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Immunodiagnostic Tests' Predictive Values for Progression to Tuberculosis in Transplant Recipients

A Prospective Cohort Study

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Background. Little is known about the predictive value for progression to tuberculosis (TB) of interferon-γ release assays and how they compare with the tuberculin skin test (TST) in assessing the risk of TB infection in transplant recipients. **Methods.** We screened 50 liver transplant (LT) and 26 hematopoietic stem cell transplant (HSCT) recipients with both QuantiFERON-TB Gold In-tube (QFT-GT) and TST and prospectively followed them for a median of 47 months without preventive chemoprophylaxis. **Results.** In the LT cohort, 1 in 22 (4.5%) QFT-GT–positive patients developed posttransplant TB, compared with none of the QFT-GT–negative patients. In the HSCT cohort, none of the 7 QFT-GT–positive patients developed TB, whereas 1 case (5.3%) progressed to active TB among the 19 QFT-GT-negative patients. Comparable results were obtained with the TST: in the LT group, 1 of 23 TST-positive and none of the 27 TST-negative patients developed TB; and in the HSCT group, none of the 8 TST-positive and one of the 18 TST-negative patients progressed to active TB. **Conclusions.** In this cohort of transplant recipients, the positive predictive value of QFT-GT for progression to active TB was low and comparable to that of TST. Although the risk of developing TB in patients with negative results at baseline is very low, some cases may still occur.

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Transplant recipients are at increased risk for tuberculosis (TB) compared to the general population,[1] although its risk varies with the type of transplant and the endemic TB burden.[2-4] In low-prevalence regions, transplant-associated TB mostly arises from the reactivation of a latent TB infection (LTBI), which can be effectively prevented with proper treatment.[5] Therefore, guidelines strongly recommend screening and treatment for LTBI for transplant candidates.[1,6,7]

The tuberculin skin test (TST) has been the reference method for targeting TB chemoprophylaxis. However, its low sensitivity in immunosuppressed patients and its limited ability to identify patients at higher risk of reactivation compromise its reliability in transplant candidates. These limitations, together with the prevailing lack of awareness of the risk of active TB and a fear of isoniazid toxicity,[8] make physicians not offer universal LTBI treatment in this population.

The T cell–based interferon-γ release assays (IGRAs) have been increasingly used for detecting LTBI in many clinical scenarios. Although published data suggest that IGRAs might perform better than TST in immunocompromised patients, such as transplant candidates,[9] little is known about their ability to predict posttransplant TB.[10-14]

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This study aimed to assess the usefulness of the Quanti - FERON-TB Gold In-tube (QFT-GT) for predicting the development of active TB in comparison to the TST in patients undergoing liver transplant (LT) and hematopoietic stem cell transplant (HSCT) in a low-TB burden setting (17.3 per 100,000 population).[15]

MATERIALS AND METHODS

We performed a prospective cohort study to evaluate the performance of TST and QFT-GT for detecting LTBI in consecutive candidates to LT and HSCT between July 2008 and July 2010 at Duran i Reynals and Bellvitge University Hospitals in Barcelona (Spain). All patients provided written informed consent before enrolment, and the ethics committee approved the study.

Transplant candidates were referred to the TB unit for clinical assessment and were asked to enrol after active TB had been excluded. In accordance with current guidelines, we followed a symptom-driven diagnostic workup for ruling out active TB in our cohort. All patients were screened for respiratory and had a chest x-ray performed. Because all our patients were asymptomatic and there were no concerning radiographic findings, no microbiologic testing was necessary to evaluate for active TB infection.

Experienced staff took a blood sample for QFT-GT testing, and TST was administered immediately after. For the TST, any induration 5 mm or greater was considered positive.[7] If the TST result was negative, another TST was administered within a week to assess any booster effect. After testing, patients were referred back to their treating physicians, who decided whether to treat them or not. In LT candidates, the risk of liver toxicity was considered to outweigh the potential benefit of chemoprophylaxis regardless of the TST or QFT-GT results. The lack of specific guidelines and the priority of treating a hematologic malignance also meant no LTBI treatment for patients in the HSCT cohort.

