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Contribution of an Interferon Gamma Released Assay to the Detection of Latent Tuberculosis in Chronic Dialysis Patients in Sub-Saharan Africa

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Abstract

Introduction: Tuberculosis (TB) is common in patients with chronic renal failure due to their immunosuppressed state. Diagnosing TB is difficult because of the latency of the clinical and biological picture. This study was conducted to assess the performance of the Interferon Gamma Released Assay (IGRA) in the diagnosis of latent TB infection in chronic dialysis patients in Senegal.

Materials and methods: This is a cross-sectional study carried out in Nephrology Department of Aristide Le Dantec University Hospital during 6 month. All patients with chronic haemodialysis or chronic peritoneal dialysis were included. A group of patients with non-dialyzed kidney disease was also included. Patients with active TB at the time of the study were not included. A tuberculin skin test (TST) and an IGRA were performed. The QuantiFERON® (QFT) was repeated 3 months later in the group of dialysis patients.

Results: Sixty-two patients were included: 22 haemodialysis (HD) patients, 19 peritoneal dialysis (PD) patients and 21 patients with non-dialyzed kidney disease (NDKD). The mean age was 44 ± 12 years with a sex ratio M/F of 1.06. Nineteen patients were vaccinated with BCG. TST was positive in 22 patients (35.4%). Subjects with a positive TST had a significantly higher rate of BCG vaccination (P=0.002) than those with a negative TST. QFT was positive in 17 patients (28%) and undetermined in 9 patients (14%). In patients with a positive QFT, six (27%) were in HD, four (21%) in peritoneal dialysis and seven (33%) in NDKD. A total of 9/17 (52%) QFT-positive patients developed active TB. Correlation (r=0.998, p=0.001) indicates that T cell functionality was not affected by the duration of renal replacement therapy.

Conclusion: These results highlight the advantage of Quantiferon test over TST for diagnosis of latent TB in immunocompromised patients, including chronic dialysis patients.

Keywords: Interferon gamma released assay; Latent tuberculosis; Dialysis patient; Senegal

Introduction

Tuberculosis (TB) is a major global health problem. In 2014, 9.6 million new TB cases were estimated [1]. Dialysis patients are particularly susceptible to developing active TB once infected with Mycobacterium tuberculosis complex bacilli, because of their immunodeficiency. In long-term dialysis patients, nosocomial transmission of TB has also been reported [2]. Compared with the general population, the prevalence of latent TB (LTB) infection is high in patients with renal impairment [3]. The risk of reactivation of LTB is up to 52.5 times higher in patients with renal impairment than in healthy individuals [4]. For preventing the progression of LTB to active TB and secondary contamination in dialysis centres, the detection of LTB infection in this population is therefore of critical importance the TST has been used for decades, as the only test for detecting LTB. However, because of a high rate of anergy that can reach 44% in dialysis patients [5,6], the results were disappointing. In addition, because of the reactivity of tuberculin with environmental mycobacteria and with the BCG (Bacillus Calmette-Guerin) vaccine, the TST can produce false-positive results [7]. As an alternative immunodiagnostic approach to TST for the detection of M. tuberculosis infection, T-cell interferon-gamma release assays (IGRA) have been developed [8,9].

In sub-Saharan Africa, an area of high TB endemicity, no study to date has been conducted to detect latent TB in chronic dialysis patients. The objective of this study was to assess the performance of the IGRA test in the diagnosis of latent TB in chronic dialysis patients in sub-Saharan Africa.

Patients and Methods

This was a cross-sectional study conducted in the Nephrology Department of Aristide Le Dantec University Hospital in collaboration with the Department of Immunology, from 1 September 2014 to 30 January 2015. The study protocol was approved by the Hospital Ethics Committee. All included patients provided written free and informed consent. All haemodialysis or peritoneal dialysis patients of more than 3 months who agreed to participate in the study were included. A group of patients with chronic kidney disease at the pre-dialysis stage

was also included. Patients with active TB at the time of the study were not included.

A physician collected the following demographic and clinical data: age, gender, BCG vaccination, TB contagiousness, history of TB infection and symptoms of chronic inflammation. All included patients underwent the TST and the IGRA test. The TST was performed by a nurse, using the Mantoux technique, by injecting five units of tuberculin intradermally into the forearm. The same nurse performed the reading 72 hours later. The TST was considered positive if the induration was ≥ 5 mm, negative if <5 mm and anergic if there was no induration.

For the IGRA test we used the QuantiFERON®-TB Gold blood test (QFT). The test was performed according to the manufacturer's instructions. In each of the three test tubes, one millilitre of blood was collected: one containing no antigen (control), one with TB antigens (ESAT-6, CFP-10 and TB7. 7) and one with mitogen (phytohemagglutinin, positive control). The three tubes were incubated at 37°C for 18-20 h. After incubation and centifugation, the plasma was removed from each tube and frozen at -20°C. IFN-γ measurement by ELISA was performed in batch testing. The results were in IU/ml, and were determined from a standard curve spread. QFT was positive if a value ≥ 0.35 IU/ml for ((IFN-γ in the TB antigen tube)-(IFN-γ in the negative control tube)) was found and negative if the IFN-γ level was <0.35 IU/ml in the TB antigenic tube and the mitogen control positive (≥ 0.5 IU/ml). The test was recorded as indeterminate if the levels of IFN-γ in the TB antigen and mitogenic tubes were below the threshold of positivity, or the level in the nil tube was >8.0 IU/ml. The QFT test was repeated 3 months later in the group of dialysis patients. The Local Ethical Committee has approved this study.

