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Heterogeneity in Patient Characteristics and Differences in Treatment Across 4 Canadian Rheumatoid Arthritis Cohorts

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ABSTRACT. ***Objective.*** To compare clinical characteristics and treatment of patients with rheumatoid arthritis (RA) across 4 Canadian cohorts.

Methods. The 4 longitudinal cohorts included the following: the Canadian Early Arthritis Cohort (CATCH; n = 2878), Ontario Best Practices Research Initiative (OBRI; n = 3734), RHUMADATA (Quebec, n = 2890), and the Rheum4U Precision Health Registry (Calgary, Alberta, n = 709). Data were from cohort inception (range 1998–2016) to 2020. Clinical characteristics and drug treatments were summarized descriptively.

Results. In total, 10,211 patients with RA were included. The percentage of patients who entered the cohort with early RA (2 yrs of disease at enrollment) ranged from 29% (Rheum4U) to 100% (CATCH). Mean age (55 yrs), sex (74% female), and seropositivity (69%) were similar between cohorts. At the time of initial disease-modifying antirheumatic drug (DMARD) use, median Disease Activity Score in 28 joints (DAS28) varied, ranging from 2.99 (Rheum4U) to 5.19 (CATCH), but were more similar at the time of the first DMARD switch (range 3.57–5.03), first biologic (bDMARD) or targeted synthetic DMARD (tsDMARD) use (range 4.01–4.67), and second bDMARD or tsDMARD (range 3.71–4.39). The initial DMARD was most commonly methotrexate, either in monotherapy (32%, range 18–40%) or dual therapy (34%, range 29–42%). The first DMARD switch was to another DMARD monotherapy in 20% (range 10–32%), dual therapy in 49% (range 39–56%), and bDMARD or tsDMARD in 24% (range 15–28%). The first bDMARD was an anti–tumor necrosis factor in 79% (range 78–82%).

Conclusion. Canadian RA cohorts demonstrate some heterogeneity in treatment, which could reflect differences in inclusion criteria, calendar year, or regional differences. This project is a first step toward conducting harmonized analyses across Canadian RA cohorts.

Key Indexing Terms: rheumatoid arthritis, registries, therapeutics

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Observational cohorts provide valuable real-world evidence on treatment patterns, disease trajectories, and clinical outcomes. Over the past 20 years, multiple rheumatoid arthritis (RA) cohorts have been established.[1,2,3] Recently, efforts have been made to conduct harmonized analyses across multiple cohorts,[4,5] the advantages of which include increased power to explore rare outcomes,[6,7] increased representativeness of patient and clinical characteristics and treatment patterns, and increased ability to study subpopulations of patients. Observational evidence can also help measure quality of care, provide important real-world context to findings from randomized trials to inform practice and health policy, and provide opportunities for comparative effectiveness. Prior studies have shown that the eligibility criteria and design of randomized trials often differ from how treatments are applied in clinical practice.[8,9]

Understanding real-world treatment patterns may provide important context when developing treatment recommendations. For strong recommendations where there is clear evidence for a given treatment approach, such as with treat-to-target strategies and using methotrexate (MTX) as the initial disease-modifying antirheumatic drug (DMARD) in patients with moderate-to-severe RA,[10,11,12] analyzing treatment patterns may point to gaps in care and/or potential barriers in implementing these recommendations. For conditional recommendations, where there is less consensus on the preferred treatment approach, such as with the use of combination DMARDs, subcutaneous (SC) MTX, and glucocorticoids (GCs),[10,11,12] treatment patterns may help contextualize recommendations by providing insight into commonly used treatment approaches in the country in which the recommendations are being applied. Treatment patterns may also indicate potential implications for implementation.

In Canada there are a number of RA cohorts, and in 2019 the RA Registry Network was formed as a special interest group within the Canadian Rheumatology Association (CRA). The present work represents the first collaborative effort of this group to review the similarities and differences between the cohorts. This work builds on earlier efforts to create an RA Core Clinical Dataset[13] to support clinical care and research efforts in Canada. While in principle the RA Core Clinical Dataset was agreed upon by members of the rheumatology community, including cohort collaborators, it is not clear whether these core elements can be implemented using existing data in the registries. The objective of this study was to compare clinical characteristics and differences in treatment across Canadian RA cohorts. We view this work as a first step toward our aim of conducting future analyses across multiple cohorts. In future, we aim to leverage this network to conduct large practice pattern studies, which will generate contextual information to be used in the future development and implementation of CRA treatment recommendations for RA.

METHODS

Study design. This project involved secondary use of cohort data. Four large Canadian cohorts are included: the Canadian Early Arthritis Cohort (CATCH),[14] Rheum4U Precision Health Registry,[15] Ontario Best Practices Research Initiative (OBRI),[16] and RHUMADATA.[17] A common analytic framework was developed by a working group representative of the 4 cohorts.

Participants and cohort characteristics. Cohort characteristics were collected, including eligibility criteria, number of patients in the cohort, location(s), start date, date of last data cut, number of sites, and percentage of patients seen in university-based clinics vs community rheumatology clinics.

Participants with RA of any duration who met cohort eligibility criteria were included. Some cohorts included patients with other rheumatic conditions and these individuals were excluded from the study. Clinical characteristics of each cohort were collected: age, sex, seropositivity, disease duration, smoking behavior, highest education achieved, race/ethnicity, and income. Responses in the cohorts' categories differed for race/ethnicity, education, and income, and for purposes of reporting some categories were collapsed.

