Diagnosis of latent tuberculosis infection among immunodeficient individuals: review of concordance between interferon-γ release assays and the tuberculin skin test

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ABSTRACT

Mycobacterium tuberculosis remains as a major threat to global health. Nearly a third of the world's population is estimated to have latent *M. tuberculosis* infection, and this is considered to be a major reservoir of potential active disease. Immunocompromised individuals, such as those with chronic renal failure requiring haemodialysis, solid organ transplant recipients, and individuals infected with the human immunodeficiency virus (HIV) have an increased likelihood of progression from latent infection to active disease, due to impaired cell-mediated immunity. Owing to the absence of a systematic review evaluating concordance between interferon-γ release assays (IGRAs) and the tuberculin skin test (TST) in the diagnosis of latent tuberculosis infection (LTBI) among immunodeficient individuals, this literature review aims to evaluate the reported agreement between IGRAs and TST in the diagnosis of LTBI. It will also assess the utility of IGRAs among individuals with weak immune systems as well as determine the degree of concordance among three diagnostic tests (TST, QuantiFERON, and TSPOT-TB) for LTBI .

KEY WORDS: Latent tuberculosis.
Immunosuppression.
Interferon-gamma release tests.

Introduction

Mycobacterium tuberculosis remains a major threat to global health. According to the latest World Health Organization (WHO) figures, there are an estimated 8.7 million incident cases of tuberculosis (TB; range: 8.3–9.0 million) globally, and approximately 125 cases per 100,000 population. Based on the estimated number of cases in 2011, most occurred in Asia (59%) and Africa (26%), followed by the Eastern Mediterranean region (7.7%), the European region (4.3%) and the Americas (3%).[1] In 2011, 1.1 million (13%) of the 8.7 million people who developed TB worldwide were human immunodeficiency virus (HIV)-positive, and an estimated 0.4 million HIV-associated TB deaths occurred.

Nearly one-third of the world's population is estimated to be latently infected with *M. tuberculosis* and this is considered to be a major reservoir of potential active disease. Immunocompromised individuals, such as those with chronic renal failure requiring haemodialysis (HD),[2–7] solid organ transplant recipients, and individuals infected with HIV have an increased likelihood of progression from latent infection to active disease, due to impaired cell-mediated immunity.[8,9]

The development of interferon-γ release assays (IGRAs) is an important advance in the diagnosis of latent tuberculosis infection (LTBI), especially in individuals who are at increased risk for the development of active tuberculosis. They are *in vitro* blood tests of the cell-mediated immune response, and measure T-cell release of interferon-γ following stimulation by antigens specific to *M. tuberculosis*.

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Two IGRAs are widely available: the QuantiFERON-TB Gold In-Tube (QFT-GIT) assay (Cellestis, Carnegie, Australia), which has replaced the second-generation Quantiferon-TB Gold (QFT-G) assay, and the T-SPOT.TB assay (Oxford Immunotec, Abingdon, UK).

The QFT-GIT assay is an enzyme-linked immunosorbent assay (ELISA)-based blood test in an 'in tube' format that uses peptides from three TB antigens (ESAT-6, CFP-10 and TB7.7). An individual is considered positive for *M. tuberculosis* infection if the IFNγ response (in iu/mL) to TB antigens is above the test cut-off.

The TSPOT-TB is an enzyme-linked immunospot (ELISpot) assay performed on counted peripheral blood mononuclear cells using ESAT-6 and CFP-10 peptides, and the result is reported as the number of IFNγ-producing T cells (spot-forming cells).[10] In contrast to the tuberculin skin test (TST), IGRAs are not affected by previous BCG vaccination or infection with most environmental non-tuberculous mycobacteria.

