Interferon-γ Release Assays in Solid Organ Transplant Recipients: Everything Begins With a Single Small Step

TO THE EDITOR—We read with interest Horne et al’s excellent article on challenges in tuberculosis in solid organ transplant (SOT) recipients, in which the authors point out the limited data on the utility of interferon-γ release assays (IGRAs) in this population [1]. We concur with the authors that there is very little literature on their reliability in this setting. Only 3 studies have reported the development of tuberculosis in SOT recipients tested with IGRAs, which is the best measure of their reliability; all 3 showed similar results in terms of their predictive values (Table 1) [2–4]. There is, however, a growing body of cross-sectional studies that deserve further comment.

First, according to the published data, the prevalence of indeterminate results with IGRAs in candidates for liver transplant ranges from 0.8% to 12.6% [5]. In this regard, the 41% rate of indeterminate results with QuantiFERON-TB Gold In-Tube (QFT) that Horne et al mention is misleading. This high rate is drawn from a large retrospective cohort study of 2392 pre-SOT patients published by Theodoropoulos et al [2], which reported 245 (10.2%) positive, 1936 (80.9%) negative, and 206 (8.6%) indeterminate results. For the comparison of the QFT-GIT results according to organ transplant type, all subjects testing positive and indeterminate (n = 451) were included in the analysis, whereas only a randomly selected 25% of individuals with negative results, did (n = 490). In the 310 liver transplant recipients analyzed, QFT-GIT results were positive in 19%, negative in 40%, and indeterminate in 41%. These proportions do not represent the whole sample, as the estimation was made with all the positive and indeterminate results, but only a quarter of the negative ones.

Second, IGRAs perform better than the tuberculin skin test (TST) in SOT candidates. We previously reported a lower proportion of positive TST results in patients with more advanced disease (MELD score ≥ 18; adjusted odds ratio [AOR], 0.2; 95% confidence interval [CI], .04–.7), whereas QFT results remained unaffected. Moreover, discordant results (TST+/QFT−) were independently associated with a MELD score ≥ 18.

Table 1. Summary of the 3 Studies Reporting Longitudinal Data on Solid Organ Transplant Recipients With Latent Tuberculosis Infection Screened With Interferon-γ Release Assays

<table>
<thead>
<tr>
<th>Author [Ref] Year, Country</th>
<th>Type of Transplant</th>
<th>Type of IGRA</th>
<th>No.</th>
<th>Follow-up</th>
<th>Tuberculosis Cases</th>
<th>PPV</th>
<th>NPV</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theodoropoulos et al [2] 2012, United States</td>
<td>SOT</td>
<td>QFT-GIT</td>
<td>694</td>
<td>10.8 mo (mean)</td>
<td>3</td>
<td>. . .</td>
<td>0.97</td>
<td>-QFT-GIT as the only screening test for latent tuberculosis. -No differences between rates of posttransplant tuberculosis with IGRA-based screening program and the previous TST-based one (0.43% vs 0.33%).</td>
</tr>
<tr>
<td>Kim et al [3] 2011, South Korea</td>
<td>Kidney</td>
<td>T-SPOT</td>
<td>312</td>
<td>1.8 y (median)</td>
<td>4</td>
<td>0.06</td>
<td>1.0</td>
<td>-Treatment decision based only on TST results. -All 4 tuberculosis cases had negative TST, but positive T-SPOT.</td>
</tr>
<tr>
<td>Lange et al [4] 2012, Germany</td>
<td>SOT</td>
<td>QFT-GIT</td>
<td>233</td>
<td>28 mo (median)</td>
<td>0</td>
<td>0.0</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IGRA, interferon-γ release assay; NPV, negative predictive value; PPV, positive predictive value; QFT-GIT, QuantiFERON–TB Gold In-tube; SOT, solid organ transplant; T-SPOT, T-SPOT® TB (an ELISPOT-based IGRA by Oxford Immunotec, Oxford, UK); TST, tuberculin skin test. * Not assessable.
(AOR, 5.0; 95% CI, 1.1–20.0). [5] As the specificity of QFT-GIT is near 100%, this finding strongly suggests that most of these patients, if not all, were truly infected, and that TST failed to detect tuberculosis infection in most of them.

Horne et al also mention 2 guidelines that recommend repeating TST if the first is negative [6, 7]. However, although 2-step ("boosting") strategy is extensively used in some countries, its benefit has not been conclusively demonstrated in any group of patients, and certainly not in SOT recipients. Our experience with 95 liver transplant candidates showed a negligible increase of 4.2% (from 42.1% to 46.3%) in positive results [5]. Even though repeating the TST may avoid missing some infected patients, the toxicity and the costs of unnecessary treatments deriving from increasing false-positive results should not be overlooked.

In summary, we believe that tuberculosis in immunocompromised patients cannot be completely prevented with the currently available diagnostic tests for latent tuberculosis. Trying to improve sensitivity by increasing the number of diagnoses may not be the best strategy as it may increase false-positive results and lead to overtreatment. While waiting for better predictors of tuberculosis development, the better accuracy and operational advantages of IGRAs argue in favor of their use in everyday clinical practice.

Notes

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