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The pros and cons of the QuantiFERON test for the diagnosis of tuberculosis, prediction of disease progression, and treatment monitoring

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ABSTRACT

Objective/Background: Tuberculosis (TB) is a re-emerging disease with the advent of human immunodeficiency virus/AIDS infections. Discovered in 1959, diagnosed by various approaches and treated with antibiotics, the treatment of TB infection still poses public health concerns. Many cases of resistance and cross-resistance are observed. Diagnosis by culture, which is considered as the standard method, takes too long (20–30 days) and is not suitable for extrapulmonary TB. QuantiFERON test, which is an indirect immunoassay based on blood, was developed. Much hope was placed in this new approach because it is based on blood, and many research teams have used it. We discuss the results of these different research groups who have used QuantiFERON for diagnosis, prediction of disease progression, or monitoring patients during the treatment of TB.

Methods: Articles published in PubMed and documents published on Google were searched with the keywords: diagnosis and TB and QuantiFERON; TB and QuantiFERON and therapeutic monitoring; interferon-γ release assay; disease progression. These articles were read and analyzed.

Results: The results were controversial with regards to using the QuantiFERON test for the diagnosis of TB according to the study population (ethnic group, bacillus Calmette–Guérin vaccine use) and according to the state of the immune system of the people studied (human immunodeficiency virus immunosuppression in cancer medication, hypertension). Also, research findings were controversial with regards to using QuantiFERON for monitoring TB patients on anti-TB medications. Also, the predictive positive value for the progression to TB among immigrant close contacts of both interferon-γ release assays was not better than that of the tuberculin skin test.

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Conclusion: The QuantiFERON has advantages and limitations depending on the type of population studied. Recommendations are made to improve the sensitivity and specificity and to differentiate between latent and active TB by adding other specific proteins in the *Mycobacterium tuberculosis* antigen cocktail.

Introduction

Roughly one-third of the world's population is infected with *Mycobacterium tuberculosis* (Mtb), and new infections occur at a rate of one per second on a global scale [1]. Insufficient access to advanced diagnostic tests has contributed to suboptimum performance in the detection of tuberculosis (TB). To date, national TB programs in disease endemic countries continue to rely largely on antiquated and not very accurate methods such as direct smear microscopy, solid culture, and chest radiography [2]. Most, if not all, of these techniques have their drawbacks. Direct microscopic examination of sputum samples and culture of mycobacteria (presently the gold standards for the diagnosis of TB) sometimes give false negative results due to poor sample collection or paucibacillary. In some cases, patients such as infants younger than 6 years lack the required expectorates and are unable to produce sputum for analysis. Diagnosis of smear-negative TB still poses substantial clinical challenges including diagnosis of extrapulmonary TB. Childhood TB is a well-known diagnostic challenge, and all available tests do poorly in cases of paucibacillary TB [3]. The absence of a gold standard for extrapulmonary TB and smear-negative TB is an important impediment to rapid assessment of new diagnostic methods in these subgroups. Diagnostic delays and misdiagnosis results in increased morbidity and mortality in patients, and allow continued transmission of TB [4].

One blood-based test which has existed since 1910 is the tuberculin skin test (TST). Its principle relies on *in vivo* detection of delayed-type hypersensitivity to purified protein derivatives, a mixture of antigens shared by many mycobacteria that gives rise to a skin reaction [5]. The main drawback of the TST is its poor specificity as previous *bacillus* Calmette–Guérin (BCG) vaccination and non-TB mycobacterial exposure can lead to false-positive results.

The other blood-based test available is the QuantiFERON test (QFT). The QFT is a type of enzyme-linked immunoassay (ELISA) used for the diagnosis of TB. There are two commercial QFTs available and approved by the United States Food and Drug Administration (FDA): the enzyme-linked immunospot-based assay T-SPOT.TB (Oxford Immunotech, Oxford, UK) and the whole blood ELISA-based format QuantiFERON-TB Gold In-Tube (QFT-GIT), provided by Cellestis (Carniege, Victoria, Australia). Memory Mtb T-cell specific antigens are used in both tests. These tests have early secretory antigen target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10) antigens in common, with QFT-GIT having TB7.7 antigen in addition. ESAT-6, CFP-10 (encoded by genomic region of difference 1), and TB7.7 (encoded by region of difference 11) are selectively restricted to Mtb while it is absent in most environmental mycobacteria and in all BCG vaccine strains [6,7]. The QFT-GIT is sometimes abbreviated to QFT-3G. The predecessor, abbreviated as QFT-2G, made use of just two antigens; CFP-10 and ESAT-6. The QFT-GIT offers a number of advantages compared with the TST, including increased specificity in persons who have had a BCG vaccination, and elimination of the need for a second visit to read the TST. The QFT-GIT is used to detect both latent and active TB but cannot distinguish between both.

