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QuantiFERON-TB gold plus in liver transplant candidates: single-center experience

Abstract

Background/Objectives: Latent tuberculosis infection (LTBI) screening prior to orthotopic liver transplant (OLT) is essential. The data on QuantiFERON-TB -Gold Plus (QFT--Plus) in OLT candidates is scarce.

Methods: QFT-Plus results performed prior to transplant among OLT recipients transplanted between 4/2019 and 8/2020 were evaluated. Previous QFT-Gold In-Tube (QFT-GIT) results were obtained, if available, to evaluate for discordant results. The infectious diseases (ID) team plan for those with positive or indeterminate QFT-Plus was obtained.

Results: We assessed 170 OLT recipients. QFT-Plus was performed in 124(73%) patients [8(6%) were positive, 20(16%) indeterminate and 96(77%) negative]. Nine (45%) of the QFT-Plus-indeterminate patients converted to negative. Twenty-one (17%) of the patients that were tested with QFT-Plus were previously tested with QFT-GIT [4(21%) of them had discordant results]. There were no differences in the survival and biopsy-proven rejection at 6 months post-transplant between QFT-Plus-positive and QFT-Plus-negative patients. ID team recommended isoniazid 300mg daily for 9 months for 7(88%) and 9(45%) patients with positive and indeterminate QFT-Plus, respectively.

Conclusions: QFT-Plus appears to be appropriate for LTBI diagnosis in OLT candidates. In our cohort, indeterminate QFT-Plus is common and QFT-Plus conversion from indeterminate to negative is frequent. In the presence of risk factors, it might be wise to treat patients with indeterminate QFT-Plus.

Keywords: latent tuberculosis infection, liver transplant, QuantiFERON-TB -Gold Plus, test performance, discordant results

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Introduction

Active tuberculosis (TB) is significantly more common in solid organ transplant (SOT) recipients than in the general population.[1] Active TB was found in 1.57% of orthotopic liver transplant (OLT) recipients in a Brazilian cohort.[2] The morbidity and mortality related to TB is higher in SOT recipients.[1,3] The short-term mortality rate was 31% in a systematic review and meta-analysis among OLT recipients.[4]

It is estimated that one third of people in the world has latent tuberculosis infection (LTBI).[5] It is recommended that SOT candidates get screened for LTBI either by tuberculin Skin Test (TST) or Interferon-Gamma Release Assays (IGRA).[1] However, IGRA testing appears to be more sensitive than TST in patients with advanced liver disease.[6] Among the IGRA, QuantiFERON-TB (QFT) is the most frequently used for diagnosing LTBI.[7]

QuantiFERON-TB gold in-tube (QFT-GIT), approved by the US Food and Drug Administration (FDA) in 2007, was used broadly for many years until QFT-Gold Plus (QFT-Plus) was approved by the FDA in 2019.[8] This newer QFT aimed to improve sensitivity, mainly in immunocompromised populations, as it targets cell-mediated immune response from CD4+ T Cells and CD8+ T Cells, whereas QFT-GIT targets a response only from CD4+ T Cells.[9] The data on QFT-Plus in OLT candidates is limited. In this manuscript, we reported the results of QFT-Plus performed prior to transplant among patients that underwent OLT at a transplant center in Miami.

Methods

Study design

This is a single-center retrospective study was conducted at Jackson Memorial Hospital (1558-licensed bed tertiary care teaching hospital in Miami, Florida)-Miami Transplant Institute (largest transplant center in the United States), and was approved by the Institutional Review Board of the University of Miami. The main objective of this study was to evaluate the performance of QFT-Plus (4th generation QFT) done prior to transplant among patients that underwent OLT at a large transplant center in Miami.

QFT-Plus

Our hospital replaced QFT-GIT with QFT-Plus in 3/2019. QFT-Plus is highly accurate and reproducible, and it has a specificity and sensitivity of >97% and >94%, respectively.[10] The QFT-GIT and QFT-Plus tests were conducted as per the manufacturer's instructions. The concentration of released interferon-gamma (IFN-γ) in each tube was calculated by subtracting the value of the nil tube. The results were considered positive when the IFN-γ concentration was ≥0.35 IU/mL and ≥25% of the nil value.[10,11] We evaluated QFT-Plus results performed prior to transplant among patients that underwent OLT between 4/2019 and 8/2020. We evaluated whether the patients with indeterminate QFT-Plus were more likely to have a high Model for End-stage Liver Disease (MELD) score at the time of listing for OLT compared to those with positive or negative QFT-Plus. In addition, we obtained previous QFT-GIT results if available to evaluate for discordant results between QFT-Plus and QFT-GIT. We evaluated how far back they were tested with QFT-GIT with respect to QFT-Plus.

