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Interferon-gamma release assays versus tuberculin skin testing for detection of latent tuberculosis in chronic haemodialysis patients

Pierre-Alain Triverio[1], Pierre-Olivier Bridevaux[2], Pascale Roux-Lombard[3], Laurent Niksic[1], Thierry Rochat[2], Pierre-Yves Martin[1], Patrick Saudan[1] and Jean-Paul Janssens[2]

[1]Division of Nephrology, [2]Division of Pulmonary Diseases and [3]Division of Immunology and Allergology, Geneva University Hospital, 1211 Geneva 14, Switzerland

Correspondence and offprint requests to: Jean-Paul Janssens; E-mail: jean-paul. janssens@hcuge.ch

Abstract

Background. End stage renal disease increases the risk of reactivating latent tuberculosis (LTBI). Interferon-γ release assays (IGRA) are an alternative to the tuberculin skin test (TST) for detecting LTBI.

Methods. Sixty-two hemodialysis patients (46 male, 16 female, aged 65 ± 15 years) from 3 hemodialysis facilities in the Geneva area were submitted to a TST, 2 IGRA (T-SPOT.TB and QuantiFERON Gold in tube: QFT), a chest radiography, and a questionnaire to record social status, country of birth, history of prior TST, tuberculosis (TB), BCG (Bacillus of Calmette-Guérin vaccine), and any cause of immuno-suppression. LTBI was defined as prior "at risk" contact with a case of contagious TB and/or a chest X-ray suggestive of prior TB infection.

Results. Positivity rate was 19% for TST, 21% for QFT and 29% for T-SPOT-TB; 8% of QFT and 11% of T-SPOT-TB were indeterminate. Agreement between IGRA was fair ($\kappa = 0.60$). After adjusting for age and BCG, OR (Odds Ratio) of having a positive QFT was 4.6-fold ($p = 0.029$) higher in patients with LTBI vs. those without LTBI. In contrast, no association was found between LTBI and having a positive T-SPOT.TB or a positive TST. As expected, there was a strong association between prior BCG vaccination and having a positive TST (OR 5.3, $p = 0.017$). QFT was the only test with a significant OR of having LTBI (adjusted OR: 4.4; 95%CI: $1.1 - 17.6$; $p = 0.034$). Among 5 patients with definite prior TB, TST and T-SPOT.TB were positive in 1 and QFT, in 2.

Conclusions. In this population, QFT was superior to TST for detecting LTBI, but both IGRAs and TST have important limitations, and are unreliable for screening for LTBI.

Keywords: chronic renal failure; haemodialysis; interferon-gamma release assays; latent tuberculosis infection

Introduction

Tuberculosis (TB) remains a major worldwide public health problem with over 9 million newly diagnosed cases in 2006 [1]. Due to their defective immune system, dialysis patients, once infected by bacilli of the *Mycobacterium tuberculosis* complex, are particularly prone to develop active tuberculosis. Nosocomial transmission of TB has also been reported in patients under long-term dialysis [2]. Studies report an 8-fold increase in tuberculosis incidence in patients on dialysis compared to the general population [3]. Detection of latent tuberculosis infection (LTBI) in this population is therefore an important issue, to prevent progression to active tuberculosis and secondary contamination to other patients and health-care workers. For decades, tuberculin skin testing (TST) has been used as the sole screening test for LTBI, but with disappointing results in dialysis patients in whom anergy rate may reach 44% [4–6]. Indeed, uraemia partly inhibits cellular immunity, which leads to false negative skin tests [7]. Moreover, specificity of TST is low, with false positive results due to either BCG (Bacillus of Calmette-Guérin) vaccination or exposure to environmental mycobacteria. Over the past 5 years, two *in vitro* T-cell-based assays have been commercialized (QuantiFERON Gold® in tube, Cellestis Ltd, Carnegie, Australia, and T-SPOT.TB®, Oxford Immunotec, UK): both measure the production of Interferon-γ (IFN-γ) by peripheral blood mononuclear cells after overnight incubation with antigens of the *M. tuberculosis* complex, which are present neither on the *BCG Mycobacterium Bovis* strain nor on most environmental mycobacteria [8]. Both tests, commonly referred to as Interferon-gamma Release Assay (IGRA) (IFN-γ Release Assays), are therefore more specific than the conventional TST, i.e. do not yield false positive results after BCG vaccination or infection with environmental mycobacteria [9,10]. Although performances of IGRAs are better than that of TST for the detection of LTBI in immuno-suppressed individuals [11], data concerning sensitivity and rate of indeterminate tests of IGRAs in haemodialyzed patients are scarce. To our knowledge, only two studies [12,13] have analysed the relative contribution of IGRAs and TST in patients on dialysis. Both showed a higher rate of positivity for the IGRA tested versus the TST; both studies also reported a higher rate of indeterminate results than that documented in immunocompetent subjects [12,13]. To date however, no study has compared diagnostic performance for LTBI of both IGRA and the TST in this population.

