The Journal of Rheumatology 2021;48:977–84
doi:10.3899/jrheum.200310
First Release March 15 2021

The Journal of Rheumatology

Use of Disease-modifying Antirheumatic Drugs, Biologics, and Corticosteroids in Older Patients With Rheumatoid Arthritis Over 20 Years

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ABSTRACT. ***Objective.*** To examine changes in prescribing patterns, especially the use of corticosteroids (CS), in patients with rheumatoid arthritis (RA) over 2 decades.

Methods. This was a secondary analysis of health administrative data using a previously validated dataset and case definition for RA. Cases were matched 1:4 by age and sex to controls within a population of approximately 1 million inhabitants with access to universal health care. Longitudinal data for incident and prevalent RA cases were studied between 1997 and 2017.

Results. There were 8240 RA cases (all ≥ 65 yrs) with a mean (SD) age 72.2 (7.5) years and 70.6% were female. Over 20 years, annual utilization of coxibs in prevalent RA cases fell with a concomitant increase in disease-modifying antirheumatic drugs (DMARDs) and biologics. Over the same period, CS use was largely unchanged. Approximately one-third of patients had at least 1 annual prescription for CS, most frequently prednisone. The mean annual dose showed a modest reduction and the duration of utilization in each year shortened. Rheumatologists prescribed CS less frequently and in lower doses than other physician groups. For incident RA cases, there was a significant fall in annual prescribed dose of prednisone by rheumatologists over time.

Conclusion. In older adults with RA, the utilization of DMARDs and biologics has increased over the past 20 years. However, the use of CS has persisted. Renewed efforts are required to minimize their use in the long-term pharmacological management of RA.

Key Indexing Terms: corticosteroids, rheumatoid arthritis

The treatment of rheumatoid arthritis (RA) has undergone substantial change in the past 20 years. Recognition of excess morbidity and mortality associated with inadequately controlled chronic inflammation stimulated a more aggressive approach to the use of pharmacotherapies. This included the earlier introduction of combination therapy with conventional disease-modifying antirheumatic drugs (DMARDs), and the development of biologics and small molecule drugs for more targeted therapies to inhibit the aberrant immune response in patients with RA. The result is that for newly diagnosed patients, there is now a reasonable expectation that their disease will either be well controlled or go into remission with current therapies. As a corollary, one would also expect a concurrent reduction in the use of corticosteroids (CS) for the treatment of disease flares or as part of maintenance therapy.

Support for this paradigm shift in the treatment of RA is derived from clinical guidelines and randomized controlled clinical trials, which provide the highest level of evidence for efficacy of new therapies. In order to determine if best practice is being used in the overall RA population, one needs to study large cohorts of patients with RA or conduct population health research by performing secondary analysis of health administrative data.

The objective of the current study was to examine the change in prescribing patterns for older adults with RA over a 20-year period using a validated health administrative database. Specifically, we aimed to determine if the anticipated changes in prescribing over 2 decades had occurred in the broader population of patients with RA and, in particular, if the use of CS fell over this time.

METHODS

Study populations and controls. This was a retrospective cohort study of patients with a diagnosis of RA within the Nova Scotia Medical Services Insurance (MSI) program. Nova Scotia is a Canadian province of approximately 1 million inhabitants. As of June 2019, there were 2677 licensed physicians in Nova Scotia, of which approximately 50% worked in primary care, 5.6% were general internists, and 0.44% were adult rheumatologists. Healthcare services, including acute and elective hospitalizations and

This study was supported by the John & Marian Quigley Endowment Fund for Rheumatology.

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The authors declare no conflict of interest.

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Accepted for publication July 13, 2020.

ambulatory physician visits, are universally provided as specified under the Canada Health Act. The eligible population for the study was Nova Scotia residents who were enrolled in the MSI program between April 1, 1997, and March 31, 2017. This excludes First Nation Canadians and members of the Canadian armed forces. Incident cases of RA were defined as those without a physician billing for the same diagnosis in the preceding 5 years.[1] Prevalent cases included both incident and nonincident cases. Patients with RA were matched 1 to 4 by age and sex to a control cohort of patients who were also enrolled in the MSI program at the time of their matched case's date of diagnosis and who never had a diagnosis of RA or other connective tissue disease (CTD).