By December 31, 2013, we checked on the statuses of patients by reviewing their medical charts and contacting their physicians. We focused on transplant procedure and the development of active TB and death. A definitive TB diagnosis was defined as the isolation of *Mycobacterium tuberculosis* complex in clinical samples, or a positive molecular test result and response to specific treatment. The incidence of active TB was calculated both as a cumulative incidence and as a density incidence (events per person-year) with 95% confidence intervals (95%CI). The positive/negative predictive values for TB progression for each test were defined as the proportion of patients with positive/negative results who did/did not develop TB within the follow-up period, respectively.

RESULTS

The initial cohort included 90 patients with end-stage liver disease and 27 patients with hematologic malignancies that were considered for LT and HSCT, respectively. However, of the patients with end-stage liver disease scheduled for LT, 24 died before transplantation, 16 improved without LT, and 50 (55.6%) eventually received LT by the follow-up date. All 27 patients with hematologic malignancies received HSCT but we excluded 1 candidate because he was screened for LTBI after transplantation.

The baseline characteristics of both cohorts are summarized in Table 1. The prevalence of LTBI according to the

TABLE 1.

Baseline Characteristics of Liver and Hematopoietic Stem Cell Transplant Recipients

Baseline Characteristics	Liver Transplant, n = 50 (%)	Hematopoietic Stem Cell Transplant, n = 26 (%)	*P*
Age: median (IQR), y	57.5 (51-64)	52.0 (39-60)	<0.01
Male sex	38 (76)	8 (30.8)	<0.01
Spanish born	45 (90)	23 (88.5)	0.56
Risk factors for TB	5 (10.0)	4 (15.4)	0.37
Birth/residence in a high-prevalence country	2 (4.0)	3 (11.5)	0.22
Exposure to active TB	2 (4.0)	1 (3.8)	0.73
Occupational exposure	1 (2.0)	—	—
Immunosuppressive treatment in the previous 6 months	3 (0.06)	24 (92.3)	<0.01
BCG scar	15 (30.0)	8 (30.8)	0.95
Primary reason for transplant			
Alcoholic or hepatitis virus cirrhosis	24 (48.0)	—	—
Hepatocellular carcinoma	20 (40.0)	—	—
Other liver diseases	6 (12.0)	—	—
Acute leukemia	—	6 (23.1)	—
Lymphoma	—	10 (38.5)	—
Multiple myeloma	—	8 (30.8)	—
Others	—	2 (7.6)	—
TST result			
Positive	23 (46.0)	8 (30.8)	0.2
Negative	27 (54.0)	18 (69.2)	0.2
QFT-GT result			
Positive	22 (44.0)	7 (26.9)	0.15
Negative	26 (52.0)	19 (73.1)	0.08
Indeterminate	2 (4.0)	—	—

BCG indicates Bacillus Calmette-Guerin.

QFT-GT was 44% and 26.9% in the LT and HSCT cohorts, respectively; 2 patients in the LT (2.6%) had indeterminate results due to low production upon stimulation with phytohemagglutinin. Regarding TST, 23 patients (46%) in the liver cohort and 8 (30.8%) in the HSCT cohort presented with positive reactions. Correlation of LTBI tests' results and traditional TB risk factors are shown in Table 2. Median time from LTBI screening and transplantation was 15 days (interquartile range [IQR], 8-23).

The LT cohort was followed up for a median of 47.5 months (IQR, 35.0-53.9) after transplantation, over which period, 7 patients died, none was lost to follow-up, and 1 patient developed TB (incidence rate, 0.6 per 100 person-years; 95% CI, 0.3-28.3). He was a 67-year-old man with hepatocellular carcinoma and positive QFT-GT and TST at baseline, who presented with abdominal pain and anorexia 11 months after an orthotopic LT. A computed tomography scan showed an ileocecal mass and a subsequent biopsy confirmed granulomatous inflammation. Culture from colonic and liver biopsies yielded *Mycobacterium tuberculosis* complex, and he made a complete recovery after a 9-month regimen of rifabutin, isoniazid, and levofloxacin.

