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

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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 occured. These date 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. (JAAD Int 2022;9:11-22.)

Key words: anxiety; depression; health care costs; psoriasis; systemic agents; trajectories.

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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 economic 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 indic-ated 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 service utilization and costs in this patient population have not been studied previously.[12,13,38]

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.

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.

PATIENTS AND METHODS

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

Abbreviations used:

AHCA:	agglomerative hierarchical cluster analysis
CST:	conventional systemic therapy
ED:	emergency department
ICD:	*International Classification of Diseases*
SA:	sequence analysis
TNFi/UST:	Tumor necrosis factor inhibitors and ustekinumab

(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, available via Mendeley at https://data.mendeley.com/datasets/wj7rshfw74/1).

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.

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.

Depression and anxiety-related health care 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, available via Mendeley at https://data.mendeley.com/datasets/wj7rshfw74/1). 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, available via Mendeley at https://data.mendeley.com/datasets/wj7rshfw74/1). Costs were converted to 2020 CAN$ using the All-item Consumer Price Index.[48]

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

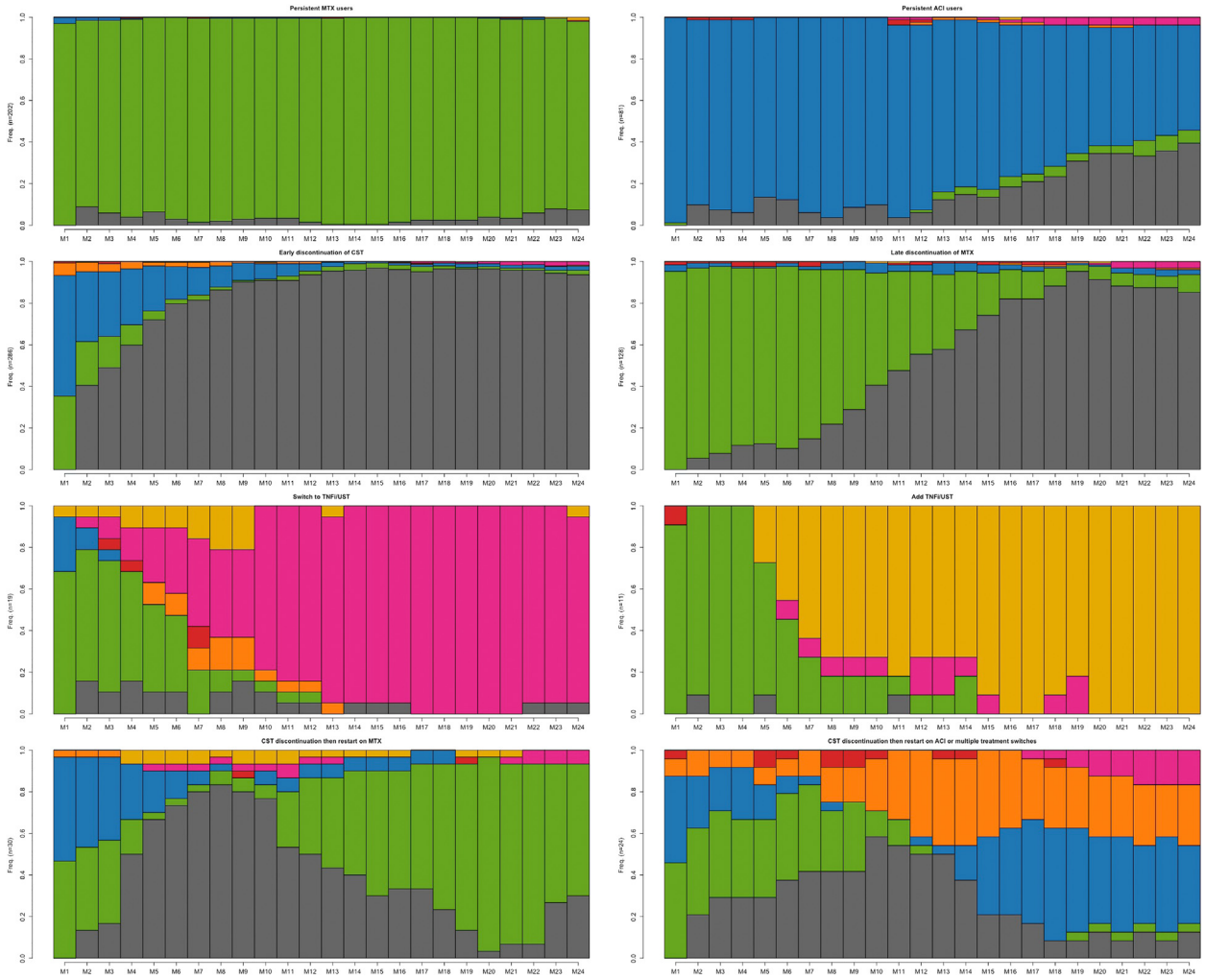

Fig 1. Tempograms describing the 8 treatment trajectories for systemic agents. Methotrexate (*green*); acitretin (*blue*); cyclosporine (*orange*); 2 CST (red); TNFi/UST (*magenta*); TNFi/UST + CST (*yellow*); other (*gray*). Chronograms: The *x-axis* indicates the monthly interval during the 24-month 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 + 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

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]

RESULTS

We included 781 patients (51.1% men, mean age 61.0 ± SD: 15.1 years) (Supplementary Fig 1, available via Mendeley at https://data.mendeley.com/datasets/wj7rshfw74/1). Dividing the data into 8 clusters was considered optimal (Supplementary Fig 2, available via Mendeley at https://data.mendeley.com/datasets/wj7rshfw74/1). 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).

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

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.

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, available via Mendeley at https://data.mendeley.com/datasets/wj7rshfw74/1 and Supplementary Table III, available via Mendeley at https://data.mendeley.com/datasets/wj7rshfw74/1). When costs for depression- and anxiety-related hospitalizations and ED visits were removed from the analyses, all trajectories, with the exception of persistent acitretin, were associated with higher health care costs for depression and anxiety (Supplementary Table III).