Table 1. Rates of positive/indeterminate results using the QFT and TST for the diagnosis of LTBI in immunodeficient patients

Study group	Country	Subjects	Social class	Year	QFT	
					Positive	
					n	(%)
Rangaka *et al*.	South Africa	74HIV$^+$ (adults)	upper middle	2005	32	43
Luetkemeyer *et al*.	USA	294 HIV$^+$ (adults)	high	–	25	8.5
Mandalakas *et al*.	South Africa	130 HIV$^+$ (children)	uppermiddle	2007–2010	22/116	19
Stephan *et al*.	Germany	286 HIV$^+$ (adults)	high	2006–2007	52/275	80.7
Talati *et al*.	Zambia	298 HIV$^+$ (adults)	low	–	109	37
Jones *et al*.	USA	207 HIV$^+$ (adults)	high	2005	11/201	5.5
Sauzullo *et al*.	Italy	207 HIV$^+$ (adults)	high	2007–2009	35	17
		195 IMIDS (adults)			35	18
Talati *et al*.	USA	336 HIV$^+$ (adults)	high	2005–2006	9	2.7
Balcells *et al*.	Chile	116 HIV$^+$ (adults)	upper middle	2006–2007	17/115	14.8
Ramos *et al*.	Spain	373 HIV$^+$ (adults)	high	2009–2010	28	75
Lattorre *et al*.	Spain	75 HIV$^+$ (adults)	high	2006–2009	5	6.7
Mandalakas *et al*.	South Africa	20 HIV$^+$ (adults)	upper middle		6/17	35.3
		23 HIV$^+$ (children)			2/12	16.7
Kim *et al*.	Korea	117 immunodeficient patients (adults)	high	2006–2009	25	21.4
Seyhan *et al*.	Turkey	100 ESRD patients (adults)	upper middle	2008	43	43
Chung *et al*.	Korea	98 ESRD patients (adults)	high	2009	43	43.9
Lee *et al*.	Taiwan	32 ESRD patients (adults)	upper middle	2005	12	40
Maden *et al*.	Turkey	96 ESRD patients (adults)	upper middle		38	39.6
Sayarlioglu *et al*.	Turkey	89 ESRD patients (adults)	upper middle		40	45
Triverio *et al*.	Switzerland	62 ESRD patients (adults)	high		13	21
Manuel *et al*.	Canada	170 ESRD patients (adults)	high	2006–2007	34/153	22.2
Chung *et al*.	Korea	167 ESRD patients (adults)	high	2008	67	45.9
Winthrop *et al*.	USA	100 ESRD patients (adults)	high		22	22
Richeldi *et al*.	Italy	120 Liver transplantation candidates (adults)	high	May 2006 to May 2007	28	23.3
		95 Haematogic malignancy (adults)			17	17.9
		116 HIV$^+$ (adults)			5	4.3
Hadaya *et al*.	Switzerland	200 renal transplant recipients (adults)	high	2009–2011	47	23.5
Stefan *et al*.	South Africa	34 children with cancer	upper middle	2007–2008	3	8.8
Silverman *et al*.	Canada	55 bladder cancer (adults)	high	2004	4	7
Cobanoglu *et al*.	Turkey	106 individuals with inflammatory disease (adults)	upper middle	2005–2006	9/61	14
Bocchirro *et al*.	Italy	69 TNFi candidates (adults)	high	2005–2006	22	31.8
Matulis *et al*.	Switzerland	142 immunodeficient patients with autoimmune disease	high		45/104	43

IMIDS: Immune–mediated inflammatory disease; ESRD: End–stage renal disease

According to different studies, recommendation for using TST or IGRA is controversial. Although the US Food and Drug Administration (FDA) has approved both the QFT-IT and TSPOT for detection of *M. tuberculosis* infection,[11] and the Centers for Disease Control and Prevention (CDC) guidelines recommend using either TST or IGRA for latent tuberculosis infection testing, many countries (e.g., UK, Canada, Spain, Italy) recommend a two-step approach (i.e., TST followed by IGRA), and this appears to be a cost-effective strategy.[12]

There are two approaches to the comparison of TST and IGRAs in the diagnosis of LTBI. The first relies on comparing