The HSCT cohort was followed up for a median of 47.51 months (IQR, 27.0-57.5), and of the 26 participants, 7 patients died, 2 were lost to follow-up (after 113 and 370 days), and 1 patient developed TB (incidence rate, 1.1 per 100 person-years; 95% CI, 0.05-5.4). This patient was a 46-year-old woman who had tested negative for TST and QFT-GT before receiving an allogeneic HSCT for acute leukemia. Three months after transplantation, she developed multiple organ dysfunction, which was attributed to progression of the leukemia. She died 15 days after being admitted to the intensive care unit. A skin biopsy culture revealed infection with *M. tuberculosis* complex. Table 3 shows the incidence rates for TB and the predictive values for progression to TB according to each diagnostic test.

DISCUSSION

This study aimed to determine the ability of the QFT-GT to predict the development of active TB in patients undergoing LT and HSCT. Our findings reveal a poor positive predictive value of QFT-GT for progression, which is comparable to that of the TST. Only 1 (4.5%) QFT-GT-positive patient among LT recipients, and none of the QFT-GT-positive HSCT recipients, developed TB within 3.5 years of transplantation. However, the risk of developing active TB among QFT-GT-negative patients was minimal.

To our knowledge, only 4 studies have reported the incidence of active TB in solid organ transplant recipients screened with IGRAs.[10-13] The incidence of TB in IGRA-positive patients could only be assessed in 2 that did not offer preventive therapy.[10,11] Kim et al[10] reported 4 cases of TB among 71 T-SPOT.TB-positive patients in a prospective cohort of 272 kidney transplant recipients, whereas Lange et al[11] found no cases of active TB among 25 QFT-GT-positive solid organ transplant recipients. Furthermore, no cases of TB occurred among the combined 409 IGRA-negative transplant patients in these retrospective studies. On the contrary, in their series of 633 and 87 patients, Jeong et al[13] and Theodoropoulos et al[12] described 1 (1.1%) and 2 (0.3%) cases of TB in QFT-GT–negative transplant patients, respectively. Although there is limited data available on IGRAs in HSCT recipients,[11,14] these also report low positive and very high negative predictive values for progression to active TB.

A recent study assessed the TST and both IGRAs to identify patients at risk for TB in different groups of immunocompromised patients in Europe.[16] Although it included a large number of solid organ transplant and HSCT recipients, both LTBI tests were carried out after the transplant procedure. Their results, including a high unexpected rate of indeterminate results, are therefore not comparable with the present study.

There is no consensus on whether TST or IGRAs should be used to assess the risk of transplant-associated TB and ultimately prevent it.[6] This uncertainty may be linked to the scarcity of longitudinal data of simultaneous screening with both tests, together with the inability of either test to predict the development of active TB.[16-18] In our study, incidence of TB and predictive values for TB progression either in the LT cohort or the HSCT cohort did not differ significantly with the 2 tests. Although 2 series of kidney and HSCT patients reported a higher incidence of TB in IGRA-positive than in TST-positive patients, the differences were not statistically significant.[10,14] These results are consistent with those reported in a previous meta-analysis, in which IGRAs showed a modest, but higher positive predictive value for TB progression than the TST with and without risk stratification.[17]

TABLE 2.