Patient outcomes and differences in treatment. Disease activity data were measured by the Disease Activity Score in 28 joints (DAS28)[18,19] and functional status was measured using the Health Assessment Questionnaire–Disability Index (HAQ-DI).[20] Outcomes and patient treatments were reported by each cohort at 4 treatment timepoints: (1) initiation of first-ever DMARD therapy as documented in the cohort (conventional synthetic [csDMARD], biologic [bDMARD], or targeted synthetic: [tsDMARD]); (2) first therapy (including csDMARD, bDMARD, or tsDMARD) switch/addition after 3 months from baseline; (3) first bDMARD or tsDMARD; and (4) second bDMARD or tsDMARD. All available biologic agents (including biosimilars) and Janus kinase (JAK) inhibitors approved for use in RA, as well as csDMARDs including MTX, sulfasalazine (SSZ), hydroxychloroquine (HCQ), and leflunomide, were considered.

Analysis. Analysis was conducted by each cohort at their central analytic site and results were compiled for review using a common data abstraction form as frequency counts, percentages, means, and standard deviation. Means were preferred for reporting over the use of medians, as we eventually intend to conduct additional analyses to compare findings to trial data that report means. Data were complete from cohort inception to September 2020 (Rheum4U) or January 2020 (other cohorts).

Ethics. All patients provided written informed consent for the collection and use of their data, and each cohort had their own ethics approval. A central ethics approval for this analysis was obtained at the University of Calgary (REB19-1759).

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RESULTS

Cohort characteristics. Cohort characteristics are shown in Table 1. The CATCH cohort is an early RA cohort including patients with a symptom duration of < 12 months, recruited from 8 Canadian provinces at 16 active sites (24 historical) since 2007 at both community- and university-based rheumatology practices. Patients in CATCH must have active RA and meet ≥ 1 additional criteria for cohort entry (Table 1). OBRI includes patients with active RA requiring treatment start or switch of csDMARD, bDMARD, or tsDMARD from 76 rheumatology sites in Ontario (both community- and university-based) since 2008. RHUMADATA includes patients with RA from 2 sites in Quebec since 1998. At inception, RHUMADATA retrospectively collected data on patients dating back to 1983. Rheum4U includes patients with a physician diagnosis of RA from 2 academic rheumatology sites (12 participating physicians) in Alberta since 2016. No additional inclusion criteria for Rheum4U or RHUMADATA were required. Across the 4 cohorts 10,211 patients were included. A distribution of patients by year of first data entry in the cohorts is shown in Figure 1. The proportion of the cohort with early RA (defined as ≤ 2 yrs since diagnosis) varied between 29.2% (Rheum4U) to 100% (CATCH). None of the participating cohorts specified any treatment protocols. Data for patients in CATCH are captured every 3 months for the first year, then at 18 months, then yearly. Data in OBRI are captured at every 6 months, or sooner if there are changes in treatment. Data in Rheum4U and RHUMADATA are captured at each rheumatology visit.

Patient characteristics. Patient characteristics at enrollment are shown in Table 2. The mean age and sex were similar between the cohorts. As expected, the median (IQR) disease duration of patients in the CATCH cohort was shorter (0.44 yrs [0.28–0.65]) compared to other cohorts, and was longest in the Rheum4U cohort (6.2 yrs [1.5–12.3]). The proportion of smokers ranged from 12% (RHUMADATA) to 17% (CATCH). Education was captured in different ways by the cohorts. The proportion

Table 1. Cohort characteristics.

	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Cohort name	CATCH	OBRI	RHUMADATA	Rheum4U
No. of sites	24 (16 active)	76	2	2
Clinic type	Academic and community	Academic and community	Academic and community	Academic
Start date	January 1, 2007	January 2008	1998	August 30, 2016
Eligibility criteria[a]				
> 18 yrs at time of consent	✓	✓	✓	✓
Disease onset after age 16 yrs		✓		
Ability to communicate in English	✓	✓		✓
Symptom duration < 12 months	✓			
Active RA	✓[b]	✓[c]		
Additional criteria	Plus 1 of the following: · RF ≥ 20 IU · anti-CCP+ · AM stiffness ≥ 45 min · Responded to NSAIDs · (+) MTP squeeze test	Starting or switching to a new RA medication		
Method of data collection	Self-report survey	Self-report interview	Self-report survey	Self-report survey
Follow-up interval	3, 6, 9, 12, 24 months, then yearly	Every 6 months or with each treatment change	At each visit	At each visit
Size of RA cohort	2878	3734	2890	709
Early RA[d], n (%)	2878 (100)	1248[e] (33)	2075 (71.8)	207/709 (29.2)
Established RA[f], n (%)	0 (0)	2486[e] (67)	815 (28.2)	502/709 (70.8)
Province, n (%)				
British Columbia	130 (5)			
Alberta	148 (4)			709 (100)
Saskatchewan	26 (1)			
Manitoba	64 (2)			
Ontario	1379 (48)	3734 (100)		
Quebec	1055 (37)		2890 (100)	
Nova Scotia	47 (2)			
Newfoundland	29 (1)			

[a] All cohorts obtained patient consent. [b] Active RA indicated by ≥ 2 swollen joints OR 1 swollen MCP or PIP joint. [c] Active RA indicated by rheumatologist assessment and recommendation of treatment with a conventional synthetic disease-modifying antirheumatic drug or advanced therapy. [d] ≤ 2 years since diagnosis at enrollment. [e] Only year of diagnosis was available; therefore, a cutoff of < 2 years since diagnosis at enrollment was used for early RA and ≥ 2 years since diagnosis at enrolment for established RA. [f] > 2 years since diagnosis at enrollment. Other cohorts completed calculations with full dates. AM: morning; anti-CCP: anticyclic citrullinated peptide antibodies; MCP: metacarpophalangeal; MTP: metatarsophalangeal; NSAID: nonsteroidal antiinflammatory drug; PIP: proximal interphalangeal; RA: rheumatoid arthritis.

