Rheumatology 2007;46;1157–1160
Advance Access publication 3 May 2007

doi:10.1093/rheumatology/kem076

Concise Report

Anti-rheumatic drug use and risk of serious infections in rheumatoid arthritis

S. Bernatsky[1], M. Hudson[1] and S. Suissa[1,2]

Objectives. To assess the risk of severe infections associated with the use of traditional disease-modifying anti-rheumatic drugs (DMARDs) and glucocorticoid agents in rheumatoid arthritis (RA).

Methods. Our study was a case-control design nested within a cohort of 23 733 RA patients studied between 1 January 1980 and 31 December 2003. Matching on age and gender, and adjusting for comorbidity and physician use, conditional logistic regression was used to estimate the effect of specific drugs on the rate ratio (RR) for infections requiring hospitalization.

Results. The risk for all infections requiring hospitalization appeared to be most elevated with current exposures to cyclophosphamide [RR: 3.26, 95% confidence interval (CI): 2.28–4.67] and systemic glucocorticoid agents (RR: 2.56, 95% CI: 2.29–2.85); azathioprine was associated with a moderate increased risk (RR: 1.52, 95% CI: 1.18–1.97). There was a suggestion of increased risk of pneumonia due to methotrexate (RR: 1.16, 95% CI: 1.02–1.33). The results were similar for the period before and after the introduction of anti-tumour necrosis factor (TNF) agents. The RR point estimate for anti-TNF agents suggested about a 2-fold increased risk for all infections, but the estimate was imprecise.

Conclusions. In this large cohort of RA patients, the most heightened risk of serious infections was seen with the use of glucocorticoid agents and immunosuppressive DMARDs. Assessments of infection risk related to newer and emerging therapies should carefully consider concomitant medication exposures, including traditional DMARDs and glucocorticoid therapy.

Key words: Rheumatoid arthritis, Disease-modifying anti-rheumatic drugs, DMARDs, Infections, Pneumonia, glucocorticoid agents.

Rheumatoid arthritis (RA) is associated with significant morbidity and reduced survival. Suggestion of an increased risk of infections complicating RA has been reported for decades [1–10] with particular concern regarding infections of the musculoskeletal system, soft-tissue and skin, as well as genitourinary and pulmonary infections. The extent to which this risk may be driven by drugs that decrease immune surveillance [notably, disease-modifying drugs, disease-modifying anti-rheumatic drugs (DMARDs) and glucocorticoid agents], is not completely clear. This issue has gained interest in light of reports of serious infections in patients receiving newer RA therapies, such as anti-tumour necrosis factor (TNF) agents [11–14].

One of the difficulties in assessing the effects of these newer agents is the paucity of precise information regarding risk of infections related to the more established 'traditional' DMARDs, including methotrexate, which, along with systemic steroids, are still widely used (and, not uncommonly, in combination with anti-TNF agents). The purpose of our study was to assess the risk in RA of serious infection associated with the use of traditional DMARDs and glucocorticoid agents. We also assessed the risk of pneumonia separately, given that it is one of the most common and life-threatening infections requiring hospitalization.

Patients and methods

We assembled a cohort of study subjects using the administrative medical databases of the Régie d'assurance maladie du Québec (RAMQ) and the Ministry of Health's Maintenance et exploitation des données pour l'étude de la clientèle hospitalière (MEDECHO). In the Province of Quebec, coverage for health services is universal; the RAMQ database maintains information on physician services for all provincial beneficiaries. Our subjects were limited to those registered in the pharmacy claims database of RAMQ, which covers provincial residents aged 65 yrs or older, those who receive social assistance and those who do not have private drug insurance through their employer. This covers about half of Quebec residents over-all (and essentially, all those of age 65 and older). The MEDECHO provincial hospital discharge summary database provides information on all hospital admissions for the entire province, including admission and discharge dates and discharge diagnoses (provided as ICD codes). These databases are linkable through a unique identifier, the personal health insurance number, a 10-digit number that provides a unique identification number for each beneficiary of the Quebec health insurance plan. Access to the denominalized data was granted by the provincial Commission d'accès à l'information, and ethical approval was obtained from the McGill University Institutional Review Board.

