Published in final edited form as:
Pharmacoepidemiol Drug Saf. 2012 June ; 21(6): 666–669. doi:10.1002/pds.3243.

ACCURACY OF PHARMACY AND CODED-DIAGNOSIS INFORMATION IN IDENTIFYING TUBERCULOSIS IN PATIENTS WITH RHEUMATOID ARTHRITIS

Christina T. Fiske[1], **Marie R. Griffin**[2], **Ed Mitchel**[2], **Timothy R. Sterling**[1], and **Carlos G. Grijalva**[2]

[1]Division of Infectious Diseases, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN, USA

[2]Department of Preventive Medicine, Vanderbilt University School of Medicine, Nashville, TN, USA

Abstract

Purpose—Previous studies suggest that disease-modifying anti-rheumatic drugs (DMARDs) increase tuberculosis (TB) risk. The accuracy of pharmacy and coded-diagnosis information to identify persons with TB is unclear.

Methods—Within a cohort of rheumatoid arthritis (RA) patients (2000–2005) enrolled in Tennessee Medicaid, we identified those with potential TB using ICD9-CM diagnosis codes and/or pharmacy claims. Using the Tennessee TB registry as the gold standard for identification of TB, we estimated the sensitivity, specificity, predictive values and the respective 95% confidence intervals for each TB case-ascertainment strategy.

Results—Ten of 18,094 RA patients had confirmed TB during 61,461 person-years of follow-up (16.3 per 100,000 person-years). The sensitivity and positive predictive value (PPV) and respective 95% confidence intervals were low for confirmed TB based on ICD9-CM codes alone (60.0% (26.2–87.8) and 1.3% (0.5–2.9)), pharmacy data alone (20% (2.5–55.6) and 4.1% (0.5–14.3)), and both (20% (2.5–55.6) and 25.0% (3.2–65.1)).

Conclusions—Algorithms that use administrative data alone to identify TB have a poor positive predictive value that results in a high false positive rate of TB detection.

Keywords

rheumatoid arthritis; anti-rheumatic drugs; tuberculosis

Corresponding author/author for reprint requests: Carlos G. Grijalva, M.D., M.P.H., Department of Preventive Medicine, Vanderbilt University School of Medicine, 1500 21st Avenue Suite 2600, The Village at Vanderbilt, Nashville, TN 37232-2637, Phone: (615) 343-5499, Fax: (615) 343-0962, carlos.grijalva@vanderbilt.edu.

Potential conflicts of interest: TRS received a research grant from Pfizer to study outcomes of HIV-infected persons; this work did not pertain to TNF-alpha inhibitors. The other co-authors have no disclosures or conflicts.

Author Contributions: Dr. Fiske was responsible for the design and execution of the study as well as data analysis and manuscript preparation. Drs. Griffin, Grijalva, and Sterling contributed to the design of the study, data analysis and review of the manuscript. Mr. Mitchel was responsible for TennCare and TIMS data acquisition, creation of the analysis files, and review of the manuscript.

This work was presented at the 47th Annual Meeting of the Infectious Diseases Society of America, Philadelphia, Pennsylvania, October 2009.

INTRODUCTION

The use of disease modifying anti-rheumatic drugs (DMARDs) is standard of care for the treatment of rheumatoid arthritis (RA).[1] The development of biologic DMARDs such as TNF-α antagonists has changed the outlook and prognosis of patients with RA. However, biologic DMARDs increase the risk of tuberculosis (TB),[2–4] most likely due to blockade of key cytokines involved in the immune response to *Mycobacterium tuberculosis.*

The reported incidence of TB associated with the use of biologic DMARDs has varied markedly in previous pharmacoepidemiologic studies. Some studies employed administrative data such as diagnostic codes and pharmacy prescription files to identify TB in persons prescribed biologic DMARDs. The accuracy of these strategies to identify the new development of TB in RA patients is unknown.

We studied the accuracy of TB case-ascertainment strategies using administrative data such as coded diagnoses and pharmacy data in a cohort of RA patients enrolled in TennCare (Tennessee Medicaid). We used the Tennessee TB registry as the gold standard to determine the sensitivity, specificity, and predictive values of these strategies.

