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ORIGINAL ARTICLE

Serious Infections in a Population-Based Cohort of 86,039 Seniors With Rheumatoid Arthritis

JESSICA WIDDIFIELD,[1] SASHA BERNATSKY,[2] J. MICHAEL PATERSON,[3] NADIA GUNRAJ,[4] J. CARTER THORNE,[5] JANET POPE,[6] ALFRED CIVIDINO,[7] AND CLAIRE BOMBARDIER[1]

Objective. **To assess risk and risk factors for serious infections in seniors with rheumatoid arthritis (RA) using a case–control study nested within an RA cohort.**

Methods. **We assembled a retrospective RA cohort age ≥66 years from Ontario health administrative data across 1992–2010. Nested case–control analyses were done, comparing RA patients with a primary diagnosis of infection (based on hospital or emergency department records) to matched RA controls. We assessed independent effects of drugs, adjusting for demographics, comorbidity, and markers of RA severity.**

Results. **A total of 86,039 seniors with RA experienced 20,575 infections, for a rate of 46.4 events/1,000 person-years. The most frequently occurring events included respiratory infections, herpes zoster, and skin/soft tissue infections. Factors associated with infection included higher comorbidity, rural residence, markers of disease severity, and history of previous infection. In addition, anti–tumor necrosis factor agents and disease-modifying antirheumatic drugs were associated with a several-fold increase in infections, with an adjusted odds ratio (OR) ranging from 1.2–3.5. The drug category with the greatest effect estimate was glucocorticoids, which exhibited a clear dose response with an OR ranging from 4.0 at low doses to 7.6 at high doses.**

Conclusion. **Seniors with RA have significant morbidity related to serious infections, which exceeds previous reports among younger RA populations. Rural residence, higher comorbidity, markers of disease severity, and previous infection were associated with serious infections in seniors with RA. Our results emphasize that many RA drugs may increase the risk of infection, but glucocorticoids appear to confer a particular risk.**

INTRODUCTION

Patients with rheumatoid arthritis (RA) have an increased risk of infection compared with the general population (1,2). Risk may be influenced by RA therapies, including biologic drugs and nonbiologic disease-modifying antirheumatic drugs (DMARDs) (3–5). Data from clinical trials, which occur outside of the "real-life" context, do not allow comparisons for real-life differences in risk of infections between various treatment strategies.

The treatment of RA in seniors requires particular vigilance, not only related to compromised host defense mechanisms, but also increasing comorbidities (e.g., diabetes mellitus, renal disease), which may also increase the risk of infection. Since seniors may have an elevated risk for infections, evaluating infection risk in this vulnerable pop-

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[1]Jessica Widdifield, BSc, PhD(c), Claire Bombardier, MD, FRCPC: University of Toronto, Toronto, Ontario, Canada; [2]Sasha Bernatsky, MD, FRCPC, PhD: McGill University, Montreal, Quebec, Canada; [3]J. Michael Paterson, MSc: Institute for Clinical Evaluative Sciences and University of Toronto, Toronto, and McMaster University, Hamilton, Ontario, Canada; [4]Nadia Gunraj, MSc: Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada; [5]J. Carter Thorne, MD, FRCPC: Southlake Regional Health Centre, Newmarket, Ontario, Canada; [6]Janet Pope, MD, MPH, FRCPC: St. Joseph's Health Care, London, Ontario, Canada; [7]Alfred Cividino, MD, FRCPC: McMaster University, Hamilton, Ontario, Canada.

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Address correspondence to Sasha Bernatsky, MD, FRCPC, PhD, Division of Clinical Epidemiology, Research Institute of the McGill University Health Centre, 687 Pine Avenue West, V-Building, Montreal, Quebec, H3A 1A1, Canada. E-mail: sasha.bernatsky@mail.mcgill.ca.

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Significance & Innovations

- Few studies have evaluated infection risk among seniors with rheumatoid arthritis (RA), a more vulnerable population than their younger counterparts, due to compromised host defense mechanisms related to disease, comorbidities, and polypharmacy. We report the rates of serious infections, overall and by type of infection, including organism- and organ-specific infections, among a population-based sample.
- Seniors with RA have significant morbidity related to serious infections. The increased rate is most strongly associated with current glucocorticoid exposure, but comorbidities are also important, as may be the disease itself.

ulation is an important undertaking, especially because they are frequently excluded from clinical trials (6).

