What defines latent infection with *Mycobacterium tuberculosis* in patients with autoimmune diseases?

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Screening for latent infection with *Mycobacterium tuberculosis* (LTBI) and treatment of test-positives is the cornerstone in the prevention of TB and should be performed preferably among individuals with risk for progression. Progression from LTBI to active TB is highest in recent contacts of patients with active TB. Moreover, it is considered particularly high in latently infected patients if they are also immunodeficient. Therefore, screening for evidence of LTBI is recommended for HIV-infected individuals, patients with chronic renal failure, individuals receiving immunosuppressive drug therapy following solid organ or stem cell transplantation, and patients with autoimmune diseases.[1 2] Since by definition LTBI lacks the gold standard of bacteriological confirmation, the condition is diagnosed indirectly by detection of an immune response towards mycobacterial antigens with either the tuberculin skin test (TST) or interferon-γ release assays (IGRA) performed from whole blood. IGRA may have test-intrinsic and operational advantages over the TST: due to the use of *M. tuberculosis*-specific antigens, IGRA have been shown to be more specific than the TST and allow distinction of infections with *M. tuberculosis* from immunity towards bacille Calmette–Guérin (BCG) or most non-tuberculous mycobacteria.[3] Moreover, unlike the TST, which has been shown to be of low sensitivity in immunocompromised patients, IGRA seem to be less affected by immunodeficiency, as frequently reflected by a higher percentage of positive test results in IGRA compared with TST in head-to-head comparative analyses.[4] Finally, as IGRA are performed along with negative and positive controls, indeterminate results due to failure of responses in the positive control (phytohaemagglutinin) may increase with increasing immunodeficiency and potentially allow to discriminate true negative from falsely negative test results. Our knowledge about the effect of immunosuppressive drugs on TST and IGRA results remains somewhat limited as the individual studies published to date suffer from sample sizes, frequently too small to show significant effects.

In this issue of the journal, Wong *et al*[5] report their results of a systematic review and meta-analysis on the effect of immunosuppressive drug treatment on LTBI testing in patients with autoimmune diseases. Studies were included where the two commercially available IGRA tests, the QuantiFERON-TB gold in tube assay (QFT) or the T-SPOT.*TB* assay, had been performed with or without the TST. Subgroup analyses were performed to address whether IGRA were affected by the underlying disease types or individual drugs. A total of 17 studies with 3197 patients were included in the analyses of which three-quarters received immunosuppressive single or combination drug therapy. Importantly, most studies (14/17) originated from low TB prevalence countries in Western Europe. Of note, the percentage of positive test results was highest in the two studies from Turkey and one study from Hong Kong, where the prevalence of TB is higher than in other parts of Western Europe.

Overall, the percentage of positive tests was adversely affected by immunosuppressive drugs in all studies. Interestingly, the OR was similar for the TST and the QFT (OR 0.51 and 0.65, respectively), indicating that the drugs affected both tests to a similar extent. In contrast, this finding was not significant for the T-SPOT.*TB* assay (OR 0.81), but this assay was used less frequently in the summarised studies. In general, the percentage of indeterminate result was rather low (1.1–17.6%) and did not differ in patients with and without immunosuppressive therapy. Subgroup analyses of patients with rheumatoid arthritis and inflammatory bowel disease, the two main groups of patients with the largest samples sizes, revealed that the adverse effect of immunosuppressive drug therapy on IGRA positivity was significant in both groups and, therefore, independent of the underlying disease. Likewise, all three main drug types, namely steroids, oral immunosuppressive drugs and tumour necrosis factor antagonists, were associated with a significant decrease in the percentage of positive IGRA tests. This result was obtained by pooling large data sets in the meta-analysis as none of the individual studies had shown statistical significance. Taken together, these data suggest that the immunosuppressive drugs used in autoimmune diseases affect both IGRA and the TST to a similar extent. It deserves further study, whether the less pronounced effect of immunosuppressive drugs on T-SPOT.*TB* results may be due to differences in the assay principle and/or the lower number of studies where this test was performed.

Looking closer at the data presented in the article, a surprising finding worth emphasising is the consistently higher percentage of positive test results in the TST compared with the IGRA. In pooled analysis, 26.6% of patients were positive in the TST, whereas only 13.6% and 16.8% had positive test results in the QFT or T-SPOT.*TB* assay, respectively. Although 57.6% of patients were BCG-vaccinated, vaccination did not seem to account for this fact as there was no relationship between TST positivity and prior BCG rates in the individual studies in the systematic review. Of note, TST positivity predominated also when stratifying patients with and without immunosuppression, indicating that the high percentage of positive TST results appears to be a particular finding in patients with autoimmune diseases. This has recently also been shown in a large multicentre study from the Tuberculosis network European trials group (TBnet).[6] In this study, test performance of TST and IGRA was compared among five different groups of immunocompromised individuals, namely HIV-infected individuals, patients with chronic renal failure, solid organ and stem cell transplant recipients and patients with rheumatoid arthritis.[6] The data showed that the percentage of positive test results was remarkably different from one patient group to the other. Interestingly, as in the present meta-analysis, patients with rheumatoid arthritis had far higher percentages of positive TSTs compared with the IGRA, which applied to both patients receiving higher and lower levels of immunosuppressive drugs.[6] This predominance of TST positivity contrasted with