The aim of the present study was therefore to determine the performances of both IGRAs versus the TST for detecting LTBI (based on patients' clinical, epidemiological and radiological data) in a group of hemodialysis patients, and to investigate the agreement between these tests in this population compared to TST and our expert physician panel.

Patients and methods

This study was performed in three haemodialysis facilities, all located in the Geneva area (450 000 inhabitants; TB incidence of $20/10^5$/year). The study protocol was approved by the Geneva University Hospital Ethics Committee, and is in agreement with the Helsinki declaration of 1975 (and as revised in 1983). The study was registered at www.clinicaltrials.gov (N°: NCT00695734). All patients included provided informed written consent. All patients under haemodialysis for end-stage renal disease for at least 3 months were eligible. Exclusion criterion was prior severe reaction to tuberculin. With the help of a standardized questionnaire and their medical records, a research nurse recorded the following demographical and clinical data: age, social status, country of birth, history of prior TST testing, TB infection and BCG vaccination, presence of scars suggesting BCG, history of HIV infection or other cause of immuno-suppression. A chest radiography was performed in all patients included.

A tuberculin skin test (TST) was performed, according to the Mantoux technique, using two units of purified protein derivative (PPD) RT 23 (Statens Serum Institute, Copenhagen, Denmark), bioequivalent to five units of the US PPD standard and read after 72 h by two experienced nurses (readings were averaged). Positivity was defined as an induration diameter >5 mm.

Blood sampling for determination of *M. tuberculosis* specific IFN-γ secreting T-cells (T-SPOT.TB® and QuantiFERON Gold In tube®) and TST were performed simultaneously. Peripheral venous blood samples (8 ml) were processed by our laboratory within 3 h.

T-SPOT.TB® was processed as previously described [14] and scored according to the supplier's instructions. Spot-forming units (SFUs) were counted with an automated ELISPOT reader (AID system, Strasberg, Germany). Tests were considered as indeterminate: (1) if SFUs in the positive control were <20, or (2) if SFUs in the negative well exceeded 10 and both antigen wells had less than twice the number of SFUs of the negative well. Results were scored as positive if SFU count in either antigen well was >6 spots above SFUs of negative control, and negative if [SFU count in highest of early secretory antigen target 6 (ESAT-6) or culture filtrate protein-10 (CFP-10) wells] – [SFUs of negative control] was ≤6 spots.

QuantiFERON Gold In tube® (QFT): the in-tube assay was performed according to the manufacturer's instructions. One millilitre of whole blood was drawn in each of three separate test tubes: one containing no antigen (nil control), one with mitogen (phytohaemagglutinin, positive control) and one with TB antigens (ESAT-6, CFP-10 and TB7.7). The three tubes were incubated for 18–20 h at 37°C. Following incubation, the tubes were centrifuged and plasma removed from each tube and frozen at −20°C. IFN-γ measurement by ELISA was subsequently performed in batch testing. Results were expressed in IU/ml, as determined from a standard curve run on each plate. According to the supplier's instruction, a value ≥0.35 IU/ml for [(IFN-γ in the TB antigen tube) – (IFN-γ in the negative control tube)] was considered a positive result. If the IFN-γ level was <0.35 IU/ml in the TB antigen tube and mitogen control was positive (≥0.5 IU/ml), the test was recorded as negative. If the level in both the TB antigen and mitogen tubes was less than the threshold of positivity, or the level in the nil tube was >8.0 IU/ml, then the test was recorded as indeterminate.

