CHEST™

Risk of Mycobacterial Infections Associated With Rheumatoid Arthritis in Ontario, Canada

Sarah K. Brode, MD; Frances B. Jamieson, MD; Ryan Ng, MSc; Michael A. Campitelli, MPH; Jeffrey C. Kwong, MD; J. Michael Paterson, MSc; Ping Li, PhD; Alexandre Marchand-Austin, BSc; Claire Bombardier, MD; and Theodore K. Marras, MD

OBJECTIVE: Patients with rheumatoid arthritis (RA) are at increased risk of TB. Little is known about the risk of nontuberculous mycobacteria (NTM) disease in these patients. We sought to ascertain the rate of NTM infection and TB in all residents of Ontario, Canada, with and without RA.

METHODS: In a cohort study, all Ontarians aged ≥ 15 years in January 2001 were followed until December 2010. Individuals with RA were identified using a validated algorithm to search hospitalization and physician billing claims. We linked Public Health Ontario Laboratory data to identify all cases of laboratory-confirmed TB and NTM disease. Analysis was performed using Cox proportional hazards regression.

RESULTS: We identified 113,558 Ontarians with RA and 9,760,075 Ontarians without RA. Relative to the non-RA group, adjusted hazard ratios (HRs) and 95% CIs for TB (1.92, [1.50-2.47]) and NTM disease (2.07, [1.84-2.32]) demonstrated increased risks in the RA group. Among those with RA, per 100,000 person-years, NTM disease (HR, 41.6; 95% CI, 37.1-46.5) was more common than TB (HR, 8.5; 95% CI, 6.5-10.8). After full adjustment, people with RA who developed NTM disease were 1.81 times as likely to die than uninfected people with RA.

CONCLUSIONS: Mycobacterial infections are more common in Ontarians with RA, with NTM disease more likely than TB. NTM disease is associated with an increased risk of death in patients with RA. Given the rising rates of NTM disease worldwide, determining whether this risk is due to the use of immunosuppressive medications vs RA itself is an important objective for future research.

CHEST 2014; 146(3):563-572

Manuscript received September 9, 2013; revision accepted December 3, 2013; originally published Online First January 2, 2014.

ABBREVIATIONS: GERD = gastroesophageal reflux disease; HMO = health maintenance organization; HR = hazard ratio; NTM = nontuberculous mycobacteria; OHIP = Ontario Health Insurance Plan; RA = rheumatoid arthritis; TNF = tumor necrosis factor

AFFILIATIONS: From the Joint Division of Respirology (Drs Brode and Marras), Department of Medicine and Toronto Western Family Health Team (Dr Kwong), University Health Network and Mount Sinai Hospital, Toronto; Westpark Healthcare Centre (Dr Brode), Toronto; Department of Medicine (Drs Brode and Marras), Department of Laboratory Medicine and Pathobiology (Dr Jamieson), Department of Family and Community Medicine (Dr Kwong), and Institute of Health Policy (Mr Paterson and Dr Bombardier), Management and Evaluation, University of Toronto, Toronto; Public Health Ontario (Drs Jamieson and Kwong and Mr Marchand-Austin), Toronto; Institute for Clinical Evaluative Sciences (Messrs Ng, Campitelli, and Paterson and Drs Kwong and Li), Toronto; Department of Family Medicine (Mr Paterson), McMaster University, Hamilton; and Toronto General Hospital Research Institute (Dr Bombardier), Toronto, ON, Canada.

Part of this article was presented in abstract form (Brode SK, Jamieson FB, Ng R, et al. *Am J Respir Crit Care Med*. 2013;187:A3793).

FUNDING/SUPPORT: The Grant-in-Aid Program of the Ontario Thoracic Society and Ontario Lung Association funded this research. This research was also supported by the Institute for Clinical Evaluative Sciences, a nonprofit research institute funded by the Ontario Ministry of Health and Long-Term Care.

CORRESPONDENCE TO: Theodore K. Marras, MD, Toronto Western Hospital, 7E 452, 399 Bathurst St, Toronto, ON, M5T 2S8, Canada; e-mail: ted.marras@uhn.ca

DOI: 10.1378/chest.13-2058

TB is a leading cause of mortality worldwide and continues to be a problem in Canada, mainly due to the immigration of infected people. Generally well-standardized, treatment of TB typically spans 6 months, with success rates exceeding 95% and low rates of recurrence.[1] Nontuberculous mycobacteria (NTM) are environmental organisms that can cause severe, predominantly pulmonary, infections without person-to-person transmission. NTM disease is increasingly common, with incidence and prevalence substantially exceeding TB in Ontario.[2] NTM disease is most common in the elderly[3] and causes important impairments in quality of life.[4] Treatment of NTM typically spans 18 months, requires multiple drugs, and has overall success rates of only about 56% and high recurrence rates.[5]

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory arthritis associated with significant morbidity and mortality that currently affects approximately 300,000 Canadians.[6] The introduction of anti-tumor necrosis factor (TNF) agents for the treatment of RA has

FOR EDITORIAL COMMENT SEE PAGE 529

raised concerns regarding the risk of TB in this patient population. Patients with RA have increased rates of TB compared with the general population, independent of anti-TNF therapy[7-10]; however, there are few data regarding NTM infection in RA. To clarify issues surrounding mycobacterial disease in patients with RA, we sought to determine the rates of NTM infection and TB in all residents of Ontario, Canada, with and without RA.

