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Original Article

Positivity rate of interferon-γ release assays for estimating the prevalence of latent tuberculosis infection in renal transplant recipients in Japan☆

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ABSTRACT

Renal transplant recipients are at increased risk of reactivating latent tuberculosis infection (LTBI) and developing active tuberculosis. QuantiFERON®-TB Gold Plus (QFT-Plus) has two TB-specific antigens tubes (TB1 and TB2). TB1 elicits CD4 T-cell response, and TB2 elicits both CD4 and CD8 T-cells responses, with expected increased sensitivity.

The aim of this study was to estimate the prevalence of LTBI in renal transplant recipients in Japan. We conducted a cross-sectional study by using two interferon-γ release assays (IGRAs), QFT-Plus and T-SPOT®.*TB* (TSPOT).

One hundred thirty-five recipients were prospectively enrolled. The median age was 49 years (range: 20 to 79). The positivity rates of QFT-Plus and TSPOT were 5.9% (95%CI 3.0−11.3) and 3.7% (95%CI 1.6−8.4), respectively, with no significant difference. The concordance rate was 95.5% (κ coefficient, 0.76). Age of 60 years and higher was related to the higher positivity rate in both QFT-Plus and TSPOT. The positivity rates of TB1 and TB2 were 5.1% (95%CI 2.5−10.2) and 5.9% (95%CI 3.0−11.2), respectively, with no significant difference. The concordance rate was 99.3% (κ coefficient, 0.93). TB2 did not show a higher positivity rate compared with TB1.

The estimated prevalence of LTBI by using the both IGRAs was 3.7−5.9% in renal transplant recipients. These results were equivalent to the IGRAs positivity rate in the general Japanese population, even under the condition of immunosuppressive therapy. In consideration of the higher risk of developing active TB from LTBI, we can use both IGRAs as acceptable tools for LTBI diagnosis in renal transplant recipients.

1. Introduction

Renal transplant recipients are at increased risk of reactivating latent tuberculosis infection (LTBI) and developing active tuberculosis (TB). Solid organ transplant recipients receive immune suppressive therapy, by which their risk of active TB is estimated to be 20 to 74 times greater than the general population [1].

LTBI is defined as a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active TB according to World Health Organization Guidelines [2]. Interferon (IFN)-γ release assays

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(IGRAs) estimate the cell-mediated immune responses to TB-specific antigens. IGRAs have been approved for LTBI diagnosis. QuantiFERON®-TB Gold Plus (QFT-Plus) (Cellestis/Qiagen, Carnegie, Australia) and T-Spot®.*TB* (TSPOT) (Oxford Immunotec, Abingdon, United Kingdom) are commercially available.

National Hospital Organization Chiba-East Hospital (CEH) is one of the renal transplantation facilities in Japan certified by the Japan Organ Transplant Network. At CEH, the total number of renal transplantation cases between April 2004 and March 2018 reached 370. Up to the present, three of the renal transplant recipients have developed active TB. Active TB is one of the important infectious diseases in renal transplant recipients. The risk for active TB disease after infection depends on several factors, the most important being the immunological status [2]. LTBI treatment by the administration of isoniazid has been shown to reduce the risk of developing active TB [3]. Accurate LTBI diagnosis and its treatment would be beneficial for patients receiving immunosuppressant treatment, such as recipients undergoing renal transplantation [4–6]. Identifying and treating LTBI is one of the key strategies for achieving TB elimination by 2050 [7–9].

QuantiFERON®-TB Gold Plus (QFT-Plus) is a 4th generation QFT, which uses two TB-specific antigen tubes, TB1 and TB2. TB1 is designed to elicit a CD4 T-cell response, like QFT-GIT. TB2 has been newly designed to elicit immune response driven by both CD4 and CD8 T-cells. This mechanism would be expected to increase the sensitivity for LTBI detection.

To estimate the prevalence of LTBI in renal transplant recipients, we conducted a study to evaluate the positivity rate by using the two IGRAs, QFT-Plus and TSPOT. We also examined the counts of CD4 and CD8 T-cells and estimated the influence in the two IGRAs on the immune responses.