The data was obtained from existing databases accessed through Health Data Nova Scotia (HDNS; previously the Population Health Research Unit) in the Department of Community Health & Epidemiology at Dalhousie University in Halifax, Nova Scotia, Canada. Within this unit, there are secure on-site research computing facilities, and access to data is governed by HDNS Data Access Guidelines and Procedures. Electronic utilization data from the Nova Scotia Senior Pharmacare Program for seniors (age ≥ 65 yrs), the Canadian Institute of Health Information (CIHI) Hospital Discharge Abstracts database, and the MSI Physician Billings database were linked by MSI number. The study protocol was reviewed and approved by the Research Ethics Board of the Nova Scotia Health Authority, central zone (CDHA-RS/2010-118). Informed consent from individual patients was not required because the study utilized secondary administrative data.

Case definition for identification of RA cases and validation. A case definition, derived from the literature and previously validated against a clinical dataset of patients with RA and controls,[2] was used to identify patients with RA. This included a MacLean-like algorithm[3] (2 nonrheumatology physician visits for RA at least 2 months apart, within a 2-yr period) or at least 1 RA code contributed by a rheumatologist or at least 1 hospitalization where RA was in the diagnostic codes and Lacaille variation, i.e., excluding individuals with at least 2 visits, at least 2 months apart, subsequent to the second visit, with 2 identical diagnoses of other inflammatory arthropathies and CTDs (psoriatic arthritis, ankylosing spondylitis, and other spondylarthropathies, systemic lupus erythematosus, systemic sclerosis, Sjögren syndrome, dermatomyositis, polymyositis, other CTDs, primary systemic vasculitis), and excluding those where a diagnosis of RA by a nonrheumatologist was not confirmed if/when the individual saw a rheumatologist.

The study population was restricted to individuals who were 65 years of age and older because the Pharmacare database used to measure drug utilization is primarily restricted to this demographic group. For prevalent cases, the denominator included individuals who had a diagnosis of RA and were eligible to receive Pharmacare. Drug utilization was only recorded following the year of an individual's 65th birthday, regardless of the age of diagnosis of RA. Incident RA cases were defined as those without a diagnosis of RA in the 5 years preceding their initial registration in the dataset. As a result, incident cases were studied between 2002 and 2017.

Data collection. Individual-level data were obtained. Computerized claims were linked by encrypted health card number to the CIHI Hospital Discharge Abstracts and MSI Physician Billings for fiscal years from April 1, 1997, to March 31, 2017. International Classification of Disease (ICD) codes were used to identify RA cases, other inflammatory arthropathies, and CTDs using ICD-9 (ICD, 9th revision) for physician billing data and ICD-10 for hospital data (Table 1).

Medication utilization. Medications were identified using the drug identification number (DIN) as administered by Health Canada. Clinical expertise and consultations with an experienced pharmacist helped to categorize drug types and groupings by DIN that were relevant to the RA population: coxibs included valdecoxib, celecoxib, meloxicam, rofecoxib; DMARDs included chloroquine, hydroxychloroquine, sulfasalazine, minocycline, penicillamine, myochrysine, azathioprine, mercaptopurine, methotrexate, cyclophosphamide, leflunomide, mycophenolic acid, cyclosporine, and tacrolimus; and biologics consisted of anakinra, infliximab, etanercept, adalimumab, golimumab, certolizumab pegol, abatacept, rituximab, and tocilizumab. CS were a single category with a subset, prednisone, selected to examine dosage trends. The specialty status of the prescribing physician was based upon information received from the College of Physicians and Surgeons of Nova Scotia, the organization responsible for physician licensing in Nova Scotia.

Utilization was measured using 2 metrics. First, the proportion of patients in each year who had any prescription for the drug type of interest. Second, for oral prednisone only, the proportion of patients with a prescription in each 3-month period per annum, and the mean annual dosage were determined. To do this, DIN numbers were queried online (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp) to determine milligrams per tablet, which was multiplied by the number of tablets to estimate dose of prednisone prescribed. Exposure time was measured by calendar year for the prevalent population, 1997–2017, and by follow-up year from the time of RA diagnosis for incident cases.

Statistical analysis. Point estimates for proportions receiving each drug type were calculated as the total number of individuals receiving any prescription for the drug divided by the total RA population in each year.

RESULTS

Patients. From 1997 to 2017, there were 8240 individuals with a diagnosis of RA. Each case was included in the denominator in every year after the diagnosis of RA until death. The average number of years of follow-up during the study period was 5.5 years, giving a total of 45,221 observations in the analysis of prevalent cases. At the initial assessment in the cohort, the mean (SD) age was 72.2 (7.5) and 70.6% were female. Of the 8240 RA cases, 4024 (48.8%) had 1 or more visits to a rheumatologist over the period of study. For those RA cases who did not see a rheumatologist, the percentage who saw an internal medicine specialist was 89.7%.

From 2002 to 2017, the number of incident cases of RA was 3194 with a mean follow-up of 4 years, giving a total of 12,796 observations in the analysis of incident cases. At the initial assessments in the cohort, the mean (SD) age was 73.1 (10.5) and the percentage of females was 69.7%.

