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ABSTRACT. ***Objective.*** Disease-modifying antirheumatic drugs (DMARD) have the greatest effect when initiated early. We evaluated the influence of early exposure to DMARD on time to joint replacement surgery among patients with incident rheumatoid arthritis (RA).

Method. Using a common protocol, we undertook 2 independent population-based cohort studies of patients with incident RA aged 66 years or older in Ontario (ON) and Quebec (QC) covering the period 2000–2013. We used Cox proportional hazards regression with time-dependent variables measuring duration of drug use in the first year, separately for methotrexate (MTX) and other DMARD, adjusting for baseline demographics, clinical factors, and other potentially confounding drug exposures. Our outcome measure was any joint replacement derived from standardized procedure codes. Adjusted HR and 95% CI were estimated.

Results. Among 20,918 ON and 6754 QC patients with RA followed for a median of 4.5 years, 2201 and 494 patients underwent joint replacement surgery for crude event rates of 2.0 and 1.4 per 100 person-years, respectively. Greater cumulative exposure to MTX (HR 0.97, 95% CI 0.95–0.98) and other DMARD (HR 0.98, 95% CI 0.97–0.99) in the first year after diagnosis was associated with longer times to joint replacement in ON, corresponding to a 2–3% decrease in the hazard of surgery with each additional month of early use. Similar results were observed in QC.

Conclusion. Greater duration of exposure to DMARD soon after RA diagnosis was associated with delays to joint replacement surgery in both provinces. Early intensive treatment of RA may ultimately reduce demand for joint replacement surgery. (First Release February 15 2016; J Rheumatol 2016;43:861–8; doi:10.3899/jrheum.151156)

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Patients with rheumatoid arthritis (RA) undergoing early intensive treatment may obtain superior clinical responses than if the same care is administered later in the disease course[1]. Therefore, the treatment paradigm has shifted to advocate for earlier and more intensive treatment strategies soon after diagnosis to preserve the structural and functional integrity of the joint. Correspondingly, there has been a general increasing trend in the use of disease-modifying antirheumatic drugs (DMARD) and biologic therapies[2,3], which coincides with a decreasing trend in orthopedic surgeries for patients with RA[4,5,6,7].

Unfortunately, delays in patient presentation, physician referral, and RA diagnosis and poor adherence to guideline-concordant care may limit the real-world effectiveness of DMARD therapy[8]. Moreover, the care of seniors with RA has often involved less intensive use of DMARD and biologic therapies and corresponding greater use of steroids[3,9,10,11,12,13,14,15].

Since early and aggressive treatment with DMARD can help reduce joint inflammation and prevent or delay joint damage, early and greater use of DMARD may ultimately delay the need for joint replacement surgery. Accordingly, we sought to evaluate the influence of early cumulative use of DMARD within the first year of diagnosis on time to joint replacement surgery among patients with incident RA in an effort to begin to quantify the population-level longterm effect of early, intensive DMARD therapy.

Our work was performed in the context of the CAnadian Network for Advanced Interdisciplinary Methods for comparative effectiveness research (CAN-AIM) group (www.canaim.ca) to develop novel methods using prospective longitudinal cohorts to study drug safety and effectiveness. Our report extended and consolidated our previous investigations of methodological approaches to evaluate cumulative drug exposures over time[16,17]. The present study further assesses the comparability and reproducibility of the longterm effects of early, intensive treatment in RA across 2 population-based cohorts from Ontario (ON) and Quebec (QC), Canada.

MATERIALS AND METHODS

Setting. Canada's publicly funded healthcare system is universal and comprehensive for both hospital care and physicians' services. Provincial health administrative databases provide wide geographic coverage and relatively complete identification of contacts with the healthcare system. Here we studied the senior residents of Canada's most populous provinces of ON and QC, which together comprise about 65% of Canada's senior population and provide comparable access to healthcare and drug insurance for persons aged 65 years and older.