2. Materials and methods

This study was a cross-sectional analysis conducted at CEH in Japan. A total of 135 renal transplant recipients were prospectively enrolled between April 2017 and March 2018. Stable renal transplant recipients who had received current immunosuppressive therapy for more than three months were eligible for inclusion in this study. We recruited 137 renal transplant recipients, and one recipient refused to participate in this study. Patient characteristics are described in Table 1.

Peripheral venous blood was collected for QFT-Plus, TSPOT, and lymphocyte subset analysis. Blood samples for QFT-Plus and TSPOT were transported to the laboratory at Chiba Foundation for Health Promotion and Disease Prevention (CFHPDP) at the appropriate temperature within 8 h, processed, and assessed according to the manufacturers' instructions. T-cell Xtend was not used for preparing peripheral blood mononuclear cells for TSPOT. Sampling tubes for QFT-Plus consisted of four tubes (TB1, TB2, negative control, positive control), and were purchased from QIAGEN (Hilden, Germany). The TB1 tube contains TB-specific antigen eliciting CD4 T-cell, and TB2 tube contains TB-specific antigens eliciting both CD4 and CD8 T-cells.

QFT-Plus was interpreted according to the supplier's instructions. The IFN-γ values for TB1 and TB2 were calculated by subtracting IFN-γ in negative control from IFN-γ in TB antigens tubes (TB1 and TB2), with a value of ≥0.35 IU/ml being considered a

Table 1
Characteristics of renal transplant patients.

	n	(%)
Total	136	
Male	81	(59.6)
Median age [years] (range)	49	(20–79)
Hemodialysis before transplantation	107	(78.7)
Duration of hemodialysis, median [days](range)	1049	(72–10472)
Duration after transplantation, median [days](range)	2238	(329–10449)
Causes of renal failure before renal transplantation		
Diabetic nephropathy	31	(22.8)
Chronic glomerulonephritis except for IgA nephropathy	27	(19.9)
IgA nephropathy	24	(17.6)
Nephrosclerosis	11	(8.1)
Polycystic kidney	8	(5.9)
Cnronic nephritis	3	(2.2)
Hypoplastic kidney	3	(2.2)
Alport syndrome	2	(1.5)
ANCA associated nephropathy	2	(1.5)
Other	11	(8.1)
Unknown	14	(10.3)
Type of renal transplantations		
Renal transplantation from living donor	125	(91.9)
Cadaveric renal transplantation	7	(5.1)
Simultaneous pancreas-kidney transplantation from living donor	2	(1.5)
Cadaveric simultaneous pancreas-kidney transplantation from living donor	2	(1.5)
Prescription of immunosupressive agents	136	(100)
Mycophenolate mofetil	124	(91.2)
Prednisolone	104	(76.5)
Tacrolimus	84	(61.8)
Cyclosporine	41	(31.4)
Everolimus	14	(10.3)
Mizoribine	8	(5.9)
WBC [/μL]median (range)	6000	(4500–7400)
Lymphocytes [/μL] median (range)	1499	(459–3936)
CD4 T-cell [/μL] median (range)	688	(146–1858)
CD8 T-cell [/μL] median (range)	491	(92–1520)
CD4/CD8 median (range)	1.35	(0.33–4.97)
Suspected tuberculosis from chest X-ray	5	(3.7)
History of tuberculosis treatment	8	(5.9)

positive result in either TB1 or TB2. If the IFN-γ value was <0.35 IU/ml and mitogen control was ≥0.5 IU/ml, the test was interpreted as negative. If the IFN-γ value was <0.35 IU/ml and mitogen control was <0.5 IU/ml, the result was considered as being indeterminate. If the negative control was >8.0 IU/ml, the result was considered as being indeterminate.

TSPOT was also scored according to the supplier's instructions. Spot-forming units (SFUs) were counted by a medical technologist. The number of spots was scored as positive if either antigen was ≥6, and negative if it was ≤5. Tests were considered as indeterminate if SFUs in positive control were <20, or SFUs in the negative well exceeded 10 and SFUs in both antigen wells had less than twice the number of SFUs of the negative well.