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 suggesting 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 discontinuing 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

Table I. Baseline characteristics according to different treatment clusters

		Clusters								
Baseline characteristics	**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)	.468
Age, y										.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)	.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)	.316
Charlson Comorbidity index										.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)	<.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)	<.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)	<.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)	.004
Other 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)	.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)	.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)	<.001

CST, Conventional systemic therapies; *TNFi/UST*, tumor necrosis factor inhibitors and ustekinumab.
*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.

Table II. Annual depression and anxiety-related health care 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	7697	11,402	2558	—	915	546	8203
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*	7932	1799	838	2685	1216	—	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	4159	6142	4892	—	—	—	—	7165
Median (Q1, Q3)*	4159 (3501, 6142)	4159	6142	2446 (1391, 3501)	—	—	—	—	7165
ED visits									
N (%)	5 (3.0)	1 (2.3)	1 (7.7)	2 (3.3)	1 (3.8)	—	—	—	—
Total cost*	7143	5747	282	934	179	—	—	—	—
Median (Q1, Q3)*	405 (282, 529)	5747	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*	7159	1566	435	2891	1164	—	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)

CST, Conventional systemic therapies; *ED*, emergency department; *Q1*, quartile 1; *Q3*, quartile 3; *TNFi/UST*, tumor necrosis factor inhibitors and ustekinumab.
*Costs in Canadian dollars.

Table III. Two-part models for depression and anxiety-related health care costs among the 8 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 restart 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 restart 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)

CST, Conventional systemic therapies; *OR*, odds ratio; *TNFi/UST*, tumor necrosis factor inhibitors and ustekinumab.

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 *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.

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.

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Conflicts of interest

Author 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. Dr 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. Dr Rahme has received funds and consulting fees from Janssen in the course of an unrelated study. Authors LeLorier, Latimer, Brouillette, and Holbrooke have no conflicts of interest to declare.

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