With the QFT-GIT based on blood and its ability to detect both latent and active TB, it should be a preferable test with respect to the drawbacks associated with TST. There have been a lot of controversies on the use of the QFT test in diagnosing TB in immunocompromised individuals and in monitoring treatment with anti-TB agents. In this systematic review, we look at the advantages and the limits of the QFT-GIT (the most recent version of the QFT test) in the diagnosis of TB and in treatment follow-up in adults. This will be of help to policy makers on strategy implementation in Mtb diagnosis and treatment follow-up, as well as researchers in orienting focus on how to upgrade the QFT-GIT to make it a better diagnostic test.

Materials and methods

We searched PubMed online, which is a free search engine accessing primarily the Medline database of references and abstracts on life sciences and biomedical topics. We searched for articles related to the topics: "QuantiFERON test in tuberculosis" and "QuantiFERON test in tuberculosis diagnosis and treatment follow-up," "IGRA and prediction of disease progression." From all the articles we were able to download, we searched their references, selected, and also downloaded related articles and reviews including the updated guidelines for using interferon-γ released assays (IGRAs) to detect Mtb infection by Centers for Disease Control in 2010 [8]. Some related articles were obtained from the Cellestis package insert on QFT TB gold (in-tube method) [9].

Results and discussion

Our search on the topic: "QuantiFERON test in tuberculosis" gave us a total of 883 papers. When we screened this number by searching for papers directly related to our topic of review ("QuantiFERON test in tuberculosis diagnosis and treatment follow-up"), the search gave a total of 54 papers which we exploited together with related references to write this review.

Origin and evolution of the QFT tests

QFT is the registered trademark of the test for TB infection or latent TB. QFT is an IGRA used in TB diagnosis. QFT-GIT, the third generation test, has replaced QFT and QFT-Gold (QFT-G), which are no longer marketed. The QFT-TB test is the first generation QFT test that was first approved by the US FDA in 2001 [10] as an aid for detecting latent Mtb infection. This test is an *in vitro* diagnostic aid that measures a component of cell-mediated immune reactivity to Mtb. The test is based on the quantification of interferon-gamma (IFN-γ) released from sensitized lymphocytes in whole blood incubated overnight with purified protein derivative from Mtb and control antigens. The QFT-G is the second generation QFT test. Some authors have abbreviated it as QFT-2G to indicate it is the second generation QFT test. This test was approved by the US FDA in 2005. For QFT-G, the antigens include mixtures of synthetic peptides representing two Mtb proteins: ESAT-6 and CFP-10. The QFT-GIT is the third most recent version of the QFT test and was approved by the US FDA in 2007 [11]. The QFT-GIT makes use of three antigens: CFP-10, ESAT-10, and TB7.7 unlike its predecessor QFT-G that had just two antigens: CFP-10 and ESAT-10. Some authors have abbreviated QFT-GIT as QFT-3G to identify the fact that it is the third generation QFT test. Presently, there are two commercial QFT tests available and approved by the US FDA: the enzyme-linked immunospot-based assay T-SPOT.TB and the whole blood ELISA-based format QFT-GIT. The change from one QFT version to another (QFT to QFT-G to QFT-GIT) has always been about increasing its performance, although it still has some limits to date.

QFT-GIT tests and treatment monitoring of TB

There have been a lot of controversies regarding the use of the QFT-GIT tests in the treatment and follow-up of TB patients. Some authors seem to approve of the idea that the QFT-GIT tests could be a monitoring tool for the treatment of TB while others are of the opposite opinion. Out of a total of 11 papers that our search gave us on this topic, just two authors (18%) were of the opinion that the QFT-GIT test could be a monitoring tool for the treatment of TB. Table 1 summarizes some of the previous work carried out on the use of QFT tests in treatment monitoring.