Blood samples for the lymphocyte subsets were analyzed by SRL Inc. (Tokyo, Japan). The percentage of lymphocytes expressing CD4 T-cell or CD8 T-cell was determined by flow cytometry after lymphocytes were stained by two-color monoclonal antibodies, anti-CD4-FITC (Fluorescein Isothiocyanate; Beckman Coulter, CA, USA) and anti-CD8-PE (Phycoerythrin; Beckman Coulter).

Renal transplant recipients volunteered to participate in the study and provided written consent following written and oral descriptions of the study. This study was approved by the Institutional Review Board of CEH and CFHPDP, and was conducted in accordance with the principles of the Declaration of Helsinki. This study was registered to UMIN, and its resistor number was R000029861.

2.1. Statistical analysis

JMP® Pro 13.0.0 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis. Chi-square test or Fisher's exact test was used to compare categorical variables. McNemar's test was used to compare paired proportions in IGRAs. Agreement between QFT-Plus and TSPOT, and between TB1 and TB2, was quantified using κ coefficients. P-value <0.05 was considered statistically significant.

3. Results

The results of QFT-Plus, including TB1 and TB2, and TSPOT are shown in Table 2. The numbers of QFT-Plus positive, negative and indeterminate were eight, 128 and none, respectively; their percentages were 5.9% [95% Confidence Interval (CI), 3.0–11.2], 94.1% [95% CI, 88.8–97.0] and 0.0%, respectively. The numbers of TSPOT positive, negative and indeterminate were five, 128 and three, respectively; their percentages were 3.7% [95% CI, 1.6–8.3], 94.1% [95% CI, 88.8–97.0] and 2.2% [95% CI, 0.8–6.3], respectively. There was no significant difference in the percentage of positive between QFT-Plus and TSPOT. The concordance rate was 95.5% between the two IGRAs. The κ coefficient for positive was 0.76 [95% CI, 0.50–1.02].

Table 2
Results of interferon-γ release assay for renal transplant recipients.

	Positive	(%)	Negative	(%)	Indeterminate	(%)
TSPOT	5	(3.7)[a]	128	(94.1)	3	(2.2)
QFT-Plus	8	(5.9)	128	(94.1)	0	(0.0)
QFT-Plus TB1	7	(5.1)[b]	129	(94.9)	0	(0.0)
QFT-Plus TB2	8	(5.9)	128	(94.1)	0	(0.0)

κ coefficient for positive was 0.76[95%CI 0.50–1.00] in the analysis of TSPOT and QFT-Plus. κ coefficient for positive was 0.93[95%CI 0.79–1.00] in the analysis of QFT-Plus TB1 and TB2.
TSPOT: T-Spot®.TB, QFT-Plus: QuantiFERON®-TB Gold Plus, CI: confidence interval.
[a] There was not significant difference in the percentage of positive between QFT and TSPOT.
[b] There was not significant difference in the percentage of positive between TB1 and TB2.

The results of TB1 and TB2, responding to TB-specific antigens of QFT-Plus, are shown in Table 2. The numbers of TB1 positive, negative and indeterminate were seven, 129 and none, respectively; their percentages were 5.1% [95% CI, 2.5–10.2], 94.9% [95% CI, 89.8–97.5] and 0.0%. The numbers of TB2 positive, negative and indeterminate were eight, 128 and none, respectively; their percentages were 5.9% [95%CI, 3.0–11.2], 94.1% [95% CI, 88.8–97.0] and none, respectively. There was no significant difference in the percentages of positive between TB1 and TB2. The concordance rate was 99.3% between TB1 and TB2., and the κ coefficient for positive was 0.93 [95% CI, 0.79–1.07].

Table 3 shows a list of eight IGRAs-positive recipients. Five of the recipients were positive in both QFT-Plus and TSPOT. Their IFN-γ values were relatively higher, and their durations of hemodialysis (HD) before renal transplantation was shorter or none.

Univariate analysis for positive in QFT-Plus and TSPOT is shown in Table 4. Eight renal transplant recipients with the history of treating TB were negative in both QFT-Plus and TSPOT. Age of 60 years or higher was related to the higher positivity rate in both IGRAs. All the recipients of renal transplantation those who did not have a history of HD had negative IGRA results.