Data sources. In ON, we used the Ontario Health Insurance Plan (OHIP) Claims History Database to identify diagnoses and procedures associated with physician services. We identified patient demographic information from the OHIP Registered Persons Database. Medication exposures were determined using the pharmacy claims database of the Ontario Drug Benefit Program. Hospital admissions were identified using the Canadian Institute for Health Information Discharge Abstract Database. These datasets are held securely in a linked coded form and analyzed at the Institute for Clinical Evaluative Sciences (ICES; www.ices.on.ca), Toronto.

In QC, we used the Quebec Health Insurance Program (RAMQ) databases to identify diagnoses and procedures associated with physician services, patient demographic information, and pharmacy claims. Hospital admissions were identified using the MED-ÉCHO (Maintenance et exploitation des données pour l'étude de la clientèle hospitalière) database. These data were denominalized by the Quebec Health Insurance Board and securely stored and analyzed in the Division of Clinical Epidemiology, McGill University Health Centre, Montreal.

Details of data availability and diagnostic coding systems within each database are provided in the Supplementary Data (available online at jrheum.org).

The research protocol was approved by the Research Ethics Boards at both the Sunnybrook Health Sciences Centre, Toronto and McGill University, Montreal, and also by the Quebec Commission for Access to Information.

Design. Using a common protocol, we conducted 2 independent population-based retrospective cohort studies in ON and QC.

Cohort definition. To identify patients with incident RA, we used a validated algorithm consisting of a minimum of 3 physician encounters with an RA diagnosis code (International Classification of Diseases, 9th ed: 714) over a 2-year period, with at least 1 such visit to a rheumatologist or an internist[18,19]. Analyses were confined to patients who were newly diagnosed after the date of their 66th birthdate (to ensure complete medication records). To identify truly incident (rather than prevalent) RA cases, we removed any patient who had any RA diagnosis codes prior to the study onset (January 1, 2000 in ON and January 1, 2002 in QC). Among those who satisfied our RA case definition, the date of the first eligible physician visit served as our diagnosis and cohort entry date. Patients were excluded if they had joint replacement surgery or died on the cohort entry date, had missing demographic information, or had followup less than or equal to 1 year.

Main exposures. The main exposures of interest were the cumulative use of methotrexate (MTX) and other DMARD (sulfasalazine, chloroquine, hydroxychloroquine, leflunomide, cyclosporine, minocycline, penicillamine, and cyclophosphamide) during the year following cohort entry. Second, we also adjusted for the cumulative use of other potentially confounding drugs, including anti-tumor necrosis factor (anti-TNF) inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab), other biologics (anakinra, rituximab, abatacept), cyclooxygenase 2 inhibitors (COXIB), nonselective nonsteroidal antiinflammatory drugs (NSAID), and glucocorticosteroids during the entire followup period. To assess time-varying drug exposures, the start date, number of pills, dosage, and days supplied were retrieved for each prescription using the pharmacy claims databases, and used to construct a daily drug exposure matrix[20]. The daily exposure matrix was then used to calculate time-dependent measures of cumulative duration of use of a specific drug, or class of drugs, until a given day during the followup

period[21]. For overlapping prescriptions of the same drug, we assumed the individual to have refilled early and completed the first prescription before starting the second. The same rule was applied to overlapping prescriptions of the same drug, but with different doses and overlapping prescriptions for different drugs within the same drug class (anti-TNF agents, glucocorticosteroids, COXIB, or NSAID). Given that combination use is common for DMARD, prescriptions for each class of DMARD were treated separately. When there was a gap of 7 days or less between 2 prescriptions of the same drug, or of different drugs within the same drug class (excluding DMARD), it was assumed that the drug was taken continuously and the gap was filled with the daily dose of the second prescription.

Other time-dependent covariates. Over the duration of followup, we used a time-varying variable identifying the number of rheumatologist visits during the followup period (log-transformed). During the 3 years prior to cohort entry and during followup, we also controlled for a time-varying indicator of the presence of extraarticular manifestations of RA [lung involvement (pleurisy, pulmonary fibrosis, rheumatoid lung, interstitial lung disease), hematological involvement (Felty's syndrome), cardiac involvement (rheumatic carditis, endocarditis, myocarditis, pericarditis), eye involvement (scleritis, sicca), dermatological complications (vasculitis, pyoderma gangrenosum), entrapment syndromes, neuropathies, and amyloidosis]. These additional time-dependent variables attempt to adjust for proxies of disease severity.