While the increased risk of bacterial infections in RA is fairly well documented, there are less data on the risk of other serious infections, particularly invasive fungal infections and viral manifestations, such as herpes zoster (HZ). Our primary objective was to determine the incidence of serious infections (identified from hospitalization or emergency room [ER] data) among seniors with RA, and to assess the influence of demographics, drug exposures, and other factors. This study was performed in the context of the Ontario Biologics Research Initiative, which is a novel undertaking performing real-world surveillance of RA outcomes in Ontario through provincial population-based administrative database analyses.

SUBJECTS AND METHODS

Setting and design. In the province of Ontario, all 13 million residents are covered by universal public health insurance, including access to hospital care and physicians' services. Universal prescription drug coverage, however, is available only to persons ages ≥65 years. Researchers routinely use Ontario's health administrative databases to study drug safety in clinical practice.

A retrospective population-based cohort of RA patients ages ≥66 years was assembled using Ontario health administrative data from April 1, 1992 to March 1, 2010. Within this cohort, we developed a case–control study to assess the risk of serious infections from 1998–2010, the period for which we had detailed information about patients' prescription drugs. The study was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre in Toronto, Ontario, Canada.

Data sources. We used the Ontario Health Insurance Plan (OHIP) Database (7) to identify physician service claim diagnoses, provided as International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (8). Medication exposures were determined using the pharmacy claims database of the Ontario Drug Benefit Program, which covers residents ages ≥65 years (9). Hospital visits were identified using the Canadian Institute for Health Information Discharge Abstract Database, which contains detailed information regarding all hospital admissions, and the National Ambulatory Care Reporting System, which records all hospital-based and community-based ambulatory care for day surgery and ERs (10). The OHIP Registered Persons Database contains a single unique record for each health care beneficiary and provides demographic information on age, sex, place of residence, death, and emigration. Socioeconomic status (SES) was estimated for each patient by linking their residential postal code to Statistics Canada Census data on neighborhood median household income. These data sets were linked in an anonymous fashion using encrypted health insurance numbers, and they have very little missing information (11).

Cohort definition. We used a previously published algorithm to identify RA patients within the OHIP billing data, based on ≥2 billing code diagnoses of RA (ICD-9-CM code 714) >60 days apart but within 5 years. This approach is similar to the approach used by researchers and by public health surveillance teams in Canada (12). As others have done (13,14), to increase our specificity of RA case ascertainment, cohort members were further required to have ≥1 prescription for an oral glucocorticoidsteroid, a DMARD, or a biologic agent. Cohort entry was the date on which all criteria were met, and patients were followed until outmigration, death, or the end of the study (March 31, 2010).

Identification of cases and controls. We defined RA patients who had an emergency department visit or hospital admission with a "most responsible" (primary) diagnosis of infection between the later of April 1, 1998 or cohort entry and March 1, 2010. For hospitalizations, we used International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes up until 2002 and the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) thereafter (specific ICD codes for each type of infection are available from the corresponding author). ER visits were captured using ICD-9 diagnosis codes until 2000 and ICD-10 codes thereafter. For those who had multiple events during the study period, the first event served as our index event. In addition to identifying cases of "any infection" overall, we identified cases by type of infection, including both organ- and organism-specific infections (where each separate outcome was analyzed separately). All types of infection were ascertained from hospital or ER ICD diagnoses, except for our case definition of HZ, which was based on ≥1 inpatient or office visit diagnosis (according to the definition employed by Smitten and colleagues [15]), since HZ generally does not require hospitalization. The HZ cases that did not require hospitalization or an ER visit were included in the HZ-specific analyses, but not the analyses of overall infection.

Cases of infection were matched on age (±5 years), sex,

and date of cohort entry (±1 year) to up to 5 controls from the same RA cohort using risk set sampling, whereby controls where matched to each case with respect to sampling time (those at risk). Since our study aim was to evaluate multiple end points (overall infections and by type), separate analyses were done for each infection outcome.

