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Discordance between Tuberculin Skin Test and Interferon Gamma Release Assay is Associated with Previous Latent Tuberculosis Infection Treatment

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Abstract

Background: The performance of Interferon gamma release assays (IGRA) in drug users and the impact of previous latent tuberculosis infection (LTBI) treatment on discordance of IGRA and tuberculin skin test (TST) are unclear.

Objective: To determine the prevalence and incidence of LTBI using TST and Quantiferon Gold In-Tube test (QFT-G-IT) in a cohort of persons with hepatitis C virus (HCV) and drug use history.

Design: Eligible participants had baseline TST and QFT-G-IT assay and were retested with QFT-G-IT after 12 months to assess prevalence and incidence of LTBI.

Results: Of 193 HCV-infected persons enrolled, 162 (84%) were HIV infected; 132 (81%) were on anti-retroviral therapy and 131 (81%) had a CD4 count >200. 190 (98%) had a history of drug use; only 19 (10%) were active intravenous drug users. 55 (28.5%) had LTBI based on TST results and 13 (7%) were diagnosed with LTBI based on QFT-G-IT. 46/193 persons (23.8%) had positive TST with negative QFT-G-IT test. History of LTBI treatment was a strong predictor of this discordance (OR=41.5; 95% CI 16.2-106.7; p<0.0001). No QFT-G-IT conversions were detected among the 101 initially QFT-G-IT negative patients retested at one year (95% CI: 0-3.6%).

Conclusions: Intravenous drug users who are not actively using drugs have a low prevalence and incidence of LTBI by IGRA. Previous LTBI treatment is associated with a positive TST and a concurrent negative QFT-G-IT.

Keywords: LTBI; TST; IGRA; High-risk groups

Introduction

A third of the world's population is infected with Latent Tuberculosis (LTBI) [1]. In the United States, the prevalence of LTBI in the general population is 4.2%, with higher percentages found in foreign-born persons, homeless individuals, prisoners, HIV patients, close contacts of persons with active tuberculosis and injection drug users [2,3]. About 10% of persons with LTBI develop reactivation TB over a lifetime; this reservoir is the most important factor in the continued occurrence of TB in the US [4].

Tuberculin skin testing (TST) has been the standard method for diagnosing LTBI for over 100 years. The TST measures the cell-mediated delayed hypersensitivity response to purified protein derivative (PPD) derived from *M. tuberculosis*. Major disadvantages of the TST include the need for trained personnel to read the TST and a second visit by the patient for test interpretation [5]. In the past decade, Interferon gamma release assays [IGRAs] have been introduced as an alternative method for detecting LTBI.

Two types of IGRAs are currently used in practice to diagnose LTBI, Quantiferon TB Gold In-Tube [QFT-G-IT; Cellestis, Victoria, Australia] and the TSPOT.TB [Oxford Immunotec, Oxford, United Kingdom]. Both of these tests use *M. tuberculosis* specific antigens, encoded by genes located in the region of difference 1 [RDI1]. The former test is an enzyme-linked immunosorbent assay to measure antigen-specific interferon-γ produced by circulating T-cells in blood and the latter uses an elispot technique to measure peripheral mononuclear cells that produce interferon- γ [5]. Studies have demonstrated moderate agreement [60-80%] between TST and IGRAs with TST being more sensitive and IGRAs being more specific for LTBI [6]. Absence of the boosting phenomenon with repeated testing, non-subjective interpretation and the requirement of only one patient visit make the test a practical alternative to TST [5,6]. Compared to TST, IGRAs are more useful in diagnosing LTBI in individuals with a history of BCG vaccination [7], however like TST; IGRA sensitivity is reduced in HIV infection and in children [8,9]. The utility of IGRAs in serial testing of populations such as health care workers, prison inmates and staff is unclear [10].

Injection and non-injection illicit drug users have been identified

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by the Centers for Disease Control and Prevention [CDC] as a high-risk group for TB infection and disease. The prevalence of LTBI in this group varies between 10 – 67% depending upon the study site, duration of drug use, HIV prevalence, and median age of the cohort [11]. Unstable lifestyle, low motivation for testing and low probability of a return office visit for TST interpretation makes IGRA an attractive test for diagnosing LTBI in this group [12]. However, the performance of IGRAs in drug users has not been clearly defined. The utility of IGRAs in detecting incident latent TB infection in drug users who undergo serial testing is also unknown [11].