Time-independent baseline covariates. Other potential confounding variables for the association between the drugs of interest and joint replacement surgery were selected *a priori* and adjusted for in the multivariable models. These included sex, age at cohort entry (in yrs and with a squared-age term added to account for nonlinear effects), place of residence (urban vs rural) derived from patients' postal codes, and socioeconomic status (derived from census data). Baseline comorbidity was defined within the 3 years prior to cohort entry using diagnostic codes from all outpatient physician and/or hospital visits [including osteoarthritis (OA), myocardial infarction, diabetes, osteoporosis, cerebrovascular disease, acute renal failure, chronic renal failure, coronary artery disease, chronic obstructive pulmonary disease/asthma, cancer, and the Charlson index[22]]. To discriminate between high and low users of the healthcare system, we adjusted for a binary indicator of high users, defined as people with at least 20 physician visits in at least 1 year of the 3 years before baseline. We also adjusted for binary indicators of exposure to anti-TNF agents, MTX, other DMARD, COXIB, NSAID, and glucocorticosteroids during the 1 year prior to cohort entry and prior joint replacement surgery up to 10 years preceding cohort entry.

Outcome. The outcome of interest was the time from RA diagnosis to the first joint replacement surgery, defined using the Canadian Classification of Health Intervention and the Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures procedure codes.

Details of all covariate and outcome definitions are provided in the Supplementary Data (available online at jrheum.org).

Statistical analysis. Descriptive statistics were used to characterize the study populations in each province. Person-time was accumulated from RA diagnosis until the first of occurrence of joint replacement surgery, death, or the end of the study period. Cumulative incidence rates were calculated for the entire study period within each database as the number of events per 100 patient-years.

We used a Cox proportional hazards regression model with time-dependent variables measuring cumulative drug use for each of MTX and other DMARD within the first year of followup only, adjusting for all baseline covariates and other time-dependent variables during the duration of followup. We determined cumulative use for drug exposures by summing the duration of all prescriptions for the relevant drugs. Adjusted HR and 95% CI were estimated.

The analyses were independently performed using R version 3.0 at McGill University, Montreal and SAS Enterprise Guide 6.1 at ICES, Toronto.

Table 1. General characteristics of the study cohorts.

Characteristic	Ontario	Quebec
Study period	Jan 1, 2000 to Mar 1, 2013	Jan 1, 2002 to Dec 31, 2011
Cohort size, n	20,918	6754
Followup time, yrs		
Median (IQR)	4.6 (2.6–7.4)	4.4 (2.6–6.7)
Maximum	13.2	10.0
Cumulative total	110,274	32,177.1
No. events, n (%)	2201 (10.5)	437 (6.5)
Description of events, frequency by joint site, n (%)		
Knee	1118 (50.8)	236 (54.0)
Hip	942 (42.8)	185 (42.3)
Pelvis	7 (0.3)	< 5
Shoulder	78 (3.5)	15 (3.4)
Other small joints*	56 (2.5)	< 5
Event rate, per 100 patient-yrs	2.0	1.4
Distribution of event times, yrs		
Median (IQR)	3.2 (1.9–5.3)	3.0 (1.9–4.4)
Maximum	12.9	8.8

* Small joint defined as elbow, hand, wrist, ankle, and feet. Significant data are in bold face. IQR: interquartile range.

RESULTS

A total of 20,918 and 6754 incident patients with RA were included in the ON and QC analyses, respectively (Table 1). Patients were followed for a median (interquartile range) of 4.6 years (2.6–7.4) and 4.4 years (2.6–6.7), respectively.

During the cumulative followup times of 110,274 patient-years in ON and 32,177 patient-years in QC, 2201 (10.5%) and 437 (6.5%) patients underwent joint replacement surgery for crude event rates of 2.0 and 1.4 per 100 patient-years in ON and QC, respectively (Table 1).