Differences between QFT-Plus-positive and negative patients

We evaluated if there were any differences in demographics variables such as gender, age and Hispanic ethnicity), LTBI-suggestive radiographic findings and post-transplant outcomes between those OLT recipients that were QFT-Plus-positive and those that were QFT-Plus-negative.

The LTBI-suggestive radiographic findings were calcified and noncalcified nodules, pleural thickening or and scarring by chest-x-rays (CXR) or chest computed tomography (CT) scans performed within one year prior to OLT. The post-transplant outcomes were length of transplant hospital stay, and survival, biopsy-proven rejection and TB reactivation at 6-month post-transplant. The transplant hospital stay was defined as the time from transplant surgery to discharge. Patients that died during the transplant stay were not included for the transplant stay analysis.

Management of positive or indeterminate QFT-Plus

The infectious diseases (ID) team in our institution evaluates all the OLT recipients right after transplantation. The post-transplant plan by the ID team for those OLT recipients with positive or indeterminate QFT-Plus was obtained.

Statistical analyses

Fisher's exact test and Chi square were used to evaluate bivariate associations between categorical variables; Mann-Whitney test or Student's *t*-test were used to compare continuous variables between groups, depending on normality of the distributions. A *P* value <0.05 was considered statistically significant.

Results

QFT-Plus

We evaluated 170 OLT recipients [130(76%) were isolated liver, 29(17%) combined liver-kidney and 11(6%) multi-visceral]. One hundred-twenty-two (72%) were Male, 94(55%) Hispanic and the median age was 58 (range: 21-75) years. QFT-Plus was performed in 124(73%) patients [86(69%) were tested once, 28(23%) twice, 8(6%) thrice and 2(2%) four times]. Eight out of 124(6%) had positive, 20(16%) indeterminate and 96 (77%) negative QFT-Plus. One of the QFT-Plus-positive patients, tested negative nine days after testing positive, and nine (45%) of the QFT-Plus-indeterminate patients converted to negative, but one of these converted back to indeterminate (Table 1). Repeating QFT-Plus testing in our cohort was performed at the discretion of the primary team.

Table 1 Liver transplant recipients with positive and indeterminate QFT-Plus

N° Patients	1st test	2nd test	3rd test	4th test
1 patient	Positive	Negative[1]	X	X
7 patients	Positive	X	X	X
8 patients	Indeterminate	Negative	X	X
1 patient	Indeterminate	Negative	Indeterminate	X
2 patients	Indeterminate	Indeterminate	Indeterminate	Indeterminate
2 patients	Indeterminate	Indeterminate	Indeterminate	X
1 patient	Indeterminate	Indeterminate	X	X
4 patients	Indeterminate	X	X	X
1 patient	Negative	Indeterminate	X	X
1 patient	Negative	Indeterminate	Indeterminate	X

QFT-Plus, QuantiFERON-TB gold in-tube. [1]tested negative nine days after testing positive.

The median MELD score was similar for QFT-Plus-indeterminate patients and those that tested positive or negative [median 28 (range 9-41) vs. median 24 (range 9-40), P=0.11, respectively]. However, there was a trend towards MELD score >25 in those patients that tested indeterminate compared to those that tested positive or negative [12/20(60%) vs. 40/104(38%), P=0.07, respectively].

Twenty-one (17%) of the patients that were tested with QFT-Plus were previously tested with QFT-GIT. They were tested with QFT-GIT at a median time of 548 (range: 26-3,532) days prior to being tested with QFT-Plus. QFT-GIT was performed in three QFT-Plus-positive patients (it was positive in two and negative in one patient), two QFT-Plus-indeterminate patients (it was negative in both), and 16 QFT-Plus-negative patients (it was positive in one and negative in 15 patients). Therefore, discordant results were found in 4(21%) of the patients.