The counts of CD4 T-cell and CD8 T-cell in peripheral venous blood were measured, and the median counts (IQR: interquartile range) were 680/μL (500–924) and 485/μL (349–680), respectively. The CD4 T-cell count was a little lower in consideration of normal range (518–1472), whereas the CD8 T-cell count was aligned within the normal range (205–924).

The recipients' background factors that were possibly associated with IGRAs were analyzed between those aged <60 years and ≥60 years (Table 5).

4. Discussion

This study analyzed the positivity rate of IGRAs to estimate the prevalence of LTBI in renal transplant recipients using two IGRAs, QFT-Plus and TSPOT. The positivity rates were 5.9% and 3.7%, respectively. The κ coefficient for positive was 0.76 between the two IGRAs, showing excellent agreement. We had previously analyzed the QFT-GIT positivity rate in renal transplant recipients, obtaining a result of 6.5% [10]. There was no significant difference in positivity between QFT-GIT and QFT-Plus. The number of renal transplantation recipients from 2004 to 2016 is 18648 as is calculated on the data by The Japan Society for Transplantation. The estimated number of LTBI patients who would be diagnosed LTBI were 690–1100 in renal transplantation recipients. The annual number of active TB patients is 18900 in 2017. The diagnosis and treatment of LTBI would be emphasized in consideration of the risk of developing active TB in renal transplantation recipients.

We then analyzed the positive renal transplant recipients (Table 3). Variability of the IFN-γ value in QFT-GIT was shown to be between 0.25 and 0.59IU/mL [11]. Others have claimed a wider variability range between 0.2 and 0.7IU/mL [12,13]. Conversion and reversion were frequently observed in serial tests in QFT. In the present study, reliable positive diagnosis with an IFN-γ value of ≥0.6 IU/mL was restricted to five of eight renal transplant recipients. There were three cases with QFT-Plus positive and TSPOT negative (Case 2, 7 and 8). IFN-γ values in Case 7 and 8 were 0.57 IU/mL and 0.36 IU/mL, respectively. Their positive results in QFT-Plus might convert to negative in the repeated tests. But, IFN-γ value in Case 2 was 1.66 IU/mL and relatively high. Although QFT-Plus revealed a little higher positivity, the two IGRAs were almost equivalent in consideration of variability range. We need further study for analyzing these discrepancies between two IGRAs, even in a limitation owing to the lack of a gold standard for the LTBI diagnosis. Better methods and biomarkers are urgently needed to

Table 3
List of positive cases in QFT-Plus and TSPOT.

Age (year)	Sex	QFT-Plus						TSPOT		CD4 (/μL)	CD8 (/μL)	CD4/CD8	Duration after RT (days)	HD duration before RT (days)
		diagnosis	IFN-γ value (IU/mL)	TB1 diagnosis	IFN-γ value(IU/mL)	TB2 diagnosis	IFN-γ value (IU/mL)	diagnosis	SFU					
62	m	positive	17.99	positive	17.99	positive	15.00	positive	19	652	646	1.0	4492	882
67	f	positive	1.66	positive	1.66	positive	1.15	negative	0	646	802	0.8	1888	120
60	f	positive	1.51	positive	1.51	positive	1.37	positive	11	757	329	2.3	768	392
69	m	positive	1.11	positive	1.06	positive	1.11	positive	16	531	313	1.7	3428	603
64	f	positive	0.68	positive	0.68	positive	0.67	positive	18	775	807	1.0	2637	1101
30	f	positive	0.54	positive	0.43	positive	0.54	positive	6	428	609	0.7	370	2493
65	m	positive	0.52	positive	0.52	positive	0.48	negative	0	645	779	0.8	4032	10472
48	f	positive	0.36	negative	−0.05	positive	0.36	negative	0	603	611	1.0	4045	5548

QFT-Plus: QuantiFERON®-TB Gold Plus, TSPOT: T-Spot®.TB, IFN: interferon, CD4: CD4 T-cell, CD8: CD8 T-cell, HD: hemodialysis, RT: renal transplantation.

