Should Tuberculin Skin Test Be Positive to Give Latent Tuberculosis Treatment Before Tumor Necrosis Factor-α Inhibitors in Selected Patients in Developing Countries?

To the Editor:

We read with interest the report by Malaviya, et al about tuberculosis (TB) and inflammatory rheumatic disease (IRD) patients receiving tumor necrosis factor-α (TNF-α) inhibitor agents. Mexico also has a "high TB burden," with estimated prevalence of at least 23 per 100,000. The tuberculin skin test (TST) has low sensitivity, including in high-risk population groups such as men and patients older than 50 years, in addition to those who have disseminated TB. In immunosuppressed patients (such as those with human immunodeficiency virus), tuberculosis anergy is reported to be > 40%, particularly in those with poor body mass index and/or severe lymphopenia. This could also be true about other immunodeficient persons, including patients with rheumatic disease who are taking disease-modifying antirheumatic drugs (DMARD) and corticosteroids.

One of 22 patients reported by Malaviya, et al who tested negative for TB (TST, Quantiferon-TB Gold, standard chest radiograph, and computed tomography scan) developed TB 8 weeks after 1 dose of TNF-α inhibitor agents. We have 5 patients with IRD and TST-negative active TB; 1 of them had systemic lupus erythematosus (SLE) treated with infliximab because of refractory polyarthritis. That patient had acute respiratory failure secondary to disseminated fulminating TB, identified in necropsy 2 weeks after death to have received the first administration of infliximab (previous normal chest radiograph). Only 1 of these patients with IRD was not treated with DMARD and received prednisone > 10 mg (Table 1).

To see whether there were differences among our cases and patients without IRD, we evaluated 54 patients without IRD and with active TB (excluding other immune-suppression causes). The average age was 39.4 years; 51.9% were female and 29.6% TST-negative; most of them had pulmonary TB (61%). We did not find TST differences between patients with pulmonary disease (70%, 23/33) and those with extrapulmonary disease (71.4%, 15/21; p > 0.05). Moreover, our healthy population has a high frequency of positive TST (> 10 mm). We found this in 65% of 650 first-year medical students (mean age 18 yrs), who had not started clinical practice and did not have any potential contact with TB patients. But we cannot explain why < 20% of our IRD patients have positive TST.

It is evident that our patients have a high risk of developing active TB independent of TST results. It is interesting that the treatment with TNF-α inhibitor agents does not decrease the sensitivity of TST. In addition, we have found that 10% of patients under biologic therapy (non-TNF-α inhibitor agents) who previously were TST-negative can change to positive. It has also been found that patients taking TNF-α inhibitor agents maintained or increased their TST positivity. Developed countries have reported patients with previous negative TST being diagnosed with TB after taking TNF-α inhibitor agents and normal chest radiograph. These considerations are important because we recognize that the TST has low sensitivity for diagnosis of latent TB. Malaviya, et al reported in India an incidence of 18.2% of TB disease flare in patients treated with TNF-α inhibitor agents with a "standard" screening strategy for latent TB, and 4.5% with the "modified" TB screening strategy.

For developing countries where latent TB has a high prevalence, and despite negative screening tests for TB, we propose that before starting TNF-α inhibitor treatment, patients should receive prophylactic therapy or treatment for latent TB. TB disease flares could be brought close to zero, or at least near 1% as quoted from randomized controlled trials of TNF-α inhibitor agents.

In Mexico, as in other developing countries having high TB prevalence, it could be reasonable to receive therapy for latent TB before taking TNF-α inhibitor agents, independent of the TST results. We do not know the maintenance time for TB therapy, because we do not have evidence that after the recommended 9 months of therapy, the TB risk could be modified. These considerations are expressed because although we had only 5 patients with IRD who developed active TB, one of them under TNF-α inhibitor therapy, the diagnosis of active TB was made in most of our patients with invasive methods.

CARLOS ABUD-MENDOZA, MD; MARCO ULISES MARTÍNEZ-MARTÍNEZ, MD, Regional Unit of Rheumatology and Osteoporosis Hospital Central, Faculty of Medicine, Universidad Autónoma de San Luis Potosí; JOSÉ DE JESÚS MACÍAS-MENDOZA, MD; MARTÍN MAGAÑA-AQUINO, MD, Faculty of Medicine, San Luis Potosí, Mexico. Address correspondence to Dr. Abud-Mendoza; E-mail: c_abud@hotmail.com

REFERENCES
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Table 1. Data of 5 patients with active TB-IRD.

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age, yrs</th>
<th>Disease</th>
<th>Time of Diagnosis</th>
<th>Treatment</th>
<th>Diagnosis of TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>22</td>
<td>AS</td>
<td>4 yrs</td>
<td>PDN, MTX</td>
<td>Bacilloscopy</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>29</td>
<td>SLE</td>
<td>5 mo</td>
<td>PDN, MTX, AZA</td>
<td>Biopsy</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>34</td>
<td>SLE</td>
<td>0 yrs</td>
<td>None</td>
<td>Biopsy</td>
</tr>
<tr>
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<td>F</td>
<td>62</td>
<td>RA</td>
<td>4 yrs</td>
<td>PDN, MTX</td>
<td>Biopsy</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>20</td>
<td>SLE</td>
<td>1 yr</td>
<td>PDN, MTX, infliximab</td>
<td>Autopsy</td>
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</tbody>
</table>

Correspondence


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