The goal of the present study is to define the prevalence and incidence of LTBI in a Hepatitis C infected drug user cohort with TST and QFT-G-IT. In addition, we sought to elucidate risk factors for discordant test results, particularly when TST was positive but QFT-G-IT was negative.

Materials and Methods

Study population

Patients were recruited for this study from the Hepatitis C, HIV and Related Morbidity [CHARM] cohort at Boston University Medical Center [BUMC]. Detailed description of this study cohort has been previously provided [13]. Briefly, the CHARM cohort was initiated in the year 2000 to prospectively evaluate the natural history of HCV infection and HIV/HCV co-infection in an inner city, predominantly drug-using population. Study participation was offered to HCV-infected persons [both male and female], 18 years of age or older, who received their primary care at BUMC, its affiliated Neighborhood Health Centers, or the Boston Veterans Administration [VA] Medical Center. Patients were excluded if they had a previous clinical liver event, if their HCV or HIV sero-status was unknown or if they did not wish to be tested. Between 2008 and 2009, CHARM patients were approached for enrollment into the proposed LTBI-related sub-study. The institutional review board at BUMC approved the study protocol, and all participants provided written informed consent.

Study data

As part of the CHARM study, participants completed a detailed baseline questionnaire and returned for follow-up interviews every 6 months. Baseline and follow-up questionnaires collected information on demographic and socioeconomic factors, tobacco, alcohol and drug use, HIV and Hepatitis C related risk factors and treatment history. For the purpose of this study, birth in Puerto Rico was considered birth outside of the United States. Race/Ethnicity questions were combined and patients were asked to classify themselves in White, African American, Hispanic and Other categories. Homelessness was defined as "living in a shelter" or living "on the street". Substance use was assessed using the Addiction Severity Index and Alcohol Use Disorders Identification Test [AUDIT] questionnaire [14,15]. A patient was considered to consume excessive/harmful amounts of alcohol if the AUDIT score was ≥8. Active drug use was defined as use of Marijuana, Cocaine and/or Heroin by any route [intravenous, nasal, oral, smoking or subcutaneous injection] within the past 30 days. Physical exams and chart reviews were obtained at baseline and every 12 months.

Patients who agreed to be part of the LTBI sub-study answered a separate questionnaire for information on BCG vaccination, LTBI risk factors, previous tuberculin skin testing [TST] and LTBI treatment. The majority of patients were receiving health care at BUMC and affiliated neighborhood health centers. Previously performed TST results were documented only after confirmation from the clinic/hospital where the test was performed. For the remaining patients, a TST was performed as part of the study and results were documented. At the time of enrollment and at the 1-year follow-up visit, blood samples were drawn, incubated in QFT-G-IT assay tubes, and sent to the Massachusetts State Laboratory for analysis. Standard guidelines were used in interpreting TST and QFT-G-IT.

Statistical analysis

Data were analyzed using SAS Version 9.3 [SAS Foundation, Cary, NC]. To identify factors that predict TST-positivity and QFT-G-IT positivity, univariate statistical associations with baseline risk factors were calculated as odds ratios [ORs] and tested for statistical significance by the chi-square and Fisher's exact test. To identify a set of independent predictors of above-mentioned outcomes, we then used conservative multivariate models to simultaneously control for the effects of the various risk factors examined. Variables with a p-value <0.20 in univariate analyses and potential confounders were considered in the multivariate models, using exact logistic regression to calculate adjusted ORs and associated 95% CI [16]. Kappa statistic was calculated to determine concordance between the two tests.

Results

Study population

The demographic characteristics of the 193 patients with known TST and QFT-G-IT results enrolled in the study are shown in (Table 1). Overall, 55/193 [28.5%, 95% CI 20.2%-39.5%] were found to have a positive tuberculin skin test and 138/193 had a negative test at baseline. Only 13/193 [6.7%, 95% CI 2.8%-14.1%] were found to have a positive baseline QFT-G-IT test; 1 [1.1%] had an indeterminate result. 43/193 [22%] persons reported previous INH treatment for LTBI. Concordance between the two tests was poor with a kappa statistic of 0.17 [95% CI=0.05-0.3, p <0.0008]. 9 persons tested positive and 133 persons tested negative with both tests. 46 persons had a positive TST with a negative QFT-G-IT test. Of 101 initially negative QFT-G-IT persons retested after 1 year, 100 were QFT-G-IT-negative and one had an indeterminate test result. The rate of QFT-G-IT conversions was therefore 0% [95% CI 0-3.6%].

