $996; 95% CI $433–$1,561, respectively). Having anxiety (N = 3,148) was associated with a significant incremental annual all-cause health cost ($4,181; 95% CI $6682–$10,091) but not with indirect costs ($267; 95% CI -$301–$832).

Cai and colleagues (2019) conducted a retrospective cohort study using MarketScan administrative databases to compare annual all-cause healthcare and indirect costs among patients with psoriasis with (vs without) treated depression and/or anxiety.[9] Patients who received a psoriasis diagnosis and were treated with a systemic agent between January and December 2014 were considered. These were followed for one year. Patients were considered treated for depression and/or anxiety if they received a diagnostic code for depression and/or anxiety followed by a prescription fill for an antidepressant, benzodiazepine or anti-psychotic agent in the following 30 days (N = 2,675). Patients with a mental health disorder were matched to patients without a mental health disorder on age, sex, type of health care plan and region of residency (1:1). Annual all-cause healthcare costs included those for outpatient, inpatient and ED visits and prescription fills. Indirect costs included those related to short-term disability. Incremental costs attributed to treated anxiety and/or depression were examined using generalized linear models with gamma distribution and log link. Patients with treated anxiety and/or depression had higher annual mean all-cause unadjusted healthcare cost of $8,077 ($p < 0.001$). Similarly, after adjustment, patients with treated anxiety and/or depression had higher annual mean all-cause healthcare cost of $5,781 ($p < 0.00$). When assessed separately, having depression and anxiety (N = 704) was associated with an incremental unadjusted annual mean all-cause cost of $12,884 ($p < 0.01$), depression alone (N = 1,128) with $8,859 ($p < 0.01$) and anxiety alone (N = 843) with $3,018 ($p = 0.09$). Short-term disability was only measured for 122 patients with an incremental unadjusted indirect annual mean cost of $1,773 ($p = 0.02$) in the presence of depression and/or anxiety.

In summary, the three reviewed studies documented the significant economic burden associated with having a comorbid psychiatric disorder such as depression and anxiety among patients with psoriasis. Nonetheless, we cannot ascertain whether the total annual incremental cost per patient was directly related to the psychiatric disorders or to other related conditions. Patients with

psoriasis are known for being at high risk of having comorbidities such as cardiovascular diseases, metabolic disorders and immune-mediated conditions that may, in turn, be associated with psychological distress, anxiety and depression.[87,155-157] The presence of psychiatric disorders could worsen psoriasis outcomes,[4] lowers response to treatments and leads to treatment failure. [4,23,76-81,101,102] Nonetheless, RCT reported significant improvement in QoL and anxio-depressive symptoms among patients with psoriasis initiating a biologic agent who previously received a CSA or were candidates to receive these agents.[26-33] Therefore, it is important to assess how mental health-related health care costs fluctuate depending on patterns of CSA and biologic agent use. Although two studies have included patients receiving systemic agents, no prior study compared mental health-related health care costs between patients receiving CSA vs biologic agents and no study examined whether certain patterns of systemic agent use were associated with incremental costs.

Table 3.2. Summary of studies examining the economic burden of mental health disorder among patients with psoriasis

Author, year of publication (Country),	Data source (Study design)	Study population	Outcome	Findings
Han, 2011 (United-States)[7]	PharMetric healthcare claims databases between 2003-2004 (Retrospective cohort study)	Patients with moderate-to-severe psoriasis with (N = 1,103) versus without a psychiatric disorder (N = 6,868)	Annual all-cause healthcare costs among those with vs without a prevalent psychiatric disorder (depression, anxiety, bipolar, delirium, dementia and/or schizophrenia)	$17,638 vs $10,363, p<0.001
Feldman, 2017 (United-States)[8]	MarketScan and Medicare health administrative databases between 2010 and 2011 (Retrospective cohort study)	Patients with psoriasis (N=56,406)	Incremental annual mean direct and indirect healthcare costs with vs without depression or anxiety	Depression: Direct: $6,765 (95% CI: $1,188–$2,081) Indirect: $996 (95% CI: $433–$1,561) Anxiety: Direct: $4,181 (95% CI: $6,682–$10,091) Indirect: $267 (95% CI: -$301–$832)
Cai, 2019 (United-States)[9]	MarketScan claims database between January 2014 and December 2015 (Retrospective cohort study)	Patients with moderate-to-severe psoriasis (N = 5,350)	Incremental annual mean direct and indirect healthcare costs with vs without treated anxiety and/or depression	Depression and/or anxiety: $8,077 (p<0.001) Depression and anxiety: $12,884 (p<0.01) Depression: $8,859 (p<0.01) Anxiety: $3,018 (p=0.09) Indirect costs: $1,773 (p=0.02)

3.3 The risk of mental health disorders and systemic agents

Seven cohort studies (four prospective and three retrospective) compared the risk of mental health outcomes between patients with psoriasis receiving CSA and those receiving biologic agents (Table 3.3).[34-40] Three of the four prospective cohort studies used BIOBADADERM registry, a national multicenter registry in Spain.[38-40] Overall, the use of biologic agents was associated with lower risks of mental health outcomes in four studies,[34-36,39] while in one study, the risk was higher among biologic agent users,[40] and in two studies, the risk was similar between users of CSA and those of the biologic agents considered.[37,38]

The definitions of mental health outcomes varied between studies. Mental health outcomes included depressive symptoms measured by the HADS-D,[34] depression and/or insomnia,[36] treated depression and/or anxiety,[37] any psychiatric disorders (depression, psychosis, bipolar suicide and suicidal ideations) examined separately and as a composite outcome,[35] and psychiatric adverse events.[38-40] In four studies, mental health disorders were the main study outcomes while in the three cohort studies using BIOBADADERM registry, psychiatric adverse events were examined alongside several other potential drug adverse events.[38-40] Two studies examined the risk of incident mental health outcomes,[34,37] one study compared the prevalence of depression/insomnia prior and after initiating a biologic agent,[36] and the other studies did not exclude patients with a history of the mental health outcome(s) under investigation.[35,38-40]

With regards to exposure groups, CSA considered by these studies included methotrexate,[34-40] cyclosporin,[34-40] acitretin,[34-36,38-40] apremilast,[35,37,40] fumarate acid esters[34] and oral steroids[34,37]. The biologic agents considered were TNFi (adalimumab,[34-40] etanercept,[34,35,37-40] infliximab,[34,35,37-40] certolizumab[37] and golimumab[35-37]), IL-12/23 inhibitors (ustekinumab),[34-40] IL-17 inhibitors (secukinumab[35,37,40] and ixekizumab[35,37]) and IL-23 inhibitors (guselukumab and tildrakizumab)[37]. Two studies considered each agent separately,[39,40] one study differentiated between TNFi and ILi,[37] and the other studies combined all biologic agents.[34-36,38]

Only one study, conducted in Taiwan by Wu and colleagues (2016), included first-time biologic agent users.[36] In this study, the authors compared the prevalence of depression and insomnia before and after initiating a TNFi among 980 patients with psoriasis and psoriatic arthritis. The authors

found that within two years of initiating these agents, the prevalence of depression and insomnia significantly decreased by 43.8% ($p < 0.001$). Similar results were found when separate analyses were conducted for different sex and age groups (< 45 and ≥ 45 years). However, the prevalence of depression and insomnia decreased more rapidly and was lower in patients with (vs without) psoriatic arthritis (decrease by 39.9% vs 62.5%) and patients with (vs without) concomitant use of methotrexate (decrease by 35.2% vs 51.4%) within two years of initiating TNFi.[36]

The three prospective cohort studies that used the BIOBADADERM registry were conducted by the same research group. In these studies, the exposed group included new biologic agent users (no prior use of the same agent) and the unexposed (comparator) group included first-time CSA users (no prior CSA or biologic agent use).[38-40] The time from the start of the treatment until its discontinuation (two consecutive missing doses) or until treatment switch was defined as a treatment cycle and patients may have had multiple treatment cycles over their follow-up. The authors assessed more than 20 adverse events, among which the psychiatric adverse events coded according to the Medical Dictionary for Regulatory Activities (MedDRA). An adverse event was associated with a treatment if it occurred during or in the 90 days following treatment exposure, although the 90-day lag period differed for some adverse events. *As reviewed below, these studies suffered from several limitations including prevalent-user bias, confounding by disease severity and reverse causality which may explain their conflicting results*.

The first of the three studies was conducted by Dauden and colleagues using the registry data from 2009 to 2018. The authors used a time-varying model that accounted for the number of treatment cycles for each patient and the treatment received during the previous cycles.[40] They used the inverse probability of treatment weighting (IPTW) to deal with confounding by disease severity and reported higher incidence rates (IR) of psychiatric adverse events for etanercept (incidence rate ratios, IRR2.6; 95% CI 1.1-6.1), infliximab (IRR 4.5; 95% CI 1.8-10.7) and adalimumab (IRR 4.2; 95% CI 2.2-8.1) when compared to methotrexate.[40] *Although the authors used a time-varying model, they did not use a time-varying IPTW to account for time-varying confounders and did not implement the inverse probability of censoring weighting (IPCW) to account for informative censoring due to discontinuation and switching.[158,159] The lack of adjustment for informative censoring may have biased the risk estimate in the biologic agent users toward a higher value,*

because Spain like Quebec have restricted access policies to biologic agents for those covered by the public drug insurance plan and biologic agents are prescribed only in individuals for whom CSA has failed or are contraindicated.[135] However, it is not clear how the lack of adjustment for time-varying IPTW has affected the results. Also, reverse causality cannot be ruled out in this study as some of the medication switches may have occurred because of psychiatric adverse events.

The second study was conducted by Carretero and colleagues using the registry data from 2008 to 2013. Patients initiating a CSA were censored at the date of a biologic agent initiation,[38] and adverse events that were related to two concomitant treatment classes, were counted with both classes. The authors implemented a time-varying Cox regression model with robust variance and reported a non-different risk of psychiatric adverse events between the biologic and CSA users (HR 0.9; 95% CI 0.4-1.8).[38] *Differences in results between this study and the one conducted by Dauden and colleagues were not explained by the latter. Of note, some events were attributed to more than one treatment; the effect of this over-counting on the results was not clear.*

The third study was conducted by Belinchon and colleagues using the registry data from 2009 to 2015. The study only reported IR of psychiatric adverse events per 100 person-years that led to treatment discontinuation: 0.33; 95% CI 0.12-0.87 for etanercept, 0.76; 95% CI 0.19-3.03 for infliximab, 0.15; 95% CI 0.04-0.60 for adalimumab, 0 for ustekinumab, 1.65; 95% CI 0.89-3.06 for acitretin, 0.66 95% CI 0.16-2.62 for cyclosporin and 0.38; 95% CI 0.16-0.92 for methotrexate.[39] These findings suggested lower rates of treatment discontinuation due to psychiatric adverse events among biologic agent users vs CSA users. *In conclusion, the three reviewed studies used the same registry and were conducted by the same research group but reported conflicting results. Differences in study designs, exposure and outcome definitions, and the choice of their statistical analyses could have led to these discrepancies.*

Margolis and colleagues conducted a retrospective cohort study using patient electronic medical records from 2007 to 2017 in the US to compare the risk of psychiatric events among patients with psoriasis receiving biologic agents vs those not receiving these agents (patients receiving CSA, phototherapy or untreated patients with ≥ 2 psoriasis diagnoses).[35] When compared to patients without biologic agents, those receiving biologic agents were at lower risk of any psychiatric

disorder (HR 0.52; 95% CI 0.51-0.53) after adjusting for potential confounders. When each psychiatric disorder was assessed separately, biologic agent users remained at lower risk for depression (HR 0.58; 95% CI 0.57-0.60), psychosis (HR 0.45; 95% CI 0.41-0.49), bipolar disorder (HR 0.53; 95% CI 0.48-0.58), suicide (HR 0.52; 95% CI 0.40-0.69) and suicidal ideation (HR 0.57; 95% CI 0.48-0.69).[35] When compared to only methotrexate users, biologic agent users remained at lower risk of psychiatric adverse events, but the point estimate increased (HR 0.91; 95% CI 0.87-0.96). When considering psychiatric disorders separately, the point estimate for the HR varied from 0.77; 95% CI: 0.65-0.91 for psychosis to 1.18; 95% CI 0.81-1.70 for suicidal ideations.[35] *It was not clear from this study if prevalent users of CSA, phototherapy and biologic agents and those with prevalent mental health disorders were excluded prior to the cohort entry date. Therefore, prevalent-user bias and reverse causality cannot be ruled out.*

To my knowledge, only two studies excluded patients with prevalent or a history of mental health disorders at the cohort entry date. However, both studies did not restrict their cohorts to first-time systemic agent users, which again could lead to prevalent-user bias. The first study was a multicenter prospective cohort study conducted by Strober and colleagues among 532 patients with moderate-to-severe psoriasis from 2007 to 2015.[34] It compared the risk of having depressive symptoms and depression between CSA (including oral steroids and femarates ester acids), phototherapy and biologic agent (TNFi and ustekinumab) users.[34] Two outcomes, depressive symptoms and depression, were measured at every 6 to 12-month visit. Depressive symptoms were measured at the visit by a HADS-D score ≥ 8 and depression was a self-reported adverse event occurring before the visit. Patients were included if they had no medical history of depression or a score lower than 8 on the HADS-D at enrollment and were followed until the first occurrence of either one of these outcomes or the end of the study period. Compared to CSA users, patients receiving biologic agents were at a lower risk of having depressive symptoms (HR 0.64; 95% CI 0.46-0.86), but those receiving phototherapy were at a similar risk (HR 1.05; 95% CI 0.71-1.54). The authors did not use a multivariable model to compare the adjusted risk of depression between treatment groups because only 37 patients reported depression as an adverse event. The IR of depression per 100 person-years was 0.21; 95% CI: 0.15-0.31 for the biologic agent users, 0.55; 95% CI 0.21-1.47 for the phototherapy users and 0.14; 95% CI: 0.03-0.55 for the CSA users. *The discordance between the observed lower risk of depressive symptoms and the higher unadjusted*

rate of depression in the biologic (vs CSA) group was not justified. Although the authors stated that depression as an adverse event could have been underestimated among CSA users because most had a score ≥ 8 on HADS-D before reporting depression as an adverse event, they did not conduct a sensitivity analysis for the combined outcome.

Lastly, Vasilakis-Scaramozza and colleagues conducted a retrospective cohort study using MarketScan databases to compare the risk of treated depression and/or anxiety among patients with psoriasis receiving CSA (methotrexate or cyclosporine), apremilast, TNFi, ILi (IL-12/23, IL-17A and IL-23) and oral corticosteroids between March 2014 and October 2018.[37] Cohort entry date was the first prescription fill of the treatment received after March 2014. Exposure to systemic agents was categorized in a time-varying scheme, including CSA, apremilast, TNFi, ILi, corticosteroids, apremilast+any non-steroids, TNFi+CSA, ILi+CSA, corticosteroids+any other treatment. Patients were excluded if they had an antidepressant or benzodiazepine use any time prior to and in the 7 days after the cohort entry date. Patients with a diagnosis of depression or anxiety in the prior six month and a prescription fill for an antidepressant or benzodiazepine within 30 days after the cohort entry date were also excluded. However, Patients with untreated depression or anxiety and those treated with a non-pharmacological approach (e.g psychotherapy) were not excluded. The outcomes were treated depression and treated anxiety. They were defined by the presence of diagnostic code for the disorder >7 days after the cohort entry date and a prescription fill for an antidepressant or benzodiazepine within 30 days of the diagnostic code. Compared to CSA users, patients receiving oral corticosteroids had significantly higher rates of treated anxiety (IRR 2.1; 95% CI 1.3-3.2), treated depression (IRR 2.0; 95% CI 1.3-3.3), and treated anxiety and depression (IRR 1.9; 95% CI: 1.0-3.4). Patients receiving oral corticosteroids in combination with any other treatment (vs CSA) also had higher rates of treated anxiety (IRR 1.6; 95% CI 1.1-2.4). TNFi (vs CSA) were associated with a non-significant increased risk of treated depression (IRR 1.4; 95% CI 1.0-1.9). Both TNFi and ILi had non-significant increased rates of treated anxiety, and treated depression or anxiety with IRR varying from 1 to 1.4. *This was the only study that implemented a latency period (>7 days after cohort entry). Nonetheless, reverse causality bias cannot be ruled out because some patients may have had a non-pharmacologically treated depression before the study entry that was later treated pharmacologically; a gap of 7 days may have been insufficient to reduce this bias.*

The association between systemic agent treatment and mental health disorders remains not clearly understood with published studies reporting contradictory results and suffering from major limitations including prevalent-user bias, reverse causality and confounding by disease severity. Limitations of the published studies were likely caused by important methodological discrepancies such as 1) inclusion of prevalent users; 2) inclusion of individuals with the outcome of interest; a history of mental health disorders; 3) inconsistency in exposure and outcomes definitions; and 4) inappropriate data analyses considering multiple treatment cycles and overcounting of events. I addressed these knowledge gaps and study limitations in my thesis by 1) including only first-time CSA and biologic agent users, 2) excluding patients with a history of mental health disorders, 3) considering a latency period of 90 days and conducting many sensitivity analyses with various length of the latency period; and 4) considering IPTW in my statistical analyses to reduce the risk of confounding by disease severity.

Table 3.3. Summary of studies comparing the risk of mental health disorders between systemic agents and other treatments among patients with psoriasis

Author, year of publication (Country),	Data source (Study design)	Study population	Exposures	Outcome	Findings
Strober, 2018 (16 countries)[34]	PSOLAR study from 2007-2015 (Multicenter prospective cohort study)	Patients with moderate-to-severe psoriasis without medical history of depression and baseline score on HADS-D <8	Biologic agents (N=412) CSA (N=80) Phototherapy (N=40)	Depressive symptoms with a HADS-D score ≥8	Biologic agents vs CSA: aHR=0.64 (95% CI: 0.46-0.86) Phototherapy vs CSA: aHR=1.05 (95% CI: 0.71-1.54)
Margolis, 2019 (United states)[35]	OptumInsight Electronic Health Records database from 2007 to 2017 (Retrospective cohort study)	Patients with psoriasis	Biologic agents (N=33,722) vs non-biologic treatments (N=228,830)	Depression, psychosis, bipolar disease, suicide and suicidal ideation	All psychiatric disorders: aHR=0.52 (95% CI: 0.51-0.53) Depression: aHR=0.58 (0.57-0.60) Psychosis: aHR=0.45 (95% CI: 0.41-0.49) Bipolar: aHR=0.53 (95% CI: 0.48-0.58) Suicide: aHR=0.52 (95% CI: 0.40-0.69) Suicidal ideation: aHR=0.57 (95% CI: 0.48-0.69)
Wu, 2016 (Taiwan)[36]	NHIRD from 1997 to 2012 (Retrospective cohort study)	Patients with psoriasis and psoriatic arthritis initiating a TNFi	Patients initiating TNFi (N=980)	Depression/insomnia in the year prior and two years after TNFi initation	Prevalence of depression/anxiety decreased by 43.8% after two years of initiating TNFi (p<0.001)
Vasilakis-Scaramozza, 2020 (United-States)[37]	MarketScan between 2014 and 2019 (Retrospective cohort study)	Patients with psoriasis and receiving systemic agents. Patients were not previously treated for depression and/or anxiety	Time-varying scheme (N at baseline): DMARD only (N=6,511) apremilast only (N=3,913) TNFi only (N=12,142) ILi only (N=4,101) Corticosteroids (N=0) Apremilast + any non-steroids (N=3) TNFi + DMARD (N=257) ILi+DMARD (N=44) Corticosteroids + other treatment (N=4,303) Untreated (N=0)	Treated depression, Treated anxiety, Treated depression and anxiety, whichever occurred first	Compared to CSA: Corticosteroids only: Treated anxiety: IRR=2.1 (95% CI: 1.3-3.2) treated depression: IRR=2.0 (95% CI: 1.3-3.3) Treated anxiety and depression: IRR=1.9 (95% CI: 1.0-3.4). Corticosteroids+any other treatment: Treated anxiety: IRR=1.6 (95% CI: 1.1-2.4) TNFi only:

					Depression: IRR=1.4 (95% CI: 1.0-1.9).
Carretero, 2015 (Spain)[38]	Spain registry of systemic therapy in psoriasis (BIOBADADERM) - from 2008 to 2013 (Prospective cohort study)	Patients diagnosed with psoriasis who initiated a CSA or a biologic agent	Multiple treatment cycle occurred CSA users (N=1572) Biologic agent users (N=2,181)	Self-reported adverse events and validated using medical records	Biologic users: IR=13 (95% CI: 9-17) per 1,000 person-years CSA users: IR=10 (6-16) per 1,000 person-years. Biologic vs CSA: (aHR=0.9; 95% CI: 0.4-1.8).
Belinchon, 2017 (Spain)[39]	Spain registry of systemic therapy in psoriasis (BIOBADADERM) - from 2008 to 2015 (Prospective cohort study)	Patients diagnosed with psoriasis who initiated a CSA or a biologic agent	Multiple treatment cycle occurred CSA users (N=2108) Biologic agent users (N=2,110)	Self-reported adverse events and validated using medical records that resulted in treatment discontinuation	IR per 100 person-year: Etanercept: 0.33 (95% CI: 0.12-0.87) Infliximab: 0.76 (95% CI: 0.19-3.03) Adalimumab :0.15 (95% CI: 0.04-0.60) Ustekinumab: 0 Acitretin:1.65 (95% CI: 0.89-3.06) Cyclosporin: 0.66 (95% CI: 0.16-2.62) Methotrexate: 0.38 (95% CI: 0.16-0.92)
Dauden, 2020 (Spain)[40]	Spain registry of systemic therapy in psoriasis (BIOBADADERM) - from 2008 to 2018 (Prospective cohort study)	Patients diagnosed with psoriasis who initiated a CSA or a biologic agent	Multiple treatment cycle occurred CSA users including apremilast (N=3,808) Biologic agent users including secukinumab (N=5,146)	Self-reported adverse events and validated using medical records	compared to methotrexate Etanercept: IRR=2.6 (95% CI: 1.1-6.1) Infliximab: IRR=4.5 (95% CI: 1.8-10.7) adalimumab: IR=4.2 (95% CI: 2.2-8.1)

aHR: adjusted hazard ratios; CI: confidence intervals; CSA: conventional systemic agents; DMARDS: Disease-modifying anti-rheumatic drugs; HADS-D: Hospital Anxiety and of Depression Scale – Depression; ILi: Interleukin inhibitors; PSOLAR: Psoriasis longitudinal Assessment and Registry

Chapter 4: Data sources

4.1 The Régie de l'Assurance Maladie du Québec (RAMQ) health administrative databases

For my thesis project, I used demographic, outpatient and inpatient physician claims, pharmaceutical claims and hospital abstract records from January 01, 1997 to December 31, 2015 obtained from the health administrative databases of the Province of Quebec. These databases include the beneficiary database (*le fichier des bénéficiaires),* the physician claims database and the pharmaceutical claims database that are maintained by RAMQ. In addition, I used the hospital abstract database, the *Maintenance et Exploitation des Données pour la Clientèle Hospitalière* (MED-ECHO) that is housed at RAMQ. These databases are linkable by a unique patient identifier.

The *fichier des bénéficiaires* includes information on sex, date of birth, area of residency, postal code, type of provincial drug insurance plan and date of death. The physician claims database contains information on all fee-for-service physician claims for services rendered in outpatient and inpatient settings, including the date of service, diagnosis codes using the International Classification of Diseases 9th revision [ICD-9] codes and procedure codes (CODE-ACT). The pharmaceutical claims database contains information on prescribed medications, including drug information number (DIN), drug common denominations (DENCOM), dispensation date, dosage, duration of supply and prescriber specialty, for those registered with the provincial drug plan. The MED-ECHO database includes hospital abstract records on all hospital admissions for all Quebec residents including admission and discharge dates, type of admission (elective or emergent), the principal and up to 15 secondary diagnoses (ICD-9 codes before April 2006 and ICD-10 codes thereafter) and procedure codes using the Canadian Classification of Health Interventions codes.

In Quebec, as in all other Canadian provinces, all residents are covered, free of charge, for their physician visits and hospitalizations. In addition, drug insurance is mandatory for all Quebec residents. By law, all residents who do not have access to a private drug insurance plan should enrol in RAMQ public drug plan. These include individuals ages 65 years or older, those receiving social assistance and those in the workforce who do not have a private drug plan through their

employer or their profession group. The RAMQ drug plan covers over 8,000 prescribed medications with the list updated yearly. Annual premium and co-payments are paid by plan members with amounts varying by plan type from 0 to a maximum of 37% of the drug price. The plan type is decided by RAMQ according to the individual's income. Among those ≥ 65 years of age, some have access and choose to remain with their private drug insurance. In 2015, about 93% of those in this age group were enrolled in the provincial drug plan of Quebec.[160]

The data available for my thesis included 55,232 patients ages ≥ 20 years who received at least one psoriasis diagnosis (ICD-9 code: 696.1 or ICD-10 code: L40.x) during an inpatient, outpatient or ED visit and were covered by RAMQ drug plan for at least one day between January 1997 and December 2015.

In addition, I also obtained the All-Patient Refined Diagnosis-Related Group (APR-DRG) database from the Ministry of Health and Social Services that I merged with MED-ECHO and RAMQ physician claims database to compute the cost of hospitalizations and ED visits. APR-DRG database includes the *Niveau d'intensité relative des ressources utilisées* (NIRRU) associated with each hospitalization or ED visit as well the as the cost of a hospitalization or ED visit per NIRRU. NIRRUs are weights representing the relative intensity level of resources used by taking into consideration the age, sex, diagnosis severity, comorbidities, the procedures carried out, complications and discharge status. NIRRU x cost per NIRRU provides an estimate for the average cost of the hospitalization not including the physician fees.

4.2 Validation of RAMQ databases

RAMQ pharmaceutical claims database was previously validated among a sample of 306 adult ages ≥ 65 years (with 723 prescription fills) who attended the internal medicine clinic of the Royal Victoria hospital in Montreal, Canada in 1990.[161] In terms of accuracy, 83% of the prescription fills, 89% of the prescribing physician specialty, 69% of the doses and 72% of the duration of supply were correctly identified in RAMQ pharmaceutical database.[161]

The diagnosis of 14 physical conditions in the RAMQ physician claims database were also validated in a sample of 14,980 adults ages ≥ 65 years against their medical chart records.[162] The

conditions included were heart block, hypertension, hypotension, CHF, Raynaud's disease, renal failure, diabetes, asthma, chronic obstructive pulmonary disease (COPD), dementia, glaucoma, gout, prostatic hypertrophy and peptic ulcer. They all had a specificity over 87.7%. However, the sensitivities for these conditions were low; the highest being for diabetes (51.8%) and hypertension (60.1%).[162] Psoriasis diagnoses were not evaluated in this study.

4.3 Validation of psoriasis cases in administrative databases

To my knowledge, psoriasis diagnostic codes were not validated in RAMQ administrative databases. One population-based study in Ontario validated the following algorithm to identify patients with psoriasis in the OHIP claims databases: ≥ 1 diagnostic code in hospital records or ≥ 2 diagnostic codes (ICD-9: 696.1 and ICD-10: L40.x) in physician claims. The sensitivity of this algorithm was 52%, the specificity was 99% and the PPV was 62%.[1] Another population-based study using Manitoba Health administrative database assessed the combined psoriasis and psoriatic arthritis ICD codes (ICD-9: 696.0, 696.1 and ICD-10: L40.x, M07.0, M07.2, M07.3) and found that ≥ 1 hospital visit, ≥ 1 physician claim or ≥ 1 treatment for psoriasis had a sensitivity of 72%, a specificity of 90% and a PPV of 25%.[163] In the same study, ≥ 1 hospital visit or ≥ 1 physician claim had a sensitivity of 44%, specificity of 97% and PPV of 44%.[163] One population-based cohort study conducted in the US using Kaiser Permanente Northern California health database found that ≥ 1 physician claim by any specialist for psoriasis (ICD-9 codes: 696.1) had a sensitivity of 100% and a PPV of 78%, while ≥ 1 claim for psoriasis by a dermatologist had a sensitivity of 91% and a PPV of 89%.[164] Finally, one study using the Swedish national health administrative database found that ≥ 1 claim for psoriasis by any specialist (ICD-10: L40.x) had a PPV of 81%.[165] In these studies, the gold standard was either patients' chart review or medical records.[1,163-165]

In my thesis, psoriasis diagnosis was defined with ≥ 1 physician claim for psoriasis by any specialist. As stated above, this definition was found to have high PPV ranging from 78% to 81%.[164,165] In addition, I restricted my cohort to patients with moderate-to-severe psoriasis by only including those receiving systemic agents. In a previous Danish cohort study, including patients with a prescription fill for a systemic therapy was a good proxy to moderate-to-severe psoriasis when validated against medical chart records (sensitivity 98%).[166]

Chapter 5: Assessing sex differences in patterns of CSA use and identifying factors associated with switch to (or add) a TNFi/UST and those associated with CSA discontinuation

In this section, I am presenting additional information on the methods used in manuscript 1 that addressed my objective 1.a

5.1 Methods

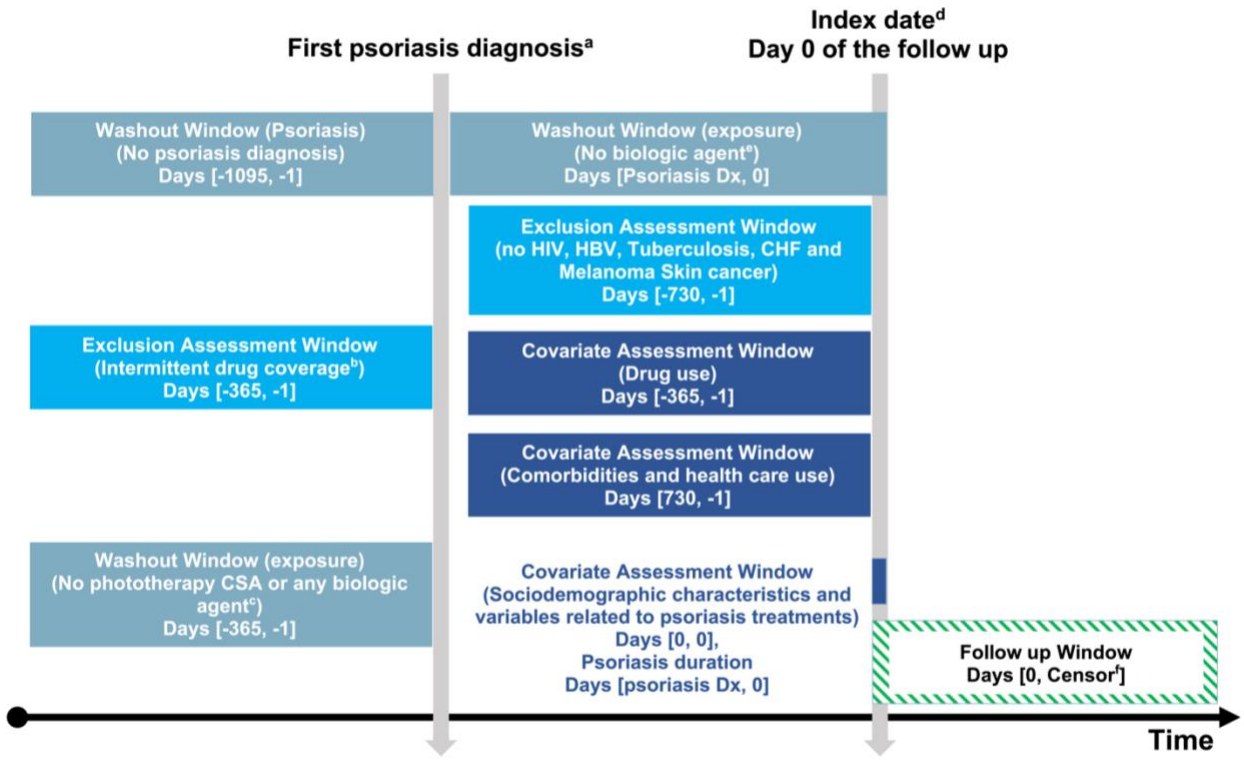
5.1.1 Cohort definition

I identified a cohort of patients ages ≥ 20 years with a first diagnostic code for psoriasis either during an inpatient, outpatient or ED visit between January 1, 2002 and September 31, 2015. Among these, I included patients with a new diagnosis for psoriasis, who were initiated on one CSA (methotrexate, cyclosporine, acitretin and Sulfasalazine). Patients with new diagnosis for psoriasis were those who did not have any diagnosis for psoriasis in the previous three years. Patients were required to be enrolled with the provincial drug plan in the previous year and those with any treatment for psoriasis, including phototherapy or a systemic agent in that year were excluded (Table 5.1). One year was deemed appropriate as increasing the duration of enrollment with the provincial drug plan would have resulted in more patients being excluded. A previous study including first-time CSA users also excluded patients without drug coverage in the 12 months prior to index date.[19]

I defined the first CSA prescription fill as the index date. I excluded patients with HIV, HBV, tuberculosis, CHF and melanoma skin cancer in the two years prior to the index date because TNFi/UST are contraindicated in patients with these conditions. I did not consider apremilast for inclusion in the cohort, but I did not exclude patients who subsequently received this agent. I used an as treated approach whereby I followed patients while they were continuously exposed to CSA as described below. A summary of the cohort construction is presented in Figure 5.1.

5.1.2 Exposure definitions

I considered CSA as a class. I adopted a 60-day grace period between CSA prescriptions and considered patients to be exposed to CSA until they had a gap exceeding 60 days between prescriptions.



[a]First psoriasis diagnosis defined as one without any diagnosis for psoriasis in the previous three years
[b]Gap of ≥90 days in the drug coverage
[c]Any biologic agent prescribed for psoriasis or any other immune-mediated condition (table 5.1)
[d]Index date defined as first CSA received following psoriasis diagnosis. Patients could only initiate on one CSA.
[e]Patients could not initiate on a biologic agent due to provincial drug formulary restrictions
[f]Patients were followed starting from index until the occurrence of the outcome of interest, death, occurrence of an ineligibility criterion (dispensed prescription for a biologic agent other than the TNFi/UST included in the study, diagnosis for HIV, HBV, CHF, tuberculosis and melanoma skin cancer), gap ≥ 90 days of enrollment in the provincial drug plan or December 31, 2015, whichever occurred first.
Abbreviations: CHF: congestive heart failure; CSA: conventional systemic agents; Dx: Diagnosis; HBV: hepatitis B virus; HIV: Human immunodeficiency virus; TNFi/UST: tumor necrosis factor inhibitors and ustekinumab

Figure 5.1. Cohort construction to address objective 1

Table 5.1. CSA and biologic agents considered in my study

Agents	Treatment considered as exposures	Treatments considered in the exclusion criteria
Conventional systemic agents	Acitretin Cyclosporine Methotrexate Sulfasalazine (objective 1) Apremilast*	Acitretin Cyclosporine Methotrexate Sulfasalazine (objective 1) Apremilast*
Biologic agents	Adalimumab Etanercept Infliximab Certolizumab pegol Golimumab Ustekinumab	Adalimumab Etanercept Infliximab Certolizumab pegol Golimumab Ustekinumab Alefacept** Efalizumab** Abatacept*** Anakinra*** Rituximab*** Tocilizumab***

*Patients could not initiate with apremilast but could receive this agent subsequently during the follow-up
**Biologic agents for psoriasis withdrawn from the market
***Biologic agents for other immune-mediated conditions

5.1.3 Outcome definitions

The biologic agents I considered in my study were the TNFi and ustekinumab (TNFi/UST). The outcomes were switch to a TNFi/UST or receiving these agents as add-on, and CSA discontinuation. IL-23 and IL-17 inhibitors were not included in my studies because they were added on the RAMQ drug plan after December 31, 2015 (Table 5.1 and Appendix B).

Switch/add TNFi/UST was defined as receiving a dispensed prescription fill for one of these agents within the CSA exposure period. An add-on of TNFi/UST occurred if the patient also refilled their CSA prescription at the time or in the 60 days following the duration of supply of the TNFi/UST prescription fill, otherwise the patient was considered to have switched to TNFi/UST.

5.1.4 Potential predictors

Baseline sociodemographic characteristics included: age (20-54, 55-64, 65-74 and ≥75 years), sex (male or female), area of residency (rural or urban based on postal code), income (low or high based on type of RAMQ drug plan with those receiving partial or total subsidies considered as low income),[160] and social deprivation index. The social deprivation index is a census area-based deprivation index that was developed by the *Institut national de santé publique du Québec* based on the proportion of persons living alone, the proportion of persons who are divorced, widowed or

separated and the proportion of single-parent families. It is divided into quintiles with 1 representing people who live in the most socially privileged areas and 5 representing those who live in the most socially deprived areas. A value of zero indicates missing value.[167]

Psoriasis treatment characteristics included year of cohort entry (2002-2010 or 2011-2015, I used a cut-off of 2011 because of all biologic agents considered in the study, ustekinumab was last to be included in the provincial drug formulary in 2011), psoriasis duration (time from first psoriasis diagnosis until the first CSA prescription fill categorized into: 0-90 days, 91-365 days and more than 365 days. This categorization was chosen based on the rounded values of the first quartile and median), specialty of the CSA prescriber (dermatologist, rheumatologist or other specialists), first CSA received (methotrexate, acitretin, sulfasalazine and cyclosporine) and use of prescribed topical agents and phototherapy in the prior year. OTC topical agents were not considered as they are not available from the RAMQ pharmaceutical database.

All-cause health care use in the prior two years (yes or no), included all-cause hospitalization and ED visits.

Physical and psychiatric comorbidities in the prior two years (yes or no for most variables) were assessed using ICD 9/10 codes (Appendix C) in at least one inpatient, outpatient or ED records (whether treated or not): psoriatic arthritis, rheumatoid arthritis, IBD, ankylosing spondylitis, clinical obesity, hypertension, ischemic heart diseases, cerebrovascular diseases, vascular diseases, cardiac arrhythmias, renal diseases, liver diseases, respiratory diseases, cancer, mental health disorders (categorized as: mood and anxiety disorders [including depression, anxiety and bipolar], adjustment, somatoform and personality disorder [without depression, anxiety and bipolar] or other mental health disorders [without having an ICD code related to the two previous categories]), and drug/alcohol abuse.

Medication use in the prior year (yes or no) was defined by having at least one dispensed prescription for the following drugs (Appendix B): antidepressants, benzodiazepines, opioids, antihypertensive agents, hypoglycemic agents, platelet inhibitors, anticoagulants, lipid-lowering agents, nonsteroidal anti-inflammatory drugs (NSAIDS) and oral corticosteroids.

5.1.5 Statistical analyses

All analyses were conducted separately for male and female patients. Both switch to TNFi/UST and receiving TNFi/UST as add-on were combined in a composite outcome switch/add TNFi/UST to increase the statistical power of the study.

5.1.5.1 The least absolute and selection operator (LASSO)

The least absolute and selection operator (LASSO) is a method that has been designed to select the best set of predictors of an outcome from a high number of candidate predictors. It does so more robustly than other model fitting methods commonly used in epidemiology such as a typical logistic regression and cox regression models with stepwise/backward variable selection.[168-171]

Cox proportional hazard models (equation 5.1) are semi-parametric models implemented to study the association between predefined predictor variables *x* and survival time.

$$h_i(t) = h_0(t)e^{\beta_1 x_{i1} + \cdots + \beta_k x_{ik}} \qquad (5.1)$$

Where $h_i(t)$ is the hazard for patient *i* at time *t* and $h_0(t)$ is the shared baseline hazard. In Cox regression models, inference is made via the partial likelihood (PL). With the PL, we are interested in determining the probability that individual *i* specifically has the event at time t_j instead of estimating the probability of observing an event at time t_j. If d individuals have distinct event times t_j, j=1, …, d then the PL is defined as follows (equation 5.2):

$$PL(\beta) = \prod_{j=1}^{d} \frac{e^{\beta_1 x_{i1} + \cdots + \beta_k x_{ik}}}{\sum_{p \in R_j} e^{\beta_1 x_{p1} + \cdots + \beta_k x_{pk}}} \qquad (5.2)$$

Where R_j is the set of patients who are still at risk at time t_j. By maximizing the log PL, we can estimate $\beta_1, \ldots, \beta_k$.

LASSO method is applied to avoid overfitting by penalizing the absolute size of the regression coefficients with the L1-regularization penalty factor λ (also known as tuning parameter).[168-170] By increasing the value of λ, non-influential baseline characteristics with weak estimates will shrink towards zero.

With Cox regression models, the log PL function is concave, thus we always use the negative partial likelihood function that can be viewed as a convex loss function similar to the squared loss function in the linear regression (equation 5.3). [170,171] The L1-penalty is applied as follows (equation 5.4):

$$\min\ [-\log\{PL(\beta)\}] \qquad (5.3)$$

$$\min\ [-\log\{PL(\beta)\} + \lambda|\beta|] \qquad (5.4)$$

The optimal λ is determined using a 10-fold cross validation (CV) process in which 500 different values of λ are tested. In a 10-fold CV, the dataset is broken down into 10 equivalent groups. Then, the model is fitted using 9 of the 10 datasets (training data) and the remainder group is used to test how well the model, that was fitted in the training data, performs in the testing data. This process is repeated ten times, each time using a different group. Ultimately, the overall performance is summarized by averaging the CV-error for each lambda within the 500 values and selecting the value of λ where the CV-error curve hits its minimum (smallest partial likelihood deviance for Cox regression models).

5.1.5.2 Variable selection

Before modelling, collinearity between binary variables was assessed using the tetrachoric correlation. If a pair was strongly correlated ($|r| \geq 0.8$), the most clinically relevant was selected. Additionally, variables with 0 outcome were excluded.

The remaining baseline characteristics were included in the Cox regression models with LASSO. Variables selected by LASSO were included in univariable Cox regression models where Hosmer and Lemeshow variable selection procedures were applied.[172] Those significant at the 0.25 level were included in a multivariable Cox regression model and standard backward variable selection procedures, based on a significance level of 0.05 and the Bayesian Information Criterion, were applied.[172] Use of a hybrid approach, a LASSO followed by the backward selection procedure, resulted in a better predictive capacity to select potential predictors when compared to the use of LASSO or backward selection procedure seperately.[173,174]

These steps were implemented for each outcome studied among male and female patients separately. The final Cox regression models for both sexes included all the variables selected in either the male and female models for each outcome.

5.1.5.3 Model fit

Internal validity of the models was assessed using the Harrel's Concordance index (discrimination measure) and calibration slopes (models' reliability).

The Harrel's Concordance index (Harrel's C index) is a rank order statistic used to estimate the degree of discrimination between individuals with and without the outcome while accounting for right censoring (as opposed to c-statistics).[175,176] An index of 0.5 was considered not useful, 0.5 to < 0.6 poor, 0.6 to < 0.7 modest, and ≥ 0.7 good discrimination. The calibration slope (models' reliability) was used to measure the agreement between the predicted and observed outcomes. A calibration slope of ≤ 0.5 was interpreted as non-informative, 0.5 < slope ≤ 0.7 as poor, and a slope > 0.7 indicated a good calibration.[174]

5.1.5.4 Other analyses

Differences in baseline characteristics between male and female patients were compared using univariable and multivariable logistic regression models. Rates of CSA discontinuation, switch/add TNFi/UST, and switch/add TNFi or a different CSA were computed using Poisson distribution.

5.1.5.5 Software

SAS studio was used for cohort construction. The packages glmnet[177] and rms[178] were used in R software (version 3.6.2) for LASSO, survival analysis and internal validity of the models. Codes are available upon request.

5.2 Manuscript 1 – Sex differences in the patterns of systemic agent use among patients with psoriasis: A retrospective cohort study in Quebec, Canada

5.2.1 Preamble to manuscript 1

The evidence to date showed that patients with psoriasis are at high risk of failing their systemic agents. However, few studies included first-time CSA users and examined the rate of switch from CSA to TNFi/UST. Additionally, sex differences in these patterns and factors associated with switch/add TNFi/UST were not assessed among patients with psoriasis, despite studies showing that male and female patients have different expectations and needs when initiating systemic agents.

To better understand how patients with psoriasis initiating a CSA are treated in Quebec, in this study, I aimed to examine sex differences in (1) patterns of systemic agent use; and (2) in factors associated with switch to TNFi/UST or receiving these agents as add-on, and CSA discontinuation among patients initiating a CSA.

Manuscript 1 was published in Frontiers in Pharmacology:
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This manuscript received attention from physician's Weekly, a trusted source of medical news and education for healthcare professionals. I conducted an e-mail-based interview with Martta Kelly, a senior editor at physician's Weekly, and the article entitled *Examining Sex Differences in the Management of Psoriasis* was published on their website.

5.2.2 Manuscript 1

5.2.2.1 Title page

Article type: Research article

Title: Sex differences in the patterns of systemic agent use among patients with psoriasis: A retrospective cohort study in Quebec, Canada

Running head: systemic agent use in psoriasis

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5.2.3 Abstract

Background: Sex differences exist in psoriasis manifestation and expectations from treatment with systemic agents, including, conventional systemic agents (CSA) and tumor necrosis factor inhibitors or ustekinumab (TNFi/UST). However, sex differences in patterns of systemic agent use, such as CSA discontinuation and switch from CSA to TNFi/UST have not been examined.

Objectives: To assess sex differences in patterns of CSA use and identify factors associated with switch to (or add) a TNFi/UST and those associated with CSA discontinuation.

Methods: We conducted a retrospective cohort study using the Quebec health administrative databases. We included patients with psoriasis initiating a CSA in 2002–2015. We excluded patients with a psoriasis diagnosis in the 3 years prior to the first diagnosis date between 2002 and 2015, and those with a systemic agent dispensation in the year prior to that date. We used Cox regression models with the Least Absolute Shrinkage and Selection Operator method to identify factors associated with Switch/add TNFi/UST, and those associated with CSA discontinuation. Separate analyses were performed for male and female patients.