Correlation of QFT-GT and TST Testing and Traditional TB Risk Factors for Both Cohorts

		Liver Transplant Candidates				HSCT Candidates			
		QFT-GT				QFT-GT			
		Pos	Neg	Indet	Global	Pos	Neg	Indet	Global
TST	Positive	18[a]	4	1	23	5	3	0	8
	No. Risk F	2[1,2]	2[1,4]	—		1[2]	1[1]	—	
	Negative	4	22	1	27	2	16[b]	0	18
	No. Risk F	—	2[2,3]	—		—	2[1]	—	
	Global	22	26	2	50	7	19	0	26

[a] Case 1: a 67-year-old Spanish man developed disseminated TB 387 days after LT (and 532 days after LTBI screening). He had no specific TB risk factors and had tested positive for TST and QFT while awaiting liver transplantation for hepatocellular carcinoma.

[b] Case 2: a 46-year-old Spanish woman developed disseminated TB 100 days after HSCT (and 116 days after LTBI screening). She had tested negative for both TST and QFT. She had no specific risk factors for TB. The reason for practicing an unrelated allogeneic bone marrow transplant was an acute leukemia.

Indet, indeterminate. No. Risk F: Number of patients with risk factors for TB, as described: being born in a high-prevalence TB country[1], previous TB close contact[2], health worker[3], (ex-) intravenous drug user[4].

TABLE 3.

The Incidence of Active Tuberculosis, and Positive Predictive Value of QFT-GT and TST in Liver and Hematopoietic Stem-Cell Transplant Recipients

	Liver Transplant (n = 50)	Hematopoietic Stem Cell Transplant (n = 26)
QFT-GT-positive	22	7
Median follow-up, mo	37.9 (35.8-54.2)	55.9 (33.0-57.1)
Person-years, p-y	81.5	25.9
TB cases	1	0
Incidence rate of TB cases per 100 p-y (95%CI)	1.2 (0.1-6.1)	—
PPV (95% CI)	4.5 (0.8-21.8)	—
QFT-GT-negative	26	19
Median follow-up, mo	42.0 (30.7-51.2)	47.3 (29.1-55.9)
Person-years, p-y	83.3	65.4
TB cases	0	1
Incidence rate of TB cases per 100 p-y (95%CI)	—	1.5 (0.1-7.5)
NPV (95%CI)	100 (87.1-100)	94.7 (75.4-99.1)
TST-positive	23	8
Median follow-up, mo	44.8 (35.4-52.1)	51.6 (24.8-59.1)
Person-years, p-y	75.0	29.3
TB cases	1	0
Incidence rate of TB cases per 100 p-y (95%CI)	1.3 (0.1-6.6)	—
PPV (95%CI)	4.4 (0.8-21.0)	—
TST-negative	27	18
Median follow-up, mo	50.8 (34.2-56.7)	47.5 (27.0-57.5)
Person-years, p-y	99.6	62.1
TB cases	0	1
Incidence rate of TB cases per 100 p-y (95% CI)	—	1.6 (0.1-8)
NPV (95% CI)	100 (87.5-100)	94.4 (74.2-99.0)

PPV indicates positive predictive value; NPV, negative predictive value.

The major advantage of IGRAs over the TST in healthy people in low-prevalence settings is that it can reduce the number of people considered for preventive chemotherapy without increasing the risk of subsequent active TB.[19] Although this characteristic cannot be applied to immunocompromised patients, in whom IGRAs may not save LTBI diagnostics as compared with TST, the negative predictive value of IGRAs for progression to active TB is consistently high in this population, and probably better than that of the TST.[17]

Therefore, with the current data available, the choice of TST or IGRAs for screening transplant candidates should be based on the expected specificity in each setting, operational factors, logistics, patients' preferences, and cost; and always keeping in mind that a negative result does not rule out the future risk of developing TB.[16]

The main limitation of our study is the small sample size and the low progression rate during follow-up, both of which preclude an accurate estimation of the incidence and predictive values for progression to active TB.

In conclusion, the rate of posttransplant TB among QFT-GT-positive patients was both low and comparable to that of the TST in this cohort of LT and HSCT recipients. Our results add to the evidence that IGRAs are poor at predicting the development of active TB in transplant recipients.

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