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. Discontinuation of CSA treatment has been previously studied in psoriasis, but switches between agents and the differences between sexes have not received much attention. 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) 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.

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. 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                                                         |                             |                          |                          |                             | —         |
| 20-45 y                                                     | 166 (17.6)                  | 21 (41.2)                | 82 (14.4)                | 12 (15.2)                   | <.001     |
| 45-64 y                                                     | 332 (35.2)                  | 20 (39.2)                | 248 (43.5)               | 26 (32.9)                   | 0.92      |
| 65-74 y                                                     | 274 (29.0)                  | 7 (13.7)                 | 148 (26.0)               | 26 (32.9)                   | 0.32      |
| ≥75 y                                                       | 172 (18.2)                  | 3 (5.9)                  | 92 (16.1)                | 15 (19.0)                   | 0.001     |
| Sex (male vs female)                                       |                             |                          |                          |                             |           |
| Area of residency (urban vs rural)                         |                             |                          |                          |                             |           |
| Income (Low vs high income)*                                 |                             |                          |                          |                             |           |
| 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†                                         |                             |                          |                          |                             |           |
| Specialty of the first CSA prescriber                      |                             |                          |                          |                             | <.001     |
| Dermatologist                                               | 458 (48.5)                  | 39 (76.5)                | 519 (91.1)               | 0 (0.0)                     | <.001     |
| Rheumatologist                                              | 238 (25.2)                  | 0 (0.0)                  | 0 (0.0)                  | 52 (65.8)                   | <.001     |
| Others†                                                     | 248 (26.3)                  | 12 (23.5)                | 51 (9.8)                 | 27 (34.2)                   | <.001     |
| 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 (%)                              |                             |                          |                          |                             |           |
| No mental health disorder                                  | 671 (71.1)                  | 32 (62.7)                | 423 (74.2)               | 65 (82.3)                   | .03       |
| Anxiety and mood disorders                                 | 208 (22.0)                  | 15 (29.4)                | 124 (21.8)               | 9 (11.4)                    | .01       |
| Dissociative, somatoform, and adjustment disorders          | 20 (2.1)                    | 0 (0.0)                  | 5 (0.9)                  | 3 (3.8)                     | .87       |
| Other mental health disorders                              | 45 (4.8)                    | 4 (7.8)                  | 18 (3.2)                 | 2 (2.5)                     | <.001     |
| 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.

ǁChi-square test or exact Fisher test for statistical significance.
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. 1Due 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/ustekinumab among male and female patients with psoriasis

| Predictors                                      | All patients (N = 1644) | Females (N = 916) | Males (N = 728) |
|------------------------------------------------|-------------------------|-------------------|-----------------|
| **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**

|                        | All patients (N = 1644) | Females (N = 916) | Males (N = 728) |
|------------------------|-------------------------|-------------------|-----------------|
| 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.

Conflicts of interest
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 conflicts of interest to declare.

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