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results from other patient groups, where the percentage of positive test results was either similar in all three assays (in patients with chronic renal failure) or where the percentage of positive test results in TST was significantly lower compared with the IGRA, as observed in HIV-infected patients, solid organ or stem cell transplant recipients (figure 1). Moreover, patients with rheumatoid arthritis were the group of individuals where all three assays showed the most pronounced association with risk factors for prior exposure towards *M. tuberculosis*. In the absence of an association with BCG vaccination, it is currently unknown why TST positivity predominated over the IGRA in patients with autoimmune diseases. One might speculate that inflammatory diseases may be associated with a favourable homing of antigen-reactive T cells into inflamed tissues, which may also favour recruitment of antigen-specific T cells to the site of tuberculin injection, thereby resulting in a relative advantage in TST positivity in autoimmune diseases. An alternative explanation could be that the underlying condition and the drug regimens used for therapy of autoimmune diseases have less impact on T cells, the key cell type mediating the delayed type hypersensitivity (DTH) response, compared with patients with HIV infection or following organ or stem cell transplantation, where T-cell function is primarily affected.

What are the practical implications of these findings for recommendations on how to best prevent TB in patients with autoimmune diseases? As both the TST and IGRA are adversely affected by immunosuppressive drugs, screening should preferably be performed before starting such treatments. Uncertainty, however, still persists regarding the choice of the screening test. While IGRA seem to be more sensitive in patients with T-cell-associated immunodeficiencies such as HIV-infected individuals or patients after solid organ and stem cell transplant recipients, this relative advantage of the IGRA over the TST is less evident for patients with autoimmune diseases. Thus, until better evidence is available, both the TST and IGRA seem viable approaches to diagnose LTBI,[7] possibly even used in combination, as recommended in screening protocols for children.[8] In our view, patients with conditions or drug regimens predominantly affecting T-cell function should preferentially be screened with IGRA as their DTH responses are more likely to be affected, as discussed above.

In clinical practice, however, the tests used should also identify those patients at highest risk for progression towards active TB in order to achieve a screening strategy and intervention with the 'best bang for your buck'—or rather your bug in this context. In this respect, interestingly, our TBnet study has shown that the incidence of TB on follow-up in the various groups of immunocompromised patients in Western Europe was not directly associated with the percentage of positive test results at the time of screening, and that TB cases were mainly observed in HIV-infected individuals with ongoing viral replication.[6 9] In contrast, despite a high percentage of positive TST and IGRA results no case of TB was observed among patients with rheumatoid arthritis.[6] This indicates that the risk for TB in patients with autoimmune diseases in low incidence countries is only poorly predicted by TST or IGRA. Thus, to increase the predictive value and to avoid unnecessary preventive chemotherapy, in our opinion screening should target patients with additional epidemiological or disease-specific risk factors. Ultimately, better biomarkers and longitudinal follow-up are needed to improve the predictive value.

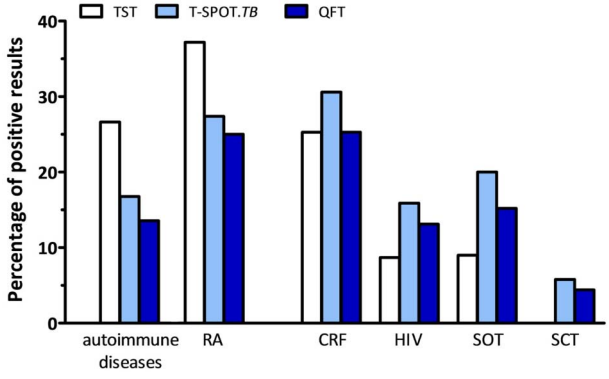

Figure 1 The percentage of positive tuberculin skin test (TST) results in patients with autoimmune diseases is higher than the percentage of positive interferon-γ release assays (IGRA) results. The percentage of positive test results in the TST and the two IGRA, the QuantiFERON TB gold in tube assay (QFT) or the T-SPOT.*TB* assay, was calculated from data derived from the meta-analysis by Wong *et al*[5] and compared with patients with rheumatoid arthritis (RA) and other patients with immunodeficiencies such as chronic renal failure (CRF), HIV-infected patients (HIV), solid organ transplant recipients (SOTs) or stem cell transplant recipients (SCTs). Data from patients with RA, CRF, HIV, SOT and SCT were reproduced from a recent TBnet study, and data sets are displayed from patients where the TST and the two IGRA results were available.[6] Patients with autoimmune diseases are the only patient group where the percentage of positive TST predominates over that of the IGRA. Data are shown for all patients irrespective of the level of immunodeficiency.

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