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BRIEF REPORT

Conversion of Tuberculosis Screening Tests During Biologic Therapy Among Veteran Patient Population With Rheumatic Disease

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Objective. The optimal strategy to detect the development of tuberculosis (TB) in subjects receiving biologic agents is not clear. The recommendations vary because there is wide variation in the reported rate of seroconversion in various parts of the world. There is a scarcity of long-term studies regarding seroconversion of TB in the United States among these patients.

Methods. This is a retrospective study among veteran populations with rheumatic diseases who received various biologic agents between 2003 and 2014. Subjects who had repeated TB screening tests and adequate follow-up periods were considered for the study.

Results. Out of 298 subjects who received biologic agents, 123 were considered for the study. After the initial negative screening test by tuberculin skin test (TST), patients were screened on an average of 1.2 years for 4.3 to 12 years. A total of 420 tests were performed, which were combination of TST and QuantiFERON-TB gold in-Tube assay. Only 1 out of 123 subjects (0.8%) seroconverted to latent TB and was treated with isoniazid for 9 months.

Conclusion. Our results are in line with a few other studies reported from the United States. We conclude that in areas with low prevalence of TB the seroconversion rate is extremely low and annual testing is unnecessary in low-risk patient populations.

INTRODUCTION

More than 80% of tuberculosis (TB) cases in the United States are associated with reactivation of longstanding, untreated latent TB infection. Testing for and treating latent TB infection in high-risk populations is the most effective way to prevent TB (1). Biologic agents (eg, TNF-α inhibitors, abatacept, tocilizumab, etc) prescribed for immune-mediated inflammatory diseases are associated with increased risk of reactivation of latent tuberculosis (2). Therefore, it is recommended that, prior to initiating these biologic agents, patients undergo screening for TB, regardless of their risk factors, either by tuberculin skin test (TST) or interferon gamma release assays (IGRA) (2,3). However, few subjects develop TB either because of reactivation or newly acquired infection despite a negative screening test while on biologic agents (4). To diagnose these new cases, repeat or serial TB testing has been recommended, but the optimal testing strategy (eg, methods and frequency) has been debated. This is due to the significant variations in the reported rate of seroconversion between patients in the United States versus other parts of the world. Given the scarcity of data available from United States regarding seroconversion, we looked at this risk among veteran subjects who have been exposed to biologic agents and followed for years.

MATERIALS AND METHODS

From January 2003 through December 2014, subjects with various rheumatic diseases who were seen at the outpatient rheumatology clinic of Veterans Affairs Medical Center, Memphis, Tennessee, and received biologic therapy were considered for the study. Subjects were routinely screened for latent TB using TST prior to the initiation of biologic therapy. Follow-up annual screening in our rheumatology clinic was done as per locally instituted protocol starting in 2002-2003 and continued until

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No potential conflicts of interest relevant to this article were reported.

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2012. In addition, testing was done when TB was suspected for concerning symptoms, possible TB exposure, and when biologic agents were switched as per the clinician's discretion. Follow up testing for latent TB was performed periodically by TST or QuantiFERON-TB gold in-Tube (QFT-GIT) assay while the subjects were receiving biologic therapy. A positive TST result was defined as skin induration of more than 5 mm, and QFT-GIT results were reported as positive or negative by our laboratory. Subjects who had at least one or more follow-up test in addition to the prebiologic screening test for latent TB were included in the study. Subjects' information (ie, demographics, comorbidities, disease type, types and duration of nonbiologic disease-modifying antirheumatic drugs [DMARDs], biologics received, etc) were extracted retrospectively from the electronic medical record through chart review by author SI. The VA Medical Center, Memphis, Tennessee, institutional review board approved the study, and all investigations were conducted in conformity with the principles of the Declaration of Helsinki

The 298 subjects who received biologic agents were considered eligible for the study. Subjects who did not have repeat TB screening tests and had not had long-term follow-up were excluded. Long-term follow-up period was defined as 2 years or more after the last TB test. Out of these, 123 subjects were included in final analysis. Descriptive statistics were used to analyze the data.

