Infection Risk in RA Linked With Comorbidities

BY KATE JOHNSON

QUEBEC CITY — The increased rate of serious infections seen in patients with rheumatoid arthritis is most strongly associated with current glucocorticoid exposure, but comorbidities are also an important factor, according to findings from a large, nested, case-control study presented at the annual meeting of the Canadian Rheumatology Association.

"When we try to predict risk of infection, we tend to focus on the drugs, particularly the immunosuppressive agents," principal investigator Dr. Claire Bombardier said in an interview. The findings from this research show that physicians need to pay more attention to other, heretofore largely overlooked risk factors, she added.

Dr. Bombardier noted that her study was limited by its reliance on data from a source that does not include complete information on exposure to biologic agents. Use of biologics has been linked to an increased risk for reactivation of tuberculosis as well as primary fungal and other infections.

In two separate posters, Dr. Bombardier presented a retrospective examination of serious infections requiring hospitalization, as well as serious fungal infections, in a cohort of 81,497 seniors with RA.

All subjects were aged older than 65 years (mean, 69 years), and were drawn from the Ontario Biologics Research Initiative administrative database, said Dr. Bombardier, professor of medicine and director of the division of rheumatology at the University of Toronto.

The first study included 14,214 patients with serious infection requiring hospitalization in 1992-2006, with the most common infection being pneumonia (7,026 patients). These subjects were matched to controls from the same cohort according to age, sex, and year of cohort entry.

Multivariate logistic regression analysis was used to assess the independent effects of demographics (age, income, rural/urban residence), comorbidity (based on the Charlson-Deyo comorbidity index), markers of RA severity (number of rheumatology visits, history of joint replacement, presence of extra-articular RA, and prescription NSAID use), and RA-related drug exposure.

Past and current drug exposures were determined based on electronic provincial prescription data, although most biologic use was probably not captured in this database because it is not covered by provincial health insurance.

After adjustment, the study found that current use of glucocorticoids was associated with the highest risk of infection, and that this risk increased with increasing doses. Compared with no exposure, a glucocorticoid dose of 5 mg or less per day was associated with an odds ratio of infection of 3.81. At 6-9 mg/day, the OR was 4.56, rising to 5.58 at a dose of 10-19 mg/day, and 5.46 at a dose of 20 mg or more per day.

Other drugs—both biologics (to the extent their effect was assessed) and disease-modifying antirheumatic drugs—were also associated with risk, but less so, with ORs ranging from 1.1 to 3.64, Dr. Bombardier said.

Within the context of these nonglucocorticoid drugs, comorbidity and markers of disease severity were associated with a similar range of risks of infection. Chronic lung disease was associated with an OR of 1.47, and renal disease with OR of 1.38. The Charlson-Deyo comorbidity index score of 1 had an OR of 1.44, whereas a score of 2 or more had an OR of 1.59.

In terms of markers of disease activity, the presence of one or more extra-articular feature of RA was associated with an OR of 1.14, and a history of joint replacement with an OR of 1.05.

Dr. Bombardier's second study focused specifically on the risk of serious fungal infections within the same cohort, because of "the flurry of interest in fungal infections recently," she said.

A total of 53 serious fungal infections occurred within the cohort, including aspergillosis, coccidioidomycosis, histoplasmosis, blastomycosis, paracoccidioidomycosis, and systemic candidiasis. As with the previous study, cases of infection were matched to 265 controls from the same cohort.

Again, univariate and multivariate logistic regression analysis assessed the independent effects of demographics, comorbidity, markers of RA severity, and RA-related drug exposure.

After adjustment, the study found that cases were more likely than controls to live in rural areas (OR, 6.8) and to have more comorbidity, most commonly lung (OR, 1.27) and renal disease (OR, 1.95).

Compared with no prednisone, there was a greater risk of fungal infection associated with prednisone doses of 10-19 mg/day (OR, 1.90) and more than 20 mg/day (OR, 4.0).

Only 17 of 53 cases were currently exposed to a DMARD at the time of the fungal infection, and no case was currently exposed to a biologic agent.

Compared with no exposure, a higher risk of infection was associated with current exposure to sulfasalazine (OR, 1.90), methotrexate (OR, 1.66), and hydroxychloroquine (OR, 1.64).

Dr. Bombardier said this information should help physicians refine decision making about adjusting RA patients' medication dose.