Predictors of TST and QFT-G-IT positivity

Predictors of TST positivity are shown in (Table 2). Univariate analysis demonstrated that patients older than 50 years had roughly a two-fold increased risk of having a positive TST [OR=2.0; 95% CI 1.0-4.1; p=0.04] and patients who did not complete high school [OR 0.5; 95% CI 0.3-1.0; p=0.06] had a decreased risk of a positive TST. After adjusting for sex, Hispanic race, homelessness, HIV infection and history of alcohol and non-injection drug use in a multiple logistic regression model, being older than 50 years [aOR 2.2; 95% CI 1.1-4.6; p=0.02] continued to be significantly association with a positive TST result. The multivariate model also showed that persons with an income <$10800/year had an increased risk [aOR 3.4; 95% CI 1.4-9.6; p=0.006] and persons not completing high school had a decreased risk [aOR 0.5; 95% CI 0.2-1.0; p=0.049] of a positive TST result compared to those with higher incomes.

Univariate analyses to assess for predictors of a positive QFT-G-IT result were limited by the small number of outcomes. However, we did find that patients with HIV infection were significantly less likely to have a positive QFT-G-IT result [OR 0.3; 95% CI 0.1-0.8; p=0.01] compared to HIV-uninfected individuals. Patients with a history of

Characteristics	N (%)
Median age in years (range)	46 (25-63)
Gender, Male	119 (62)
Race/Ethnicity	
White, non-Hispanic	43 (22)
Black, non-Hispanic	87 (45)
Hispanic	57 (30)
Other	6 (3)
Education, Less than high school	89 (46)
Unemployment (n=190)	158 (83)
Family income < $10800/year (n=192)	143 (74)
Place of birth	
United States	148 (77)
Puerto Rico	42 (22)
Other	3 (1)
Married or with partner	39 (20)
Homelessness (n=73)	21 (29)
Ever incarcerated	142 (74)
Received BCG vaccination n=(186)	49 (26)
History of receiving INH prophylaxis	43 (22)
History of cigarette smoking	175 (91)
Current harmful alcohol use	20 (10)
Illicit drug use history	
Active intravenous drug users	19 (10)
Active non-intravenous drug users	59 (31)
History (current and past) of intravenous drug use	165 (85)
History (current and past) of non-intravenous drug use	190 (98)
Total current drug (ivdu and non-ivdu) users	69 (36)
Total with past history of drug (ivdu and non-ivdu) use	173 (90)
HIV infected	162 (84)
Receiving/received ART (n=162)	132 (81)
History of opportunistic infections (n=148)	19 (13)
CD4 count at the time of Quantiferon TB Gold In-tube test (n=161)	
CD4 count < 200	30 (19)
CD4 count 200-350	45 (28)
CD4 count >350	86 (53)
Median HIV viral copies/ml (range) (n=162)	75 (50-500000)
< 75 copies/ml	90 (56)
> 75 copies/ml	72 (44)

TB: Tuberculosis; HIV: Human Immunodeficiency virus; HCV: Hepatitis C virus; BCG: Bacille Calmette Guerin; ART: Anti-retroviral treatment; INH: Isoniazid
*Data not available in all subjects for all recorded characteristics.

Table 1: Demographic, TB risk factors, and HIV related characteristics of cohort (n=193)*.

homelessness in the past 6 months [OR 3.5; 95% CI 1.02-12.2; p=0.06] were more likely to have a positive QFT-G-IT result. HIV infection [OR 0.3; 95% CI 0.09-0.9]; p=0.02] was found to have the strongest association for a positive QFT-G-IT result in a multivariate model after adjusting for homelessness and income.

Predictors of positive TST with negative QFT-G-IT

Overall, 46 patients had a positive TST and a negative QFT-G-IT while only 4 had a negative TST and a positive QFT-G-IT. The relationship between demographic factors and a positive TST with negative QFT-G-IT discordant result is shown in Table 3. Univariate and a multivariate model including age, sex, education, income, BCG vaccination history, HIV status, and illicit non-injection drug usage showed that history of LTBI treatment with INH was the only significant predictor of a positive TST and negative QFT-G-IT result.