Results

Sixty-two (62) patients were included in total, including 22 patients on HD, 19 on PD and 21 patients with chronic renal disease in the pre-dialysis stage. The mean age was 44 ± 12 years. There were 32 men and 30 women, a male: female sex ratio of 1.06. Nineteen (19) patients were vaccinated with BCG: 8 on HD, 2 on PD and 9 ND patients. Three patients had had active TB in the past: two on HD and one ND patient (Table 1).

Parameters	Results
Age (years)	44 ± 12
Gender (%)	
Men	32 (52.00)
Women	30 (48.00)
Antecedent of tuberculosis	03 (0.04)
Contact with a TB patient (%)	06 (1.00)
BCG vaccination (%)	19 (30.6)

Table 1: Socio-demographic parameters and antecedents.

At the clinical examination, no patients had fever, six had anorexia and four had weight loss. Biologically, all patients had normal white blood cell counts. C-reactive protein was elevated in two patients on HD. The median number of CD4+T cells was greater than 600 cells/l. The TST was positive in 22 patients (35.4%). Induration was greater than 10 mm in 2 patients and greater than 5 mm in 20 patients. The TST was negative in 4 patients (6.4%) and anergic in 36 (58%) patients (Figure 1). Of the patients with positive TST, 14 were on HD, 1 was on PD and 7 were ND patients. Subjects with a positive TST had a significantly higher rate of BCG vaccination (P=0.002) than those with a negative TST.

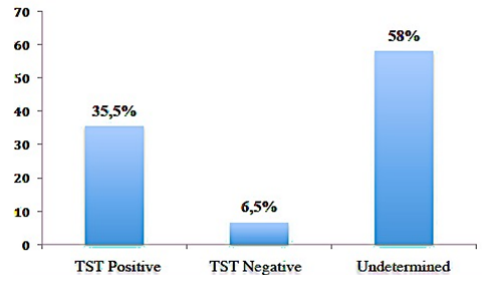

Figure 1: TST response.

The IGRA test was positive in 17 patients (28%), negative in 36 patients (58%) and undetermined in 9 (14%) patients (Figure 2). Of the patients with a positive IGRA test, six (27%) were on HD, four (21%) were on PD and seven (33%) were ND patients.

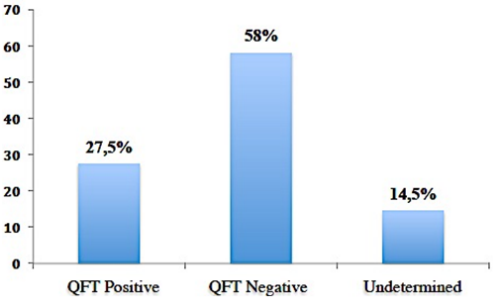

Figure 2: QFT response.

TST positive	BCG vaccine		Total	p
	Yes	No		
Yes	17	9	36	0.002
No	2	34	26	
Total	19	43	62	

Table 2: Correlation between TST and BCG Vaccine.

All six patients in the HD group with a positive IGRA test remained positive after 3 months (M3) and all developed active pulmonary TB after 6 months. Two patients (2/4) in the PD group with a positive IGRA test also developed active TB. One had a pulmonary location and the other a peritoneal location. Of the ND patients with a positive IGRA test, one was diagnosed with active TB during hospitalization. For the 6 others, we could not repeat the IGRA test because they were lost to follow-up at M3. In total, 9/17 (52%) patients who tested IGRA-

positive developed active TB, with a 100% conversion rate from LTB to active TB in the HD group. However, all patients with a positive IGRA test had a negative TST (Table 2).

A comparison of the TB antigen response in HD and ND patients showed no statistically significant difference (p=0.68) (Figure 3).

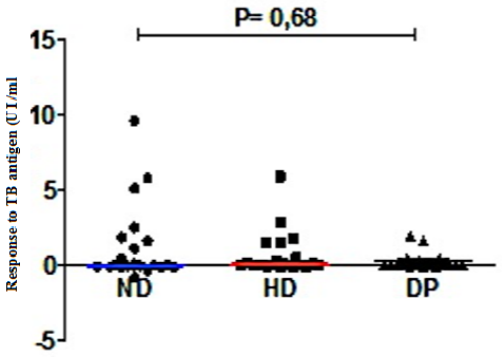

Figure 3: Repartition of the different groups compared to the response to TB antigens.

Similarly, a comparison of the net mitogen response in HD, PD and ND patients did not show a statistically significant difference (p=0.121) (Figure 4). Thus, T-cell functionality was not affected by the duration of renal replacement therapy.