Demographic and clinical characteristics. A comparison of baseline patient demographics demonstrated a comparable mean (SD) age of 75 years (6) with ≥ 65% of patients being women and most residing in urban locations (Table 2). We identified slight differences in baseline comorbidity profiles of the 2 cohorts (Table 2). The most notable differences were in the prevalence of OA (51% in ON vs 38% in QC) and osteoporosis (9% in ON vs 19% QC).

RA drug exposures. Prior use of glucocorticosteroids, NSAID, and COXIB within the 1-year pre-baseline (prior to RA diagnosis) varied slightly between the 2 cohorts (Table 3).

Similar differences were also observed when we assessed the proportion of patients receiving each drug during at least 1 day during their followup (Table 3), with fewer patients being exposed to COXIB in ON than in QC (31% vs 49%) and greater use of NSAID in ON than in QC (58% vs 38%). During followup, the proportion of patients prescribed with MTX was similar (48% vs 53%), and 53% versus 61% of patients with RA were prescribed with other DMARD in ON and QC, respectively.

Table 2. Demographic and clinical characteristics of study cohorts at baseline. Values are mean ± SD or n (%).

Characteristic	Ontario, n = 20,918	Quebec, n = 6754
Demographic		
Age at diagnosis	74.9 ± 6.3	74.5 ± 5.9
Female	14,136 (67.6)	4369 (64.7)
Urban residence	17,830 (85.2)	5437 (80.5)
Clinical*		
Osteoarthritis	10,676 (51.0)	2549 (37.7)
COPD/asthma**	6538 (31.3)	1755 (26.0)
Diabetes**	4677 (22.4)	1231 (18.2)
Coronary artery disease	3737 (17.9)	1571 (23.3)
Cancer	3712 (17.7)	1030 (15.3)
Extraarticular RA features	3296 (15.8)	1203 (17.8)
Osteoporosis	1849 (8.8)	1295 (19.2)
Acute myocardial infarction	884 (4.2)	243 (3.6)
Chronic renal failure	715 (3.4)	257 (3.8)
Acute renal failure	540 (2.6)	256 (3.8)
Cerebrovascular disease	296 (1.4)	50 (0.7)
Charlson index	0.6 ± 1.3	1.6 ± 2.1
Prior joint replacement†	2285 (10.9)	328 (4.9)
High healthcare use at baseline††	3623 (17.3)	2082 (30.8)
No. rheumatology visits‡	0.8 ± 2.0	0.8 ± 1.5

* Ascertained over the 3 years prior to baseline unless specified otherwise below. ** Ascertained over all available records (1990 onwards) in Ontario, but over 3 years in Quebec. † Ascertained up to 10 years prior to baseline. †† Defined by having at least 20 outpatient physician visits in at least 1 year of the 3 years before baseline. ‡ Ascertained over the 1 year prior to baseline. COPD: chronic obstructive pulmonary disease; RA: rheumatoid arthritis.

Table 3. Baseline and followup drug exposures. Values are n (%).

Drug Exposures*	Ontario, n = 20,918	Quebec, n = 6754
In the 1-yr pre-baseline		
Methotrexate	1763 (8.4)	722 (10.7)
Other DMARD**	2336 (11.2)	986 (14.6)
Anti-TNF agents***	47 (0.2)	21 (0.3)
Glucocorticosteroids	7520 (35.9)	3437 (50.9)
NSAID	9971 (47.7)	3065 (45.4)
COXIB	4357 (20.8)	3922 (58.1)
During followup		
Methotrexate	9958 (47.6)	3606 (53.4)
Other DMARD**	11,076 (52.9)	4106 (60.8)
Anti-TNF agents***	796 (3.8)	324 (4.8)
Glucocorticosteroids	15,409 (73.7)	5250 (77.7)
NSAID	12,043 (57.6)	2581 (38.2)
COXIB	6530 (31.2)	3338 (49.4)
No methotrexate or other DMARD exposure	6306 (30.1)	1566 (23.2)

* Proportion of patients using each drug at least 1 day. ** Other DMARD: sulfasalazine, chloroquine, hydroxychloroquine, leflunomide, cyclosporine, minocycline, penicillamine, and cyclophosphamide. *** Anti-TNF agents: adalimumab, certolizumab, etanercept, golimumab, and infliximab. DMARD: disease-modifying antirheumatic drug; anti-TNF: anti-tumor necrosis factor; NSAID: nonsteroidal antiinflammatory drug; COXIB: cyclooxygenase 2 inhibitors.