QFT		TST			Agreement QFT/TST (%)	Kappa	QFT/TST *P* value	BCG vaccination (%)	Ref.
Indeterminate		Cut–off	*n*	%					
n	(%)								
5	7	5	35	52	80	0.6	<0.001		22
		10	33	49	80	0.6	<0.001		
		15	25	37	74	0.49	<0.001		
15	5.1	5	19	9.3	89.3	0.37	<0.001		21
5/130	4	5	84/247	34		0.56	0.032	93	25
1	0.4	5	33/275	12		0.57	0.003	6.64	26
–	–	5	128	43	75	0.53	0.006	75	33
10/201	5	5	13/201	6.4	21	0.38	–		23
16	8	5	81	41	68	0.3		14	24
26	13	5	58	30	81.6	0.52		8.7	
–	–	5	7	2.5		0.23		7.4	
–	–	5	10/110	10.9		0.59	0.0001	–	16
10	2.7	5	46	12.3	–	0.548	–	15.8	15
–	–	5	9	12	0.89%	0.373	–	10.6	18
3/20	15	5	10/16	62.5		0.46		70	29
–	–	5	6/23	26.1		0.44		91.3	
25	21.4	5	12	10.3		0.38	0.001		36
–	–	10	26	26	65	0.26	0.01	72	38
13	8	10	26	26.5	73.5	0.472		67.3	37
		5	20/32	62.5	68.8	0.39	0.01	71.9	4
–	–	10	20/32	62.5	65.6	0.32			
–	–	15	18/32	36.3	62.5	0.25			
–	–	18	9/32	28.1	62.5	0.23			
3	3.1	10	42	43.8	71.9	0.427	–	69.8	40
		5	56	58.3	61.5	0.247			
–	–	10	28	31.5	73	0.44	0.001	68.5	41
5	8	5	12/62	19	–	0.6	<0.001	23	7
–	–	5	37/153	24.2	85.1	0.6	<0.001	116/142 (81.6)	45
–	–	10	38	23.5	–	0.276	–	67.3	5
		5	26	26	79	0.57		–	39
12	10	10	20	16.7	85.2	0.57	0.47	3.3	19
5	5.3	10	10	10.5	91	0.65	0.40	1.1	
7	6	5	6	5.2	95.4	0.52	0.16	6	
–	–	5	9	4.5	–	0.11	0.01		35
5	14.7	10	3	8.8	–	0.26	–	99	42
–	–	5	21	38	45.5	0.14	–	40	43
–	–	10	37/61	6	–	0.18		100	2
2	2.8	5	18	26	–	0.26	<0.001		17
2/106	1	5	27/101	27	–	0.17	0.02		46

the results of the TST with those of the IGRAs directly, and then calculating the degree of agreement, while in the second approach, researchers design studies in order to establish the extent to which test performance fits a defined attribute (e.g., likelihood of infection based on clinical or epidemiological characteristics).[13]

In view of the lack of a systematic evaluation of concordance between IGRAs and the TST in the diagnosis of LTBI among immunodeficient individuals, this review focuses on reported agreement between IGRAs and TST in the diagnosis of LTBI. It also assesses the utility of using IGRAs in individuals with a weakened immune

Table 2. Rates of positive/indeterminate results using TSPOT and TST for the diagnosis of LTBI in immunodeficient patients

