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Dynamic changes in positive interferon-gamma release assay in a dialysis population: An observational cohort study

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Summary *Background:* Interferon-gamma release assay (IGRA) is popular for detecting latent tuberculosis infection (LTBI), but its dynamic change is uncertain in high-risk groups such as dialysis patients.
Methods: Patients undergoing dialysis were prospectively enrolled. The QuantiFERON-TB Gold In-Tube (QFT-GIT) was used to detect LTBI. After 6 and 12 months, QFT-GIT was repeated to monitor dynamic changes.
Results: Only 204 of 391 enrolled patients completed the study. The initial QFT-GIT positive rate of 22.1% decreased to 19.6% after 6 months and to 14.2% after 12 months. The 6-month reversion rate was 45.9% while the conversion rate was 7.7%. Sub-population with new QFT-GIT positivity had 87.5% reversion rate, higher than the 20.8% of patients with persistent QFT-GIT positivity. The QFT-GIT response was independently associated with persistent QFT-GIT positivity. Using 0.93 IU/ml of the initial QFT-GIT response as the threshold can detect 79% persistent positivity in 6-month follow-up. Prior TB had a borderline significance for predicting conversion.

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Conclusions: In the dialysis population, reversion and conversion occur frequently within six months. The QFT-GIT positive population is heterogeneous and sub-populations have different reversion rates. Higher QFT-GIT positivity threshold can identify patients with persistent QFT-GIT positivity to prioritize follow-up and LTBI therapy.

Introduction

Tuberculosis (TB) is one of the most common global infectious diseases with high mortality.[1] For preventing further TB transmission, control should focus on early diagnosis and treatment of latent TB infection (LTBI).[2] Next to TB contacts, the dialysis population, growing as a consequence of global ageing, is a known risk group due to attenuated immunity.[3–5] Defined by interferon-gamma release assays (IGRAs), LTBI has been associated with a decline in renal function[6] and increasing prevalence to around 21–40% in the dialysis population.[7–10]

Although IGRAs are currently used to identify LTBI cases and are useful even in immuno-compromised hosts,[11–13] it should be interpreted carefully because around 7.7% of IGRA has discordant results in a duplicated test and most are located in a range near the cut-off value.[14] Moreover, there is a high proportion of IGRA reversion in serial follow-up studies,[15,16] while lower positive IGRA response is associated with reversion.[15] Thus, some investigators suggest using a grey zone instead of a cut-off value to avoid over-diagnosing LTBI.[14,17,18]

However, little is known about the impact of impaired cellular immunity in dialysis on IGRA results.[19,20] Longitudinal follow-up and outcome correlation are critical for redefining IGRA positivity in dialysis patients, especially for grey zone values, to prove clinical efficacy and prioritize resources. This cohort study was conducted to investigate dynamic changes in IGRA results and measure reversion and conversion rates. The clinical significance of IGRA positivity, as well as its cut-off value, was also studied.

Methods

This prospective cohort study was conducted at National Taiwan University Hospital, a tertiary referral center in northern Taiwan, and its branch hospital in southern Taiwan. The hospital's institutional review board approved the study, which was registered in ClinicalTrial.gov (NCT01311999). All of the participants provided written informed consent. From March to November 2011, adult patients (age $\geq$20 years) under long-term ($>$3 months) dialysis were enrolled. Those with human immuno-deficiency virus (HIV) infection, liver cirrhosis of Child-Pugh class C, active tuberculosis within the last three years, or cancer receiving regular chemotherapy were excluded. Clinical history and chest radiography were obtained to exclude active TB disease. Acid-fast smear and mycobacterial culture from three sputum samples were performed as previously described if TB was suspected.[21]

Upon enrollment, QuantiFERON-TB Gold In-Tube assay (QFT-GIT) (Celestis, Australia) was performed according to the manufacturer's instructions (www.cellestis.com). Results were interpreted as positive, negative, or indeterminate. A three-tube system of QFT-GIT was used, including the negative control tube, positive control tube (Phytohemagglutinin A as the stimulant), and the TB-antigen tube. After overnight culture, the QFT-GIT response (IU/ml) was calculated as the interferon-gamma (IFN-γ) level in the supernatant of the TB-antigen tube minus that of the negative control tube. The maximal level of IFN-γ detected by QFT-GIT enzyme-linked immuno-sorbent assay (ELISA) was 10 IU/ml and values greater than this was reported as 10 IU/ml.

The QFT-GIT test was examined at the initial (QFT-GIT1) and at six (QFT-GIT2) and 12 months (QFT-GIT3) after to determine dynamic changes. Reversion was defined as the QFT-GIT result changing from positive to negative in either QFT-GIT2 or QFT-GIT3, while conversion was defined as the change from negative to positive.

Sample size calculation

A previous study revealed that around 7.7% of IGRA had discordant results in a duplicated test.[14] Two recent studies with serial QFT-GIT examinations within one year showed conversion and reversion in 12.9% of all study subjects.[18,22] As such, to have a power of 0.8 and an alpha error of 0.05 in a one-sided test where the proportion of event cases is 12.9%, which is 5.2% higher than the discordant rate, the calculated sample size was 193. Assuming a 50% drop-out rate, at least 386 patients should be enrolled.

Data collection

Clinical and demographic data, including age, sex, comorbidity, prior TB history, contact history of TB, respiratory and constitutional symptoms, smoking status, and blood hemoglobin and albumin levels were recorded using a standardized case report form. Dialysis mode was defined as its use in the past three months prior to enrollment. Cough $\geq$3 weeks was defined as chronic cough, while current smoker was defined as those who smoked $>$100 cigarettes, with the latest time of smoking within one month prior to the study.[23] Chest radiography was interpreted by a pulmonologist blinded to the QFT-GIT results.

Statistical analysis

Inter-group differences were analyzed by the student *t* test for numerical variables, the Mann–Whitney *U* test for QFT-GIT response and IFN-γ level in the positive control tube, and the chi-square test for categorical variables. Population confidence interval was estimated according to the