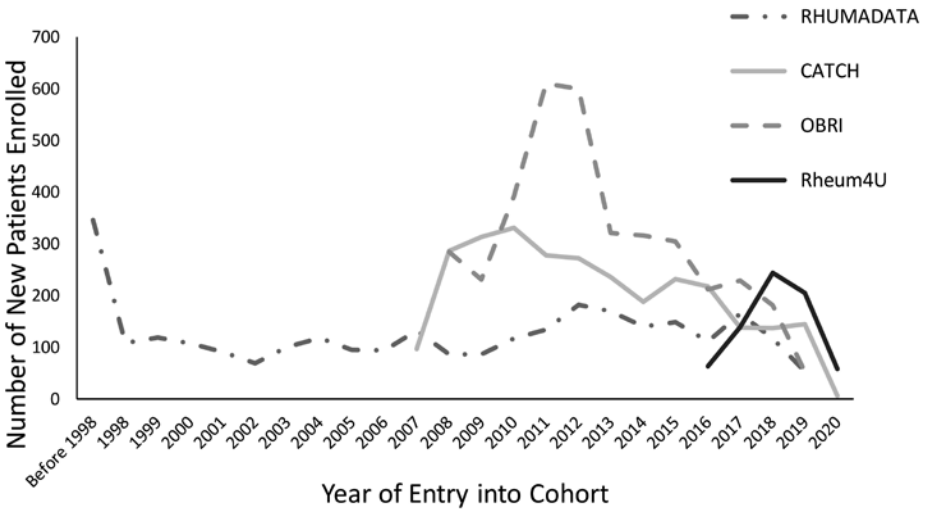

Figure 1. Number of new patients enrolled in each cohort by year.

Table 2. Clinical characteristics.

	CATCH, n = 2878	OBRI, n = 3734	RHUMADATA, n = 2890	Rheum4U, n = 709
Age, yrs, mean (SD)	55 (15)[a]	57.9 (13.2)	52.8 (13.6)	55.4 (13.9)
Age, yrs, median (IQR)	56.0 (45.0–67.0)	58.8 (49.5–67.2)	53.9 (43.4–62.2)	57.1 (46.5–65.2)
Sex, female	2031/2816 (72.1)	2902 (77.7)	2145/2890 (74.2)	510/693 (73.6)
Seropositive				
RF	1615/2717 (59.4)	2504/3460 (72.4)	1703/2890 (58.9)	NA
Anti-CCP	1324/2373 (55.8)	978/1591 (61.5)	1316/2890 (45.5)	NA
Either	1852/2585 (71.6)	1131/1553 (72.8)	1846/2890 (63.9)	NA
Disease duration (from diagnosis), yrs				
Mean (SD)	0.48 (0.25)[b]	8.2 (9.8)	3.2 (7.8)	9.0 (9.8)
Median (IQR)	0.44 (0.28–0.65)	4.0 (1.0–13.0)	0 (0–3.2)	6.2 (1.5–12.3)
Smoking, current	473/2787 (17.0)	562/3534 (15.9)	345/2890 (11.9)	105/691 (15.2)
Education[c]				
Elementary	207/2816 (7.4)	314/3534 (8.9)	150/2890 (5.2)	NA
High school	979/2816 (34.8)	1209/3534 (34.1)	785/2890 (27.2)	145/693 (20.9)
Postsecondary	1550/2816 (55.0)	2020/3534 (57.0)	1218/2890 (42.1)	467/693 (67.4)
Ethnicity[d]				
White	2369/2824 (83.9)	2985/3540 (84.3)	NA	553/693 (79.8)
Indigenous	114/2824 (4.0)	41/3540 (1.2)	NA	41/693 (5.9)
Other	372/2824 (13.2)	514/3540 (14.5)	NA	112/693 (16.2)
Prefer not to say	NA	NA	NA	22/693 (3.2)
Comorbidity[e]				
Heart disease	333/2878 (11.6)	462/3554 (13.0)	127/2890 (4.4)	35/691 (5.1)
High blood pressure	768/2878 (26.7)	1259/3554 (35.5)	511/2890 (17.7)	172/691 (24.9)
Lung disease	394/2878 (13.7)	493/3554 (13.9)	227/2890 (7.9)	59/691 (8.5)
Diabetes	269/2878 (9.3)	347/3554 (9.8)	132/2890 (4.6)	53/691 (7.7)
Ulcer or stomach disease	113/2878 (3.9)	516/3554 (14.5)	64/2890 (2.2)	39/691 (5.6)
Kidney disease	41/2878 (1.4)	136/3554 (3.8)	57/2890 (2.0)	8/691 (1.2)
Anemia or other blood disease	200/2878 (6.9)	691/3554 (19.5)	63/2890 (2.2)	50/691 (7.2)
Cancer	189/2878 (6.6)	361/3554 (10.2)	125/2890 (4.3)	26/691 (3.8)
Depression	300/2878 (10.4)	895/3554 (25.5)	159/2890 (5.5)	108/691 (15.6)
Liver disease	60/2878 (2.1)	115/3554 (3.2)	47/2890 (1.6)	0/691 (0)
Back pain	296/2878 (10.3)	1571/3554 (44.3)	234/2890 (8.1)	215/691 (31.1)
OA or degenerative arthritis	503/2878 (17.5)	1162/3554 (32.7)	963/2890 (33.3)	189/691 (27.4)