Exposure assessment. We determined the use of methotrexate, leflunomide, azathioprine, cyclophosphamide, sulfasalazine, hydroxychloroquine, other DMARDs (gold, cyclosporine, penicillamine, and chloroquine), anti–tumor necrosis factor (anti-TNF) agents, and other biologic agents from pharmacy claims. We also examined oral glucocorticoid prescriptions and converted those other than prednisone to prednisone-equivalent dosages and categorized each prednisone-equivalent dosage into low (≤5 mg/day), medium (6–9 mg/day), high (10–19 mg/day), and very high (≥20 mg/day) (16,17). In addition, methotrexate was further dichotomized into ≤10 mg/day or >10 mg/day.

Drug exposures were identified using prescription drug claims in the 365 days preceding the index date for each case–control set. Current exposures were those that included the index date (based on duration of the drug supplied, plus 21 days for DMARDs and other drugs, e.g., steroids) and a variable period for biologic agents based on half-life (17). Past exposures were then defined as any noncurrent drug prescriptions in the preceding year before the event. The analyses of drug effects considered all past and current drug exposures in a single model, which therefore controlled for multiple concurrent DMARD exposures. This enabled us to estimate the specific effect of each exposure, independent of whether or not the patients were concomitantly receiving other medications. We also controlled for current use of nonsteroidal antiinflammatory drugs (NSAIDs) and selective cyclooxygenase (COX) inhibitors as part of our efforts to control for disease activity/severity. Since proton-pump inhibitors and H_2 receptor antagonists are commonly coprescribed with NSAIDs/COX inhibitors and may heighten the risk of infection, we also included these in our model.

Covariate information. Covariates included age, SES, urban versus rural residence, and clinical factors (comorbidity and proxies for disease severity). SES was defined as the patient's neighborhood income quintile from the Statistics Canada Census, and the rurality index was based on each patient's postal code at the time of an event. Comorbid conditions were identified from both outpatient and inpatient physician encounters. In addition to including the Deyo-Charlson Comorbidity Index derived from inpatient diagnoses over the previous 5 years (18,19), we counted both the number of distinct prescription drugs each patient received (20) and the number of days in the hospital in the preceding year. We also evaluated specific comorbid conditions that could confound our results (being potentially associated with both drug use and infection risk). Here we used case definitions for diabetes mellitus that have been validated (≥1 hospitalization code OR ≥2 diagnosis codes within 2 years of each other) (21), as well as renal and chronic lung disease algorithms (≥2 diagnosis codes separated by ≥2 months, in each case). We also considered the possible effect of channeling bias, adjusting for the history of each infection end point prior to cohort entry (which could also affect both drug prescriptions and the risk of an event) (22). Finally, since administrative data do not allow direct measures of RA severity or activity, we included proxies of this covariate in our model (2,14,23). These proxies included the number of rheumatology visits between cohort entry and the index date, history of joint replacement, extraarticular RA features (pulmonary involvement, ocular involvement, Felty's syndrome, and vasculitis) and, as mentioned previously, use of NSAIDs and COX inhibitors.

Table 1. Rates of serious infections in a cohort of 86,039 seniors with rheumatoid arthritis: overall, organ-specific, and organism-specific infection event rates for serious infections

Types of infection*	No. of events	Event rate, events/1,000 patient-years
Infections, overall†	20,575	46.36
Respiratory infections, overall	11,545	23.50
Bacterial pneumonia	8,839	17.43
Herpes zoster	4,368	8.54
Skin or soft tissue infections	4,198	8.12
Septicemia	2,056	3.87
Postoperative infections	853	1.61
Pyelonephritis	574	1.08
Septic arthritis	232	0.43
Osteomyelitis	195	0.36
Fungal infections	49	0.09
Endocarditis	35	0.07
Tuberculosis	30	0.05
Meningitis	19	0.04
Central nervous system abscess	16	0.03
Encephalitis	11	0.02

* All types of infection were ascertained from hospital or emergency room International Classification of Diseases, Ninth Revision, Clinical Modification and International Statistical Classification of Diseases and Related Health Problems, Tenth Revision diagnoses, except for our case definition of herpes zoster, which was based on ≥1 inpatient or office visit diagnosis.
† Types of infections are not mutually exclusive. The number of events for overall infections does not equate to the sum of each individual type of infection, since organism- and organ-specific infections can be counted twice (e.g., bacterial pneumonia and respiratory infections).