Study group	Country	Subjects	Social class	Year	TSPOT	
					Positive	
					n	(%)
Rangaka *et al*.	South Africa	74 HIV+ (adults)	upper middle	2005	38	52
Ramos *et al*.	Spain	373 HIV+ (adults)	high	2009–2010	69	18.5
Karam *et al*.	Senegal	285 HIV+ (adults)	low	2003–2005	125/247	50.6
Zhang *et al*.	China	93 HIV+ (adults)	upper middle		16	17/2
Mandalakas *et al*.	South Africa	130 HIV+ (children)	upper middle	2007–2010	16/114	14
Stephan *et al*.	Germany	286 HIV+ (adults)	high	2006–2007	66/275	24
Elzi *et al*.	Switzerland	242 HIV+ (adults)	high	1993–2005	25/64	39
Talati *et al*.	Zambia	298 HIV+ (adults)	low	–	109	37
Talati *et al*.	USA	336 HIV+ (adults)	high	2005–2006	14	4.2
Mandalakas *et al*.	South Africa	20 HIV+ (adults)	upper middle		13/18	72.7
		23 HIV+ (children)			12/23	52.2
Chung *et al*.	Korea	98 ESRD patients (adults)	high	2009	57	58.2
Passalent *et al*.	Canada	203 ESRD patients (adults)	high	2005	72	35.5
Triverio *et al*.	Switzerland	62 ESRD patients (adults)	high		18	29
Chung *et al*.	Korea	167 ESRD patients (adults)	high	2008	96	60.4
Winthrop *et al*.	USA	100 ESRD patients (adults)	high		27	27
Lee *et al*.	Taiwan	32 ESRD patients (adults)	upper middle	2005	15/32	46.9
Richeldi *et al*.	Italy	120 Liver transplantation candidates (adults)	high	2006–2007	32	26.7
		95 Haematologic malignancy (adults)			25	26.3
		116 HIV+ (adults)			4	3.5
Kim *et al*.	South Korea	209 kidney transplant candidates (adults)	high	2008–2009	65/209	30
Hadaya *et al*.	Switzerland	200 renal transplant recipients (adults)	high	2009–2001	40	20.5
Stefan *et al*.	South Africa	34 children with cancer	upper middle	2007–2008	6	17.6
Bocchino *et al*.	Italy	69 TNFi candidates (adults)	high	2005–2006	21	30.4

ESRD: End-stage renal disease

system and determines the degree of concordance reported among three diagnostic tests (TST, QFT, and TSPOT) for LTBI

Search methodology

The authors used PubMed, Scopus and Web of Science for relevant studies by searching on terms included 'interferon gamma release assay', 'T cell–based assay', 'T-cell response', 'interferon', 'interferon-gamma', 'gamma-interferon', 'IFN', 'TSPOT', 'enzyme-linked immunosorbent spot', 'Quantiferon', 'Quantiferon-TB', 'HIV, human immunodeficiency virus, 'immunodeficiency', 'cancer', 'hemodialysis', 'renal failure', 'transplant' and 'latent tuberculosis'. In addition to database searches, the reference sections of primary studies were reviewed for anything that could have been missed using the electronic search, along with bibliographies of reviews and guidelines. The methodological quality of each selected paper assessed independently by at least two reviewers.

Inclusion and exclusion criteria

Studies were deemed eligible for inclusion if the study subjects were adults or children, with immunosuppressive conditions but were free of active disease, in any longitudinal study design (e.g., prospective or retrospective cohort) in any setting (i.e., low-income, middle-income or high-income country).

Data were synthesised for each commercial IGRA and by each group with immunosuppressive conditions (i.e., HIV, end-stage renal disease [ESRD], transplant candidates, patients with liver or arthritic disease). The prespecified subgroups minimised heterogeneity related to differences in testing performance for each group. Full-text papers reporting on human studies in which data on agreement (concordance) between TST and IGRA results in individuals with immunosuppressive conditions were evaluated.

The following were excluded from the review: i) studies that evaluated non-commercial IGRAs in non-blood