Values are expressed as n/N (%) unless otherwise stated. [a] Calculation is an approximate as only year of birth was available. [b] Calculation made with duration from symptoms onset due to high missingness of diagnosis date data. [c] Cohorts offered varying response options for types of post-secondary education and data was collapsed into a single category for analysis. Some cohorts offered "Other" and/or "Prefer not to say" categories, which have been omitted from the table; therefore, proportions presented do not represent 100% of patients. [d] > 1 ethnicity could be selected by each patient. Response options have been grouped due to between-cohort variations in response options and low proportions of patients identifying as ethnic minorities. [e] CATCH and RHUMADATA collected additional comorbidity data, but only common elements across all 4 cohorts were used for analysis. Anti-CCP: anticyclic citrullinated peptide antibodies; CATCH: Canadian Early Arthritis Cohort; NA: not available; OA: osteoarthritis; OBRI: Ontario Best Practices Research Initiative; RF: rheumatoid factor.

Table 3. Disease activity and functional status comparison between 4 Canadian RA cohorts at key treatment timepoints.

	CATCH[a]	OBRI	RHUMADATA	Rheum4U
Initial DMARD therapy[b]				
DAS28	n = 1544	n = 512	n = 472	n = 112
Mean (SD)	5.17 (1.36)	4.91 (1.39)	4.50 (2.73)	3.00 (1.64)
Median (IQR)	5.19 (4.24–6.16)	4.97 (3.98–5.91)	4.43 (3.62–5.39)	2.99 (1.72–7.58)
HAQ-DI	n = 1544	n = 420	n = 638	n = 155
Mean (SD)	1.06 (0.70)	1.16 (0.74)	0.93 (0.67)	0.72 (0.72)
Median (IQR)	1.00 (0.50–1.50)	1.13 (0.50–1.75)	0.88 (0.38–1.38)	0.50 (0.13–1.19)
First therapy switch/addition[c]	N = 655	N = 214	N = 1504	N = 197
DAS-28	n = 655	n = 173	n = 560	n = 22
Mean (SD)	3.82 (1.53)	4.93 (1.35)	4.27 (1.40)	3.54 (1.39)
Median (IQR)	3.78 (2.63–4.90)	5.03 (3.94–6.04)	4.18 (3.27–5.29)	3.57 (2.66–4.28)
HAQ-DI	n = 655	n = 127	n = 795	n = 32
Mean (SD)	0.72 (0.63)	1.20 (0.73)	0.91 (0.65)	0.87 (0.64)
Median (IQR)	0.63 (0.13–1.13)	1.38 (0.75–1.75)	0.88 (0.38–1.38)	0.88 (0.25–1.38)
First advanced therapy[d]	N = 231	N = 873	N = 1392	N = 276
DAS28	n = 231	n = 864	n = 527	n = 37
Mean (SD)	4.49 (1.55)	4.62 (1.46)	4.58 (1.40)	4.23 (1.45)
Median (IQR)	4.57 (3.29–5.60)	4.67 (3.61–5.71)	4.63 (3.66–5.62)	4.01 (3.08-4.79)
HAQ-DI	n = 231	n = 717	n = 827	n = 47
Mean (SD)	0.92 (0.66)	1.29 (0.72)	1.22 (0.66)	1.32 (0.74)
Median (IQR)	0.88 (0.38–1.38)	1.38 (0.75–1.88)	1.25 (0.75–1.75)	1.50 (0.63–2.00)
Second advanced therapy	N = 59	N = 363	N = 1134	N = 115
DAS28	n = 59	n = 296	n = 448	n = 16
Mean (SD)	4.16 (1.42)	4.32 (1.52)	3.82 (1.57)	3.59 (1.28)
Median (IQR)	4.34 (2.95–5.31)	4.39 (3.33–5.45)	3.87 (2.58–4.87)	3.71 (2.68–4.49)
HAQ-DI	n = 59	n = 177	n = 781	n = 25
Mean (SD)	0.99 (0.63)	1.24 (0.78)	1.03 (0.70)	0.94 (0.73)
Median (IQR)	0.99 (0.38–1.44)	1.25 (0.63–1.75)	1.0 (0.38–1.63)	1.00 (0.25–1.50)

[a] Only patients who were DMARD naïve at entry to cohort or who started an initial DMARD ≤ 4 weeks before entry to cohort were included in analysis. [b] All DMARD therapies added within a 3-month baseline period from date of first DMARD initiation. [c] The first time after the 3-month baseline period when a new therapy was added. [d] Advanced therapy defined as biologic, biosimilar, or targeted synthetic therapy (JAKi). CATCH: Canadian Early Arthritis Cohort; DAS28: Disease Activity Score in 28 joints; DMARD: disease-modifying antirheumatic drug; HAQ-DI: Health Assessment Questionnaire–Disability Index; JAKi: Janus kinase inhibitor; OBRI: Ontario Best Practices Research Initiative; RA: rheumatoid arthritis.

with postsecondary education was lowest in RHUMADATA (42%) and highest in Rheum4U (67%). The 3 cohorts with available data were ≥ 80% White in race/ethnicity. The most commonly reported comorbidities included back pain (range 8.1% RHUMADATA to 44.3% OBRI), high blood pressure (range 17.7% RHUMADATA to 35.5% OBRI), osteoarthritis/degenerative arthritis (range 17.5% CATCH to 33.3% RHUMADATA), and depression (range 5.5% RHUMADATA to 25.5% OBRI). Data on income/household income were collected using different categories in each cohort, making comparisons challenging, and there were high rates of missing data (Supplementary Table 1, available with the online version of this article).