Blood samples remained anonymous as they were not used for clinical decision making.

Statistical analysis

Univariate and parsimonious multivariate logistic regression were used to identify which factors were associated with the probability of a positive test. Main predictor of interest was 'latent tuberculosis infection' (LTBI) defined by chest radiography suggestive of prior infection (calcified granuloma or adenopathy, suggestive fibrotic scars) and/or established 'at risk' contact with a patient with contagious TB. Covariates (age, BCG status) were included a priori into the models. Analyses were run separately for T-SPOT.TB, QFT and TST. Hosmer and Lemeshow goodness-of-fit test was applied to evaluate model fit: model fit is considered adequate if $P > 0.05$.

Agreement between tests was quantified using Kappa statistics [15]. Kappa values range from $\kappa = 1$ (full agreement) to $\kappa = -1$(full disagreement). The null value ($\kappa = 0$) corresponds to an agreement equalling chance alone. Kappa statistics were then interpreted according to Landis and Koch: ($\kappa > 0.75$: excellent agreement, $\kappa = 0.40$ to 0.75: fair to good agreement, $\kappa < 0.40$: poor agreement).

All statistical analyses were performed with STATA™ version 10 (Stata corporation, College Station Texas, USA).

Results

Among 95 patients followed by the three haemodialysis facilities, 62 patients (46 male, 16 female) fulfilled inclusion criteria and accepted to be included in the present study. Characteristics of the patients are summarized in Table 1. Three patients were under low doses of prednisolone (2.5–5mg/day). Two patients had HIV infection, with respectively 232 and 495 CD4 lymphocytes/mm^3. Twenty-three percent had prior BCG vaccination, and 13 (21%) had probable LTBI (as previously defined).

Of 10 patients originating from high incidence countries, 4 had positive IGRAs (3 with the QFT and 3 with the T-SPOT.TB), and only 1 had a TST ≥ 5 mm.

Indeterminate tests occurred in seven (11%) subjects with T-SPOT.TB versus five (8%) with QFT. Among patients with indeterminate results, two were indeterminate with both IGRAs, one received 2.5 mg of prednisolone/day, four had a low lymphocyte count, including one patient with HIV infection and 232 CD4 lymphocytes/mm^3.

TST induration was >10 mm in 9 subjects and >5 mm in 12 subjects. Subjects with a positive (>5 mm) TST had a significantly higher rate of BCG vaccination ($P = 0.01$) than those with a negative TST (Table 1).

Rate of LTBI (as defined in the 'Statistical analysis section') was higher in patients with positive QFT (46.2%) compared to those with negative QFT (16.3%) ($P = 0.02$). Agreement between TST and IGRAs was poor ($\kappa = 0.16$ for QFT; $P = 0.116$, $\kappa = 0.32$ for T-SPOT.TB; $P = 0.007$), whereas agreement between IGRAs was fair ($\kappa = 0.60$; $P < 0.001$).

Table 2 shows the association between relevant clinical items and T-SPOT.TB, QFT or TST results. In univariate analysis, the OR of having a positive QFT was 4.5-fold higher ($P = 0.029$) in patients with LTBI compared to those without LTBI. After adjusting for age and BCG status, the association between LTBI and QFT remained significant (OR 4.6, $P = 0.029$). In contrast, no association was found between LTBI and having either a positive T-SPOT.TB or a positive TST. As expected, there was a strong association between BCG status and having a positive TST (OR 5.3, $P = 0.017$). Accuracies of the models were fair for QFT and TST with areas under the curve of 0.69 [95% CI: 0.56–0.81] and 0.71 [95% CI: 0.58–0.81], respectively.

Among five patients with definite prior TB, TST and T-SPOT.TB were positive in one and QFT, in two.