Results: We included 1,644 patients (55.7% females, mean age 60.3 years), among whom 60.4% discontinued their CSA and 7.4%, switched/added TNFi/UST (3.4% switched and 4.0% added) within a median of 0.78 years of follow-up. Among male and female patients, rates of Switch/add TNFi/UST per 1,000 person-year were 49.1 and 41.0 and rates of CSA discontinuation were 381.2 and 352.8. Clinical obesity in male patients (HR 3.53, 95% CI 1.20–10.35), and adjustment/somatoform/dissociative disorders (HR 3.17, 95% CI 1.28–7.85) and use of nonsteroidal anti-inflammatory drugs (HR 2.70, 95% CI 1.56–4.70) in female patients were associated with Switch/add TNFi/UST. Male patients followed by a rheumatologist (HR 0.66, 95% CI 0.46–0.94) and those with a prior hospitalization (HR 0.70, 95% CI 0.57–0.87) were at lower risk of CSA discontinuation, while those initiated on acitretin (vs methotrexate) were at higher risk to discontinue their CSA (HR 1.61, 95% CI 1.30–2.01). Female patients with rheumatoid arthritis comorbidity (HR 0.69, 95% CI 0.51–0.93), those with a dispensed lipid-lowering agent (HR 0.72, 95% CI 0.59–0.88) and hypoglycemic agent (HR 0.75, 95% CI 0.57–0.98) and those initiated on methotrexate (vs all other CSA) were less likely to discontinue their CSA. Male and female

patients entering the cohort between 2011 and 2015 were at reduced risk of CSA discontinuation compared to those entering the cohort before 2011.

Conclusion: Most male and female patients discontinued their CSA within 1 year of follow-up. Our study highlighted sex differences in patients' characteristics associated with switch/add a TNFi/UST and CSA discontinuation; treatment switch and discontinuation may be indications of treatment failure in most patients.

5.2.4 Introduction

Psoriasis is a chronic inflammatory skin condition affecting 1 to 3.2% of the population in western countries (Canadian Agency for Drugs and Technologies in Health, 2007; Rachakonda et al., 2014). About 21.5% of patients have a moderate-to-severe form of psoriasis (Canadian Dermatology Association, 2009; Armstrong et al., 2021). Psoriasis treatments vary by disease severity and include topical agents, phototherapy, conventional systemic agents (CSA) and biologic agents (Canadian Dermatology Association, 2009). Clinical guidelines for the management of psoriasis recommend treatment with systemic agents, including CSA and biologic agents, for moderate-to-severe psoriasis. Randomized controlled trials (RCT) have found biologic agents, including tumor necrosis factor alpha inhibitors (TNFi) and interleukin inhibitors, to be more effective than placebo and the CSA, methotrexate, in achieving complete or nearly complete skin clearance and maintaining it over a longer period of time in patients with moderate-to-severe psoriasis (Gordon et al., 2006; Mahil et al., 2020). An important barrier to biologic agents' use is their high acquisition costs. The provincial drug plan in Quebec approves reimbursement for biologic agents in psoriasis only when CSA are contraindicated or ineffective (Régie de l'assurance maladie du Québec, 2020); a policy adopted by several other public drug insurance plans (Ighani et al., 2019; National Institute for Health and Care Excellence, 2020).

Although the prevalence of psoriasis is similar in male and female populations (Amur et al., 2012), sex differences in disease manifestation have been reported. Male and female patients with psoriasis differ in presence of comorbidities (Mahler et al., 2009; Love et al., 2011; Sondermann et al., 2020), and needs and goals from therapy (Uttjek et al., 2005; Mahler et al., 2009; Papp et al., 2010; Maul et al., 2019). Because male patients are at higher risk of moderate-to-severe psoriasis than female patients, they may be more likely to receive a systemic agent (biologics or CSA) (Hotard et al., 2000; White et al., 2012; Hagg et al., 2017). Female patients reported having higher treatment expectations and thus increased potential for perceived treatment failure and requests for treatment change (Generali et al., 2016; Maul et al., 2019). Differences in CSA prescribing and switching in male and female patients have not been clearly described (Generali et al., 2016). Switching and discontinuing treatment are indications of treatment failure and are associated with worsening of psoriasis severity, lower quality of life and psychiatric morbidity (Thorneloe et al., 2013; Michalek et al., 2016; Bell et al., 2020).

Most studies examining patterns of systemic agents' use in psoriasis considered only those using biologic agents and examined treatment discontinuation and switch between these agents (No et al., 2018; Mourad et al., 2019). Little is known about the patterns of CSA use in this population (Tabolli et al., 2015; Higa et al., 2019). Our objectives were to assess among patients with psoriasis, sex differences in 1) the patterns of CSA use, 2) factors associated with switch/add a TNFi or ustekinumab (TNFi/ UST), and 3) factors associated with CSA discontinuation.

5.2.5 Patients and methods

5.2.5.1 Study design and data source

We conducted a retrospective cohort study using the province of Quebec health administrative databases housed at the Régie de l'assurance maladie du Québec (RAMQ). Quebec has a universal health care system offering free of charge physician and hospital services to all residents. Drug insurance is mandatory since 1997. Individuals in the working force who do not have a private drug insurance plan with their employer, all those ≥65 years and all those receiving social assistance are registered in the public drug insurance plan. In 2015, 44.3% of all Quebec residents were covered by the provincial drug plan (Régie de l'Assurance Maladie du Québec, 2015). Socio-demographic, physician and prescription drug claims and hospital records were obtained from RAMQ for the period from January 1997 to December 2015. The pharmaceutical claims database contains information on prescribed medications, including dispensation date, dosage, duration of supply and prescriber specialty, for those covered by RAMQ drug plan. The medical claims database contains information on all outpatient physician claims for all Quebec residents (International Classification of Diseases 9th revision, ICD-9 codes). The hospital abstract records provide information on all hospital admissions including the admission/discharge dates and primary and secondary discharge diagnoses (ICD-9 codes before April 2006 and ICD-10 codes thereafter).

5.2.5.2 Study population

We selected individuals ages ≥20years who received a first diagnostic code for psoriasis either in-hospital, during an emergency department (ED) or outpatient visit between January 2002 and September 2015 (ICD-9 code 696.1 and ICD-10 code L40.x). We considered those who were continuously enrolled in the provincial drug plan in the previous year and examined their treatment

utilization until the first gap ≥90days in their enrolment plan (eligibility period). We defined a new patient with psoriasis as one without any diagnosis code for psoriasis in the previous 3 years and any psoriasis treatment (phototherapy, CSA or a biologic agent) in the previous year. Among new patients, we included those initiating a CSA (methotrexate, cyclosporine, acitretin and sulfasalazine) anytime during their eligibility period. The date of the first CSA prescription fill was their index date. We excluded those who received any biologic agent in the prior year and those with less than 3 months of data following their index date. We also excluded those with a diagnosis of Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), active tuberculosis, congestive heart failure (CHF) and melanoma skin cancer in the prior 2 years because TNFi/UST are contraindicated in these conditions (Elmets et al., 2019; Enbrel® (Etanercept), 2000; Humira® (Adalimumab), 2004; Nardone et al., 2014; Remicade® (Infliximab), 2017; Simponi® (Golimumab), 2018; Stelara® (Ustekinumab), 2017).

5.2.5.3 Outcomes

For this study, we considered all CSA as a single class. Our outcomes were 1) Switch/add TNFi/UST (etanercept, infliximab, adalimumab, golimumab, certolizumab pegol and ustekinumab); and 2) CSA discontinuation. These outcomes were determined based on the comparison between the time between the preceding CSA fill and the time to the next refill with the permissible treatment gap. For each CSA prescription fill, the duration of supply was available in the RAMQ pharmaceutical database. To the duration of supply, we added a 60-days grace period to compute the permissible gap. We defined Switch/add TNFi/UST as receiving a dispensed prescription for one of these agents within the permissible gap. An add-on occurred if the patient also refilled their CSA prescription within the permissible gap, while a switch occurred if they did not. We defined CSA discontinuation as no supply for any CSA for a period exceeding the permissible gap. We combined switch and add-on of TNFi/UST for statistical power purposes.

5.2.5.4 Follow-up

We followed the study individuals from index date until the first date of Switch/add TNFi/UST, CSA discontinuation, death, occurrence of an ineligibility criterion (dispensed prescription for a biologic agent not indicated for psoriasis, diagnosis for HIV, HBV, active tuberculosis, CHF and

melanoma skin cancer), a gap ≥ 90 days in the provincial drug plan enrollment or 31 December 2015, whichever occurred first.

5.2.5.5 Baseline characteristics

We assessed the following potential predictors at baseline: socio-demographic characteristics: age, sex, area of residency (rural/urban), income (low/high based on receiving partial or total subsidies), social deprivation index (quintiles with 5 representing the most socially deprived); all-cause healthcare use in the prior 2 years: all-cause hospitalization and ED visits; psoriasis treatment characteristics: year of cohort entry (2002–2010 vs 2011–2015), psoriasis duration, specialty of the CSA prescriber, first CSA received, and use of topical agents and phototherapy in the prior year; comorbidity in the prior 2years using ICD codes during at least one inpatient, outpatient or ED visit (whether treated or not): PSa, rheumatoid arthritis (RA), inflammatory bowel diseases (IBD), ankylosing spondylitis (AS), clinical obesity, hypertension, ischemic heart diseases, cerebrovascular diseases, vascular diseases, cardiac arrhythmias, renal diseases, liver diseases, respiratory diseases, cancer, mental health disorders and drug/alcohol abuse; and medication use in the prior year defined by having at least one dispensed prescription for the following drugs: antidepressants, benzodiazepines, opioids, antihypertensive agents, hypoglycemic agents, platelet inhibitors, anticoagulants, lipid-lowering agents, nonsteroidal anti-inflammatory drugs (NSAIDS) and oral corticosteroids.

5.2.5.6 Statistical analyses

We reported baseline characteristics by sex and compared them using univariable and multivariable logistic regression models. We conducted all remaining analyses in male and female patients separately. We reported crude incident rates (IR) of Switch/add TNFi/UST and CSA discontinuation per 1,000 person-years. We plotted Kaplan Meier curves for our primary outcomes by sex. We employed the Least Absolute Shrinkage and Selection Operator (LASSO) method to select potential baseline characteristics associated with Switch/add TNFi/UST and CSA discontinuation. LASSO method is applied to avoid overfitting by penalizing the absolute size of the regression coefficients with the L1-regularization penalty factor λ (Tibshirani, 1996; Kumar et al., 2019). By increasing the value of λ, non-influential baseline characteristics with weak estimates will shrink towards zero. The optimal λ was determined using a 10-fold cross validation

(CV) and 500 iterations to reduce potential instability in the results. We selected the value of λ where the CV-error curve hits its minimum (Tibshirani, 1996; Simon et al., 2011; Kumar et al., 2019).

Before modelling, we assessed collinearity between binary variables using the tetrachoric correlation. If a pair was strongly correlated ($r \geq \pm 0.8$), the most clinically relevant was selected. The remaining baseline characteristics were included in the Cox regression models with LASSO. Variables selected by LASSO were included in univariable Cox regression models. Those significant at the 0.25 level were included in a multivariable Cox regression model and standard backward variable selection procedures, based on a significance level of 0.05 and the Bayesian Information Criterion (BIC), were applied (Hosmer et al., 2008). The final Cox regression models for both sexes included all the variables selected in either the male and female models for each outcome. We verified the proportional hazard assumption using the Schoenfeld residuals. We assessed internal validity of the models by the Harrel's Concordance index (discrimination measure) and calibration slopes (models' reliability) (Harrell, 2011). We reported hazard ratios (HR) and 95% confidence intervals (CI).

In sensitivity analyses, to test the robustness of our main findings, we repeated the main analyses 1) in each of the age groups < 65 years and ≥65 years separately; 2), for each of the time periods defined by the year of cohort entry 2002–2010 and 2011–2015, separately. The analyses by time periods were conducted to control for a potential change in psoriasis management over time as TNFi and ustekinumab were included in the provincial drug formulary for psoriasis in late 2008 and 2011 respectively; before then, they were prescribed for psoriasis on the exceptional patient basis; 3) excluding patients with PSa at cohort entry; 4) considering only patients receiving their initial CSA from a dermatologist, rheumatologist, internal medicine specialist or a general practitioner; 5) not excluding patients with CHF because TNFi/UST are only contraindicated in patients with moderate-to-severe CHF (Remicade® (Infliximab), 2017; Simponi® (Golimumab), 2018; Humira® (Adalimumab), 2004); 6) varying the grace period from 60 to 30 and 90 days; and 7) excluding sulfasalazine from the list of CSA prescribed for psoriasis.

Cohort development and statistical analyses were performed using SAS (version 9.4) and R studio (version 3.6.2).

5.2.6 Results

5.2.6.1 Study population

We included 1,644 patients with psoriasis who initiated a CSA (Supplementary eFigure S1), among whom 55.7% were females (Table 1). Most male (63.5%) and female (60.5%) patients were prescribed their first CSA by a dermatologist with methotrexate being the CSA most often prescribed (females: 58.5% and males: 56.0%) followed by acitretin, sulfasalazine and cyclosporine. Unadjusted and adjusted odds ratios and 95% CI are presented in Table 1. After adjusting for all baseline characteristics, compared to female patients, male patients were younger (mean age 58.6 ± 15.7 vs 61.4 ± 15.1years), more likely to have higher income, ischemic heart diseases, cancer, renal diseases, and alcohol/drug abuse, and to use lipid-lowering drugs. Male patients were less likely to live in urban areas, to have vascular diseases, respiratory diseases, dissociative, somatoform and adjustment disorders and to use antidepressants and benzodiazepines.

5.2.6.2 Patterns of systemic agents' use

Patients were followed for a median of 0.78 years (quartiles: 0.39 and 1.87). During the follow-up, 993 (60.4%) patients discontinued their treatment, and 121 patients (7.4%) had a Switch/add TNFi/UST; 56 (3.4%) switched to a TNFi/UST and 65 (4.0%) received a TNFi/UST as an add-on. The IRs per 1,000 person-years in male vs female patients were: Switch/add TNFi/UST 49.1 vs 41.0 and CSA discontinuation 381.2 vs 352.8 (Table 2). Among the 121 patients who had Switch/add TNFi/UST, most (92.6%) received a TNFi, specifically adalimumab and etanercept, in both sexes (Table 3). Nine patients (5 females and 4 males) received ustekinumab. Kaplan Meier curves exhibited a non-significant higher tendency to Switch/add TNFi/UST in male versus female patients (Supplementary eFigure S2).

5.2.6.3 Variable selection for the models

In both sexes, hypertension and prior use of antihypertensive agents had a correlation coefficient $r > 0.8$. We chose to include hypertension in the model and not antihypertensive agents because of the possibility that these agents were prescribed for an indication other than hypertension. For the patient characteristics associated with Switch/add TNFi/UST in male patients, renal diseases, liver

diseases and cancer were not considered in the model because 0 patients with these comorbidities switched/added TNFi/UST. For the female model, inflammatory bowel diseases and renal diseases were also not considered (0 switch/add-on in patients with these conditions as well). All variables were considered when examining factors associated with CSA discontinuation in both sexes.

5.2.6.4 Factors associated with switch/add TNFi/UST

In male patients, compared to those ages 20–54 years, patients ages 55–64 years, 65–74 years and ≥75 years were at lower risk of Switch/add TNFi/UST (HR = 0.26, 95% CI: 0.12–0.56; HR = 0.21, 95% CI: 0.09–0.45; and HR = 0.10, 95% CI: 0.02–0.40, respectively) while in female patients only those ages ≥75 years were at lower risk of Switch/add TNFi/UST (HR = 0.17, 95% CI: 0.04–0.71) (Table 4). Male patients with clinical obesity (HR = 3.53, 95% CI: 1.20–10.35) and duration of psoriasis >12 months vs 0–3 months (HR = 2.34, 95% CI: 1.09–5.03) were at higher risk of Switch/add TNFi/UST. Female patients, with (vs without) dissociative, somatoform and adjustment disorders were at higher risk of Switch/add TNFi/UST (HR = 3.17, 95% CI: 1.28-7.85). Female patients entering the cohort between 2011–2015 (vs 2002–2010) and those with prescribed NSAID use in the prior year were at higher risk (HR = 1.81, 95% CI: 1.05–3.12 and HR = 2.70, 95% CI: 1.56–4.70 respectively) while those with RA were at lower risk (HR = 0.41, 95% CI: 0.19–0.89) of Switch/add TNFi/UST.

5.2.6.5 Factors associated with CSA discontinuation

Male and female patients entering the cohort between 2011–2015 were at lower risk of CSA discontinuation when compared to those entering the cohort between 2002–2010 (females: HR = 0.78, 95% CI: 0.65–0.93; males: HR = 0.70, 95% CI: 0.57–0.86). Compared to patients receiving methotrexate as a first CSA, initiating acitretin in both sexes (females: HR = 2.07, 95% CI: 1.69–2.5; males: HR = 1.61, 95% CI: 1.30–2.01), and cyclosporine and sulfasalazine in female patients were associated with increased risks of CSA discontinuation (Table 5). Male patients prescribed their first CSA by a rheumatologist (vs dermatologist) and those with (vs without) prior hospitalizations were at lower risk of CSA discontinuation (HR = 0.66, 95% CI: 0.46–0.94 and HR = 0.70, 95% CI: 0.57–0.87 respectively). Female patients with RA, and those with prior use of hypoglycemic and lipid-lowering agents were at a decreased risk of discontinuation by at least 25%.

5.2.6.6 Sensitivity analyses

Overall, results of the sensitivity analyses were consistent with those of the main analyses (Supplementary eTables S1–S10), except for the two analyses including patients aged ≥65 years and those entering the cohort after 2011. None of the predictors for Switch/add TNFi/UST were significant among male and female patients aged ≥ 65 years (Supplementary eTable S2), most likely due to the smaller sample sizes (N = 737, N = 420 females and N = 317 males) and the lower risk of receiving these agents at this age as shown in our main analyses. Similarly, none of the predictors for Switch/add TNFi/UST were significant for patients entering the cohort after 2011 (Supplementary eTable S4), again perhaps due to the smaller sample sizes (N = 740, n = 421 females and N = 319 males). Nonetheless, it is worth noting that in both analyses, the direction of HR estimates remained the same as in the main analyses.

In the sensitivity analyses with grace periods of 30 and 90 days, female patients receiving their first CSA prescription by a rheumatologist were also at a reduced risk of CSA discontinuation (Supplementary eTable S8 and Supplementary eTable S9), while the result was borderline non-significant in the main analysis (HR = 0.75, 95% CI: 0.55–1.01).

5.2.7 Discussion

To our knowledge, this is the first study to assess sex differences in factors associated with Switch/add TNFi/UST and CSA discontinuation among individuals with psoriasis who initiated a CSA. Despite the sex differences in baseline characteristics, there were no statistically significant differences in the rates of CSA discontinuation and Switch/add TNFi/UST among male and female patients. Nonetheless, most of the factors associated with these outcomes were sex specific. Factors associated with Switch/ add TNFi/UST included younger age for both sexes, psoriasis duration and clinical obesity in male patients, and mental health disorders, RA and prior use of NSAIDS in female patients. Factors associated with CSA discontinuation included the CSA received at cohort entry, and cohort entry date after 2011 for both sexes, and the prescriber specialty and hospitalization in the prior year for male patients and RA, lipid-lowering and hypoglycemic agent use for female patients.

In our study, 7.4% of patients who initiated a CSA received a TNFi/UST in follow-up. A similar result was reported by a United States study where 6.3% of patients switched CSA treatment and 81.3% of them switched to a biologic agent (Higa et al., 2019). The decision to prescribe TNFi/UST for our psoriasis patients using CSA was not influenced by the physician specialty or the CSA received. Clinical obesity was associated with Switch/add TNFi/UST only in males. Obesity has been previously associated with increased psoriasis severity (Naldi et al., 2008), which may partially explain our result. However, it is not clear why this result was only observed in males. Previous studies also reported that older adults are less likely to receive biologic agents due to the increased risk of infections at this age (DeWitt et al., 2009; Geale et al., 2016).

Male patients with >12 months (vs ≤ 12 months) psoriasis duration were at higher risk of Switch/add TNFi/UST. Patients with longer disease durations may have had a more severe disease manifestation. To examine this possibility, we assessed the number of phototherapy sessions received in the previous 3 months. Among those with psoriasis duration >12 months, 11.2% received phototherapy (median 15; quartiles 9–24 sessions) compared to 7.1% of those with a disease duration of 0–3 months (median 5; quartiles 4–17 sessions).

Our female patients with dissociative, somatoform and adjustment disorders were more likely to Switch/add TNFi/ UST. Over 30% of patients with psoriasis suffer from mental health disorders (Kotrulja et al., 2010; Ferreira et al., 2016; Wu et al., 2017), with higher prevalence observed among females (Wu et al., 2016; Duvetorp et al., 2020). TNFi/UST are prescribed on a weekly to 3 months basis, therefore, adherence with TNFi/UST may be improved over that of CSA (Osterberg & Blaschke, 2005). In addition, reduced risk of mental health disorders, fatigue and quality of life have been reported among those treated with biologic agents during RCT (Tyring et al., 2006; Gooderham et al., 2016; Strober et al., 2018). Perceived better adherence and improved quality of life may explain the higher rate of switch among our female patients with mental health disorders. It is worth noting that prior opioids use was high in our cohort (21.4%), similar to what have been previously reported in individuals with moderate-to-severe psoriasis (Noe et al., 2020). However, prior opioid use was not significantly different between both sexes.

The presence of RA as a comorbidity in our female patients decreased the risk of switch/add, while the presence of PSa was not associated with switch/add. This was surprising as TNFi/UST are recommended in Psa and TNFi are recommended in RA (Menter et al., 2008).

Prior use of prescribed NSAIDs was associated with an increased risk of Switch/add TNFi/UST in our female patients. NSAIDs have analgesic and anti-inflammatory properties and are indicated for RA, AS, Psa and other arthropathies. Female patients with psoriasis using NSAIDs report less pain, less burning sensations and less depressive feelings (Maul et al., 2019), but may have higher expectations from CSA treatments which may explain their higher risk of switch (Maul et al., 2019).

In our study, methotrexate was the CSA most often prescribed in both sexes and was associated with less CSA discontinuation. A recent systematic review including 6 observational studies also reported high rates of CSA discontinuation in 1 year of follow-up (Mason et al., 2019). In this review, 50.3% of patients initiated on methotrexate remained persistent at 1 year vs 42.2 and 23.3% of patients initiated on acitretin and cyclosporine, respectively (Davila- Seijo et al., 2016; Mason et al., 2019). However, results from this review cannot be compared to ours as all included studies considered new and prevalent CSA users with only one study differentiating between these users in the analysis (Mason et al., 2019). We found only two published retrospective cohort studies that included first time CSA users (Bergqvist et al., 2019; Higa et al., 2019). Similar to our findings, these studies reported high rates of CSA discontinuation within 1year of follow-up (≥75%) with acitretin having the highest rate, followed by cyclosporine and methotrexate (Bergqvist et al., 2019; Higa et al., 2019). Acitretin has a teratogenic effect and is contraindicated in young women (Canadian Dermatology Association, 2009). Nonetheless, in our study, discontinuation rate remained significant in the age stratified analyses for both sexes, which suggest that other reasons may be the cause.

Among male and female patients, the risk of CSA discontinuation was higher among those entering the cohort in 2011–2015 (vs 2002–2010), while the risk of Switch/add TNFi/UST was higher only among female patients entering the cohort in 2011–2015 (vs 2002–2010). This reflects the changes in the standard of care for patients with moderate-to-severe psoriasis in Quebec between 2008 and 2011 following the update of the Canadian clinical guideline for the management of plaque

psoriasis in 2009 and the inclusion of TNFi and UST on the provincial drug formulary in late 2008 and 2011 respectively (Canadian Dermatology Association, 2009; Hagg et al., 2017).

In the sensitivity analyses with grace periods of 30 and 90 days, male and female patients who received their initial CSA from a rheumatologist (vs a dermatologist) were less likely to discontinue their CSA. Further investigation is needed to better understand the nature of this association because patients treated by a rheumatologist may have concomitant rheumatic manifestations.

Prior use of lipid-lowering and hypoglycemic agents were associated with lower risks of CSA discontinuation in our female patients. Similar to our study, dyslipidemia was associated with persistence to CSA in a previous study (Bergqvist et al., 2019). However, it is not clear why this association was only observed in female patients in our study. Differences in the metabolic syndromes risks and types have been reported between males and females with psoriasis. While higher risks of metabolic syndromes have been reported in female versus male patients, (Love et al., 2011; Danielsen et al., 2015; Sondermann et al., 2020), female patients in our study were more likely to receive hypoglycemic agents and male patients were more likely to receive lipid-lowering agents.

In our study, prior all-cause hospitalization was associated with a lower risk of CSA discontinuation among male patients. Hospitalization is an indicator of frailty and males may be at higher risk of psoriasis complications (Gordon et al., 2017; Zhang et al., 2018). Therefore, they may be more closely monitored which may have improved their adherence to therapy (Gordon et al., 2006; Zhang et al., 2018).

5.2.7.1 Limitations

Our study has some limitations. First, our database does not include direct information on psoriasis severity. We have considered the use CSA as indication of moderate-to-severe psoriasis. Although this definition has been used by many authors and was previously validated (Egeberg et al., 2016; Executive Board, 133, 2013), it is not a gold standard and as such our study may have included some patients with mild psoriasis. Second, psoriasis types may be associated with TNFi/UST use. However, we were unable to distinguish the psoriasis type in our study because such information

was not available in the database. Third, in our study, obesity may have been underestimated because it was based on clinical diagnoses which may mostly include morbid obesity. Fourth, because only 7.4% of our study patients switched/added TNFi/UST with about half of them switching and the other half adding the treatment, our analysis considered the combination of both outcomes to increase the statistical power. As predictors of switching from CSA to TNFi/UST may differ from those of adding TNFi/UST to CSA and information regarding these differences is lacking in the literature, our results should be interpreted with caution. To manage model overfitting and perform variable selection, we used LASSO regularization, a method widely used in several machine learning algorithms (Kumar et al., 2019; Tibshirani, 1996). Our models showed good overall performances with Harrel's Concordance index and calibration slopes ≥0.6 (Table 4, Table 5). Fifth, while most of our patients have initiated on methotrexate, our analyses did not consider switch and add-on between CSA. Sixth, over-the-counter pain-relief medicines are not included in the RAMQ pharmaceutical claims database. Therefore, we may have misclassified users of the over-the-counter NSAIDS as non-users which may have biased our results toward the null. The effect of NSAIDS use on Switch/add TNFi/UST may have been stronger than that reported in our study (Carrasco- Garrido et al., 2010). Seventh, our study did not include newer generations of biologic agents approved after 2015. Therefore, our results may not be generalizable to all biologic agents. Eighth, our results may not be generalizable to patients covered by private drug insurance plans. However, individuals from different socioeconomic statuses are covered by the RAMQ drug plan and in our study the variable income, based on the type of drug coverage with RAMQ, was not associated with both outcomes (Régie de l'Assurance Maladie du Québec, 2015). Lastly, our study is observational in nature and may suffer from residual confounding due to unmeasured confounders such as body mass index, pain, and smoking.

5.2.8 Conclusion

In our study, a high proportion of male and female patients with psoriasis discontinued their CSA within the first year of initiating their systemic treatment. Our findings suggest that factors associated with Switch/add TNFi/UST include mostly characteristics related to patients' clinical profile such as mental health disorders in female, and clinical obesity and disease duration in male patients. However, CSA discontinuation among male and female patients was also influenced by the initial CSA received and the speciality of the prescriber. Additional studies examining sex

differences in systemic agents' use are needed to confirm our findings and their impact on clinical practice and provincial drug policy. The identification of such factors may help improve the management of male and female patients with moderate-to-severe psoriasis when initiating systemic agents.

5.2.9 Statements

Data availability statement: The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement: Approval to conduct the study was obtained from the McGill University Health Centre Ethics Review Board (ERB). The study uses anonymized data from the Provincial administrative database. Study participants cannot be identified, and informed consent is not required by the ERB for such studies.

Author contributions: Study concept and design: All authors. Drafting of manuscript: RM and ER. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: RM.

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5.2.10 References

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Table 1. Baseline patient characteristics by sex: logistic regression model comparing baseline characteristics in male vs female patients

	All patients (N = 1,644)	Females (N = 916)	Males (N = 728)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[‖]
Mean age (SD)	60.3 (15.4)	61.4 (15.1)	58.9 (15.7)	–	–
Mean duration of follow-up in years (SD)	1.66 (2.2)	1.70 (2.3)	1.59 (2.0)	–	–
Median duration of follow-up in years (Q1, Q3)	0.78 (0.39, 1.87)	0.76 (0.39, 2.01)	0.81 (0.38, 1 .77)	–	–
Socio-demographic variables, N (%)					
Age					
20-54 years	537 (32.7)	263 (28.7)	274 (37.6)	Ref	Ref
55-64 years	370 (22.5)	233 (25.4)	137 (18.8)	0.56 (0.43-0.74)	0.57 (0.43-0.77)
65-74 years	455 (27.7)	253 (27.6)	202 (27.7)	0.77 (0.60-0.99)	0.70 (0.52-0.95)
≥75 years	282 (17.2)	167 (18.2)	115 (15.8)	0.66 (0.49-0.89)	0.56 (0.39-0.82)
Social deprivation index					
Unknown	205 (12.5)	110 (12.0)	95 (13.0)	0.9 (0.62-1.31)	1.08 (0.72-1.63)
Most socially privileged	239 (14.5)	122 (13.3)	117 (16.1)	Ref	Ref
Privileged socially	251 (15.3)	150 (16.4)	101 (13.9)	0.70 (0.49-1.00)	0.70 (0.48-1.03)
Average socially deprivation	283 (17.2)	162 (17.7)	121 (16.6)	0.78 (0.55-1.10)	0.78 (0.54-1.13)
Deprived socially	328 (20.0)	173 (18.9)	155 (21.3)	0.93 (0.67-1.30)	1.07 (0.75-1.53)
Most socially deprived	338 (20.6)	199 (21.7)	139 (19.1)	0.73 (0.52-1.02)	0.90 (0.62-1.29)
Area of residency (urban vs rural)	1320 (80.3)	755 (82.4)	565 (77.6)	0.74 (0.58-0.94)	0.69 (0.52-0.90)
Income (Low vs high income)[†]	963 (58.6)	558 (60.9)	405 (55.6)	0.80 (0.66-0.98)	0.77 (0.62-0.96)
Variables related to CSA and other psoriasis treatments, N (%)					
Year of cohort entry (2011-2015 vs 2002-2010)	740 (45.0)	421 (46.0)	319 (43.8)	0.92 (0.75-1.12)	0.81 (0.65-1.01)
Psoriasis duration[‡]					
0–3 months	458 (27.9)	261 (28.5)	197 (27.1)	Ref	Ref
>3-12 months	315 (19.2)	185 (20.2)	130 (17.9)	0.93 (0.70-1.25)	0.92 (0.67-1.26)
>12 months	871 (53.0)	470 (51.3)	401 (55.1)	1.13 (0.90-1.42)	1.22 (0.95-1.57)
Specialty of the first CSA prescriber					
Dermatologist	1016 (61.8)	554 (60.5)	462 (63.5)	Ref	Ref

Rheumatologist	290 (17.6)	172 (18.8)	118 (16.2)	0.82 (0.63-1.07)	0.79 (0.53-1.17)
Others[§]	338 (20.6)	190 (20.7)	148 (20.3)	0.93 (0.73-1.20)	0.90 (0.66-1.22)
First CSA received					
Methotrexate	944 (57.4)	536 (58.5)	408 (56.0)	Ref	Ref
Cyclosporine	51 (3.1)	25 (2.7)	26 (3.6)	1.37 (0.78-2.40)	1.15 (0.62-2.15)
Acitretin	570 (34.7)	316 (34.5)	254 (34.9)	1.06 (0.86-1.30)	0.97 (0.76-1.25)
Sulfasalazine	79 (4.8)	39 (4.3)	40 (5.5)	1.35 (0.85-2.13)	1.42 (0.85-2.39)
Use of topical agents in the prior year	1389 (84.5)	775 (84.6)	614 (84.3)	0.98 (0.75-1.28)	0.93 (0.68-1.27)
Use of phototherapy in the prior year	206 (12.5)	111 (12.1)	95 (13.0)	1.09 (0.81-1.46)	1.09 (0.78-1.51)
All-cause health care use and comorbidities in the prior 2 years, N (%)					
Hospitalizations	552 (33.6)	311 (34.0)	241 (33.1)	0.96 (0.78-1.18)	0.88 (0.68-1.14)
Emergency department visits	899 (54.7)	496 (54.1)	403 (55.4)	1.05 (0.86-1.28)	1.13 (0.90-1.43)
Psoriatic arthritis	242 (14.7)	129 (14.1)	113 (15.5)	1.12 (0.85-1.47)	1.24 (0.90-1.70)
Rheumatoid arthritis	233 (14.2)	148 (16.2)	85 (11.7)	0.69 (0.52-0.91)	0.71 (0.50-1.02)
Inflammatory bowel diseases	27 (1.6)	14 (1.5)	13 (1.8)	1.17 (0.55-2.51)	1.02 (0.44-2.38)
Ankylosing spondylitis	23 (1.4)	13 (1.4)	10 (1.4)	0.97 (0.42-2.22)	1.34 (0.55-3.30)
Obesity	78 (4.7)	47 (5.1)	31 (4.3)	0.82 (0.52-1.31)	0.85 (0.50-1.44)
Hypertension	591 (35.9)	345 (37.7)	246 (33.8)	0.85 (0.69-1.04)	0.91 (0.68-1.20)
Ischemic heart diseases	95 (5.8)	43 (4.7)	52 (7.1)	1.56 (1.03-2.37)	1.66 (1.03-2.67)
Cerebrovascular diseases	41 (2.5)	19 (2.1)	22 (3.0)	1.47 (0.79-2.74)	1.37 (0.68-2.74)
Vascular diseases	139 (8.5)	89 (9.7)	50 (6.9)	0.69 (0.48-0.98)	0.59 (0.39-0.91)
Cardiac Arrhythmias	90 (5.5)	47 (5.1)	43 (5.9)	1.16 (0.76-1.78)	1.32 (0.81-2.16)
Renal diseases	51 (3.1)	18 (2.0)	33 (4.5)	2.37 (1.32-4.24)	4.09 (2.10-7.95)
Liver diseases	51 (3.1)	25 (2.7)	26 (3.6)	1.32 (0.76-2.31)	1.43 (0.76-2.68)
Respiratory diseases	311 (18.9)	196 (21.4)	115 (15.8)	0.69 (0.53-0.89)	0.61 (0.46-0.82)
Cancer[¶]	190 (11.6)	95 (10.4)	95 (13.0)	1.30 (0.96-1.76)	1.56 (1.11-2.20)
Mental health disorders, N (%)					
No mental health disorder	1191 (72.4)	640 (69.9)	551 (75.7)	Ref	Ref
Anxiety and mood disorders	356 (21.7)	228 (24.9)	128 (17.6)	0.65 (0.51-0.83)	0.83 (0.62-1.12)
Dissociative, somatoform and adjustment disorders	28 (1.7)	21 (2.3)	7 (1.0)	0.39 (0.16-0.92)	0.34 (0.13-0.89)

Other mental health disorders	69 (4.2)	27 (2.9)	42 (5.8)	1.81 (1.10-2.97)	2.36 (1.37-4.05)
Drug and/or alcohol abuse	74 (4.5)	28 (3.1)	46 (6.3)	2.14 (1.32-3.46)	2.65 (1.53-4.59)
Drug use in the prior year, N (%)					
Antidepressants	382 (23.2)	258 (28.2)	124 (17.0)	0.52 (0.41-0.67)	0.56 (0.42-0.76)
Benzodiazepines	478 (29.1)	303 (33.1)	175 (24.0)	0.64 (0.51-0.80)	0.69 (0.54-0.90)
Opioids	351 (21.4)	200 (21.8)	151 (20.7)	0.94 (0.74-1.19)	1.11 (0.84-1.47)
Antihypertensive agents	793 (48.2)	451 (49.2)	342 (47.0)	0.91 (0.75-1.11)	0.93 (0.69-1.26)
Hypoglycemic agents	258 (15.7)	141 (15.4)	117 (16.1)	1.05 (0.81-1.38)	0.96 (0.69-1.32)
Lipid-lowering drugs	569 (34.6)	298 (32.5)	271 (37.2)	1.23 (1.00-1.51)	1.47 (1.13-1.93)
Platelet inhibitors	471 (28.6)	251 (27.4)	220 (30.2)	1.15 (0.93-1.42)	1.13 (0.85-1.51)
Anticoagulants	59 (3.6)	35 (3.8)	24 (3.3)	0.86 (0.51-1.46)	0.90 (0.48-1.69)
Nonsteroidal anti-inflammatory drugs	658 (40.0)	378 (41.3)	280 (38.5)	0.89 (0.73-1.09)	0.95 (0.75-1.21)
Oral corticosteroids	423 (25.7)	232 (25.3)	191 (26.2)	1.05 (0.84-1.31)	1.27 (0.97-1.66)

[‖]The multivariate logistic regression model was adjusted for all variables included in table 1. The reference group was female patients. OR >1 indicates higher likelihood among male patients. OR<1 indicates lower likelihood among male patients.

[†]Income (high vs low) was based on the type of drug plan they had with those receiving partial or total subsidies classified as low income

[‡]Time from first psoriasis diagnosis until the first conventional systemic agent prescription fill

[§]The others category included mostly general practitioners (63.9%) and internal medicine doctors (25.1%). Only 5 (1.8%) received their first CSA from a gastroenterologist.

[¶]22 female patients and 21 male patients had non-melanoma skin cancer

List of abbreviations: OR: odds ratios; CSA: conventional systemic agent; CI: confidence interval; Q1: first quartile; Q3: third quartile; ref: reference group; SD: standard deviation

Table 2. Crude rates of switch to a TNFi/UST or add-on and treatment discontinuation among male and female patients with psoriasis

	All (N=1,644)		Females (N=916)		Males (N=728)	
	Number of events	IR per 1000 person-years (95% CI)	Number of events	IR per 1000 person-years (95% CI)	Number of events	IR per 1000 person-years (95% CI)
Switch to TNFi/UST or add-on	121	44.5 (37.0-53.1)	64	41.0 (31.6-52.3)	57	49.1 (37.2-63.7)
Switch to TNFi/UST	56	20.6 (15.5-26.7)	27	17.3 (11.4-25.1)	29	25.0 (16.7-35.9)
Add-on of TNFi/UST	65	23.9 (18.4-30.4)	37	23.7 (16.7-32.7)	28	24.1 (16.0-34.9)
CSA discontinuation	993	364.9 (342.6-388.3)	551	352.8 (324.0-383.6)	442	381.2 (346.5-418.4)

List of abbreviations: CSA: conventional systemic agent; CI: confidence interval; IR: Incident rate; TNFi: Tumor necrosis factor inhibitor; UST: Ustekinumab

Table 3. Biologic agents received during the follow-up

	All patients N=121 (%)	Females N=64 (%)	Males N=57 (%)
Tumor necrosis factor inhibitors	112 (92.6)	59 (92.2)	53 (93.0)
Adalimumab	52 (43.0)	27 (42.1)	25 (43.9)
Etanercept	34 (28.1)	17 (26.6)	17 (29.8)
Infliximab	17 (14.1)	9 (14.1)	8 (14.0)
Golimumab	8 (6.6)	5 (7.8)	3 (5.3)
Certolizumab pegol	1 (0.8)	1 (1.6)	0 (0)
Ustekinumab	9 (7.4)	5 (7.8)	4 (7.0)

Table 4. Predictors of switch to a TNFi/UST or add-on among males and female patients with psoriasis - Cox proportional Hazard models with LASSO

	All patients (N=1,644)	Females (N=916)	Males (N=728)
	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Age			
20-54 years	Ref	Ref	Ref
55-64 years	0.50 (0.32-0.78)	0.80 (0.44-1.44)	0.26 (0.12-0.56)
65-74 years	0.36 (0.23-0.58)	0.61 (0.32-1.15)	0.21 (0.09-0.45)
≥75 years	0.12 (0.04-0.32)	0.17 (0.04-0.71)	0.10 (0.02-0.40)
Sex	1.15 (0.79-1.67)	–	–
cohort entry between 2011-2015	1.55 (1.04-2.31)	1.81 (1.05-3.12)	1.28 (0.71-2.30)
Psoriasis duration[†]			
0–2.99 months	Ref	Ref	Ref
3-12 months	0.61 (0.33-1.16)	0.48 (0.22-1.04)	0.93 (0.30-2.86)
>12 months	1.25 (0.80-1.95)	0.76 (0.43-1.36)	2.34 (1.09-5.03)
Rheumatoid arthritis	0.67 (0.40-1.12)	0.41 (0.19-0.89)	1.33 (0.63-2.82)
Clinical obesity	1.60 (0.76-3.33)	1.09 (0.38-3.12)	3.53 (1.20-10.35)
Mental health disorders			
No mental health disorder	Ref	Ref	Ref
Anxiety and mood disorders	1.24 (0.81-1.89)	1.06 (0.59-1.91)	1.54 (0.85-2.81)
Dissociative, somatoform and adjustment disorders	2.95 (1.24-7.01)	3.17 (1.28-7.85)	NA[‡]
Other mental health disorders	1.51 (0.72-3.17)	1.58 (0.37-6.65)	1.45 (0.59-3.52)
Prior use of NSAIDS	1.87 (1.27-2.73)	2.70 (1.56-4.70)	1.04 (0.58-1.86)
Internal validity of the models			
Harrel's C index (95% CI)	0.69 (0.66-0.72)	0.68 (0.64-0.72)	0.70 (0.61-0.78)
Calibration slope	0.90	0.62	0.81

[†]Time from first psoriasis diagnosis until the first conventional systemic agent prescription fill

[‡]In male patients, only 7 patients had dissociative, somatoform and adjustment disorders; therefore, they were combined with had also anxiety and mood disorders

List abbreviations: aHR: adjusted Hazard ratios, CI: confidence intervals; Harrel's C index: Harrel's Concordance index; LASSO: least absolute shrinkage and selection operator; NSAIDS: Non-steroidal anti-inflammatory drugs; ref: reference group; TNFi: Tumor necrosis factor inhibitor; UST: Ustekinumab

Table 5. Predictors of CSA discontinuation among males and female patients with psoriasis - Cox proportional Hazard models with LASSO

	All patients (N=1,644)	Females (N=916)	Males (N=728)
	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Sex	0.99 (0.87-1.12)	–	–
cohort entry between 2011-2015	0.76 (0.66-0.86)	0.78 (0.65-0.93)	0.70 (0.57-0.86)
Specialty of the CSA prescriber			
Dermatologist	Ref	Ref	Ref
Rheumatologist	0.70 (0.56-0.89)	0.75 (0.55-1.01)	0.66 (0.46-0.94)
Other specialists	0.85 (0.71-1.03)	0.89 (0.69-1.14)	0.83 (0.62-1.10)
First CSA received			
Methotrexate	Ref	Ref	Ref
Cyclosporine	1.45 (1.01-2.08)	2.14 (1.30-3.55)	1.03 (0.62-1.73)
Acitretin	1.84 (1.59-2.13)	2.07 (1.69-2.53)	1.61 (1.30-2.01)
Sulfasalazine	1.44 (1.04-2.00)	1.56 (1.00-2.42)	1.31 (0.80-2.12)
Prior hospitalization	0.86 (0.75-0.99)	0.99 (0.82-1.19)	0.70 (0.57-0.87)
Rheumatoid arthritis	0.75 (0.60-0.94)	0.69 (0.51-0.93)	0.84 (0.59-1.19)
Prior use of Hypoglycemic agents	0.82 (0.68-1.00)	0.75 (0.57-0.98)	0.97 (0.72-1.29)
Prior use of lipid-lowering agents	0.78 (0.68-0.91)	0.72 (0.59-0.88)	0.90 (0.72-1.11)
Internal validity of the models			
Harrel's C index (95% CI)	0.63 (0.61-0.65)	0.65 (0.59-0.70)	0.61 (0.59-0.64)
Calibration slope	0.94	0.95	0.79

List abbreviations: aHR: adjusted Hazard ratios, CI: confidence intervals; Harrel's C index: Harrel's Concordance index; LASSO: Least absolute shrinkage and selection operator; ref: reference group; TNFi: Tumor necrosis factor inhibitor; UST: Ustekinumab

Chapter 6: Assessing switch/add-on to a TNFi/UST or a different CSA (whichever occurred first), and identify sex differences in factors associated with these switches/add-on

In this section, I am presenting additional information on the methods used in manuscript 2 that addressed my objective 1.b.

6.1 Methods

To address objective 1.b, I used the same cohort, set of potential confounders and statistical analyses as those described in chapter 5 to address objective 1.a. Therefore, in this study I included patients who were initiated on one CSA (methotrexate, cyclosporine, acitretin and Sulfasalazine). However, contrary to the previous study where CSA were considered as a class, in the current study CSA were considered separately. Therefore, the exposure and outcome definitions differed from those described in chapter 5, and these will be detailed below.

6.1.1 Exposure definition

I adopted a grace period of 60 days between prescriptions and considered patients to be continuously exposed to their initial CSA until they had a gap exceeding 60 days between prescriptions for that agent.

6.1.2 Outcome definition

The outcome was switch/add TNFi/UST or a CSA that was different from the initial CSA received. Switch and add-on were defined as in chapter 5. The CSA considered in the outcome definition included methotrexate, acitretin, cyclosporine, sulfasalazine and apremilast.

6.2 Manuscript 2 – Sex differences in factors associated with switch between systemic agent use among patients with psoriasis: A retrospective cohort study in Quebec, Canada

6.2.1 Preamble to manuscript 2

Manuscript 2 is a continuum to manuscript 1. In manuscript 1, switches and add-on between CSA were not examined because all CSA were considered as a single class. Therefore, in manuscript 2, I aimed (1) to assess among patients initiating a CSA, the rates of switch/add to either TNFi/UST or a different CSA, whichever occurred first; and (2) to examine among these patients, the sex differences in factors associated with switch/add between systemic agents.