Table 4
Univariate analysis of positive in interferon-γ release assays in renal transplant recipients.

		n	QFT-Plus Positive	(%)	P value[a]	TSPOT Positive	(%)	P value[a]
Male	yes	81	3	(3.7)	n.s	2	(2.5)	n.s
	No	55	5	(9.1)		3	(5.5)	
Age of 60 years or more	yes	47	6	(12.8)	0.02	4	(8.5)	0.048
	no	89	2	(2.3)		1	(1.1)	
HD before transplantation	yes	109	8	(7.3)	n.s	5	(4.6)	n.s
	no	27	0	(0.0)		0	(0.0)	
Diabetes mellitus	yes	33	2	(6.1)	n.s.	1	(3.0)	n.s
	no	102	6	(5.9)		4	(3.9)	
Chronic liver disease	yes	5	0	(0.0)	n.s	0	(0.0)	n.s
	no	131	8	(6.1)		5	(3.8)	
History of TB treatment	yes	8	0	(0.0)	n.s	0	(0.0)	n.s
	no	128	8	(6.3)		5	(3.9)	
Suspected previous TB in chest X-ray	yes	5	1	(20.0)	n.s	0	(0.0)	n.s
	no	131	7	(5.3)		5	(3.7)	

QFT-Plus: QuantiFERON®-TB Gold Plus, TSPOT: T-Spot®.TB, HD: hemodialysis, TB: tuberculosis, n.s.: not significant.
[a] Difference between yes and no.

Table 5
Differences in the two age groups of <60yr. and ≥60 yr.

	<60 years old		≥60 years old		P value
	n = 89	(%)	n = 47	(%)	
Male	56	(62.9)	24	(52.2)	n.s.
Transplantation from living donor	84	(94.4)	40	(85.1)	n.s.
HD before transplantation	67	(75.3)	40	(85.1)	n.s.
Duration of HD, median [days](IQR)	754	(321–2610)	1417	(612–3156)	n.s.
Duration after transplantation, median [days](IQR)	2161	(1332–3271)	2637	(1462–3347)	n.s.
Suspected previous TB in chest X-ray	2	(2.3)	3	(6.4)	n.s.
History of TB treatment	4	(4.5)	4	(8.5)	n.s.
WBC [/μL](IQR)	6100	(4450–7600)	5800	(4600–7000)	n.s.
Lymphocyte [/μL](IQR)	1487	(1167–2005)	1539	(1112–1769)	n.s.
CD4 T-cell [/μL](IQR)	714	(497–936)	653	(502–922)	n.s.
CD8 T-cell [/μL](IQR)	497	(346–727)	485	(363–645)	n.s.
CD4/CD8(IQR)	1.34	(1.00–1.97)	1.39	(0.86–1.97)	n.s.
IFN-γ value in positive control in QFT-Plus (IQR)	24.3	(20.3–32.5)	24.9	(20.7–29.6)	n.s.

HD: hemodialysis, IQR: Interquartile Range, TB: tuberculosis, CD4: CD4 T-cell, CD8: CD8 T-cell, IFN: interferon, QFT-Plus: QuantiFERON®-TB Gold Plus.

select LTBI treatment in immunocompromised conditions specifically [14]. LTBI diagnosis should be based on not only interpretation of the cut-off value but also on epidemiological and clinical assessment [15]. Therefore, we need to be cautious when interpreting QFT-Plus results with an IFN-γ value of <0.6 IU/mL and TSPOT results of 6 or 7 SFUs.

The positivity rates of QFT-Plus and TSPOT rose to 13.0% and 8.5% in elderly renal transplant recipients of aged 60 years or more, respectively, significantly higher rates compared with younger recipients. These results reflected the higher TB infection rate in elderly people in Japan. The QFT-GIT positivity rate in the general Japanese aged 60 years and older was 9.4–15.7%, and TSPOT was 7.1–26.3% [16]. The rates were 3.9% and 3.6%, respectively, in those less than 60 years old [16]. In this study, the positivity rates of both QFT-Plus and TSPOT were similar to those of the general Japanese population. Therefore, the prevalence of LTBI in renal transplant recipients was estimated to be similar to that of the general Japanese population. The relative risk for solid organ transplantation

recipients to develop active TB from LTBI is estimated to be 20–74 times [1]. The treatment regimen for LTBI among renal transplant recipients by using isoniazid have been supported by several studies [17]. The introduction of IGRAs in renal transplant recipients would be appropriate for the selection of INH treatment candidates and lead to a reduction in the number of those developing active TB.