Disease activity and functional status. Median (IQR) disease activity, as measured by the DAS28, at initial therapy was highest in CATCH (5.19 [4.24–6.16]) and lowest in Rheum4U (2.99 [1.72–7.58]; Table 3). At the first addition or switch of DMARD 3 months after initiation of therapy, the median (IQR) DAS28 was highest in OBRI at 5.03 (3.94–6.04) and lowest in Rheum4U at 3.57 (2.66–4.28). Median (IQR) DAS28 scores were similar between the cohorts at the time of first bDMARD or tsDMARD (range: Rheum4U 4.01 [3.08–4.79] to OBRI 4.67 [3.61–5.71]) but varied more at the time of second bDMARD or tsDMARD (Rheum4U 3.71 [2.68–4.49] to OBRI 4.39 [3.33–5.45]). Median HAQ-DI scores showed similar trends across cohorts, and cohorts with higher DAS28 scores generally had higher HAQ-DI scores (Table 3).

Treatment differences: initial therapy, first treatment switch, and GC use. RA treatments are shown in Table 4. At initial treatment, MTX was used in 64–78% of patients across the cohorts, most commonly as monotherapy (18–40%), dual therapy (29–42%), or triple therapy (1–10%). Rates of SC MTX at initial therapy were highest in the CATCH cohort (49% of patients using MTX) and Rheum4U (44%) compared to OBRI (18%) and RHUMADATA (11%). HCQ used as monotherapy varied between 14–29%, although the range dropped to 11–16% when considering only patients with moderate or high disease activity (Supplementary Table 2, available with the online version of this article).

At the time of first treatment switch (3 months after initial therapy; Table 4), higher rates of dual therapy were seen

Table 4. DMARD treatment patterns: initial treatment and first treatment switch.

	CATCH	OBRI	RHUMADATA	Rheum4U
Initial DMARD therapy[a]	N =1544	N = 546	N = 2890	N = 324
Monotherapy	924/1544 (60)	321/546 (59)	1777/2890 (61)	147/324 (45)
MTX	615/1544 (40)	214/546 (39)	823/2890 (28)	57/324 (18)
SC (% of MTX users)	300/615 (49)	38/214 (18)	90/823 (11)	25/57 (44)
Oral (% of MTX users)	315/615 (51)	176/214 (82)	733/823 (89)	32/57 (56)
HCQ	281/1544 (18)	75/546 (14)	839/2890 (29)	81/324 (25)
Other DMARD monotherapy	28/1544 (2)	32/546 (6)	115/2890 (4)	9/324 (3)
SSZ		26/546 (5)	88/2890 (3)	7/324 (2)
LEF		5/546 (1)	27/2890 (1)	2/324 (1)
AZA		1/546 (< 1)	0/2890 (0)	0/324 (0)
Dual therapy	521/1544 (34)	173/546 (32)	1065/2890 (37)	147/324 (45)
MTX + HCQ	456/1544 (30)	115/546 (21)	975/2890 (34)	131/324 (40)
MTX + SSZ	13/1544 (1)	19/546 (3)	29/2890 (1)	4/324 (1)
MTX + LEF	31/1544 (2)	22/546 (4)	14/2890 (< 1)	1/324 (< 1)
Other DMARD dual therapy	21/1544 (1)	17/546 (3)	47/2890 (2)	11/324 (3)
Triple therapy	89/1544 (6)	52/546 (10)	18/2890 (1)	24/324 (7)
MTX + HCQ + SSZ	89/1544 (6)	36/546 (7)	15/2890 (1)	18/324 (6)
Other DMARD triple therapy	0/1544 (0)	16/546 (3)	3/2890 (< 1)	6/324 (2)
DMARD + Advanced Therapy	10/1544 (1)			6/324 (2)
Anti-TNF ± csDMARD	7/1544 (< 1)			5/324 (2)
Non-TNF ± csDMARD	3/1544 (< 1)			1/324 (< 1)
First therapy change[b]				
None	889/1544 (58)	332/546 (61)	800/2890 (28)	191/387 (49)
Monotherapy[c]	87/655 (13)	68/214 (32)	453/2090 (22)	20/196 (10)
MTX	14/655 (2)	14/214 (7)	180/2090 (9)	5/196 (3)
SC (% of MTX)	1/14 (7)			4/5 (80)
Oral (% of MTX)	13/14 (93)			1/5 (20)
HCQ	37/655 (6)	16/214 (7)	60/2090 (3)	5/196 (3)
Other DMARD monotherapy	36/655 (6)	38/214 (18)	213/2090 (10)	10/196 (5)
SSZ		13/214 (6)	97/2090 (5)	4/196 (2)
LEF		24/214 (11)	116/2090 (6)	5/196 (3)
AZA		1/214 (< 1)	0/2090 (0)	0/196 (0)
Chloroquine		0/214 (0)	0/2090 (0)	1/196 (1)
Dual therapy	370/655 (56)	84/214 (39)	1013/2090 (48)	92/196 (47)
MTX + HCQ	239/655 (37)	30/214 (14)	770/2090 (37)	66/196 (34)
MTX + SSZ	33/655 (5)	12/214 (6)	60/2090 (3)	5/196 (3)
MTX + LEF	55/655 (8)	29/214 (14)	61/2090 (3)	6/196 (3)
Other DMARD dual therapy	43/655 (7)	13/214 (6)	122/2090 (6)	15/196 (8)
Triple therapy	86/655 (13)	30/214 (14)	37/2090 (2)	39/196 (20)
MTX + HCQ + SSZ	83/655 (13)	11/214 (5)	20/2090 (1)	18/196 (9)
Other DMARD triple therapy	3/655 (< 1)	19/214 (9)	17/2090 (1)	21/196 (11)
Quadruple therapy	0/655 (0)	0/214 (0)	1/2090 (<1)	4/196 (2)
MTX + HCQ + SSZ + LEF	0/655 (0)	0/214 (0)	1/2090 (< 1)	4/196 (2)
bDMARD or tsDMARD	112/655 (17)	32/214 (15)	586/2090 (28)	41/196 (21)
Anti-TNF ± csDMARD	95/655 (14)	25/214 (12)	458/2090 (22)	34/196 (17)
Non-TNF ± csDMARD	9/655 (1)	6/214 (3)	99/2090 (5)	5/196 (3)
JAKi ± csDMARD	8/655 (1)	1/214 (< 1)	29/2090 (1)	2/196 (1)
Cross-sectional oral GC[d]				
≤ 2 yrs after first DMARD	45/218 (21)	36/175 (21)	5/114 (4)	4/97 (4)
> 2 yrs after first DMARD	68/665 (10)	379/2235 (17)	75/2283 (3)	38/513 (7)
Overall	113/883 (13)	415/2410 (17)	80/2397 (3)	42/610 (7)