Initially, manuscript 2 was submitted as a research article to the Journal of the American Academy of Dermatology International (JAAD international). After reviewing the manuscript, the editor of the journal proposed to publish the results as a research letter. The analyses not included in the research letter were added as additional results in section 6.3, because JAAD international does not allow the inclusion of electronic supplementary materials and more than 3 tables/figures in research letters.

Milan R, LeLorier J, Brouillette MJ, Holbrook A, Litvinov IV, Rahme E. *Sex differences in factors associated with switch between systemic agents among individuals with psoriasis: A retrospective cohort study in Quebec, Canada*. JAAD Int. 2021 Jul 31;4:79-83.

6.2.2 Manuscript 2

6.2.2.1 Title page

Article type: Research letter

Title: Sex differences in factors associated with switch between systemic agents among individuals with psoriasis: A retrospective cohort study in Quebec Canada

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Raymond Milan holds a doctoral training award from the *Fonds de Recherche du Québec – Santé* (FRQS). Ivan Litvinov is supported by a Junior I Clinician Scientist award from the FRQS and has received consulting fees from Novartis, Janssen, Galderma and Bristol-Myers Squibb in the course of unrelated studies. Elham Rahme has received funds and consulting fees from Janssen in the course of an unrelated study. Jacques LeLorier, Marie-Josée Brouillette and Anne Holbrooke have no conflict of interest to disclose.

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Figures: 1

Tables: 2

6.2.3 Research letter

Conventional systemic agents' (CSA) are indicated in moderate-to-severe psoriasis. CSA switch to another CSA and/or a biologic agent including a tumor necrosis factor inhibitor and ustekinumab (TNFi/UST) may be an indication of dissatisfaction with treatment.[1] Discontinuation of CSA treatment has been previously studied in psoriasis, but switches between agents and differences between sexes have not received much attention.[2-4] We examined sex differences in factors associated with CSA treatment switch among patients with psoriasis.

We conducted a retrospective cohort study using Quebec health administrative databases. We considered new patients with psoriasis ≥20 years, enrolled in the public drug plan (≥65 years, <65 years with no private drug plan or receiving social assistance) in 2002-2015. New patients were those with no psoriasis diagnosis in the prior three years and no psoriasis treatment (phototherapy, CSA or a biologic agent) in the prior year. We included those initiated on a CSA (methotrexate, cyclosporine, acitretin and sulfasalazine)[1] and followed them until the first date of a switch, CSA discontinuation (no supply for any CSA for ≥60 days), death or end of public drug plan enrollment. A switch was a prescription for another CSA or TNFi/UST during the days supplied for the initial CSA or a 60-day grace period. Cox regression models with Least Absolute Shrinkage and Selection Operator method identified factors associated with switch in male and female patients, separately.[5] In sensitivity analyses 1) sulfasalazine was not considered among the CSA prescribed for psoriasis (sulfasalazine is prescribed when other CSA are contraindicated and in those with other immune-mediated conditions); and 2) both prevalent and incident psoriasis patients were studied.

We included 1,644 patients with psoriasis who initiated a CSA (55.7% females: mean age 61.4±15.1 vs 58.9±15.7 yrs for males). Most patients initiated a methotrexate, followed by acitretin, sulfasalazine and cyclosporine (57.4%, 34.7%, 4.8% and 3.1%, respectively) with no difference between sexes (Table 1). Most methotrexate, acitretin and cyclosporine prescriptions were by a dermatologist (48.5%, 91.1% and 76.5%, respectively) and 65.8% of sulfasalazine prescriptions were by a rheumatologist.

In total, 312 patients switched their initial CSA (different CSA: 82.7% and TNFi/UST: 17.3%) (Figure 1). Most switched to methotrexate (29.8%), followed by acitretin (21.1%), sulfasalazine (18.9%), cyclosporine (12.2%), adalimumab (6.7%) and etanercept (5.5%).

In both sexes, age was associated with a decreased risk of switch while receiving sulfasalazine vs methotrexate was associated with an increased risk (Table 2). In male patients, psoriatic arthritis, and longer disease duration were associated with increased risks. In female patients, disease duration of 3-12 vs 0-2.99 months was associated with a 47% decreased risk of switch and the presence of somatoform/dissociative/adjustment disorders and prior use of nonsteroidal anti-inflammatory drugs were associated with an increased risk.

Results of the sensitivity analyses were consistent with those of the main analysis (data not shown), although a higher proportion of patients switched to TNFi/UST when sulfasalazine was not considered (29.8% vs 17.3%).

In our study, physical comorbidities increased the risk of switch in male patients, while in female patients, mental health disorders increased that risk.

Figure legends

Figure 1: Sankey diagram describing switches between systemic agents among patients with psoriasis initiating a CSA while accounting for switches between CSA (N=312 switches occurred)

[§]Due to drug formulary restrictions, patients could not initiate on apremilast but can receive this agent after failing their index CSA

List of abbreviations: ACI: acitretin; ADA: Adalimumab; APR: Apremilast; CSA: Conventional systemic agent; CER: Certolizumab pegol; CYC: Cyclosporin; ETA: Etanercept; GOL: Golimumab; INF: Infliximab; MTX: Methotrexate; SUL: Sulfasalazine; UST: Ustekinumab

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Table 1. Baseline characteristics by the initial CSA received

	Methotrexate N=944 (57.4)	Cyclosporine N=51 (3.1)	Acitretin N=570 (34.7)	Sulfasalazine N=79 (4.8)	p-Value[e]
Mean duration of follow-up in years (SD)	1.83 (2.37)	0.98 (1.26)	0.92 (1.33)	0.96 (1.58)	–
Median duration of follow-up in years (Q1, Q3)	0.83 (0.38, 2.22)	0.50 (0.31,1.09)	0.49 (0.26, 0.95)	0.35 (0.25, 0.65)	–
Socio-demographic variables, N (%)					
Age					<0.001
20-45 years	166 (17.6)	21 (41.2)	82 (14.4)	12 (15.2)	
45-64 years	332 (35.2)	20 (39.2)	248 (43.5)	26 (32.9)	
65-74 years	274 (29.0)	7 (13.7)	148 (26.0)	26 (32.9)	
≥75 years	172 (18.2)	3 (5.9)	92 (16.1)	15 (19.0)	
Sex (male vs female)	408 (43.2)	26 (51.0)	254 (44.6)	40 (50.6)	0.44
Area of residency (urban vs rural)	754 (79.9)	43 (84.3)	456 (80.0)	67 (84.8)	0.64
Income (Low vs high income)[a]	567 (60.1)	37 (72.5)	314 (55.1)	45 (57.0)	0.04
Variables related to CSA and other psoriasis treatments, N (%)					
Year of cohort entry (≥2009-2015 vs 2002-2008)	564 (59.7)	28 (54.9)	363 (63.7)	38 (48.1)	0.04
Psoriasis duration[b]					<0.001
0–2.99 months	243 (25.7)	18 (35.3)	182 (31.9)	15 (19.0)	
3-12 months	162 (17.2)	13 (25.5)	127 (22.3)	13 (16.5)	
Over 12 months	539 (57.1)	20 (39.2)	261 (45.8)	51 (64.6)	
Specialty of the first CSA prescriber					<0.001
Dermatologist	458 (48.5)	39 (76.5)	519 (91.1)	0 (0.0)	
Rheumatologist	238 (25.2)	0 (0.0)	0 (0.0)	52 (65.8)	
Others[c]	248 (26.3)	12 (23.5)	51 (8.9)	27 (34.2)	
Use of topical agents in the prior year	759 (80.4)	43 (84.3)	533 (93.5)	54 (68.4)	<0.001
Use of phototherapy in the prior year	85 (9.0)	8 (15.7)	112 (19.6)	1 (1.3)	<0.001
Comorbidities in the prior 2 years, N (%)					

Psoriatic arthritis	176 (18.6)	3 (5.9)	38 (6.7)	25 (31.6)	<0.001
Rheumatoid arthritis	192 (20.3)	0 (0.0)	13 (2.3)	28 (35.4)	<0.001
Inflammatory bowel diseases	18 (1.9)	1 (2.0)	5 (0.9)	3 (3.8)	0.12
Ankylosing spondylitis	14 (1.5)	0 (0.0)	3 (0.5)	6 (7.6)	<0.001
Obesity	42 (4.4)	5 (9.8)	25 (4.4)	6 (7.6)	0.17
Renal diseases	22 (2.3)	5 (9.8)	21 (3.7)	3 (3.8)	0.02
Liver diseases	29 (3.1)	6 (11.8)	13 (2.3)	3 (3.8)	0.01
Cancer[d]	109 (11.5)	6 (11.8)	64 (11.2)	11 (13.9)	0.92
Mental health disorders, N (%)					0.03
No mental health disorder	671 (71.1)	32 (62.7)	423 (74.2)	65 (82.3)	
Anxiety and mood disorders	208 (22.0)	15 (29.4)	124 (21.8)	9 (11.4)	
Dissociative, somatoform and adjustment disorders	20 (2.1)	0 (0.0)	5 (0.9)	3 (3.8)	
Other mental health disorders	45 (4.8)	4 (7.8)	18 (3.2)	2 (2.5)	
Drug and/or alcohol abuse	42 (4.4)	2 (3.9)	25 (4.4)	5 (6.3)	0.87
Drug use in the prior year, N (%)					
Antidepressants	235 (24.9)	11 (21.6)	124 (21.8)	12 (15.2)	0.16
Benzodiazepines	287 (30.4)	18 (35.3)	151 (26.5)	22 (27.8)	0.30
Antihypertensive agents	472 (50.0)	22 (43.1)	262 (46.0)	37 (46.8)	0.40
Hypoglycemic agents	148 (15.7)	12 (23.5)	88 (15.4)	10 (12.7)	0.40
Lipid-lowering drugs	342 (36.2)	10 (19.6)	193 (33.9)	24 (30.4)	0.07
Platelet inhibitors	266 (28.2)	14 (27.5)	171 (30.0)	20 (25.3)	0.78
Anticoagulants	38 (4.0)	3 (5.9)	12 (2.1)	6 (7.6)	0.02
Nonsteroidal anti-inflammatory drugs	455 (48.2)	11 (21.6)	131 (23.0)	61 (77.2)	<0.001
Oral corticosteroids	301 (31.9)	17 (33.3)	76 (13.3)	29 (36.7)	<0.001

[a]Income (high vs low) was based on the type of drug plan they had with those receiving partial or total subsidies classified as low income
[b]Time from first psoriasis diagnosis until the first conventional systemic agent prescription fill
[c]The others category included mostly general practitioners (63.9%) and internal medicine doctors (25.1%). Only 5 (1.8%) received their first CSA from a gastroenterologist.

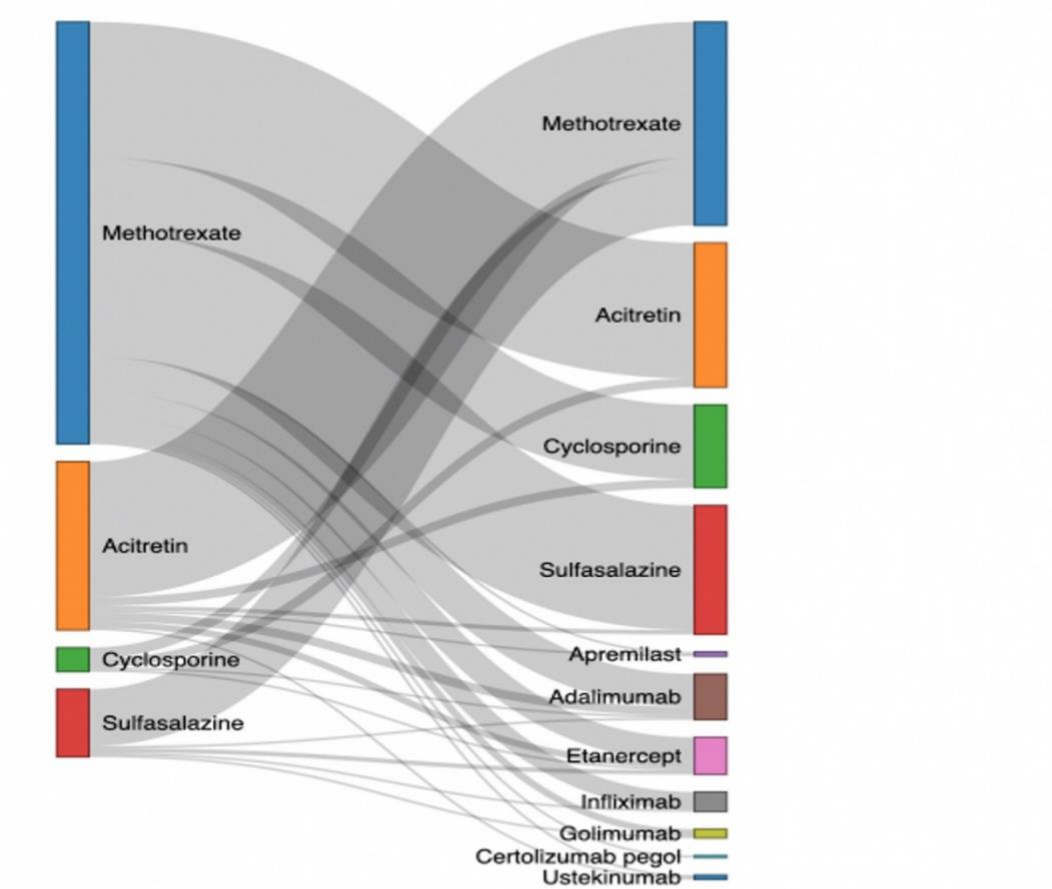
[d]43 patients had non-melanoma cancer: 22 female patients and 21 male patients had non-melanoma skin cancer. With regards to the CSA received, 27 patients with methotrexate, 1 patient with cyclosporine, 11 patients with acitretin and 4 patients with sulfasalazine had non-melanoma skin cancer.
[e]Chi-square test or exact Fisher test for statistical significance
List of abbreviations: aOR: Adjusted odds ratios; CSA: conventional systemic agent; CI: confidence interval; Q1: first quartile; Q3: third quartile; ref: reference group; SD: standard deviation

Table 2. Predictors of switch to either a CSA or a tumor necrosis factor inhibitor/Ustekinumab among males and female patients with psoriasis

	All patients (N=1,644)	Females (N=916)	Males (N=728)
	aHR (95% CI)	**aHR (95% CI)**	**aHR (95% CI)**
Age			
20-54 years	Ref	Ref	Ref
55-64 years	0.70 (0.52-0.93)	0.68 (0.45-1.01)	0.72 (0.48-1.11)
65-74 years	0.46 (0.33-0.64)	0.44 (0.28-0.70)	0.47 (0.28-0.76)
≥75 years	0.32 (0.21-0.50)	0.35 (0.19-0.62)	0.29 (0.14-0.59)
Psoriasis duration			
0–2.99 months	Ref	Ref	Ref
3-12 months	0.65 (0.45-0.94)	0.50 (0.31-0.81)	0.90 (0.49-1.65)
Over 12 months	1.13 (0.87-1.48)	0.89 (0.63-1.25)	1.61 (1.03-2.53)
First CSA received			
Methotrexate	Ref	Ref	Ref
Cyclosporine	1.29 (0.69-2.41)	1.15 (0.42-3.19)	1.69 (0.74-3.82)
Acitretin	1.17 (0.88-1.55)	1.24 (0.85-1.81)	1.16 (0.75-1.80)
Sulfasalazine	3.05 (2.07-4.49)	3.06 (1.81-5.18)	3.34 (1.84-6.05)
Psoriatic arthritis	1.28 (0.96-1.70)	1.15 (0.77-1.69)	1.52 (1.02-2.31)
Mental health disorders			
No mental health disorder	Ref	Ref	Ref
Anxiety and mood disorders	1.03 (0.76-1.38)	0.90 (0.62-1.32)	1.20 (0.74-1.95)
Dissociative, somatoform and adjustment disorders	1.82 (0.95-3.49)	2.18 (1.04-4.57)	NA[b]
Other mental health disorders	1.56 (0.97-2.51)	1.83 (0.91-3.72)	1.37 (0.72-2.60)
Prior use of NSAIDS	1.30 (1.02-1.66)	1.50 (1.09-2.06)	1.14 (0.78-1.65)
Performance measures for internal validation			
Harrel's C index (95% CI)	0.63 (0.59-0.66)	0.61 (0.59-0.62)	0.61 (0.55-0.67)
Calibration slope	0.81	0.66	0.77

[a]In male patients, only 7 patients had dissociative, somatoform and adjustment disorders; therefore, they were combined with those who had anxiety and mood disorders.

List of abbreviations: aHR: Adjusted hazard ratios; CI: confidence interval; CSA: conventional systemic agent; Harrel's C index: Harrel's Concordance index; NSAIDS: nonsteroidal anti-inflammatory drugs; ref: reference group



Initial CSA	Systemic agent received during the switch (N = 312)											Total of switch	Incidence rate per 1,000 person-year
	CSA (N = 258)					Biologic agent (N = 54)							
	MTX	ACI	CYC	SUL	APR§	ADA	ETA	IFN	GOL	CER	UST		
MTX (N=944)	0	62	34	57	1	15	11	8	3	1	1	193	111.6
ACI (N=570)	62	0	4	2	1	4	3	0	0	0	1	77	147.4
CYC (N=51)	5	4	0	0	0	1	1	0	0	0	0	11	220.4
SUL (N=79)	26	0	0	0	0	1	2	1	1	0	0	31	407.6
Total	93	66	38	59	2	21	17	9	4	1	2	312	131.3

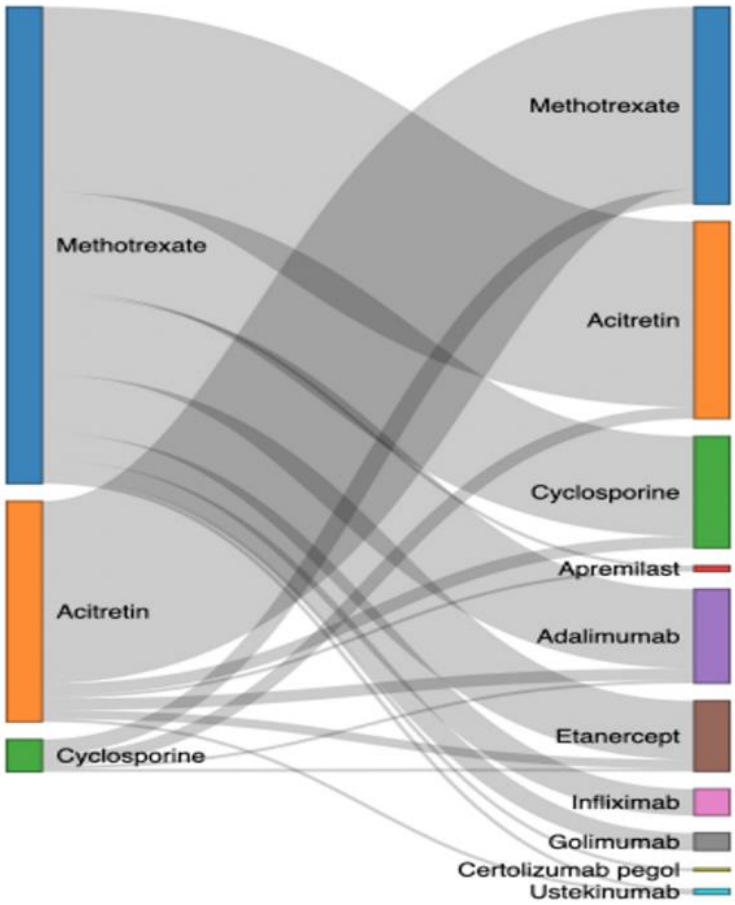
Figure 1. Sankey diagram describing switches between systemic agents among patients with psoriasis initiating a CSA while accounting for switches between CSA (N=312 switches occurred)

6.3 Additional results

The results presented below are the sensitivity analyses that were not included in the research letter. As previously stated, in JAAD international, I could only include 3 tables/figures and supplementary materials were not allowed.

Sensitivity analysis without considering sulfasalazine as a CSA (N = 1,613). In total, 248 patients switched their initial CSA, with 70.2% received a different CSA and 29.8% received a TNFi/UST (Figure 6.1). In this sensitivity analysis, a higher percentage of patients switched to a TNFi/UST versus the main analysis (29.8% vs 17.3%). Overall, predictors of switch to a different systemic agent were consistent with those of the main analysis (Table 6.1), except for psoriatic arthritis (HR 1.45, 0.90-2.33) which became non-significant among male patients and the use of NSAIDS which also became non-significant among female patients (HR 1.11, 95% CI: 0.77-1.59).

Sensitivity analysis without excluding patients with a diagnosis in the prior three years, thus including prevalent and incident cases of psoriasis (N = 2,486). This analysis was performed to answer one of the reviewer's comments that suggested that by excluding patients with a previous psoriasis diagnosis, I might have excluded younger patients. Indeed, I found that in the entire cohort, patients with a psoriasis diagnosis in the prior three years were slightly younger than patients without a diagnosis in the prior three years (mean age: 56 ± 18 vs 60 ± 17 years, $p < 0.001$). In this analysis, 470 patients switched their initial CSA, with 82.1% received a different CSA and 17.8% received a TNFi/UST (Figure 6.2), with the same percentage of patients switching to a TNFi/UST vs in the main analysis (17.8% vs 17.3%). In addition, all predictors of switch to a different systemic agent were consistent with those of the main analysis (Table 6.2).



Initial CSA	Systemic agent received during the switch (N = 248)										Total of switch	Incidence rate per 1,000 person-year
	CSA (N = 174)				Biologic agent (N = 74)							
	MTX	ACI	CYC	APR[a]	ADA	ETA	IFN	GOL	CER	UST		
MTX (N=991)	0	63	34	1	27	20	9	6	1	1	162	86.4
ACI (N=571)	62	0	4	1	4	3	0	0	0	1	75	143.3
CYC (N=51)	5	4	0	0	1	1	0	0	0	0	11	220.4
Total	67	67	38	2	32	24	9	6	1	2	248	101.3

[a]Due to drug formulary restrictions, patients could not initiate on apremilast but can receive this agent after failing their index CSA
List of abbreviations: ACI: acitretin; ADA: Adalimumab; APR: Apremilast; CSA: Conventional systemic agent; CER: Certolizumab pegol; CYC: Cyclosporin; ETA: Etanercept; GOL: Golimumab; INF: Infliximab; MTX: Methotrexate; UST: Ustekinumab

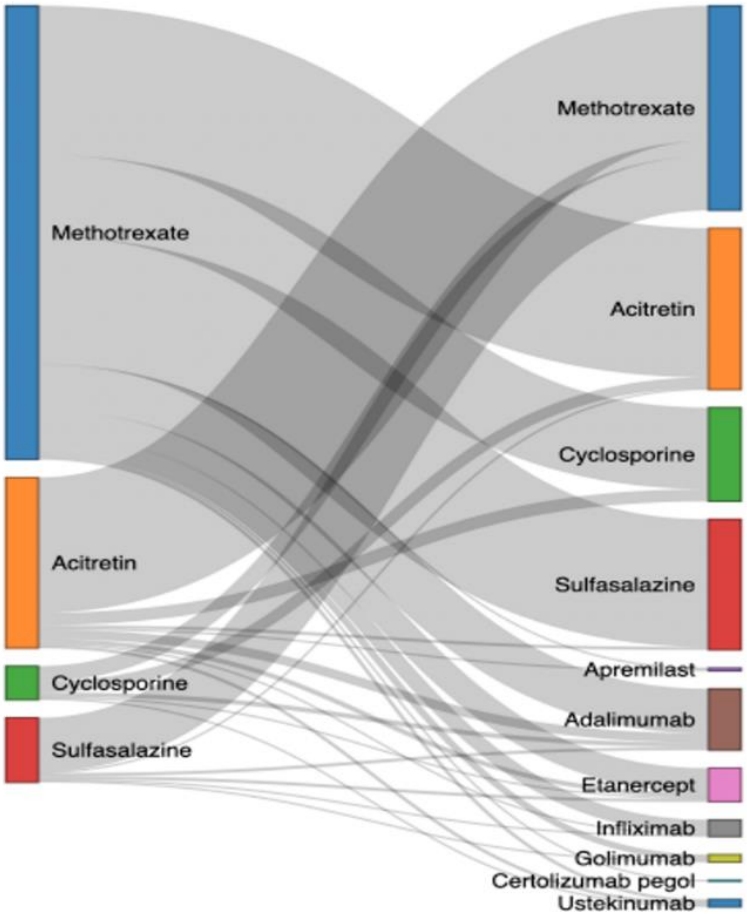
Figure 6.1. Sankey diagram describing switches between systemic agents among patients with psoriasis initiating a CSA while accounting for switches between CSA (N = 248 switches occurred) – Without considering Sulfasalazine

Table 6.1. Predictors of switch to either a CSA or a tumor necrosis factor inhibitor/Ustekinumab among males and female patients with psoriasis (without considering sulfasalazine)

	All patients (N=1,613)	**Females (N=903)**	**Males (N=710)**
	aHR (95% CI)	**aHR (95% CI)**	**aHR (95% CI)**
Age			
20-44 years	Ref	Ref	Ref
45-64 years	**0.67 (0.49-0.92)**	0.63 (0.40-1.00)	0.71 (0.45-1.11)
65-74 years	**0.45 (0.31-0.66)**	**0.44 (0.26-0.75)**	**0.48 (0.28-0.82)**
≥75 years	**0.26 (0.15-0.44)**	**0.26 (0.13-0.54)**	**0.27 (0.12-0.58)**
Psoriasis duration			
0–2.99 months	Ref	Ref	Ref
3-12 months	**0.66 (0.44-0.98)**	**0.45 (0.26-0.76)**	1.17 (0.61-2.24)
Over 12 months	1.03 (0.76-1.38)	0.70 (0.48-1.02)	**1.80 (1.09-2.98)**
First CSA received			
Methotrexate	Ref	Ref	Ref
Cyclosporine	1.51 (0.80-2.85)	1.41 (0.50-3.94)	1.84 (0.81-4.20)
Acitretin	**1.40 (1.04-1.88)**	**1.57 (1.05-2.34)**	1.25 (0.79-1.96)
Psoriatic arthritis	1.29 (0.93-1.80)	1.19 (0.74-1.90)	1.45 (0.90-2.33)
Mental health disorders			
No mental health disorder	Ref	Ref	Ref
Anxiety and mood disorders	1.03 (0.74-1.42)	0.91 (0.60-1.40)	1.17 (0.70-1.96)
Dissociative, somatoform and adjustment disorders	1.92 (0.92-3.97)	**2.15 (1.05-4.45)**	NA[b]
Other mental health disorders	1.62 (0.97-2.69)	1.77 (0.76-4.16)	1.57 (0.82-3.02)
Prior use of NSAIDS	1.00 (0.76-1.32)	1.11 (0.77-1.59)	0.90 (0.59-1.36)
Performance measures for internal validation			
Harrel's C index (95% CI)	0.59 (0.55-0.64)	0.59 (0.57-0.60)	0.59 (0.51-0.67)
Calibration slope	0.820	0.634	0.489

[a]In male patients, only 7 patients had dissociative, somatoform and adjustment disorders; therefore, they were combined with had also anxiety and mood disorders.

List of abbreviations: aHR: Adjusted hazard ratios; CI: confidence interval; CSA: conventional systemic agent; Harrel's C index: Harrel's Concordance index; NSAIDS: nonsteroidal anti-inflammatory drugs; ref: reference group



Initial CSA	Systemic agent received during the switch (N = 470)										Total of switch	Incidence rate per 1,000 person-year
	CSA (N = 386)				Biologic agent (N = 84)							
	MTX	ACI	CYC	APR[a]	ADA	ETA	IFN	GOL	CER	UST		
MTX (N=1,391)	0	97	53	83	29	16	9	4	1	2	295	122.9
ACI (N=806)	88	0	8	2	6	3	1	0	0	2	111	147.4
CYC (N=80)	10	7	0	0	3	1	0	0	0	1	22	293.1
SUL (N=109)	35	1	0	0	0	2	2	1	1	0	42	401.5
Total	133	105	61	85	2	40	22	11	5	1	470	141.8

[a]Due to drug formulary restrictions, patients could not initiate on apremilast but can receive this agent after failing their index CSA
List of abbreviations: ACI: acitretin; ADA: Adalimumab; APR: Apremilast; CSA: Conventional systemic agent; CER: Certolizumab pegol; CYC: Cyclosporin; ETA: Etanercept; GOL: Golimumab; INF: Infliximab; MTX: Methotrexate; UST: Ustekinumab

Figure 6.2. Sankey diagram describing switches between systemic agents among patients with psoriasis initiating a CSA while accounting for switches between CSA (N = 470 switches occurred) – Without excluding patients with a diagnosis of psoriasis in the prior three years

Table 6.2. Predictors of switch to either a CSA or a tumor necrosis factor inhibitor/Ustekinumab among males and female patients with psoriasis – Without excluding patients with a diagnosis in the prior three years

	All patients (N=2,386)	Females (N=1,277)	Males (N=1,109)
	aHR (95% CI)	**aHR (95% CI)**	**aHR (95% CI)**
Age			
20-44 years	Ref	Ref	Ref
45-64 years	**0.75 (0.59-0.94)**	0.78 (0.55-1.10)	0.72 (0.52-1.00)
65-74 years	**0.48 (0.37-0.62)**	**0.57 (0.39-0.83)**	**0.40 (0.27-0.59)**
≥75 years	**0.40 (0.28-0.58)**	**0.45 (0.28-0.73)**	**0.36 (0.21-0.63)**
Psoriasis duration			
0–2.99 months	Ref	Ref	Ref
3-12 months	0.74 (0.53-1.03)	**0.65 (0.43-0.98)**	0.80 (0.46-1.40)
Over 12 months	**1.28 (1.01-1.62)**	1.00 (0.74-1.36)	**1.74 (1.18-2.56)**
First CSA received			
Methotrexate	Ref	Ref	Ref
Cyclosporine	**1.86 (1.19-2.91)**	1.89 (0.94-3.78)	**2.09 (1.15-3.81)**
Acitretin	1.12 (0.89-1.41)	1.15 (0.84-1.57)	1.11 (0.78-1.56)
Sulfasalazine	**2.81 (2.02-3.91)**	**2.77 (1.76-4.34)**	**2.93 (1.79-4.80)**
Psoriatic arthritis	**1.33 (1.06-1.66)**	1.14 (0.84-1.55)	**1.58 (1.14-2.20)**
Mental health disorders			
No mental health disorder	Ref	Ref	Ref
Anxiety and mood disorders	1.15 (0.91-1.47)	0.99 (0.72-1.35)	1.45 (0.99-2.12)
Dissociative, somatoform and adjustment disorders	1.68 (0.94-3.02)	1.70 (0.95-3.27)	NA
Other mental health disorders	1.46 (0.97-2.20)	1.56(0.81-2.99)	1.47 (0.87-2.50)
Prior use of NSAIDS	**1.26 (1.04-1.53)**	**1.42 (1.10-1.84)**	1.11 (0.83-1.48)
Performance measures for internal validation			
Harrel's C index (95% CI)	0.62 (0.60-0.63)	0.59 (0.57-0.62)	0.64 (0.62-0.67)
Calibration slope	0.90	0.68	0.62

[a]In male patients, only 7 patients had dissociative, somatoform and adjustment disorders; therefore, they were combined with had also anxiety and mood disorders.

List of abbreviations: aHR: Adjusted hazard ratios; CI: confidence interval; CSA: conventional systemic agent; Harrel's C index: Harrel's Concordance index; NSAIDS: nonsteroidal anti-inflammatory drugs; ref: reference group

Chapter 7: Describing longitudinal trajectories of systemic agent use and assessing whether certain trajectories are associated with depression- and anxiety-related health care costs

In this section, I am presenting additional information on the methods used in Manuscript 3 that addressed my objective 2

7.1 Methods

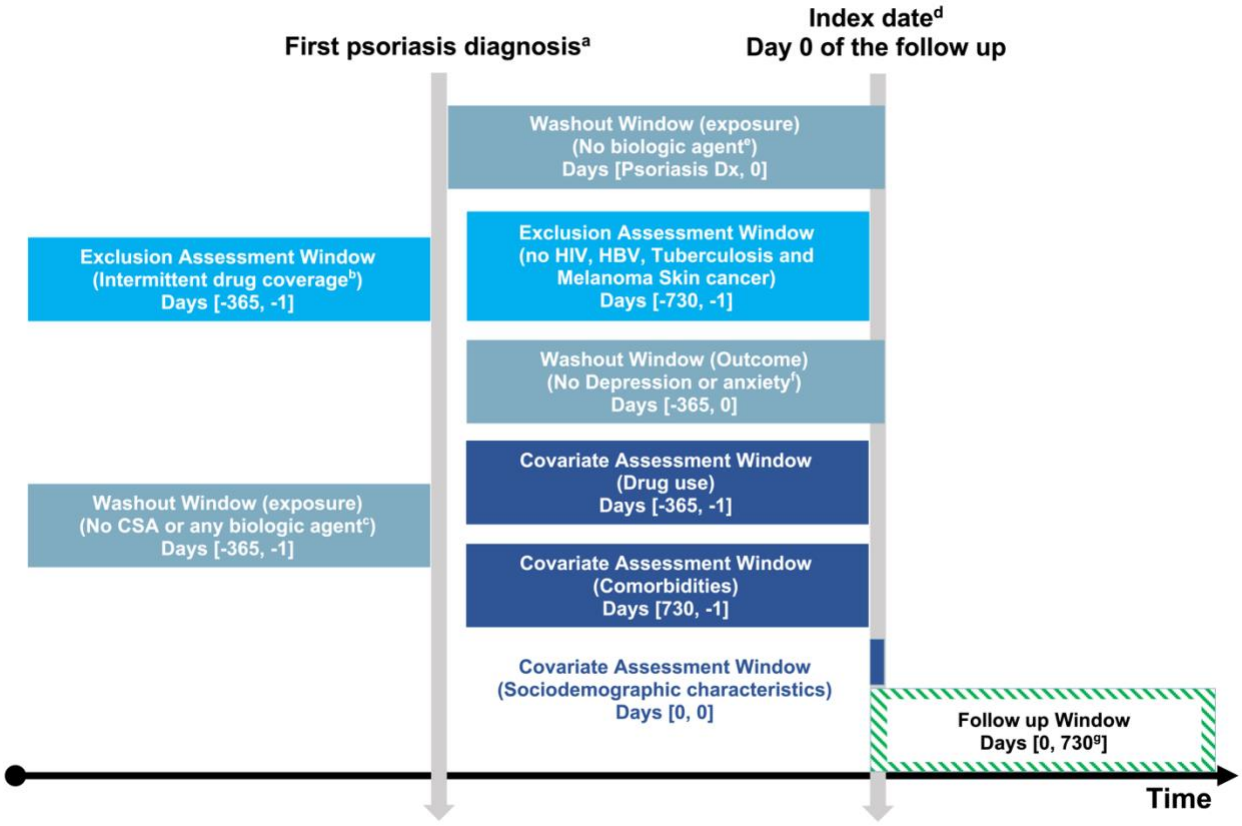
7.1.1 Cohort definition

To address objective 2, I included patients who received at least one psoriasis diagnosis in inpatient, outpatient or ED records between January 01, 2002 and December 31, 2013. Patients with a systemic agent use prior to the psoriasis diagnosis were excluded, but contrary to my first 2 studies, I did not exclude those with a previous diagnosis for psoriasis, because this would have unnecessarily decreased my sample size. Patients were also required to initiate a CSA including methotrexate, cyclosporine and acitretin. Sulfasalazine was not considered due to its off-label use for psoriasis. Patients were included if they received more than one CSA, but those initiating on a biologic agent prior to receiving a CSA were excluded. Index date was defined as the date of first CSA prescription fill. Patients with HIV, HBV, tuberculosis and melanoma skin cancer in the two years prior to index date were also excluded because TNFi/UST are contraindicated in patients with these conditions. In this study, I did not exclude patients with CHF, because TNFi are only contraindicated in patients with severe disease (CHF class III/IV according to the New York Heart Association). In patients with milder CHF severity, monitoring is recommended after initiating a TNFi. A summary of the cohort construction to address objective 2 is presented in Figure 7.1.

7.1.2 Exposure definitions

Longitudinal trajectories of systemic agent use were assessed over two years. Each patient had a two-year follow-up divided into monthly intervals. In each interval, exposure was assessed as follows: only methotrexate, only acitretin, only cyclosporine, 2 CSA, only TNFi/UST, TNFi/UST+CSA or other. The latter included patients untreated or patients receiving topical agents or phototherapy. If the duration of supply of the systemic agent received during a certain interval surpassed the end of that interval, the patient was considered treated until the end of their

supply. I then used a combination of sequence and hierarchical cluster analysis to combine patients with similar trajectories into clusters.[179] Additional details regarding sequence and cluster analysis can be found in section 7.1.5.



[a]First psoriasis diagnosis between January 01, 2002 and December 31, 2013.
[b]Gap of ≥90 days in the drug coverage
[c]Any biologic agent prescribed for psoriasis or any other immune-mediated condition (Table 5.1)
[d]Index date defined as first CSA received following psoriasis diagnosis. Patients could receive more than one CSA
[e]Patients could not initiate on a biologic agent due to provincial drug formulary restrictions
[f]Depression or anxiety based on ICD 9/10 codes or a prescription fill for an antidepressant and a benzodiazepine
[g]Patients were followed starting from index until the index date+730 days, death, occurrence of an ineligibility criterion (dispensed prescription for a biologic agent other than the TNFi/UST included in the study, diagnosis for HIV, HBV, tuberculosis and melanoma skin cancer), gap ≥ 90 days of enrollment in the provincial drug plan or December 31, 2015, whichever occurred first.
Abbreviations: CSA: conventional systemic agents; HBV: hepatitis B virus; HIV: Human immunodeficiency virus; TNFi/UST: tumor necrosis factor inhibitors and ustekinumab.

Figure 7.1. Cohort construction to address objective 2

7.1.3 Outcome definitions

The outcome was mental health-related healthcare costs associated with depression and anxiety during the two-year follow-up period. The costs were analysed from the health care system perspective. The costs included those of antidepressants, benzodiazepine, physician outpatients and ED encounters for depression or anxiety, and hospitalisations with depression and anxiety as the primary or secondary diagnosis. ICD-9 and ICD-10 codes were used to retrieve medical encounters for these disorders (Appendix C). The costs were converted to 2020 Canadian dollars (CAN$) using the all-item consumer price index.[180] The cost of antidepressants and benzodiazepines were available from RAMQ pharmaceutical database and considered RAMQ reimbursement and pharmacist fees. The costs of physician visits for depression and anxiety representing the reimbursement costs for physician fee-for-service claims with a depression or anxiety diagnosis, were available from RAMQ medical database. The costs of ED and inpatients visits with depression as a primary or secondary diagnosis were computed as follows: the sum of the physician claims during a certain hospitalization or ED visit plus the product of the NIRRU associated with that visit times the unit cost per NIRRU (physician claims + NIRRU*unit cost per NIRRU). Physician claims were retrieved from RAMQ medical database. If a hospitalization had a missing NIRRU value, the cost was computed by multiplying the length of stay of that hospitalization with the average daily cost for these conditions (Table 7.1).[181] These daily costs were provided by the Canadian Institute for Health Information for the year 2019 (CIHI).[181] An additional analysis was conducted in which adjustment disorder was also considered.

Table 7.1. Average daily cost for a hospitalization related to depression, anxiety and adjustment disorder

	Average cost of a hospitalization in 2019*	Average cost of a hospitalization in 2020**	Average length of stay*	Average daily cost
Depression	7,572	7630	12	636
Anxiety	6,501	6549	7.1	923
Adjustment disorder	4,581	4615	4.8	962

*As indicated by the Canadian Institute for Health Information
**Converted to 2020 CAN$ using the consumer price index (cost*137/136)

7.1.4 Potential confounders

Sociodemographic characteristics included age (20-44, 45-64, 65-74 and ≥75 years), sex (male or female), income (low or high) and area of residency (urban or rural).

Comorbidities in the prior two years included psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, IBD, mental health disorders (other than depression and anxiety) and Charlson Comorbidity Index (CCI; 0, 1 or ≥2).[182] Rheumatoid arthritis was not included in the calculation of CCI because it was considered a separate comorbidity. Also, CCI did not account for HIV because patients with this disorder were excluded. All other comorbidities were binary variables (yes or no). ICD-9/10 codes for these comorbidities are included in Appendix C.

Treatment use in the prior year (yes or no) included those related to psoriasis treatments such as topical agents and phototherapy (Appendix B).

7.1.5 Statistical analyses

7.1.5.1 Sequence analysis and hierarchical cluster analysis

To determine the different trajectories of systemic agent's use in psoriasis, sequence analysis and agglomerative hierarchical clustering analysis (AHCA) were used to group individual patterns with similar treatment trajectories into trajectory clusters. Sequence analysis, originally used in computer and social sciences, helps measure the degree of dissimilarity between two individual patterns (or sequences) to construct the hierarchical cluster.

In sequence analysis, optimal matching is the most commonly used method to measure dissimilarities. Optimal matching assigns a cost or a weight to the number of operations needed to allow two trajectories to become strictly similar. The lower the weight, the higher is the similarity between two trajectories.[183,184] Three operations can be used in sequence analysis: substitution, insertion and deletion:

- Substitution: AAB and BAB → substitute the first A by B → BAB and BAB
- Deletion: BBB and BB → Delete the first B BBB → BB and BB
- Insertion: AA and AAA → Insert an A at the beginning → AAA and AAA

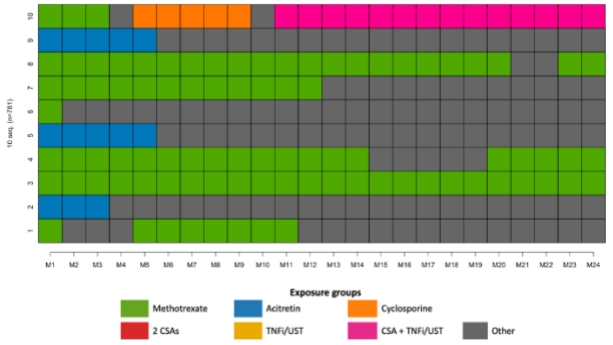
Since all patient in the study have treatment trajectories of equal lengths (two years), substitution is the only operation needed. Hamming distance measures, a type of optimal matching, can be used

because they only take into consideration substitutions.[183] These measures include the Dynamic Hamming Measure (DHM), Hamming distance and simple Hamming.

For this study, DHM was used because it accounts for the type of substitution and its timing by introducing time-varying weights inversely proportional to the transition rate from one treatment group to another between three consecutive intervals (except for the first and last treatment interval).[179] These substitution weights are used to calculate a dissimilarity matrix, which is the macro representation of the individual trajectories between all the different treatment groups. At each interval (with a total of 24 intervals), a substitution cost matrix is built to calculate the weights for replacing one treatment by another using the following formula (equation 7.1):

$$DHM = \begin{cases} 4 - 2\,[p(X_{t+1} = a \mid X_t = b) + p(X_{t+1} = b \mid X_t = a)], & \boldsymbol{if\ a \neq b\ and\ t = 1} \\ 4 - [p(X_t = a \mid X_{t-1} = b) + p(X_t = b \mid X_{t-1} = a) + p(X_{t+1} = a \mid X_t = b) + p(X_{t+1} = b \mid X_t = a)], & \boldsymbol{if\ a \neq b\ and\ 1 < t < 24} \\ 4 - 2\,[p(X_t = a \mid X_{t-1} = b) + p(X_t = b \mid X_{t-1} = a)], & \boldsymbol{if\ a \neq b\ and\ t = 24} \end{cases} \quad (7.1)$$

In the formula, a and b represent two different exposure categories and *t* represents the time interval. With DHM, the weight considers simultaneously the probabilities of transitioning from *a* to *b* and from *b* to *a* before (*t*-1) and after (*t*+1) the interval of interest (*t*). If the two consecutive intervals are the same (example: TNFi/UST$_{time\ t}$ and TNFi/UST$_{t+1}$) then the weight is 0. Because the weights are inversely proportional to the transition rate, lower weights occur with higher probability of transitioning. The last step is to sum the substitution weights for all 24 intervals between two patients (which is done for all patient pairs) to compute the dissimilarity matrix (Figure 7.2).



	[,1]	[,2]	[,3]	[,4]	[,5]	[,6]	[,7]	[,8]	[,9]	[,10]
[1,]	0.00	37.71	61.30	41.96	41.59	26.61	14.93	53.56	41.59	86.38
[2,]		0.00	92.47	73.14	7.23	11.10	46.10	84.73	7.23	85.15
[3,]			0.00	19.33	92.98	87.91	46.37	7.74	92.98	83.50
[4,]				0.00	73.65	68.57	27.03	27.08	73.65	83.33
[5,]					0.00	18.33	46.61	85.24	0.00	89.37
[6,]						0.00	41.54	80.16	18.33	80.58
[7,]							0.00	38.63	46.61	82.81
[8,]								0.00	85.24	83.37
[9,]									0.00	89.37
[10,]										0.00

Note: left) Individual trajectories for the first 10 patients in my cohort; right) Dissimilarity matrix between patient pairs for all 10 patients. Patients 5 and 9 have the same treatment trajectories, therefore, their final weight is 0. Patients 5 and 9 both have the highest weight when compared to patient 3 (final weight of 92.98), therefore the trajectory of patient 3 is the most dissimilar to patients 5 and 9.
CSA: conventional systemic agents; M1-M24: month 1 to month 24; TNFi/UST: tumor necrosis factor inhibitors/ustekinumab.