QFT-Plus introduced TB2 for estimating both CD4 T-cell and CD8 T-cell immune responses to TB-specific antigens. We expected that TB2 would boost the sensitivity of LTBI diagnosis, in addition to TB1. However, both TB1 and TB2 showed almost complete agreement. The κ coefficient for positive was 0.93 between TB1 and TB2, showing excellent agreement.

We also analyzed the relation of lymphocyte subsets with IGRAs diagnosis. Compared with the reference range of CD4 and CD8 T-cells, CD4 T-cell counts of the renal recipients were slightly lower, CD8 T-cell normal.

There were eight renal transplant recipients with TB treatment histories, and they were negative in both QFT-Plus and TSPOT. Some studies have reported that T-cell IFN-γ production in response to TB-specific antigens declines or even disappears in patients receiving anti-TB treatment [18–20]. Anti-TB therapy greatly reduces the 。 bacterial load, and then the frequency of effector T cells also decreases. Immunosuppressive therapy would also attenuate IFN-γ production still more, resulting in IGRAs negative response. Longer duration of HD presents a higher risk of developing active TB [21]. In this study, all IGRAs-positive renal transplant recipients had histories of HD, whereas none was IGRA positive among direct renal transplant recipients (without preceding HD). HD might be a risk for LTBI. HD its self is a risk factor of developing active TB. Our results support the possible TB transmission in the HD fasciitis.

The indeterminate rate in QFT-Plus and TSPOT was 0.0% and 2.2%, respectively. In the former study of renal transplant recipients, QFT-GIT and TSPOT in renal transplant recipients showed an indeterminate rate of 2.2% in each IGRA [10]. Both IGRAs would be available for LTBI diagnosis in low immunosuppressive status like the stable renal transplant recipients.

There are some limitations. First, the present study was conducted in a single facility. The number of renal transplantation from 2004 to 2016 is 18648 as is calculated on the data by The Japan Society for Transplantation. The renal transplantation in CEH is 380, indicating 2.0% of total renal transplantation in Japan. Second, the number of positive recipients was small in the present study. Therefore, the factors associated with IGRA results, including TB1 and TB2, were not analyzed sufficiently. Additional studies are needed to attain clearer findings of the immune response. Finally, the risk of developing active TB in solid organ transplantation recipients was relatively higher within 1–3 years of renal transplantation [22]. In our study, the median duration after renal transplantation was about 2238 days (6.1 years). In comparison, in Taiwan, the mean duration from renal transplantation to active TB development was reported to be 58 months [23]. Our present study demonstrated the efficacy of IGRA estimation to some extent.

Our study examined the prevalence of LTBI in renal transplant recipients, showing 5.2% in QFT-Plus and 3.7% in TSPOT. QFT-Plus was found to be similar positivity rate to TSPOT. These results were also equivalent to the IGRAs positivity rate in the general Japanese population, even under the condition of immunosuppressive therapy. In consideration of the higher risk of developing active TB from LTBI, we can use both IGRAs as acceptable tools for LTBI diagnosis in renal transplant recipients.

Authors' contributions

Hidetoshi Igari: Study planning, Data analysis.

Naotake Akutsu Study planning, Data analysis.

Satoru Ishikawa: Study planning, Data analysis.

Hiromichi Aoyama Recruitment of subjects and blood specimen sampling.

Kazunori Otsuki Recruitment of subjects and blood specimen sampling.

Masayuki Hasegawa Recruitment of subjects and blood specimen sampling.

Michihiro Maruyama Recruitment of subjects and blood specimen sampling.

Kenichi Saigo Study planning, Data analysis.

Mizue Tsuyuzaki Laboratory staff for QFT and TSPOT.

Kiminori Suzuki Study planning.

Conflicts of interest

None declared.

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