Multivariable analysis. In the multivariable analyses in ON, after adjustment for all covariates, greater exposure to MTX (HR 0.97, 95% CI 0.95–0.98) and other DMARD (HR 0.98, 95% CI 0.97–0.99) within the first year of diagnosis were independently associated with longer time to joint replacement in both provinces, corresponding to a 2–3% decrease in the hazard of joint replacement with each additional month of DMARD use in the first year of followup (Table 4). Similar point estimates for MTX (HR 0.96, 95% CI 0.94–0.98) and other DMARD (HR 0.99, 95% CI 0.97–1.00) were observed in QC.

The strongest independent predictors of a shorter time to joint replacement were previous joint replacement surgery (HR 1.87 in ON, 2.48 in QC), coexisting OA (HR 1.49 in ON, 1.97 in QC), increasing age (HR 1.36 in ON, 2.02 in QC), and greater cumulative exposure to both NSAID (HR 1.20 in ON, 1.33 in QC) and COXIB (HR 1.11 in ON, 1.22 in QC) during the entire followup period (Table 4).

DISCUSSION

Our findings suggest that joint replacement surgeries are not uncommon in seniors with new-onset RA and that greater cumulative exposures to MTX and other DMARD within the first year of RA diagnosis are associated with longer times to joint replacement surgery.

By using a common protocol across 2 independent population-based RA cohorts, we were able to conduct a comparative analysis of patient characteristics and outcomes. Despite our best efforts to standardize data definitions across databases, database heterogeneity (e.g., data availability, coding systems) may have contributed to slight variation among comorbidity profiles between our RA cohorts. For example, 11% of ON patients versus 5% of QC patients had a joint replacement surgery prior to cohort entry. This difference may reflect reduced differential access to orthopedic surgeons across provinces (e.g., overall practice patterns, surgeon availability). Moreover, different screening patterns for comorbid conditions may also potentially explain differences observed between the 2 populations. In addition, while use of our main exposures of MTX and other DMARD were somewhat similar, differences in the use of NSAID and COXIB during followup may reflect different marketing, physician prescription patterns, or drug coverage policy in the 2 provinces. Similarly, primary care models (i.e., outpatient visits) also differed between the provinces[23].

Despite some differences observed, using standardized definitions for study populations and outcomes over a similar time period identified comparable rates and risk for joint replacement surgery among both RA cohorts studied. Further, our findings support previous studies that early use of DMARD results in both short-term and longterm benefits[24,25,26,27] and earlier treatment initiation is more beneficial when compared with a delayed start[26,27]. Unfortunately, definitions of joint surgery used in previous studies all

Table 4. Multivariable analyses.