For the period between 1 January 1980 and 31 December 2003, we identified all subjects with a diagnosis of RA using the physician billing codes (ICD-9 code 714) and who were dispensed at least one DMARD after 1 January 1980. Cohort entry was defined by the date of the first of these DMARD prescriptions. The DMARDs included methotrexate, hydroxychloroquine, chloroquine, sulphasalazine, azathioprine, leflunomide, cyclophosphamide, cyclosporine, gold compounds, minocycline, penicillamine and TNF-α antagonists (the anti-TNF agents were only listed on the provincial formulary for the study population as of 2002, and no other biologic agents were available for the study period).

Subjects were all followed from the cohort entry date up to the earliest of three possible events: the outcome of interest, death or the end of study period (31 December 2003). Subjects were required to have more than 3 months of eligibility in the health insurance plan prior to cohort entry, and to have no record of a hospitalization for infection at any time prior to their cohort entry date.

[1]Division of Clinical Epidemiology, McGill University Health Centre and [2]Department of Epidemiology and Biostatistics, McGill University, Montreal, Canada.

Submitted 26 October 2006; revised version accepted 2 March 2007.

Correspondence to: Dr S. Bernatsky, Division of Clinical Epidemiology, McGill University Health Centre, 687 Pine Avenue West, V-Building, Montreal, Quebec H3A 1A1, Canada. E-mail: sasha.bernatsky@mail.mcgill.ca

The outcome of interest was the first occurrence of an infection requiring hospitalization during follow-up. These events were identified from hospitalization discharge diagnoses (primary or non-primary); in the administrative database, each hospitalization may have up to 15 discharge diagnoses. Thus our outcome event was defined as a hospitalization discharge diagnosis (primary or non-primary) with an ICD-9 code of 001–139 (the ICD categories for infections of various types, excluding pneumonia) or 480–486 (the ICD categories for pneumonia). Pneumonia was thus included in the main analyses for all infections, and also analysed as an outcome separately.

Due to the complexity of the time-dependent drug exposures, we used a nested case-control design, due to its computational efficiency [15]. For each case of hospitalization for infection that occurred in the cohort, we randomly selected 10 controls, matching on age, gender, month and year of cohort entry, and ensuring that each control was still at risk for a first-time occurrence of infection on the day the case occurred. The date of hospitalization for infection was designated as the index date for each case-control set. All drugs dispensed during the year prior to the index date were identified from the prescription database.

Because disease severity and comorbidity are potentially associated with infection risk, and possibly also with medication exposures, we adjusted for these factors in the following way. We did not have a direct measure of disease severity, but we did assess and control for the average number of physician visits per patient, as a correlate of disease severity. Comorbidity was identified from diagnoses made prior to the index date, from ICD-9 codes for physician encounters (in-patient or out-patient) of diabetes mellitus, cancer, renal disorders, circulatory disease and chronic respiratory conditions. These comorbidity items were chosen because of their potential associations with both medication exposures and the outcomes of interest.

Data analysis

Person-years of follow-up within the cohort were totalled to estimate the incidence rates in the cohort for a first-time infection requiring hospitalization. Within the nested case-control sample, we used conditional logistic regression to estimate the rate ratio (RR) of hospitalization for infection for each of the drug exposures of interest, including DMARDs and systemic glucocorticoid agents, along with 95% confidence intervals (CIs) for the adjusted estimates. Current exposure to each drug was defined as a prescription dispensed during the 45-day period prior to the index date; the adjusted estimates reflect the specific effect of each exposure, independent of whether or not the subjects were concomitantly receiving the other medications.

The DMARDs were analysed in terms of time-dependent current use, assessing the independent effects of the most commonly used DMARD types (Table 2). Systemic glucocorticoid exposures included any oral or parenteral administration. All drugs were included in conditional regression models that controlled concurrently for the other medications and comorbidity. In secondary analyses, we considered the subgroup of individuals aged 65 or older, and the calendar period prior to (*vs* after) the introduction of anti-TNF-α agents.

