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[1]. Mexico also has a "high TB burden," with estimated prevalence of at least 23 per 100,000[2]. 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[3,4]. In immunosuppressed patients (such as those with human immunodeficiency virus), tuberculin anergy is reported to be > 40%, particularly in those with poor body mass index and/or severe lymphopenia[5]. This could also be true about other immunodeficient persons, including patients with rheumatic disease who are taking disease-modifying antirheumatic drugs (DMARD) and corticosteroids[6,7].

One of 22 patients reported by Malaviya, *et al* who tested negative for TB (TST, Quanti-FERON-TB Gold, standard chest radiograph, and computed tomography scan) developed TB 8 weeks after 1 dose of TNF-α inhibitor agents[1]. We have 5 patients with IRD with 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[8]. Developed countries have reported patients with previous negative TST being diagnosed with TB after taking TNF-α inhibitor agents and normal chest radiograph[9]. 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[1].

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[10].

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.

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

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

TB: tuberculosis; IRD: inflammatory rheumatic disease; AS: ankylosing spondylitis; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; PDN: prednisone; MTX: methotrexate; AZA: azathioprine.

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