Medication utilization by prevalent RA cases and controls. The proportion of cases and controls prescribed coxibs, CS, nonbiologic DMARDs, and biologics on an annual basis is summarized in Figure 1. Over the 20 years of observation, the utilization of coxibs fell from 51.6% to 24% with a concurrent increase in DMARDs (33.8% to 64.9%) and biologics (0% to 20.4%). Over the same period, CS use changed very little from 34.3% to 32.5%. Prednisone use was slightly lower but also remained static over time (28.3% to 27.6%; data not shown in Figure 1).

Prescribing of CS by physician groups. The source of CS prescribing for RA cases is summarized in Figure 2. Family physicians were responsible for the majority of prescriptions that remained stable over time between 70.8% and 76.7% of all annual CS prescriptions between 1997 and 2017. The proportion of CS prescriptions by nonfamily physicians was also stable between 23.3% and 29.2%. Within the latter group, rheumatologists were responsible for 14.1% to 19.4% of CS prescriptions.

CS utilization by incident RA cases. The proportion of cases receiving CS and the prescribing source following the diagnosis of RA is summarized in Figure 3. In the first 3 years, the

Table 1. ICD-9 and ICD-10 codes for RA, other inflammatory arthropathies, and CTD.

Diagnosis	ICD-9 Code	ICD-10 Code
RA	714.0, 714.1, 714.2	MO5–MO5.9, MO6.0, MO6.8, MO6.9
Other inflammatory arthropathies and CTD		
Psoriatic arthritis	696.0	L40.5
Ankylosing spondylitis	720.0	M45
Other spondylarthropathies	720.1, 720.2, 720.8, 720.9	M46.0, M46.1, M46.2, M46.3, M46.4, M46.5, M46.8, M46.9
Systemic lupus erythematosus	710.0	M32, M32.1, M32.8, M32.9
Systemic sclerosis	710.1	M34
Sjögren syndrome	710.2	M35.0
Dermatomyositis	710.3	M33.1, M33.9
Polymyositis	710.4	M33.2
Other CTD	710.5, 710.8, 710.9	M35.1, M35.2, M35.8, M35.9

CTD: connective tissue diseases; ICD-9: International Classification of Diseases, 9th revision; RA: rheumatoid arthritis; SSc: systemic sclerosis.

proportion of cases receiving CS fell from 41.8% to 27.1% but increased slowly thereafter. Comparison of the prescribing patterns by rheumatologists and nonrheumatologists indicated that rheumatologists contributed to most of the decline in the use of CS (17.4% to 6.7%). In contrast, the nonrheumatology physician group had a more modest reduction in CS prescribing (33.7% to 20%).

Prednisone utilization by prevalent and incident RA cases. As prednisone was the most frequently used CS, the change in prednisone utilization in RA cases was of particular interest and is illustrated in Figure 4. The top panel shows the trend by calendar year in the mean annual dose. For prevalent RA cases, the average annual dose was relatively stable over 20 years and was always lower when prescribed by rheumatologists. However, as shown on the lower panel, there was a change in the duration of time in each 12-month period that patients received prednisone. Thus, the proportion of RA cases receiving prednisone for more than 9 months of the year rose between 1997 and 2008, following which it fell steadily. Conversely, the proportion receiving prednisone for less than 3 months fell until 2002, at which point it began to increase. For incident RA cases, the average annual dose of prednisone prescribed by nonrheumatologists was always higher than the dose prescribed by rheumatologists (Figure 5). In addition, the average dose prescribed by rheumatologists fell from 1235 mg/year in the first year of diagnosis to 450 mg/year in the 14th year since diagnosis. For nonrheumatologists, there was a change from 1602 mg/year in the first diagnosis year to 1335 mg/year in the 14th year.

DISCUSSION

The current study examines the change in medication utilization derived from prescribing patterns in health administrative data for older adults with RA between 1997 and 2017. During these 20 years of observation, there were substantive changes in the therapeutic approach to RA that included more aggressive use of conventional DMARDs and the introduction of biologics. The increased utilization of disease-modifying therapies is particularly encouraging. The results of our study in an older adult population with universal access to health care indicate that many of the important outcomes from RA clinical trials were translated into clinical practice, as well as implementation of practice guidelines developed by many professional rheumatology organizations. However, the use of CS was largely unchanged over time. Given the risks associated with chronic CS use, especially in older adults, renewed efforts are required to minimize their use in the long-term pharmacological management of RA.