In the studies carried out by Katiyar et al. [12] and Helmy et al. [14], there were significant decreases in the proportion of positive responders to the IFN-γ tests during the treatment compared with that at the beginning of the therapy. These results strengthen the idea of the use of the QFT-GIT tests for monitory treatment response. But it is difficult to draw a conclusion on the use of QFT-GIT for treatment monitoring of TB as some individuals cured of TB still had positive QFT-GIT tests results. Other studies [13,15–17], however, tend to demonstrate a significantly large number of QFT-test positive

Table 1 – A summary of some previous work carried out by different authors on the use of the QuantiFERON test in treatment monitoring.

Authors	Tests used	Results obtained			Author's conclusions
		T0 (before treatment)	T2 (after 2 mo of treatment)	T6 (after 6 mo of treatment; end of treatment)	
Katiyar et al. (2008) [12]	Microscopy &/or culture	76 positives	–	–	The QFT-G can potentially be used as a tool to monitor the efficacy of anti-TB treatment
	QFT (QFT-GIT)	–	17 positives 59 negatives	–	
Bocchino et al. (2010) [13]	Microscopy &/or culture	60 positives	–	60 negatives	QFT adds no significant information to clinicians for treatment monitoring due to IFN-γ persistence even after successful cure
	QFT (QFT-GIT)	53 positives 7 negatives		38 positives 22 negatives	
Helmy et al. (2012) [14]	Microscopy &/or culture	29 positives	03 positives 24 negatives	25 negatives	There is a correlation between clinical treatment outcome & changes in IFN-γ response to Mtb
	QFT (QFT-GIT)	24 positives 5 negatives	04 positives 23 negatives	04 positives 21 negatives	
Denkinger et al. (2013) [15]	Microscopy &/or culture	149 positives	18 positives 119 negatives	–	QFT results do not offer much value for treatment monitoring of TB disease
	QFT (QFT-GIT)	133 positives 16 negatives	125 positives 19 negatives	108 positives 26 negatives	
Mansour et al. (2014) [16]	Microscopy &/or culture	25 positives	–	2 positives 23 negatives	The QFT (T-SPOT) is a weak test for use in treatment monitory. The QFT test should not be considered as a surrogate marker for a cure
	QFT (T-SPOT TB)	–	–	21 positives 4 negatives	

Note. IFN-γ = interferon-gamma; mo = month; Mtb = *Mycobacterium tuberculosis*; QFT = QuantiFERON; QFT-G = QuantiFERON-Gold; QFT-GIT = QuantiFERON-Gold In-tube; TB = tuberculosis; T0 = pretreatment test carried out before initiation of treatment; T2 = results obtained after 2 months of treatment with anti-TB; T6 = results obtained after 6 months of treatment with anti-TB.

Table 2 – A summary of some previous work carried out on the QuantiFERON tests and immunocompromised persons.

Authors	Population/country of study	Description of immunocompromised conditions	QFT test results	Authors' conclusions	Final verdict
Kobashi et al. (2007) [24]	This study was carried out in Kawasaki Japan	252 immunocompromised patients suspected of TB among whom were; 74 with malignant diseases (CD4 count 208 ± 31), 72 with immunosuppressive treatment (CD4 count 114 ± 29), 52 with diabetes mellitus (CD4 count 220 ± 36), 50 with chronic renal failure (CD4 count 212 ± 32), & 4 with HIV (CD4 count 40)	The positive rate of the QFT-TB test for the diagnosis of TB infection (active or latent TB infection) was 78%. An indeterminate result for the QFT-TB test was recognized in 12.7% (32 out of 252 immunocompromised patients) & it appeared most frequently in patients receiving immunosuppressive treatments who presented with lymphocytopenia (especially CD4 lymphocytopenia)	The QuantiFERON TB-2G test result showed an indeterminate response for patients receiving immunosuppressive treatment, especially with lymphocytopenia due to severe underlying diseases. Therefore, care must be taken when making a diagnosis of tuberculosis in immunocompromised patients based on QuantiFERON TB-2G test results	The authors' conclusion support the opinion that, immunosuppression affects the performance of the QuantiFERON test
Hornum et al. (2008) [25]	This study was carried out in Copenhagen Denmark	4 active TB patients confirmed by culture among whom; 1 HIV positive patient with CD4 count of 290, two kidney-transplanted patients on immunosuppressive drugs (steroids, mycophenolate mofetil, & cyclosporin), & 1 malnourished patient who was a smoker & had a history of alcohol abuse	All 4 patients gave a false negative QFT-2G test	A negative IFN-γ test does not exclude TB disease in immunosuppressed patients	These authors are in support of the opinion that immunosuppressiveness affects the performance of the QuantiFERON test
Kobashi et al. (2009) [26]	This study was carried out in Kawasaki in Japan	140 patients were confirmed with active TB. 10 of the 140 had a CD4 count of 254 ± 28. 115 of the 140 had a CD4 count of 392 ± 30	All 10 TB patients with CD4 count of 254 ± 28 showed a false negative QFT test while the other TB patient group of 115 with CD4 count of 392 ± 30 showed a positive QFT-2G test	False negative results in the QFT test may originate from a decrease in IFN-γ production due to lymphocytopenia, advanced age of patient, or lack of ability to produce IFN-γ	Authors are in support of the opinion that the performance of the QuantiFERON test is affected by immunosuppressiveness