Differences between QFT-Plus-positive and negative patients

There were no differences in gender, age and Hispanic ethnicity between QFT-Plus-positive and QFT-Plus-negative. There was also no difference in the prevalence of LTBI-suggestive radiographic findings by CXR or chest CT scan between both groups. Regarding the post-transplant outcomes, there were no differences in the length of transplant hospital stay, and survival and biopsy-proven rejection at 6 months post-transplant between QFT-Plus-positive and QFT-Plus-negative. None of the patients from either group had TB reactivation at 6 months post-transplant (Table 2).

Management of positive or indeterminate QFT-Plus

During the post-transplant evaluation, the ID team recommended isoniazid 300 mg daily for 9 months for 7/8 (88%) and 9/20 (45%) patients with positive and indeterminate QFT-Plus, respectively. Isoniazid was not recommended in one case of positive QFT-Plus as patient was previously treated.

Discussion

The data on QFT-Plus (newer QFT) to diagnose LTBI among OLT candidates is scarce. In this manuscript, we reported our experience from a large cohort of OLT recipients that were tested with QFT-Plus prior to transplant. LTBI is common in Miami, a rate of 21% was demonstrated in a cohort of pregnant women with human immunodeficiency virus (HIV),[12] and a rate of 16% was found in a cohort of kidney transplant candidates.[13] Interestingly, in our study, only eight out of 124(6%) tested positive, which might seem low considering that more than half of the patients were Hispanic. The considerably high rate of indeterminate result of 16% could have affected the total rate of positive result. Our high rate of indeterminate result is not surprising, as this has been reported in OLT candidates. The rate of indeterminate QFT-GIT was 27% in a cohort of OLT candidates, and patients with a MELD score greater than 25 were >16 times more likely to have an indeterminate result.[14] Our study, also revealed that a MELD score >25 was more frequent among QFT-Plus indeterminate patients. Ryu, et al, reported that the rate of indeterminate result was similar between QFT-GIT and QFT-Plus in immunosuppressed patients.[15]

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QFT-Plus was found to be more sensitive than QFT-GIT for diagnosis of LTBI among older adults in long-term facilities.[16] A high degree of agreement between the results of QFT-GIT and QFT-Plus for the screening of LTBI was demonstrated among SOT candidates. However, the proportion of OLT candidates in that cohort was not reported.[15] Twenty-one (17%) of our patients that were tested with QFT-Plus were previously tested with QFT-GIT. Discordant results were found in 4(21%) of them. It is unclear if the occurrence of discordant results in our results could have been due the difference of the QFT (Plus vs. GIT) and/or to the fact that the QFT-Plus and QFT-GIT were done in a different times. Large studies are needed to evaluate whether there are differences in performance between both tests among OLT candidates.

In our study, almost one third of the patients were tested with QFT-Plus more than once. Reversion of QFT-Plus from a positive to negative result, was noted in one patient and conversion from indeterminate to a negative result was found in nine patients, as it was illustrated in Table 1. Therefore, we highlight the importance of repeating QFT-Plus in OLT candidates with an indeterminate QFT-Plus result. The reproducibility of QFT-GIT testing among patients with low pre-test probability for LTBI is poor as it was seen in healthcare workers (HCW) that were screened for LTBI in Arkansas, USA.[17] Conversions or reversions were observed in 52% of HCW who underwent monthly testing with GFT-GIT for one year.[18] In the study by Ryu et al, the reproducibility for both QFT-GIT and QFT-Plus had the same variability of 5.4%.[15]

We found no differences in the LTBI-suggestive radiographic findings between those that were QFT-Plus positive and those who were negative. This could be explained by the small sample size as only a small proportion of our patients had a chest CT scan performed. Chest CT is more likely to reveal signs of LTBI than a CXR in OLT candidates.[19]

Following OLT, ID team recommended isoniazid 300mg daily for 9 months in all the patients that tested positive, except for one which was already treated prior to transplant. Almost half of the patients with indeterminate QFT-Plus were treated with isoniazid as per the discretion of the ID team based on patients' risk factors for TB. Our study has the limitations that are inherent to its retrospective design. We did not obtain information about patients' immune status, which might have facilitated the interpretation of QFT-Plus results, particularly in patients with indeterminate results. The data collection of other risk factors for LTBI such as imprisonment or known TB contacts, was not feasible as this information was usually unavailable. In addition, our comparison between QFT-Plus and QFT-GIT would have been more enlightening if the sample size would have been larger and both tests performed around the same time.