METHODS

Sources of data

We modified a previously assembled cohort of RA patients enrolled in TennCare to allow the identification of patients with available TB registry information in the state of Tennessee (January 2000–December 2005). TennCare, the Medicaid managed-care program in Tennessee, maintains a computerized registry of all enrollees and records of patient-provider encounters and pharmacy benefits usage that allow the reconstruction of medication exposures and the identification of study outcomes.

Information for confirmed TB cases was obtained from the Tuberculosis Information Management System (TIMS), which is a surveillance and case management software application used by TB control programs throughout the U.S. Four criteria are used to confirm TB cases in this registry: (1) Isolation of *M. tuberculosis* from a clinical specimen, (2) A positive stain for acid fast bacilli, (3) Clinical diagnosis, or (4) Provider diagnosis.[5] Personal identifiers common to both TennCare and TIMS were used to identify confirmed TB in the TennCare RA cohort.

Study population

Patients with RA were identified using physician's ICD9-CM coded diagnosis (714.**, except 714.3, juvenile RA). Potential cohort members were considered eligible if they were aged ≥18 years and met ≥1 of the following criteria: (1) One RA-coded healthcare encounter plus any DMARD prescription filled; or (2) Two RA-coded healthcare encounters ≥30 days apart plus an oral glucocorticoid prescription filled.[6]

Follow-up started either on the first day of 2000 for RA patients who fulfilled eligibility criteria on that date or before, or on the date when eligibility criteria were met. Follow-up continued through the earliest of either the date of TB identification, the end of the study, the date of death, or when eligibility criteria were no longer met. All cohort members had at least 180 days of continuous enrollment in TennCare before cohort entry to allow the collection of baseline characteristics.

TB case-ascertainment strategies

We evaluated three strategies to identify TB: (1) a physician encounter coded with an ICD9-CM code for TB (010–018, V12.01, V01.1, and 647.3); (2) pharmacy claims data for ≥2 anti-TB medications (isoniazid, rifampin, rifabutin, pyrazinamide, ethambutol, cycloserine, ethionamide, streptomycin, amikacin, capreomycin, quinolone, and combination isoniazid/rifampin) filled on the same day; and (3) a physician encounter coded for TB *and* pharmacy claims data for ≥2 anti-TB medications filled on the same day (30 days before or after the coded physician encounter).

Confirmed TB cases

Confirmed TB cases were those RA patients who were diagnosed with TB as per the TIMS registry during the study period. The TB identification date was the date that the TB case was reported to the Tennessee Department of Health or the day that anti-TB therapy was initiated, whichever occurred first.

Statistical Analysis

Using TIMS data as the gold standard for identification of persons with TB, we estimated the sensitivity, specificity, predictive values and the respective 95% confidence intervals for each TB case-ascertainment strategy.

The incidence of TB was calculated by dividing the number of confirmed TB cases by the total person-years of follow-up. For comparison, the incidence rates of TB in Tennessee and the U.S. were also calculated by dividing the number of TB cases in TIMS by the cumulative mid- year population census estimates.[7]

All statistical analyses were done in Stata 10.0. The Vanderbilt University Institutional Review Board and the Bureau of TennCare approved the study protocol.

RESULTS

Incidence of TB in the RA cohort

The TennCare cohort (2000–2005) included 18,094 RA patients. During 61,461 person-years of follow-up ten persons with confirmed TB were identified for a crude incidence rate of 16.3 per 100,000 person-years. In contrast, the estimated rates for Tennessee and the U.S. were 5.6 and 5.2 cases per 100,000 person-years, respectively.[8]

Accuracy of TB case-ascertainment strategies

Our TB case-ascertainment strategies yielded very different results, with the number of potential TB cases identified ranging from 8 to 449 (Table 1A). The sensitivities and positive predictive values (PPV) of the three strategies were low. The false positive rates of TB case detection were high when ICD9-CM and pharmacy criteria were employed alone (98.7% and 95.8% respectively). When the criteria were used together, six false positive cases were identified (false positive rate of 75%). The pharmacy and medical claims of these six cases were manually reviewed. None of them received ≥3 months of anti-TB medications, and three of the six had alternative diagnoses identified after the TB diagnosis (atypical mycobacterial infection and blastomycosis).