Maximilian & Rieger, 2009 [27]	This study was carried out in Vienna Austria	830 HIV infected patients diagnosed with the QFT-GIT. Only 11 were confirmed at the end of study period to have active TB	Out of the 830 HIV-infected patients, 44 (4 with CD4 count < 200, 12 with CD4 count between 200 & 350, & 28 with CD4 count > 350) showed a positive QFT test result, 739 (107 with CD4 count < 200, 180 with CD4 count between 200 & 350, & 452 with CD4 count > 350) showed negative QFT results while 47 (25 with CD4 count < 200, 8 with CD4 count between 200 & 350, & 14 with CD4 count > 350) showed indeterminate QTF results	The QFT-GIT assay may be a sensitive tool for the detection & prediction of active tuberculosis in HIV-1-infected individuals	This conclusion does not tally with presented results. Authors are against the opinion that immunosuppressiveness affects the performance of the QuantiFERON test
Lange et al. (2010) [23]	This study was carried out in Freiburg Germany	Patients had either undergone organ transplantation or stem cell transplantation (39% rheumatoid arthritis, 12% systemic lupus erythematosus, 5% chronic inflammatory bowel disease, 44% other autoimmune diseases), had been receiving immunosuppressive therapy for at least 6 mo & had primary immunodeficiencies (82% with chronic variable immunodeficiency syndrome) or HIV-infection (mean CD4 count: 435)	The overall rate of indeterminate result in immunocompromised patients was significantly higher than in the control group ($p = .001$)	Different disease groups bear an independent risk of indeterminate results in the QFT-GIT. Low lymphocytes, low CD8 T-cells, & hemoglobin levels are better predictors of indeterminate QFT results than disease group or immunosuppressive medication	Are for the opinion that the performance of the QuantiFERON test is affected by immunosuppression

Note. CD4 values are reported as mean ± standard deviation. HIV = human immunodeficiency virus; IFN-γ = interferon-gamma; mo = month; QFT = QuantiFERON; QFT-G = QuantiFERON-Gold; QFT-GIT = QuantiFERON-Gold In-tube; TB = tuberculosis.

individuals after 6 months of treatment (complete therapy) who have been declared cured of TB. According to Chee et al. [18], T-cell response to ESAT-6 may persist as a scar of previously treated or quiescent infection, whereas that to CFP-10 may be more indicative of active infection because this response appears to be influenced by TB treatment (it decreases over time upon successful treatment). With respect to this point, the QFT-GIT, which is the latest improvement from the previous in-plate format, is of limited usefulness since all the antigens are tested simultaneously in a single tube. These antigens could be re-evaluated by testing each individually, but this would reduce the test sensitivity. This test assesses the Mtb specific central memory T-cell responses to selected Mtb antigens. These cells are long lived cells, and will therefore give positive QTF-GIT test results for already cured people. Quantifying the relative amount of IFN-γ released as treatment goes on could be a suitable approach to increase the usefulness of the QFT-GIT in treatment management.

Wu-Hsieh and collaborators [19] also showed that cured TB patients could retain strong ESAT-6 responses for several years after completion of treatment. Eum et al. [20], showed that the regulation of tumor necrosis factor (TNF) during therapy might be better than IFN-γ in predicting sputum conversion at 6 months. The QFT-GIT test therefore has a limit in that it cannot be used to monitor treatment of TB. Modifications in the QFT tests might be of enormous importance for treatment follow-up like re-evaluating CFP-10, looking for a possibility of using TNF as another marker, or modifying the cut-off levels [21].