Conclusion

QFT-Plus appears to be an appropriate test for LTBI diagnosis in OLT candidates. Our cohort reveals that indeterminate QFT-Plus is common and conversion from indeterminate QFT-Plus to negative is frequent. Therefore, repeating QFT-Plus is essential as it could prevent patients from being treated for LTBI unnecessarily. However, in the presence of TB risk factors, it might be prudent to treat patients with indeterminate QFT-Plus.

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Conflicts of interest

The authors declare no conflicts of interest.

References

1. Subramanian AK, Theodoropoulos NM. Mycobacterium tuberculosis infections in solid organ transplantation:Guidelines from the infectious diseases community of practice of the American Society of Transplantation. *Clin Transplant.* 2019;33(9):e13513.
2. Clemente WT, Faria LC, Lima SS, et al. Tuberculosis in liver transplant recipients:a single Brazilian center experience. *Transplantation*. 2009;87:397–401.
3. Singh N, Paterson DL. Mycobacterium tuberculosis infection in solid--organ transplant recipients:impact and implications for management. *Clin Infect Dis*. 1998;27:1266–1277.
4. Holty JE, Gould MK, Meinke L, et al. Tuberculosis in liver transplant recipients:a systematic review and meta-analysis of individual patient data. *Liver Transpl*. 2009;15:894–906.
5. Centers for Disease Control and Prevention. Tuberculosis: Data and Statistics. 2022.
6. Casas S, Munoz L, Moure R, et al. Comparison of the 2–step tuberculin skin test and the quantiFERON–TB Gold In–Tube Test for the screening of tuberculosis infection before liver transplantation. *Liver Transpl.* 2011;17:1205–1211.
7. Lalvani A, Pareek M. A 100 year update on diagnosis of tuberculosis infection. *Br Med Bull.* 2010;93:69–84.
8. The United States Food and Drug Administration. 2022.
9. Barcellini L, Borroni E, Brown J, et al. First independent evaluation of QuantiFERON-TB Plus performance. *Eur Respir J*. 2016;47:1587–1590.
10. QIAGEN- QuantiFERON Products. 2022.
11. Mazurek GH, Jereb J, Vernon A, et al. Updated guidelines for using Interferon Gamma Release Assays to detect Mycobacterium tuberculosis infection - United States, 2010. *MMWR Recomm Rep.* 2010;59(RR-5):1–25.
12. Schulte JM, Bryan P, Dodds S, et al. Tuberculosis skin testing among HIV-infected pregnant women in Miami, 1995 to 199. *J Perinatol*. 2002;22(2):159–162.
13. Simkins J, Kraus K, Morris MI. Demographics and prevalence of positive QuantiFERON-TB Gold In-Tube test in renal transplant candidates. *Transpl Infect Dis.* 2016;18(1):5–13.
14. Hand J, Sigel K, Huprikar S, et al. Tuberculosis after liver transplantation in a large center in New York City:QuantiFERON ® -TB Gold-based pre-transplant screening performance and active tuberculosis post-transplant. *Transpl Infect Dis*. 2018;20:e12845.
15. Ryu MR, Park MS, Cho EH, et al. Comparative Evaluation of QuantiFERON-TB Gold In-Tube and QuantiFERON-TB Gold Plus in Diagnosis of Latent Tuberculosis Infection in Immunocompromised Patients. *J Clin Microbiol*. 2018;56:e00438–e00418.
16. Chien JY, Chiang HT, Lu MC, et al. QuantiFERON-TB Gold Plus Is a More Sensitive Screening Tool than QuantiFERON-TB Gold In-Tube for Latent Tuberculosis Infection among Older Adults in Long-Term Care Facilities. *J Clin Microbiol.* 2018;56:e00427–e00418.
17. Joshi M, Monson TP, Joshi A, et al. IFN-γ release assay conversions and reversions. Challenges with serial testing in U.S. health care workers. *Ann Am Thorac Soc.* 2014;11(3):296–302.
18. Park JS, Lee JS, Kim MY, et al. Monthly follow-ups of interferon-γ release assays among health-care workers in contact with patients with TB. *Chest.* 2012;142:1461–1468.
19. Lyu J, Lee SG, Hwang S, et al. Chest computed tomography is more likely to show latent tuberculosis foci than simple chest radiography in liver transplant candidates. *Liver Transpl.* 2011;17:963–968.

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