Values are expressed as n/N (%) unless otherwise stated. [a] All DMARD therapies added within a 3-month baseline period from date of first DMARD initiation. [b] The first time after the 3-month baseline period when a new therapy was added or switched. [c] Reported as (%) using the denominator of those individuals with a first therapy change (n = 655) unless otherwise specified. [d] Denominators specify individuals ≤ 2 years, > 2 years, or overall, for each entire cohort (not only those receiving initial DMARDs or DMARD therapy changes). AZA: azathioprine; bDMARD: biologic DMARD; CATCH: Canadian Early Arthritis Cohort; csDMARD: conventional synthetic DMARD; DMARD: disease-modifying antirheumatic drug; GC: glucocorticoid; HCQ: hydroxychloroquine; JAKi: Janus kinase inhibitor; LEF: leflunomide; MTX: methotrexate; OBRI: Ontario Best Practices Research Initiative; SC: subcutaneous; SSZ: sulfasalazine; TNF: tumor necrosis factor; tsDMARD: targeted synthetic DMARD.

Table 5. bDMARD and tsDMARD treatment patterns.[a,b]

	CATCH	OBRI	RHUMADATA	Rheum4U
First bDMARD or tsDMARD (%)	N = 231	N = 873	N = 1388	N = 274
Anti-TNF	185/231 (80)	712/873 (82)	1091/1388 (79)	214/274 (78)
ADA	59/231 (26)	180/873 (21)	230/1388 (17)	70/274 (26)
CZP	22/231 (9)	91/873 (10)	93/1388 (7)	15/274 (5)
ETN	85/231 (37)	306/873 (35)	473/1388 (34)	105/274 (38)
GOL	12/231 (5)	95/873 (11)	131/1388 (9)	15/274 (5)
IFX	7/231 (3)	40/873 (5)	164/1388 (12)	9/274 (3)
Non-TNF	25/231 (11)	93/873 (11)	233/1388 (17)	39/274 (14)
ABA	7/231 (3)	37/873 (4)	118/1388 (9)	20/274 (7)
Anakinra	0/231 (0)	0/873 (0)	22/1388 (2)	0/274 (0)
RTX	6/231 (3)	28/873 (3)	35/1388 (3)	8/274 (3)
Sarilumab	2/231 (1)	0/873 (0)	9/1388 (1)	0/274 (0)
TCZ	10/231 (4)	28/873 (3)	49/1388 (4)	11/274 (4)
JAKi	21/231 (9)	68/873 (8)	64/1388 (5)	21/274 (8)
Baricitinib	0/231 (0)	0/873 (0)	2/1388 (< 1)	0/274 (0)
TOF	21/231 (9)	68/873 (8)	62/1388 (4)	21/274 (8)
Second bDMARD or tsDMARD	N = 59/231	N = 363/873	N = 1131	N = 113
Anti-TNF	20/59 (34)	209/363 (58)	830/1131 (73)	61/113 (54)
ADA	6/59 (10)	59/363 (16)	171/1131 (15)	32/113 (28)
CZP	2/59 (3)	28/363 (8)	66/1131 (6)	1/113 (1)
ETN	6/59 (10)	61/363 (17)	365/1131 (32)	19/113 (17)
GOL	3/59 (5)	35/363 (10)	72/1131 (6)	6/113 (5)
IFX	3/59 (5)	26/363 (7)	156/1131 (14)	3/113 (3)
Non-TNF	33/59 (56)	106/363 (29)	253/1131 (22)	45/113 (40)
ABA	14/59 (24)	28/363 (8)	105/1131 (9)	17/113 (15)
Anakinra	0/59 (0)	0/363 (0)	8/1131 (1)	0/113 (0)
RTX	7/59 (12)	22/363 (6)	55/1131 (5)	6/113 (5)
Sarilumab	2/59 (3)	7/363 (2)	10/1131 (1)	0/113 (0)
TCZ	10/59 (17)	49/363 (13)	75/1131 (7)	22/113 (19)
JAKi	6/59 (10)	48/363 (13)	48/1131 (4)	7/113 (6)
Baricitinib	0/59 (0)	1/363 (< 1)	1/1131 (< 1)	2/113 (2)
TOF	6/59 (10)	47/363 (13)	47/1131 (4)	5/113 (4)
No. of lifetime bDMARDs or tsDMARDs				
0	1313/1544 (85)	1750/2672 (65)	1498/2890 (52)	346/691 (50)
1	172/1544 (11)	471/2672 (18)	721/2890 (25)	145/691 (21)
2	46/1544 (3)	196/2672 (7)	328/2890 (11)	80/691 (12)
3	7/1544 (< 1)	116/2672 (4)	174/2890 (6)	54/691 (8)
4	5/1544 (< 1)	61/2672 (2)	95/2890 (6)	66/691 (10)
5	0/1544 (< 1)	33/2672 (1)	41/2890 (1)	16/691 (2)
6	1/1544 (< 1)	17/2672 (< 1)	13/2890 (< 1)	4/691 (1)
≥ 7	0/1544 (0)	28/2672 (1)	20/2890 (1)	11/691 (2)
No. of refractory[c] patients	17/1544 (1)	519/2672 (19)	232/2890 (8)	105/691 (15)