Results

The cohort included 23 733 individuals who had a diagnosis of RA, were dispensed a DMARD prescription, and had no recent history of infection. Average age at cohort entry was 61.7 yrs; as expected in RA, the majority (69.9%) was women. Drug exposures at cohort entry were as listed in Table 1; the prevalence of drug use for each agent reflects both combination therapy and monotherapy. The entire RA cohort generated 156 520 person-yrs of follow-up time, for an average follow-up of 6.3 yrs. During this time, 1970 cases of serious infection occurred, for an incidence rate of 129.1 events per 10 000 person-years; of these infections, the most common event was pneumonia with 1315 cases, for an incidence rate of 83.4 per 10 000 person-years. There were only 21 cases of tuberculosis recorded.

The mean ages for cases and their matched controls were 71.0 and 71.5 yrs, respectively, and these subjects were 65.5% female. The events occurred at a mean time of 5.5 (S.D. 4.7) yrs after cohort entry. The average yearly number of physician visits in the cases was 5.5, similar to the average of 5.1 for controls.

The adjusted RR estimates reflecting the specific effect of each exposure, independent of whether or not the subjects were concomitantly receiving the other medications, is given in Table 2. As indicated by these estimates, the risk for all infections requiring hospitalization appeared to be most elevated with current exposures to cyclophosphamide (RR: 3.3, 95% CI: 2.3–4.7) and systemic glucocorticoid agents (RR: 2.6, 95% CI: 2.3–2.9); azathioprine was associated with a moderate increased risk (RR: 1.5, 95% CI: 1.2–2.0). Similar effects were seen with pneumonia as the outcome. For methotrexate, there was a trend towards increased risk for all infections, and a moderate increased risk for pneumonia (RR: 1.2, 95% CI: 1.0–1.3). Otherwise, specifically for hydroxychloroquine and for other DMARDs, there was no definite evidence of an increased risk of infection. Limiting our sample to subjects aged 65 yrs and older, the estimates were similar, but with the suggestion of slightly more pronounced effects, noted particularly for methotrexate (adjusted RR: 1.3; 95% CI: 1.1–1.5).

Regarding the RR estimates for the time period prior to (*vs* after) the introduction of anti-TNF agents into the Quebec formulary, the calendar year-specific RR point estimates were, for each agent, slightly lower in the period from 2002–04, although in all cases, for a given drug, the CIs for the calendar year-specific estimates were overlapping. The RR point estimate for anti-TNF agents suggested about a 2-fold increased risk for all infections, but due to the limited number of subjects exposed to these agents, the CI was wide and included the null value (RR: 1.9, 95% CI: 0.7–5.3).

Discussion

We demonstrated, in a large cohort of RA patients, the effects of current drug exposures on risk of serious infection. As might be expected, the highest risk estimates were associated with the agents that had the greatest immunosuppressant effects, including cyclophosphamide and glucocorticoids. The increase in pneumonia related to glucocorticoids is similar to what has been recently reported by Wolfe *et al.* [16].

We saw a moderate increase in the relative risk of infections with azathioprine exposure, and a mild to moderate increased risk of pneumonia with methotrexate exposure. Anti-malarial agents, including hydroxychloroquine and chloroquine, did not appear to be associated with a greatly increased risk of infection.

TABLE 1. Characteristics of RA subjects at cohort entry ($n = 23\ 733$)

Mean age, yrs (±S.D.)	61.7 ± 14.5
Female gender (%)	69.9
DMARD[a] at cohort entry: *n* (%)	
Methotrexate	7044 (29.7)
Azathioprine	453 (1.9)
Cyclophosphamide	380 (1.6)
Anti-malarial agent[b]	9415 (39.7)
Anti-TNF agents[c]	261 (1.1)
All other DMARDs[d]	6180 (26.0)

[a]DMARD, disease-modifying anti-rheumatic drug. The prevalence of drug use for each agent reflects both combination therapy and monotherapy. [b]Anti-malarial agents include hydroxychloroquine and chloroquine. [c]TNF, tumour necrosis factor. Anti-TNF agents (infliximab and etanercept) were first listed on the Quebec provincial formulary in 2002. [d]All other DMARDs: sulphasalazine, leflunomide, cyclosporine, gold compounds, minocycline, penicillamine.