Statistical analysis. The rates of serious infections, overall and by type of infection, including organism- and organ-specific infections, were determined from the later of April 1, 1998 or cohort entry to the end of followup or March 31, 2010. Rates were estimated by dividing the number of cases observed during the observation period (1998–2010) by the number of years of person-time contributed by individuals for the observation period (1998–2010). Multivariate conditional logistic regression analyses were performed to estimate the effect of factors (demographics, comorbidity, history of previous infection, markers of RA severity, and RA-related drug exposures) on

Table 2. Descriptive characteristics for cases with any serious infection (between April 1, 1998 and March 31, 2010) and their matched controls and the influence of baseline factors and antirheumatic drug exposures on risk of infection*

	Cases (n = 20,575)	Controls (n = 102,860)	Crude OR (95% CI)	Adjusted OR (95% CI)†
Demographics				
Age, mean ± SD years	79.00 ± 6.57	78.70 ± 6.19	1.05 (1.04–1.05)	1.05 (1.04–1.06)
Women	14,259 (69.3)	71,290 (69.3)	–	–
Rural (ref. urban)	4,014 (19.5)	12,872 (12.5)	1.70 (1.64–1.77)	1.51 (1.44–1.58)
Income quintile (ref. 1 − lowest)	4,548 (22.1)	21,265 (20.7)	–	–
2	4,539 (22.1)	22,057 (21.4)	1.04 (1.00–1.08)	1.02 (0.96–1.07)
3	4,106 (20)	20,273 (19.7)	1.01 (0.98–1.05)	1.02 (0.96–1.08)
4	3,697 (18)	18,912 (18.4)	0.97 (0.93–1.01)	1.01 (0.95–1.07)
5	3,596 (17.5)	19,952 (19.4)	0.88 (0.85–0.92)	0.99 (0.93–1.04)
Clinical characteristics				
Deyo-Charlson Comorbidity Index (ref. 0)	5,447 (26.5)	27,186 (26.4)	–	–
1	3,612 (17.6)	12,444 (12.1)	1.56 (1.49–1.62)	1.34 (1.27–1.42)
≥2	5,057 (24.6)	12,006 (11.7)	2.51 (2.42–2.60)	1.44 (1.36–1.52)
No. of distinct medications used (1 year prior to index date), mean ± SD	13.3 ± 6.38	10 ± 5.47	1.10 (1.10–1.11)	1.03 (1.02–1.03)
No. of rheumatologist visits between cohort entry and index date, mean ± SD	8.8 ± 19.48	7.9 ± 17.8	1.00 (1.00–1.00)	0.99 (0.99–0.99)
No. of days in the hospital in the 365 days preceding the index date, mean ± SD	5.6 ± 14.82	2.3 ± 9.7	1.02 (1.02–1.02)	1.01 (1.00–1.01)
Past infection	8,713 (42.3)	28,573 (27.8)	1.96 (1.90–2.02)	1.51 (1.45–1.57)
Diabetes mellitus	5,078 (24.7)	21,002 (20.4)	1.28 (1.24–1.33)	0.97 (0.93–1.01)
Chronic lung disease	7,280 (35.4)	22,774 (22.1)	1.94 (1.88–2.00)	1.31 (1.25–1.36)
Renal disease	1,976 (9.6)	4,849 (4.7)	2.17 (2.05–2.29)	1.26 (1.18–1.36)
Joint replacement	4,984 (24.2)	22,083 (21.5)	1.17 (1.13–1.22)	1.01 (0.97–1.06)
Extraarticular features of RA	5,962 (29)	22,576 (21.9)	1.45 (1.41–1.50)	1.11 (1.07–1.16)
Drug exposures (ref. nonuse)‡				
Anti-TNF agent				
Current use	129 (0.6)	169 (0.2)	3.85 (3.06–4.85)	1.60 (1.19–2.15)
Past use	28 (0.1)	57 (0.1)	2.46 (1.56–3.86)	1.97 (1.10–3.52)
Methotrexate dose, mg				
≤10	2,661 (12.9)	3,513 (3.4)	4.40 (4.17–4.65)	2.38 (2.22–2.56)
>10	64 (0.3)	63 (0.1)	5.18 (3.64–7.35)	2.97 (1.90–4.64)
Past use	905 (4.4)	2,322 (2.3)	2.00 (1.85–2.17)	1.36 (1.23–1.50)
Hydroxychloroquine				
Current use	2,290 (11.1)	3,025 (2.9)	4.23 (3.99–4.48)	2.21 (2.05–2.38)
Past use	757 (3.7)	2,546 (2.5)	1.51 (1.39–1.64)	1.27 (1.14–1.41)
Sulfasalazine				
Current use	356 (1.7)	629 (0.6)	2.87 (2.52–3.28)	1.16 (0.98–1.37)
Past use	273 (1.3)	868 (0.8)	1.59 (1.38–1.82)	0.98 (0.82–1.18)
Leflunomide				
Current use	307 (1.5)	444 (0.4)	3.52 (3.04–4.08)	1.29 (1.07–1.56)
Past use	156 (0.8)	470 (0.5)	1.67 (1.39–2.00)	0.81 (0.63–1.03)
Azathioprine				
Current use	242 (1.2)	182 (0.2)	6.72 (5.54–8.15)	2.48 (1.94–3.18)
Past use	115 (0.6)	189 (0.2)	3.08 (2.44–3.89)	1.53 (1.11–2.11)
Cyclophosphamide				
Current use	33 (0.2)	19 (0)	8.68 (4.94–15.27)	2.54 (1.24–5.22)
Past use	36 (0.2)	47 (0)	3.83 (2.48–5.91)	1.97 (1.12–3.46)
Other drugs				
Current use	383 (1.9)	412 (0.4)	4.74 (4.12–5.46)	2.78 (2.32–3.32)
Past use	255 (1.2)	787 (0.8)	1.63 (1.41–1.88)	1.42 (1.18–1.71)
NSAIDs/COX inhibitors				
Current use	5,041 (24.5)	6,627 (6.4)	4.82 (4.63–5.03)	3.49 (3.31–3.67)
Past use	4,345 (21.1)	11,772 (11.4)	2.09 (2.01–2.18)	1.97 (1.88–2.07)
H_2 receptor antagonists/PPIs				
Current use	6,391 (31.1)	8,068 (7.8)	6.43 (6.17–6.71)	3.10 (2.95–3.26)
Past use	1,774 (8.6)	4,471 (4.3)	2.11 (1.99–2.23)	2.02 (1.88–2.17)