TSPOT		TST			Agreement TSPOT/TST (%)	Kappa	TSPOT/TST *P* value	BCG vaccination (%)	Ref.
Indeterminate		Cut–off	*n*	%					
n	(%)								
1	1	5	35	52	79	0.58	<0.001		22
		10	33	49	76	0.52	<0.001		
		15	25	37	66	0.31	0.006		
26	7	5	46	12.3	–	0.397	–	15.8	15
–	–	5	61	21.4	61.1	0.23	0.95		31
–	–	5	3	3.3	82.8	0.23	0.0001	100	32
–	–	5	84/247	34		0.37	0.013	93	25
8	2/9	5	33/275	12		0.53	0.006	6.64	26
21/64	33	5	22/44	50		0.14	0.177		27
–	–	5	128	43	76	0.4	0.005	75	33
–	–	5	7	2.5		0.16		7.4	28
2/20	10	5	10/16	62.5		0.43		70	29
–	–	5	6/23	26.1		–0.02		9.3	
7	4	10	26	26.5	70.4	0.402		67.3	37
14	7	10	19	9.4		0.25			6
7	11	5	12/62	19		0.32	0.007	23	7
–	–	10	38	23.5	–	0.163		67.3	5
–	–	5	26	26	71	0.61		–	39
		5	20/32	62.5	68.80	0.39	0.01	71.9	4
		10	20/32	62.5	65.60	0.32			
		15	18/32	56.3	62.50	0.25			
		18	9/32	28.1	62.50	0.23			
1	0.8	10	20	16.7	80.6	0.47		3.3	19
1	1.1	10	10	10.5	80.9	0.40		1.1	
0	0	5	6	5.2	92.7	0.16		6	
25	12	10	21	10		0.24	< 0.001	48/145 (33%)	36
–	–	5	9	4.5	–	0.09	0.034		35
4	11.8	10	3	8.8	–	0.33	–	99	42
4	5.8	5	18/69	26		0.21	0.0002		17

specimens; ii) studies focused on the effect of anti-TB treatment on IGRA response; iii) studies reporting insufficient data to determine the degree of concordance among diagnostic tests for LTBI (TST, IGRA); and iv) conference abstracts and letters without original data and reviews.

All data were extracted including study design, participants, country, period of recruitment, proportions of participants, IGRA method (assay used), TST method (cut-off point used), history of BCG vaccination and outcome data (e.g., IGRA or TST concordance).

Concordance between test results for TST and the IGRAs was assessed using Kappa (κ) coefficients.[14] The authors used the following definitions for primary outcomes: Kappa values range (κ=1 [full agreement] to κ=–1 [full disagreement]). The null value (κ=0) corresponds to an agreement equaling chance alone. Kappa statistics were then interpreted according to Landis and Koch, as follows: κ>0.75 (excellent agreement), κ=0.40–0.75 (fair to good agreement), κ<0.40 (poor agreement).

Study characteristics

Among the studies that addressed the concordance between IGRAs and TST for detection of LTBI in HIV-infected individuals, eight evaluated both the IGRA test and TST, five studies compare agreement between QFT and TST, and three studies evaluated the degree of concordance between TSPOT and TST.

Five studies evaluated both the IGRA test and TST in ESRD patients. Three studies and two studies compared agreement between TSPOT/TST and QFT/TST, respectively, in these patients.

Two studies addressed the concordance between IGRA and TST for LTBI in transplant candidates, but only one study compare the agreement between TSPOT and TST in this group.

Two studies evaluated both the IGRA test and TST in patients with cancer or haematologic malignancy. One study compared the performance of both the IGRA test and TST in candidates for anti-TNFγ treatment, and one study

evaluated QFT and TST in immunosuppressed patients with autoimmune disease and patients with chronic inflammatory disease.

Twenty-one studies were reported from high-income countries, 11 from upper middle-income countries and two from low-income countries.

Review of concordance

The proportion of indeterminate IGRA results among HIV-infected patients varied considerably, with 0–15% among studies by QFT,[15–30] and 0–33% among studies by TSPOT.[15,19,20,22,25–29,31–34] The proportion of indeterminate results for IGRAs was 0–12% among transplant candidates with immunosuppressive conditions,[19,35,36] as well as 0–8% by QFT[4,5,7,37–41] and 0–11% by TSPOT among ESRD patients.[4-7,35,37,39]

Stefan *et al*. reported that 14.7% and 11.8% of children aged under 16 years with cancer had indeterminate IGRA by QFT and TSPOT, respectively,[42] while in another study of 55 adult bladder cancer cases, no indeterminate IGRA results were obtained.[43] Although indeterminate IGRA results in other immunocompetent individuals, including patients with chronic liver disease, inflammatory disease, rheumatoid arthritis and in anti-TNFα candidates, accounted for less than 2.8%,[2,44–46] some studies reported higher figures (5.8% in anti-TNFα candidates[17] and 13% in patients with immune-mediated inflammatory disease).