We note that, possibly due to differences in study populations and methodology, the rates of infection in RA patients in earlier studies have varied; our estimates fall within the range of these. Doran *et al*. [10] reported on the rate of hospitalization for infection in 609 subjects with RA, but over a time period earlier than ours (1955–94), and based their case ascertainment on medical records, not administrative data. These two factors may have contributed to higher rates of hospitalizations for infections, both in the RA population (where the rate was 957 infections requiring hospitalization per 10 000 person- years) and the age- and gender-matched control general population (where the rate was 509 infections requiring hospitalization per 10 000 person-yrs). Dixon *et al*. [12] found, in DMARD-treated RA patients, a rate of serious infections equal to 414 events per 10 000 patient-years Conversely, Kroesen *et al*. [17] examined data from a registry of 60 RA patients for the 2-yr period prior to 1999. The rate of infections was surprisingly low (80 cases per 10 000 person-years), which may be explained partly because these RA patients were relatively young (median age ~53 yrs) and also because of some selection bias.

We acknowledge both the strengths and potential limitations of our study. In the setting of a rare disease (RA) and a relatively rare outcome (infection requiring hospitalization), administrative claims databases are extremely useful to conduct analyses with large samples and within a relatively short time frame. On the other hand, the use of administrative databases also has potential limitations. Our approach did not permit confirmation of the diagnosis of RA or the outcome of serious infection. Concerning the diagnosis of RA, other musculoskeletal conditions [particularly osteoarthritis (OA), which is relatively common [18]] may be misclassified as RA if one relies solely on physician diagnostic billing codes. However, combining physician encounter data with a dispensed prescription for a DMARD optimizes the validity of the RA diagnosis, since DMARDs are essentially excluded from the regular treatment options for OA [19]. We also note that the demographics (age and gender distribution) of our study cohort is very similar to that of clinical RA cohorts [20].

With respect to the outcome, we considered only infections requiring hospitalization; we acknowledge that not all cases of infections are hospitalized. However, we wished to look at severe cases of infection, hence our inclusion of only those requiring hospitalization; this approach has been successfully used by others [10,17]. We do note that our methods would not include deaths occurring due to acute infections if these deaths occurred without a hospitalization. However, we note that hospitalizations due to infections occur much more commonly than deaths due to infections; the crude mortality rate for infectious causes in Quebec according to Statistics Canada was 14.8 per 100 000 population in 2003 [21], and most of these deaths would have occurred in hospital. Regardless, even if these deaths were not picked up as events through the hospitalization data, according to the estimated rates of deaths due to infections, they would only constitute a small fraction (numbering only about 20 cases, as opposed to the almost 700 cases picked up by hospitalization).

An important potential source of bias in pharmacoepidemiology studies is 'channelling', whereby drug exposure occurs differentially according to pre-existing risk for the outcome event. We were aware of this possibility and did attempt to control for it. Firstly, since our main exposure of interest was DMARD use, we aimed to study a homogeneous population with respect to the likelihood of drug exposure. This was done by assembling an RA cohort whose members 'all' were exposed to DMARDs, and examining risk of infection with respect to DMARD type. We also attempted to exclude subjects with a history of recent serious infection, and to adjust for major comorbidity that might be associated with both exposure and outcome, including diabetes mellitus, cancer, renal disorders, circulatory disease and chronic respiratory conditions. Other studies of this issue have documented the usefulness of this course [10], which would presumably adjust at least for some severe extra-articular RA features, such as lung involvement.

