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

To the Editor: Conventional systemic agents (CSAs) 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 the 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 the Quebec health administrative databases. We considered new patients with psoriasis aged ≥20 years who were enrolled in the public drug plan (aged ≥65 years or <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 3 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 the 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 the 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 CSAs prescribed for psoriasis (sulfasalazine is prescribed when other CSAs are contraindicated and in those with other immune-mediated conditions) and (2) both prevalent and incident psoriasis patients were studied.

We included 1644 patients with psoriasis who initiated a CSA (55.7% females: mean age ±SD 61.4 ± 15.1 years vs 58.9 ± 15.7 years for males). Most patients initiated methotrexate, followed by

acitretin, sulfasalazine, and cyclosporine (57.4%, 34.7%, 4.8%, and 3.1%, respectively) with no difference between sexes (Table I). 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 (to a different CSA: 82.7% and to TNFi/UST: 17.3%) (Fig 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, higher age was associated with a decreased risk of switch whereas receiving sulfasalazine versus methotrexate was associated with an increased risk (Table II). In male patients, psoriatic arthritis and longer disease duration were associated with increased risks. In female patients, disease duration of 3 to 12 versus 0 to 2.99 months was associated with a 50% decreased risk of switch, and the presence of somatoform/dissociative/adjustment disorders and prior use of nonsteroidal antiinflammatory drugs were associated with an increased risk.

The 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 this study, physical comorbidities increased the risk of switch in male patients, whereas in female patients, mental health disorders increased that risk.

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Table I. Baseline characteristics by the initial conventional systemic agent received

Patient characteristics	Methotrexate N = 944 (57.4)	Cyclosporine N = 51 (3.1)	Acitretin N = 570 (34.7)	Sulfasalazine N = 79 (4.8)	P value[‖]
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)	—
Sociodemographic variables, N (%)					
Age					<.001
20-45 y	166 (17.6)	21 (41.2)	82 (14.4)	12 (15.2)	
45-64 y	332 (35.2)	20 (39.2)	248 (43.5)	26 (32.9)	
65-74 y	274 (29.0)	7 (13.7)	148 (26.0)	26 (32.9)	
≥75 y	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)	.44
Area of residency (urban vs rural)	754 (79.9)	43 (84.3)	456 (80.0)	67 (84.8)	.64
Income (Low vs high income)*	567 (60.1)	37 (72.5)	314 (55.1)	45 (57.0)	.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)	.04
Psoriasis duration[†]					<.001
0-2.99 mo	243 (25.7)	18 (35.3)	182 (31.9)	15 (19.0)	
3-12 mo	162 (17.2)	13 (25.5)	127 (22.3)	13 (16.5)	
>12 mo	539 (57.1)	20 (39.2)	261 (45.8)	51 (64.6)	
Specialty of the first CSA prescriber					<.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[‡]	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)	<.001
Use of phototherapy in the prior year	85 (9.0)	8 (15.7)	112 (19.6)	1 (1.3)	<.001
Comorbidities in the prior 2 years, N (%)					
Psoriatic arthritis	176 (18.6)	3 (5.9)	38 (6.7)	25 (31.6)	<.001
Rheumatoid arthritis	192 (20.3)	0 (0.0)	13 (2.3)	28 (35.4)	<.001
Inflammatory bowel diseases	18 (1.9)	1 (2.0)	5 (0.9)	3 (3.8)	.12
Ankylosing spondylitis	14 (1.5)	0 (0.0)	3 (0.5)	6 (7.6)	<.001
Obesity	42 (4.4)	5 (9.8)	25 (4.4)	6 (7.6)	.17
Renal diseases	22 (2.3)	5 (9.8)	21 (3.7)	3 (3.8)	.02
Liver diseases	29 (3.1)	6 (11.8)	13 (2.3)	3 (3.8)	.01
Cancer[§]	109 (11.5)	6 (11.8)	64 (11.2)	11 (13.9)	.92
Mental health disorders, N (%)					.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)	.87
Drug use in the prior year, N (%)					
Antidepressants	235 (24.9)	11 (21.6)	124 (21.8)	12 (15.2)	.16
Benzodiazepines	287 (30.4)	18 (35.3)	151 (26.5)	22 (27.8)	.30
Antihypertensive agents	472 (50.0)	22 (43.1)	262 (46.0)	37 (46.8)	.40
Hypoglycemic agents	148 (15.7)	12 (23.5)	88 (15.4)	10 (12.7)	.40
Lipid-lowering drugs	342 (36.2)	10 (19.6)	193 (33.9)	24 (30.4)	.07
Platelet inhibitors	266 (28.2)	14 (27.5)	171 (30.0)	20 (25.3)	.78
Anticoagulants	38 (4.0)	3 (5.9)	12 (2.1)	6 (7.6)	.02
Nonsteroidal antiinflammatory drugs	455 (48.2)	11 (21.6)	131 (23.0)	61 (77.2)	<.001
Oral corticosteroids	301 (31.9)	17 (33.3)	76 (13.3)	29 (36.7)	<.001

CI, Confidence interval; *CSA*, conventional systemic agent; *Q1*, first quartile; *Q3*, third quartile; *ref*, reference group; *SD*, standard deviation.

*Income (high vs low) was based on the type of drug plan the patients had with those receiving partial or total subsidies classified as low income.

[†]Time from first psoriasis diagnosis until the first CSA 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.

[§]43 patients had nonmelanoma cancer: 22 female patients and 21 male patients had nonmelanoma 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 nonmelanoma skin cancer.