In studies from South Africa, concordance between TST and IGRAs has been reported as fair[22,25,27,29,33] or poor.[29,42] The reported kappa statistics have been inconsistent (range: 0.02–0.6 among HIV-infected patients, 0.16–0.61 in ESRD individuals, 0.09–0.57 in transplant candidates, and 0.14–0.65 in patients with cancer). Several other studies have shown fair[16,26] to poor[15,17,18,21,23,24,28,31,32] concordance in HIV-infected individuals.

Among those with various immunosuppressive conditions screened for LTBI, published comparisons of TSPOT with TST generally demonstrate either similar proportions of positive results[20,22,28,39] or more frequent positives.[5–7,15,17,19,26,29,32,35–37,42] However, some studies have reported higher proportions of TST-positive results in comparison to TSPOT.[4,25,27,33]

In the majority of studies, similar proportions of positive results for QFT in comparison to TST[7,21,23,28,36,39,40,42,45] or a higher proportion of QFT in comparison to TST[5,15–17,19,22,26,30,35,37,38,41,44,46] were observed. In contrast, several studies reported a higher proportion of TST positives.[2,4,18,22,24,25,27,29]

Among studies that compared the performance of IGRAs and TST, prevalence of LTBI in transplant candidates ranged from 20.5% to 30% by IGRA and from 4.5% to 16.7% by TST.[10,35,36] Among studies comparing the performance of IGRAs and TST, prevalence of LTBI in ESRD patients range from 21% to 60.4% by IGRA and from 9.4% to 73.5% by TST[4–7,37–41,45]

In the Mandalakas *et al*. study, a high level of discordant IGRA results in HIV-infected adults and in children was observed. In adults, there was fair agreement between the TST and TSPOT (κ=0.43) and the TST and QTF (κ=0.46), while in children, in spite of fair agreement between TST and QTF (κ=0.44), very poor concordance between TST and TSPOT (κ=–0.02) was observed.[29]

In previous studies determining the performances of IGRA results versus TST for detecting LTBI in ESRD cases, agreement between these tests were variable, from fair[7,37,39,41] to poor concordance,[4–6,38] and excellent agreement was not observed. Maden *et al*. found fair to moderate agreement between QFT and TST with a TST cut-off of 5 mm (κ=0.24) and 10 mm (κ=0.427) in ESRD patients on haemodialysis.[40] In the study by Lee *et al*., in spite of considering different TST cut-off values (i.e., 5, 10, 15 and 18 mm), very poor concordance between TST and QFT was observed.[4]

Discussion

Several studies addressed the diagnostic performances of IGRA for LTBI in immunocompromised persons, such as those with HIV infection,[15–30,34,47] in ESRD cases[4–7,37–41] or in patients with chronic liver disease,[45] and in transplant candidates with immunosuppressive conditions.[19,35,36] However, few data are available on this issue in patients with cancer.[42,43]

As there is no diagnostic 'gold standard' test for LTBI, the authors evaluated concordance between IGRAs and TST. Several studies demonstrated that IGRAs produce a higher number of positive results than TST, and show poor agreement.[18,21–23,26,29,34,48–50] Observed discrepancies between IGRAs may be related to several technical and interpretation aspects related to test methodology, such as differences in T-cell count for TSPOT, discrepancies in volume of blood added,[29] or differences in participant age,[29] race, prior BCG vaccination, recent TST, and coexisting diseases, including non-tuberculous mycobacterial infection and immunosuppressive conditions. It has been reported that increasing age is associated more strongly with TST results than with IGRA results.[4,27,40,51,52]