Disease severity in RA is potentially associated with both infection risk and with medication exposures. Though we did not have a direct measure of disease severity, we did assess and control for the average number of physician visits per patient, as a correlate of disease severity. Interestingly, Maradit-Kremers *et al*. [22] recently found that in RA subjects, DMARD use was not associated with disease severity characteristics such as disease

TABLE 2. Crude and adjusted RR, by drug exposure, 1 January 1980 to 31 December 2003

	All infections requiring hospitalization (ICD 9 codes 001–139, 480–486)				
	Cases ($n=1970$)	Controls ($n=19\,700$)	Crude	Adjusted[a]	
Drug exposure[b]	Number exposed	Number exposed	RR	RR	(95% CI[c])
Methotrexate	697	5937	1.29	1.10	(0.98–1.23)
Azathioprine	87	364	2.46	1.52	(1.18–1.97)
Cyclophosphamide	73	116	6.75	3.26	(2.28–4.67)
Anti-malarial agents[d]	542	5350	1.02	1.06	(0.94–1.19)
Anti-TNF agents[e]	5	24	2.14	1.93	(0.70–5.34)
All other DMARDs[f]	347	3403	1.03	0.92	(0.80–1.05)
Glucocorticoids	1344	8150	3.20	2.56	(2.29–2.85)
	Pneumonia only (ICD-9 codes 480–486)				
	Cases ($n=1315$)	Control (13 150)	Crude	Adjusted	
Drug exposure	Number exposed	Number exposed	RR	RR	(95% CI)
Methotrexate	477	3856	1.41	1.16	(1.02–1.33)
Azathioprine	52	259	2.06	1.30	(0.94–1.79)
Cyclophosphamide	31	66	4.87	2.64	(1.60–4.36)
Anti-malarial agents	368	3551	1.06	1.06	(0.92–1.22)
Anti-TNF agents	3	20	1.54	1.29	(0.36–4.67)
All other DMARDs	230	2180	1.07	0.99	(0.84–1.16)
Glucocorticoids	906	5529	3.22	2.07	(2.37–3.08)

[a]Cases and controls are age- and gender-matched. All variables are adjusted for each other and for number of physician visits. [b]Drug exposure is the prescription within the 45 days prior to the index date; includes both oral and parenteral exposures, where applicable. [c]CI, confidence interval. [d]Anti-malarial agents include hydroxychloroquine and chloroquine. [e]TNF tumour necrosis factor; these were first listed on the population provincial formulary only in 2002. [f]DMARD, disease-modifying anti-rheumatic drug. All other DMARDs: sulphasalazine, leflunomide, cyclosporine, gold compounds, minocycline, penicillamine.

duration, rheumatoid factor positivity, joint counts, radiographic changes, nodules and RA complications. In that event, though RA disease severity may be associated with infection incidence (as Doran *et al.* [23] have shown), disease severity may not function as an important confounder of the effects of DMARDs on infection incidence (since a confounder must be associated with both exposure and outcome).

Still, we acknowledge the possibility of residual confounding in our study. Our estimates for the effects of DMARDs and glucocorticoid agents could partially reflect differential prescription habits by physicians according to risk factors for infection, especially if there was substantial error for measurement of comorbidity. However, there is considerable support for our findings on the basis of immunological changes caused by cyclophosphamide, glucocorticoid agents and similar drugs [24].

In summary, we demonstrated, in a large cohort of RA patients, the degree of risk for infection, related to drug exposures. Assessments of infection risk related to emerging therapies should take into careful consideration concomitant medication exposures, particularly immune-suppressive traditional DMARDs and glucocorticoid agents.

Acknowledgements

S.B. is the recipient of career awards from the Canadian Institutes for Health Research (CIHR), Fonds de Recherche en Sante du Quebec (FRSQ), Canadian Arthritis Network, and of support from the McGill University Research Institute and Faculty of Medicine. S.S. is the recipient of the James McGill professorship and the CIHR distinguished investigator award. M.H. is funded by CIHR.

The authors have declared no conflicts of interest.