(continued)

Table 2. *(Cont'd)*

	Cases (n = 20,575)	Controls (n = 102,860)	Crude OR (95% CI)	Adjusted OR (95% CI)†
Prednisone-equivalent dosage, mg/day				
Low: ≤5	2,091 (10.2)	2,519 (2.4)	4.55 (4.28–4.83)	3.96 (3.67–4.27)
Medium: 6–9	541 (2.6)	562 (0.5)	4.93 (4.38–5.56)	4.28 (3.70–4.96)
High: 10–19	1,526 (7.4)	1,167 (1.1)	7.11 (6.56–7.69)	5.98 (5.42–6.59)
Very high: ≥20	1,569 (7.6)	1,195 (1.2)	7.29 (6.73–7.89)	7.57 (6.87–8.34)
Past use	4,978 (24.2)	14,711 (14.3)	2.04 (1.97–2.13)	2.28 (2.17–2.39)

* Values are the number (percentage) unless otherwise indicated. OR = odds ratio; 95% CI = 95% confidence interval; RA = rheumatoid arthritis; anti-TNF = anti–tumor necrosis factor; NSAIDs = nonsteroidal antiinflammatory drugs; COX = cyclooxygenase; PPIs = proton-pump inhibitors.
† Adjusted for all covariates, including demographics (age, socioeconomic status, urban versus rural residence), clinical factors (comorbidity and proxies for disease severity), and current and past use of RA therapies (methotrexate, leflunomide, azathioprine, cyclophosphamide, sulfasalazine, hydroxychloroquine, other DMARDs [gold, chloroquine], anti-TNF agents, NSAIDs and selective COX inhibitors, PPIs, and H_2 receptor antagonists).
‡ Drug exposures were identified using prescription drug claims in the 365 days preceding the index date for each case–control set. Current exposures were those that included the index date (based on the duration of the drug supplied, plus 21 days for DMARDs and other drugs, e.g., steroids, and a variable period for biologic agents based on half-life). Past exposures were then defined as any noncurrent drug prescriptions in the year before the event.

the risk of serious infections overall. Using the same methods, we produced separate estimates for risk of the 4 most commonly occurring infections: respiratory infections, bacterial pneumonia, HZ, and skin or soft tissue infections. Crude and adjusted odds ratio (OR) estimates with 95% confidence intervals (95% CIs) were generated. Detailed results are shown only for overall infections; results for other selected outcomes are shown in Supplementary Table 1 (available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.21812/abstract).