Variable	Adjusted* HR (95% CI)	
	Ontario	Quebec
Time-dependent variables		
Main exposures, cumulative use in the first yr, mos**		
Methotrexate	0.97 (0.96–0.98)	0.96 (0.94–0.98)
Other DMARD	0.98 (0.97–1.00)	0.99 (0.97–1.00)
Other exposures, cumulative use over followup, yrs***		
Glucocorticosteroids	1.02 (0.99–1.06)	0.97 (0.89–1.05)
NSAID	1.20 (1.16–1.24)	1.33 (1.18–1.49)
COXIB	1.11 (1.06–1.16)	1.22 (1.10–1.35)
Anti-TNF	2.50 (0.72–8.65)	1.13 (0.91–1.39)
Other biologics	1.01 (0.95–1.07)	0.17 (0.00–36.07)
Extraarticular RA†	0.93 (0.85–1.02)	1.14 (0.93–1.39)
Rheumatology visits over followup††	1.10 (1.05–1.16)	1.22 (1.07–1.39)
Time-independent baseline variables		
Age	1.36 (1.14–1.63)	2.02 (1.26–3.25)
Sex, reference: male	0.81 (0.73–0.89)	0.76 (0.61–0.94)
Rheumatology visits in 1 yr prior††	0.97 (0.90–1.06)	1.22 (1.07–1.39)
High healthcare use at baseline‡, reference: low	1.14 (1.02–1.27)	0.96 (0.76–1.21)
Prior joint replacement	1.87 (1.67–2.10)	2.48 (1.83–3.35)
Baseline comorbidities		
Acute myocardial infarction	1.17 (0.90–1.53)	0.79 (0.40–1.55)
Diabetes	0.86 (0.76–0.96)	0.91 (0.67–1.23)
Osteoporosis	0.92 (0.79–1.07)	0.79 (0.61–1.02)
Cerebrovascular disease	1.06 (0.69–1.64)	1.38 (0.43–4.41)
Acute renal failure	0.96 (0.65–1.42)	0.86 (0.45–1.63)
Chronic renal failure	0.92 (0.65–1.29)	2.11 (1.13–3.95)
Coronary artery disease	0.89 (0.79–1.02)	1.14 (0.89–1.46)
COPD/asthma	0.96 (0.87–1.06)	0.91 (0.71–1.16)
Cancer	1.12 (1.00–1.26)	1.07 (0.74–1.54)
Osteoarthritis	1.49 (1.36–1.64)	1.97 (1.61–2.41)
Drug use 1 yr prior to cohort entry‡‡, reference: non-use		
Methotrexate	1.17 (0.99–1.39)	1.18 (0.82–1.71)
Other DMARD	0.97 (0.84–1.13)	0.99 (0.73–1.34)
Glucocorticosteroids	1.12 (1.01–1.23)	1.18 (0.95–1.45)
Anti-TNF	0.49 (0.13–1.90)	1.20 (0.32–4.49)
NSAID	1.03 (0.95–1.13)	0.78 (0.63–0.96)
COXIB	1.08 (0.98–1.19)	0.87 (0.71–1.07)

* Adjusted for all covariates including socioeconomic status (defined by census data), age (squared), patient residence, and Charlson index. ** HR expressed as per month of additional use. *** HR expressed as per year of additional use. † Extraarticular RA manifestations. †† Log-transformed. ‡ Binary indicator reflecting at least 20 outpatient physician visits in at least 1 year of the 3 years before baseline. ‡‡ Binary indicator reflecting use during the 1-year prior to cohort entry. DMARD: disease-modifying antirheumatic drug; NSAID: nonsteroidal anti-inflammatory drug; COXIB: cyclooxygenase-2 inhibitor; anti-TNF: anti-tumor necrosis factor; RA: rheumatoid arthritis; COPD: chronic obstructive pulmonary disease.

differed, as did the ages and periods studied, thus impeding direct comparisons with the data at hand.

Current healthcare quality improvement measures predominantly focus on system-level and provider/process measures (what providers do in delivering care, e.g., prescribing treatment) rather than patient outcome measures, which typically require years to accurately quantify[28]. For example, there has been increasing access to rheumatologists[29] and RA treatment[2] over time (according to established quality improvement measures[30]), but uncertainty to what extent early therapy can ultimately improve population-health of patients with RA, such as reducing the need for later joint surgery. Joint replacement surgeries are costly — and only indicated after irreparable joint damage because they impose a greater risk of complications to patients with RA[31,32] — yet they are highly effective procedures to improve physical function[33]. Thus, targeted efforts to reduce joint damage through early access to and greater duration of treatment soon after diagnosis may ultimately lead to reductions in costly surgical interventions, and thus benefit society by improving RA health at the population level. For instance, the HR for our time-dependent covariates for MTX and other DMARD were found to be both statistically significant and clinically meaningful. The 2–3% decrease per month is clinically

important relative to the cumulative use over time (e.g., persistent use of MTX within the first full year would correspond to a > 36% reduction in joint replacement surgery over 12 mos).