A number of previous studies, cross-sectional[4,5,6,7,8] and longitudinal,[9,10,11] have used health administrative data to evaluate medication utilization in RA at a population level. To our knowledge, the current study in RA has the longest duration to date. Some of the changes in utilization are in line with expectations. For example, the temporal fall in coxib prescribing in both RA and control populations is in keeping with the effect of regulatory changes and prescribing patterns for this drug class. At study onset, the use of DMARDs was low but comparable to the findings in another Canadian jurisdiction by Lacaille, *et* al,[1] who reported that only 43% of patients with RA received a DMARD at least once over 5 years between 1996 and 2000. In our study over 20 years of observation, there was a progressive increase in DMARD use that had almost doubled by 2017. Once biologics became available to the insured population of the current study, there was also a steady increase in utilization over time. In light of these changes, in particular with the increased use of disease-modifying therapies, it was surprising to find that almost one-third of patients received some exposure to CS on an annual basis and that the prevalent use of CS did not change appreciably over the 20 years of observation. A comparable trend, albeit with slightly lower utilization, was seen when the analysis was confined to prednisone only.

The frequency of CS use in RA is variable and influenced by a number of factors. In a cross-sectional study of 10,262 patients with RA in the United States, 23% were receiving CS.[6] In another US study,[4] 10% of 8125 patients with RA received

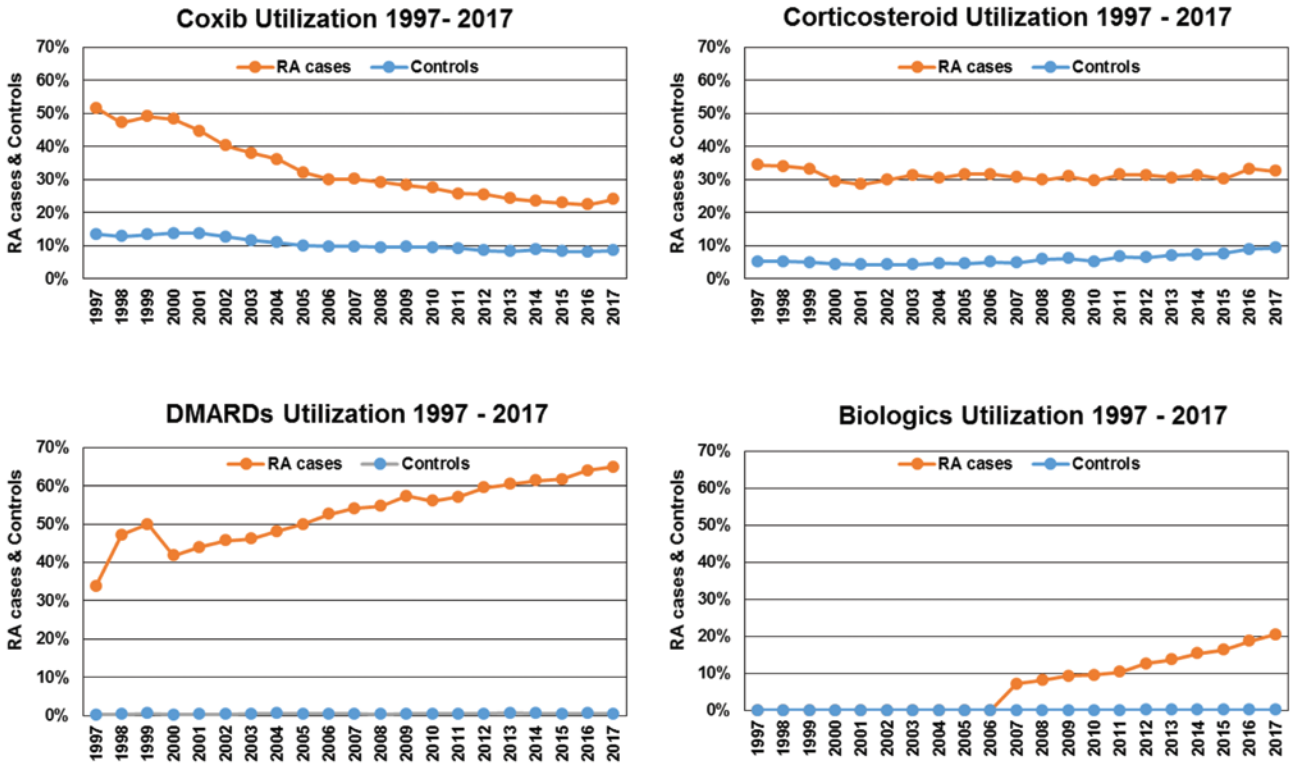

Figure 1. Annual utilization of coxibs, corticosteroids, DMARDs, and biologics over 20 years as indicated by the proportion of RA cases and controls who received one or more prescriptions per year. DMARD: disease-modifying antirheumatic drugs; RA: rheumatoid arthritis.