RESULTS

The baseline patient characteristics are summarized in **Table 1**. Among the study patient population, mean age was 55.5 years, and the majority of the subjects were males. In terms of the rheumatic diseases, a majority of the subjects had been diagnosed with rheumatoid arthritis (RA) followed by undifferentiated inflammatory arthritis, ankylosing spondylitis, and psoriatic arthritis. Median duration of disease was 9.5 years. The interquartile range (IQR) for disease duration was 16 years. The subjects were followed anywhere from 4.3 to 12 years. A majority of the subjects were on nonbiologic DMARDs; methotrexate was the most frequently used agent followed by sulfasalazine, hydroxychloroquine, azathioprine, and leflunomide. One-third of the subjects were receiving prednisone at a mean dose of 7.5 mg/day. Out of the 123 subjects who received biologic agents, the majority (55%) were exposed to multiple biologic agents (etanercept, adalimumab, infliximab, or abatacept). The details of biologic agents' exposure have been summarized in **Table 2**. Variables associated with TB screening tests have been summarized in **Table 3**. A total of 420 screening tests were performed. All subjects had an initial screening test with TST, and subsequent testing was done with either TST or QFT-GIT. Median duration between testing was 1.2 years. The IQR for testing was 1.3 years. Sixty-eight percent had multiple follow-up tests. The various risk factors for TB are presented in **Table 4.** Sixty percent of subjects had no apparent risk factors. Information regarding nonclinical risk factors for TB exposure, such as travel to endemic areas and prison visits, was not available in the chart.

Table 1. Baseline Demographic, disease and treatment characteristics of population

Characteristics	Value
Age (years, Mean ± SD)	55.5±11.5
Sex	
Male	113 (91.9%)
Female	10 (8.1%)
Disease Duration in years (Median)	9.5
Interquartile range (IQR)	16
Corticosteroid (Prednisone) use	30 (24%)
Rheumatic Disease	
Rheumatoid arthritis	67 (54.5%)
Psoriatic arthritis	13 (6.5%)
Ankylosing spondylitis	17 (13.8%)
Inflammatory bowel disease associated arthritis	1 (0.8%)
Undifferentiated inflammatory arthritis	25 (20.3%)
DMARDs	
Methotrexate	61 (48.8%)
Leflunomide	19 (15.2%)
Azathioprine	21 (16.8%)
Hydroxychloroquine	24 (19.2%)
Sulfasalazine	23 (18%)

Table 2. Biologics Agents exposure. Data in parenthesis represents exposure to a drug in terms of patient years

Biologic agents	Value
Infliximab	N=22 (50.6)
Etanercept	N=118 (232.3)
Adalimumab	N=88 (183.3)
Abatacept	N=3 (6.1)

Only 1 out of 123 subjects (0.8%) who received the biologic agents developed a positive TB test 4 years after initial negative screening test. That subject was a male patient who had RA and was treated with methotrexate and infliximab before seroconversion. However, he did not develop active TB and was treated with 9 months of isoniazid (INH) therapy.

DISCUSSION

This is the first study among the US veteran population examining the conversion of TB screening tests in patients with rheumatic disease who are receiving biologic therapy. In our study, 1 out of 123 subjects (0.8%) seroconverted in 4 years after the initial negative test at annual incidence rate of 2.5 per 10 000 patient years. Prior to the positive test, he had another negative TST. He had no apparent exposure to active TB and had no additional risk factors. The chest X-ray was negative, and he received 9 months of INH therapy. This result has important implications in monitoring of rheumatic disease patients on biologic therapy.

The seroconversions during longitudinal testing could result from true latent infection from later exposure or intraindividual variability in the testing method, including initial false-negative

Table 3. TB screening tests

Characteristics	Value
Total test Performed (TST + QFT GIT)	420
QFT GIT	37 (9%)
Time duration between testing (Median)	1.2 year
People with baseline and 1 follow-up test	39 (32%)
People with baseline and 2 follow-up tests	28 (23%)
People with baseline and 3 follow-up tests	22 (17%)
People with baseline and 4 follow-up tests	34 (28%)