Sensitivity analyses. Three separate sensitivity analyses were performed for the outcome of "bacterial pneumonia" and are shown in Supplementary Table 2 (available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.21812/abstract). To investigate the robustness of our definition of serious infection, we first restricted our definition of infection to include hospitalization visits only (and not to incorporate ER visits as done in our primary analysis). A separate analysis was also performed to include both primary and secondary diagnoses of infection. One additional sensitivity analysis was performed, narrowing our risk window for drug exposures (eliminating the grace period following exposure to immunosuppressant agents).

RESULTS

We identified 86,039 seniors with RA from 1992–2010. As expected, the majority (59,658 [69.3%]) were women, and the mean ± SD age at cohort entry was 72.4 ± 6.98 years; only a minority (14,452 [16.8%]) resided in rural areas.

Over the 443,803 patient-years of followup from 1998–2010, there were 20,575 infections requiring hospitalization or an ER visit, for a rate of 46.4 events/1,000 patient-years. The numbers of events, as well as organ-specific and organism-specific infections, are shown in Table 1. The most common events were respiratory infections (n = 11,545; 23.5 events/1,000 patient-years), including bacterial pneumonia (n = 8,839; 17.4 events/1,000 patient-years), HZ (n = 4,368; 8.5 events/1,000 patient-years), and skin or soft tissue infections (n = 4,198; 8.1 events/1,000 patient-years). In addition, there were 49 serious fungal infections (0.09 event/1,000 patient-years) and 30 cases of tuberculosis (TB; 0.05 event/1,000 patient-years).

For overall infections, when the 20,575 cases were compared to 102,860 matched controls without infection, cases were more often from rural areas and had more comorbidities, drug prescriptions, rheumatology visits, extraarticular features of RA, joint replacements, previous infections, and prior hospitalizations (Table 2). The strongest independent demographic and clinical associations were rural residence, previous infections, higher comorbidity, and extraarticular features.

Table 2 also shows the specific drug exposures and the crude and adjusted ORs (for serious infections overall) for each exposure, adjusted for concomitant medications at the index event date. The most common current drug exposures included glucocorticoids (27.8% cases versus 5.3% controls), methotrexate (13.2% cases versus 3.5% controls), and hydroxychloroquine (11.1% cases versus 2.9% controls). Only 129 cases (0.6%) and 169 controls (0.2%) were currently receiving an anti-TNF agent at the time of the index date. After adjusting for covariates, an increased risk of serious infection was elevated for current use of anti-TNF agents (OR 1.60, 95% CI 1.19–2.15). Among DMARDs, the highest ORs were for cyclophosphamide (OR 2.54, 95% CI 1.24–5.22) and azathioprine (OR 2.48, 95% CI 1.94–3.18) and methotrexate. A dose-response relationship was observed for low-dose methotrexate (OR 2.38, 95% CI 2.22–2.56) and high-dose methotrexate (OR 2.97, 95% CI 1.90–4.64). In addition, previous drug exposures appeared to confer risk as well. However, the highest OR point estimates were found for current exposure to glucocorticoids, with an increasing trend to infection risk at higher doses, and an OR ranging from 3.96 (95% CI 3.67–4.27) at low doses to 7.57 (95% CI 6.87–8.34) at high doses. Similar results demonstrating increasing risk with increasing steroid doses were seen among the 4 most common occurring infections: respiratory infections, bacterial pneumonia,

HZ, and skin or soft tissue infections (see Supplementary Table 1, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.21812/abstract). Sensitivity analyses surrounding our definition of serious infection and narrowing our risk windows for drug exposures did not change the ORs appreciably (see Supplementary Table 2, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.21812/abstract).

DISCUSSION

Experiencing a hospitalization or an ER visit with a primary diagnosis of infection was relatively common in seniors with RA, occurring at a rate of 46.4 events/1,000 patient-years. Smitten et al (2), who defined a serious infection as one requiring hospitalization or outpatient parenteral antibiotics with both primary and secondary diagnoses, showed a lower rate (38.6 events/1,000 patient-years) for serious infections in persons with RA, but only 7.2% of patients were seniors and the majority of patients (77%) had no comorbidities.