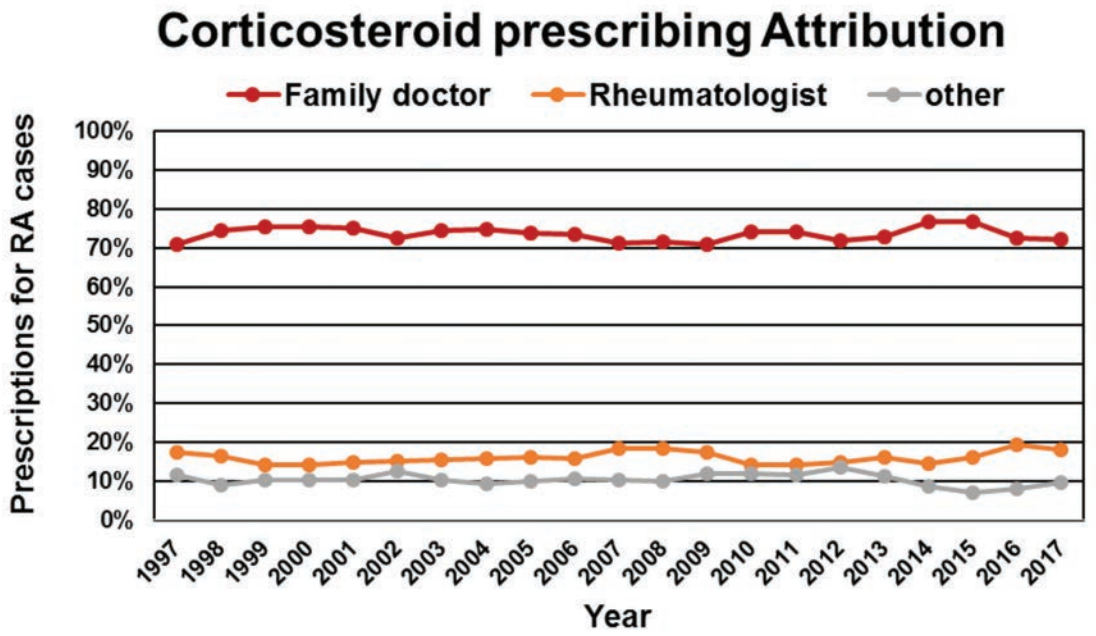

Figure 2. The annual proportion of total corticosteroid prescriptions for RA cases provided by family physicians and nonfamily physicians over 20 years. RA: rheumatoid arthritis.

CS without DMARDs and were more likely to be older, had lower incomes, and less likely to have seen a rheumatologist compared to DMARD users. In a UK study of 38,884 patients with RA over 17 years, 47% of patients received oral CS for a median percentage of 26.3% of follow-up time and CS were more commonly prescribed in older patients.[11] In a Canadian study of 16,207 patients with RA over 65 years of age, 35% of patients received CS.[8] Finally, in an incident RA cohort, 63%