Table 3 displays the OR of having latent TB using the three different tests. All tests showed a positive association with latent TB, but QFT was the only one with a significant

Table 1. Patient characteristics

	All ($n = 62$)	T-SPOT.TB ($n = 62$)		QFT GOLD ($n = 62$)		TST > 5 mm ($n = 62$)	
		Positive	Negative	Positive	Negative	Positive	Negative
Test, positive/negative (*n*)		18	37	13	44	12	50
Positivity rate (%)		29		21		19	
Indeterminate (%)		7(11)		5(8)		0	
Age, mean (SD)	65 (15)	66 (13)	62 (17)	66 (19)	64 (15)	62 (15)	65 (16)
TB incidence in country of origin							
Low ($<50\times10^5$ year^{-1}); *n*, (%)	52 (84)	15 (83)	30 (81)	10 (77)	37 (84)	11 (92)	41 (82)
High ($\geq50\times10^5$ year^{-1}); *n*, (%)	10 (16)	3 (17)	7 (19)	3 (23)	7 (16)	1 (8)	9 (18)
BCG performed; *n* (%)	14 (23)	4 (22)	8 (22)	2 (15)	11 (25)	6 (50)	8 (16)[†]
Contact with TB patients, *n* (%)	8 (13)	3 (17)	5 (14)	3 (23)	5 (11)	1 (8)	7 (14)
Chest X-rays suggestive of tuberculosis, *n* (%)	8 (13)	1 (6)	5 (14)	3 (23)	5 (11)	2 (17)	6 (12)
Latent tuberculosis[b], *n* (%)	13 (21)	4 (22)[a]	7 (19)[a]	6 (46)	7 (16)[‡]	3 (25)	10 (20)

QFT Gold: QuantiFERON Gold in tube.
[a] Total number of T-SPOT.TB in patients with latent TB is 11 versus 13 because of two indeterminate results.
[b] Latent tuberculosis defined as chest X-ray suggestive of prior TB and/or prior 'at risk' contact with a case of contagious TB. Percentages refer to the total number of subjects with either positive or negative IGRA or TST.
[†] $P = 0.011$ for X^2 comparing positive and negative TST.
[‡] $P = 0.022$ for X^2 comparing positive and negative QuantiFERON Gold. For all other positive and negative tests, P values were >0.05.

Table 2. Logistic regression models and odds ratios for positive tests

	Univariate OR (95% CI)	Multivariate OR[a,b] (95% CI)
T-SPOT.TB		
Age, years	1.02 (0.98–1.06)	1.02 (0.98–1.06)
High incidence of TB in country of origin	0.86 (0.19–3.81)	–
Prior BCG	1.04 (0.26–4.03)	1.11 (0.28–4.40)
Latent tuberculosis[c]	1.22 (0.3–4.88)	1.18 (0.29–4.81)
QuantiFERON Gold		
Age, years	1.01 (0.97–1.05)	1.00 (0.96–1.05)
High incidence of TB in country of origin	1.58 (0.35–7.27)	–
Prior BCG	0.55 (0.10–2.85)	0.51 (0.09–2.89)
Latent tuberculosis[c]	4.53 (1.17–17.6)	4.59 (1.16–18.4)
TST >5 mm		
Age, years	0.98 (0.95–1.02)	0.98 (0.94–1.02)
High incidence of TB in country of origin	0.41 (0.05–3.06)	–
Prior BCG	5.25 (1.34–20.5)	5.30 (1.34–20.9)
Latent tuberculosis[c]	1.33 (0.30–5.85)	1.47 (0.31–7.10)

BCG: bacillus of Calmette-Guérin.
[a]Adjusted for age and BCG status.
[b]Hosmer & Lemeshow goodness-of-fit test statistic: all $P \geq 0.2$ ($P > 0.05$ indicates adequate model fit).
[c]Latent tuberculosis defined as chest X-ray suggestive of prior TB and/or prior 'at risk' contact with a case of contagious TB.

Table 3. Logistic regression models for odds ratio of latent tuberculosis

	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)	Adjusted OR[b] (95% CI)
T-SPOT.TB	1.2 (0.3–4.9)	1.2 (0.3–4.8)	1.2 (0.3–4.8)
QuantiFERON Gold	4.5 (1.2–17.6)	4.6 (1.2–18.1)	4.4 (1.1–17.6)
TST > 5 mm	1.3 (0.3–5.9)	1.4 (0.3–7.0)	1.7 (0.3–8.5)

Latent tuberculosis defined as chest X-ray suggestive of prior TB and/or prior 'at risk' contact with a case of contagious TB.
[a]Adjusted for age and BCG status.
[b]Adjusted for age, BCG status and TB incidence in country of origin.

association (adjusted OR: 4.4; 95% CI: 1.1–17.6; $P = 0.034$).