Discussion

Users of intravenous and other illicit drugs are at high-risk for acquisition of both TB and HIV [3,11]. Our study found moderate prevalence of LTBI by TST [28.5%], low prevalence by QFT-T-IT [7%] and no incidence by QFT-G-IT in a population of persons with a history of drug use. This is in contrast to two previous studies that examined the prevalence of LTBI in drug using populations using QFT-G-IT. Grimes et al. studied LTBI among 119 crack cocaine drug users in Houston, Texas. Of these subjects, 28% tested positive for LTBI with a TST and 34% tested positive for LTBI with QFT-G-IT. Over 90% of this cohort reported smoking crack 48 hours before LTBI screening [17]. Garfein et al. showed that 67% [621/1020] of an IV drug user cohort in Tijuana, Mexico tested positive for LTBI with QFT-G-IT, but TST was not performed. All study subjects were active IV drug users [18]. In contrast, in our study only 36% of subjects were active drug [injection and non-injection] users. Therefore, we conclude that the differences between our results and those found previously are related to an increased risk for recent TB infection associated with active drug use.

Another difference between our cohort and the previous two studies is the prevalence of HIV infection. In our study, 84% of study subjects were HIV-infected, compared with only 7% in the study of Grimes and 4% in the Garfein study [17,18]. However, our HIV-infected subjects were largely on effective antiretroviral regimens with low viral loads and near-normal CD4 counts, thus potentially diminishing differences between the populations. Moreover, lack of QFT-G-IT conversions during the 1-year follow up supports the conclusion that they were at low risk for exposure to TB.

We also found that a large number of our study subjects had discordance between TST and QFT-G-IT, nearly all of whom were TST positive/QFT-G-IT negative [46/50, or 92%]. This pattern of discordance was strongly associated with previous treatment for LTBI. Neither of the previous two studies [17,18], commented on LTBI treatment history among the participants in their studies. If LTBI treatment successfully eliminates viable tubercle bacilli from the host, this might provide an explanation for the observed discordance. Several studies have documented a decline in IFN-γ levels or reversion to test negativity measured by IGRA in patients during TB disease treatment [19-22]. Two prospective follow-up studies of persons with LTBI treated with isoniazid have been reported; in both, IGRA+ recent convertors or close contacts of TB disease cases were followed for up to two years [23,24]. In both studies modest decreases in IFN-gamma production were observed, but IGRA tests did not generally revert to negative. However, it is possible that IGRA tests might have become negative with longer follow-up.

Our study has a number of limitations. First, the small number of patients with a positive QFT-G-IT limited our ability to perform an analysis of risk factors for a positive test. Second, we did not have accurate information about the timing of or adherence to INH treatment in those who reported receiving it. Nonetheless, the very strong association between Isoniazid treatment history and TST positive/QFT-G-IT negative status is unlikely to have occurred by chance. Third, there were missing data, particularly among covariates such as employment, family income, and history of opportunistic infections. Fourth, our inability to successfully locate and retest 117 of the subjects testing negative with QFT-G-IT at baseline limits the reliability of our estimate of the one-year LTBI incidence rates.

Risk factors	TST positive n/total (%)	Unadjusted OR (95%CI)	p-value	Adjusted OR(95% CI), p-value
Age, > 50 yrs	**22/55 (40)**	**2.0 (1.0-4.1)***	**0.04**	**2.3 (1.0-5.0), 0.04**
Gender, Male	38/119 (32)	1.6 (0.8-3.3)	0.24	
Race/Ethnicity				
White, non-Hispanic	11/43 (26)	0.8 (0.3-1.9)	0.78	
Black, non-Hispanic	27/87 (31)	1.3 (0.6-2.5)	0.58	
Hispanic	12/57 (21)	0.6 (0.3-1.3)*	0.19	0.6 (0.2-1.3), 0.18
Education, Less than high school	**19/89 (21)**	**0.5 (0.3-1.0)***	**0.06**	**0.5 (0.2-1.0), 0.049**
Unemployment	45/158 (29)	0.9 (0.4-2.2)	0.90	
Family income, < $10800/yr	**46/143 (32)**	**2.1 (0.9-5.3)***	**0.09**	**3.4 (1.4-9.6), 0.006**
Place of birth, Outside US	12/45 (27)	0.9 (0.4-2.0)	0.91	
Married or with partner	11/39 (28)	1.0 (0.4-2.3)	1.00	
Homelessness	5/21 (24)	0.8 (0.2-2.3)	0.83	
Ever incarcerated	42/142 (30)	1.2 (0.6-2.8)	0.71	
Received BCG vaccination	18/56 (32)	1.3 (0.6-2.8)	0.53	
History of cigarette smoking	50/175 (29)	1.0 (0.3-3.9)	1.00	
Current harmful alcohol use	3/20 (15)	0.4 (0.1-1.5)	0.24	
Illicit drug use history				
Active intravenous drug user	4/19 (21)	0.6 (0.1-2.2)	0.64	
Active non-intravenous drug user	17/59 (29)	1.0 (0.5-2.1)	1.00	
History (current and past) of intravenous drug use	47/165 (28)	1.0 (0.4-2.8)	1.00	
History (current and past) of non-intravenous drug use	53/190 (28)	0.2 (0.003-3.8)*	0.39	0.2 (0.0-3.9), 0.39
HIV infected	49/162 (30)	1.8 (0.7-5.7)*	0.31	2.0 (0.7-6.6), 0.24