We also repeated our case-ascertainment evaluation using a pharmacy definition described in a recent study in which TB cases were identified when a person filled isoniazid and rifampin on the same day or filled pyrazinamide at any time during the study period[9](Table 1B). Compared with our original pharmacy strategy, the use of this alternate pharmacy definition yielded a similar sensitivity and the PPV improved only slightly.

DISCUSSION

In the current study, we demonstrated that a number of TB case-ascertainment strategies using coded diagnosis data and pharmacy claims had low accuracy. Our estimated rate of TB (16.3 cases per 100,000 person-years) was much lower than that reported by a previous study that used ICD9-CM codes alone and reported a rate of 219 per 100,000 person-years in another U.S. RA cohort[4]. In our cohort, use of ICD9-CM codes alone would have resulted in 449 rather than 10 cases of TB. Two additional studies reported TB rates of 13.4 per 100,000 person-years when only hospital discharge diagnoses for TB were included[10] and 45.8 per 100,00 person-years when both hospital discharges and outpatient diagnoses for TB coupled with 6 months of two anti-TB drugs were included.[11] Although the second of these strategies was likely more sensitive, the accuracy of either of these approaches is unknown. Patients may be falsely coded as having TB if they were being evaluated for TB and it was later excluded or if they are diagnosed with latent *M. tuberculosis* infection. Identifying TB using pharmacy data is also difficult because most U.S. patients receive their anti-tuberculosis medication from public health departments. A recent study that used data from a private healthcare insurance system and the Veterans Affairs (VA) Administration, found TB diagnostic codes to have a poor PPV that improved with the addition of pharmacy data.[9] Notably, the improvement was substantial in the private system but modest in the VA. In our study of Medicaid patients with RA, we did not find an acceptable improvement by adding pharmacy data to diagnostic codes. Our pharmacy criteria were quite broad in order to maximize sensitivity of detecting persons with TB. When we repeated our analysis using the authors' more specific pharmacy definition we found only a marginal improvement in PPV for identifying TB. This difference may be due to differences in the pharmacy claims systems used to identify TB in the different healthcare systems. Since misclassification introduced by inaccurate definitions could obscure medication effects of interest, our findings suggest that for pharmacoepidemiologic research, validation of administrative claims for identification of TB is necessary.

Our study has several limitations. First, TB is a rare disease in the U.S.[8] and we identified a small number of confirmed TB cases during the study period. However, our count is based on confirmed TB cases rather than relying on ICD9-CM codes and pharmacy data. Second, the sensitivity of TIMS data to detect all TB cases depends on compliance of laboratory and healthcare professionals to guidelines that mandate reporting of TB to public health authorities. A previous study of the Tennessee registry indicated that it was 94% complete.[12] Finally, Tennessee Medicaid enrollees may not be representative of the general population and caution is suggested in extrapolating our findings to other settings.

In summary, our study of RA patients enrolled in Tennessee Medicaid indicates that use of administrative data alone is suboptimal to identify TB cases for pharmacoepidemiologic research. The addition of pharmacy data resulted in only a slight improvement in TB case detection. Our findings suggest that, when feasible, confirmed TB cases should be used in future pharmacoepidemiologic research in order to avoid false representations of the risk of TB associated with medications used to treat RA.

Acknowledgments

We acknowledge the Tennessee Bureau of TennCare of the Department of Finance and Administration and the Tennessee Department of Health, Office of Health Statistics which provided the TennCare data and the Department of Health (Jon Warkentin, M.D. M.P.H.), which provided the tuberculosis data.

Financial support: This work was supported by the Vanderbilt Multidisciplinary Clinical Research Center (National Institutes of Health / National Institute of Arthritis, Musculoskeletal, and Skin Diseases grant [P60 AR056116]), the Institutional National Research Service Award [T32 HS 013833] from the Agency of Healthcare Research and Quality (AHRQ), and a National Institutes of Health K24 [AI065298].

