Minimizing Tuberculosis Risk in Patients Receiving Anti-TNF Therapy

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Systemic anti-TNF therapy has improved the management of immune-mediated inflammatory conditions, such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease. These drugs work by neutralizing TNF- α , which contributes to inflammation at the site of disease. However, TNF- α is also an important cytokine for macrophage activation and of critical importance in host control of *Mycobacterium tuberculosis* (*Mtb*) (1). As a result, anti-TNF therapies (in particular, monoclonal antibody preparations, such as infliximab and adalimumab) are associated with a moderate risk of reactivating latent tuberculosis (TB) of approximately two- to eightfold (2, 3). Of those who develop active TB, the majority do so within 3–6 months of commencing infliximab. Mortality can be considerable (4).

Screening for TB before commencing anti-TNF therapy is therefore important, and many guidelines have been developed recommending a variety of approaches to TB screening (5). Evaluation of these approaches is often difficult, as the TB incidence is low in many countries where anti-TNF therapy is most commonly prescribed. For example, in a recent study covering 7,210 person-years follow-up in the United States of anti-TNF therapy prescribed for inflammatory bowel disease, 72–86% of patients received TB screening, and only two patients developed active TB (6).

In this issue of *AnnalsATS*, Lee and colleagues (pp. 690–697) report a cohort of 10,863 patients commenced on anti-TNF therapy for a variety of indications in South Korea between 2011 and 2013 (7). This country has an intermediate TB burden (TB incidence 86/100,000). The study was conducted after the introduction of national guidelines for TB screening before anti-TNF therapy. Those guidelines recommended that patients be screened for latent infection by either an IFN- γ release assay (IGRA) or a tuberculin skin test (TST) with 10-mm cut-off, along with a chest radiograph before initiation of anti-TNF therapy (8). The incidence of active TB was ascertained through analysis of national insurance claims according to whether or not they had received prior preventive drug therapy with rifampin, isoniazid, or both.

The incidence of active TB was significantly lower in the 22.7% who received any preventive therapy compared with those who did not (4.07/1,000 person-years vs. 12.34/1,000 person-years; incidence rate ratio = 0.33). The risk reduction was greatest in those who completed a full course of preventive therapy, highlighting the importance of adherence.

The strength of the study was the broad population coverage achieved by using a database covering nearly 100% of residents in South Korea. The study is therefore a valuable programmatic evaluation at

a national level of TB screening for those commencing anti-TNF therapy. The study also highlights the value of preventive therapy and shows that a substantial number of cases of TB (over 100 in 3 yr) occurred in patients who did not receive prior preventive therapy.

A limitation of the study was that the authors did not have access to TB screening data and were therefore not able to shed light on whether these findings reflected a failure to implement guidelines or whether the guidelines, although implemented correctly, failed to identify all those at risk of reactivation. Evidence from a smaller study in Korea showed that, by 2013, screening by IGRA occurred in up to 90% of patients, although TST was performed in less than 40% (9). Other possible explanations for the high rates of TB in those not receiving preventive therapy are that patients declined therapy or that infection was acquired after screening. The findings by Lee and coauthors likely reflect all these possibilities.

In the absence of a true gold standard for latent TB, there is a fundamental question about the best approach to identify people asymptotically infected with viable *Mtb* with the potential to reactivate. This is particularly important in the context of anti-TNF therapy. Current tests for latent TB (TST and IGRA [QuantiferonTB-Gold and T-SPOT.TB]) are immunodiagnostics that merely demonstrate immune sensitization by

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detecting a cell-mediated immune response after *in vivo* or *ex vivo* stimulation with mycobacterial antigens. They do not indicate the presence of viable *Mtb*, and often remain positive after treatment (10). In addition, conditions or therapies that impair cell-mediated immune responses may compromise sensitivity of these tests.

Approximately 80% of patients for whom anti-TNF therapy is being considered are on immunosuppressive disease-modifying agents (DMARDS) that frequently include a corticosteroid (9, 11). Steroid prescription at the time of TST is associated with increased likelihood of a negative result. For that reason, IGRAs are becoming the preferred investigation method for latent TB in patients receiving DMARDS (12). However, the IGRA result may also be affected by corticosteroid use, in particular by increasing the likelihood of an indeterminate result (13). Relying on a single IGRA result to guide preventive therapy, which may have been the case in many patients in the study by Lee and coauthors, may be inadequate in high-risk populations.

Discordance between positive TST (sometimes strongly positive) and negative IGRA is common, as is discordance between QuantiFERON-TB-Gold and T-SPOT.TB (14). Boosting of the TST response by repeat two-step testing—as is recommended in some guidelines, including those from Korea—may increase likelihood of a positive result, but also increases logistical complexity, and is often not performed (15).

The likelihood of a positive IGRA may also be boosted by a prior TST, as we have recently shown in HIV-1 coinfecting patients, although this has yet to be investigated in patients taking DMARDS (16).

Given the limitations of these immunodiagnosics in this high-risk population, some guidelines additionally favor providing preventive therapy based on epidemiological risk. For example, in the United Kingdom, preventive therapy is recommended for those in whom the annual risk of TB (on anti-TNF therapy) exceeds the risk of hepatotoxicity with preventive therapy (e.g., those born in South Asia or Africa [3]). However, extending criteria for preventive therapy is not without consequences. It inevitably increases the number needed to treat to prevent a case of TB, leading to unnecessary adverse events and delays in initiating anti-TNF therapy, all of which needs to be taken into consideration along with cost effectiveness.

The timing of TB screening is often before commencing anti-TNF therapy, but the duration of such therapy may be prolonged. Patients reinfected while on anti-TNF therapy may be at high risk of progression to active disease. This may be particularly relevant in countries like Korea with higher burdens of TB.

In a recent French/Swiss study of 44 cases of TB occurring in patients after anti-TNF therapy who had an initially negative TB screen (25 by TST alone, 15 IGRA^{+/−} TST), 57% of cases occurred more than

12 months after initiation of therapy and 36% had risk factors for exposure to TB after anti-TNF therapy. This suggests that the initial screen may be truly negative in some cases with subsequent infection, and that consideration of ongoing screening in patients at risk of TB exposure may be indicated (17). In the study by Lee and associates, the time between prescription of anti-TNF therapy and the duration of TB therapy was not discussed, which may have been informative as to whether cases were related to reactivation or reinfection.

Current tests for latent TB are suboptimal. A next generation of tests is proposed for which target product profiles have been developed. Under development is a test for incipient TB with high predictive value for developing TB. Also in development is a test for persistent infection, which, if negative, would rule out risk of reactivation (18).

Pending the potential development of such tests, screening algorithms need to be optimized to the circumstances of individual countries: there is no one-size-fits-all solution. Nonadherence with guidelines has been shown to increase the probability of developing TB (15). Monitoring of adherence to, and efficacy of, TB screening is critical, and additional studies, such as that by Lee and colleagues, will be valuable in providing an overview of the effectiveness of such programs. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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