According to Balcells *et al*., the degree of agreement between TST and QFT varied among those individuals for whom no known risk factor for TB was found (κ=0.17), and those individuals with known possible latent TB risk factor (κ=0.86).[16]

There are many confounders that lead to false-negative and false-positive results. Alcoholism, gastrectomy or intestinal bypass, haematologic or lymphoreticular disorders, HIV, inaccurate reading of induration, live virus vaccines (e.g., measles, mumps, rubella and polio virus), malnutrition, renal failure, sarcoidosis, and systemic viral, bacterial and fungal infection may cause a false-negative TST result. On the other hand, boosting phenomena, cross-reaction with non-tuberculous mycobacterial antigens, error in administering the test, and BCG vaccination may lead to a false-positive TST result.[53–55]

It has been reported that IGRA performance in immunosuppressed patients, with indeterminate IGRA results, tend to have lower CD4 counts, as well as negative TST responses.[21,49] These findings highlighted the risk of TST anergy in HIV-infected individuals with lower CD4 counts.[29,56,57] However, Bruzzese *et al*. reported that IGRA performance is not associated with age, gender, blood leucocyte count, or immunosuppressive treatment duration in HIV-negative, immunocompromised children.[58] According to Bruzzese *et al*., IGRAs are of little help in TB infection management for immunocompromised children due to high rates of discordant and indeterminate results, particularly in a country in which the prevalence of the disease is low.[58]

Immunosuppression due to HIV infection and immunosuppressive therapy in solid organ transplant recipients are recognised risk factors for false-negative TST reactions.[15,26,29,31,32,59] Liver transplantation recipients had an 18-fold increase in the risk of TB reactivation and a four-fold increase in the case fatality rate compared with the general population.[60]

A relatively high rate of indeterminate QFT test results versus TST (12.6% versus <1%) was observed in liver transplantation patients.[61] Kim *et al*. reported that the TSPOT test was more frequently positive than TST for detecting LTBI in renal transplant recipients.[36]

Patients with chronic renal failure are at high-risk of reactivation (relative risk: 10.0–25.3) compared to the general population,[4,62,63] and all patients with a positive reaction are recommended for prophylaxis.[39,64,65]

Patients with ESRD may show cutaneous anergy to skin test antigens.[3,6,66–68] Although the rate of anergy is variable, recent reports suggest that 22.6–81% of HD patients are anergic.[3,66–69] In addition, the likelihood of false-negative TST results in these patients makes interpretation of negative results unreliable.[39] However, anergic reaction is common among patients requiring HD; therefore, TST may not be a sensitive means to detect LTBI.[12]

Although responses to IGRA are slightly reduced in immunosuppressed subjects, when compared with immunocompetent individuals, IGRA positivity rate is substantially higher than that of TST.[5,6,15,26,29,31,34,35,37–39,44,70] Using the QFT test in patients with ESRD can bypass the problems associated with anergy in response to TST or cross-reactivity in patients with a history of BCG vaccination.[71] Among ESRD patients receiving HD, the IGRA-positive rate is reported to be 22–60.4%,[4–7,37-41,72] while 0–11% of patients have indeterminate IGRA results.[4–7,37–41,72,73]

Overall, IGRAs (both QFT and TSPOT) have been shown to be more sensitive than the TST for the diagnosis of latent TB in ESRD patients.[5–7,36,39,73] The TST is very insensitive in HD patients, and false-positives may occur in patients born in countries where BCG vaccine has been used.