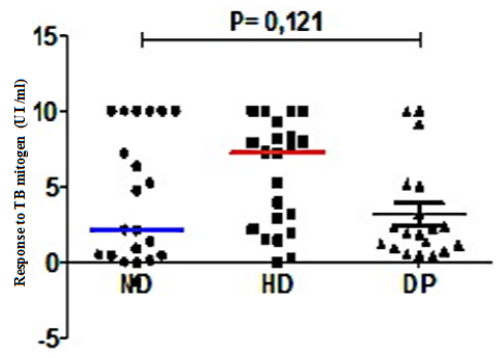

Figure 4: Repartition of the different groups compared to the response to mitogen.

Discussion

The high prevalence of TB in our region requires the detection of LTB, especially among people at risk. Patients with CKD, particularly chronic HD and renal transplant patients are exposed to multiple infectious complications due to their immunosuppressed state. The TST has long been used in the detection of LTB and now appears to be obsolete because of the high rate of anergy in immunocompromised patients, such as dialysis patients, and interaction with the BCG vaccine. Thus, the IGRA test has been developed for the diagnosis of LTB. Our study appears to be the first, to our knowledge, to detect LTB in patients with CKD in sub-Saharan Africa.

In this study, we proposed, on the one hand, to highlight the value of the QuantiFERON®-TB Gold blood test compared with that of the TST in patients with CKD by determining the proportion of these patients with LTB according to the two tests and secondly, to evaluate the impact of dialysis on the QuantiFERON®-TB Gold blood test response. The immune status of our study population was assessed by CD4+T cell counts. The median CD4 count in the different groups of our study population was greater than 600 cells/µl. This indicates that the subjects in our study population did not exhibit quantitative immunosuppression. Indeed, it has been shown that in dialysis patients, the peripheral lymphocyte level is slightly decreased [10], but this decrease would not be comparable with that observed in patients infected with HIV.

The TST was positive in 22 patients (35.4%) in our study. The induration was greater than 10 mm in 2 patients and between 5 and 10 mm in 20 patients. These results differed from those of Trivero, who found 9 patients with an induration greater than 10 mm and 12 patients with an induration greater than 5 mm. Grant had also found in a population of 79 chronic haemodialysis patients, 2 patients with an induration greater than 10 mm and 1 patient with an induration between 5 and 10 mm. Anergy was present in 36 patients (58%). This high rate of anergy present in our study is also found in the literature, with rates of about 44%. This could be explained by the state of immunosuppression created by CKD, which appears to be an abnormality of delayed hypersensitivity due to either a defect in antigen presentation or a lack of T-cell function [11].

By studying the response to the IGRA test, we found a positivity rate of 28%. This result corroborates that of Grant, who found a 28% IGRA test positivity rate in chronic HD patients in the US [12]. However, Trivero [13] and Juno [14] found slightly lower rates of 21% and 18.75%, respectively, in chronic HD patients in Switzerland and Canada. Among patients with a positive IGRA test, 27% were on HD, 21% were on PD and 33% were ND patients, with no statistically significant difference. This shows that the proportions of IGRA positivity were comparable between the different groups.

At the third month of follow-up (M3), 9/17 (52%) IGRA-positive patients developed active TB with a 100% rate of conversion from LTB to active TB in the HD group. This high rate of LTB to active TB conversion requires early diagnosis. This rate would probably be increased if we could see the patients who were lost to follow-up who were IGRA-positive. Indeed, in our study, all chronic haemodialysis patients who had latent TB evolved into active TB. In our study, a high proportion of patients tested negative in the TST and positive in the QuantiFERON TB Gold® test. Indeed, all IGRA-positive patients tested negative by TST. The IFN-γ assay in vitro may be less affected by immunosuppression in patients with kidney disease than in vivo evaluation with TST. In a study of the immune response to purified protein derivative (PPD)-specific T cells, both in vivo and in vitro in patients with chronic kidney disease it was found that a large number of patients who responded to in vitro tests were TST-negative. This suggests a high rate of cutaneous anergy in the TST in the dialysis population [15]. On the other hand, there was a correlation in our study between TST positivity and BCG vaccination (p=0.002). In fact, 19 out of 26 patients with active TB had been vaccinated with BCG. Reactivity of BCG with tuberculin has been shown.

Although a positive IGRA test is not 100% equivalent to LTB, the IGRA has several advantages over TST in terms of convenience and precision [15,16]. The correlation between the duration of dialysis and the response to the QuantiFERON TB Gold showed that in HD

patients, the dialysis duration has no influence on the QuantiFERON response. However, in patients on PD, a negative correlation was found between the response of T cells to TB antigen and the duration of peritoneal dialysis. Thus, the longer the duration of peritoneal dialysis, the less T cells responded to the TB antigen. This result would challenge the sensitivity of the IGRA test in patients on long-term peritoneal dialysis. Few studies have been done on this subject, which makes it difficult to interpret this result.

Conclusion

Our results highlight the benefit of the IGRA test for the diagnosis of LTB in immunocompromised patients. This would support the thesis that the IGRA test is more sensitive than the TST in screening for LTB in patients with RCM.

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