References

1 Mitchell WS, Brooks PM, Stevenson RD, Buchanan WW. Septic arthritis in patients with rheumatoid disease: a still underdiagnosed complication. J Rheumatology 1976;3:124–33.
2 Rimoin DL, Wennberg JE. Acute septic arthritis complicating chronic rheumatoid arthritis. JAMA 1966;196:617–21.
3 Baum J. Infection in rheumatoid arthritis. Arthritis Rheum 1971;14:135–7.
4 Goldenberg DL. Infectious arthritis complicating rheumatoid arthritis and other chronic rheumatic disorders. Arthritis Rheum 1989;32:496–502.
5 Mutru O, Laakso M, Isomaki H, Koota K. Ten year mortality and causes of death in patients with rheumatoid arthritis. Br Med J 1985;290:1797–9.
6 Prior P. Cause of death in rheumatoid arthritis. Br J Rheumatology 1984;23:92–9.
7 Myllykangas-Luosujarvi R, Aho K, Kautiainen H, Isomaki H. Shortening of life span and causes of excess mortality in a population-based series of subjects with rheumatoid arthritis. Clin Exp Rheumatol 1995;13:149–53.
8 Reilly PA, Cosh JA, Maddison PJ, Rasker JJ, Silman AJ. Mortality and survival in rheumatoid arthritis: a 25-year prospective study of 100 patients. Ann Rheum Dis 1990;49:363–9.
9 Doran MF, Pond GR, Crowson CS, O'Fallon WM, Gabriel SE. Trends in incidence and mortality in rheumatoid arthritis in Rochester, Minnesota, over a forty-year period. Arthritis Rheum 2002;46:625–31.
10 Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls a population-based study. Arthritis Rheum 2002;46:2287–93.
11 Baghai M, Osmon DR, Wolk DM, Wold LE, Haidukewych GJ, Matteson EL. Fatal sepsis in a patient with rheumatoid arthritis treated with etanercept. Mayo Clin Proc 2001;76:653–6.
12 Dixon WG, Watson K, Lunt M *et al.* and British Society for Rheumatology Biologics Register Control Centre Consortium. Serious infection rates, including site-specific and bacterial intracellular infection rates, in rheumatoid arthritis patients treated with anti-TNFalpha therapy: Results from the British Society for Rheumatology Biologics Register (BSRBR). Arthritis Rheum 2006;54:2368–76.
13 Listing J, Strangfeld A, Kary S *et al.* Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis Rheum 2005;52:3403–12.
14 Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA 2006;295:2275–85.
15 Suissa S. Novel approaches to pharmacoepidemiology study design and statistical analysis. In: Strom BL, ed. Pharmacoepidemiology. New York, NY: John Wiley & Sons Ltd, 2000;785–805.
16 Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. Arthritis Rheum 2006;54:628–34.
17 Kroesen S, Widmer AF, Tyndall A, Hasler P. Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-{alpha} therapy. Rheumatology 2003;42:617–21.
18 Reginster JY. The prevalence and burden of arthritis. Rheumatology 2002;41(Supp 1):3–6.
19 Walker-Bone K, Javaid K, Arden N, Cooper C. Regular review: medical management of osteoarthritis. Br Med J 2000;321:936–40.
20 Sany J, Bourgeois P, Saraux A *et al.* Characteristics of patients with rheumatoid arthritis in France: a study of 1109 patients managed by hospital based rheumatologists. Ann Rheum Dis 2004;63:1235–40.
21 Mortality, Summary List of Causes. Catalogue no. 84F0209X ISSN1701-2023. 2006. Ottawa, Statistics Canada.
22 Maradit-Kremers H, Nicola P, Crowson C, O'Fallon W, Gabriel S. Patient, disease, and therapy-related factors that influence discontinuation of disease-modifying antirheumatic drugs: a population-based incidence cohort of patients with rheumatoid arthritis. J Rheumatol 2006;33:248–55.
23 Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Predictors of infection in rheumatoid arthritis. Arthritis Rheum 2002;46:2294–300.
24 Gluck T, Kiefmann B, Grohmann M, Falk W, Straub RH, Scholmerich J. Immune status and risk for infection in patients receiving chronic immunosuppressive therapy. J Rheumatol 2005;32:1473–80.