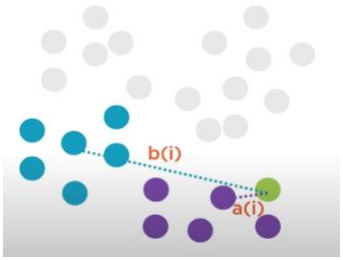
Figure 7.2. Individual treatment trajectories for the first 10 patients of the study cohort and their dissimilarity matrix using the Dynamic Hamming Measure

I used AHCA with Ward's minimum variance criterion to create homogenous clusters of patients with similar individual trajectories, based on their dissimilarity weights. Initially, with agglomerative clustering, each observation constitutes its own cluster, and pairs of clusters are merged as one moves up in hierarchy. At each step, Ward's criterion finds the pair of clusters that leads to a minimum increase in total within-cluster variance after being merged. In sequence analysis, Ward's criterion is the most implemented linkage method when dissimilarity matrices are used to measure the similarity between trajectories.[185,186]

The average silhouette width (ASW) is often used to determine the optimal number of clusters. Other methods are available, but most AHCA based on dissimilarity matrices employ ASW.[179,185] Silhouette coefficients compare the average packing of points within one cluster to the average distance of points to the closest cluster to which these points do not belong (Figure 7.3). ASW is the average of all silhouette coefficients and can vary from -1 to 1. A high ASW value implies that the clusters are homogeneous and well separated from each other. ASW is computed for several number of clusters (at least 2) and the one with the highest value is chosen (equation 7.2).

$$silhouette\ coefficient\ S(i) = \frac{b(i) - a(i)}{\max\left[a(i), b(i)\right]}, \boldsymbol{if\ C_n > 1} \qquad (7.2)$$

In equation 7.2, *a(i)* indicates the average distance inside a cluster and *b(i)* the average distance to the nearest other cluster. The denominator refers to the highest value between *a(i)* and *b(i)*. C_n refers to the number of clusters.



Note: a(i) is the average distance inside a cluster; b(i) is the average distance to the nearest cluster
Ideally, a(i) = 0 and b(i) = infinity → S(i) = 1
Worst case scenario, a(i) = infinity and b(i) = 0 → S(i) = -1

Figure 7.3. Example on how to compute the silhouette coefficient

7.1.5.1.1 Comparing sequence analyses to other latent class methods

Latent class methods, including Group-based trajectories modeling (GBTM) and growth mixture modeling (GMM), are often used in longitudinal studies to measure trajectories.[187-190] In both methods, individuals are assigned to latent trajectory groups based on their probability of membership to that group. Similar to sequence analysis, these methods have an individual centred perspective, thus they seek to identify relationships between individuals' patterns and form groups based on these patterns. Additionally, these methods are used when trajectories cannot be classified *a priori*, hence the name *latent* class. However, differences are also noted.

GBTM is a semi-parametric statistical model that is designed to identify a finite number of groups of individuals following similar trajectories over time.[189,190] Studies using GBTM to determine patterns of medication use have often considered adherence as the outcome of interest. Adherence in these studies was measured by the medication possession ratio or proportion of days covered[191] over a few time intervals (three to six time-points) to allow variability and avoid having many intervals with either perfect or null adherence.[191] On the other hand, this method can include co-variable adjustments. GMM is a parametric statistical model that also examines the evolution of trajectories over time.[187,189,192] As opposed to both sequence analysis and GBTM, GMM allows

for the inclusion of continuous, and categorical variables, and multiple types of trajectories can be examined simultaneously. Thus, GMM allows for residual variation within the trajectory groups (or random effect). However, GMM can be computationally intense, and researchers tend to reduce the number of intervals when using this method, thus possibly underestimating the variation of trajectories over time. Additionally, in both GBTM and GMM, the optimal number is chosen based on either the Lo-Mendell-Ruben likelihood ratio test, the Bayesian Information Criterion, and Akaike Information Criteria.

Because of these differences, studies assessing life course trajectories in social sciences using these methods concluded that sequence analysis and latent class methods should not be expected to yield similar trajectories.[187,188] In the present study, I used sequence analysis because (1) it is less computationally intense than GMM, and (2) as opposed to GBTM, the use of DHM as a dissimilarity measure allowed the inclusion of time-varying transition weights to describe more than one type of patterns, including restart of therapy, persistence, discontinuation and/or switch between treatments.[187]

7.1.5.2 Two-part models

When examining mental-health related health care costs, the analyses should account for excess zero costs as most patients will not have depression- and anxiety-related healthcare costs.[193] Therefore, I used two-part models to assess the adjusted cost ratios between the different trajectories. The first part was a multivariate logistic regression modeling the probability of having a nonzero cost (yes versus no), and the second part was a generalized linear model estimating cost values with a gamma distribution and log link function conditional on having a nonzero cost. Gamma distribution with log link was used to account for the skewness of cost data. The models were adjusted for the potential confounders listed in section 7.1.4 in addition to the clusters. Predicted annual mean costs per patient were calculated by multiplying the predicted estimates from the first- and second-part models (equation 7.3). The bootstrap resampling method with 10,000 iterations was used to estimate the predicted mean annual cost ratios per patient between the trajectories and their bias-corrected and accelerated 95% CI.[194,195]

$$predicted\ mean\ cost\ for\ each\ patient\ in\ the\ cohort = \hat{p} \times \hat{y} \qquad (7.3)$$

With $\hat{p}$ representing the propensity of having a nonzero cost for depression and anxiety estimated from the first part of the model, and $\hat{y}$ representing the predicted mean cost for depression and anxiety estimated from patients who had a nonzero cost in the second part of the model.

7.1.5.3 Software

SAS studio was used for cohort construction and the two-part model. The packages TraMineR[184] and WeightedCluster[196] were used in R software (version 3.6.2) for sequence and hierarchical analyses. Codes are available upon request.

7.2 Manuscript 3 – Trajectories of systemic agent use and associated depression and anxiety-related healthcare costs among patients with psoriasis

7.2.1 Preamble to manuscript 3

In manuscripts 1 and 2, the presence of mental health disorders was associated with increased risk of switch/add of TNFi/UST or to a different CSA among patients with psoriasis initiating a CSA. Systemic agent treatment failure can lead to psoriasis exacerbation and aggravates psoriasis severity, which in turn can worsens patient's psychological health. Hence, the choice of the systemic agent can have an impact on the patient's psychological health as shown in RCT comparing the efficacy of biologic agents to that of methotrexate or placebo. Mental health disorders have an important clinical and economic burden on patients with psoriasis.

While previous observational studies reported incremental all-cause annual health care costs in the presence of a psychiatric comorbidity among patients with psoriasis, no prior study has assessed the incremental health care costs related to having an incident mental health disorder such as depression and anxiety, and no study has examined whether certain patterns of systemic agent use were associated with higher costs. Therefore, using a novel approach to describe longitudinal treatment trajectories, in my third study, I aimed to assess depression and anxiety related health care costs associated with trajectories of systemic agent use among patients with psoriasis.

Manuscript 3 was published in JAAD international:
Milan R, LeLorier J, Latimer EA, Brouillette MJ, Holbrook A, Litvinov IV, Rahme E.
Trajectories of systemic agent use and associated depression- and anxiety-related health care costs among patients with psoriasis. JAAD Int. 2022 Jun 25;9:11-22.

In this manuscript, I replaced conventional systemic agents (CSA) by conventional systemic therapies (CST) as requested by a reviewer. In the section additional results, I present the results of three additional analyses that I conducted. 1) I compared depression and anxiety-related healthcare costs among male and female patients, 2) I considered 10 clusters instead of 8 clusters, and 3) I also included adjustment disorder as an outcome.

7.2.2 Manuscript 3

7.2.2.1 Title page

Article type: Research article

Trajectories of systemic agent use and associated depression and anxiety-related healthcare costs among patients with psoriasis.

Running head: depression and anxiety-related healthcare costs among patients with psoriasis.

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Statement of ethics: The study was approved by the Research Ethics Board (REB) of the Research Institute of the McGill University Health Centre

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Conflicts of Interest: Raymond Milan is supported by the *Fonds de Recherche du Québec – Santé* (FRQS, Quebec foundation for Health Research) doctoral training award and the Canadian Institutes of Health Research (CIHR) Drug Safety and Effectiveness Cross-Disciplinary Training (DSECT) program award. Ivan Litvinov is supported by a Junior I Clinician Scientist award from the FRQS and has received consulting fees from Novartis, Janssen, Galderma and Bristol-Myers Squibb in the course of unrelated studies. Elham Rahme has received funds and consulting fees from Janssen in the course of an unrelated study. Jacques LeLorier, Eric A Latimer, Marie-Josée Brouillette and Anne Holbrooke have no conflict of interest to disclose.

Reprint requests: Elham Rahme

Figures: 1
Tables: 3

Supplementary figures: 3

Supplementary tables: 2

Keywords: Psoriasis, systemic agents, trajectories, depression, anxiety, healthcare costs

7.2.3 Abstract

Background: Systemic treatment patterns and related mental health disorders and economic burden among patients with psoriasis are largely unknown.

Objective: To assess systemic treatment patterns and associated depression and anxiety-related health care costs among patients with psoriasis initiating a conventional systemic treatment (CST).

Methods: Using a retrospective cohort design with sequence and cluster analyses, we assessed systemic treatment trajectories (CST and tumor necrosis factor inhibitors or ustekinumab, [TNFi/UST]) over a 2-year period following CST initiation. We compared health care costs between trajectories using 2-part models.

Results: We included 781 patients and identified 8 trajectories: persistent methotrexate users, persistent acitretin users, early CST discontinuation, late methotrexate discontinuation, switch to TNFi/UST, adding TNFi/UST, discontinuation then restart on methotrexate, and discontinuation then restart on acitretin or multiple CST switches. Overall, 165 (21%) patients incurred depression- and anxiety-related health care costs (median annual cost, CAN$56; quartiles, $14-$127). Compared with persistent methotrexate users, adding a TNFi/UST (cost ratio, 3.63; 95% CI, 1.47-5.97) and discontinuation then restart on acitretin or multiple switches between systemic agents (cost ratio, 13.3; 95% CI 5.76-22.47) had higher costs.

Limitations: Trajectory misclassification may have occurred. These data represent an association, and causality cannot be inferred, particularly given the risk of confounding.

Conclusion: Depression- and anxiety-related health care costs were high among patients adding TNFi/UST and those discontinuing then restarting on acitretin or experiencing multiple switches between systemic agents.

Capsule summary

- The burden of mental health disorders among patients with moderate-to-severe psoriasis is substantial.
- Monitoring depression and anxiety among patients with psoriasis, especially those who need to add a biologic agent to their conventional systemic therapies and those who experience several switches or discontinue their initial conventional systemic therapies and restart on acitretin, may help decrease the burden.

Abbreviations

AHCA: Agglomerative hierarchical cluster analysis

CCI: Charlson Comorbidity Index

CI: confidence interval

CST: conventional systemic therapies

ED: emergency department

RAMQ: Régie de l'Assurance Maladie du Québec

SA: sequence analysis

TNFi/UST: Tumor necrosis factor inhibitors and ustekinumab

7.2.4 Introduction

Psoriasis is an immune-mediated chronic skin condition affecting 2.5% of the Canadian population,[1] among whom 21.5% have moderate-to-severe disease.[2] Psoriasis is associated with pain, pruritus, disability, inflammation, and impaired quality of life.[3-6] Compared with the general population, patients with moderate-to- severe psoriasis are at increased risk for depression and anxiety.[7-12] The eco- nomic burden of psoriasis is significant. The total annual cost was estimated at US$112 billion in the United States in 2013, of which, 56.4% were for direct health care costs.[13]

Systemic agents, including conventional systemic therapies (CST), such as methotrexate, cyclosporine, and acitretin, and biologics, such as tumor necrosis factor inhibitors (TNFi) and interleukin inhibitors, are indicated for the management of moderate-to-severe psoriasis.[14] In double-blind randomized controlled trials, biologic agents were more effective than CST and placebo in achieving skin clearance and improving anxio-depressive symptoms and quality of life.[15-22] However, because of their high acquisition costs, the Canadian province of Quebec and several other jurisdictions with similar public drug insurance plans cover biologic agents for psoriasis only when treatment with CST fails or is contraindicated.[23-25]

The rate of treatment failure with CST is high, and patients tend to cycle through multiple systemic agents throughout their disease life course, with loss of efficacy and adverse events as the main reasons for treatment failure.[26-29]

Treatment failure can lead to psoriasis exacerbation and aggravate disease severity,[14] which increases the risk for depression and anxiety.[7-12] In turn, the patient's psychological health has been associated with treatment failure in many chronic physical conditions,[30,31] including psoriasis.[32] Additionally, sustained depressive symptoms were found to worsen psoriasis clinical outcomes[32,33] through decreased sensitivity and poor adherence to treatment.[32]

Therefore, the choice of the systemic treatment may have a significant effect on the mental health outcomes of patients with psoriasis. Previous studies have reported substantial incremental all-cause annual health care costs of up to US$12,884 per patient among those with and without mental health disorders.[13,34-36] Identifying longitudinal patterns of systemic treatment and their association with depression and anxiety-related health services utilization and costs may raise awareness

toward earlier detection of depression and anxiety in those at higher risk. Early detection and management of depression and anxiety may improve perceived psoriasis severity, adherence to therapies, and decrease resource utilization.[12,37] Nonetheless, longitudinal patterns of systemic treatment and their association with depression and anxiety-related health ser- vice utilization and costs in this patient population have not been studied previously.[12,13,38]

Although biologic agents are more costly than CST, improving access to these agents for those at high risk of CST failure may decrease the patient's psychological burden and create some cost offset. In the present study, we aimed to describe the trajectories of systemic agents used over a 2-year period among patients with psoriasis initiating a CST and assess depression and anxiety-related health care costs associated with these trajectories.

7.2.5 Patients and methods

7.2.5.1 Study design and data source

This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology statement for cohort studies.[39]

We conducted a retrospective cohort study using the Canadian province of Quebec health administrative databases linked by a unique patient identifier. For this study, data were available from January 1997 to December 2015. Sociodemographic characteristics, physician claims, inpatient and prescription drug records were obtained from the provincial health insurance agency, *Régie de l'assurance maladie du Québec.* The physician claims database contains information on all outpatient physician claims (including costs) and emergency department (ED) visits for all Quebec residents (International Classification of Diseases, Ninth Revision [ICD-9] codes). The pharmaceutical claims database contains information on prescribed medications (dispensation date, dosage, duration of supply, prescriber specialty, and cost) for those registered with the provincial drug plan (individuals in the workforce who do not have private drug insurance through their employer, those $65 years of age and those receiving social assistance). Drug insurance is mandatory for all Quebec residents. In 2015, 44.3% of all Quebec residents were covered by the provincial drug plan.[40] Hospital abstract records were obtained from the *Maintenance et exploitation des données pour l'étude de la clientèle hospitalière* (MedEcho) database. MedEcho

provides information on all acute care hospital admissions, including admission and discharge dates, and the principal and up to 15 secondary diagnoses (using ICD-9 codes before April 1, 2006, and ICD-10 codes thereafter). Hospitalizations and ED visits cost data were obtained from the *Ministère de la santé et services sociaux*–the All-Patient Refined Diagnosis Related Groups database (Supplementary Material I).

7.2.5.2 Study population and follow-up

We selected individuals ages $20 years who received $1 diagnostic code for psoriasis (ICD-9: 696.1 and ICD-10: L40.x) either in-hospital, during an ED or outpatient visit between January 2002 and December 2013. We considered those who were continuously enrolled in the provincial drug plan in the previous year. Patients who did not receive any systemic agent in that year were eligible for the study. We included those initiated on a CST (methotrexate, cyclosporine, or acitretin) and the date of the first CST prescription fill was their index date. Study patients may have had more than one CST at the index date, but those with a CST and a biologic agent at that date were excluded. We also excluded those with a diagnosis of human immunodeficiency virus, hepatitis B virus, tuberculosis, and melanoma skin cancer in the prior 2 years because TNFi and ustekinumab (TNFi/UST) are contraindicated in these conditions.[41-47] In addition, we excluded patients with a diagnosis of depression or anxiety and those with a prescription fill for an antidepressant or benzodiazepine in the year before the index date. Study individuals were followed from the index date until the first date of death, the occurrence of an ineligibility criterion, a gap ≥90 days in the provincial drug plan enrollment, or 31 December 2015. All included patients were required to have at least 2 years of follow-up data.

7.2.5.3 Exposure to systemic agents

Patterns of systemic agent use were examined over 2 years. For each individual, we divided the follow-up into monthly intervals. We classified each interval into one of 7 groups according to the treatment received: (1) only methotrexate; (2) only acitretin; (3) only cyclosporine; (4) 2 CSTs; (5) only TNFi/UST; (6) TNFi/UST + CST, or (7) other (no CST or TNFi/UST). The latter group included untreated individuals and those treated with a topical agent or phototherapy. If the

duration of supply of the systemic agent received during a certain interval surpassed the end of that interval, the patient was considered treated until the end of their supply.

7.2.5.4 Depression and anxiety-related healthcare costs

Using the health care system perspective, we assessed the direct medical costs of patients using ≥1 health care service or treatment for depression or anxiety (Supplementary Table I). Costs were assessed during the 2-year follow-up and included those of antidepressants and benzodiazepines, physician outpatient and ED encounters for depression and anxiety, and hospitalization with depression or anxiety as the primary or secondary diagnosis (Supplementary Material I). Costs were converted to 2020 CAN$ using the All-item Consumer Price Index.[48]

7.2.5.5 Statistical analyses

We assessed treatment patterns using sequence analysis (SA).[49-51] This method, alongside agglomerative hierarchical clustering analysis (AHCA) with Ward's minimum variance criterion,[52-54] portrayed the dynamic changes in psoriasis treatment over time and allowed the combination of patients with similar trajectories into clusters. The optimal number of clusters was chosen empirically by the average silhouette width.[54]

We used 2-part models to assess the adjusted cost ratios between the different clusters.[55] The first part was a multivariable logistic regression model to assess the probability of having a non-zero cost (yes/no), and the second part was a multivariable generalized linear model with a gamma distribution to compare the log-transformed costs among those with non-zero costs. Predicted annual mean costs per patient were calculated by multiplying the corresponding estimates from the first- and second- part models. The bootstrap resampling method was used to calculate the cost ratios between the clusters and their 95% confidence interval (CI).[56,57] The models adjusted for age, sex, income, area of residency, Charlson Comorbidity Index, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel diseases, other mental health disorders, and prior use of topical agents and phototherapy.

Two sensitivity analyses were conducted to test the robustness of our findings. First, to increase the sample sizes of trajectory clusters, we considered 5 exposure groups instead of 7 by combining

all CST into a single category. Second, we repeated the analyses after removing the costs of hospitalizations and ED visits because these costs were elevated and only a few of them can skew the total cost associated with the trajectories.

The cohort development and statistical analyses were performed using SAS (version 9.4) and R Studio (version 3.6.2). SA and AHCA were performed using the ‘‘TraMineR’’ and ‘‘WeightedCluster’’ packages in R Studio.[49,54]

7.2.6 Results

We included 781 patients (51.1% men, mean age 61.0, SD: 15.1 years) (Supplementary Fig 1). Dividing the data into 8 clusters was considered optimal (Supplementary Fig 2). We labeled the 8 clusters identified according to their most frequent treatment trajectory observed (Fig 1): persistent methotrexate users (25.8%), persistent acitretin users (10.4%), early CST discontinuation (36.6%), late methotrexate discontinuation (16.4%), switch to TNFi/UST (2.4%), adding TNFi/UST (1.4%), CST discontinuation then restart on methotrexate (3.8%), and CST discontinuation then restart on acitretin or multiple switches between systemic agents (3.1%).

A higher proportion of patients in the trajectory cluster who switched to TNFi/UST were younger than 65 years (79.0%) and had a Charlson Comorbidity Index score of 0 (73.7%), whereas a higher proportion of patients in the persistent methotrexate users were older than 65 years (56.9%) and had a Charlson Comorbidity Index score ≥1 (51.0%). Patients in the cluster adding TNFi/UST had the highest proportion of psoriatic arthritis and rheumatoid arthritis (36.4% and 45.5%, respectively), and patients in the cluster with persistent acitretin users had the lowest proportions (7.4% and 1.2%) (Table I).

7.2.6.1 Cost of depression and anxiety-related health care services

In the cohort, 165 patients (21.1%) incurred a depression- or anxiety-related health care cost. For these patients, the median annual cost was $56 (quartiles, $14-$127) per patient (Table II). Hospitalizations accounted for 50.1% of the total costs followed by antidepressants and benzodiazepines (17.8%), outpatient visits (16.1%), and ED visits (16.0%).

The predicted annual mean cost derived from the 2-part models for the entire cohort (including those with zero costs) was $60 (95% CI, $51-$77) per patient (Table III). The mean costs per patient in each trajectory cluster were: $40 ($31-$57) for persistent methotrexate users, $54 ($42-$75) for persistent acitretin users, $47 ($40-$58) for early discontinuation of CST, $44 ($31-$70) for late discontinuation of methotrexate, $141 ($79-$249) for adding TNFi/UST, $19 ($14-$27) for CST discontinuation then restart on methotrexate, and $514 ($297-$931) for CST discontinuation then restart on acitretin or multiple switch between systemic agents. When compared with persistent methotrexate, the costs in the trajectory cluster adding a TNFi/UST were 3.6 times higher (cost ratio, 3.63; 95% CI, 1.47-5.97) and those in the CST discontinuation then restart on acitretin or multiple switches between systemic agents were 13.3 times higher (cost ratio, 13.30; 95% CI, 5.76-22.47). The trajectory cluster CST discontinuation and restart on methotrexate were associated with lower costs (cost ratio, 0.49; 95% CI, 0.29-0.71).

Overall, results from the sensitivity analyses were consistent with those of the main analysis (Supplementary Table II and Supplementary Table III). When costs for depression- and anxiety-related hospitalizations and ED visits were removed from the analyses, all trajectories, except for persistent acitretin, were associated with higher health care costs for depression and anxiety (Supplementary Table III).

7.2.7 Discussion

To our knowledge, this is the first study to assess trajectories of systemic agent use and their association with depression- and anxiety-related health care costs among patients with psoriasis. Our study identified 8 treatment trajectories. In line with previous studies,[27] most patients in our cohort discontinued their CST during the 2 years of follow-up. On the other hand, by using SA and AHCA, we were able to differentiate between patients with early and late discontinuation, patients restarting their therapy after discontinuation and those who did not, patients switching to a TNFi/UST, and those receiving these agents as an add-on, and patients with multiple treatment switches.

In our study, the predicted mean cost for health care services and treatments for depression and anxiety was $60 per patient. The predicted mean cost is close to the unadjusted median cost of $56

for the 165 patients with health care services and treatment for depression and anxiety, thus suggest- ing that the 2-part model corrected for the skewness in the cost data caused by a few patients having very high costs. Based on the prevalence of psoriasis in Canada (2.5%) and the percentage of patients with the moderate-to-severe disease (21.5%),[1,2,58] we project that $10 million ($2.26 million in Quebec) are spent annually on total direct health care costs to managing depression and anxiety among Canadian patients with moderate-to-severe psoriasis. This projection is still an underestimation of the true total cost to manage these mental health conditions because we did not account for psychotherapy and indirect costs.

Thus far, 3 studies conducted in the United States have reported incremental all-cause health care costs ranging from US$4,181 to US$12,077 per patient for patients with moderate-to-severe psoriasis experiencing depression or anxiety versus those not experiencing these conditions.[34-36] These studies did not assess separately the cost of depression and anxiety-related health care costs. Their results cannot be compared with ours because a large proportion of the incremental cost could have been to treat comorbidities such as cardiovascular disease and metabolic disorders[59-61] that are more prevalent among those with depression and anxiety.[62-65] Furthermore, none of these studies differentiated between prevalent and new cases of depression and anxiety. Our study adds to the existing literature by examining direct health care costs associated with new diagnoses or new episodes of depression and anxiety, and whether having certain treatment trajectories for psoriasis was associated with these costs.

The trajectory cluster adding TNFi/UST and CST discontinuation then restart on acitretin or multiple switches between systemic agents were both associated with increased depression and anxiety-related health care costs when compared with persistent methotrexate users.

In real-world practice, receiving a combination of TNFi/UST, CST and restarting on a CST after dis- continuing their initial CST and multiple switches between systemic agents are indicators of nonresponse to therapy, disease severity, and perhaps psoriasis exacerbation, while being persistent on methotrexate indicates stable psoriasis, especially since methotrexate is recommended as first-line therapy for moderate-to-severe psoriasis.[14,66] Furthermore, methotrexate is often added to TNFi to reduce immunogenicity and increase its efficacy.[67,68] A

possible explanation for the reduced costs in patients who discontinued their initial CST and restarted on methotrexate is that methotrexate is the most effective CST.[69]

While no prior study assessed the impact of systemic agent failure on mental health outcomes, previous studies found that the presence of psychiatric disorders was associated with treatment failure among biologic agent users.[32,33] Two prospective cohort studies conducted in China among patients receiving the TNFi etanercept reported worse psoriasis clinical outcomes when patients had sustained depressive symptoms after 6 months of therapy, [32,33] while in patients achieving $75% reduction on the Psoriasis Area and Severity Index, anxio-depressive symptoms were improved.[32] In our study, patients without a history of anxiety or depression who switched to a TNFi/UST after initiating a CST did not have any health care service or treatments for these mental health disorders during the follow-up as opposed to other trajectory clusters, thus confirming that the choice of the systemic agent may have a significant effect on mental health outcomes.

Our study has some limitations. First, information on the reason for treatment switch and discontinuation was not available in the *Régie de l'assurance maladie du Québec* databases. Nonetheless, side effects and loss of efficacy were reported as the main reasons for discontinuing and switching CST and TNFi/UST.[27,70] Second, with AHCA, individual trajectories can be misclassified (included in a cluster in which they do not belong) and SA does not account for other covariables while measuring transition rates. Third, because of our study sample, some clusters included a small number of participants, therefore, care should be taken while interpreting the results. Fourth, we have accounted for the full cost of anxiety and depression-related hospitalization and ED visits. An unknown proportion of these costs were because of physical ailments. However, this has unlikely biased our results as the removal of the entire costs of hospitalizations and ED visits from the analyses did not affect our conclusion. Fifth, the total direct health care costs associated with depression and anxiety may have been underestimated because we did not account for the cost of non-pharmacological therapies such as psychotherapy. Information on this type of service is incomplete in the provincial health administrative database as most patients in Quebec seek psychotherapy in the private sector. Sixth, the trajectories and health care services and treatments for depression and anxiety were examined simultaneously; therefore, we could not confirm the temporality of events. Finally, our study did not consider

biologic agents approved for psoriasis after 2015, which could affect the generalizability of our findings.

7.2.8 Conclusion

Among all treatment trajectories identified in our study, patients adding TNFi/UST, those discontinuing their CST then restarting on acitretin, and patients with multiple switches between systemic agents had higher rates of depression and anxiety and higher health care costs related to these conditions.

Figure legends

Figure 1: Tempograms describing the eight treatment trajectories for systemic agents

Methotrexate (green); acitretin (blue); cyclosporine (orange); 2 CST (red); TNFi/UST (magenta); TNFi/ UST 1 CST (yellow); other (gray).

Tempograms: The x-axis indicates the monthly interval during the 24-month follow-up. The y-axis indicates the frequency (0 to 1) of each exposure group within each monthly interval.

Persistent MTX users: From month 1 until month 24, more than 90% of patients consistently received methotrexate (color green). ***Persistent ACI users***: From month 1 until month 15, more than 80% of patients consistently received acitretin (color blue), and from month 16 until month 24, more than 50% of patients received acitretin. ***Early CST discontinuation:*** At month 1, more than 90% of patients were treated with methotrexate (green) or acitretin (blue). This percentage decreased between months 2 and 3, whereas the category other (gray) started to increase gradually to reach more than 50% at month 4 and over 90% at month 24, thus most patients stopped taking their CST early during the trajectory. ***Late MTX discontinuation***: At month 1, more than 90% of patients received methotrexate (green). This percentage gradually decreased to less than 50% at month 13, whereas the percentage of the category other (gray) gradually increased starting from month 2 and reached 50% at month 13 and 80%-90% between months 19 and 24. ***Switch to TNFi/UST***: From month 1 to month 4, 80%-90% of patients were treated with methotrexate (green). This percentage gradually decreased starting from month 5, whereas the category TNFi/UST (magenta) started to increase as of month 5 to become the majority. This indicates that patients switched to TNFi/ UST. ***Adding TNFi/UST***: From month 1 to month 4, 80%-90% of patients were treated with methotrexate (green). This percentage gradually decreased starting from month 5, whereas the category TNFi/UST 1 CST (yellow) started to increase as of month 5 to become the majority. This indicates that patients remained treated with methotrexate and received a TNFi/UST as an add-on. ***CST discontinuation then restarts on MTX***: At month 1, most patients were treated with methotrexate (green) or acitretin (blue) and their use gradually decreased from month 2 until month 10, then treatment with methotrexate (green) increased between months 11 and 24. On the other hand, the category other (gray) gradually increased from month 2 until month

10 and then decreased as of month 11, thus indicating that patients discontinued their initial CST and then restarted on methotrexate. ***CST discontinuation then restarts on ACI or multiple switches between systemic agents***: This is the most heterogeneous cluster including patients who received multiple systemic agents during the follow-up (methotrexate [green], acitretin [blue], cyclosporine [orange] and TNFi/UST [magenta]), and patients discontinuing their initial CST between months 2 and 14 (gray) then restarting on acitretin (blue).

ACI, Acitretin; CST, conventional systemic therapy; CYC, cyclosporine; Freq, frequency, M1-M24, month 1 until month 24; MTX, methotrexate; TNFi/UST, tumor necrosis factor inhibitors and ustekinumab.

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Table 1. Baseline characteristics according to different treatment clusters

	Clusters									
	All study sample (N=781)	**Persistent methotrexate users (N=202)**	**Persistent acitretin users (N=81)**	**Early discontinuation of CST (N=286)**	**Late discontinuation of methotrexate (N=128)**	**Switch to TNFi/UST (N=19)**	**adding TNFi/UST (N=11)**	**CST discontinuation then restart on methotrexate (N=30)**	**CST discontinuation then restart on acitretin or multiple switches between systemic agents (N=24)**	**p-Value ‡**
Male sex	399 (51.1)	93 (46.0)	43 (53.1)	152 (53.1)	67 (52.3)	10 (52.6)	6 (54.5)	12 (40.0)	16 (66.7)	0.468
Age (years)										0.006
20-44	153 (19.6)	26 (12.9)	11 (13.6)	66 (23.1)	29 (22.7)	6 (31.6)	4 (36.4)	5 (16.7)	6 (25.0)	
45-64	289 (37.0)	61 (30.2)	39 (48.1)	108 (37.8)	46 (35.9)	9 (47.4)	4 (36.4)	13 (43.3)	9 (37.5)	
65-74	208 (26.6)	59 (29.2)	20 (24.7)	74 (25.9)	37 (28.9)	3 (15.8)	2 (18.2)	7 (23.3)	6 (25.0)	
≥75	131 (16.8)	56 (27.7)	11 (13.6)	38 (13.3)	16 (12.5)	1 (5.3)	1 (9.1)	5 (16.7)	3 (12.5)	
Urban area (vs rural)	619 (79.3)	155 (76.7)	63 (77.8)	232 (81.1)	104 (81.2)	11 (57.9)	7 (63.6)	27 (90.0)	20 (83.3)	0.136
Low income (vs high)†	425 (54.4)	118 (58.4)	44 (54.3)	153 (53.5)	66 (51.6)	7 (36.8)	5 (45.5)	21 (70.0)	11 (45.8)	0.316
Charlson Comorbidity index										0.027
0	453 (58.0)	99 (49.0)	46 (56.8)	192 (67.1)	67 (52.3)	14 (73.7)	7 (63.6)	15 (50.0)	13 (54.2)	
1	199 (25.5)	61 (30.2)	21 (25.9)	63 (22.0)	33 (25.8)	2 (10.5)	3 (27.3)	8 (26.7)	8 (33.3)	
≥2	129 (16.5)	42 (20.8)	14 (17.3)	31 (10.8)	28 (21.9)	3 (15.8)	1 (9.1)	7 (23.3)	3 (12.5)	
Psoriatic arthritis	122 (15.6)	49 (24.3)	6 (7.4)	26 (9.1)	22 (17.2)	3 (15.8)	4 (36.4)	5 (16.7)	7 (29.2)	<0.001
Rheumatoid arthritis	105 (13.4)	60 (29.7)	1 (1.2)	11 (3.8)	22 (17.2)	1 (5.3)	5 (45.5)	4 (13.3)	1 (4.2)	<0.001
Ankylosing spondylitis	12 (1.5)	3 (1.5)	1 (1.2)	1 (0.3)	5 (3.9)	0 (0.0)	1 (9.1)	1 (3.3)	0 (0.0)	<0.001
Inflammatory bowel diseases	8 (1.0)	3 (1.5)	0 (0.0)	2 (0.7)	2 (1.6)	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)	0.004
Mental health disorders	61 (7.8)	19 (9.4)	7 (8.6)	17 (5.9)	14 (10.9)	1 (5.3)	1 (9.1)	0 (0.0)	2 (8.3)	0.465
Topical agent use in the prior year	657 (84.1)	161 (79.7)	73 (90.1)	251 (87.8)	99 (77.3)	17 (89.5)	6 (54.5)	27 (90.0)	23 (95.8)	0.002
Phototherapy use in the prior year	129 (16.5)	20 (9.9)	14 (17.3)	55 (19.2)	21 (16.4)	2 (10.5)	1 (9.1)	4 (13.3)	12 (50.0)	<0.001

†Income (high vs low) was based on the type of drug plan they had with those receiving partial or total subsidies classified as low income
‡Chi-square test or Fisher's exact test
Abbreviations: ACI: acitretin; CST: Conventional systemic therapies; MTX: methotrexate; Q1: quartile 1; Q3: quartile 3; TNFi/UST: Tumor necrosis factor inhibitors and ustekinumab

Table 2. Annual depression and anxiety-related healthcare costs in Canadian dollars associated with different systemic agents' trajectories

	All study sample (N=781)	Persistent methotrexate users (N=202)	Persistent acitretin users (N=81)	Early discontinuation of CST (N=286)	Late discontinuation of methotrexate (N=128)	Switch to TNFi/UST (N=19)	adding TNFi/UST (N=11)	CST discontinuation then restart on methotrexate (N=30)	CST discontinuation then restart on acitretin or multiple switches between systemic agents (N=24)
N (%)	165 (21.1)	43 (21.3)	13 (16.0)	60 (21.0)	26 (20.3)	0 (0.0)	5 (45.4))	7 (23.3)	11 (45.8)
Among patients with a non-zero cost for depression and anxiety									
Overall									
Total cost†	44,593	13,272	7,697	11,402	2,558	–	915	546	8,203
Median (Q1, Q3)†	56 (14, 127)	30 (9, 90)	97 (34, 249)	58 (25, 116)	73 (21, 137)	–	70 (40, 115)	36 (6, 172)	46 (6, 193)
Medications									
N (%)	130 (78.8)	37 (86.1)	11 (84.6)	45 (75.0)	18 (69.2)	–	4 (80.0)	6 (85.7)	9 (81.8)
Total cost†	7,932	1,799	838	2,685	1,216	–	639	121	635
Median (Q1, Q3)†	26 (7, 73)	14 (6, 44)	65 (14, 113)	29 (11, 90)	33 (15, 74)	–	31 (18, 301)	13 (6, 40)	6 (5, 34)
Hospitalizations									
N (%)	5 (3.0)	1 (2.3)	1 (7.7)	2 (3.3)	–	–	–	–	1 (9.1)
Total cost†	22,359	4,159	6,142	4,892	–	–	–	–	7,165
Median (Q1, Q3)†	4,159 (3,501, 6,142)	4,159	6,142	2,446 (1,391, 3,501)	–	–	–	–	7,165
ED visits									
N (%)	5 (3.0)	1 (2.3)	1 (7.7)	2 (3.3)	1 (3.8)	–	–	–	–
Total cost†	7,143	5,747	282	934	179	–	–	–	–
Median (Q1, Q3)†	405 (282, 529)	5,747	282	467 (405, 529)	179	–	–	–	–
Outpatient visits									
N (%)	64 (38.8)	14 (32.5)	3 (23.1)	25 (41.7)	12 (46.2)	–	3 (60.0)	3 (42.8)	4 (36.4)
Total cost†	7,159	1,566	435	2,891	1,164	–	276	425	403
Median (Q1, Q3)†	83 (56, 137)	74 (59, 127)	136 (93, 206)	83 (52, 138)	80 (56, 143)	–	114 (45, 115)	128 (36, 261)	85 (58, 144)

Abbreviations: ACI: acitretin; CST: Conventional systemic therapies; MTX: methotrexate; Q1: quartile 1; Q3: quartile 3; TNFi/UST: Tumor necrosis factor inhibitors and ustekinumab

Table 3. Two-part models for depression and anxiety-related healthcare costs among the eight treatment trajectory clusters

Clusters	Part 1 model Adjusted OR (95% CI)	Part 2 model β (95% CI)	Predicted mean costs 95% bias corrected bootstrap CI)	Cost ratio (95% bias corrected bootstrap CI)
Overall (N=781)			60 (51, 77)	
Clusters				
Persistent methotrexate users (N=202)	reference	reference	40 (31, 57)	reference
Persistent acitretin users (N=81)	0.89 (0.43, 1.85)	1.18 (0.11, 2.25)	54 (42, 75)	1.40 (0.85, 1.98)
Early discontinuation of CST (N=286)	1.31 (0.80, 2.15)	0.78 (0.03, 1.54)	47 (40, 58)	1.22 (0.82, 1.66)
Late discontinuation of methotrexate (N=128)	1.07 (0.60, 1.90)	0.25 (-0.61, 1.11)	44 (31, 70)	1.14 (0.66, 1.81)
Switch to TNFi/UST (N=19)	–	–	–	–
Adding TNFI/UST (N=11)	3.72 (1.04, 13.55)	0.75 (-0.64, 2.14)	141 (79, 249)	3.63 (1.47, 5.97)
CST discontinuation then re-start on methotrexate (N=30)	1.21 (0.47, 3.14)	0.02 (-1.21, 1.25)	19 (14, 27)	0.49 (0.29, 0.71)
CST discontinuation then re-start on acitretin or multiple switches between systemic agents (N=24)	4.56 (1.78, 11.68)	2.36 (0.97, 3.75)	514 (297, 931)	13.30 (5.76, 22.47)

Abbreviations: CI: confidence interval; CST: Conventional systemic therapies; OR: Odds ratio; SD: Standard deviation; TNFi/UST: Tumor necrosis factor inhibitors and ustekinumab

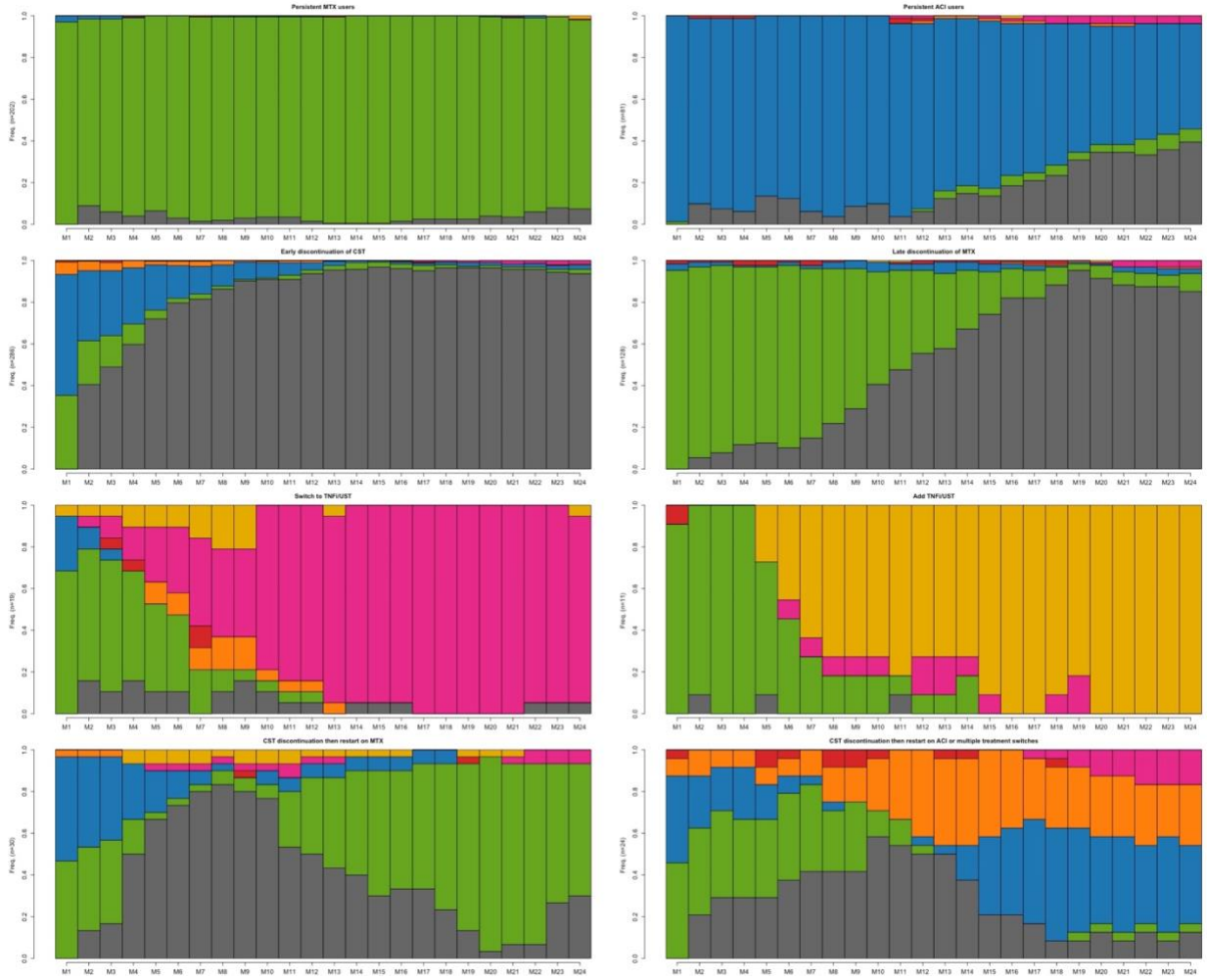


Figure 1. Tempograms describing the eight treatment trajectories for systemic agents

7.3 Additional results

In this section, I present the results of the three additional analyses that I conducted.

I the first additional analysis, I compared depression and anxiety-related healthcare costs among male and female patients. The results of this analysis (Table 7.2) showed that female patients had higher predicted mean costs by 1.89 folds when compared to male patients (CAN$ 78 vs CAN$ 43).

Table 7.2. Two-part models for depression and anxiety-related healthcare costs among male and female patients

	Predicted mean costs 95% bias corrected bootstrap CI)	Cost ratio (95% bias corrected bootstrap CI)
Male patients	43 (32, 71)	Reference
Female patients	78 (67, 106)	1.89 (1.11, 2.69)

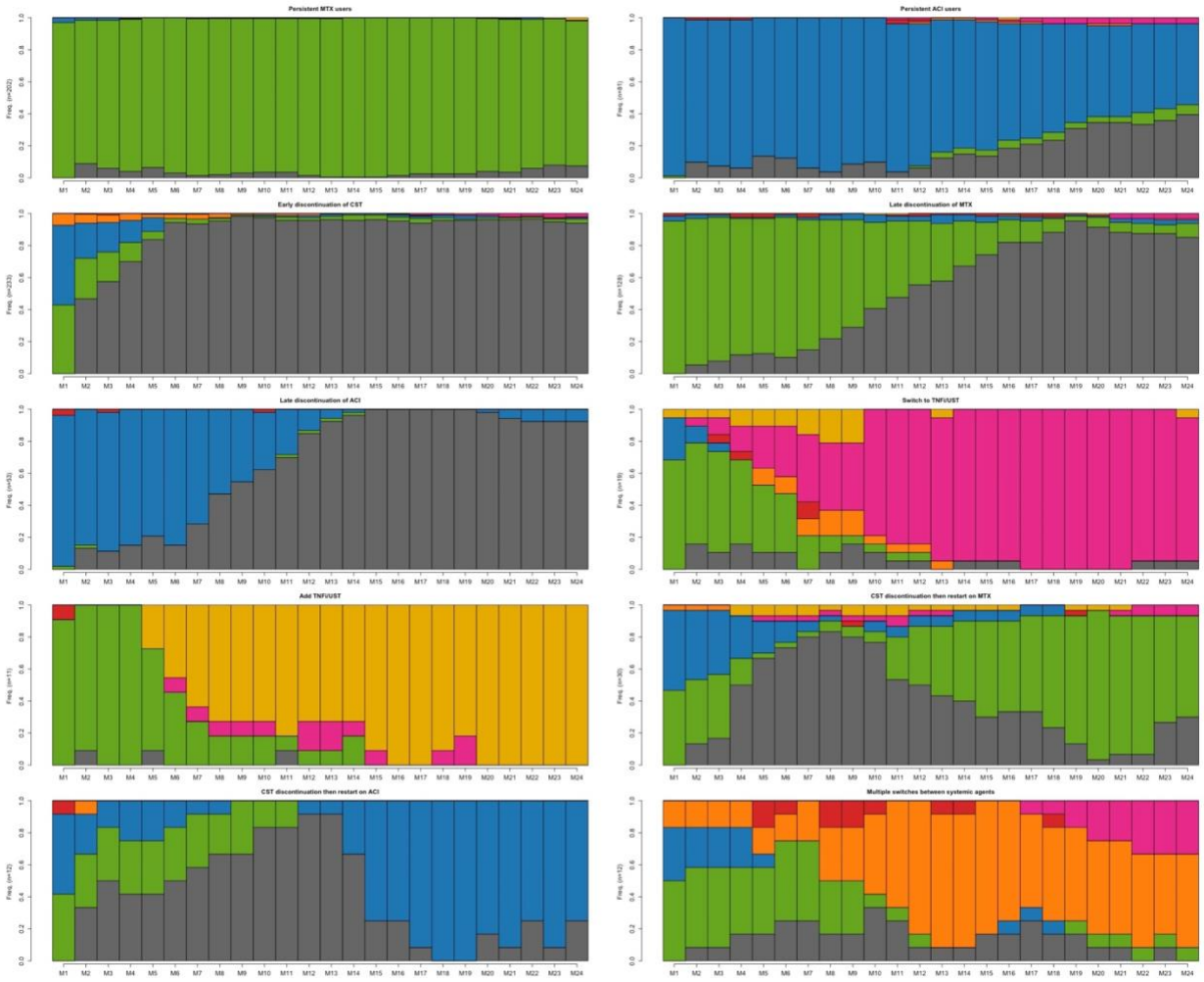
Abbreviations: CI: confidence interval

In the second additional analysis, I repeated the analyses considering 10 clusters instead of 8 clusters (Figure 7.4 & Table 7.3). The initial cluster *Early discontinuation of CSA* (N = 286) was further divided into *early discontinuation of CSA* (N = 233) and *late discontinuation of acitretin* (N = 53). The trajectory *CSA discontinuation then re-start on acitretin or multiple switches between systemic agents* (N = 12) was further divided into *CSA discontinuation then re-start on acitretin* (N = 12) and *multiple switches between systemic agents* (N = 12). Compared to persistent methotrexate users, the trajectory *late discontinuation of acitretin (*cost ratio 1.9, 95% CI: 1.19-2.64)*, adding TNFi/UST* (cost ratio3.1, 95% CI: 1.4-5.1)*, CSA discontinuation then re-start on acitretin* (cost ratio 31.7 95% CI: 11.9-66.0) *and multiple switches between systemic agents* (cost ratio 5.3 95% CI: 1.3-10.3) had higher depression and anxiety-related health care costs.

