

Making Tumor Necrosis Factor Blockers Safer: A Prescriber's Consumptive Challenge



Latent tuberculosis (TB) infection is firmly on the prescriber's agenda

Until recently the diagnosis and treatment of latent TB infection (LTBI) has been the preserve of countries with a low prevalence of TB (under 10 patients per 100,000 population per year). These countries were seeking to eliminate the epidemic and sought to target treatment of the asymptomatic infection in high-risk individuals. The notion was to nearly eliminate the 5%–10% chance of TB reactivation in the person with LTBI, and thus prevent TB in that person, as well as preventing about 12 new infections that would be the consequence of a new infectious case.

Such a strategy was largely ignored by European countries even though they had low levels of TB. However, with the advent of TNF blockers and the association of infliximab and adalimumab use with TB reactivation, LTBI diagnosis and treatment has become more than just a cautious prescriber's preference¹. A number of countries now have specific advice on how to screen and treat LTBI in patients with rheumatologic illnesses²⁻⁷. This is because the consequences of failing to diagnose and treat LTBI may include TB disease, which is frequently disseminated, difficult to diagnose and treat, and is associated with a high mortality rate in this vulnerable group^{1,8}.

Screening and treating LTBI in the setting of TNF blockers works

The BIOBADASER group has shown in Spain that if their LTBI diagnosis and treatment guidelines are adhered to, reactivation cases of TB are unlikely to occur⁹. Perez, *et al* have shown similar data for adalimumab use¹⁰.

LTBI diagnostic challenges in the immunosuppressed patient

The diagnosis of LTBI traditionally relies on a positive tuberculin skin test (TST), in an asymptomatic patient. A chest radiograph is performed to rule out active TB. But of

course the TST is an immunological test that relies on an intact immune system to function properly¹¹. So it is not surprising that anergy has been shown to accompany immunosuppression and immunosuppressive illnesses¹². This limits the utility of a negative TST in ruling out LTBI. Specifically, Raval, *et al* reported 34 patients with a negative TST that went on to develop TB after starting infliximab⁸. The failure of this one-step TST may be compensated for by the use of a 2-step TST in populations of moderate TB prevalence. The Spanish registry used a 2-step TST approach to good effect⁹. Another alternative to the TST in LTBI diagnosis are the new interferon- γ release assays (IGRA), which are convenient blood tests. These tests are more specific than the TST in bacillus Calmette-Guerin (BCG) vaccinated populations, but they are also immune tests, and may have issues in the immunosuppressed^{13,14}.

IGRA in rheumatic patients

The study by Vassilopoulos¹⁵, *et al*, published in this issue of *The Journal*, is to be welcomed, since there have been few publications to date that specifically look at IGRA performance in this high-risk immunosuppressed population who are uniquely susceptible to TB¹⁶⁻¹⁸. The authors compared the ELISPOT IGRA to the TST in rheumatic patients scheduled for TNF blockers. They found agreement between tests to be around 70%. As observed in other patient groups, the blood test seems to be more specific than the TST in BCG-vaccinated persons. Although their numbers of TST-/ELISPOT+ cases were small, steroid use did not seem to interfere with the blood test. This is important, as steroid use has been associated with reactivation of TB¹⁹.

A clinical risk profile, including history of TB or TB contact and radiographic findings, can probably serve as a surrogate marker for LTBI²⁰. Of note, Matulis, *et al*¹⁶ demonstrated that an IGRA based on the QuantiFERON TB-Gold In Tube assay correlated better with a clinical risk profile for LTBI than TST. Their study and the current one

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both end by asking for further prospective evaluation of the TST-/IGRA+ group who remain untreated with isoniazid; if a number of these untreated patients proceed to develop reactivation TB, this would support the contention that IGRA are more sensitive at diagnosing LTBI than TST. If this fails to occur, then maybe the TST is the true test, and the IGRA is a false-positive. Such a study would be more readily answered if done in a country of high prevalence, yet withholding prophylaxis from IGRA+ patients may be an ethical issue.

Lack of a gold standard for LTBI is a limitation of this and many other studies that seek to establish the sensitivity of these new tests²¹. The gold standard for LTBI is the observation that, over a number of years (or even decades), the patient with the latent infection will proceed to reactivating TB.

Never off the hook

Given the immune basis of the TST and the IGRA, it is likely that a negative test in either will not rule out LTBI in all cases that are immunosuppressed¹⁴. Neither the patient nor the prescriber can feel completely “off the hook” with respect to TB reactivation risk when starting TNF blockers. In this regard, a diligent risk assessment with a good history and chest radiograph remain important, and continued surveillance is clearly the prudent path.

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