tests (4). The conversion rate of latent tuberculosis during biologic therapy depends on the baseline prevalence of TB in the geographical area where the study was performed, and the type of screening method employed (eg, TST vs. IGRAs (4)). Studies performed by TST reported a conversion rate of 0% to 13.6% in Spain, Italy, and Austria (countries with low prevalence of TB) vs. 25% to 37% in high prevalence areas (eg, Turkey, Taiwan, South Korea, etc (4–6)). The conversion rate was 0% to 37% in studies performed using TST vs. 0% to 12% in studies performed by IGRAs (4). To our knowledge, there are few longitudinal studies looking at the conversion of TB screening tests in the United States where TB prevalence is low. These studies mostly presented as an abstract form reporting a conversion rate of 1% or lower (7–9). Another study from Southern California reported a conversion rate of 9.4% (10). Per the authors, the risk of conversion was greater among patients of Hispanic ethnicity and those treated with infliximab, but there were no known risk factors for TB or exposure among these subjects. The authors recommended annual screening for their patient population. Our study's reported conversion rate conforms with a couple of other studies from the United States, though it involves a unique patient population. The VA Medical Center, Memphis, Tennessee, serves more than 196 000 veterans living in a 53-county area of western Tennessee, northern Mississippi, and northwest Arkansas. The incidence rate of TB in these three states is relatively low and varies from 1.5 to 3.0 cases per 100 000 (11). Thus, the extremely low rate of seroconversion in our patients is likely due to the low prevalence rate of TB in the area served by this VA medical center. The high rate of seroconversion in the study from Southern California reflects higher prevalence of TB in California, particularly in the Los Angeles area, compared with other reported studies from United States (11).

Table 4. Risk factors for TB

Characteristics	Value
None	75 (61%)
Diabetes mellitus	29 (23%)
Lung diseases	8 (6%)
ESRD on dialysis	0
Hematological malignancy	1 (0.8%)
Solid cancer	5 (4%)
Small cell carcinoma	0
HIV	0
Solid organ transplant	0
Multiple	5 (4%)

The clinical significance of positive seroconversion is not clear as repeat testing 6 months later showed the majority of the tests to be negative (12,13). Most of the conversions among health care workers in low TB incidence settings appears to be false-positives and were more common with IGRAs than TST, so the authors recommended repeat testing to avoid unnecessary treatment for latent TB (13). Furthermore, in a recent study, Moses et al demonstrated that serial testing for latent TB using the currently available QFT-GIT assay in health care workers in North America would result in overdiagnosis and overtreatment of latent TB (eg, 30 false positives for every true infection diagnosed (14)). Given the low incidence of TB in the general population in the United States and the low rate of seroconversion shown in the handful of studies, including ours, serial testing would result in unnecessary treatment, adverse events, and increased cost. We did not see such an increase in false-positive tests in our sample population, which could be due to the low number of subjects. Two additional studies from the United States reported positive tests without known risk factor or exposure (9,10). There is no information on whether these tests were confirmed by repeat testing, and we speculate that a good percentage of those tests might be false positives. We agree with the American College of Rheumatology (ACR) and Centers for Disease Control and Prevention (CDC) recommendation that annual screening is unnecessary among low-risk patients who are being treated with biologic agents and that follow-up testing is only required in subjects with apparent risk factors and exposure (3,15,16). Though the utility of repeated testing is limited in areas of low disease prevalence like ours, development of active TB can be catastrophic and thus follow-up screening is recommended as per ACR and CDC guidelines. The number of individuals with positive immunodiagnostic results needed to treat to prevent a case of TB among immunocompromised patients vary from 50 to 80 per one study (17). The study subjects included rheumatoid arthritis patients, but it did not mention if they received biologics or not.

Our study has several strengths. This is the first study among the veteran patient population, a high-risk group with multiple comorbidities. Studies have shown that veterans tend to have higher rates of hypertension, diabetes, osteoarthritis, chronic pain, and lung disease (18). Our study reflects data from routine clinical practice and has a relatively longer follow-up duration compared with other studies from the United States.

Our study has certain limitations that are due to the retrospective nature of data and lack of retesting on an exact annual basis after the 1-year time point. The other limitation includes having a mix of QFT-GIT assay as a follow-up screening test after the initial TST.

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AUTHOR CONTRIBUTIONS

Study conception and design. Pattanaik, Islam.
Acquisition of data. Islam.
Analysis and interpretation of data. Pattanaik, Gupta, Islam, Singhal, Raza.

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