Considering the low sensitivity and low specificity of TST in HD patients, the use of IGRAs as the screening test in this group, including renal transplantation candidates prior to surgery, is recommended.[74]

The impact of HIV infection on the immune response of LTBI is poorly understood. In cases with discordant result, it is not easy to decide which test gives the true result, due to lack of a gold standard for detection of LTBI.[18] There are few data on IGRA performance in immunocompromised children.[25,29,42,75] In the Mandalakas *et al*. study, among 23 HIV-infected, a greater rate of positive results with TSPOT (52.2%) than with TST (26.1%) was seen,[29] which suggested greater sensitivity of TSPOT for detection of LTBI in this group. In another study, among 34 children with cancer, TSPOT showed a high rate of positive results compare with TST (17.6% versus 4.5%).[42]

Although use both of IGRA and TST increased the overall rate of LTBI detection in immunocompromised children,[76] QFT might not provide a determinate test result in a substantial proportion due to young age and immuno-deficiency.[25,29,76] Indeterminate results, predominately because of poor mitogen responses, are observed more frequently in younger children (range: 0–14.7%).[25,29,42,58]

Although, there are insufficient data on which factors influence indeterminate results, age, female gender, lower CD4+ count, lymphopenia, advanced liver disease, diabetes mellitus, immunodeficiency, cancer chemotherapy and immunosuppressive treatment may be associated with indeterminate results.[30,45,77]

BCG vaccination status has been shown to be a risk factor for discordant results between TST and QFT.[41] Vaccination with BCG can cause difficulties in interpretation of the TST, due to the genetic similarities between BCG and *M. tuberculosis*.[78] TST-positive/IGRA-negative discordance may occur 1.1- to 25-fold more often in BCG-vaccinated persons.[4,25,29,33,40,51,79]

In the study by Sayarlioglu *et al*., BCG-vaccinated patients had a low agreement (κ=0.36) between TST and QFT, while among non-vaccinated HD patients this concordance was 82% (κ=0.61).[41] However, Manuel *et al*. reported that BCG vaccination was not associated with discordant results between tests.[45,70] Silverman *et al*. reported that bladder cancer patients with a history of BCG vaccination were significantly more likely to have a positive TST than a positive QFT.[43]

The decision about which test to use will also depend on resource and logistic considerations, as well as the country guidelines.[10] Many countries (e.g., Portugal, Czech Republic, Ireland, Slovakia, The Netherlands, South Korea, Croatia and UK) recommend simultaneous testing with TST and IGRA. However, Germany, Switzerland, Bulgaria, Japan, France, Poland and Austria recommend IGRA as the initial test of choice. Countries such as Canada, Italy, Ireland, Saudi Arabia, and Spain recommend IGRA testing only if the initial TST is negative,[10,80] while Brazil recommends performing TST alone.[80] According to Saudi guidelines, in patients with immunodeficiencies, IGRAs might be useful to rule out LTBI if a false-negative TST result is suspected.[12]

Currently, the choice about which IGRA test to use in immunodeficient patients is under debate. It has been reported that IGRAs, especially the T-SPOT.TB assay, are less affected by HIV-related immunosuppression than is TST.[80] Among studies which evaluated the performance of the two commercially available IGRA assays (TSPOT and QFT),[4,5,7,15,17,19,20,22,25,26,28,29,33,35,37,39,42] the highest proportion of positive tests was identified by TSPOT.[4,5,7,19,22,28,29,37,39,42] However, other studies report a higher proportion of QFT-positive results[15,20,25,26] or similar proportions in comparison to TSPOT.[17,33,35] Among ESRD patients in all studies, considering both IGRAs assays (TSPOT and QFT), the highest proportion of positive tests were identified by TSPOT.[4,5,7,37,39]

The major limitations of IGRAs for diagnosing LTBI are lack of differentiating between LTBI and active TB, as well as inadequate reference standards for diagnosis of LTBI. Thus, studies of LTBI testing are generally limited by this lack of an adequate reference standard, particularly among patient populations with immunosuppressive conditions.

It has been reported that antibody measurement may predict ongoing progression from latent to active TB in immunodeficient patients (e.g., HIV-positive subjects), particularly in those with a negative TST or an indeterminate IGRA result.[13] Therefore, measurement of cytokines such as IFNγ, interleukin (IL)-2 and IL-10 released after stimulation with selected antigens in order to differentiate active TB from LTBI, principally in a high risk-population such as immunodeficient patients, is highly recommended. □

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