Tumour necrosis factor α inhibitors: screening for tuberculosis infection in inflammatory bowel disease

Arun Gupta, Alan C Street and Finlay A Macrae

ABSTRACT

- Tumour necrosis factor (TNF) α inhibitors such as infliximab are becoming more widely used for the treatment of selected patients with Crohn's disease, rheumatoid arthritis, and other inflammatory disorders.
- TNFα inhibitors increase the risk of serious infections, including tuberculosis.
- Screening for and treatment of latent tuberculosis infection before infliximab therapy reduces the risk of developing active tuberculosis.
- New blood tests that measure interferon γ production are an alternative to traditional tuberculin skin testing and offer some significant advantages over skin testing for screening of latent tuberculosis infection.

MJA 2008; 188: 168–170

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Monoclonal antibody therapies have become important in many different areas of medicine, from haematological malignancies to inflammatory bowel disease. Infliximab is a chimeric human–mouse immunoglobulin G_1 antibody which binds to and blocks tumour necrosis factor α (TNFα), a proinflammatory cytokine. TNFα is thought to play an important role in causing inflammation, which characterises Crohn's disease. TNFα induces two major signalling cascades: the apoptotic (cell death) pathway, and the inflammatory pathway.[1] In Crohn's disease, infliximab causes apoptosis of T lymphocytes in the lamina propria of the mucosal wall.[2]

In Crohn's disease, infliximab is used for patients with moderate to severe mucosal disease refractory to conventional therapy, and for patients with fistulising disease. For patients with mucosal disease, infliximab has been approved for use in Australia under the Pharmaceutical Benefits Scheme beginning in October 2007. For ulcerative colitis, there is evidence for use of infliximab in a severe acute exacerbation refractory to conventional therapy as a means of avoiding surgery,[3] and in induction and maintenance therapy in moderate disease.[4] Other TNFα inhibitors with trial evidence for use in inflammatory bowel disease include adalimumab[5] and certolizumab pegol.[6] The soluble TNFα receptor etanercept has not been shown to be efficacious in inflammatory bowel disease, possibly because of less inhibition of lipopolysaccharide-induced interleukin 1β production compared with other TNFα inhibitors.[7]

Use of TNFα inhibitors is not without risks. A meta-analysis of TNFα inhibitor use in rheumatoid arthritis showed that the risk of serious infection is doubled.[8] Reported infections include conventional bacterial infections, such as pneumonia and intravenous line-related sepsis, and opportunistic infections, such as tuberculosis (TB), varicella zoster and histoplasmosis. The effect of TNFα inhibitors on chronic or latent viral infections is less well characterised. Worsening of hepatitis B or hepatitis C infection is possible, and a recent review suggested that all patients should be screened for hepatitis B and C before infliximab therapy.[9] Viral reactivation of cytomegalovirus, Epstein–Barr virus or human herpesvirus 6 does not seem to occur.[10]

Screening for tuberculosis

Infliximab increases the risk of developing TB fivefold.[11] TNFα plays an essential role in host defences against TB through its role in granuloma formation and activation of macrophages.[12] Tuberculosis complicating infliximab therapy almost always occurs in patients with pre-existing latent TB infection (LTBI), which is reactivated by the TNFα inhibitor. A third of the world's population is thought to have LTBI,[12] although the proportion is much lower in Australia. Risk factors for LBTI include being born in or having lived in a TB-endemic area, contact with a patient with pulmonary TB, and a prior history of untreated or inadequately treated TB. LTBI is by definition asymptomatic, and only 10% of people with LTBI normally go on to develop active TB.

Treatment of patients for LTBI before TNFα inhibitor use decreases the incidence of active TB by more than 80%.[13,14] Traditionally, screening for LTBI has been based on tuberculin (Mantoux) skin testing. However, the Mantoux test has important limitations. False positive results can occur because of BCG vaccination or exposure to environmental (atypical) mycobacteria. False negative results may occur because of immunosuppressive medications or immune deficiency states such as HIV infection. In patients with Crohn's disease, a false negative Mantoux test may result from either immunosuppressive therapy or from anergy associated with the disease itself.[15]