Discussion

This study is to our knowledge the first to compare simultaneously the performance of both commercially available IGRAs with TST for the detection of latent tuberculosis infection (LTBI) in end-stage renal failure patients under haemodialysis. Our results show that association between probable LTBI (defined as: chest radiography suggestive of prior infection and/or established 'at risk' contact with a patient with contagious TB) and results of one of the IGRA tested (QuantiFERON Gold In tube test: QFT) was highly significant. This was not the case, however, for the T-SPOT.TB or the TST. In this study, QFT was twice as effective at detecting probable LTBI (46%, Table 1) as either the T-SPOT.TB (22%) or TST (25%). Even after adjustment for age, and previous BCG vaccination, haemodialysis patients with probable LTBI had an OR of 4.6 of having a positive QFT (Table 2). Conversely, OR for detecting latent tuberculosis for either T-SPOT.TB or TST was not significant. Furthermore, detection of patients with prior TB was very low: among five patients with prior TB, T-SPOT.TB and TST identified only one, while QFT identified two. As previously reported, the best predictor of a positive TST was prior BCG vaccination. QFT (8%) and T-SPOT.TB (11%) had similar rates of indeterminate tests.

IGRAs have been studied in various groups of immunocompromised subjects (HIV infection, immuno-suppressed haematology patients, auto-immune diseases, silicosis, cancer) [11,12,16]. Although responses to IGRA are slightly reduced in immuno-suppressed subjects, when compared with immuno-competent individuals, positivity rate of IGRA is substantially higher than that of TST [11]. Two studies specifically included patients with chronic renal failure. Kobashi *et al.* [12] performed simultaneously TST and QFT in 252 immuno-compromised patients among

which 50 had chronic renal failure. Indeterminate rate was 4% for QFT in these 50 subjects (versus 12.7% for all patients included). The rate of indeterminate tests was associated with immunosuppressive treatments, but not with underlying disease. The sensitivity of QFT in this specific group is not reported. Passalent *et al.* [13] studied 203 patients with end-stage renal disease and dialysis: in this report, a positive T-SPOT.TB was strongly associated with age, history of TB, high incidence of TB in country of birth and radiological markers of TB, which was not the case for TST. Conversely, as in our study, a positive TST was associated with BCG vaccination. Among patients with self-reported history of TB, sensitivity of T-SPOT.TB was 78.6% versus 21.4% for the TST, i.e. 4-fold higher. Based on these findings, the authors advocate a combination of T-SPOT.TB and medical assessment to diagnose latent tuberculosis instead of relying on the TST [13]. The rate of indeterminate T-SPOT.TB results was 7%.

Our results confirm the higher predictive value of the QFT for detecting LTBI versus TST (Tables 1–3). However, the sensitivity of the T-SPOT.TB was lower in this particular subset of patients (22%, Table 1) and similar to that of TST (25%). This result was surprising, since sensitivity of the T-SPOT.TB is usually reported as at least equivalent to that of the QFT [11]. As mentioned, all blood samples were transported within 3 h to our laboratory, which has several years of experience in IGRA processing. The rate of indeterminate results is also slightly higher for both IGRA than previously reported in chronic renal failure, although similar to that encountered in malignant disease [12]. Among possible explanations are low lymphocyte counts ($n = 4$), and age above 75 years ($n = 7$) that have been shown to increase indeterminate IGRA results [17].

Our study has a few limitations that should be mentioned. First, the presumptive diagnosis of latent TB infection in our study was based on a composite of history of exposure and radiological features, and as such is not a true gold standard. This is an inevitable limitation of diagnostic tests for LTBI, since there is no gold standard for LTBI. The definition of LTBI is therefore probabilistic, based either on scores of exposures and/or contagiousness of index case in the case of recent exposure, or on epidemiological items clearly related to risk of LTBI such as age, incidence of TB in country of origin and history of contact with a case of active TB. Relying on chest X-rays suggestive of prior TB only would require a substantially larger group of subjects.