Materials and Methods

Study Population and Setting

We conducted a population-based cohort study using linked health administrative data and Public Health Ontario Laboratory data from Ontario. We included all people in Ontario's Registered Persons Database aged ≥ 15 years on January 1, 2001, and followed them until the earliest of emigration, death, or December 31, 2010. Ontario residents have universal public health insurance under the Ontario Health Insurance Plan (OHIP), the single payer for medically necessary services. We excluded people who were ineligible for OHIP coverage (eg, immigrants during their initial 3 months of residence). We obtained ethics approval from the research ethics boards of the University of Toronto (26090) and University Health Network (11-1018-AE), both in Toronto, Canada.

Data Sources and Definitions

The Registered Persons Database, which contains demographic and vital status information about every Ontario resident with a valid health card, was used to identify and characterize our cohort. To identify individuals with RA and comorbidities, we used the Canadian Institute for Health Information Discharge Abstract Database, which contains diagnostic and procedural information recorded during admissions to acute care hospitals, and the OHIP Claims History Database, which contains physician billing claims for inpatient and outpatient services. We used a validated algorithm to identify individuals with RA (Fig 1).[11-17] Comorbidities, including diabetes mellitus, chronic kidney disease, HIV infection, asthma, COPD, and gastroesophageal reflux disease (GERD), were also identified with validated algorithms.[18-23] We looked back from cohort entry to April 1, 1991 (the earliest date available), to identify RA and comorbidities.

Outcomes were identified by linking patient records from health administrative databases with the Public Health Ontario Laboratory database, which captures isolates from 100% of TB cases and approximately 95% of NTM cases in Ontario.[2] Microbiologic methods are described in e-Appendix 1. Case definitions of TB and NTM are presented in Figure 1. Consistent with accepted guidelines, NTM infection was defined as either "isolation" or "disease." Findings relating to NTM disease are presented in this article, while findings relating to NTM isolation are presented in e-Appendix 2. We also assessed the relative frequencies of individual NTM species associated with disease in patients with RA and those without RA by pulmonary vs nonpulmonary disease.

Statistical Analysis

Characteristics of Ontarians with and without RA were compared using one-way analysis of variance for continuous variables and χ^2 tests for categorical variables. Incidence of TB and NTM (collectively referred to as mycobacterial syndromes) was expressed relative to follow-up time (person-years) among Ontarians with and without RA. For the non-RA group, follow-up time began on January 1, 2001, and was censored at death, RA diagnosis (date of first diagnosis code), or end of the study period, whichever came first. Follow-up time for patients with RA began on January 1, 2001 (for prevalent cases), or the date of the first diagnosis code for RA, and was censored at death or end of the study period, whichever came first. Thus, patients in the non-RA group who were subsequently diagnosed with RA contributed person-years to the non-RA group until the date of RA diagnosis and contributed person-years to the RA group after diagnosis. Follow-up was not censored at the time of diagnosis of a mycobacterial syndrome for incidence calculations, but was censored at diagnosis of a mycobacterial syndrome for determination of hazard ratios (HRs).

We attributed TB and NTM cases to RA if the patient was in the RA cohort before the occurrence of the mycobacterial syndrome. We looked back 3 years prior to the study period to find preexisting cases of mycobacterial syndromes. Due to the chronic nature of NTM lung disease, cases of incident NTM were excluded in any patient who previously had the same NTM species isolated during the look-back period. However, cases of TB were included in any given patient who previously had TB isolated, as long as the interval between positive TB culture results was at least 18 months.

Incidence was calculated as events per 100,000 person-years with Poisson 95% CIs. HRs comparing RA and non-RA groups were calculated using Cox proportional hazards regression. A time-dependent variable for the diagnosis of RA was used in the analysis to account for patients developing RA during follow-up. Adjustment was made for age, sex, income, rurality, and comorbidities known to increase the risk of TB and NTM; comorbidities were modeled in a time-varying fashion. Among patients with RA, mortality risk after mycobacterial disease was modeled using Cox proportional hazards regression with time-dependent covariates used to switch patients with RA from uninfected to infected with TB or NTM during follow-up. To control for RA disease severity in mortality analyses, we included extraarticular RA as a covariate.[24] Analyses were performed using SAS, version 9.2 (SAS Institute Inc) and Stata, version 9.2 (StataCorp LP). All tests were two-tailed with the type 1 error (α) rate set at 5%.