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NOTE

Living donor and recipient screening for latent tuberculosis infection by tuberculin skin test and interferon-gamma releasing assay in a country with an intermediate burden of tuberculosis

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Abstract There are few data on donor screening for latent tuberculosis infection (LTBI) using the tuberculin skin test (TST) and interferon-gamma releasing assay (IGRA). In South Korea, most renal allografts involve living donors (average, 80 %). Hence, we have an opportunity to evaluate donor and recipient screening for LTBI by TST and IGRA. All donors and recipients admitted for kidney transplantation during a 20-month period were evaluated prospectively by using TST and *Mycobacterium tuberculosis*-specific enzyme-linked immunosorbent spot (ELISPOT) assay. The study population consisted of 205 living donor–recipient pairs (≥16 years) including 15 (7 %) who yielded indeterminate donor or recipient ELISPOT results. Of the 205 donors, 63 (31 %) gave a positive TST ≥5 mm, 33 (16 %) a positive TST ≥10 mm, and 96 (47 %) a positive ELISPOT. Of the 205 recipients, 9 (5 %) gave a positive TST ≥5 mm, 3 (2 %) a positive TST ≥10 mm, and 79 (39 %) had a positive ELISPOT. Of the 205 donor–recipient pairs, only 59 (29 %) gave negative donor and recipient ELISPOT results and 139 (68 %) negative donor and recipient TSTs (<5 mm) ($P < 0.001$). One third of donor–recipient pairs tends to be positive in the TST, and two thirds of the donor–recipient pairs tends to be positive in the ELISPOT. Given the high positive rate of LTBI obtained by screening donors, further studies on the clinical value of solid organ transplant donors with positive TST or ELISPOT and health economics analysis in countries with intermediate burden of TB are needed for policy decisions on isoniazid (INH) prophylaxis.

Keywords Tuberculosis · Tuberculin skin test · ELISPOT · Kidney transplantation

Because tuberculosis (TB) is one of the most important opportunistic infections in transplant recipients [1], it has been recommended that all recipients undergo a tuberculin

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Clinical Trial Registration Number: Clinical Trial No. NCT01087190

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skin test (TST) before transplantation [2]. However, because of anergy, only 20–25 % of all cases of active TB after transplantation occur in patients who give positive TST reactions before transplantation [3], indicating that the ability of TST to diagnose latent tuberculosis infection (LTBI) in transplant candidates is poor. The interferon (IFN)-gamma releasing assay (IGRA), a new generation of diagnostic TB assays, has shown promise in diagnosing LTBI [4]. Recently, we demonstrated in a longitudinal study that positive enzyme-linked immunosorbent spot (ELISPOT) results predict the subsequent development of TB in kidney transplantation (KT) recipients who lack clinical risk factors for LTBI or in whom LTBI cannot be detected by TST [5]. In this context, we note that the recent U.S. guidelines recommended that IGRA may be used in place of TST for diagnosing LTBI [6].

Although the majority of TB developed after solid organ transplantation (SOT) is caused by activation of LTBI in the recipient, TB can also be transmitted through the donor allograft [1]. Because transmission of TB from SOT donor to SOT recipient is increasing in frequency as a result of global travel and immigration, donor-derived TB is an emerging issue. However, to the best of our knowledge, there is little information on donor screening for latent tuberculosis infection (LTBI) using TST and IGRA. In South Korea, living donors provide most of the renal allografts (average, 80 %), and thus we have a unique opportunity to screen both KT donors and recipients for LTBI. Hence, we have performed a prospective study to evaluate donor and recipient screening for LTBI using TST and IGRA. The incidence of TB has been reported to be 90 cases per 100,000 among Koreans [7] and 4.6 % among Korean KT recipients (14 new TB cases among 304 KT recipients between 1984 and 1994) [8].

All donors and recipients admitted for living-donor transplantation to a renal transplant unit between June 2010 and August 2011 in a 2,700-bed, tertiary-care hospital in Seoul, South Korea, were prospectively screened. Donors and recipients were interviewed by a trained nurse to assess clinical risk factors for LTBI (i.e., close contact with an active TB patient, history of untreated or inadequately treated TB, or recent history of TST) 2 to 5 days before the scheduled transplant surgery for living-donor transplantation. Simultaneously, tests for LTBI (i.e., chest radiography, TST) were performed by a trained nurse 2 to 5 days before the scheduled transplant surgery for living-donor transplantation. If the chest radiographic findings were abnormal, a sputum acid-fast bacillus (AFB) smear and computed tomography (CT) scan were performed to rule out active pulmonary TB. Exclusion criteria were refusal of informed consent, presence of active TB, presence of skin disease that precluded TST, pediatric renal transplant candidature (<16 years of age), and presence of any contraindication for KT (e.g., malignancy). Pancreas transplantation only was also excluded. All individuals were informed of the nature of the study, and all provided written informed consent. This study presents cross-sectional data derived from our ongoing randomized trial, in which an INH prophylaxis group and a no prophylaxis group are randomly assigned to all KT recipients with a positive recipient ELISPOT assay regardless of the results of recipient TST or donor ELISPOT/TST results (Clinical Trial No. NCT01087190). This investigation was approved by the hospital Institutional Review Board.

A peripheral venous blood sample (8 ml) using a heparinized tube was collected from each patient to perform ELISPOT assays for IFN-gamma producing T-cell responses (i.e., T-SPOT.TB; Oxford Immunotec, Abingdon, UK). Within 6 h of collection, peripheral blood mononuclear cells (PBMCs) were isolated by use of a Ficol-Hypaque density gradient. The prepared PBMCs were then suspended in AIM-V media (GIBCO) and distributed to each well at concentrations of 2.5×10^5 cells/well. After 18 h incubation, the resulting spots were counted using an automatic microscope (ELiSpot 04 HR; Autoimmune Diagnostika). The criteria used for positive, negative, and indeterminate outcomes have been described [9]. The TST was performed by the Mantoux technique, injecting a 2-TU (tuberculin unit) dose of purified protein derivative RT23 (Statens Serum Institut, Copenhagen, Denmark) intradermally into the forearm. At 48 h after inoculation, the single well-trained nurse used the ballpoint-pen technique to measure the maximum diameters of indurations.

All tests of significance were two tailed; a P value < 0.05 was considered to indicate statistical significance. The categorical variables were compared by Pearson χ^2 tests. Calculations were performed with SPSS for Windows software, version 14.0K (SPSS, Chicago, IL, USA).

During the study period, 276 patients were admitted for kidney transplantation. Of these, we excluded 63 (23 %) patients who received deceased donor transplants, 4 (1 %) of age <18 years, and 4 (1 %) who refused informed consent. In the end, 205 donor–recipients for living donor transplants were included. Six (3 %) of the 205 KT recipients received simultaneous pancreas–kidney transplants. Demographic data for the study group are shown in Table 1. None of 205 KT recipients reported a history of treatment for LTBI. Five recipients had clinical risk factors for LTBI (Table 1), namely, abnormal chest radiography with history of untreated or inadequately treated TB. Of the 205 KT recipients, 146 (71 %) had histories of BCG vaccination or scars. None of the KT donors reported previous treatment for LTBI. Two donors had clinical risk factors for LTBI (Table 1): one with abnormal chest radiography with a history of untreated or inadequately treated TB, and the other with

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