Secondly, no booster testing was performed for TST. Indeed, a significant increase in the rate of positive TST after one or two booster injections has been reported [18–21]. However, the problem of the low specificity of the TST is not improved by booster injections: correlation of TST with chest X-ray images suggestive of prior TB or history of prior TB, when reported, is either weak or non-significant [20, 21]. Because it is time consuming, subject to variability between different readers, and does not improve specificity, we did not perform booster injections and chose to compare IGRA with a unique TST, which is the current procedure in our institution.

Finally, samples sizes limit the reliability of any direct comparison of performances of both IGRAs.

In summary, our results confirm the poor diagnostic value of TST testing in haemodialysis patients and question the use of TST alone for screening for latent tuberculosis infection. The best predictor of a positive TST was prior BCG, which illustrates the limited specificity of the TST. Although one of the IGRAs tested (QFT) showed a 2-fold increase in sensitivity for detecting LTBI, when compared to TST, results of the T-SPOT.TB were not significantly related to a presumptive diagnosis of LTBI. As expected, agreement between IGRA and TST was low; more surprisingly, agreement between IGRAs was only fair. Detection of patients with prior TB was very low with TST and both IGRA. The rate of indeterminate tests was rather high for both tests. These results suggest that, in our population, the QFT was superior to TST for detecting LTBI, but both IGRAs and TST have important limitations. Based on our results, we would recommend that detection of latent tuberculosis in haemodialysis patients be based on a combination of an IGRA and a thorough evaluation of risk factors, and radiological assessment. Whether QFT is clearly superior to T-SPOT.TB in this population should be confirmed by further studies.

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Conflict of interest statement. There are no conflicts of interest related to this publication for Pierre-Alain Triverio, Pierre-Olivier Bridevaux, Pascale Roux-Lombard, Laurent Niksic, Thierry Rochat, Pierre-Yves Martin, Patrick Saudan and Jean-Paul Janssens.

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Protocol adherence and the ability to achieve target haemoglobin levels in haemodialysis patients

Kevin Chan[1], John Moran[2], Mark Hlatky[3] and Richard Lafayette[1]

[1]Department of Nephrology, [2]Satellite Healthcare, Inc, Mountain View, CA and [3]Health Research and Policy, Stanford University School of Medicine, Stanford, CA, USA

Correspondence and offprint requests to: Kevin Chan; E-mail: Kevinchan9999@hotmail.com

Abstract

Background. Anemia management remains complicated in patients with endstage renal disease on hemodialysis. We wished to evaluate the effect of protocol adherence to EPO and intravenous iron dosing on achieving the desired range of hemoglobin levels.

Methods. A cohort of hemodialysis patients was studied to evaluate the rate of adherence to EPO and iron dosing protocols over a 5 month period. A database was completed to evaluate all known comorbidities, demographic factors, and facility issues that might affect hemoglobin levels. A logistic regression model was employed to evaluate the effect of adherence to the anemia protocols on the probability of achieving a hemoglobin level below, within or above the targeted range of 11–12.5g/dl.

Results. Among 2114 patients, we found that adherence to both the EPO and iron dosing protocol resulted in the greatest probability of achieving the target hemoglobin range ($56 \pm 5\%$ in anemia protocol adherent patients versus $42 \pm 7\%$ in non adherent patients). This was predominantly due to a lowered risk of having above target hemoglobin levels rather than below. The use of the anemia protocols was associated with lower rates of hospitalization (9 ± 0.7 visits/100 months in adherent group vs 15 ± 2 in non adherent group) and lower utilization of both EPO and intravenous iron. Furthermore, patients in the adherent groups had less variability of their hemoglobin levels month by month, at least as judged by standard deviation.

Conclusion. Adherence to anemia protocols, as practiced in the dialysis units included in this cohort, may improve hemodialysis patients' ability to achieve target hemoglobin levels, and by avoiding above target hemoglobin values, lower drug utilization and reduce variability of hemoglobin levels.

Keywords: anaemia management; ESRD; processes of care