Table 7.3. Two-part models for depression and anxiety-related healthcare costs among the ten treatment trajectory clusters

Clusters	Predicted mean costs in CAN$ (95% CI)	Cost ratio (95% CI)
Overall	65 (52, 101)	
Clusters		
Persistent methotrexate users (N=202)	39 (31, 56)	Reference
Persistent acitretin users (N=81)	47 (36, 67)	1.2 (0.7, 1.8)
Early discontinuation of CSA (N=233)	41 (34, 53)	1.1 (0.7, 1.5)
Late discontinuation of methotrexate (N=128)	44 (33, 76)	1.2 (0.7, 1.9)
Late discontinuation of ACI (N=53)	73 (59, 101)	1.9 (1.2, 2.6)
Switch to TNFi/UST (N=19)	–	–
Adding a TNFi/UST (N=11)	119 (72, 210)	3.1 (1.4, 5.1)
CSA discontinuation then re-start on MTX (N=30)	42 (35, 70)	1.1 (0.6, 1.4)
CSA discontinuation then re-start on acitretin (N=12)	1227 (584, 2998)	31.7 (11.9, 66.0)
Multiple switch between systemic agents (N=12)	202 (68, 445)	5.3 (1.3, 10.3)

Abbreviations: CI: confidence interval; CSA: Conventional systemic agents; TNFi/UST: Tumor necrosis factor inhibitors and ustekinumab



Abbreviations: ACI: Acitretin, CST: conventional systemic therapies, CYC: Cyclosporine, Freq: Frequency, M1-M24: Month 1 until month 24, MTX: methotrexate, TNFi/UST: Tumor necrosis factor inhibitors and ustekinumab.
Notes: Methotrexate (green); acitretin (blue); cyclosporine (orange); 2 CST (red); TNFi/UST (magenta); TNFi/UST + CST (yellow); other (grey).

Figure 7.4. Tempograms describing the ten treatment trajectories for systemic agents

In the third additional analysis, I considered adjustment disorder in the outcome alongside depression and anxiety (Table 7.4). Even after considering patients with a history of adjustment disorder in the exclusion criteria, the final study sample remained unchanged (N = 781). The mean predicted annual cost for depression, anxiety and adjustment disorder-related health care costs per patient slightly increased to CAN$ 73, but results of the main analysis did not change. Among the eight treatment trajectories, patients in the trajectories *adding TNFi/UST* (cost ratio 2.81 95% CI 1.14-4.72) and *CSA discontinuation then restart on acitretin or multiple switches between CSA*

(cost ratio 8.76, 95% CI 4.29-4.37) were associated with incremental costs when compared to persistent methotrexate users.

Table 7.4. Two-part models for depression, anxiety and adjustment disorder-related healthcare costs among the eight treatment trajectory clusters

Clusters	Predicted mean costs 95% bias corrected bootstrap CI)	Cost ratio (95% bias corrected bootstrap CI)
Overall (N=781)	73 (63, 93)	
Clusters		
Persistent methotrexate users (N=202)	69 (54.72, 96.44)	reference
Persistent acitretin users (N=81)	55 (42.25, 91.55)	0.81 (0.50, 1.21)
Early discontinuation of CSA (N=286)	54 (47.32, 64.72)	0.80 (0.56, 1.06)
Late discontinuation of methotrexate (N=128)	41 (31.87, 58.15)	0.71 (0.48, 1.02)
Switch to TNFi/UST (N=19)	–	–
Adding TNFI/ust (N=11)	190 (102.6, 351.5)	2.81 (1.14, 4.72)
CSA discontinuation then re-start on methotrexate (N=30)	29 (21.86, 40.59)	0.43 (0.26, 0.61)
CSA discontinuation then re-start on acitretin or multiple switches between systemic agents (N=24)	592 (363.3, 1057.3)	8.76 (4.29, 14.37)

Abbreviations: CI: confidence interval; CSA: Conventional systemic agents; TNFi/UST: Tumor necrosis factor inhibitors and ustekinumab

Chapter 8: Comparing the risk of depression, anxiety and adjustment disorder among patients with psoriasis initiating a CSA and subsequently received a TNFi/UST versus those who did not receive these agents

In this section, I am presenting additional information on the methods used in manuscript 4 that addressed my objective 3.

8.1 Methods

8.1.1 Cohort definition

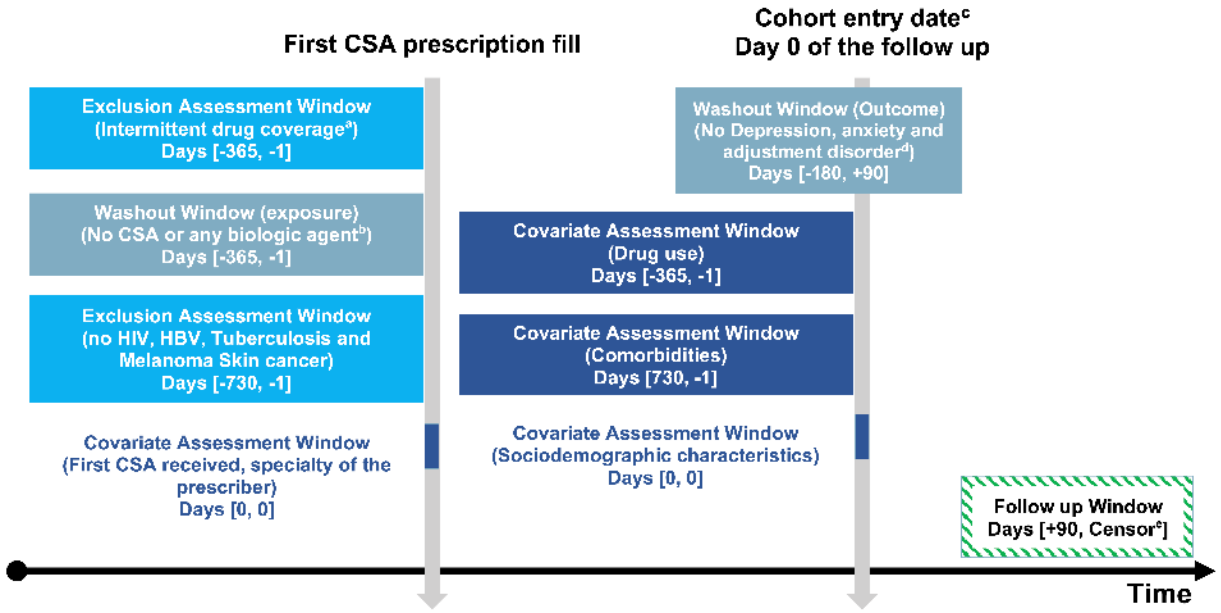
I considered all individuals who have received at least one psoriasis diagnosis in inpatient, outpatient or ED records between January 01, 1999 and December 31, 2014 followed by a prescription fill for at least one CSA (methotrexate, cyclosporine and acitretin). As for my previous cohorts, patients were required to be continuously enrolled in the provincial drug plan in the year prior to the first CSA dispensed. Those who did not receive any systemic agent in that year or a diagnosis of HIV, HBV, tuberculosis and melanoma skin cancer in the prior two years were included (Figure 8.1).

8.1.2 Exposure definitions

I divided my cohort participants into two groups, those who subsequently received a TNFi/UST (TNFi/UST user), as switch or add-on, after being initiated on a CSA and those who did not receive a TNFi/UST (TNFi/UST non-user). The date of the first TNFi/UST prescription fill was the index date for each TNFi/UST user. I used prescription time-distribution matching to selected an index date for TNFi/UST non-users (Figure 8.2).[197] The number of days between the first CSA and first TNFi/UST prescription fills was assessed for all TNFi/UST users (set of durations). Then, this set of durations was used to assign an index-date for each TNFi/UST non-user based on the following criteria: (1) The date of the first CSA prescription fill of the non-user was within 365 days of that of the TNFi/UST user; and (2) the assigned index-date is within the non-user's follow-up period (defined below). For patients with more than one potential index-date, a date was randomly selected. The TNFi/UST non-users were further separated into two groups: 1) current CSA users

included those who had a supply for a CSA at or within 90 days of their index-date and 2) previous CSA users included those with no such supply.

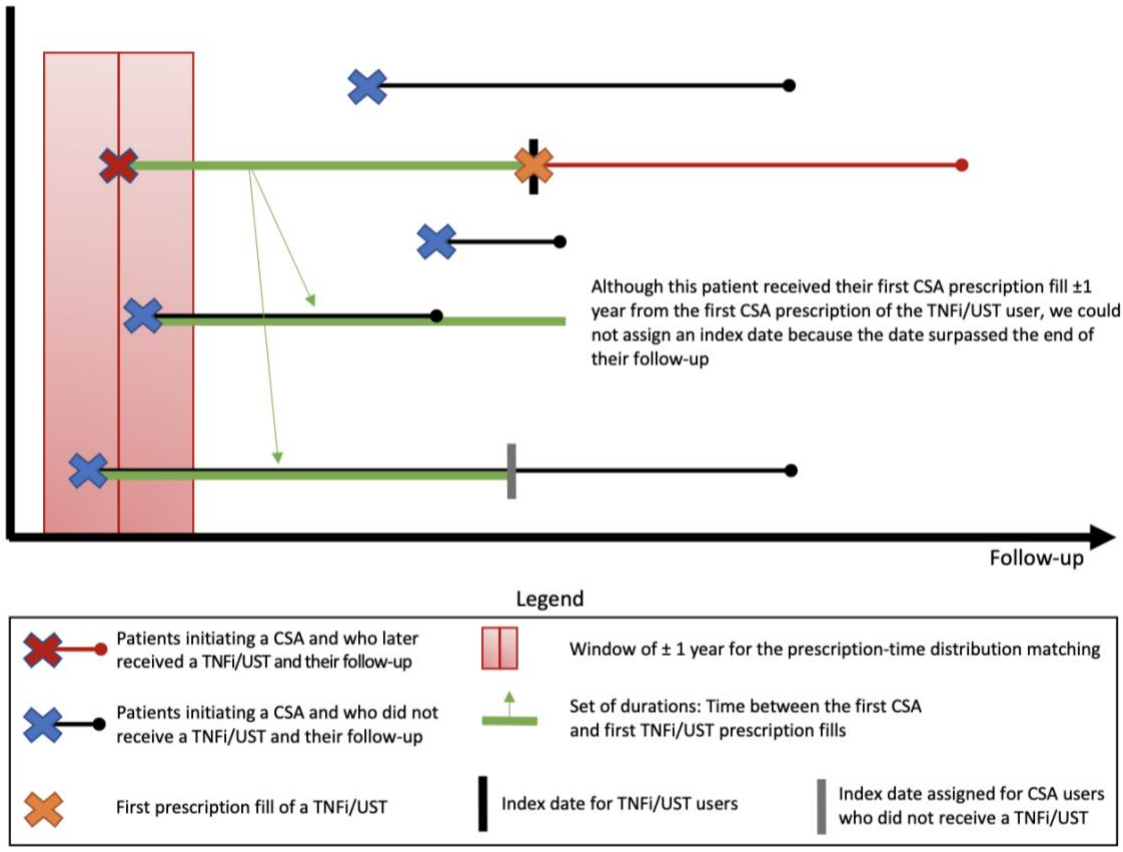
In this study, all TNFi/UST agents and CSA were considered as a single class of treatment. For the TNFi/UST and current CSA exposure group, patients were considered exposed to their index treatment (TNFi/UST or CSA) until a gap ≥ 90 days occurred in their treatment supply. A 90-day gap was deemed appropriate as most studies examining patterns of biologic agent used this duration. Others have considered 60 days and up to 120 days (because of ustekinumab); I also considered these durations in sensitivity analyses. I considered previous CSA users as unexposed until they re-initiated their CSA treatment, defined by a new prescription fill for any CSA.



[a]Gap of ≥90 days in the drug coverage
[b]Biologic agents indicated for psoriasis and other immune-mediated conditions
[c]Index date for TNFi/UST users was the date of the first prescription fill of the TNFi/UST received. Index date for current and previous CSA users was assigned using prescription time-distribution matching, conditional on: (1) having received their first CSA prescription fill within one year of the first CSA prescription fill of the TNFi/UST user with the assigned duration; and (2) having an index date assigned before the end of their follow-up.
[d]ICD 9/10 codes or a prescription fill for an antidepressant and benzodiazepine
[e]Patients were followed starting three months after index date until the occurrence of the outcome of interest, death, occurrence of an ineligibility criterion (dispensed prescription for a biologic agent other than the TNFi/UST included in the study, diagnosis for HIV, HBV, tuberculosis and melanoma skin cancer), gap ≥ 90 days of enrollment in the provincial drug plan, end of exposure to their index treatment (for TNFi/UST and current CSA users) or unexposure period (for previous CSA users) or December 31, 2015, whichever occurred first.

CSA: conventional systemic agents; HBV: Hepatitis B virus; HIV: Human Immunodeficiency Virus; ICD: International Classification of Diseases; TNFi/UST: tumor necrosis factor inhibitors and ustekinumab

Figure 8.1. Cohort construction to address objective 3



CSA: conventional systemic agents; TNFi/UST: tumor necrosis factor inhibitors and ustekinumab

Figure 8.2. Example of a prescription-time distribution matching

8.1.3 Outcome definitions

The main outcome was at least one outpatient physician claim, ED visit or a hospitalization (principle or secondary diagnosis) for depression, anxiety and/or adjustment disorder (Appendix C), whichever occurred first. To ensure that these were incident cases of depression, anxiety and/or adjustment disorder, patients with a diagnosis for these conditions and those with a dispensed antidepressant or benzodiazepine prescription in the 180 days prior and 90 days post index-date were excluded. A 90-day lag was deemed appropriate to reduce the possibility of reverse causality whereby the TNFi/UST would be prescribed to patients experiencing depression and anxiety symptoms or adjustment disorder because of CSA failure (Figure 8.1).[26,28-31]

8.1.4 Potential confounders

Sociodemographic characteristics included age (20-44, 45-64, 65-74 or ≥75 years), sex (male or female), area of residency (urban or rural), social deprivation index (divided into quintiles with 1 representing people who live in the most socially privileged areas and 5 representing those who live in the most socially deprived areas. A value of zero indicates missing value),[167] and income (low or high).

Comorbidities in the prior two years included CCI (0, 1 or ≥2), psoriatic arthritis, rheumatoid arthritis, IBD, ankylosing spondylitis, mental health disorders (other than depression, anxiety and adjustment disorder) and drug and alcohol abuse (Appendix C). All comorbidities were binary variables (yes or no) except for CCI.

Drug use in the prior year (Appendix B) included NSAIDS, antihypertensive agents, lipid-lowering agents, hypoglycemic agents, anticoagulants, platelet inhibitors, opioids, antipsychotic agents and oral corticosteroids (yes or no).

Variables related to psoriasis treatments included time from first CSA prescription fill to index date (continuous variable in years), first CSA received at index date (methotrexate, cyclosporine and acitretin), specialty of the CSA prescriber (dermatologist, rheumatologist and other specialists) and use of phototherapy in the prior year (yes or no).

8.1.5 Statistical analyses

To compare the risk of depression, anxiety and adjustment disorder between the three exposure groups, marginal structural Cox regression models with robust variance estimators were applied to minimize confounding by disease severity.[158,159,198] Robust variance was implemented because it reduces variance when using marginal structural models.[198] To do so, a multinomial logistic regression model was first used to estimate the propensity score for each patient. The propensity score was the probability of being a TNFi/UST user or current CSA user vs previous CSA user, adjusted for all potential confounders listed in section 8.1.4. The variable duration between the first CSA prescription fill and index-date was included in the model using a restricted cubic spline with five knots. The use of five knots helps minimize bias caused by model misspecification from

linearity assumptions. Then, patients in the non-overlapping regions of the propensity score distributions were excluded. Lastly, the inverse of these propensity scores stabilized by the crude probability of exposure were used to compute the IPTW (equation 8.1). Covariate balance between the treatment groups before and after weighting was evaluated by measuring the standardized mean differences (SMD) using a threshold of 0.1.[199] If a covariable had an SMD > 0.1 after weighting, it was adjusted for in the final marginal cox regression models.

$$IPTW = \frac{p(T)}{p(T|X)} \qquad (8.1)$$

p(T) represents the crude probability of exposure T and *p(T|X)* represents the propensity score: probability of exposure conditional on X (a vector including all potential confounders).

8.1.5.1 Software

SAS studio was used for cohort construction and all statistical analyses. Codes are available upon request.

8.2 Manuscript 4 – Depression, anxiety and adjustment disorder among patients with psoriasis receiving systemic agents: A retrospective cohort study in Quebec, Canada

8.2.1 Preamble to manuscript 4

In Chapters 5 and 6, I observed that patients with (vs without) mental health disorders, especially female patients, were at higher risks of switching to or adding a TNFi/UST after initiating a CSA. In Chapter 7, among patients without depression and anxiety at baseline, I observed higher mental health related health care costs during follow-up among those receiving TNFi/UST as add-on when compared to persistent methotrexate users, but not among those switching to TNFi/UST. These results were consistent when adjustment disorder was included as part of the outcome. These findings highlighted the important economic burden associated with mental health disorders, as well as the possible association of these disorders with the choice of therapy.

On the other hand, in RCT, patients treated with biologic agents reported significant improvement in HRQoL, depressive and anxiety symptoms when compared to placebo and methotrexate. Nonetheless, the seven observational studies conducted on this topic have reported discordant results due to methodological limitations and heterogeneity of the study populations. In the present study, I have addressed these limitations by comparing the incidence of depression, anxiety and adjustment disorder among patients initiating a CSA who subsequently received a TNFi/UST as a switch or add-on vs patients who did not receive these agents.

Manuscript 4 was published in the Journal of the European Academy of Dermatology and Venereology Clinical Practice (JEADV clin pract):
Milan R, LeLorier J, Brouillette MJ, Holbrook A, Litvinov IV, Rahme E. *Depression, anxiety and adjustment disorders among patients with psoriasis receiving systemic agents: A retrospective cohort study in Quebec, Canada.* JEADV clin pract. 2022;1-14.

This manuscript received attention from HCP Live, a news page for health care professionals on health care research, treatment, and drug development. I conducted an e-mail-based interview with Jenna Lorenz, a reporter at HCP Live, and the article entitled *Biologic Agents May Reduce Risk of Mental Health Disorders in Some Patients with Psoriasis* was published on their website.

8.2.2 Manuscript 4

8.2.2.1 Title page

Article type: Research article

Depression, anxiety and adjustment disorder among patients with psoriasis receiving systemic agents: A retrospective cohort study in Quebec, Canada

Running head: Depression, anxiety and adjustment disorder among patients with psoriasis.

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Statement of ethics: The study was approved by the Research Ethics Board (REB) of the Research Institute of the McGill University Health Centre.

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Conflicts of interest: Raymond Milan is supported by the Fonds de Recherche du Québec—Santé (FRQS, Quebec Foundation for Health Research) doctoral training award. Raymond Milan has also received stipends from the Canadian Institutes of Health Research (CIHR) Drug Safety and Effectiveness Cross-Disciplinary Training (DSECT) pro- gram and from the Réseau Québecois sur le suicide, les troubles de l'humeur et les troubles associés (RQSHA). Ivan Litvinov is supported by a Junior I Clinician Scientist award from the FRQS and has received consulting fees from Novartis, Janssen, Galderma and Bristol-Myers Squibb in the course of unrelated studies. Elham Rahme has received funds and consulting fees from Janssen in the course of an unrelated study. The remaining authors declare no conflicts of interest.

Data availability statement: The data are subject to third party restrictions.

Reprint requests: Elham Rahme

Figures: 2

Tables: 3

Supplementary figures: 3

Supplementary tables: 11

Keywords: Psoriasis, biologic agents, conventional systemic agents, depression, anxiety, adjustment disorder

8.2.3 Abstract

Introduction: Patients with psoriasis are at risk of depression, anxiety and adjustment disorder (DAAD). Randomized control trials reported improve- ment in depression and anxiety symptoms among patients with psoriasis receiving tumour necrosis factor inhibitors and ustekinumab (TNFi/UST) versus placebo and conventional systemic agents (CSA). The risk of DAAD among TNFi/UST versus CSA users was not assessed in real-world settings.

Objective: To compare DAAD incidence among patients with psoriasis using CSA and subsequently received (vs. not) TNFi/UST.

Methods: We conducted a retrospective cohort study using the province of Quebec health administrative databases (1997–2015). Among adult patients with a diagnosis of psoriasis and initiating a CSA, we included those who later initiated a TNFi/UST, as a switch or add-on, at the date of their first prescription fill (index-date). We also included TNFi/UST nonusers at a date chosen to match the time between the first CSA and the index date of a random TNFi/UST user. TNFi/UST nonusers were classified into current or previous CSA users according to their last CSA received in the 90 days before or after their index date. Marginal structural Cox regression models weighted by the inverse probability of exposure compared the risk of DAAD between TNFi/UST, current and previous CSA users. Additional analyses were conducted by age group and sex.

Results: Our cohort included 1333 patients with psoriasis: 183 TNFi/UST users, 625 current CSA users and 525 previous CSA users. TNFi/UST users were at a lower risk of DAAD versus previous CSA users (hazard ratio 0.48, 95% confidence intervals: 0.28–0.94). The reduction in risk among TNFi/UST users was not statistically significant versus current CSA users. Similar results were observed across different age groups and sex.

Conclusion: Among patients with psoriasis receiving CSA, those who were subsequently dispensed TNFi/UST were at a lower risk of DAAD compared to those who did not receive these agents.

8.2.4 Introduction

Psoriasis is an immune-mediated skin disorder affecting 2%–3.1% of the North American population.[1-5] It manifests itself with thick erythematous plaques, which can be painful, pruritis and disfiguring.[6] Psoriasis imposes a high clinical and economic burden on patients and healthcare systems.[7] Psoriasis has a negative effect on body image and self-esteem, thus reducing patients' quality of life (QoL) and work productivity.[6,8] Patients with psoriasis are at increased risk of depression, anxiety and adjustment disorder (DAAD) compared to the general population.[9-19] Higher risks of DAAD have been consistently reported among female patients and patients with increased psoriasis severity,[11,13,20-25] with varying effects of age.[21,22,26]

Biologic agents, including tumour necrosis factor inhibitors (TNFi) and interleukin inhibitors (IL), have revolutionized the management of patients with moderate-to-severe plaque psoriasis.[6] In double-blind randomized controlled trials (RCT), biologic agents were more effective than placebo and methotrexate, a conventional systemic agent (CSA), in achieving at least 75% improvement in the Psoriasis Area and Severity Index (PASI) after 10–12 weeks of therapy.[27-34] Additionally, significant improvement in anxiety and depressive symptoms, health-related QoL (HRQoL) and fatigue were reported by these RCT in the biologic arm, especially among patients with ≥75% improvement in PASI.[27-34]

In the Canadian province of Quebec as in many other jurisdictions, because of their high acquisition costs, biologic agents are reimbursed by the provincial drug plan for patients with moderate-to-severe psoriasis as well as for those with other immune-mediated conditions only when CSA are contraindicated or ineffective.[35-37]

To date, seven cohort studies have examined the effect of biologic agents versus CSA on mental health disorders (MHD).[21,38-43] These studies, reported lower,[21,38,39,41] similar[42,43] and higher[40] MHD risks with biologic agents. Variations in populations mix and outcome/exposure definitions may explain these discrepancies. Thus, we aimed to compare DAAD incidence among patients with psoriasis initiating a CSA and subsequently receiving (vs. not) a TNFi or ustekinumab (TNFi/UST).

8.2.5 Patients and methods

8.2.5.1 Study design and data source

This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cohort studies.[44]

We conducted a retrospective cohort study using Quebec health administrative databases. The databases include demographic, physician and pharmaceutical claims and hospital abstract summary records and are linkable by a unique patient identifier. For this study, data were available from January 1997 to December 2015. The physician claims database contains information on all outpatient, emergency department (ED) and inpatient physician encounters for all residents (International Classification of Diseases 9th revision [ICD-9] codes). The pharmaceutical claims database contains information on prescribed medications (dispensation date, dosage, duration of supply and prescribed speciality), for those registered with the provincial drug plan (about 44% of the population including all individuals in the workforce who do not have private drug insurance through their employer or a family member plan, those ≥65 years and those receiving social assistance).[45] Hospital abstract records provide information on all hospital admissions including admission and discharge dates and the principal and up to 15 secondary diagnoses (ICD-9 codes before April 2006 and ICD-10 codes thereafter).

8.2.5.2 Study population

We identified patients ≥20 years with a physician claim for psoriasis (ICD-9: 696.1 and ICD-10: L40.x) between January 1999 and December 2014. To include those with moderate-to-severe psoriasis, we retained only those who filled at least one CSA (methotrexate, cyclosporine or acitretin) prescription post psoriasis diagnosis. Patients were required to be continuously enrolled in the provincial drug plan in the year before the first CSA was dispensed. Those who did not receive any systemic agent (biologic or CSA) in that year and did not have a diagnosis for a disease for which TNFi/UST is contra- indicated (human immunodeficiency virus [HIV], hepatitis B, tuberculosis or melanoma skin cancer)[46-52] in the prior 2 years were included (Supporting Information: eFigure 1).

8.2.5.3 Outcome

We defined DAAD by having at least one physician outpatient visit, an ED visit or a hospitalization (principal or secondary diagnosis) with an ICD-code for DAAD (Supporting Information: eTable 1).

8.2.5.4 Exposure assessment

Among the study patients, we identified those who were prescribed a TNFi/UST (etanercept, infliximab, adalimumab, golimumab, certolizumab pegol and ustekinumab) following their first CSA prescription. The date of the first TNFi/UST prescription fill was the index date. We included patients for whom TNFi/UST use was added to or replaced CSA. For study patients who did not receive a TNFi/UST in the study period (TNFi/UST nonusers), we used prescription time-distribution matching to define their index date (Supporting Information: eFigure 2).[53] First, for each TNFi/UST user, we assessed the number of days between their first CSA and first TNFi/UST prescription fills (duration). Then, we used this set of durations to assign an index date for each TNFi/UST nonuser based on the following criteria: (1) The date of the first CSA prescription fill of the nonuser was within 365 days of that of the TNFi/UST user; and (2) the assigned index-date is within the nonuser's follow-up period (defined below). For patients with more than one potential index date, we randomly selected one date. The TNFi/UST nonusers were separated into two groups: (1) current CSA users included those who had a supply for a CSA within 90 days of their index date and (2) previous CSA users included those with no such supply.

We did not differentiate between individual TNFi/ UST and CSA agents. For the TNFi/UST and current CSA exposure group, patients were considered exposed to their index treatment (TNFi/UST or CSA) until a gap ≥90 days occurred in their treatment supply. Previous CSA users were considered unexposed until they reinitiated their CSA treatment, defined by a new prescription fill for any CSA.

We excluded patients with a diagnosis of DAAD and those with a dispensed antidepressant or benzodiazepine prescription in the 180 days prior and 90 days post-index- date (Supporting Information: eFigure 1). A 90-day lag was deemed appropriate to reduce the possibility of reverse

causality whereby the TNFi/UST would be prescribed to patients experiencing DAAD symptoms because of CSA failure.[21,29-32]

Patients were followed starting 90 days post-index- date until the occurrence of the outcome of interest, death, the occurrence of an ineligibility criterion (dispensed prescription for a biologic agent other than the study TNFi/UST, diagnosis for HIV, HBV, tuberculosis and melanoma skin cancer), gap ≥90 days in their provincial drug plan, end of exposure to their index treatment (for TNFi/UST and current CSA users) or unexposure period (for previous CSA users) or 31 December 2015, whichever occurred first.

8.2.5.5 Statistical analysis

We calculated crude incidence rates of DAAD per 1000 person-years with 95% confidence intervals (CI) based on the Poisson distribution by exposure group. To compare DAAD risk between exposure groups, we applied marginal structural Cox regression models with robust variance estimators to minimize confounding by disease severity.[54-56] First, we fitted a multinomial logistic regression model to estimate the propensity score for each patient. The propensity score was the probability of being a TNFi/UST user or current CSA user versus a previous CSA user, adjusted for all potential confounders listed in (Table 1) in addition to the duration between the first CSA prescription fill and index-date using a restricted cubic spline with five knots. Patients in the nonoverlapping regions of the propensity score distributions were excluded (Supporting Information: eFigure 3). We used the inverse of the propensity score stabilized by the crude probability of exposure to compute inverse probability-of-treatment weights (IPTW). Covariate balance between the treatment groups before and after weighting was evaluated by standardized mean differences (SMD) using a threshold of 0.1.[57] We reported the results in hazard ratios (HR) and 95% CI.

We performed four secondary analyses. First, we fitted two marginal structural Cox regression models to assess separately the risk of depression and anxiety/ depression combined. Second, we repeated the main analyses among male and female patients, separately. Third, we conducted separate analyses according to age groups. Lastly, we compared TNFi/UST users to current and previous CSA users combined.

We performed 10 sensitivity analyses to test the robustness of our findings. First, we changed the lag from 90 to 0, 180 and 365 days. Second, we varied the gap period between prescriptions from 90 to 60 days. Third, we used a restrictive definition for psoriasis (≥1 dermatologist visit, hospitalization or ED visit or ≥2 outpatient visits with other specialists). Fourth, patients with any MHD in the 180 days pre-index-date were excluded. Fifth, patients with a history of DAAD in the 365 days pre-index-date were excluded. Sixth, the first eligibility criterion for the nonuser index-date selection (date of first CSA fill being within 365 days of that of the TNFi/UST user) was changed to within 180 days. Seventh, we did not consider golimumab and certolizu- mab pegol as TNFi because, at the time of our study, these agents were not approved for psoriasis but were indicated for other immune-mediated conditions such as psoriatic arthritis that is present in up to 35% of patients with moderate-to-severe psoriasis.[3] Eighth, we did not consider acitretin among the CSA because this agent was previously associated with depressive symptoms. Ninth, we fitted an adjusted Cox proportional hazard model with all potential confounders instead of using IPTW. Lastly, we did not perform propensity score trimming.

We computed the E-value to assess the strength of our treatment-outcome association.[58] The E-value is the minimum strength of association that an unmeasured confounder would need to have with both the treatment and the outcome to fully explain away the findings.[58] All analyses were conducted using SAS 9.4 and R Studio 1.4.

8.2.6 Results

We included 183 TNFi/UST users, 625 current CSA users and 525 previous CSA users (Figure 1). Before weighting, the mean time from first CSA prescription fill to index date was 3.1 ± 2.7, 2.0 ± 2.2 and 3.2 ± 2.9 years for previous CSA, current CSA and TNFi/UST users, respectively (Table 1). While most patients were initiated on metho- trexate and acitretin, the proportions were imbalanced between previous CSA users (55.6% and 39.4%), current CSA (71.7% and 25.4%) and TNFi/UST users (71.0% and 25.1%). More than half of our cohort received their initial CSA prescription by a dermatologist, with an imbalance between the three exposure groups (73.9%, 56.3% and 62.8%). TNFi/UST users were younger, with higher social deprivation index, higher unadjusted proportions of psoriatic arthritis, ankylosing spondylitis, NSAIDS and hypoglycaemia agent prescription fills when compared to current and previous CSA users. Current CSA users had

lower unadjusted proportions of RA and prescription fills for lipid-lowering agents when compared to previous CSA and TNFi/UST users. Previous CSA users had higher unadjusted proportions of prescription fill for oral corticosteroids when compared to current CSA and TNFi/UST users. After weighting, the three exposure groups were well balanced on all baseline characteristics (SMD < 0.1).

Kaplan–Meier curves showed a nonsignificant decreased DAAD risk among TNFi/UST users when compared to current and previous CSA users (Figure 2). Crude DAAD incidence rates per 1000 person-years were 33.5 (95% CI: 18.9–55.3) for TNFi/UST users, 55.6 (42.3–71.8) for current CSA users and 63.3 (50.6–78.1) for previous CSA users (Table 2). The marginal structural models showed that TNFi/UST users were at a 52% lower risk of DAAD when compared to previous CSA users (HR 0.48, 95% CI: 0.28–0.94). The result for TNFi/UST users versus current CSA users pointed to lower risk (0.60, 0.31–1.20), but was not statistically significant.

In secondary analyses (Table 3), when only depres- sion was assessed, a nonsignificant decreased risk was observed in TNFi/UST users compared to previous and current CSA users, respectively (0.60, 0.22–1.63 and 0.70, 0.26–1.88). Similar results were found when anxiety and depression were assessed in combination. The risk of DAAD was similar across different sex and age groups (Table 3). After combining current and previous CSA users, TNFi/UST users remained at a lower risk of DAAD (0.53, 0.27–1.01).

8.2.6.1 Sensitivity analyses

Overall, findings from sensitivity analyses were consist- ent with those of the main analyses. When TNFi/UST users were compared to previous CSA users, HR (95% CI) ranged from 0.36 (0.13–1.00) for the 365-day lag to 0.74 (0.23–2.33) for the analysis without considering acitretin (Supporting Information: eTables 2–11).

The E-value analysis showed that the HR of 0.48 that we found in the TNFi/UST versus previous CSA users could be explained away by an unmeasured confounder whose association with each of the treatment and outcome is 2.72-fold higher. The upper bound of the CI in the main analysis (0.94) could be moved to include 1 by an unmeasured confounder that is associated with both the treatment and outcome by 1.25-fold each.

8.2.7 Discussion

Our study investigated the association between TNFi/ UST use and DAAD incidence among patients with psoriasis. TNFi/UST users were at a lower risk of DAAD when compared to previous and current CSA users, although the latter association was not statistically significant. Although there were no significant associations between the exposure groups across the different MHD assessed separately and across age groups and sex, the HR estimates remained in the same direction as in the main analyses, thus suggesting no effect modification by sex or age. RCT assessing TNFi/UST efficacy in patients with moderate-to-severe psoriasis also sought to determine the effect of these agents on HRQoL and anxiety/depressive symptoms as secondary efficacy endpoints.[27-34] These RCT consistently reported significant improvement in HRQoL and anxiety/depressive symptoms in patients treated with TNFi/UST when compared to placebo and methotrexate after 10–24 weeks of therapy, with most RCT examining the effect at 12 weeks. The beneficial effect of TNFi/UST on these secondary efficacy endpoints persisted during the extension periods, lasting up to 3 years after treatment initiation.[31,32,34]

The seven observational studies that examined the association between systemic agents and MHD among patients with psoriasis have reported inconsistent findings.[21,38-43] In a retrospective cohort study, the prevalence of depression/insomnia significantly decreased after initiating TNFi/UST.[21] In a prospective cohort study, TNFi/UST (vs. CSA) users were at a lower risk of incident self-reported depressive symptoms (HR 0.76, 95% CI: 0.59–0.98).[38] A lower risk of depression, psychosis, suicide

and bipolar disorder was found among biologic (vs. nonbiologic) agent users (HR 0.52, 95% CI 0.51–0.53) and versus methotrexate (HR 0.91, 95% CI 0.87–0.96) in one study.[39] In three cohort studies using the same registry, higher,[40] similar[42] and lower[41] MHD risks were reported with biologic agents versus CSA use. Heterogeneity in the study populations including patients with[39-42] or without MHD history,[38,43] variation in outcome definition[21,38-43] and inclusion of prevalent systemic agent users creating a possible prevalent-user bias[59] may explain these discrepancies.

Our study is in line with these previous RCT and four observational studies. We found that patients receiving TNFi/UST were at reduced risk of incident DAAD versus previous CSA users. The

beneficial effect persisted when considering a 365-day lag, thus indicating a long-term mental-health benefit with TNFi/UST. Although not statistically significant, our findings pointed to reduced risks of DAAD in TNFi/UST users versus current CSA users and of anxiety/depression in TNFi/UST users versus current or previous CSA users. Further investigation is needed to determine the reasons for CSA discontinuation including those that may improve mental health such as skin clearance and those that may deteriorate it such as lack of compliance, lack of efficacy or adverse events. Countries with universal drug plans cover biologic agents for patients with moderate-to- severe psoriasis in whom CSA treatment had failed. Failure to these agents is expected to increase the risk of DAAD.[25,60] Therefore, our findings are reassuring.

Our study considered adjustment disorders as part of the outcome. An adjustment disorder is an emotional or a behavioural reaction to a stressful event and may be misdiagnosed as anxiety/depressive disorder.[61] This is the case in three of the seven studies that examined the risk of mental health outcomes among patients receiving systemic agents.[21,39,43] In these retrospective studies, ICD-9 codes for adjustment disorders such as 309.0 (adjustment disorder with depressed mood), 309.1 (prolonged depressive reaction) and 309.28 (adjustment disorder with mixed anxiety and depressed mood) were included with the diagnosis of depression.[21,39,43] The few published studies that assessed adjustment disorder among patients with psoriasis were cross-sectional and reported prevalence ranging from 13.3% to 62.5%.[15,17-19] Based on our findings, adjustment disorder should be considered in future studies related to MHD in psoriasis.

Both depression and psoriasis share similar pathological pathways mediated by inflammatory cytokines.[62] However, it is not clear whether the effect of TNFi/UST on depression is directly related to the reduction in inflammation associated with biologic agent use, or is a consequence of psoriasis skin clearance, reduced pain and pruritus and improved QoL or a combination of both.[11]

8.2.7.1 Strengths and Limitations

Our study has several strengths. First, the use of prescription time-distribution matching helped reduce Ref 1.28 (0.88–1.87) 0.61 (0.31–1.22) survival bias.[53] Because of provincial drug formulary restrictions, patients with moderate-to-severe psoriasis must initiate a CSA before receiving a biologic agent. The prescription time-distribution matching we used rendered the index dates of

those exposed to TNFi/UST comparable to those of the CSA groups. Second, we reduced confounding by disease severity with marginal structural models by estimating the average treatment effect of the population to increase the comparability between the three exposure groups.[55,56] Lastly, the 90-day lag reduced detection bias and reverse causality as shown in our sensitivity analyses where no association was observed with a 0-day lag, with more events occurring in patients in the TNFi/UST group, as opposed to a 90-, 180- and 365-day lag.

Our study is subject to some limitations. First, RAMQ databases do not include information on psoriasis severity, patient's HRQoL or physician advocacy for access to restricted biologics. Although we reduced the risk of confounding by disease severity by only including patients receiving systemic agents, residual confounding may have remained. The upper bound of the 95% CI of the HR for TNFi/UST versus current CSA users in the main analysis (0.28–0.94) could be moved to include 1 by an unmeasured confounder associated with both the exposure and outcome by ≥1.25-fold. Larger studies are needed to confirm the strength of this unmeasured confounder, because in general, increasing the sample size can narrow the CI. On the other hand, a strong unmeasured confounder whose association with each of the treatments and outcome is ≥2.72-fold is required to change the HR of 0.48 for the TNFi/UST users versus CSA users to a null result, which is reassuring. Second, we could not assess each biologic agent individually, because only 183 patients received TNFi/UST. However, in RCT, all TNFi/UST was associated with improved HRQoL and anxiety/depressive symptoms when compared to placebo and methotrexate.[27-34] Third, we did not consider switches between CSA and switches between TNFi/UST. Treatment switch is an indicator of nonresponse to therapy or adverse events,[63-65] which in turn, can increase the risk of MHD.[60] Lastly, our study did not include newer generation of biologic agents, such as IL-23 and IL-17 inhibitors, approved for psoriasis after 2015, which could affect the generalizability of our findings. However, the reduced risk of DAAD among the newer generation of biologic agents should remain significant when compared to previous CSA users, because during RCT, IL-23 and IL-17 inhibitors were more effective than TNFi/UST in improving anxio-depressive symptoms and HRQoL.[66-74]

8.2.8 Conclusion

The findings of the present retrospective study indicate that among patients with psoriasis using a CSA, those who subsequently received a TNFi/UST may be at reduced risk of DAAD compared to those who did not. These findings warrant examination of a newer generation of biologic agents.

Figure legends

Figure 1: Study flowchart

Abbreviations:

CSA: conventional systemic agents, TNFi/UST: Tumor necrosis factor inhibitors and ustekinumab; HBV: hepatitis B virus; HIV: Human Immonodeficiency Virus; ps: propensity score

Figure 2: Weighted and unweighted Kaplan Meier curves for the risk of depression, anxiety and adjustment disorder between TNFi/UST users, current CSA users and previous CSA users

Notes:

Kaplan Meier curves were weighted by the inverse probability of exposure

Abbreviations:

CSA: conventional systemic agents, TNFi/UST: Tumor necrosis factor inhibitors

Supplement figure legends

eFigure 1: Cohort construction

Notes:

[a]Gap of ≥90 days in the drug coverage

[b]Biologic agents indicated for psoriasis and other immune-mediated conditions

[c]Cohort entry date or index date: Index date for TNFi/UST users was the date of the first prescription fill of the TNFi/UST received. Index date for current and previous CSA users was assigned using prescription time-distribution matching, conditional on: (1) having received their first CSA prescription fill within one year of the first CSA prescription fill of the TNFi/UST user with the assigned duration; and (2) having an index date assigned before the end of their follow-up.

[d]ICD 9/10 codes or a prescription fill for an antidepressant and benzodiazepine

[e]Patients were followed starting three months after index date until the occurrence of the

outcome of interest, death, occurrence of an ineligibility criterion (dispensed prescription for a biologic agent other than the TNFi/UST included in the study, diagnosis for HIV, HBV, tuberculosis and melanoma skin cancer), gap ≥ 90 days of enrollment in the provincial drug plan, end of exposure to their index treatment (for TNFi/UST and current CSA users) or exposure period (for previous CSA users) or December 31, 2015, whichever occurred first.