Respiratory infections (23.5 events/1,000 patient-years) were our leading cause of site-specific infections in our sample, with bacterial pneumonia (17.4 events/1,000 patient-years) being a key contributor to this burden. Few studies have addressed the risk of pneumonia among seniors with RA; however, our estimates are in line with reports by researchers from the National Data Bank for Rheumatic Diseases, who reported 17 events/1,000 patient-years, and their rate reached its maximum among the age group 75–84 years (24). When our definition of serious infection for pneumonia was restricted to those who were hospitalized only, our event rate (9.3 events/1,000 patient-years) was similar to findings published in Quebec, Canada (8.3 events/1,000 patient-years) (14) that used a similar approach to identify cases of infection.

Our rate of HZ (8.5 events/1,000 patient-years) is higher than the rates of HZ estimated from sampling within the US general population (approximately 2–3 events/1,000 patient-years) (25,26). Population-based data have also estimated the burden of HZ to be substantially higher among seniors in the general population versus younger individuals (25,27). Previous reports among patients with RA using a similar definition of HZ within administrative data are similar to our study (9.9 cases/1,000 patient-years) (15,28). Estimates from clinically confirmed RA cohorts have been of a similar magnitude (29–31). However, somewhat varying estimates of risk by country are likely due to differences in RA study populations, drug exposures, and methodology. Our data, being unselected and population based, likely represent a somewhat different patient profile from that seen in clinical registries. However, the lack of standard reporting of disease activity measures in administrative data further highlights the importance of disease registries.

We present novel data on the incidence of serious fungal infections in our cohort (0.09 event/1,000 patient-years). While others have reported that the frequency of serious fungal infections is increasing in immunosuppressed patients (32), the risk of serious fungal infections in RA has only been reported sporadically, with the main emphasis on the surveillance of RA patients undergoing biologic therapy (33).

In our data set, nonpharmacologic factors associated with infection included higher comorbidity, rural residence, markers of disease severity, and history of previous infection. We also observed associations of both previous and current antirheumatic drug use with an increasing infection risk for both overall and specific infections. While some observational data have pointed to the same phenomenon, other studies have been unable to show a definite increased risk of overall infection in RA related to DMARDs (24,34). In fact, other authors have suggested a decreased risk of serious infections with DMARDs that, although counterintuitive, could be a marker for uncontrolled disease activity (35). Methodologically, the studies suggesting a decreased infection risk (2,36) related to DMARDs were different from ours in that they included younger, and therefore less vulnerable, patients. The RA case definition in these studies also differed from ours, relying only on physician diagnoses (not RA treatment). We suspect that since we required some RA treatment in order to enter our cohort, our RA sample may be more homogeneous (in terms of clinical status) and, on average, more severely affected than patients in other administrative data–based studies. In addition, the conflicting results observed that showed a protective effect related to DMARDs may have been due to some channeling bias, such that those with a higher baseline risk of infection may not have been prescribed DMARDs, particularly ones that do have strong immunosuppressive properties. Finally, depletion of susceptible patients is an important consideration in these previous studies, which may have caused an apparent reduction in infection risk due to DMARD exposures and may partially explain why the magnitude of our risk estimates for each drug exposure is higher than that reported in previous studies (37).

In our study, the drug category with the highest estimate of an independent effect was current glucocorticoid exposure, with a trend for an increasing risk at higher doses. Recently, concerns have emerged regarding glucocorticoids and both serious infections (16,17,36,38) and nonserious infection in RA (39). Of course, again the effects of channeling could be at play, since theoretically in very high-risk patients, physicians might avoid the use of DMARDs and biologic agents (which have relatively long-term immunosuppressive effects) in favor of glucocorticoids, whose immunosuppressive effects may resolve more quickly upon discontinuation. While we did not explore the duration of glucocorticoid use, more recent data have suggested a more delayed impact on infection risk (40).

Regarding anti-TNF agents, Curtis et al recently showed that risk of hospitalization with a physician-confirmed infection was approximately 2-fold higher overall and 4-fold higher in the first 6 months among patients receiving anti-TNF agents versus patients receiving methotrexate alone (41). We also observed an approximately 2-fold increase in risk of serious infection among those receiving anti-TNF agents after adjusting for concomitant drug use.