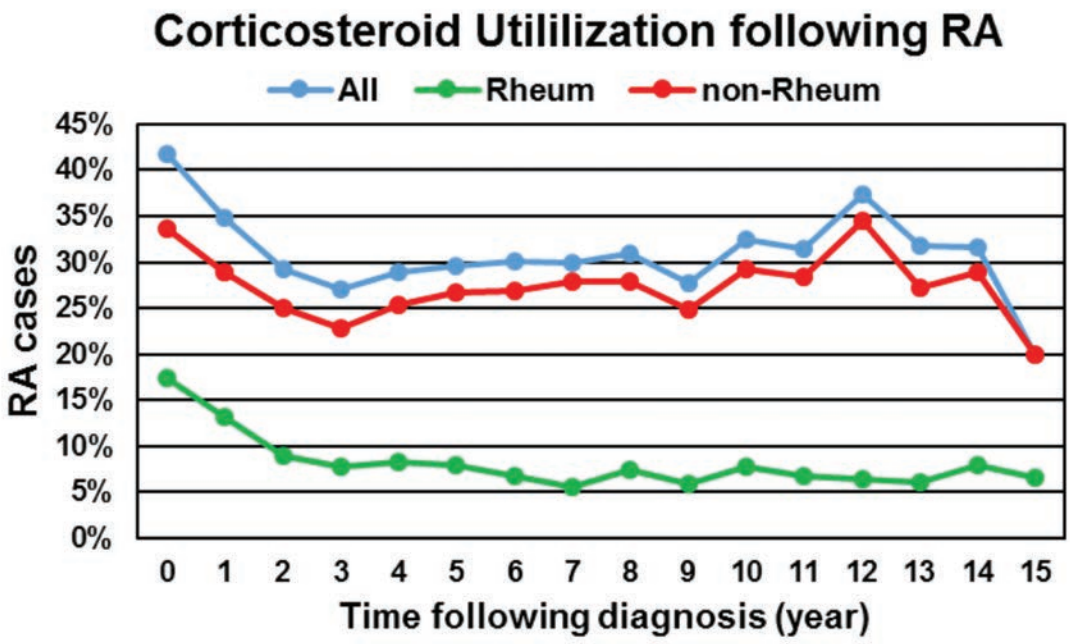

Figure 3. The proportion of all incident RA cases receiving 1 or more prescriptions for corticosteroids per year for up to 15 years following the diagnosis of RA. Attribution of prescriptions to rheumatologists (Rheum) and other physician groups (non-Rheum) is also shown. Some patients received prescriptions from both rheumatologists and other physicians in the same year. RA: rheumatoid arthritis.

of 3992 patients received CS within 12 months following diagnosis.[10] The current study confirms and expands these observations. In our prevalent RA cohort, approximately one-third of cases had an annual exposure to CS compared to up to 10% of controls, and the majority of prescribing was by family physicians. Although there was little change in the mean annual dose of prednisone over time, it was encouraging that the duration of exposure in any given year fell consistently over the latter 10 years of observation. For all physician groups, CS were more frequently prescribed close to the time of RA diagnosis, but less frequently by rheumatologists who also curtailed subsequent prescribing over a follow-up of 14 years. A similar trend was seen when the analysis was restricted to prednisone use and the annual dose of prednisone.

CS play an important role in gaining prompt control of acute polyarthritis in patients with RA. However, there are concerns surrounding their long-term use, even in low doses. Although clinical trials of up to 2 years in duration have suggested less radiographic joint destruction in patients with RA treated concurrently with low-dose CS,[12,13,14] this has not been replicated in a more recent observation study of 5 years' duration.[15] Further, as reflected in recent European League Against Rheumatism guidelines for management of RA,[16] in the era of synthetic and biologic DMARDs, the potential benefit of long-term CS, even in low doses, is now challenged by expert opinion. The reasons responsible for the persistent use of CS in our study were not explored and are currently unknown. Possible explanations include reluctance by both patients and physicians to intensify treatment with DMARDs or to commence with biologics due to a fear of drug toxicity or some degree of CS dependency because of adrenal suppression from prolonged use.

What is perhaps less controversial is evidence of toxicity associated with long-term CS in patients with RA. This is particularly persuasive when examining the association with infection. Severe infections,[17] some requiring hospitalization,[18,19] nonserious infections,[8] and infection risk above that seen with methotrexate[20] are all associated with CS use. The frequency of use, even in low doses, is also an important factor. For example, Dixon, *et al*[17] found that the use of 5 mg prednisolone for 3 months, 6 months, and 3 years was associated with a 30%, 46%, and 100% increased risk of serious infection compared to patients with RA who did not use CS. Concern about using CS is also shared by patients with RA, with 68% of 158 consecutive ambulatory patients with RA seen in 1 center declining to take them.[21] Notwithstanding the possibility of confounding by indication due to disease activity and severity,[21] there is a compelling need to minimize and preferably eliminate the use of low-dose CS in the long-term management of RA.

What steps can be taken to lower long-term CS exposure in patients with RA? As acknowledged by previous[22] and more current[16] treatment guidelines for RA, CS can play an important role in the management of patients with RA. Prompt control of active disease at presentation or with subsequent flares provides a bridging strategy to allow time for conventional or biologic DMARDs to take effect. Rapid tapering of CS is universally recommended, with total exposure of less than 3 months in the majority of cases.[16] The use of long-term CS, even in doses of prednisone 5 mg/day, are not recommended.[16] In the Canadian healthcare system, and in many others, the role of primary care