Abbreviations:

CSA: conventional systemic agents; HBV: Hepatitis B virus; HIV: Human Immunodeficiency Virus; ICD: International Classification of Diseases; TNFi/UST: tumor necrosis factor inhibitors and ustekinumab

eFigure 2: Example of a prescription-time distribution matching

Abbreviations:

CSA: conventional systemic agents; TNFi/UST: tumor necrosis factor inhibitors and ustekinumab

eFigure 3: Propensity score trimming

Notes:

Previous CSA users (Blue), current CSA users (yellow) and TNFi/UST (green)

Abbreviations:

CSA: conventional systemic agents; ps: propensity score; TNFi/UST: tumor necrosis factor inhibitors and ustekinumab

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Table 1. Baseline characteristics

Variables	Before weighting [a]				After weighting [b]			
	Previous CSA users (N=525)	**Current CSA users (N=625)**	**TNFi/UST users (N=183)**	**SMD**	**Previous CSA users**	**Current CSA users**	**TNFi/UST users**	**SMD**
Variables related to psoriasis treatments								
Time from first CSA prescription fill to index date in years, mean (SD)	3.1 (2.7)	2.0 (2.2)	3.2 (2.9)	0.34	2.6 (2.6)	2.6 (2.7)	2.5 (2.7)	0.03
First CSA received				0.24				0.07
Acitretin	207 (39.4)	159 (25.4)	46 (25.1)		31.3	30.1	26.9	
Cyclosporine	26 (5.0)	18 (2.9)	7 (3.8)		4.2	4.5	3.7	
Methotrexate	292 (55.6)	448 (71.7)	130 (71.0)		64.5	65.3	69.4	
Specialty of the first CSA prescriber				0.29				0.09
Dermatologist	388 (73.9)	352 (56.3)	115 (62.8)		62.3	63.6	63.0	
Rheumatologist	56 (10.7)	144 (23.0)	40 (21.9)		16.6	18.3	20.7	
Other specialists	81 (15.4)	129 (20.6)	28 (15.3)		21.1	18.1	16.3	
Phototherapy use	64 (12.2)	91 (14.6)	28 (15.3)	0.06	11.7	13.0	13.4	0.03
Socio-demographic characteristics								
Age				0.33				0.07
20-44 years	96 (18.3)	93 (14.9)	47 (25.7)		18.7	16.9	16.2	
45-64 years	183 (34.9)	190 (30.4)	77 (42.1)		30.6	34.4	32.8	
65-74 years	146 (27.8)	218 (34.9)	40 (21.9)		30.9	29.4	31.8	
≥75 years	100 (19.0)	124 (19.8)	19 (10.4)		19.9	19.3	19.2	
Male sex	292 (55.6)	334 (53.4)	108 (59.0)	0.08	52.8	55.2	51.7	0.05
Living in urban area	439 (83.6)	494 (79.0)	144 (78.7)	0.08	82.2	80.9	81.4	0.02
Social deprivation index				0.16				0.07
Unknown	63 (12.0)	70 (11.2)	15 (8.2)		10.0	10.5	10.9	
Most socially privileged	102 (19.4)	103 (16.5)	41 (22.4)		19.1	18.7	19.6	
Privileged socially	82 (15.6)	118 (18.9)	30 (16.4)		18.0	18.0	16.5	
Average socially deprivation	91 (17.3)	106 (17.0)	30 (16.4)		18.1	16.6	15.0	
Deprived socially	91 (17.3)	116 (18.6)	39 (21.3)		17.4	18.5	20.0	
Most socially deprived	96 (18.3)	112 (17.9)	28 (15.3)		17.4	17.7	18.0	
Low income	264 (50.3)	322 (51.5)	85 (46.4)	0.07	51.1	49.6	48.8	0.03
Comorbidities in the prior two years								
Charlson comorbidity index				0.07				0.09
0	306 (58.3)	358 (57.3)	108 (59.0)		58.3	58.5	57.1	
1	115 (21.9)	133 (21.3)	42 (23.0)		21.9	21.5	18.6	
≥2	104 (19.8)	134 (21.4)	33 (18.0)		19.9	20.0	24.3	

Psoriatic Arthritis	67 (12.8)	139 (22.2)	48 (26.2)	0.23	20.1	19.3	18.8	0.02
Rheumatoid Arthritis	31 (5.9)	104 (16.6)	26 (14.2)	0.23	13.3	12.3	12.8	0.02
Inflammatory bowel diseases	3 (0.6)	7 (1.1)	2 (1.1)	0.04	0.6	0.9	0.3	0.04
Ankylosing spondylitis	2 (0.4)	7 (1.1)	5 (2.7)	0.13	1.2	0.9	1.1	0.02
Other mental health disorders	24 (4.6)	26 (4.2)	6 (3.3)	0.04	4.4	4.3	5.9	0.04
Drug and alcohol abuse	6 (1.1)	7 (1.1)	2 (1.1)	0.01	0.8	0.8	1.9	0.06
Drug use in the prior year								
Non-Steroidal Anti-Inflammatory drugs	126 (24.0)	196 (31.4)	69 (37.7)	0.20	29.4	30.3	30.6	0.02
Anti-Hypertensive agents	246 (46.9)	324 (51.8)	86 (47.0)	0.07	47.0	49.6	51.9	0.07
Lipid-lowering agents	174 (33.1)	254 (40.6)	64 (35.0)	0.10	34.2	36.3	40.2	0.08
Hypoglycemic agents	83 (15.8)	118 (18.9)	40 (21.9)	0.10	17.1	17.7	19.6	0.04
Anticoagulants	24 (4.6)	33 (5.3)	9 (4.9)	0.02	5.2	4.5	6.8	0.07
Platelet inhibitors	125 (23.8)	182 (29.1)	47 (25.7)	0.08	24.6	26.8	28.1	0.05
Opioids	63 (12.0)	88 (14.1)	29 (15.8)	0.07	13.8	13.2	12.2	0.03
Antipsychotic agents	4 (0.8)	6 (1.0)	1 (0.5)	0.03	0.9	0.8	1.5	0.04
Oral corticosteroids	49 (9.3)	130 (20.8)	32 (17.5)	0.22	16.0	16.8	16.7	0.02

Abbreviation: CSA: conventional systemic agent; SMD: standardized mean difference; TNFi/UST: Tumor necrosis factor inhibitors and ustekinumab

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[B] Data are presented as percentage of patients unless otherwise indicated.

Table 2. Primary analyses examining the association between exposure to systemic agents and the risk of depression, anxiety and adjustment disorders – Marginal structural models

	N of event	Person-year	Incidence rate (95% CI)	Marginal HR (95% CI)	Marginal HR (95% CI)
Previous CSA users (N=525)	86	1359	63.3 (50.6-78.1)	Ref	1.28 (0.88-1.87)
Current CSA users (N=625)	59	1064	55.6 (42.3-71.8)	0.78 (0.54-1.13)	Ref
Current TNFi/UST users (N=183)	15	447	33.5 (18.8-55.3)	0.48 (0.24-0.93)	0.61 (0.31-1.22)

Abbreviation: CI: confidence interval; CSA: conventional systemic agent; HR: hazard ratios; TNFi/UST: Tumor necrosis factor inhibitors and ustekinumab

Table 3. Secondary analyses examining the association between exposure to systemic agents and the risk of depression, anxiety and adjustment disorder – Marginal structural model

	N of event	Person-year	Incidence rate (95% CI)	Marginal HR (95% CI)	Marginal HR (95% CI)
Depression					
Previous CSA users (N=789)	50	2201	22.7 (16.8-29.9)	Ref	1.15 (0.71-1.86)
Current CSA users (N=888)	33	1443	22.8 (15.7-32.1)	0.87 (0.53-1.41)	Ref
Current TNFi/UST users (N=278)	9	690	13.0 (6.0-24.8)	0.60 (0.22-1.63)	0.70 (0.26-1.88)
Depression and anxiety					
Previous CSA users (N=569)	71	1533	46.2 (36.1-58.4)	Ref	0.94 (0.63-1.40)
Current CSA users (N=654)	58	1060	54.7 (41.5-70.7)	1.06 (0.71-1.59)	Ref
Current TNFi/UST users (N187)	15	468	32.1 (17.9-52.8)	0.73 (0.35-1.55)	0.69 (0.33-1.46)
Combining previous and current CSA users					
CSA users (N=1172)	152	2488	61.1 (51.7-71.6)	Ref	–
Current TNFi/UST users (N=187)	15	455	32.9 (18.4-54.3)	0.53 (0.27-1.01)	
By age					
20-64 years					
Previous CSA users (N=254)	38	708	53.6 (37.9-73.6)	Ref	1.89 (0.93-3.87)
Current CSA users (N=224)	13	332	39.1 (20.8-66.9)	0.52 (0.26-1.07)	Ref
Current TNFi/UST users (N=108)	10	272	36.6 (17.6-67.4)	0.64 (0.28-1.43)	1.21 (0.48-3.05)
≥65 years					
Previous CSA users (N=237)	41	576	71.1 (51.0-96.5)	Ref	1.03 (0.63-1.69)
Current CSA users (N=336)	36	640	56.3 (39.4-77.9)	0.98 (0.59-1.59)	Ref
Current TNFi/UST users (N=55)	2	117	17.0 (2.1-61.5)	0.25 (0.05-1.16)	0.26 (0.05-1.20)
By sex					
Male patients					
Previous CSA users (N=282)	43	761	56.5 (40.8-76.1)	Ref	1,06 (0.61-1.85)
Current CSA users (N=301)	25	494	50.5 (32.7-74.6)	0.94 (0.54-1.64)	Ref
Current TNFi/UST users (N=104)	7	230	30.5 (12.2-62.8)	0.55 (0.17-173)	0.59 (0.18-1.90)
Female patients					
Previous CSA users (N=217)	35	542	64.5 (44.9-89.7)	Ref	1.18 (0.69-1.99)
Current CSA users (N=283)	32	499	64.0 (43.0-90.4)	0.85 (0.50-1.44)	Ref
Current TNFi/UST users (N=69)	7	170	41.1 (16.5-84.6)	0.57 (0.21-1.51)	0.67 (0.25-1.18)

Abbreviation: CI: confidence interval; CSA: conventional systemic agent; HR: hazard ratios; TNFi/UST: Tumor necrosis factor inhibitors and ustekinumab

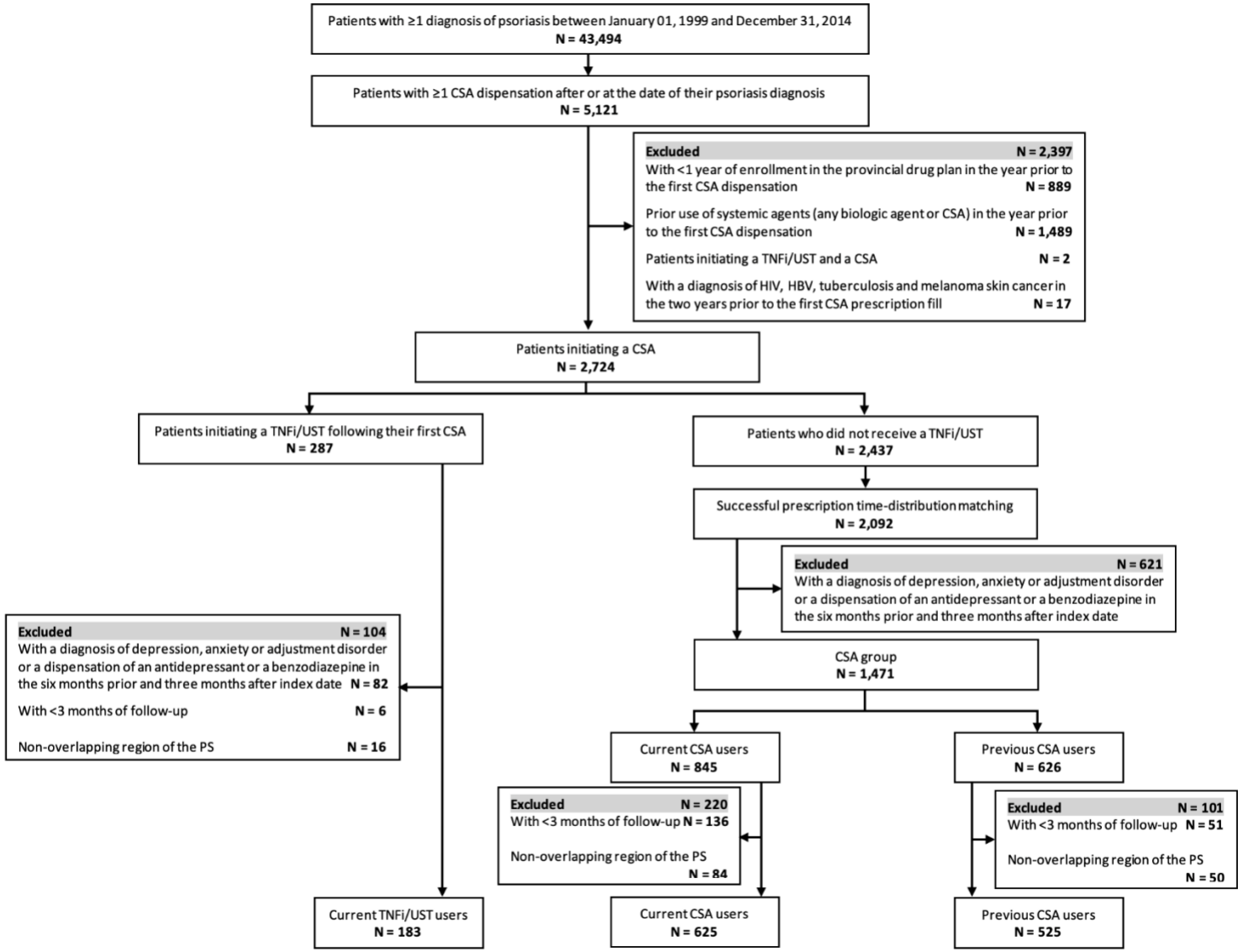

Figure 1. Study flowchart

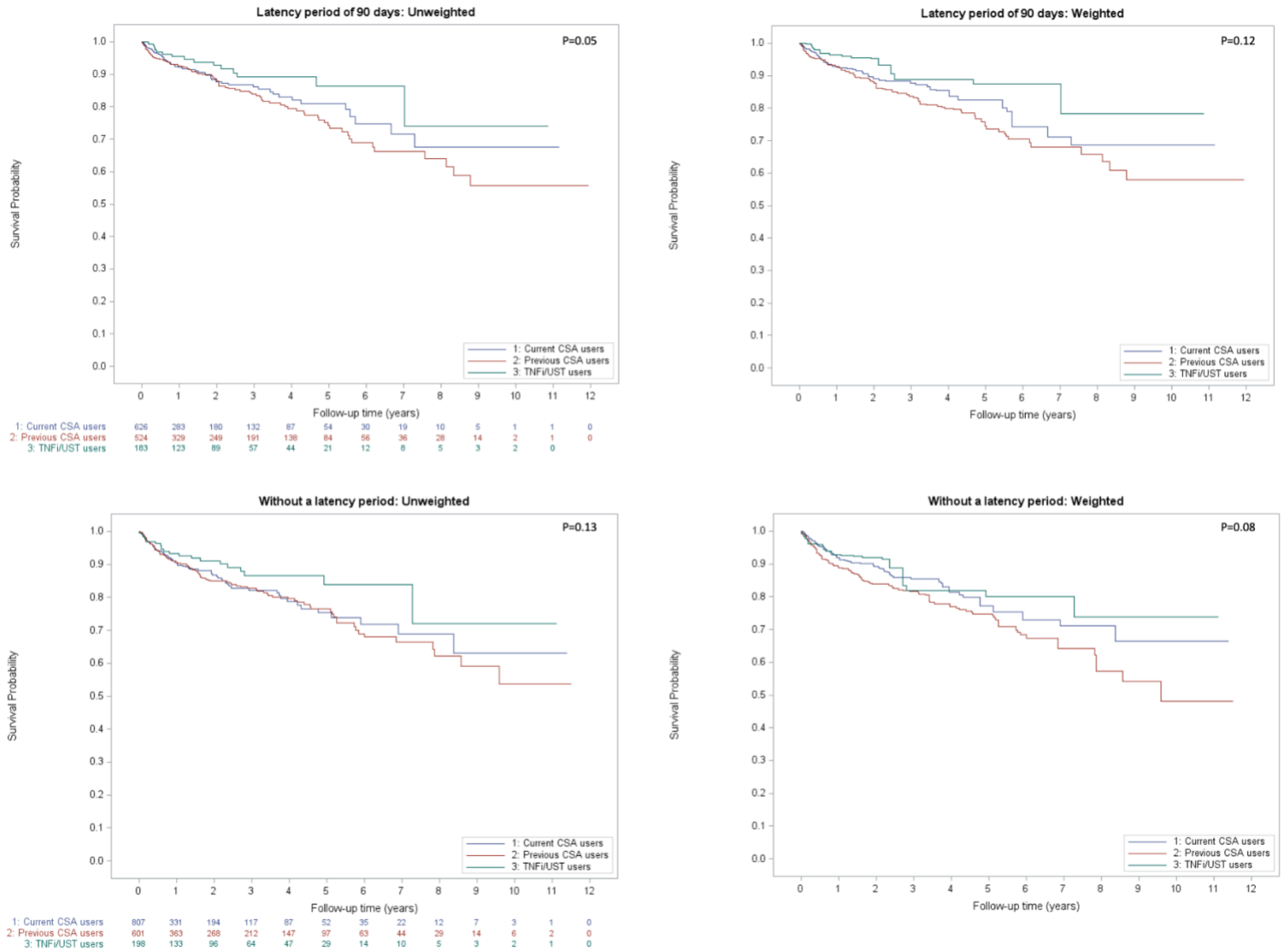

Figure 2. Weighted and unweighted Kaplan Meier curves for the risk of depression, anxiety and adjustment disorder between TNFi/UST user, current CSA users and previous CSA users

Chapter 9: Discussion

This thesis was conducted to fill important gaps in knowledge, while addressing some of the methodologic limitations in the published literature regarding utilization of systemic agents and associated mental health outcomes. In particular, among patients with psoriasis, I sought to (1) describe patterns of systemic agent use, including CSA and TNFi/UST; (2) determine if the association of these agents with depression, anxiety and adjustment disorders; and (3) assess the direct health care costs of these mental health outcomes.

9.1 Summary of research findings

9.1.1 Objective 1

In manuscripts 1 and 2, I examined sex differences in patterns of systemic agent use and factors associated with switch/add TNFi/UST, switch/add TNFi/UST or a different CSA and CSA discontinuation among patients initiating a CSA. I conducted a retrospective cohort study using RAMQ databases. My cohort included 1,644 patients with psoriasis initiated on a CSA between 2002 and 2015, and followed until the first date of CSA discontinuation, switch/add TNFi/UST, death, the occurrence of a contraindication to TNFi/UST or the end of the study period.

In manuscript 1, I considered CSA as a single class, and did not account for switches between these agents. During a median follow-up of 0.7 years, 60.4% of study participants discontinued their CSA with similar rates between male and female patients (381.2 and 352.8 per 1,000 person-year). My findings were in range with previous observational studies reporting that up to 85% of patients discontinued their CSA within one year of follow-up.[12,14-17,19,152] My findings were also similar to those of the one study that assessed the risk of systemic agent discontinuation in male and female patients and reported similar risks between sexes.[21] However, that study did not differentiate between biologic agents and CSA and included both first-time and prevalent systemic agent users.

My study found sex differences in factors associated with CSA discontinuation. Male patients followed by a rheumatologist (versus dermatologist) and those with a prior hospitalization were at

lower risk of CSA discontinuation, while those initiated on acitretin (vs methotrexate) were at higher risk. Among female patients, the presence of rheumatoid arthritis and receiving at least one prescription fill for a hypoglycemic agent or a lipid-lowering agent were associated with reduced risks of CSA discontinuation, while those initiated on acitretin, cyclosporine or sulfasalazine (vs methotrexate) were at increased risk of CSA discontinuation. All patients entering the cohort after 2011 (versus 2002-2010) were at a reduced risk of CSA discontinuation regardless of the sex. To my knowledge, only one previous study reported that male patients were at higher risk of CSA discontinuation than female patients[17] and no previous study assessed whether factors associated with discontinuation varied between sexes. However, similar to my study, previous studies have reported an association between metabolic disorders with a reduced risk of CSA discontinuation,[15,17] and higher risks with cyclosporine and acitretin.[12,14,15,17,18] As opposed to my findings, other studies found that age ≥ 40 years (versus < 40 years),[17] the presence of IBD,[17] hypertension,[17] metabolic diseases,[15,17] cancer,[17] liver disease[17] and kidney disease[17] were associated with lower risks of CSA discontinuation. While my study did not find an association between psoriatic arthritis and CSA discontinuation, findings from previous studies regarding this association were discordant. One study conducted in France reported a lower risk of CSA discontinuation among patients with both psoriasis and psoriatic arthritis,[17] while a study conducted in Israel reported a higher risk.[15]

In my study, over a median of 0.7 years of follow-up, 7.4% of study patients received a TNFi/UST during the follow-up, with 3.4% switching to a TNFi/UST and 4.0% receiving these agents as add-on. The rates of switch/add TNFi/UST in my study were similar between male and female patients (49.1 and 41.0 per 1,000 person-years). To my knowledge, only two previous studies examined switch from CSA to a biologic agent. One study was conducted in Italy and reported that 34% of patients receiving a CSA switched to a biologic agent over an average follow-up of 2.4 years.[154] The other study was conducted in the US including only first-time CSA users. It reported that only 5% of those initiated on a CSA switched to a biologic agent in an average follow-up of 1.29 years.[19] Both of these studies suffered from important limitations that may have overestimated the rate of switch in the first study and underestimate it in the second. The first study included incident and prevalent CSA users. It considered treatment cycles as the unit of analysis and allowed multiple

treatment cycles per patient. On the other hand, the second study did not account for treatment add-on and defined a switch as one that occurred after a discontinuation of therapy.

In my study, most predictors of switch/add of TNFi/UST were sex specific. Among male, but not among female patients, longer psoriasis disease duration and obesity were associated with an increased risk of switch/add TNFi/UST. Among female, but not among male patients, prior use of NSAIDS and the presence of mental health disorders such as adjustment, personality and somatoform disorders increased the risk of switch/add TNFi/UST, while female patients with rheumatoid arthritis as a comorbidity were at 60% reduced risk of switch/add TNFi/UST. Among both male and female patients, older age was associated with reduced risk of switch/add TNFi/UST. Only one previous study assessed factors associated with switch/add a biologic agent among CSA users. In that study, only age was associated with a lower risk of switch to a biologic agent. However, that study did not account for sex differences and was methodologically limited by the inclusion of prevalent CSA users and the analysis of multiple treatment cycles per patient.[154]

My findings suggest that the decision of the health care professional to prescribe a biologic agent for male and female patients with psoriasis was mostly based on their clinical profile. To my surprise, psoriatic arthritis was not associated with the risk of switch in both male and female patients, while rheumatoid arthritis was associated with a decreased risk in female patients. Psoriatic arthritis and rheumatoid arthritis are immune-mediated conditions for which biologic agents can be also prescribed. Thus, one would assume that patients with psoriasis and these comorbidities would be more likely to receive biologic agents. Additional research is warranted to better understand the reduced risk of switch/add of TNFi/UST among female patients with both psoriasis and rheumatoid arthritis.

In manuscript 2, I considered switch and add-on between systemic agents (CSA and TNFi/UST). I found that among the 1,644 patients initiated on a CSA, 342 (20.8%) switched to or added another systemic agent during the follow-up with 82.7% of them receiving a different CSA and 17.3% receiving a TNFi/UST. In male patients, the presence of psoriatic arthritis and longer psoriasis disease (> 12 months versus 0-3 months) increased the risk of switch, while among female patients, those with a disease duration of 3-12 months (versus 0-3 months) were at lower risk of switch.

Additionally, female patients receiving a prescription fill for an NSAIDs and those with adjustment, somatoform and dissociative disorders were at increased risks of switch to a different systemic agent. In both sexes, older age was associated with a reduced risk of switch, while sulfasalazine vs methotrexate increased the risk of switch/add of a different systemic agent. Overall, these factors are consistent with those identified in my first study as associated with switch/add TNFi/UST, with the exception of sulfasalazine and psoriatic arthritis in male patients, and disease duration, NSAIDS and sulfasalazine in female patients. It is worth noting that sulfasalazine is prescribed off-label for psoriasis, while it is indicated for psoriatic arthritis and other immune-mediated conditions, which may explain the higher risk of switch found in patients initiated on sulfasalazine. This was confirmed in a sensitivity analysis that did not find any association between psoriatic arthritis and switch/add a different systemic agent when those initiated on sulfasalazine were removed from the analysis.

9.1.2 Objective 2

In manuscript 3, I examined the longitudinal trajectories of systemic agent use among patients initiating a CSA and determined whether certain of these trajectories were associated with depression- and anxiety-related health care costs. Using RAMQ administrative databases and a retrospective cohort design, I included 781 patients with psoriasis initiated on a CSA after excluding those with a history of depression and anxiety and those with less than two years of potential follow-up data. I assessed depression and anxiety-related health care costs from the health care system's perspective and used two-part models to compare these costs between the trajectories.

I used sequence and cluster analyses which identified eight treatment trajectories that I labeled according to their most frequent treatment pattern used (1) persistent methotrexate users, (2) persistent acitretin users, (3) early CSA discontinuation, (4) late methotrexate discontinuation, (5) switch to TNFi/UST, (6) adding TNFi/UST, (7) CSA discontinuation then restart on methotrexate, and (8) CSA discontinuation then restart on acitretin or multiple switches between systemic agents.

In this study, the predicted annual mean direct health care costs for depression and anxiety were CAN$ 60 per patient. Thus, I estimated that approximately 10 million dollars would be expected

to be spent annually to manage depression and anxiety among patients with moderate-to-severe psoriasis treated with systemic agents. This projection remains an underestimation of the true cost associated with managing depression and anxiety, as access to psychotherapy is limited in the public health sector and costs associated with psychotherapy are not available in the RAMQ databases. Psychotherapy is more costly than antidepressants and benzodiazepines agents as these are mostly prescribed in their generic forms. Previous studies reported that the presence of a psychiatric disorder as a comorbidity, including depression and anxiety, was associated with an incremental annual all-cause health care costs ranging from US$4,181 to US$12,077 per patients.[7-9] Based on my findings, it is unlikely that these incremental costs were directly related to management of psychiatric disorders, but could perhaps be more likely related to management of comorbidities, such as cardiovascular diseases and metabolic syndromes, that are prevalent among patients with mental health disorders.[87,155-157] Furthermore, these studies only assessed mental disorders at the cohort entry date, thus including prevalent cases of psychiatric disorders.[7-9] In addition, patients who developed a mental health disorder during the follow-up were considered in the no psychiatric disorder group in that study.

My findings also showed differences in depression and anxiety-related health care costs between treatment trajectories. Predicted annual costs in each trajectory ranged from CAN$39 for persistent methotrexate users to CAN$119 for patients adding TNFi/UST and CAN$514 for patients in the trajectory CSA discontinuation then restart on acitretin or with multiple switches between systemic agents. The latter two trajectories were associated with higher costs by 3.1-fold (95% CI 1.4-5.1) and 13.3-fold (95% CI 5.8-22.77) when compared to persistent methotrexate users. Patients in the trajectory switch to TNFi/UST did not have any depression- and anxiety-related health care costs. My findings remained consistent after adding health care costs associated with adjustment disorder.

Additionally, when the trajectory CSA discontinuation then restart on acitretin or with multiple switches between systemic agents was separated into two clusters, both CSA discontinuation then restart on acitretin (cost ratio 31.7, 95% CI 11.9-66.0) and multiple switches between systemic agents (cost ratio 5.3, 95% CI 1.3-10.3) were associated with higher depression- and anxiety-related health care costs when compared to persistent methotrexate users.

In my study, sex differences were also noted, with female patients having higher health care costs for depression and anxiety when compared to male patients. This finding is in line with previous studies reporting higher mental health burden among female patients with psoriasis when compared to male patients. However, because of the small sample size, I could not assess sex differences in depression and anxiety-related healthcare costs between the trajectories.

To the best of my knowledge, sequence analysis has not been previously used in pharmacoepidemiology to describe longitudinal treatment patterns in real-world settings. Other techniques such as time-to-event analysis and latent class methods have been used for that purpose.[188,200,201] As opposed to time-to-event analysis and GBTM, sequence analysis measures simultaneously several types of patterns such as persistence, switch, add-on and re-start of therapy while taking into consideration the timing and the heterogeneity in pathways of treatment use.[179] In addition, sequence analysis is less computationally intense than GMM, thus allowing the use of multiple time points to examine treatment trajectories.[188,200,201]

9.1.3 Objective 3

In manuscript 4, I examined the risk of depression, anxiety and adjustment disorder among patients with psoriasis initiating a CSA and subsequently receiving a TNFi/UST vs those who did not receive these agents. Using RAMQ administrative databases, I conducted a retrospective cohort study including 1,333 patients initiated on a CSA between 1999 and 2015. I included those who subsequently received a TNFi/UST as a switch or add-on in the TNFi/UST group at the switch/add date (N = 183) and divided those who did not receive TNFi/UST into current CSA users (N = 625) and previous CSA users (N = 525) using prescription-time distribution matching to define the cohort entry date for TNFi/UST non-users.

After implementing marginal structural Cox regression models, study patients receiving TNFi/UST were at 52% reduced risk for depression, anxiety and adjustment disorder when compared to previous CSA users (HR 0.48, 95% CI 0.28-0.93) but not when compared with current CSA users (HR 0.60, 95% CI 0.31-1.20). When mental health outcomes were assessed separately, TNFi/UST users were at a non-significant reduced risk of depression (HR 0.60, 95% CI 0.22-1.63 and HR 0.70, 95% CI 0.26-1.88) and anxio-depression (HR 0.73, 95% CI 0.35-1.55 and HR 0.69,

95% CI 0.33-1.46) when compared to previous CSA users or current CSA users, respectively. My results also suggested no effect modification by age and sex. When both CSA groups were combined, biologic agent users remained at lower risk of depression, anxiety and adjustment disorders by 47% (HR 0.53, 95% CI 0.27-1.01), but the decrease in risk was not statistically significant.

Previous observational studies comparing the risk of mental health outcomes between systemic agents reported inconsistent findings.[34-40] Overall, the use of biologic agents was associated with lower mental health outcomes when compared to CSA or to patients with psoriasis not receiving biologic agents in four studies.[34-36,39] Nonetheless, in the four studies, mental health outcomes definitions varied widely and included depressive symptoms,[34] prevalent depression and insomnia before and after initiating a TNFi/UST,[36] psychiatric illness including a composite outcome of depression, anxiety, suicide, bipolar and psychosis,[35] and any psychiatric adverse event.[39]

In a retrospective cohort study conducted in the US by Margolis and colleagues (2019) among 262,552 patients with moderate-to-severe psoriasis receiving systemic agents or phototherapy, biologic agents were associated with a 48% reduced risk of psychiatric illness when compared to patients with moderate-to-severe psoriasis not receiving these agents (HR 0.52, 95% CI 0.51-0.53). Biologic agents were also associated with a 9% reduced risk when compared to only methotrexate users (HR 0.91, 95% CI 0.87-0.96). These findings were similar to mine, although the confidence intervals were narrower, partly because of the larger sample size. Patients in that study who did not receive a biologic agent may be similar to my study patients in the current and previous CSA users' groups combined, while methotrexate users in that study could be similar to the current CSA users in my study. However, it is worth noting that the study by Margolis and colleagues may be subject to reverse causality and prevalent user biases, as the authors did not indicate whether patients included in the study were first-time systemic agent users and whether patients with a history of psychiatric illnesses were excluded.[35]

In fact, these methodologic limitations were present in most of the published studies on this topic (section 3.3). To my knowledge, only two studies included patients without a history of mental health disorders,[34,37] and one also implemented a latency period of 7 days to ensure that the event

occurred after treatment initiation.[37] Strober and colleagues (2018) reported that patients treated with biologic agents were at lower risk of depressive symptoms when compared to CSA users (HR 0.76, 95% CI 0.59-0.98).[34] On the other hand, Vasilakis-Scaramozza and colleagues (2020) reported no differences in the risk of treated depression, treated anxiety and treated depression and anxiety among patients receiving TNFi and IL with or without a CSA when compared to those receiving only a CSA, with HR estimates varying from 0.7 to 1.4 and none of them reaching statistical significance.[37] Additionally, no differences were observed between CSA users and untreated patients in that study, which corroborates my finding.

Wu and colleagues reported that the prevalence of depression and insomnia significantly decreased by 43.8% within two years of initiating a TNFi/UST when compared to the period before initiation ($p < 0.001$).[36] In the same study, similar results were observed when separate analyses were conducted for different sex and age groups, thus also suggesting no effect modification by age and sex.

My study showed the importance of introducing a latency period to reduce the risk of reverse causality and detection bias, as shown in my sensitivity analysis where no association was observed between TNFi/UST and previous CSA users with a 0-day lag (HR 0.65, 95% CI 0.35-1.19) because more events occurred early on in the TNFi/UST group as opposed to the 90-day lag (HR 0.48, 95% CI 0.28-0.93), 180-day lag (HR 0.53, 95% CI 0.26-1.11) and 365-day lag (HR 0.36, 95% CI 0.13-1.00).

I implemented the IPTW to reduce confounding by disease severity.[158,159] Most of the previous studies included exposure to systemic agents as a time-varying exposure,[37-40] but only one implemented IPTW to reduce confounding[40] and none of the studies implemented IPCW to account for informative censoring.[158] In my study, IPCW was not included in the MSM, because I did not use a time-varying approach for the exposure groups. The goal of MSM is to estimate the treatment effect in the entire population by creating a pseudo-population in which everyone has the same probability of being included in one of the three exposure groups.[158,159,202] This is particularly helpful because the three exposure categories in my study included patients currently

treated with systemic agents defined by TNFi/UST and current CSA users as well patients not currently treated with any systemic agents defined as previous CSA users.

9.2 Limitations of this thesis

While I discussed the study-specific limitations in each manuscript, there are certain limitations that are common across these studies and warrant further discussion.

I used the RAMQ health administrative databases in manuscripts 1 to 4 of this thesis. Although the RAMQ databases were previously validated against medical chart records and are reliable sources to measure treatment patterns and health outcomes,[161,162] they have certain limitations. First, the RAMQ pharmaceutical claims database does not include information on treatment indication, which could lead to misclassification of disease status when based on medication use. Therefore, I could not determine whether the CSA and TNFi/UST received were prescribed for psoriasis or for a different, concomitant, immune-mediated condition for which these treatments are also indicated. However, in a previous study conducted using the Danish National administrative databases and health care registries, receiving a systemic agent anytime following a psoriasis diagnosis was a good indicator of moderate-to-severe psoriasis (sensitivity 98%).[166] Second, RAMQ pharmaceutical claims database includes information on medications dispensed and not on drug intake, which could overestimate persistence to therapy. However, pharmaceutical claim databases are a reliable resource to measure persistence and adherence.[203] Third, RAMQ pharmaceutical claims database does not include information on the reason for treatment discontinuation. However, in several prospective cohort studies, loss of efficacy and adverse events were the main reasons for discontinuing CSA and TNFi/UST among patients with moderate-to-severe psoriasis.[12,13] Fourth, RAMQ medical claims database was designed for billing purposes and therefore does not capture variables related to psoriasis severity (BSA, PASI, DLQI), laboratory tests, BMI, HRQoL and lifestyle habits such as smoking and alcohol consumption. These variables can influence psoriasis severity, the choice of treatment, response to therapy and mental health outcomes, which could lead to confounding.[4,46,87,88,155-157,204] To reduce confounding by disease severity, I only included patients initiated on a CSA as these agents are recommended as a first-line treatment for moderate-to-severe psoriasis, and in Quebec patients are required to initiate a CSA before receiving a TNFi/UST unless the former is contraindicated.[11] In addition, in

the first three manuscripts, all the analyses were adjusted for baseline characteristics, chronic physical and psychiatric comorbidities, and prior drug use to reduce confounding bias. In manuscript 4, I used MSM to further reduce confounding by disease severity when comparing TNFi/UST to CSA users.[158,159]

Health administrative databases can underestimate the number of patients with mental health disorders because they only capture those who are actively seeking medical help. In fact, validation studies of depression and anxiety in RAMQ and other Canadian health administrative databases reported low sensitivity (16% to 79%) and low PPV (25% to 86%) when compared to electronic medical records and standardized tests for these disorders.[205-208] These studies differed by 1) the ICD codes that were included to detect health care services for depression and/or anxiety, 2) the number of health care services for these conditions; and 3) whether prescription fills for antidepressants or benzodiazepines were considered. Studies had higher sensitivity and PPV when anxiety and depression were combined and when a combination of health care services and pharmacotherapy was considered.[205-208] The low incidence and prevalence of mental health disorders in health administrative databases may be due to the stigma and discrimination associated with these conditions that may prevent patients from seeking professional help.[209] Additionally, while the usual pathway into healthcare in the province of Quebec is a general practitioner, two meta-analyses revealed that general practitioners identified less than half of the patients with a depressive disorder.[210,211] Thus, a large percentage of patients remain untreated for depression (and other mental health disorders) and will not be identified in studies based on the RAMQ administrative databases. Finally, patients who only seek psychotherapy for depression, anxiety or adjustment disorder are not captured in RAMQ administrative databases due to low access to these services in the public sector. In manuscripts 3 and 4, the outcomes were depression, anxiety and/or adjustment disorder. These mental health outcomes were identified using ICD-9 and ICD-10 codes in both manuscripts, and by also including patients with a prescription fill for an antidepressant or benzodiazepine in manuscript 3. Although, RAMQ databases may underestimate the incidence of these mental disorders, the risk of misclassification is more likely to be non-differential between all treatment trajectories and exposure groups. Therefore, my findings may be biased toward the null, thus underestimating the true strength of association between my exposure groups and mental health outcomes.

The variable sex in RAMQ administrative databases represents the biological sex at birth (male or female) and not gender (how individuals perceive themselves). Although some individuals may identify differently from their biologic sex on their RAMQ health card, only 0.35% of Canadian residents identify as a gender that differs from the sex they were assigned at birth (transgender or non-binary).[212] Therefore, I do not believe that our inability to adjust for gender had a substancial impact on the findings in manuscripts 1 and 2, especially since the potential predictors included in the studies were not gender specific (comorbidities, prior drug use and socio-demographic characteristics). However, future studies should account for gender and gender-specific predictors such as patients' body image, expectation from treatment, self-confidence, stigma and QoL in the analyses. These variables may be associated with both the treatment choice and patients' mental health and could confound the result if not adjusted for.[3,24,25]

In manuscript 1, CSA and TNFi/UST were examined as a single class and not individually to increase the statistical power. However, regardless of the sample size, I used LASSO regularization to manage model overfitting and perform variable selection, and my models showed good overall performances with Harrel's Concordance index and calibration slopes ≥ 0.6.[168,169] Nonetheless, I could not separate patients who switched to TNFi/UST from those who received these agents as add-on. These groups of patients (switch vs add) could differ in baseline characteristics, especially since in manuscript 3, patients switching to a TNFi/UST did not have any mental health-related healthcare cost, while those who received these agents as add-on did. Therefore, my results should be interpreted with caution. In manuscript 3, while CSA were examined separately, I considered all TNFi/UST as a single class. Therefore, my trajectories could not identify patients who switched to a different biologic agent during the two-year follow-up. Additional analyses revealed that only 9 patients received ustekinumab during the follow-up and 67% of them were included in the trajectory switch to TNFi/UST. Patients included in the trajectory adding TNFi/UST were all TNFi users.

My study only included biologic agents such as TNFi and ustekinumab approved by Health Canada for psoriasis before December 2015. Therefore, IL-17 and IL-23 inhibitors were not considered in this thesis. However, I believe that my findings are still generalizable and relevant to current patients with psoriasis receiving newer generation of biologic agents, because drug

formulary restrictions for TNFi/UST and other biologics remain unchanged in psoriasis. These agents are reimbursed only if treatments with CSA failed or is contraindicated. Therefore, patterns of systemic agent use and their association with mental health-related health care costs have unlikely changed either. Additionally, recent RCT for IL-23 and IL-17 inhibitors often included TNFi or ustekinumab as an active comparator. In these RCT, newer generation of biologic agents were more effective in improving anxio-depressive symptoms and QoL when compared to older generation of biologic agents.[142-150] Therefore, the reduced risk of depression, anxiety and adjustment disorder among biologic agents should remain significant when compared to previous CSA users. Lastly, my results may not be generalizable to patients with psoriasis covered by a private drug plan as the provincial drug plan only covers 43% of Quebec residents (93% of adults ages ≥ 65 years and about 33% of the people in the working force). However, individuals from different socio-economic statuses are covered by RAMQ drug plan and in my studies,[160] the variable income (high vs low), based on type of drug coverage with RAMQ was similar between exposure groups at baseline and was not associated with the outcomes.

9.3 Strengths of this thesis

Despite these limitations, the present thesis had several strengths. In this thesis, I addressed many important methodological limitations of previous studies, such as prevalent-user bias, reserve causality and survival bias. In manuscripts 1 to 4, I reduced the risk of prevalent-user bias by only including patients with psoriasis who were initiated on a CSA instead of including prevalent and incident users as done in previous studies. I excluded patients with a prescription fill for any systemic agent, CSA or biologic, in the year prior to the first CSA received during the study period. Previous experience with drug effectiveness and side effects can affect the current choice of therapy, which in turn can be associated with failure to treatments and influence the pattern of therapy use. In addition, if the use of biologic agents decreases the risk of depression, anxiety and adjustment disorder compared to other treatment alternatives, as reported in RCT, then by including prevalent users of biologic agents, we might overestimate the true association.[153]

In manuscripts 3 and 4, I reduced the risk of reverse causality by excluding patients with a history of depression, anxiety and adjustment disorder or a prescription for an antidepressant or benzodiazepine in the prior year (manuscript 3) or the prior six months (manuscript 4). Among

patients with psoriasis, the risk of depression and anxiety is increased with disease severity. Therefore, I had to ensure that these mental health outcomes occurred after initiating the CSA, which can be used as a proxy for moderate-to-severe psoriasis.[166] In some studies, patients with a history of mental health disorders were not excluded, thus it is difficult to conclude from these studies whether the events occurred after initiating the systemic agent, or whether failure of a previous treatment resulted in a switch/add of treatment, which in turn would be associated with an increased risk of depression and anxiety. In manuscript 4, I also implemented a latency period of 90 days to ensure that depression, anxiety or adjustment disorder occurred after initiating a TNFi/UST and are not the consequence of treatment failure on CSA that resulted in the switch/add-on of TNFi/UST.

Survival bias can occur when comparing different treatments that are not from the same line of therapy. In the case of moderate-to-severe psoriasis in Quebec and other countries with a similar public drug plan, biologic agents are reimbursed only if previous treatment with CSA failed or is contraindicated. Therefore, survival bias, a type of time-related bias, can occur because the exposure to TNFi/UST requires that patients are event free from first CSA prescription fill until the date they receive this agent. During that time-window, if patients developed the outcome, they would be excluded. It is usually difficult to estimate the magnitude of this bias because it depends on the length of the time-window and the risk of the outcome in this period.[213] Only three of seven studies addressed the issue of survival bias by implementing a time-varying approach and they reported discordant results.[37,39,40] In my study, I reduced survival bias by using prescription-time distribution matching to render the index dates of patients exposed to TNFi/UST comparable to those of the non-exposed group. A previous study comparing different methods to reduce the risk of survival bias concluded that both, time-varying analysis, and prescription-time distribution matching, provided a good control for survival bias and yielded similar results.[197]

9.4 Implication of findings

To my knowledge, this is the first Canadian study assessing patterns of CSA use, factors associated with receiving a TNFi/UST among patients with psoriasis and mental health outcomes associated with receiving these agents. Findings of this thesis are pertinent to clinicians and to the public health care system interested in improving access to biologic agents for patients with moderate-to-

severe psoriasis and reduce the burden associated with mental health disorders among this population. The studies included in this thesis support the importance of considering depression, anxiety and adjustment disorder when assessing if patients with moderate-to-severe psoriasis using CSA are candidate to receive a biologic agent. My studies further support the importance of shared decision making between health care professionals and patients with psoriasis when initiating systemic agents and suggest that patients should be informed and encouraged to have realistic expectations regarding treatment efficacy. Based on the treatment trajectories, those receiving a TNFi/UST as add-on, those with multiple switches during the follow-up and those who discontinued their initial CSA then restarted on acitretin had higher incremental health care costs for depression and anxiety. These patterns are often indicators of treatment failure and non-response to therapy, which could in part explain the higher costs associated with mental health outcomes in these trajectories, as dissatisfaction with treatment can lead to stress, depression and anxiety. Encouraging adherence to therapy and early screening and management of depression, anxiety and adjustment disorder could reduce health care costs associated with these mental health disorders, especially those related to hospitalizations as they accounted for 50% of the total cost in my study. In addition to finding that none of the patients in the trajectory switch to TNFi/UST had depression, anxiety and adjustment disorder-related health care costs, my study found that patients receiving TNFi/UST were indeed at lower risk of these mental health disorders by at least 50% when compared to previous CSA users who are currently not using any systemic treatment and tended to be at lower risk when compared to current CSA users, although the latter was not statistically significant. One would assume that patients receiving a TNFi/UST should be at higher risk of mental health outcomes because of provincial drug formulary restrictions by which patients tend to receive these agents as a last resort. However, my findings suggest otherwise, which is reassuring.

My findings support the importance of considering sex differences when prescribing a TNFi/UST for patients with psoriasis who previously received a CSA. Improving access to biologic agents for male patients who are obese and for those who have lived with psoriasis for a while and for female patients who experienced pain or mental health symptoms may save them the burden of going through a failed treatment experience and help improve their psoriasis outcomes faster, especially since biologic agents are known for being more effective than CSA. In addition, my

finding suggests that female patients without a history of depression and anxiety are more likely to have incident depression and anxiety-related health care costs when compared to male patients after having initiated a CSA. These findings are in line with previous studies reporting that the risk of having mental health disorder is increased among female patients with psoriasis because they are more affected by the disease in terms of self-esteem and QoL, and often have higher expectations than male patients when initiating a systemic agent.[3-6,24,25] Nonetheless, when the risk of incident depression, anxiety and adjustment disorder was compared between TNFi/UST and CSA users, no sex differences were noted, thus suggesting that the effect of biologic agents on these mental health outcomes is not sex specific.

My study is in line with previous RCT reporting improvement in anxio-depressive symptoms.[26-33] However, with the administrative data I used, I could not determine if it is directly related to reduced inflammation, since depression and psoriasis share inflammatory pathway[100] or if it is indirectly related to skin clearance, improved HRQoL, pain and fatigue.[26-33]

My study supports the consideration of adjustment disorder when assessing the risk of mental health outcomes among patients with psoriasis. Adjustment disorder is an emotional or a behavioral reaction to a stressful event.[111] Previous cross-sectional studies reported a high prevalence of adjustment disorder ranging from 13.3% to 62.5% among patients with psoriasis.[107-110] Patients can have adjustment disorder with depression symptoms, which, if not well managed, can lead to depressive disorders, anxiety disorders and even suicidality. Adjustment disorder remain under-researched and can be misdiagnosed as an anxiety or depressive disorder.[111] This is the case in three of the seven studies that examined the risk of mental health outcomes among patients receiving systemic agents. In these retrospective studies, ICD-9 codes for adjustment disorder such as 309.0 (adjustment disorder with depressed mood), 309.1 (prolonged depressive reaction) and 309.28 (adjustment disorder with mixed anxiety and depressed mood) were included with the diagnosis of depression.[35-37]

9.5 Future directions

The next stages would be for me to include a larger sample size of patients with moderate-to-severe psoriasis initiated on a CSA by conducting a national Canadian study using health

administrative data from all the Canadian provinces and by considering newer generation of biologic agents including IL-12 and IL-17 inhibitors. These studies should assess factors associated with switch to biologic agents and receiving a biologic agent as an add-on separately. A longitudinal prospective cohort study is optimal to also consider psoriasis severity measures, BMI, HRQoL, laboratory tests, measures of lifestyle habits such as smoking and alcohol consumption, and reasons for treatment discontinuation, switch, or add-on.

In terms of cost analysis, future studies should consider costs related to psychotherapy and the studies should be done from the societal perspective to also account for out-of-pocket costs and indirect costs such as short-term and long-term loss of productivity.

In addition, future studies should compare the risk of depression, anxiety, and adjustment disorder in all biologic agents to corroborate findings from RCT reporting that IL-12 and IL-17 inhibitors are more effective than TNFi/UST at improving depressive and anxiety symptoms and QoL.[142-150] Furthermore, to determine if biologic agents are directly associated with improvement in mental health outcomes or if they are indirectly related to improvement in QoL and skin clearance, mediation analyses should be conducted.[214] These studies will determine the additional risk of having depression, anxiety and adjustment disorder in patients who have versus those who have not improved QoL and/or skin clearance and will help understand if these clinical measures are full, partial or are not mediators in the association between biologic agents and mental health outcomes.