"When you're worrying about a patient, don't focus just on the drugs. Think about whether they have renal disease, or whether they have lung disease. That is as important [as], if not more important than, worrying about the drugs," she said. ■

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Link Between RA and Carotid Artery Stenosis Questioned

BY MITCHEL L. ZOLER

PHILADELPHIA — The increased atherosclerotic disease that generally accompanies rheumatoid arthritis may not consistently involve carotid artery stenosis, according to two reports at the annual meeting of the American College of Rheumatology.

In one study with 195 rheumatoid arthritis patients and a nearly equal number of controls, carotid atherosclerosis was not clearly linked with coronary atherosclerosis in patients with RA, although the link existed in control patients, said Dr. Jon T. Giles, a rheumatologist at Johns Hopkins Medical Center, Baltimore.

Results from a second study, a meta-analysis of 22 prior reports in a total of 1,384 RA patients, showed that the mean extent of carotid intima-media thickness was "far less than expected." Patients' average carotid stenosis corresponded to about a 10%-15% increase in cardiovascular risk, compared with similar people without RA, said Dr. Michael T. Nurmohamed, a rheumatologist at the Free University Medical Center in Amsterdam.

But the relationship between RA and carotid disease is more complex, according to other results reported by Dr. Nurmohamed. Preliminary results from measurement of carotid intima-media thickness in 100 patients with RA showed a mean thickness of 0.83 mm—"comparable" to the thickness in patients with type 2 diabetes—and enough stenosis to produce "a significantly increased cardiovascular risk," Dr. Nurmohamed said.

"What is the best way to assess atherosclerosis in RA patients? For now, there is no recommendation on how to measure" subclinical cardiovascular disease, Dr. Giles said in an interview. No one can say whether measuring coronary disease is better or worse than measuring carotid atherosclerosis. If an RA patient "does not have carotid atherosclerosis, you can't be comfortable that nothing is going on," he said.

He reported on 195 RA patients seen at the arthritis center at Johns Hopkins during October 2004–May 2008 and enrolled in the ESCAPE-RA (Evaluation of Subclinical Cardiovascular Disease and Predictors of Events in Rheumatoid Arthritis) study. Patients were 45-84 years old at enrollment and met the 1987 ACR classification criteria for RA. Enrollment excluded patients with clinically apparent cardiovascular disease. RA patients were matched by age, sex, and ethnicity with 198 controls who did not have RA and who had been enrolled in the Baltimore cohort of MESA (Multi-Ethnic Study of Atherosclerosis).

The results showed that carotid stenosis was linked to a high level of coronary calcium in both the RA patients and controls. But many RA patients without carotid atherosclerosis nonetheless had an increased prevalence of coronary calcium, an incongruous combination that was not seen in the controls.

"The absence of carotid atherosclerosis cannot rule out coronary atherosclerosis in RA patients in the same way that it does in the general population," Dr. Giles said. The implication is that "using subclinical carotid atherosclerosis as a surrogate for coronary atherosclerosis in studies of RA patients may be inaccurate."

The meta-analysis of 22 studies by Dr. Nurmohamed and his associates involved a total of 1,147 controls as well as more than 1,300 RA patients. In 17 of the studies, the carotid intima-media thickness was greater in the RA patients than in the controls. But the average intima-media thickness in the RA patients was 0.71 mm, an average of 0.09 mm larger than in the controls, a difference that corresponds to a modest 10%-15% higher rate of cardiovascular risk.

'The absence of carotid atherosclerosis cannot rule out coronary atherosclerosis in RA patients.'

DR. NURMOHAMED

The low risk level may have occurred because the studies excluded people with cardiovascular disease or risk factors at baseline, a step that may have led to an underestimate of the difference in carotid intima-media thickness between the RA patients and controls.

The carotid data collected directly by Dr. Nurmohamed and his associates came from the CARRÉ (Cardiovascular Research and Rheumatoid Arthritis) study, a prospective study that tracked the incidence of cardiovascular events in patients with RA and in controls. A report from CARRÉ published in September showed the substantially higher level of cardiovascular disease events in 294 patients with RA (13%), compared with 258 controls (5%) (Ann. Rheum. Dis. 2009;68:1395-400).

Additional prospective, controlled studies are needed to further define the cardiovascular disease risk in RA patients, Dr. Nurmohamed said. ■

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