Had we examined specifically the first 6-month period of exposure, we may have seen an even higher OR for these drugs in our senior population. Since treatment duration can have varying effects on the patient and study outcome, with longer exposures not only leading to clinical improvement but depletion of susceptible patients (healthy drug survivor effect), we opted for the computationally efficient nested case–control design (42).

Our study has both strengths and limitations. Population-based administrative data can be used to generate reasonably precise, generalizable estimates for the risk of infrequent events. The conduct and reporting of this study are in line with recent standards for the use of administrative data in rheumatology research and surveillance (43).

While our approach did not permit confirmation of the RA diagnosis or the serious infection, we combined claims data with dispensed prescriptions to increase the specificity of a diagnosis of RA (2,14). And while exposure to DMARDs was low among cases and controls at the time of our index date, all patients were required to have at least had one exposure to a DMARD, biologic agent, or oral glucocorticoid at the time of cohort entry. We additionally explored variations in the criteria for cohort entry (first RA code versus requiring all criteria to have been met), and our results were robust with respect to the elevated adjusted ORs seen across drug exposures. Our sample was limited to persons ages >65 years, but this is not a limitation per se, since this population has a relatively high prevalence of RA and represents a subgroup most vulnerable to infection.

Our primary analyses limited our definition of serious infection to diagnoses requiring either hospitalization or an ER visit, which underestimates the full burden of infections. We also employed a more comprehensive and sensitive definition to identify HZ, since these cases are more often seen in the outpatient setting. In contrast, we employed a more restricted definition to identify serious cases of TB only (those requiring a hospitalization or at least 2 ER visits) than the methods employed by other researchers, who identified cases of TB based on outpatient visits and anti-TB therapy (44). However, we are cautious in reporting our estimates of TB and interpreting previously reported TB rates determined from administrative data because administrative data routinely overestimate TB risk in rheumatic populations, presumably because of heightened awareness of TB risk in persons exposed to immunosuppressants. Therefore, many of the events that provide TB data are likely to actually rule out TB visits and admissions.

The use of pharmacy claims to classify risk windows for drug exposures can be challenging, but our comprehensive sensitivity analyses confirm the robustness of our results. Because there is no standard approach to represent exposures, our preferred way was to show the effects of all drugs estimated, adjusted for concomitant exposures, relative to no exposure to that drug. We have performed additional sensitivity analyses (which are available upon request from the corresponding author) in which patients were placed into mutually exclusive groups based on a hierarchy of drug exposures. ORs remained high for all drug categories; however, because of the hierarchical nature of the categories, we observed what appeared to be additive effects. Finally, our case–control study was nested within a cohort of seniors with universal health coverage. This is a strength, since several reports have identified an apparent risk reduction over time that may be due to loss to followup (38).

Although we adjusted for proxies of disease activity/severity, residual confounding may exist. However, there are conflicting data on the impact of disease activity on infection risk, with the possibility that there may be an indirect association via the use of glucocorticoids and a decline in function (38,45). Therefore, most of the excess infection seen among medication groups was likely due to medication, as opposed to residual confounding by RA activity. Also, despite our inability to fully adjust for disease activity, adjustment using surrogate markers resulted in risk estimates similar to those reported previously (38). Confounding by indication or channeling bias may have played a role, since seniors at the highest risk for infections may not have been prescribed biologic agents or other immunosuppressive agents. This may have resulted in conservatively low risk estimates for these exposures. We did attempt to control for this by adjusting for comorbidity that heightens infection risk (diabetes mellitus, etc.) as well as history of infection. However, to date, no perfect proxy for disease activity exists for administrative data (23); this is a future research priority.

In summary, these comprehensive analyses present novel findings and confirm previous data from observational studies using large administrative databases, patient registries, and postmarketing surveillance systems on the safety of antirheumatic therapy in clinical practice. Rural residence, higher comorbidity, markers of disease severity, and previous infections were associated with serious infections in older individuals with RA. Our results suggest that both previous and current antirheumatic drug use also increase risk among seniors, although some of the observed effect may be due to channeling. Glucocorticoids appear to confer particular risk. While the relative risk of serious infection was elevated across all antirheumatic treatments, the message should not be that nonuse is the way to reduce infection risk in seniors. Rather, seniors with RA have significant morbidity related to serious infections and require enhanced vigilance in the management of their pharmacotherapy and comorbidities.

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Bernatsky had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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