Lastly, there have been some concerns regarding the use of IL-17 inhibitors and increased risk of suicidality, especially with brodalumab (IL-17 receptor inhibitor).[142,215,216] During the RCT and their extensions, brodalumab was more effective than ustekinumab and placebo in achieving PASI-75.[145] However, four male patients in the brodalumab group died by suicide compared to 0 patients in the ustekinumab and placebo group, which lead to approval of this biologic for moderate-to-severe psoriasis with a black box warning for potential risk of suicidal behavior and ideation. [142,215,216] Pharmacovigilance reports and other RCT data also revealed several cases of suicidality with TNFi and IL inhibitors when used for psoriasis and other indications.[32] Nonetheless, a causal association cannot be inferred from these reports because of incomplete reporting and lack of

comparator group. Some even suggested that depression could be a mediator in this association, especially in the case of brodalumab because the RCT were pragmatic and did not exclude patients with a history of a mental health disorder, including the four patients who died by suicide.[117,215] However, this has not been clearly delineated and sex-differences have not been explored. A mediation analysis could be helpful in better understanding if depression is a full, partial, or not a mediator in the association between biologic agents and suicidality in male and female patients with moderate-to-severe psoriasis.

Chapter 10: Conclusion

This thesis provides an important contribution to the understanding on how patients with moderate-to-severe psoriasis are treated with systemic agents and who are the potential candidates for receiving a TNFi/UST. This thesis also highlights the importance of considering mental health outcomes when prescribing TNFi/UST. In this doctoral thesis, I examined patterns of systemic agent use and whether certain patterns are associated with incremental depression, anxiety and adjustment disorder-related health care costs, and I compared the risk of occurrence of these mental health disorders among patients with psoriasis receiving TNFi/UST vs those who did not receive these agents. Findings from this thesis suggest that although the rates of CSA discontinuation and switch/add TNFi/UST were similar between male and female patients, most of the factors associated with these outcomes were sex specific. In addition, patients discontinuing their initial CSA then restarting on acitretin, those with multiple switches between systemic agents and those receiving a TNFi/UST as an add-on had significantly higher depression, anxiety and adjustment-related health costs when compared to patients persistent to methotrexate. Sex differences were also noted with female patients incurring higher costs when compared to male patients. Finally, this thesis suggests that patients receiving TNFi/UST are at lower risk of depression, anxiety and adjustment disorder when compared to those receiving other treatment alternatives. Improving access to biologic agents among patients with psoriasis may save patients from the burden of going through a failed treatment experience and help improve psoriasis outcomes faster. Future studies should include a larger sample size and consider newer generations of biologic agents.

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Appendices

Appendix A. Certificate of ethical approval

Centre universitaire de santé McGill — McGill University Health Centre

2021-03-08

Dr. Elham Rahme
Epidemiology
email: elham.rahme@mcgill.ca

RE: Final REB Approval of a New Research Project
Treatment patterns and risks of major cardiovascular, cardio-metabolic and mental health adverse events and associated costs in individuals with psoriasis **(12-056 / 2020-6340)**

MUHC REB Co-Chair for the CTGQ panel: Me Marie Hirtle

Dear Dr. Rahme,

Thank you for submitting your responses and corrections for the research project indicated above, as requested by the McGill University Health Centre (MUHC) Research Ethics Board (REB).

The MUHC REB, more precisely its Cells, Tissues, Genetics & Qualitative (CTGQ) research panel provided conditional approval for the research project after a delegated review provided by its member(s).

On 2021-03-08, a delegated review of your responses and corrections was provided by member(s) of the MUHC REB. The research project was found to meet scientific and ethical standards for conduct at the MUHC.

The following documents were approved or acknowledged by the MUHC REB:

- Initial Submission Form (F11-53538)
- REB Conditions & PI Responses Form(s) (F20-55437, F20-56468, F20-57396)
- Research protocol
  - (Proposal_V7.docx) [Date: 2020-03-23, Version: 7]

This will be reported to the MUHC REB and will be entered accordingly into the minutes of the next CTGQ meeting. Please be advised that you may only initiate the study after all required reviews and decisions are received and documented and you have received the MUHC authorization letter.

The approval of the research project is valid until 2022-03-08.

All research involving human subjects requires review at recurring intervals. To comply with the regulation for continuing review of at least once per year, it is the responsibility of the investigator to submit an *Annual Renewal Submission Form* (F9) to the REB prior to expiry. Please be advised that should be protocol reach its expiry before a Continuing review has been submitted, the data collected after the expiry date may not be considered valid. However, should the research conclude for any reason prior to approval expiry, you are required to submit

a *Completion (End of Study) Report* (F10) to the board once the data analysis is complete to give an account of the study findings and publication status.

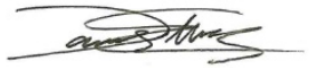
Furthermore, should any revision to the project or other development occur prior to the next continuing review, you must advise the REB without delay. Regulation does not permit initiation of a proposed study modification prior to its approval by the REB.

The MUHC REB is registered and works under the published guidelines of the *Tri-Council Policy Statement 2*, in compliance with the *Plan d'action ministériel en éthique de la recherche et en intégrité scientifique* (MSSS, 1998) and the *Food and Drugs Act* (2001.06.07), acting in conformity with standards set forth in the (US) *Code of Federal Regulations* governing human subjects research and functioning in a manner consistent with internationally accepted principles of good clinical practice.

We wish to advise you that the MUHC REB "working procedures" completely satisfies the requirements for Research Ethics Board Attestation (REBA) as stipulated by Health Canada. Neuro and MUHC research that is subject to US Federal Wide Assurance is conducted under FWA00000840.

We trust this will prove satisfactory to you. Thank you for your consideration in this matter.

Best Regards,



James Ellasus
MUHC REB Coordinator
for MUHC Co-chair mentioned above

Centre universitaire de santé McGill | McGill University Health Centre

Annual renewal submission form - Harmonized

Titre du protocole : **Treatment patterns and risks of major cardiovascular, cardio-metabolic and mental health adverse events and associated costs in individuals with psoriasis**

Project number(s): **2020-6340**
Form: **F9H-89768**
Nagano identifier: **12-056**
First submit date: **2022-01-20**
Principal investigator: **Elham Rahme**
Last submit date: **2022-02-10**
Project's REB approbation date: **2021-03-08**
Form status: **Form approved**

Administration - REB

1. **MUHC REB Panel & Co-chair(s):**
   Cells, tissues, genetics & qualitative research (CTGQ)
   Co-chair: Marie Hirtle
   reb.ctgq@muhc.mcgill.ca

2. **REB Decision:**
   Approved - REB delegated review

3. **Renewal Period Granted:**
   From 2022-03-09 to 2023-03-08.

4. **Date of the REB final decision & signature**
   2022-02-14
   Signature

James Ellasus
MUHC REB Coordinator
for MUHC Co-chair mentioned above
2022-02-14 11:28

General information

Appendix B. DENCOM and DIN codes for prescription drug fills and code act for phototherapy sessions in RAMQ pharmaceutical and medical databases

	DENCOM or code act*	DIN
Topical agents	39042 00780 33530 00949 46588 46585 37768 02548 46664 38405 03978 46471 46494 03991 04550 17758 46420 04563 33413 46390 39055 45581 09737 43722 47043 47039 46350 40589 46367 39003 46470 00663 46740 14118 19310 38171 42175 45469 43332 43839 39107 46811	Except**: 00374407 00422053 00828548 00872318 00872326 00872334 00893633 00897353 00899135 01923935 01950002 02172712 02213710 02213729 02215055 02216531 02228300 02238796 02242029 02242030 99000393 02162504 00862371 00030910 00030929 00230316 00900761 02112736 00332151 00404411 00436275 00579335 00607789 00607797 00704458 00906689 01980661 02128446 02179547 02209764 02210517 02236399 02240112 02242798 02247691 02387239 99100959 99100960 02243595 02243596 01913328 01964054 01977563 01999761 01999788 01999869 02213834 02219271 02229540 02229550 99100592 00481815 00481823 00824291 00891738 00891746 02145839
Phototherapy*	00820 20061	
Methotrexate	47651 00338 00351 46301	
Cyclosporine	44060 46329 46375	Except**: 02355655 99100387 00593257
Acitretin	47101 46237	
Apremilast	48031	
Sulfasalazine	45420	Except**: 02064499 00613568
Adalimumab	47522	
Etanercept	47438 46711	
Infliximab	47416 48034 46739	
Certolizumab pegol	47796 47968	
Golimumab	47798	
Ustekinumab	47757	
Alefacept	47529	
Efalizumab	47581	
Abatacept	47618	
Anakinra	46829	
Rituximab	47370	
Tocilizumab	47841	
Antidepressants	00429 00442 46836 43696 14781 02522 03198 04784 37443 06578 46835 08294 09906 46543 47317 47553 47971 45504 45633 47061 46164 45630 47714 48075 46435 47285 46744 47408 46235 47093 43137 46244 47118 47770 42058 46427 47005 7280 9698	
Benzodiazepine	37872 43501 46440 37950 43488 06786 01807 14768 46161 02717 42045 41590 39029 04095 46818	

Antipsychotics	45580 46318 47197 47567 46413 47052 46156 47278 01820 01924 01950 14768 03250 41863 43202 34284 04069 04056 38236 04394 46292 43826 43540 46296 37612 40745 34219 05746 07150 07176 46011 33465 41707 08047 08164 46187 47047 46320 09555 09568 09594 09620 10400 098020 3440 47136 47137 47138	
Opiods	02119 17641 38184 38496 46013 46098 46168 46172 46368 46372 46871 47155 48207 03809 33855 46478 47038 04615 17771 46790 05603 46412 45373 46707 06305 19063 43527 06838 44541 06838 06799 46651 47846 47908 46036 46037 46344 38847 44528 44515 06708 46038 47835 47725 34375 46045 46255 46323 46503 47860	
Hypoglycemic agents	00091 01937 04264 04823 04888 05824 09672 15184 18296 18309 18322 18335 18348 39120 39133 39146 39159 39172 39185 39458 39484 39497 39523 41655 43033 43735 44151 44164 44476 44489 44502 44996 45405 45415 45483 45511 45531 45534 46056 46300 46322 46536 46537 46538 46568 46592 46602 46603 46607 46642 46678 46798 46799 46810 46862 47004 47151 47206 47208 47329 47357 47371 47392 47424 47426 47427 47536 47586 47615 47652 47749 47807 47832 47836 47867 47964 47965 48013 48017 48039 48044 48062 48085 48117 47715 47817 47881 48018	
Antihypertensive agents	00806 01846 01976 03562 04173 04381 04524 04537 06110 06136 07800 08229 08671 09100 09763 10751 19440 37742 38158 38197 38275 38314 39016 40550 40563 41759 41772 42071 42162 42708 43228 43397 43670 44814 44866 45243 45408 45440 45463 45476 45520 45532 45571 45572 45576 45624 45625 45629 46157 46216 46258 46284 46315 46319 46325 46388 46418 46441 46459 46469 46529 46572 46573 46587 46760 46763 46780 46786 47002 47006 47021 47040 47049 47056 47079 47117 47135 47199 47207 47247 47250 47259 47282 47301 47309 47320 47333 47354 47355 47369 47389 47412 47413 47439 47440 47449 47532 47534 47655 47686 47732 47751 47763 47764 47609 47889	
Lipid-lowering agents	45500 45564 45570 46240 46355 46425 46584 46860 47083 47169 47232 47272 47595 47604 47609 02067 44879 44905 45574 46575 47092 47366 47373 47596 47754 06487 19089 46079 46147	
Antiplatelets	00143 46353 38132 38184 46036 46094 46098 46128 46172 46198 46232 46344 46368 47365 47595 47751 46077 46372 46486 47307 47834 47866 45617 47189 47348 47337 03094	
Anti-coagulants	00013 04407 10205 10218 18179 45497 45538 46095 46268 46415 46436 46604 47026 47098 47125 47163 47264 47279 47443 47653 47756 47802 47944	
NSAIDS	47327 47346 47385 07462 60851 04810 40381 37664 47078 41694 47059 47122 46256 46006 47066 46150 47107 43150 44749 42019 46638 45592 04745 46654 19752 46152 46335 46626 38691 33803 45407 45514 46347 47506 47570 44359 46546 46596 46858 47631 47084 46228 46679 44437 47890	
Oral corticosteroids		00021695 00156876 00232378 00252417 00271373 00312770 00550957 00607517 00610623 00016438 00016446 00280437 00285471 00295094

	00354309 00489158 01946897 01964070 01964968 01964976 02237046 02240684 02240687 02250055 02261081 02279363 02311267 02086026 00030910 00030929 00030988 00036129 00021679 02152541 02230619 02245532 02194090 02229293

*Code act only for phototherapy because it is not a pharmacologic treatment. Phototherapy sessions were retrieved from RAMQ medical database
**Not in a format recommended for psoriasis
DENCOM: Common denominator; DIN: Drug Identification Number

Appendix C. ICD-9/10 codes for all physical and psychiatric comorbidities considered in the studies

		ICD-9	ICD-10
Psoriasis		696.1	L40.x
Psoriatic arthritis		696.0	M07.x
Rheumatoid arthritis		714.x	M05.x, M06.x, M08.x, M09.x
Ankylosing spondylitis		720.x	M45.x
Inflammatory bowel diseases		555.x, 556.x	K50.x, K51.x
Melanoma cancer		172.x	C43.x
Non melanoma cancer (other malignant neoplasms of skin)		173.x	C44.x
Any malignancy except melanoma and other malignant neoplasms of skin		140.x-171.x, 174.x-195.8, 196.x-208.x, 238.6	C00.x–C26.x, C30.x–C34.x, C37.x– C41.x, C45.x–C58.x, C60.x–C85.x, C88.x, C90.x–C97.x
Obesity		278.0	E66.x
Renal diseases		403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0–583.7, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x	I12.0, I13.1, N03.2–N03.7, N05.2– N05.7, N18.x, N19.x, N25.0, Z49.0– Z49.2, Z94.0, Z99.2
Liver diseases		070.44, 070.54, 070.6, 070.9, 456.0–456.2, 570.x, 571.x, 572.2–572.8, 573.3, 573.4, 573.8, 573.9, V42.7	B18.x (except B18.0 and B18.1), I85.x, I86.4, I98.2, K70.x, K71.1, K71.3– K71.5, K71.7, K72.x– K74.x, K76.0, K76.2– K76.9, Z94.4
Cardiovascular diseases (Myocardial infarction and angina)		410.x, 412.x, 413.x, 411.1	I20.x, I21.x, I22.x, I25.2
Cerebrovascular diseases		362.3, 430.x, 431.x, 432.x, 433.x, 434.x, 435.x	I60.x-I65.x, H34.x, G45.x
Vascular diseases	**Atherosclerosis**	440.x	I70.x
	Systemic arterial embolism	444.x	I74.x
	Venous thromboembolism (DVT and VE)	415.x, 451.x, 452.x, 453.x	I26.x, I80.x, I81.x, I82.x
	Peripheral vascular disease	093.0, 437.3, 441.x, 443.1–443.9, 447.1, 557.1, 557.9	I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9
	Pulmonary circulation disorders	416.x, 417.0, 417.8, 417.9 (or 417.x)	I26.x, I27.x, I28.0, I28.8, I28.9 (or I28.x)
Congestive heart failure		398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4–425.9, 428.x	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43.x, I50.x, P29.0
Cardiac arrhythmias	**Atrial fibrillation**	427.3	I48.x
	Other cardiac arrhythmias	426.0, 426.13, 426.7, 426.9, 426.10, 426.12, 427.0–427.2, 427.4, 427.6–427.9, 785.0, 996.01, 996.04, V45.0, V53.3	I44.1–I44.3, I45.6, I45.9, I47.x, I49.x, R00.0, R00.1, R00.8, T82.1, Z45.0, Z95.0
chronic pulmonary diseases	**COPD**	490.x–492.x, 496.x	J40.x–J44.x
	Other chronic pulmonary diseases	416.8, 416.9, 493.x–495.x, 497.x–505.x, 506.4, 508.1, 508.8	I27.8, I27.9, J45.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3

Tuberculosis	010.x–0.18.x, 137.x	A15.x–A.18.x, B.90.x, J65.x
HIV/AIDS	042.x–044.x	B20.x–B22.x, B24.x
Hepatitis B	070.2, 070.3	B16.x, B18.0, B18.1
Bipolar disorder	296.x (except 296.2 and 296.3)	F30.x, F31.x
Schizophrenia and psychotic disorders	295.x, 297.x, 298.x (except 298.0)	F20.x (except F20.4), F22–F25.x, F28.x, F29.x
Depression	296.2, 296.3, 298.0, 300.4, 311.x	F32.x, F33.x, F20.4, F34.1, F41.2
Anxiety	300.0, 300.2	F40.x, F41.x (except for F41.2)
Adjustment disorder	308.x, 309.x	F43.x
Somatoform	306.x, 300.7, 300.8, 300.11	F45.x, F44.4, F44.5, F44.6, F48.0
Personality disorder	301.x	F34.0, F60.x, F61.x
Drug/substance abuse	292.x, 304.x, 305.x (except 305.0, 305.1), 648.3, V654.2	F11.x, F12.X, F13.X, F14.X, F15.X, F16.X, F18.x, F19.x, Z71.5, Z72.2, O993.2
Alcoholism	980.x, 291.x (except 291.0, 291.4), 265.2, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, V11.3	F10.x, E52.x, T51.x, G621, I42.6, K70.x, K70.9, K29.2, Z50.2, Z71.4, Z72.1
Other mental, behavioural, and neurodevelopmental disorders	All other ICD-9 codes (290.x-319.x)	All other ICD-10 codes (F00.x-F99x)

ICD-9/10: International classification of diseases ninth and tenth editions

Appendix D. Electronic supplement materials for manuscript 1

Supplementary eTable S1. Sensitivity analysis – Predictors of switch to a TNFi/UST or add-on and CSA discontinuation among males and females with psoriasis – Patients < 65 years (N=907)

Supplementary eTable S2. Sensitivity analysis – Predictors of switch to a TNFi/UST or add-on and CSA discontinuation among males and females with psoriasis –Patients ≥ 65 years (N=737)

Supplementary eTable S3. Sensitivity analysis – Predictors of switch to a TNFi/UST or add-on and CSA discontinuation among males and females with psoriasis – Patients entering the cohort between January 01, 2002 until December 31, 2010 (N=904)

Supplementary eTable S4. Sensitivity analysis – Predictors of switch to a TNFi/UST or add-on and CSA discontinuation among males and females with psoriasis – Patients entering the cohort between January 01, 2011 until December 31, 2015 (N=740)

Supplementary eTable S5. Sensitivity analysis – Predictors of switch to a TNFi/UST or add-on and CSA discontinuation among males and females with psoriasis – Patients without psoriatic arthritis at baseline (N=1,402)

Supplementary eTable S6. Sensitivity analysis – Predictors of switch to a TNFi/UST or add-on and CSA discontinuation among males and females with psoriasis – Patients receiving their initial CSA from a dermatologist, rheumatologist, internal medicine specialist or a general practitioner (N=1,607)

Supplementary eTable S7. Sensitivity analysis – Predictors of switch to a TNFi/UST or add-on and CSA discontinuation among males and females with psoriasis – Without excluding patients with congestive heart failure (N=1,755)

Supplementary eTable S8. Sensitivity analysis – Predictors of switch to a TNFi/UST or add-on and CSA discontinuation among males and females with psoriasis – Grace period of 30 days (N=1,644)

Supplementary eTable S9. Sensitivity analysis – Predictors of switch to a TNFi/UST or add-on and CSA discontinuation among males and females with psoriasis – Grace period of 90 days (N=1,644)

Supplementary eTable S10. Sensitivity analysis – Predictors of switch to a biologic agent and CSA discontinuation among males and females with psoriasis – Without considering sulfasalazine as a CSA (N=1,610)

Supplementary eFigure S1: Study flowchart

Supplementary eFigure S2: Kaplan Meier estimates of switch to (a) TNFi/UST or add-on; and (b) CSA discontinuation

Supplementary eTable S1. Sensitivity analysis – Predictors of switch to a TNFi/UST or add-on and CSA discontinuation among males and females with psoriasis – Patients < 65 years (N=907)

	Switch a TNFi/UST or add-on		CSA discontinuation	
	Females (N=496)	Males (N=411)	Females (N=496)	Males (N=411)
Number of events	46	47	249	249
	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Cohort entry after 2011	1.53 [0.79, 2.95]	1.30 [0.69, 2.46]	0.85 [0.66, 1.08]	0.56 [0.42, 0.74]
Age				
20-54 years	Ref	Ref	–	–
55-64 years	0.79 [0.44, 1.44]	0.27 [0.12, 0.57]		
Time to first CSA prescription				
0–2.99 months	Ref	Ref	–	–
3-12 months	0.52 [0.21, 1.30]	0.83 [0.24, 2.89]		
>12 months	0.81 [0.41, 1.61]	2.09 [0.91, 4.80]		
Specialty of the CSA prescriber				
Dermatologist	–	–	Ref	Ref
Rheumatologist			0.83 [0.55, 1.25]	0.58 [0.35, 0.97]
Other specialists			0.85 [0.60, 1.19]	0.77 [0.52, 1.14]
First CSA received				
Methotrexate	–	–	Ref	Ref
Cyclosporine			1.79 [0.97, 3.29]	1.05 [0.59, 1.86]
Acitretin			2.13 [1.61, 2.82]	1.75 [1.31, 2.34]
Sulfasalazine			1.47 [0.81, 2.65]	0.77 [0.33, 1.81]
Prior hospitalization	–	–	1.11 [0.86, 1.43]	0.68 [0.49, 0.93]
Rheumatoid arthritis	0.39 [0.15, 1.04]	1.49 [0.63, 3.53]	0.78 [0.52, 1.18]	0.41 [0.20, 0.82]
Obesity	1.36 [0.46, 4.02]	5.89 [1.90, 18.27]	–	–
Mental health disorders				
No mental health disorder	Ref	Ref	–	–
Anxiety and mood disorders	1.02 [0.51, 2.02]	1.54 [0.80, 2.97]		
Dissociative, somatoform and adjustment disorders	3.88 [1.40, 10.72]	NA[a]		
Other mental health disorders	1.06 [0.14, 8.15]	2.02 [0.79, 5.12]		
Prior use of Hypoglycemic agents	–	–	0.72 [0.49, 1.07]	0.81 [0.51, 1.30]
Prior use of lipid-lowering agents	–	–	0.68 [0.51, 0.92]	0.84 [0.60, 1.16]
Prior use of NSAIDS	3.53 [1.75, 7.09]	1.05 [0.54, 2.04]	–	–

[a]In male patients, only 4 patients had dissociative, somatoform and adjustment disorders; therefore, they were combined with had also anxiety and mood disorders

List of abbreviations: aHR: Adjusted hazard ratios; CI: confidence interval; NSAIDS: nonsteroidal anti-inflammatory drugs

Supplementary eTable S2. Sensitivity analysis – Predictors of switch to a TNFi/UST or add-on and CSA discontinuation among males and females with psoriasis –Patients ≥ 65 years (N=737)

	Switch a TNFi/UST or add-on		CSA discontinuation	
	Females (N=420)	Males (N=317)	Females (N=420)	Males (N=317)
Number of events	18	10	242	193
	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Cohort entry after 2011	2.96 [1.01, 8.70]	1.08 [0.24, 4.86]	0.69 [0.53, 0.90]	0.86 [0.63, 1.17]
Age				
65-70 years	Ref	Ref	–	–
≥75 years	0.24 [0.05, 1.08]	0.48 [0.10, 2.30]		
Time to first CSA prescription				
0–2.99 months	Ref	Ref	–	–
3-12 months	0.67 [0.15, 3.08]	1.30 [0.08, 21.34]		
>12 months	1.08 [0.32, 3.60]	4.04 [0.49, 33.03]		
Specialty of the CSA prescriber				
Dermatologist	–	–	Ref	Ref
Rheumatologist			0.66 [0.42, 1.05]	0.67 [0.39, 1.12]
Other specialists			0.94 [0.64, 1.37]	0.84 [0.54, 1.31]
First CSA received				
Methotrexate	–	–	Ref	Ref
Cyclosporine			4.69 [1.86, 11.79]	1.04 [0.25, 4.30]
Acitretin			2.01 [1.50, 2.70]	1.44 [1.02, 2.04]
Sulfasalazine			1.82 [0.93, 3.56]	2.17 [1.17, 4.02]
Prior hospitalization	–	–	0.87 [0.66, 1.14]	0.76 [0.56, 1.04]
Rheumatoid arthritis	0.50 [0.13, 1.87]	0.93 [0.18, 4.89]	0.60 [0.39, 0.93]	1.24 [0.77, 1.97]
Obesity	NA	NA	–	–
Mental health disorders				
No mental health disorder	Ref	Ref	–	–
Anxiety and mood disorders	1.72 [0.52, 5.63]	1.24 [0.25, 6.20]		
Dissociative, somatoform and adjustment disorders	1.71 [0.20, 14.47]	NA[a]		
Other mental health disorders	1.76 [0.21, 14.48]	NA		
Prior use of Hypoglycemic agents	–	–	0.80 [0.55, 1.16]	1.14 [0.78, 1.68]
Prior use of lipid-lowering agents	–	–	0.75 [0.57, 0.98]	0.83 [0.61, 1.13]
Prior use of NSAIDS	0.92 [0.24, 3.51]	0.92 [0.24, 3.51]	–	–

[a]In male patients, only 3 patients had dissociative, somatoform and adjustment disorders; therefore, they were combined with had also anxiety and mood disorders

List of abbreviations: aHR: Adjusted hazard ratios; CI: confidence interval; NSAIDS: nonsteroidal anti-inflammatory drugs

Supplementary eTable S3. Sensitivity analysis – Predictors of switch to a TNFi/UST or add-on and CSA discontinuation among males and females with psoriasis – Patients entering the cohort between January 01, 2002 until December 31, 2010 (N=904)

	Switch a TNFi/UST or add-on		CSA discontinuation	
	Females (N=495)	Males (N=409)	Females (N=495)	Males (N=409)
Number of events	34	35	352	291
	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Age				
20-54 years	Ref	Ref	–	–
55-64 years	0.83 [0.37, 1.84]	0.20 [0.07, 0.55]		
65-74 years	0.33 [0.10, 1.07]	0.19 [0.07, 0.52]		
≥75 years	0.28 [0.06, 1.30]	0.17 [0.04, 0.74]		
Time to first CSA prescription				
0–2.99 months	Ref	Ref	–	–
3-12 months	0.57 [0.21, 1.59]	0.85 [0.15, 4.71]		
>12 months	0.8 [0.35, 1.84]	3.84 [1.30, 11.35]		
Specialty of the CSA prescriber				
Dermatologist	–	–	Ref	Ref
Rheumatologist			0.71 [0.5, 0.90]	0.65 [0.43, 1.00]
Other specialists			0.88 [0.65, 1.20]	0.70 [0.49, 1.01]
First CSA received				
Methotrexate	–	–	Ref	Ref
Cyclosporine			3.87 [2.01, 7.47]	0.87 [0.46, 1.62]
Acitretin			1.97 [1.53, 2.54]	1.60 [1.21, 2.10]
Sulfasalazine			1.34 [0.79, 2.29]	1.17 [0.64, 2.14]
Prior hospitalization	–	–	1.00 [0.79, 1.26]	0.67 [0.51, 0.88]
Rheumatoid arthritis	0.25 [0.07, 0.88]	1.18 [0.48, 2.92]	0.71 [0.50, 1.01]	0.82 [0.55, 1.22]
Obesity	0.98 [0.21, 4.50]	9.23 [1.88, 45.26]	–	–
Mental health disorders				
No mental health disorder	Ref	Ref	–	–
Anxiety and mood disorders	1.30 [0.60, 2.83]	1.28 [0.58, 2.84]		
Dissociative, somatoform and adjustment disorders	12.25 [3.38, 44.36]	NA[a]		
Other mental health disorders	1.47 [0.19, 11.66]	1.64 [0.47, 5.67]		
Prior use of Hypoglycemic agents	–	–	0.66 [0.47, 0.93]	0.91 [0.61, 1.36]
Prior use of lipid-lowering agents	–	–	0.76 [0.59, 0.96]	0.93 [0.71, 1.21]
Prior use of NSAIDS	3.29 [0.79, 7.82]	0.88 [0.42, 1.87]	–	–

[a]In male patients, only 5 patients had dissociative, somatoform and adjustment disorders; therefore, they were combined with had also anxiety and mood disorders

List of abbreviations: aHR: Adjusted hazard ratios; CI: confidence interval; NSAIDS: nonsteroidal anti-inflammatory drugs

Supplementary eTable S4. Sensitivity analysis – Predictors of switch to a TNFi/UST or add-on and CSA discontinuation among males and females with psoriasis – Patients entering the cohort between January 01, 2011 until December 31, 2015 (N=740)

	Switch a TNFi/UST or add-on		CSA discontinuation	
	Females (N=421)	Males (N=319)	Females (N=421)	Males (N=319)
Number of events	30	22	199	151
	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Age				
20-54 years	Ref	Ref	–	–
55-64 years	0.93 [0.36, 2.39]	0.39 [0.12, 1.25]		
65-74 years	0.98 [0.41, 2.32]	0.22 [0.06, 0.78]		
≥75 years	NA	NA		
Time to first CSA prescription				
0–2.99 months	Ref	Ref	–	–
3-12 months	0.50 [0.15, 1.69]	1.06 [0.23, 4.97]		
>12 months	0.81 [0.34, 1.91]	1.62 [0.52, 5.08]		
Specialty of the CSA prescriber				
Dermatologist	–	–	Ref	Ref
Rheumatologist			0.89 [0.49, 1.62]	0.63 [0.32, 1.24]
Other specialists			0.90 [0.58, 1.40]	1.08 [0.68, 1.72]
First CSA received				
Methotrexate	–	–	Ref	Ref
Cyclosporine			1.32 [0.60, 2.89]	1.79 [0.71, 4.54]
Acitretin			2.17 [1.56, 3.03]	1.64 [1.13, 2.39]
Sulfasalazine			2.40 [1.08, 5.35]	1.66 [0.73, 3.79]
Prior hospitalization	–	–	0.93 [0.69, 1.26]	0.78 [0.55, 1.06]
Rheumatoid arthritis	0.68 [0.25, 1.85]	1.78 [0.44, 7.27]	0.60 [0.34, 1.09]	1.09 [0.50, 2.36]
Obesity	1.03 [0.23, 4.67]	2.08 [0.44, 9.77]	–	–
Mental health disorders				
No mental health disorder	Ref	Ref	–	–
Anxiety and mood disorders	0.93 [0.36, 2.43]	2.04 [0.76, 5.47]		
Dissociative, somatoform and adjustment disorders	1.13 [0.26, 5.01]	NA[a]		
Other mental health disorders	1.43 [0.18, 11.57]	1.55 [0.39, 6.15]		
Prior use of Hypoglycemic agents	–	–	0.95 [0.61, 1.48]	1.05 [0.68, 1.64]
Prior use of lipid-lowering agents	–	–	0.65 [0.46, 0.92]	0.85 [0.59, 1.23]
Prior use of NSAIDS	2.20 [1.03, 4.73]	1.24 [0.47, 3.25]	–	–

[a]In male patients, only 2 patients had dissociative, somatoform and adjustment disorders; therefore, they were combined with had also anxiety and mood disorders

List of abbreviations: aHR: Adjusted hazard ratios; CI: confidence interval; NSAIDS: nonsteroidal anti-inflammatory drugs

Supplementary eTable S5. Sensitivity analysis – Predictors of switch to a TNFi/UST or add-on and CSA discontinuation among males and females with psoriasis – Patients without psoriatic arthritis at baseline (N=1,402)

	Switch a TNFi/UST or add-on		CSA discontinuation	
	Females (N=787)	Males (N=615)	Females (N=787)	Males (N=615)
Number of events	47	41	493	391
	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Cohort entry after 2011	2.29 [1.21, 4.32]	1.32 [0.64, 2.69]	0.75 [0.62, 0.91]	0.72 [0.58, 0.90]
Age				
20-54 years	Ref	Ref	–	–
55-64 years	0.63 [0.32, 1.26]	0.30 [0.13, 0.68]		
65-74 years	0.57 [0.27, 1.20]	0.14 [0.05, 0.41]		
≥75 years	NA	0.14 [0.03, 0.61]		
Time to first CSA prescription				
0–2.99 months	Ref	Ref	–	–
3-12 months	0.24 [0.08, 0.73]	1.27 [0.38, 4.30]		
>12 months	0.81 [0.42, 1.56]	2.10 [0.85, 5.18]		
Specialty of the CSA prescriber				
Dermatologist	–	–	Ref	Ref
Rheumatologist			0.79 [0.56, 1.13]	0.77 [0.50, 1.20]
Other specialists			0.96 [0.73, 1.24]	0.86 [0.64, 1.16]
First CSA received				
Methotrexate	–	–	Ref	Ref
Cyclosporine			2.31 [1.39, 3.83]	1.20 [0.71, 2.02]
Acitretin			2.10 [1.71, 2.59]	1.57 [1.25, 1.98]
Sulfasalazine			1.31 [0.78, 2.21]	1.65 [0.95, 2.85]
Prior hospitalization	–	–	1.03 [0.85, 1.26]	0.65 [0.51, 0.81]
Rheumatoid arthritis	0.64 [0.27, 1.51]	1.23 [0.52, 2.93]	0.64 [0.46, 0.90]	0.68 [0.45, 1.02]
Obesity	1.61 [0.54, 4.79]	3.76 [0.85, 16.62]	–	–
Mental health disorders				
No mental health disorder	Ref	Ref	–	–
Anxiety and mood disorders	1.02 [0.50, 2.07]	1.71 [0.84, 3.49]		
Dissociative, somatoform and adjustment disorders	4.23 [1.51, 11.80]	NA[a]		
Other mental health disorders	2.03 [0.47, 8.74]	1.75 [0.64, 4.80]		
Prior use of Hypoglycemic agents	–	–	0.71 [0.53, 0.95]	0.90 [0.66, 1.23]
Prior use of lipid-lowering agents	–	–	0.75 [0.61, 0.92]	0.94 [0.75, 1.18]
Prior use of NSAIDS	2.93 [1.55, 5.53]	1.23 [0.61, 2.49]	–	–

[a]In male patients, only 7 patients had dissociative, somatoform and adjustment disorders; therefore, they were combined with had also anxiety and mood disorders

List of abbreviations: aHR: Adjusted hazard ratios; CI: confidence interval; NSAIDS: nonsteroidal anti-inflammatory drugs

Supplementary eTable S6. Sensitivity analysis – Predictors of switch to a TNFi/UST or add-on and CSA discontinuation among males and females with psoriasis – Patients receiving their initial CSA from a dermatologist, rheumatologist, internal medicine specialist or a general practitioner (N=1,607)

	Switch a TNFi/UST or add-on		CSA discontinuation	
	Females (N=898)	Males (N=709)	Females (N=898)	Males (N=709)
Number of events	63	55	538	432
	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Cohort entry after 2011	1.82 [1.05, 3.14]	1.44 [0.80, 2.60]	0.79 [0.66, 0.95]	0.70 [0.57, 0.86]
Age				
20-54 years	Ref	Ref	–	–
55-64 years	0.75 [0.42, 1.37]	0.26 [0.12, 0.57]		
65-74 years	0.59 [0.31, 1.12]	0.21 [0.09, 0.45]		
≥75 years	0.16 [0.04, 0.69]	0.09 [0.02, 0.39]		
Time to first CSA prescription				
0–2.99 months	Ref	Ref	–	–
3-12 months	0.51 [0.23, 1.11]	0.85 [0.28, 2.63]		
>12 months	0.80 [0.44, 1.45]	2.21 [1.03, 4.75]		
Specialty of the CSA prescriber				
Dermatologist	–	–	Ref	Ref
Rheumatologist			0.74 [0.54, 1.01]	0.67 [0.46, 0.96]
Other specialists			0.83 [0.64, 1.08]	0.86 [0.64, 1.16]
First CSA received				
Methotrexate	–	–	Ref	Ref
Cyclosporine			1.88 [1.08, 3.26]	1.11 [0.64, 1.93]
Acitretin			2.05 [1.67, 2.50]	1.65 [1.32, 2.07]
Sulfasalazine			1.70 [1.08, 2.67]	1.37 [0.82, 2.30]
Prior hospitalization	–	–	0.98 [0.81, 1.18]	0.71 [0.57, 0.88]
Rheumatoid arthritis	0.42 [0.19, 0.90]	1.31 [0.61, 2.83]	0.67 [0.49, 0.91]	0.84 [0.58, 1.20]
Obesity	1.13 [0.39, 3.25]	2.62 [0.77, 8.85]	–	–
Mental health disorders				
No mental health disorder	Ref	Ref	–	–
Anxiety and mood disorders	1.00 [0.55, 1.83]	1.55 [0.83, 2.87]		
Dissociative, somatoform and adjustment disorders	3.09 [1.25, 7.64]	NA[a]		
Other mental health disorders	1.56 [0.37, 6.56]	1.88 [0.78, 4.55]		
Prior use of Hypoglycemic agents	–	–	0.75 [0.57, 0.98]	0.94 [0.70, 1.27]
Prior use of lipid-lowering agents	–	–	0.72 [0.59, 0.88]	0.92 [0.74, 1.13]
Prior use of NSAIDS	2.61 [1.50, 4.54]	1.02 [0.57, 1.84]	–	–

[a]In male patients, only 7 patients had dissociative, somatoform and adjustment disorders; therefore, they were combined with had also anxiety and mood disorders

List of abbreviations: aHR: Adjusted hazard ratios; CI: confidence interval; NSAIDS: nonsteroidal anti-inflammatory drugs

Supplementary eTable S7. Sensitivity analysis – Predictors of switch to a TNFi/UST or add-on and CSA discontinuation among males and females with psoriasis – Without excluding patients with congestive heart failure (N=1,755)

	Switch a TNFi/UST or add-on		CSA discontinuation	
	Females (N=973)	Males (N=782)	Females (N=973)	Males (N=782)
Number of events	66	62	595	487
	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Cohort entry after 2011	1.80 [1.05, 3.07]	1.42 [0.81, 2.49]	0.82 [0.69, 0.97]	0.74 [0.61, 0.90]
Age				
20-54 years	Ref	Ref	–	–
55-64 years	0.79 [0.44, 1.42]	0.30 [0.15, 0.59]		
65-74 years	0.65 [0.35, 1.20]	0.22 [0.11, 0.47]		
≥75 years	0.14 [0.03, 0.60]	0.13 [0.04, 0.42]		
Time to first CSA prescription				
0–2.99 months	Ref	Ref	–	–
3-12 months	0.50 [0.24, 1.07]	0.65 [0.22, 1.92]		
>12 months	0.75 [0.42, 1.34]	1.96 [0.98, 3.92]		
Specialty of the CSA prescriber				
Dermatologist	–	–	Ref	Ref
Rheumatologist			0.77 [0.58, 1.03]	0.71 [0.51, 0.99]
Other specialists			0.90 [0.71, 1.14]	0.82 [0.62, 1.07]
First CSA received				
Methotrexate	–	–	Ref	Ref
Cyclosporine			2.05 [1.24, 3.39]	1.15 [0.72, 1.84]
Acitretin			2.08 [1.71, 2.52]	1.65 [1.33, 2.04]
Sulfasalazine			1.65 [1.09, 2.49]	1.28 [0.82, 2.00]
Prior hospitalization	–	–	0.99 [0.83, 1.17]	0.73 [0.60, 0.89]
Rheumatoid arthritis	0.46 [0.22, 0.95]	1.25 [0.60, 2.58]	0.72 [0.54, 0.94]	0.84 [0.61, 1.18]
Obesity	1.29 [0.50, 3.35]	2.30 [0.89, 5.93]	–	–
Mental health disorders				
No mental health disorder	Ref	Ref	–	–
Anxiety and mood disorders	0.98 [0.54, 1.78]	1.30 [0.72, 2.34]		
Dissociative, somatoform and adjustment disorders	3.17 [1.28, 7.83]	NA[a]		
Other mental health disorders	1.42 [0.34, 5.98]	1.41 [0.59, 3.39]		
Prior use of Hypoglycemic agents	–	–	0.80 [0.63, 1.02]	0.98 [0.75, 1.27]
Prior use of lipid-lowering agents	–	–	0.74 [0.62, 0.90]	0.90 [0.74, 1.10]
Prior use of NSAIDS	2.71 [1.58, 4.67]	1.11 [0.64, 1.92]	–	–

[a]In male patients, only 8 patients had dissociative, somatoform and adjustment disorders; therefore, they were combined with had also anxiety and mood disorders

List of abbreviations: aHR: Adjusted hazard ratios; CI: confidence interval; NSAIDS: nonsteroidal anti-inflammatory drugs

Supplementary eTable S8. Sensitivity analysis – Predictors of switch to a TNFi/UST or add-on and CSA discontinuation among males and females with psoriasis – Grace period of 30 days (N=1,644)

	Switch a TNFi/UST or add-on		CSA discontinuation	
	Females (N=916)	**Males (N=728)**	**Females (N=916)**	**Males (N=728)**
Number of events	59	40	607	496
	aHR (95% CI)	**aHR (95% CI)**	**aHR (95% CI)**	**aHR (95% CI)**
Age	1.87 [1.07, 3.29]	1.09 [0.54, 2.20]	0.79 [0.66, 0.93]	0.82 [0.68, 0.99]
20-54 years	Ref	Ref	–	–
55-64 years	0.67 [0.36, 1.25]	0.25 [0.10, 0.63]		
65-74 years	0.61 [0.32, 1.16]	0.17 [0.07, 0.46]		
≥75 years	0.08 [0.01, 0.60]	0.13 [0.03, 0.56]		
Time to first CSA prescription				
0–2.99 months	Ref	Ref	–	–
3-12 months	0.44 [0.19, 1.02]	0.50 [0.13, 1.91]		
>12 months	0.78 [0.42, 1.42]	1.38 [0.61, 3.08]		
Specialty of the CSA prescriber				
Dermatologist	–	–	Ref	Ref
Rheumatologist			0.71 [0.53, 0.95]	0.61 [0.43, 0.85]
Other specialists			0.79 [0.62, 1.00]	0.73 [0.56, 0.96]
First CSA received				
Methotrexate	–	–	Ref	Ref
Cyclosporine			2.23 [1.40, 3.56]	0.85 [0.51, 1.43]
Acitretin			1.99 [1.65, 2.42]	1.47 [1.19, 1.80]
Sulfasalazine			1.53 [1.01, 2.34]	1.27 [0.80, 2.03]
Prior hospitalization	–	–	0.98 [0.82, 1.17]	0.76 [0.62, 0.93]
Rheumatoid arthritis	0.43 [0.20, 0.93]	1.48 [0.63, 3.48]	0.73 [0.56, 0.97]	0.93 [0.67, 1.30]
Obesity	1.09 [0.37, 3.18]	4.85 [1.60, 14.70]	–	–
Mental health disorders				
No mental health disorder	Ref	Ref	–	–
Anxiety and mood disorders	1.20 [0.65, 2.22]	1.28 [0.59, 2.77]		
Dissociative, somatoform and adjustment disorders	3.32 [1.33, 8.30]	NA		
Other mental health disorders	2.35 [0.54, 10.32]	1.93 [0.71, 5.23]		
Prior use of Hypoglycemic agents	–	–	0.81 [0.63, 1.03]	0.91 [0.70, 1.20]
Prior use of lipid-lowering agents	–	–	0.71 [0.59, 0.86]	0.90 [0.74, 1.10]
Prior use of NSAIDS	2.65 [1.47, 4.75]	1.29 [0.64, 2.57]	–	–

[a]In male patients, only 7 patients had dissociative, somatoform and adjustment disorders; therefore, they were combined with had also anxiety and mood disorders

List of abbreviations: aHR: Adjusted hazard ratios; CI: confidence interval; NSAIDS: nonsteroidal anti-inflammatory drugs

Supplementary eTable S9. Sensitivity analysis – Predictors of switch to a TNFi/UST or add-on and CSA discontinuation among males and females with psoriasis – Grace period of 90 days (N=1,644)

	Switch a TNFi/UST or add-on		CSA discontinuation	
	Females (N=916)	**Males (N=728)**	**Females (N=916)**	**Males (N=728)**
Number of events	69	63	507	403
	aHR (95% CI)	**aHR (95% CI)**	**aHR (95% CI)**	**aHR (95% CI)**
Age	1.86 [1.11, 3.13]	1.24 [0.71, 2.15]	0.75 [0.62, 0.90]	0.67 [0.54, 0.83]
20-54 years	Ref	Ref	–	–
55-64 years	0.78 [0.45, 1.37]	0.32 [0.16, 0.64]		
65-74 years	0.54 [0.29, 1.00]	0.20 [0.10, 0.42]		
≥75 years	0.15 [0.03, 0.63]	0.09 [0.02, 0.38]		
Time to first CSA prescription				
0–2.99 months	Ref	Ref	–	–
3-12 months	0.47 [0.22, 1.02]	1.04 [0.39, 2.74]		
>12 months	0.85 [0.49, 1.49]	2.02 [1.01, 4.05]		
Specialty of the CSA prescriber				
Dermatologist	–	–	Ref	Ref
Rheumatologist			0.71 [0.52, 0.98]	0.61 [0.42, 0.90]
Other specialists			0.85 [0.65, 1.10]	0.80 [0.59, 1.08]
First CSA received				
Methotrexate	–	–	Ref	Ref
Cyclosporine			2.17 [1.29, 3.65]	1.14 [0.67, 1.94]
Acitretin			1.93 [1.57, 2.38]	1.62 [1.29, 2.04]
Sulfasalazine			1.56 [0.98, 2.48]	1.28 [0.76, 2.16]
Prior hospitalization	–	–	1.04 [0.86, 1.27]	0.73 [0.58, 0.92]
Rheumatoid arthritis	0.44 [0.21, 0.91]	1.25 [0.60, 2.60]	0.70 [0.51, 0.95]	0.95 [0.66, 1.36]
Obesity	1.27 [0.49, 3.27]	3.64 [1.25, 10.54]	–	–
Mental health disorders				
No mental health disorder	Ref	Ref	–	–
Anxiety and mood disorders	1.06 [0.61, 1.85]	1.40 [0.78, 2.52]		
Dissociative, somatoform and adjustment disorders	3.05 [1.25, 7.48]	NA[a]		
Other mental health disorders	1.51 [0.36, 6.34]	1.77 [0.78, 4.02]		
Prior use of Hypoglycemic agents	–	–	0.77 [0.58, 1.02]	0.92 [0.67, 1.25]
Prior use of lipid-lowering agents	–	–	0.69 [0.56, 0.85]	0.89 [0.72, 1.12]
Prior use of NSAIDS	2.71 [1.60, 4.60]	1.06 [0.61, 1.84]	–	–