[‖]Chi-square test or exact Fisher test for statistical significance.
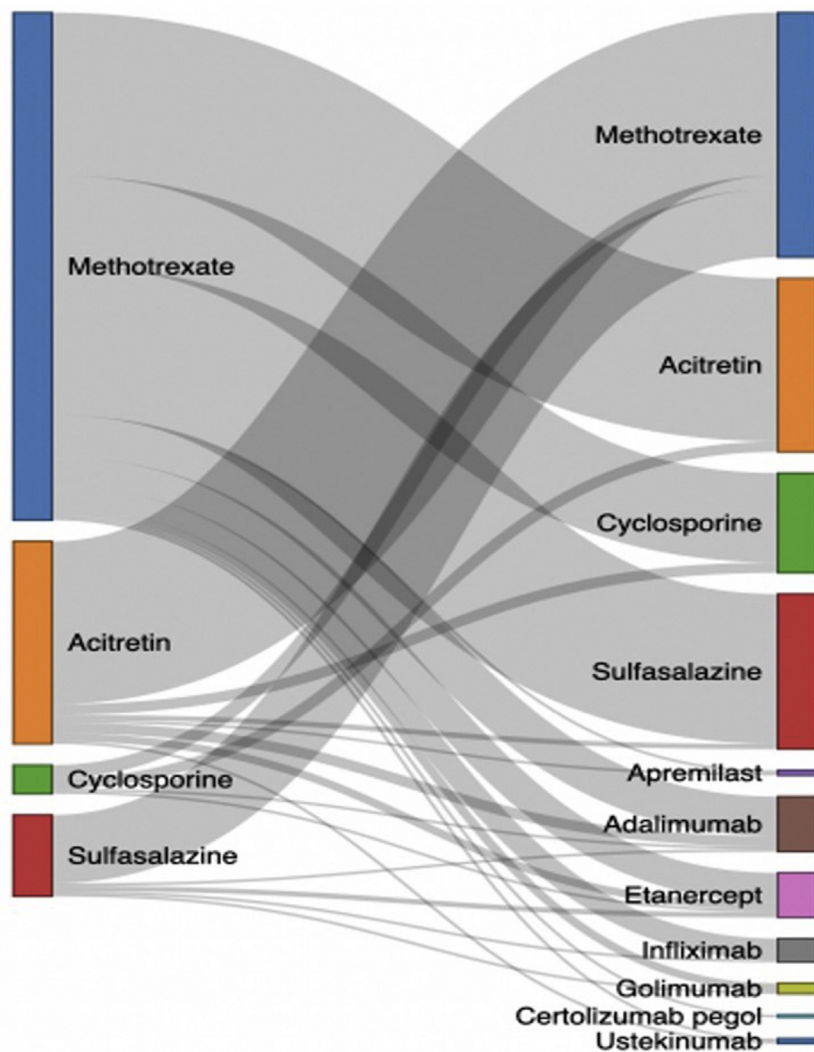
| Initial CSA | Systemic agent received during the switch (N = 312) | | | | | | | | | | | Total of switch | Incidence rate per 1,000 person-year |
| | CSA (N = 258) | | | | | Biologic agent (N = 54) | | | | | | | |
	MTX	ACI	CYC	SUL	APR§	ADA	ETA	IFN	GOL	CER	UST		
MTX (N=944)	0	62	34	57	1	15	11	8	3	1	1	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

Fig 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). *ACI,* Acitretin; *ADA,* adalimumab; *APR,* apremilast; *CSA,* conventional systemic agent; *CER,* certolizumab pegol; *CYC,* cyclosporine; *ETA,* etanercept; *GOL,* golimumab; *INF,* infliximab; *MTX,* methotrexate; *SUL,* sulfasalazine; *UST,* ustekinumab. §Due to drug formulary restrictions, patients could not initiate on apremilast but can receive this agent after failing their index CSA.

Table II. Predictors of switch to either another CSA or a tumor necrosis factor inhibitor/usterkinumab among male and female patients with psoriasis

Predictors	All patients (N = 1644) aHR (95% CI)	Females (N = 916) aHR (95% CI)	Males (N = 728) aHR (95% CI)
Age			
20-54 y	Ref	Ref	Ref
55-64 y	**0.70 (0.52-0.93)**	0.68 (0.45-1.01)	**0.72 (0.48-1.11)**
65-74 y	**0.46 (0.33-0.64)**	**0.44 (0.28-0.70)**	**0.47 (0.28-0.76)**
≥75 y	**0.32 (0.21-0.50)**	**0.35 (0.19-0.62)**	**0.29 (0.14-0.59)**
Psoriasis duration			
0-2.99 mo	Ref	Ref	Ref
3-12 mo	**0.65 (0.45-0.94)**	**0.50 (0.31-0.81)**	0.90 (0.49-1.65)
>12 mo	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)**	1.83 (0.91-3.72)	NA*
Other mental health disorders	1.56 (0.97-2.51)	**2.18 (1.04-4.57)**	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

Bold denotes significant associations.
aHR, Adjusted hazard ratio; *CI*, confidence interval; *CSA*, conventional systemic agent; *Harrel's C index*, Harrel's Concordance index; *NA*, not applicable; *NSAIDS*, nonsteroidal antiinflammatory drugs; *ref*, reference group.
*In male patients, only 7 patients had dissociative, somatoform, and adjustment disorders; therefore, they were combined with those who had anxiety and mood disorders.

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