QFT tests and immunocompromised individuals

Our search gave us a total of 12 articles on the QFT tests and immunocompromised persons. Three authors (25%) were of the opinion that immunosuppressiveness does not affect the performance of the QFT tests, while the other nine authors, 75%, were of the opposite opinion in that it does affect the performance of the tests. Immunocompromised patients include stem cell and solid organ transplant recipients, patients with autoimmune diseases, patients with chronic renal failure, HIV-positive patients, and those receiving immunosuppressive drugs. False-negative results on the QFT-GIT test for patients with latent and active TB disease have been reported with a frequency of 4–38% [22]. The growing list of data existing on the reliability of IGRAs in immunocompromised patients show that the prevalence of indeterminate results may vary depending on the degree of immunosuppression and the IGRA test used [23]. Table 2 shows a summary of some previous work carried out on the QFT test and immunocompromised individuals.

Maximilian and Rieger [27] reported that the QFT-GIT assay may be a sensitive tool for the detection and prediction of active TB in HIV-1 infected individuals based on the small proportion of indeterminates (47 indeterminates in 830 immunocompromised patients) they got from their study. An intrinsic problem of this study is that all patients with active TB disease may not have been identified. Individuals with a positive QFT-GIT assay result were monitored more closely than those with a negative test result. Thus, it is more likely that patients with TB infection were missed in the group with negative QFT-GIT assay results. Out of the 739 patients with negative QFT-GIT results, up to 107 had a CD4 count <200. Most of these negatives could have been false negatives. Many previous studies [25,26,28–31] have confirmed the idea that immunocompromised patients with a CD4 count around or below 200 show false-negative QFT-GIT results.

The QFT-GIT test depends on the release of IFNγ by T-cells previously sensitized to Mtb-specific antigens (ESAT-6, CFP-10, TB 7.7). Peripheral blood mononuclear cells are stimulated *in vitro* to produce IFN-γ which is quantified using ELISA. Lymphocytopenia causes decreased production of IFN-γ and lower responses to ESAT-6, CFP-10, and TB7.7 antigens [24]. Secondly, immunosuppressive drugs directly reduce the production of inflammatory cytokines such as IFN-γ, interleukin-1, TNF-α, from T-lymphocytes [32–34]. The decrease in IFN-γ induces false negative and indeterminate results due to lower mitogen, ESAT-6, CFP-10, and TB7.7 antigens levels. Care should therefore be taken when interpreting negative QFT-GIT test results in immunocompromised patients because they may be false-negative results. This is a limit to the use of the QFT-GIT test in the diagnosis of immunocompromised patients.

Limit in distinguishing latent from active TB

Exposure to Mtb may result in latent TB infection. A person with latent TB infection usually lives a healthy life without developing active TB disease. Two billion people have latent TB infection but only a fraction (<10 million/y) fall sick with active TB disease [35]. IGRAs are designed to detect indistinctly both latent and active TB infections. They are "indirect tests" because they do not detect the actual TB bacilli but instead an immune response that suggests past or present exposure to TB bacilli.

IGRAs, as well as the TST, cannot distinguish between latent TB infection and active TB disease [31]. In high TB burden communities, with positive QFT-GIT test results in individuals without any clinical signs of TB, it becomes difficult to say with certainty whether it is latent TB. In the course of our work, no report was found on the prediction of values of the IGRAs to permit the distinction of latent TB from active TB. A possible approach to this problem would be to find out further distinguishing antigens if there are any or to associate various diagnosis tools/methods with QFT-GIT results. Generally QFT-GIT is interpreted with clinical features or with results from other direct-detecting assays.

Studies still need to be done to evaluate the concentration of IFN-γ released in latent TB patients in comparison with those with active TB in order to come up with some predictive values or cut-off values which might help distinguish latent from active TB.

Limit in predicting disease progression

QFT-GIT and T-SPOT.TB are not better in predicting disease progression than the TST in immigrant contact [36].

Conclusions

The QFT-GIT test is probably not a very accurate diagnostic technique to be used in monitoring TB treatment. Modifications in the QFT-GIT test might be of enormous importance for treatment follow-up like, for example, looking into the possibility of adding TNF or other distinguishing antigens to this test or modifying the cut-off values. Care must be taken when interpreting QFT-test results in immunocompromised patients, especially in those who are severely immunocompromised because a negative test result might not completely mean absence of TB. Studies oriented towards coming up with predictive values to distinguish between latent TB infection and active TB disease or associating it to other diagnostic tools/methods will help increase the practicality of the QFT tests.

Conflicts of interest

The authors declare that they have no competing interests.

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