Our study has both strengths and limitations. We studied 2 large population-based RA cohorts, which have wide geographic population representation, with detailed drug prescription data over a long followup time. Our collaborative approach to harmonize data definitions to systematically characterize both RA cohorts and our standardized methodological approach to assess patient outcomes achieved highly consistent and comparable findings. To study the effects of early and aggressive treatment on time to joint surgeries, it is important to account for timing of drug use since drug use and dose varies across users and over time. This was accomplished by conducting the appropriate analytic approach using incident patients with RA, using a new user drug design, and assessing time-varying drug exposures (i.e., daily exposures over followup).

While administrative data preclude confirmation of diagnosis, we used a RA case definition that has a high positive predictive value, sensitivity, and specificity based on validation with patient clinical records in ON[18,19]. Many patients had RA-related drug exposures during followup within both cohorts. Yet, in our senior populations, 23–30% of patients were not exposed to any DMARD (including MTX) during followup. A recent study similarly identified 28% of patients with incident RA were also not exposed to DMARD in a US population-based cohort[15]. Similar to our study, individuals not exposed to DMARD tended to be older than those treated with DMARD, and to have more comorbidities at baseline. This combination of increased age and comorbidity may represent a relative contraindication to DMARD use in this subgroup.

While both provinces also have a similar prevalence of RA[34,35], ON has a larger source population, and we had more years of data available in ON than in QC at the time of analysis, thus our RA cohorts were not equivalent in size.

A potential caveat is that our data sources lacked information on potential confounders including detailed clinical information such as RA severity and physical function. To overcome this limitation, we attempted to adjust for proxies of disease severity[36] (such as extraarticular manifestations of RA, number of rheumatology visits, and use of concomitant medications such as glucocorticoids), yet residual confounding may be present. For example, the association of greater use of NSAID and COXIB leading to more joint surgeries in our samples does not necessarily represent a causal effect, rather an indirect effect representing the complex relationship of NSAID/COXIB use, preexisting OA, prior joint surgery, and our outcome studied. Other studies, which were able to adjust for clinical measures of disease activity, have similarly identified NSAID use and the presence of extraarticular disease to be associated with joint surgeries[7,37]. Likewise, the decision-making and timing for orthopedic and pharmacologic interventions are complex issues because of the polyarticular involvement. In addition, the multifaceted characteristics between RA and OA (preexisting or secondary to RA) and the need for surgery is often established by an interdisciplinary team that includes rheumatologists and orthopedic surgeons[38].

There is also some evidence from clinical trials that erosive damage is gradually decreasing over time in RA, irrespective of the type of treatment used[39]. Perhaps better access to care, improvements in overall population health, and comorbidity management may be involved. We did not assess period effects and our data lack clinical measures of disease severity to make this determination. Seniors with RA may also differ from patients enrolled in clinical trials. For example, they tend to have more comorbidity than their younger counterparts and may be excluded from clinical trials. However, we did study contemporary patients with RA (diagnosed after 2000) relevant to clinical practice today.

Dates of symptom onset are not identified in our data sources, thus some patients with RA may not have been truly incident and damage may have already been present at cohort entry. However, as part of our previous validation exercises, we found that the timing of RA diagnostic codes and physician diagnosis are fairly well defined in health services data[19], yet information on joint damage at the time of diagnosis was not available to us. Moreover, seropositivity status was not available to us. Finally, our analyses were confined to seniors with new-onset RA; however, this is not a limitation per se because patients with RA presenting at higher age often have more severe joint damage[40].

We evaluated the influence of early cumulative use of DMARD within the first year of diagnosis on time to joint replacement surgery among incident RA seniors. We found that greater cumulative exposures to MTX and other DMARD within the first year of RA diagnosis were associated with longer time to joint replacement surgeries, which could be reflective of the joint-sparing effects of DMARD. Thus, early intensive treatment to prevent joint damage and restore physical function may ultimately reduce the need for joint replacement surgeries and improve overall population health among patients with RA. Our coordinated approach across provincial data sources identified highly comparable and consistent findings.

ONLINE SUPPLEMENT

Supplementary data for this article are available online at jrheum.org.

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