Values are expressed as n/N (%) unless otherwise stated. [a] Advanced therapy may have been taken in combination with ≥ 1 DMARDs. [b] Only patients naïve to advanced therapies were included in the analysis. [c] *Refractory* is defined as failure of at least 1 anticytokine (anti-TNF and/or IL-6 directed) and 1 cell-targeted (B cell depletion and/or T cell costimulation blockade) bDMARD. ABA: abatacept; ADA: adalimumab; bDMARD: biologic DMARD; CATCH: Canadian Early Arthritis Cohort; CZP: certolizumab pegol; DMARD: disease-modifying antirheumatic drug; ETN: etanercept; GOL: golimumab; IL: interleukin; IFX: infliximab; JAKi: Janus kinase inhibitor; OBRI: Ontario Best Practices Research Initiative; RTX: rituximab; TCZ: tocilizumab; TNF: tumor necrosis factor; TOF: tofacitinib; tsDMARD: targeted synthetic DMARD.

(39–56%) compared to rates of monotherapy (10–32%). Triple therapy rates also increased in most cohorts (2–20%). bDMARDs or tsDMARDs were introduced as the first switch or addition in 15–28% of patients across cohorts, with anti–tumor necrosis factor (TNF) therapy as the most frequent choice. Cross-sectional oral GC use at the last available visit ranged from ranged between 4–21% for patients with early disease (≤ 2 yrs since first DMARD) and between 3–17% for patients with more established disease (> 2 yrs).

bDMARD and tsDMARD use. Across all cohorts, an anti-TNF was the bDMARD or tsDMARD used in 78–82%, with etanercept being the most common, followed by adalimumab (Table 5). Non-TNF biologics were used first in 11–17% of patients, and JAK inhibitors were used in 5–9% of patients across cohorts.

For individuals requiring a second bDMARD or tsDMARD, anti-TNFs were used in 34–73% of cases, non-TNF biologics in 22–56%, and JAK inhibitors in 4–13% (Table 5).

At the time of last available follow-up, the proportion of patients who had used at least 1 bDMARD or tsDMARD varied from 15% (CATCH) to 50% (Rheum4U). Lifetime number of bDMARDs or tsDMARDs over follow-up are shown in Table 5. Rates of patients with refractory disease, defined as inefficacy of at least 1 anticytokine agent and 1 cell-targeted agent,[21] varied between 1% (CATCH) and 19% (OBRI).

DISCUSSION

This study represents the largest Canadian collaboration of RA cohorts to date and provides some important insights on the similarities and differences between the RA cohorts, as well as preliminary insights into differences in treatment. Importantly, this work highlights considerations and challenges for future collaborations. While some similarities were seen among the cohorts in the types of data collected, there were areas of important variation observed.

The demographic and clinical characteristics of patients with RA from across Canada provide some useful insights. Age, sex, and seropositivity rates were similar to known values from other international cohorts.[1] There was a low percentage of non-White patients, and a relatively high level of postsecondary education, indicating a potential for selection bias. Disease activity and HAQ-DI scores were similar to international cohorts[1] but lower than mean scores observed in clinical trials. For initial therapy, the range scores in our cohorts was 3.00–5.17 for DAS28 and 0.72–1.16 for HAQ-DI, compared to mean scores of 5.87 for DAS28 and 1.33 for HAQ-DI in clinical trials of DMARD-naïve patients.[22] These differences were more pronounced in patients requiring a switch in therapy. In our cohorts, mean DAS28 scores varied between 3.54–4.93 and HAQ-DI scores between 0.87–1.20, compared to mean values from trials in patients with inadequate responses to MTX of 6.15 (DAS28) and 1.45 (HAQ-DI).[22] This highlights what others have shown: patients treated in clinical practice differ systematically from those enrolled in clinical trials.[23] Future work by our network will aim to investigate predictors of treatment choice and the association with patient outcomes to better understand variation in care and its impact.