OR: Odds Ratios; US: United States; BCG: Bacille Calmette Guerin; HIV: Human Immunodeficiency virus
*Variables included in a multivariate model.

Table 2: Prevalence and association of baseline risk factors with Latent Tuberculosis (LTBI) diagnosed by Tuberculin skin test (TST).

Risk factors	Patients with positive TST and negative QFT-G-IT test			
	n/total (%)	Unadjusted OR (95%CI)	p-value	Adjusted OR(95% CI); p-value
Age, > 50 yrs	18/55 (33)	1.8 (0.9-3.7)*	0.09	
Gender, Male	32/115 (28)	1.6 (0.8-3.3)*	0.18	
Race/Ethnicity				
White, non-Hispanic	10/42 (24)	1.0 (0.4-2.1)	0.91	
Black, non-Hispanic	22/85 (26)	1.1 (0.6-2.2)	0.68	
Hispanic	11/55 (20)	0.7 (0.3-1.5)	0.36	
Education, Less than high school	14/85 (16)	0.4 (0.2-0.9)*	0.02	
Unemployment	37/154 (24)	0.8 (0.3-1.8)	0.56	
Family income, < $10800/yr	38/138 (28)	1.9 (0.8-4.5)*	0.12	
Place of birth, Outside US	11/44 (25)	1.0 (0.5-2.3)	0.93	
Married or with partner	10/38 (26)	1.1(0.5-2.6)	0.77	
Homelessness	3/20 (15)	0.5 (0.1-1.8)	0.41	
Ever Incarcerated	35/138 (25)	1.2 (0.6-2.6)	0.64	
History of BCG vaccination	15/46 (33)	1.7 (0.8-3.6)*	0.18	
History of receiving INH	**34/43 (79)**	**41.5 (16.2-106.7)**	**<0.0001**	**41.5(15.0-114.8); <0.0001**
History of cigarette smoking	41/170 (24)	0.8 (0.3-2.5)	0.7	
Current harmful alcohol use	3/20 (15)	0.5 (0.1-1.8)	0.41	
Illicit drug use history				
Active intravenous drug user	4/19 (21)	0.8 (0.3-2.6)	0.71	
Active non-intravenous drug user	16/57 (28)	1.3 (0.6-2.7)	0.45	
History (current and past) of intravenous drug use	41/160 (26)	1.6 (0.6-4.4)	0.38	
History (current and past) of non-intravenous drug use	44/185 (24)	0.16 (0.01-1.8)*	0.15	
HIV infected	43/159 (27)	3.2 (0.9-11.2)*	0.06	

OR: Odds Ratios; US: United States; BCG: Bacille Calmette Guerin; INH: Isoniazid; HIV: Human Immunodeficiency virus
*Variables adjusted for in a multivariate model.

Table 3: Association of baseline risk factors with a positive Tuberculin skin test (TST) and negative Quantiferon Gold In-tube (QFT-G-IT) assay.

Conclusion

We conclude that the incidence and prevalence of latent tuberculosis infection by QFT-G-IT is low in drug users who are not actively using illicit drugs. Serial screening for LTBI may therefore not be useful or cost-effective in patient populations with demographic characteristics similar to ours. Previous treatment of LTBI with Isoniazid was strongly

associated with a positive TST and negative QFT-G-IT, potentially suggesting cure of LTBI.

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