References

1. Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum. 2008; 59:762–784.10.1002/art.23721 [PubMed: 18512708]
2. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med. 2001; 345:1098–1104.10.1056/NEJMoa011110 [PubMed: 11596589]
3. Gomez-Reino JJ, Carmona L, Valverde VR, et al. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. Arthritis Rheum. 2003; 48:2122–2127.10.1002/art.11137 [PubMed: 12905464]
4. Brassard P, Kezouh A, Suissa S. Antirheumatic drugs and the risk of tuberculosis. Clin Infect Dis. 2006; 43:717–722.10.1086/506935 [PubMed: 16912945]
5. Centers for Disease Control and Prevention. Case definitions for infectious conditions under public health surveillance. MMWR Recomm Rep. 1997; 46:1–55.
6. Kim SY, Servi A, Polinski JM, et al. Validation of rheumatoid arthritis diagnoses in health care utilization data. Arthritis Res Ther. 2011; 13:R32.10.1186/ar3260 [PubMed: 21345216]
7. United States Census Bureau. Current Population Survey (Basic). www.census.gov
8. Centers for Disease Control. Reported Tuberculosis in the United States, 2007. U.S. Department of Health and Human Services; Atlanta, GA: Sep. 2008
9. Winthrop KL, Baxter R, Liu L, et al. The reliability of diagnostic coding and laboratory data to identify tuberculosis and nontuberculous mycobacterial disease among rheumatoid arthritis patients using anti-tumor necrosis factor therapy.
10. Bernatsky S, Hudson M, Suissa S. Anti-rheumatic drug use and risk of serious infections in rheumatoid arthritis. Rheumatology (Oxford). 2007; 46:1157–1160. [PubMed: 17478469]
11. Brassard P, Lowe AM, Bernatsky S, et al. Rheumatoid arthritis, its treatments, and the risk of tuberculosis in Quebec, Canada. Arthritis Rheum. 2009; 61:300–304. [PubMed: 19248128]
12. Yokoe DS, Coon SW, Dokholyan R, et al. Pharmacy data for tuberculosis surveillance and assessment of patient management. Emerg Infect Dis. 2004; 10:1426–1431. [PubMed: 15496244]

Key messages

- Algorithms relying on ICD9-CM codes and pharmacy data to identify TB have poor predictive value and may lead to falsely high prevalence estimates.
- Confirmation of tuberculosis is recommended for studies that rely on administrative data to identify persons with tuberculosis

Pharmacoepidemiol Drug Saf. Author manuscript; available in PMC 2013 June 01.

Table 1

Diagnostic Test Characteristics of TB case-ascertainment strategies using ICD9-CM data and two different sets of pharmacy criteria. A) ICD9-CM coded patient-provider encounters (010–018, V12.01, V01.1, and 647.3) and pharmacy data (two anti-tuberculosis medications (isoniazid, rifampin, pyrazinamide, ethambutol, rifabutin, amikacin and fluoroquinolones) filled on the same day). B) ICD9-CM coded patient-provider encounters and pharmacy data (isoniazid and rifampin filled on the same day, or any prescription for rifamate (isoniazid/rifampin combination) or pyrazinamide)

TABLE 1A. Diagnostic Test Characteristics of strategies based on ICD-9CM[a] and pharmacy[b] data for diagnosis of TB

TB Definition	N TB cases	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
ICD9-CM	449	60 (26.2–87.8)	97.6 (97.3–97.8)	1.3 (0.5–2.9)	99.9 (99.9–100)
Pharmacy	49	20 (2.5–55.6)	99.7 (99.7–99.8)	4.1 (0.5–14.3)	99.9 (99.9–100)
Both	8	20 (2.5–55.6)	99.9 (99.9–100)	25 (3.2–65.1)	99.9 (99.9–100)

TABLE 1B. Diagnostic Test Characteristics of strategies based on ICD9-CM[a] and pharmacy[c] data for diagnosis of TB

TB Definition	N TB cases	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
ICD9-CM	449	60 (26.2–87.8)	97.6 (97.3–97.8)	1.3 (0.5–2.9)	99.9 (99.9–100)
Pharmacy	12	20 (2.5–55.6)	99.9 (99.9–100)	16.7 (2.1–48.4)	100 (99.9–100)
Both	6	20 (2.5–55.6)	100 (99.9–100)	33.3 (4.3–77.7)	100 (99.9–100)