This study also offers important direction for future investigation into RA treatment patterns in Canada that will be used to provide contextual information during ongoing updates of the CRA RA guidelines. The existing CRA guidelines recommend MTX as the preferred initial DMARD unless contraindicated.[24] This is in accordance with current guidance from the European Alliance of Associations for Rheumatology[12] and the American College of Rheumatology.[11] What is perhaps surprising about our analysis is that while MTX monotherapy use was common as initial therapy, there were unexpectedly high rates of HCQ monotherapy (14–29%), although this did decrease when considering only patients with moderate or high disease activity. The reasons for this are likely varied and could include patient age, treatment preference, comorbidities, pregnancy, pregnancy planning, or lactation; therefore, further exploration of this observed treatment pattern from a provider and patient perspective is warranted. Future analyses are planned to investigate these findings while accounting for calendar year, province of practice, and patient characteristics.

We also observed high rates of SC MTX use in CATCH and Rheum4U as initial therapy; this may be due to differences in cohort characteristics such as local prescribing practices influenced by insurance criteria for biologics, physician preferences, and/or year of cohort inception. Current Canadian guidelines do not suggest a preference for SC MTX; however, many Canadian public and private insurance programs require a trial of it as one of the requirements prior to accessing advanced therapies (Supplementary Table 3, available with the online version of this article), which may contribute to physicians' prescription patterns.[25] SC MTX use has also been shown to be associated with lower rates of treatment changes and some improvements in disease control in early RA, as demonstrated previously in the CATCH cohort.[26]

Over one-third of patients across cohorts were given initial combination therapy with 2 agents, most commonly HCQ and MTX. This is in accordance with current Canadian guidelines, which suggest that initial combination therapy be considered, especially in patients with moderate-to-high disease activity and in those with poor prognostic features.[24] The use of triple therapy across cohorts was low. While triple therapy is not explicitly recommended in Canadian RA guidelines, a 2016 Cochrane network metaanalysis showed moderate-quality evidence that triple therapy (MTX, SSZ, and HCQ) is similarly effective in controlling disease compared to MTX in addition to most advanced therapies.[22] The use of triple therapy prior to biologics is also cost effective[27]; however, a trial of triple therapy is currently not required by most public insurance programs.[25] Providers cite the complexity of the triple therapy regimen and possible increased side effects as reasons for not offering triple therapy to patients, although evidence from patient preference studies suggest many patients may prefer triple therapy as initial treatment.[28]

Initial choice of bDMARD or tsDMARD was similar between cohorts, with approximately 80% of patients having an anti-TNF as the first agent. The choice of second bDMARD or tsDMARD therapy varied more substantially between cohorts, which could be reflective of cohort characteristics (e.g., cohorts with earlier cohort inception dates may have had fewer agents available), provincial regulations regarding access to biologic agents, or local/regional treatment patterns. We did not examine the prevalence of use of biosimilar agents in our analyses, although future investigative efforts in our network on this important topic are planned. tsDMARD treatment is another emerging therapy in RA and has only been on the market in Canada since approximately 2014. Given the low numbers of use in our cohorts, it remains to be seen how the increasing availability of these agents will affect treatment patterns.

Our study also provides insight into some of the challenges when conducting analyses across multiple cohorts. Variables that were easily compared included disease activity, functional status,

and DMARD treatments. Variables that were more challenging to assess included comorbidities due to potential variability during collection. This likely contributed to the large variations in the reported prevalence of comorbid conditions. In future, we would suggest trying to standardize reporting of comorbidities using validated indices such as the Rheumatic Disease Comorbidity Index.[29] Additionally, sociodemographic information, including race/ethnicity, household income, and education, were collected differently between cohorts, necessitating some additional collapsing of variables for reporting. For specific research questions involving data such as household income, additional efforts to harmonize analyses through variable conversion will be necessary. Efforts to harmonize data collection for research and quality improvement efforts are underway. In 2017, the Canadian Rheumatoid Arthritis Core Clinical Dataset was proposed with input from members representing the major RA cohorts[13]; however, as evidenced by the present study, there are additional steps required for implementation of the dataset.

While our study represents the largest evaluation of Canadian RA cohorts, to our knowledge, there are some limitations. As discussed above, the cohorts varied in collection of some key patient characteristics, and may affect interpretation of results. The cohorts had varying dates of inception, and this may have affected treatments, in particular for bDMARDs and tsDMARDs. As with any cohort data, there may be a selection bias for included participants; this could have affected treatment if patients included in the cohorts differed in important ways from other patients with RA. Nevertheless, although treatment data may be available from pharmacy databases in some Canadian provinces, these data sources lack important patient variables including disease activity and functional status.

This study provides baseline work as we plan future collaborative efforts to better understand RA treatment patterns; these will be considered when updating CRA RA guidelines. Importantly, this work has also provided an opportunity to collaborate among cohorts along with 2 patient partners (DPR and LP) and paves the way for future analyses of other research questions that may not be readily answerable with smaller sample sizes (e.g., for rare outcomes or outcomes in smaller subgroups). Future efforts will work to foster collaboration among the cohorts in harmonizing data collection and streamlining data sharing to maximize advancements in RA cohort research in Canada.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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