[a]In male patients, only 7 patients had dissociative, somatoform and adjustment disorders; therefore, they were combined with had also anxiety and mood disorders

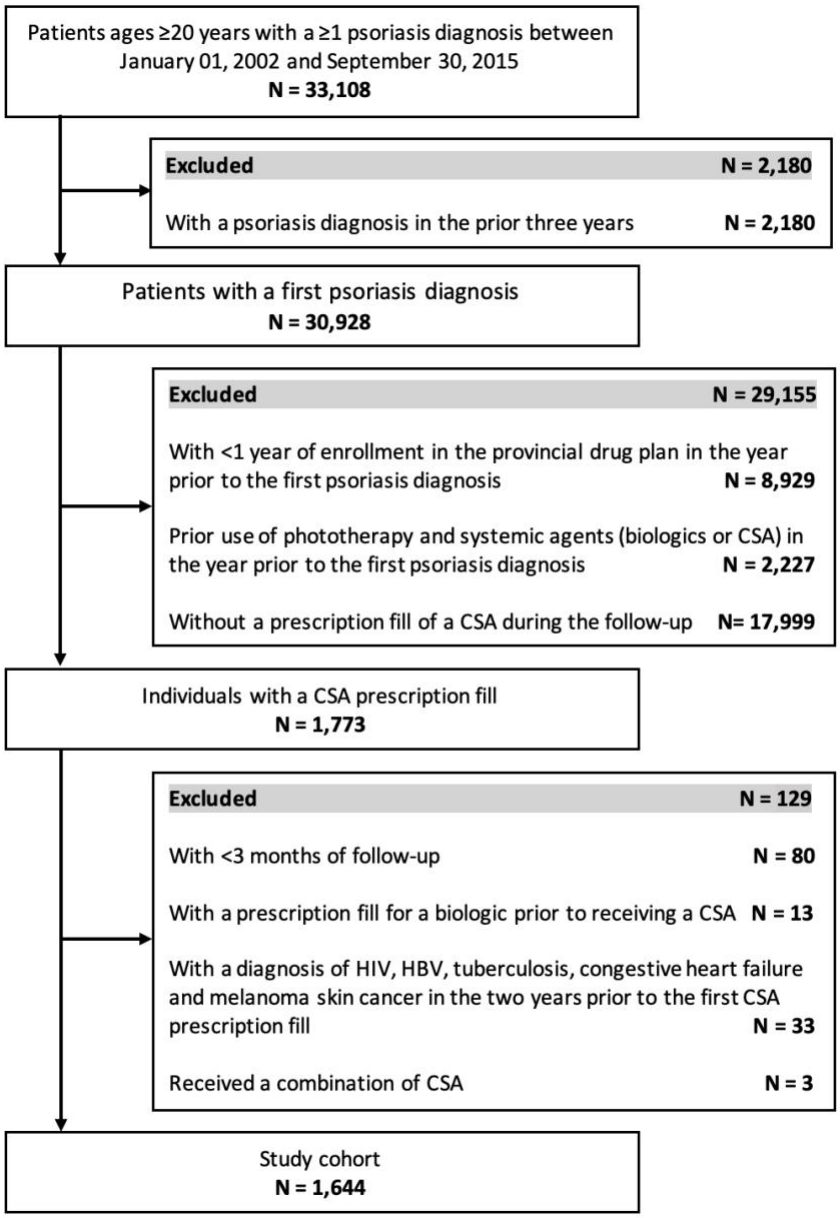
List of abbreviations: aHR: Adjusted hazard ratios; CI: confidence interval; NSAIDS: nonsteroidal anti-inflammatory drugs

Supplementary eTable S10. Sensitivity analysis – Predictors of switch to a biologic agent and CSA discontinuation among males and females with psoriasis – Without considering sulfasalazine as a CSA (N=1,610)

	Switch a TNFi/UST or add-on		CSA discontinuation	
	Females (N=901)	Males (N=709)	Females (N=901)	Males (N=709)
Number of events	59	56	544	434
	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Cohort entry after 2011	1.91 [1.08, 3.38]	1.16 [0.65, 2.08]	0.77 [0.64, 0.92]	0.70 [0.57, 0.86]
Age				
20-54 years	Ref	Ref	–	–
55-64 years	0.81 [0.44, 1.48]	0.29 [0.13, 0.61]		
65-74 years	0.58 [0.30, 1.12]	0.21 [0.09, 0.45]		
≥75 years	0.08 [0.01, 0.61]	0.09 [0.02, 0.39]		
Time to first CSA prescription				
0–2.99 months	Ref	Ref	–	–
3-12 months	0.43 [0.19, 0.97]	1.95 [0.67, 5.68]		
>12 months	0.72 [0.39, 1.31]	2.80 [1.18, 6.67]		
Specialty of the CSA prescriber				
Dermatologist	–	–	Ref	Ref
Rheumatologist			0.77 [0.57, 1.05]	0.63 [0.44, 0.90]
Other specialists			0.96 [0.75, 1.23]	0.88 [0.66, 1.17]
First CSA received				
Methotrexate	–	–	Ref	Ref
Cyclosporine			2.09 [1.26, 3.45]	0.98 [0.58, 1.64]
Acitretin			2.03 [1.66, 2.47]	1.60 [1.29, 1.99]
Prior hospitalization	–	–	0.96 [0.80, 1.16]	0.71 [0.58, 0.89]
Rheumatoid arthritis	0.54 [0.26, 1.13]	1.62 [0.79, 3.34]	0.65 [0.48, 0.89]	0.85 [0.59, 1.22]
Obesity	0.80 [0.24, 2.65]	3.23 [1.11, 9.39]	–	–
Mental health disorders				
No mental health disorder	Ref	Ref	–	–
Anxiety and mood disorders	1.16 [0.63, 2.14]	1.46 [0.80, 2.67]		
Dissociative, somatoform and adjustment disorders	3.48 [1.39, 8.69]	NA[a]		
Other mental health disorders	1.68 [0.40, 7.13]	1.56 [0.64, 3.81]		
Prior use of Hypoglycemic agents	–	–	0.74 [0.57, 0.97]	1.06 [0.79, 1.41]
Prior use of lipid-lowering agents	–	–	0.70 [0.58, 0.86]	0.82 [0.66, 1.02]
Prior use of NSAIDS	2.61 [1.47, 4.61]	1.06 [0.58, 1.90]	–	–

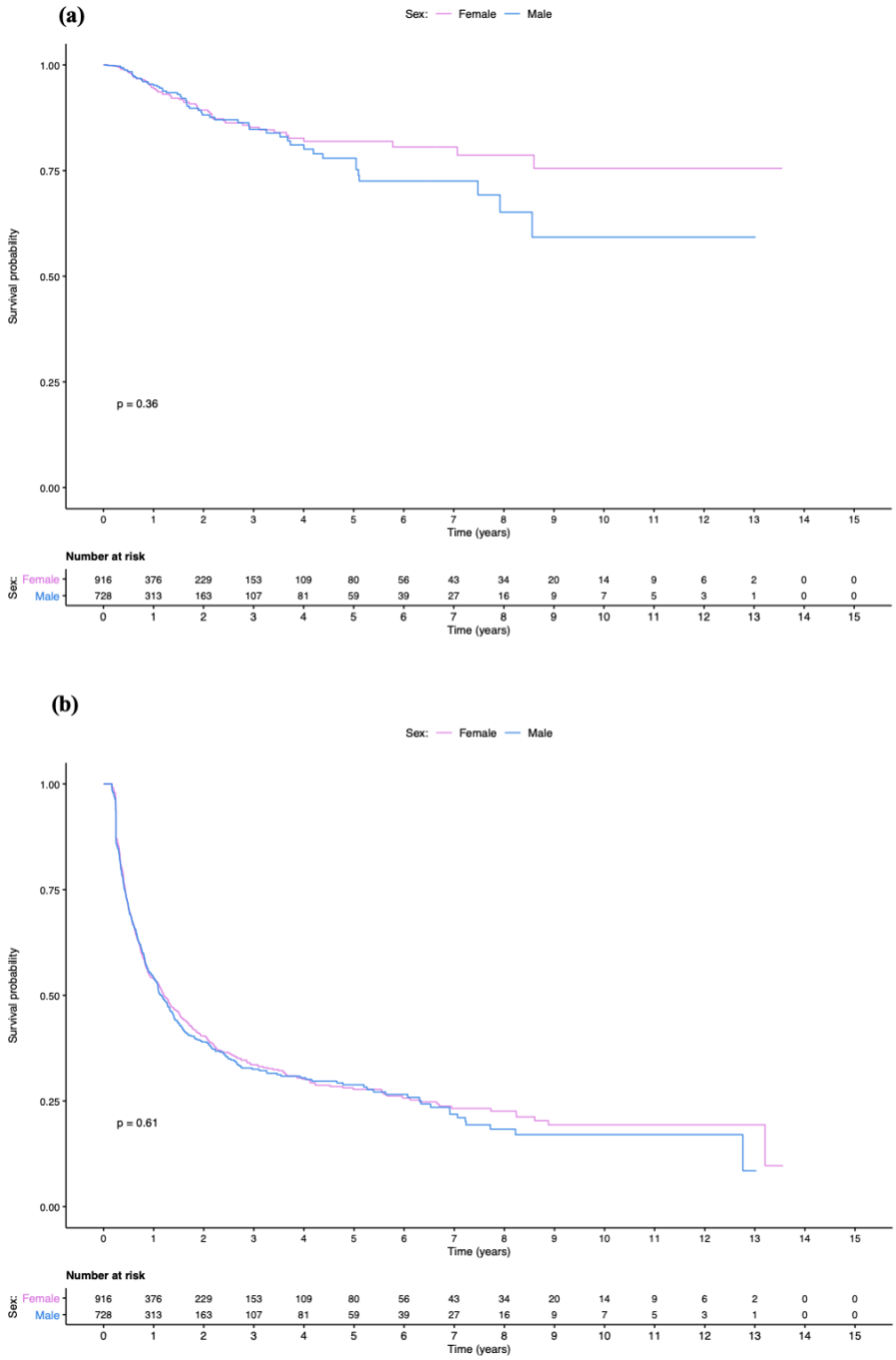
[a]In male patients, only 6 patients had dissociative, somatoform and adjustment disorders; therefore, they were combined with had also anxiety and mood disorders

List of abbreviations: aHR: Adjusted hazard ratios; CI: confidence interval; NSAIDS: nonsteroidal anti-inflammatory drugs



List of abbreviations: CSA: conventional systemic agent; HBV: Hepatitis B virus, HIV: Human immunodeficiency virus

Supplementary eFigure S1. Study flowchart



List of abbreviations: CSA: Conventional systemic agents; TNFi/UST: Tumor necrosis factor inhibitors and ustekinumab

Supplementary eFigure S2. Kaplan Meier estimates of switch to (a) TNFi/UST or add-on; and (b) CSA discontinuation

Appendix E. Electronic supplement materials for manuscript 3

Supplement material 1. Depression and anxiety-related healthcare costs

Supplementary eTable S1. International classification of diseases (ICD) 9th and 10th edition

Supplementary eTable S2. Sensitivity analysis with 5 exposure groups

Supplementary eTable S3. Sensitivity analysis excluding the costs of depression- and anxiety-related hospitalizations and ED visits

Supplementary eFigure S1. Study flowchart

Supplementary eFigure S2. Determining the optimal number of clusters

Supplement material 1. Depression and anxiety-related healthcare costs

Cost of antidepressants and benzodiazepines were available from RAMQ pharmaceutical database and considered RAMQ reimbursement and pharmacist fees. The costs of physician visits for depression and anxiety representing the reimbursement costs for physician fee-for-service claims with a depression diagnosis, were available from the RAMQ medical database. The costs of ED and inpatients visits with depression as a primary or secondary diagnosis were computed as follows: the sum of the physician claims during a certain hospitalization or ED visit plus the product of the *Niveau d'intensité relative des ressources utilisées* (NIRRU) associated with that visit times the unit cost per NIRRU (physician claims + NIRRU*unit cost per NIRRU). Physician claims were retrieved from RAMQ medical database. NIRRU and unit cost per NIRRU were provided by the "All Patient Refined Diagnosis-Related Group" database of the Ministry of health and social services of Quebec. NIRRUs are weights representing the relative intensity level of resources used. The unit cost per NIRRU represents the average provincial cost of an admission for a physical condition. If a hospitalization had a missing NIRRU value, the cost was computed by multiplying the length of stay of that hospitalization with the average daily cost of $636 and $923 for depression and anxiety respectively.[1]

Supplementary eTable S1. International classification of diseases (ICD) 9th and 10th edition

	ICD-9	ICD-10
Psoriasis	696.1	L40.x
Depression	296.2, 296.3, 298.0, 300.4, 311.x	F20.4, F32.x, F33.x, F34.1, F41.2
Anxiety	300.0, 300.2	F40.x, F41.x (excluding F41.2)

Supplementary eTable S2. Sensitivity analysis with 5 exposure groups

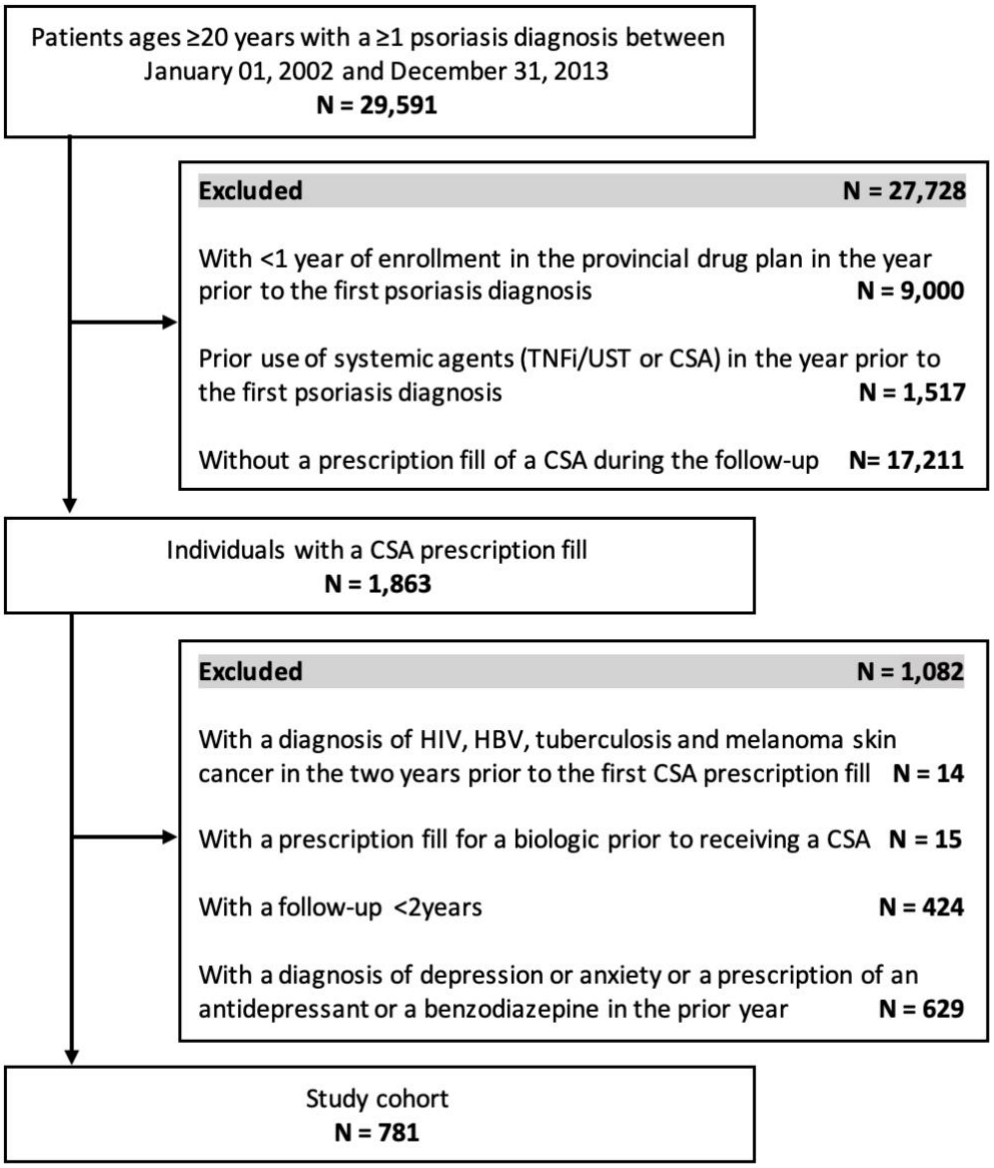
Clusters	Predicted mean costs 95% bias corrected bootstrap CI)	Cost ratio (95% bias corrected bootstrap CI)
Overall (N=781)	56 (50, 65)	
Six Clusters		
Persistent CST users (N=269)	52 (42, 67)	Reference
Early discontinuation of CST (N=312)	47 (39, 60)	0.92 (0.67, 1.26)
Late discontinuation of methotrexate (N=124)	46 (37, 60)	0.90 (0.62, 1.21)
Switch to TNFi/UST (N=20)	–	–
Adding TNFI/UST (N=11)	114 (67, 200)	2.24 (1.07, 3.64)
CST discontinuation then re-start on CST (N=45)	165 (132, 239)	3.23 (2.16, 4.48)

Abbreviations: CI: Confidence interval; CST: conventional systemic therapies; TNFi/UST: Tumor necrosis factor inhibitors and ustekinumab

Supplementary eTable S3. Sensitivity analysis excluding the costs of depression- and anxiety-related hospitalizations and ED visits

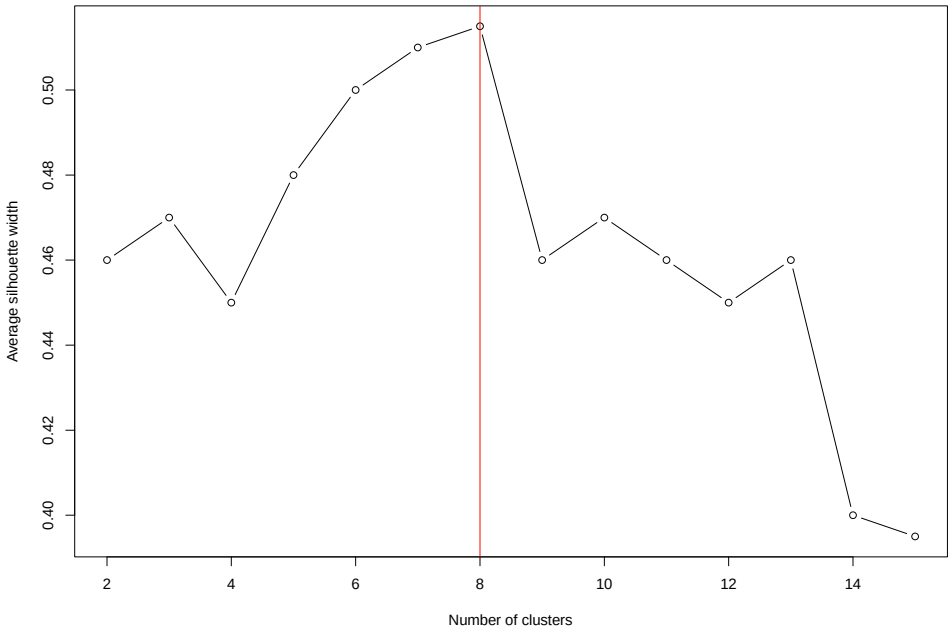
Clusters	Predicted mean costs 95% bias corrected bootstrap CI)	Cost ratio (95% bias corrected bootstrap CI)
Overall (N=781)	21 (19, 22)	
Clusters		
Persistent methotrexate users (N=202)	15 (13, 16)	reference
Persistent acitretin users (N=81)	17 (15, 20)	1.18 (0.97, 1.42)
Early discontinuation of CST (N=286)	21 (19, 23)	1.43 (1.24, 1.65)
Late discontinuation of methotrexate (N=128)	19 (17, 23)	1.34 (1.11, 1.61)
Switch to TNFi/UST (N=19)	–	–
Adding TNFI/UST (N=11)	84 (55, 119)	5.80 (3.62, 8.20)
CST discontinuation then re-start on methotrexate (N=30)	17 (13, 22)	1.14 (0.83, 1.50)
CST discontinuation then re-start on acitretin or multiple switches between systemic agents (N=24)	60 (47, 85)	4.17 (3.03, 5.67)

Abbreviations: CI: Confidence interval; CST: conventional systemic therapies; ED: Emergency department; TNFi/UST: Tumor necrosis factor inhibitors and ustekinumab

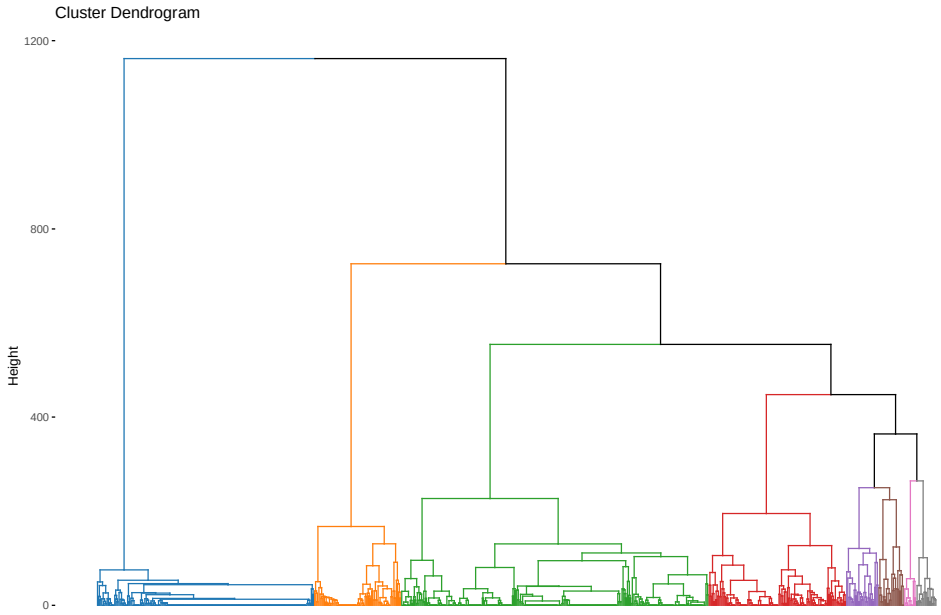


Supplementary eFigure S1. Study flowchart

a)



b)



Supplementary eFigure S2. Determining the optimal number of clusters

Figure 2, a: The average silhouette width (ASW) can vary from -1 to 1 and a high ASW-value implies that clusters are homogeneous and well separated from each other. In our study the highest ASW values was for 8 clusters with a value of 0.515.

Figure 2, b: The dendrogram divided into 8 clusters

Cluster 1: Persistent methotrexate users

Cluster 2: Persistent acitretin users

Cluster 3: Early discontinuation of CST

Cluster 4: Late discontinuation of methotrexate

Cluster 5: Switch to TNFi/UST

Cluster 6: Adding TNFi/UST

Cluster 7: CST discontinuation then restart on methotrexate

Cluster 8: CST discontinuation then restart on acitretin or multiple witches between systemic agents

Abbreviations: CST: conventional systemic therapies; TNFi/UST: Tumor necrosis factor inhibitors and ustekinumab

Supplementary references

1. Canadian Institute for Health Information (CIHI). Patient Cost Estimator – Across Canada. Accessed August 5, 2020, https://apps.cihi.ca/mstrapp/asp/Main.aspx

Appendix F. Electronic supplement materials for manuscript 4

Supplementary eTable 1. ICD-9 and ICD-10 codes for depression, anxiety and adjustment disorders

Supplementary eTable 2. Sensitivity analyses with latency periods of 0, 180 and 365 days

Supplementary eTable 3. Sensitivity analysis with a treatment gap of 60 days

Supplementary eTable 4. Sensitivity analysis with a restrictive definition for psoriasis: Patients with ≥1 outpatient diagnosis for psoriasis by a dermatologist, ≥2 outpatient visits by other specialists, an ED visit or a hospitalisation with psoriasis as a main or secondary diagnosis

Supplementary eTable 5. Sensitivity analysis excluding patients with any mental health disorders and those with a prescription fill for an anti-psychotic

Supplementary eTable 6. Sensitivity analysis excluding patients with depression, anxiety, somatoform and adjustment disorders in the prior year

Supplementary eTable 7. Sensitivity analysis: The requirement of having the first CSA prescription fill within a 12-month period in the prescription time-distribution matching was changed to a 6-month period

Supplementary eTable 8. Sensitivity analysis without including certolizumab pegol and golimumab

Supplementary eTable 9. Sensitivity analysis without including acitretin

Supplementary eTable 10. Sensitivity analysis in which the cox regression models were adjusted for all potential confounders

Supplementary eTable 11. Sensitivity analysis without propensity score trimming

Supplementary eFigure 1. Cohort construction

Supplementary eFigure 2. Example of a prescription-time distribution matching

Supplementary eFigure 3. Propensity score trimming

Supplementary eTable 1. ICD-9 and ICD-10 codes for depression, anxiety and adjustment disorders

	ICD-9	ICD-10
Depression	296.2, 296.3, 298.0, 300.4, 311.x	F32.x, F33.x, F20.4, F34.1, F41.2
Anxiety	300.0, 300.2	F40.x, F41.x (except for F41.2)
Adjustment disorder	308.x, 309.x	F43.x

ICD 9/10: International classifications of diseases 9th and 10th revisions

Supplementary eTable 2. Sensitivity analyses with latency periods of 0, 180 and 365 days

	Number of events	Person-year	IR* (95% CI)	Marginal HR (95% CI)	Marginal HR (95% CI)
0 days					
Previous CSA users (N=601)	100	1515	65.8 (53.6-80.1)	Ref	1.39 (1.01-1.93)
Current CSA users (N=897)	85	1203	70.6 (56.4-87.3)	0.71 (0.52-0.99)	Ref
Current TNFi/UST users (N=198)	21	502	41.8 (25.9-63.9)	0.65 (0.35-1.19)	0.90 (0.49-1.66)
180 days					
Previous CSA users (N=437)	63	1164	54.1 (41.6-69.2)	Ref	1.39 (0.88-2.21)
Current CSA users (N=481)	44	819	53.7 (39.0-72.1)	0.72 (0.45-1.14)	Ref
Current TNFi/UST users (N=168)	14	401	34.9 (19.1-58.5)	0.53 (0.26-1.11)	0.75 (0.36-1.55)
365 days					
Previous CSA users (N=333)	52	956	54.4 (40.6-71.3)	Ref	1.63 (0.92-2.90)
Current CSA users (N=328)	23	684	33.6 (21.3-50.4)	0.61 (0.34-1.09)	Ref
Current TNFi/UST users (N=123)	8	305	26.1 (11.3-51.5)	0.36 (0.13-1.00)	0.58 (0.20-1.74)

*Per 1,000 person-year
CI: confidence intervals; CSA: conventional systemic agents; HR: hazard ratios; IR: incidence rates; TNFi/UST: tumor necrosis factor inhibitors and ustekinumab

Supplementary eTable 3. Sensitivity analysis with a treatment gap of 60 days

	Number of events	Person-year	IR* (95% CI)	Marginal HR (95% CI)	Marginal HR (95% CI)
Previous CSA users (N=579)	88	1522	57.8 (46.3-71.2)	Ref	1.05 (0.72-1.55)
Current CSA users (N=607)	56	900	62.3 (47.0-80.8)	0.95 (0.65-1.39)	Ref
Current TNFi/UST users (N=179)	14	380	36.8 (20.1-61.8)	0.56 (0.27-1.17)	0.59 (0.28-1.27)

*Per 1,000 person-year
CI: confidence intervals; CSA: conventional systemic agents; HR: hazard ratios; IR: incidence rates; TNFi/UST: tumor necrosis factor inhibitors and ustekinumab

Supplementary eTable 4. Sensitivity analysis with a restrictive definition for psoriasis: Patients with ≥1 outpatient diagnosis for psoriasis by a dermatologist, ≥2 outpatient visits by other specialists, an ED visit or a hospitalisation with psoriasis as a main or secondary diagnosis

	Number of events	Person-year	IR* (95% CI)	Marginal HR (95% CI)	Marginal HR (95% CI)
Previous CSA users (N=503)	83	1336	62.0 (49.4-77.0)	Ref	0.97 (0.65-1.46)
Current CSA users (N=597)	57	886	64.3 (48.7-83.4)	1.03 (0.68-1.55)	Ref
Current TNFi/UST users (N=174)	12	429	27.9 (14.5-48.8)	0.42 (0.20-0.88)	0.41 (0.18-0.87)

*Per 1,000 person-year
CI: confidence intervals; CSA: conventional systemic agents; HR: hazard ratios; IR: incidence rates; TNFi/UST: tumor necrosis factor inhibitors and ustekinumab

Supplementary eTable 5. Sensitivity analysis excluding patients with any mental health disorders and those with a prescription fill for an anti-psychotic

	Number of events	Person-year	IR* (95% CI)	Marginal HR (95% CI)	Marginal HR (95% CI)
Previous CSA users (N=518)	86	1309	65.7 (52.5-81.5)	Ref	1.41 (0.96-2.06)
Current CSA users (N=609)	54	1022	52.8 (39.6-68.9)	0.71 (0.48-1.04)	Ref
Current TNFi/UST users (N=178)	14	422	33.1 (18.1-55.6)	0.45 (0.22-0.92)	0.63 (0.30-1.33)

*Per 1,000 person-year
CI: confidence intervals; CSA: conventional systemic agents; HR: hazard ratios; IR: incidence rates; TNFi/UST: tumor necrosis factor inhibitors and ustekinumab

Supplementary eTable 6. Sensitivity analysis excluding patients with depression, anxiety, somatoform and adjustment disorders in the prior year

	Number of events	Person-year	IR* (95% CI)	Marginal HR (95% CI)	Marginal HR (95% CI)
Previous CSA users (N=515)	72	1309	55.0 (43.0-69.3)	Ref	0.89 (0.60-1.31)
Current CSA users (N=589)	62	972	63.7 (48.9-81.7)	1.12 (0.76-1.65)	Ref
Current TNFi/UST users (N=179)	14	426	32.8 (17.9-55.0)	0.52 (0.26-1.09)	0.48 (0.23-0.99)

*Per 1,000 person-year
CI: confidence intervals; CSA: conventional systemic agents; HR: hazard ratios; IR: incidence rates; TNFi/UST: tumor necrosis factor inhibitors and ustekinumab

Supplementary eTable 7. Sensitivity analysis: The requirement of having the first CSA prescription fill within a 12-month period in the prescription time-distribution matching was changed to a 6-month period

	Number of events	Person-year	IR* (95% CI)	Marginal HR (95% CI)	Marginal HR (95% CI)
Previous CSA users (N=523)	72	1353	53.2 (41.6-67.0)	Ref	0.98 (0.65-1.47)
Current CSA users (N=608)	60	964	62.2 (47.8-80.1)	1.02 (0.68-1.54)	Ref
Current TNFi/UST users (N=173)	14	409	34.2 (18.7-57.3)	0.48 (0.24-0.97)	0.47 (0.23-0.96)

*Per 1,000 person-year
CI: confidence intervals; CSA: conventional systemic agents; HR: hazard ratios; IR: incidence rates; TNFi/UST: tumor necrosis factor inhibitors and ustekinumab

Supplementary eTable 8. Sensitivity analysis without including certolizumab pegol and golimumab

	Number of events	Person-year	IR* (95% CI)	Marginal HR (95% CI)	Marginal HR (95% CI)
Previous CSA users (N=537)	84	1336	62.8 (50.1-77.8)	Ref	1.21 (0.83-1.75)
Current CSA users (N=657)	62	1060	58.4 (44.8-75.0)	0.83 (0.57-1.20)	Ref
Current TNFi/UST users (N=176)	14	410	34.1 (18.6-57.2)	0.49 (0.25-0.95)	0.72 (0.35-1.48)

*Per 1,000 person-year
CI: confidence intervals; CSA: conventional systemic agents; HR: hazard ratios; IR: incidence rates; TNFi/UST: tumor necrosis factor inhibitors and ustekinumab

Supplementary eTable 9. Sensitivity analysis without including acitretin

	Number of events	Person-year	IR* (95% CI)	Marginal HR (95% CI)	Marginal HR (95% CI)
Previous CSA users (N=259)	34	743	45.7 (31.7-63.9)	Ref	1.17 (0.72-1.90)
Current CSA users (N=463)	38	819	46.4 (32.8-63.7)	0.85 (0.53-1.38)	Ref
Current TNFi/UST users (N=88)	8	224	35.7 (15.4-70.4)	0.74 (0.23-2.33)	0.86 (0.27-2.75)

*Per 1,000 person-year
CI: confidence intervals; CSA: conventional systemic agents; HR: hazard ratios; IR: incidence rates; TNFi/UST: tumor necrosis factor inhibitors and ustekinumab

Supplementary eTable 10. Sensitivity analysis in which the cox regression models were adjusted for all potential confounders

	Number of events	Person-year	IR* (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)
Previous CSA users (N=525)	86	1359	63.3 (50.6-78.1)	Ref	1.11 (0.78-1.59)
Current CSA users (N=625)	59	1060	55.6 (42.3-71.8)	0.90 (0.63-1.29)	Ref
Current TNFi/UST users (N=183)	15	447	33.5 (18.8-55.3)	0.51 (0.29-0.91)	0.57 (0.31-1.02)

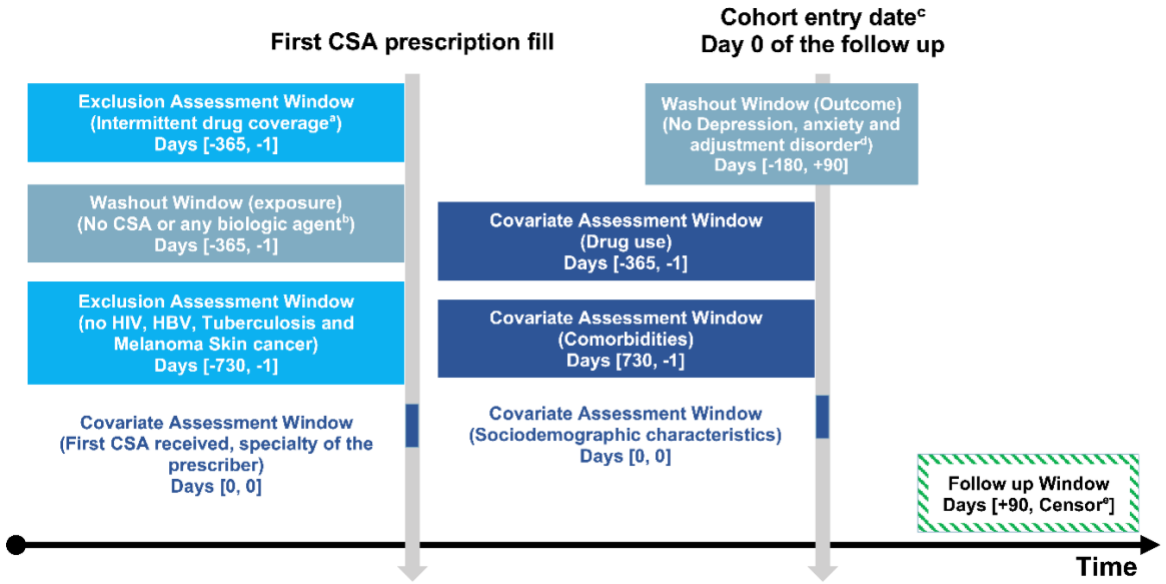
*Per 1,000 person-year
CI: confidence intervals; CSA: conventional systemic agents; HR: hazard ratios; IR: incidence rates; TNFi/UST: tumor necrosis factor inhibitors and ustekinumab

Supplementary eTable 11. Sensitivity analysis without propensity score trimming

	Number of events	Person-year	IR* (95% CI)	Marginal HR (95% CI)	Marginal HR (95% CI)
Previous CSA users (N=575)	93	1484	62.7 (50.6-76.8)	Ref	1.06 (0.73-1.53)
Current CSA users (N=709)	71	1181	60.1 (46.9-75.8)	0.95 (0.65-1.37)	Ref
Current TNFi/UST users (N=199)	16	484	33.1 (18.9-53.7)	0.50 (0.26-0.95)	0.52 (0.27-1.03)

*Per 1,000 person-year
CI: confidence intervals; CSA: conventional systemic agents; HR: hazard ratios; IR: incidence rates; TNFi/UST: tumor necrosis factor inhibitors and ustekinumab

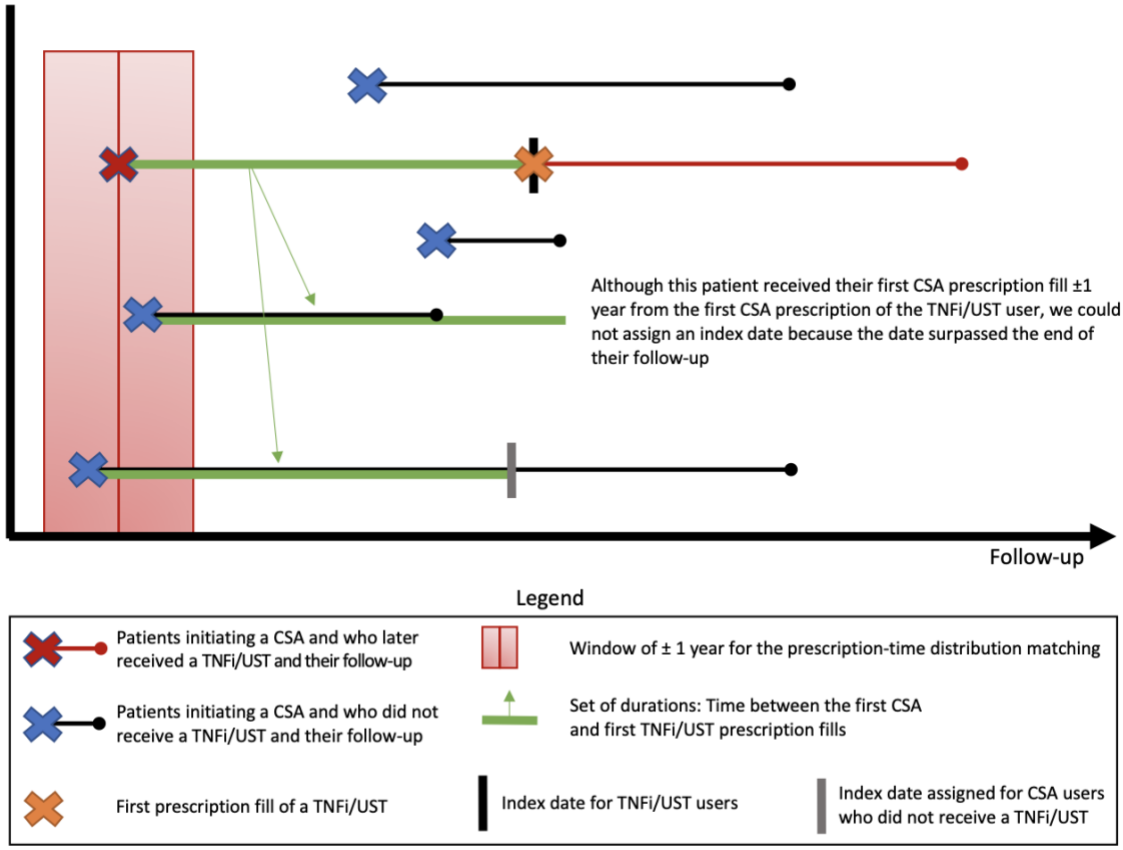
Supplementary eFigure 1. Cohort construction



[a]Gap of ≥90 days in the drug coverage
[b]Biologic agents indicated for psoriasis and other immune-mediated conditions
[c]Cohort entry date or index date: Index date for TNFi/UST users was the date of the first prescription fill of the TNFi/UST received. Index date for current and previous CSA users was assigned using prescription time-distribution matching, conditional on: (1) having received their first CSA prescription fill within one year of the first CSA prescription fill of the TNFi/UST user with the assigned duration; and (2) having an index date assigned before the end of their follow-up.
[d]ICD 9/10 codes or a prescription fill for an antidepressant and benzodiazepine
[e] Patients were followed starting three months after index date until the occurrence of the outcome of interest, death, occurrence of an ineligibility criterion (dispensed prescription for a biologic agent other than the TNFi/UST included in the study, diagnosis for HIV, HBV, tuberculosis and melanoma skin cancer), gap ≥ 90 days of enrollment in the provincial drug plan, end of exposure to their index treatment (for TNFi/UST and current CSA users) or unexposure period (for previous CSA users) or December 31, 2015, whichever occurred first.

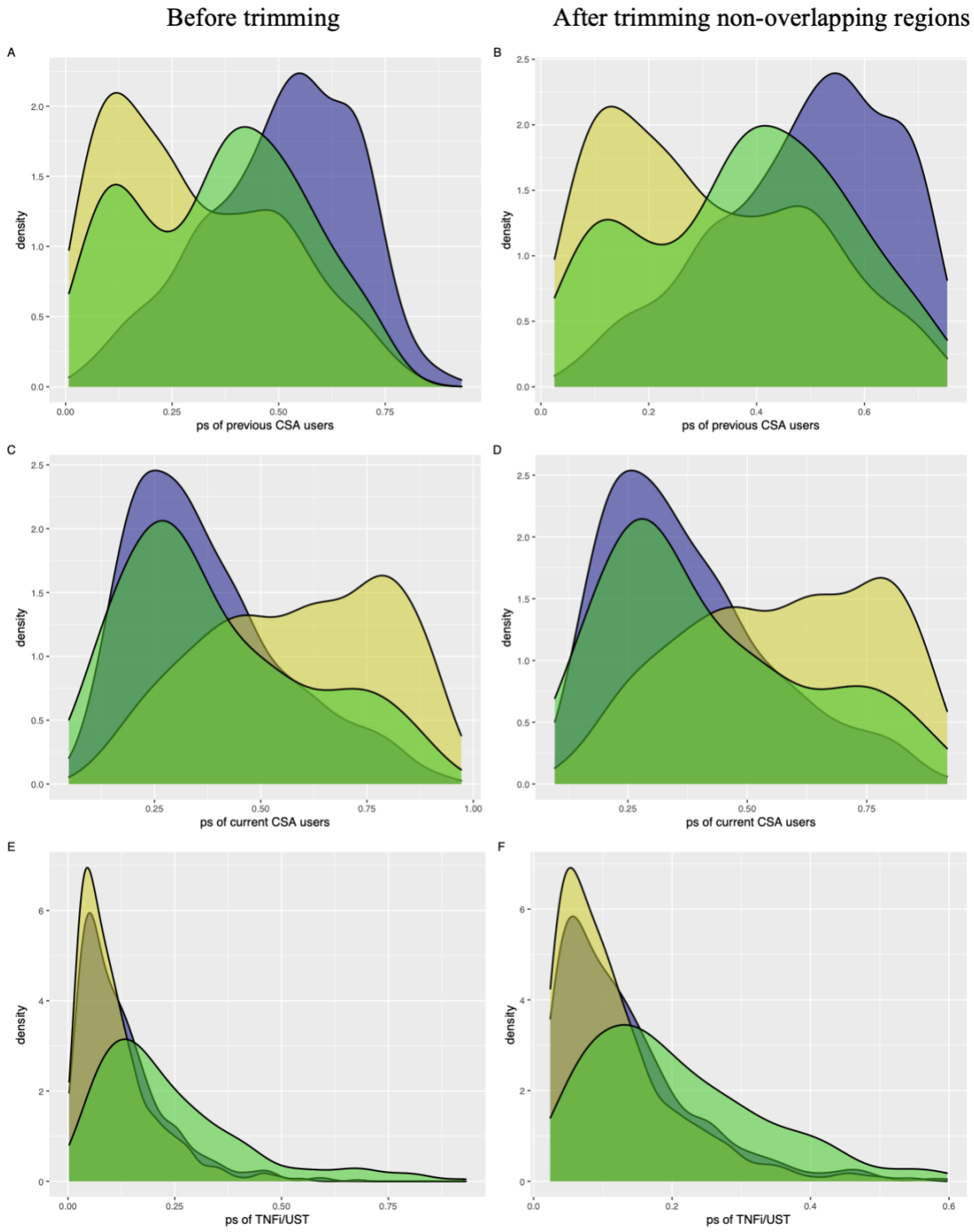
CSA: conventional systemic agents; HBV: Hepatitis B virus; HIV: Human Immunodeficiency Virus; ICD: International Classification of Diseases; TNFi/UST: tumor necrosis factor inhibitors and ustekinumab

Supplementary eFigure 2. Example of a prescription-time distribution matching



CSA: conventional systemic agents; TNFi/UST: tumor necrosis factor inhibitors and ustekinumab

Supplementary eFigure 3. Propensity score trimming



Previous CSA users (Blue), current CSA users (yellow) and TNFi/UST (green)
CSA: conventional systemic agents; ps: propensity score; TNFi/UST: tumor necrosis factor inhibitors and ustekinumab