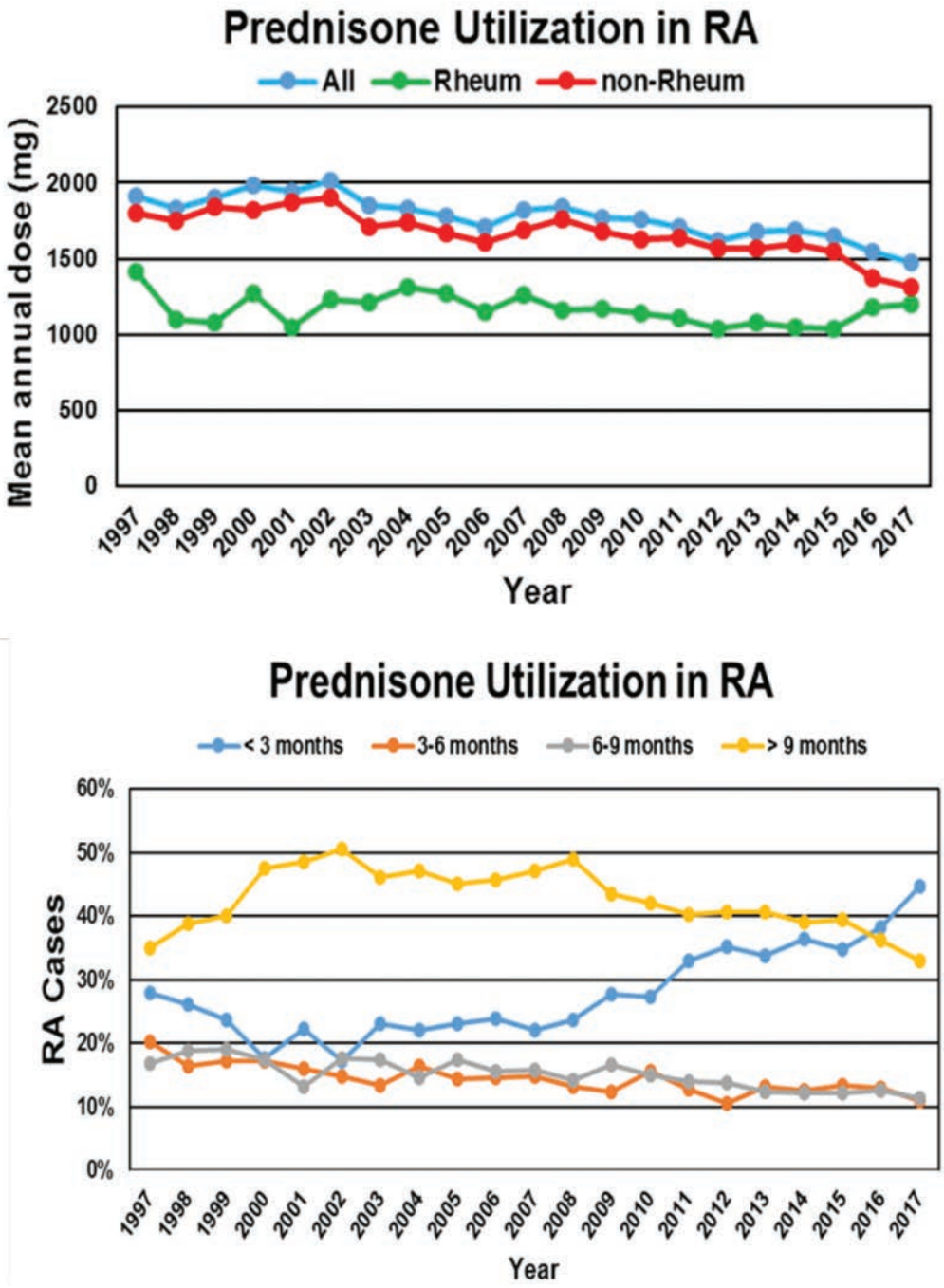

Figure 4. The change in annual utilization of prednisone in RA cases over 20 years. Top panel: change in mean annual dose of prednisone in RA cases and the attribution of prescriptions to rheumatologists (Rheum) and other physician groups (non-Rheum). Some patients received prescriptions from both rheumatologists and other physicians in the same year. Bottom panel: change in the annual duration of exposure to prednisone in RA cases as assessed by 1 or more prescriptions in each 3-month interval. RA: rheumatoid arthritis.

physicians (PCP) is central to the treatment of patients with RA at presentation, during flares, and in the long term. The current study indicates that not only are the majority of CS for older patients with RA prescribed by PCPs but in contrast to rheumatologists, the dose is usually higher and is tapered less aggressively over time. This difference in practice patterns could be addressed though enhanced medical education for PCPs, more communication between rheumatologists and PCPs, and improved access to rheumatologists. The proportion of patients with RA who were seen by a rheumatologist in our study (48.8%) is similar to that reported in another Canadian population health study (48%).[1] In both studies, the remaining patients were seen by general internists and PCPs. Renewed efforts to educate patients on the risks associated with long-term use of CS

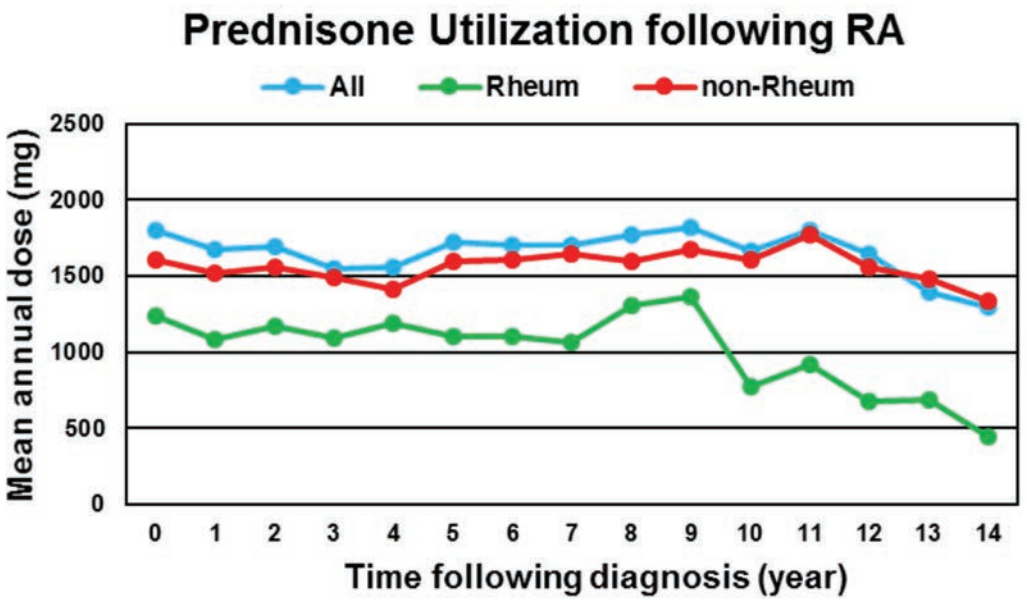

Figure 5. The change in mean annual dose of prednisone in incident RA cases receiving 1 or more prescriptions for prednisone per year for up to 14 years following the diagnosis of RA. Attribution of prescriptions to rheumatologists (Rheum) and other physician groups (non-Rheum) is also shown. Some patients received prescriptions from both rheumatologists and other physicians in the same year. RA: rheumatoid arthritis.

may also be required because for some patients, the symptomatic benefit of low-dose CS may outweigh what appears to be a low risk of toxicity. Finally, in some situations, improved and timelier access to biologic and synthetic DMARDs may be beneficial, especially in view of the prompt onset of action of these agents that may diminish the need for bridging therapy with CS.

Strengths of the current study include prior validation of the case definition for RA against a clinical dataset,[2] a prolonged duration of observation, and the fact that the Nova Scotia population is stable with a mix of urban and rural communities and a range of socioeconomic groups representative of a general Canadian population. There are also some limitations to the study. First, due to the homogenous nature of the Nova Scotia population, it was not possible to examine the effect of race/ethnicity on medication utilization. Second, although the Canada Health Act provides universal coverage for inpatient health services, public payment for medication outside of hospital is restricted predominantly to individuals 65 years of age and older. The health administrative data for the current study were limited to this older adult population, many of whom likely had well-established RA. This was addressed in part by the identification of an incident RA cohort in whom the pattern of CS utilization was comparable to that seen in the prevalent RA cohort. Although the definition of incident cases was in agreement with traditional methodology in population health studies,[1] it would not have excluded patients with RA with longstanding disease who relocated to Nova Scotia during the period of study. Very likely, this represented a minority of RA cases. Third, the cases were not stratified for disease activity or severity, which may have influenced medication utilization patterns. Finally, the possibility of bias due to misclassification of CS exposure needs to be considered. In a UK study[23] that compared the "true" CS utilization determined by patient report with prescription data, ascertainment agreement was high with 86% accuracy but was still considered large enough to lead to important misclassification bias.

Despite these limitations, the current study provides a high-level overview of changes in medication utilization over a 20-year period during which the pharmacological approach to the treatment of RA underwent several paradigm shifts. Many of the transformative outcomes of clinical trials in RA and RA treatment guidelines from rheumatology organizations are reflected in this population health study. Despite the many advances in disease-modifying therapies, an important finding of the current study is the durable utilization of CS that needs to be addressed. The findings presented here provide a benchmark to determine the effect of future efforts to reduce the long-term use of low-dose CS in older adults with RA.

ACKNOWLEDGMENT

The data (or portions of the data) used in this report were made available by Health Data Nova Scotia of Dalhousie University. Although this research is based on data obtained from the Nova Scotia Department of Health and Wellness, the observations and opinions expressed are those of the authors and do not represent those of either Health Data Nova Scotia or the Department of Health and Wellness.

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