Interferon gamma release assays

New blood tests for detection of TB infection have been introduced recently. These tests are based on measuring the production of interferon γ by T cells in response to in-vitro stimulation by antigens specific to *Mycobacterium tuberculosis* (and some atypical mycobacteria that are very rare causes of human disease). The QuantiFERON-TB Gold (QFT-G) test (Cellestis, Melbourne, Vic) is an enzyme-linked immunoassay type test that has been endorsed by the United States Centers for Disease Control and Prevention (CDC) for use as an alternative to the Mantoux test for screening selected populations for LTBI. However, the CDC suggest caution in immunosuppressed patients.[16] The T-SPOT.*TB* (Oxford Immunotec, Oxford, UK) is a similar test based on the enzyme-linked immunosorbent spot method.[17]

Interferon γ release assays (IGRAs) are more convenient and may provide results more quickly than the Mantoux test, and have the advantage of being more specific for *M. tuberculosis* infection. However, given the lack of a gold standard test for LTBI, determining the true sensitivity of IGRAs is difficult. Studies in patients with culture-proven TB show that IGRAs are at least as sensitive as Mantoux testing.[18] Studies in patients at risk of latent TB, such as household contacts of smear-positive pulmonary TB patients, also

indicate similar if not superior sensitivity to Mantoux testing, using extent of exposure to the index case as a surrogate marker of likelihood of latent infection.[18]

Data concerning use of IGRAs in immunosuppressed patients (such as patients on immunomodulator drugs) are still limited. Studies in patients with HIV and in immunosuppressed haematology patients suggest that IGRAs are more sensitive than Mantoux testing for detecting LTBI.[19,20] A recent study of patients with inflammatory rheumatic conditions on immunosuppressive medications used risk factors for LTBI as a surrogate marker; this showed a closer association between these risk factors and the IGRA result than with the Mantoux test. Although the Mantoux result was positive more often than the IGRA, this may have represented false positive results due to the high rate of BCG vaccination (83%) in that United Kingdom study, rather than superior sensitivity.[21] These immunosuppressed populations may not directly translate to our population of patients with inflammatory bowel disease, but do offer us some information about LTBI screening in the setting of immunosuppression.

Guidelines for screening for LTBI

Current recommendations for LTBI screening in patients being considered for TNFα inhibitor therapy vary. The British Thoracic Society recommends asking about TB risk factors and performing a chest x-ray, but not a Mantoux test, because of the latter's reduced sensitivity in the setting of immunosuppression. Treatment of LTBI is considered for selected patients with epidemiological risk factors, even if the chest x-ray is normal (in addition to those with chest x-ray changes or past history of TB).[11] The CDC guidelines suggest Mantoux testing of patients with TB risk factors. A chest x-ray is performed only if treatment of LTBI is planned, to exclude active TB. Treatment of LTBI may be considered in patients with a negative Mantoux test if there are convincing epidemiological risk factors.

Alternative screening guideline incorporating an IGRA in Australia

We propose an approach that incorporates an IGRA as an alternative to the Mantoux test (Box). All patients for whom TNFα inhibitor therapy is being considered should have:

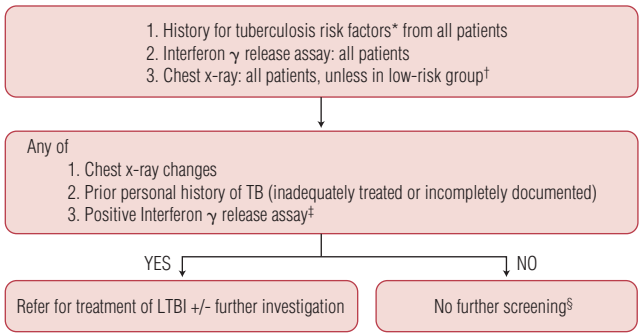
- an IGRA (such as QFT-G); and
- a history taken for TB risk factors and for current symptoms suggestive of active TB; and
- a chest x-ray, unless in a low-risk group (Australian-born and younger than 50 years with no other risk factors on history).

Patients should be considered for treatment of LTBI (previously known as chemoprophylaxis) and referred to an appropriate specialist if any of the following criteria are met:

- positive IGRA;
- radiographic lesions suggestive of past TB infection (eg, calcified nodular lesions, apical fibrosis, pleural scarring); or
- a history of previous TB (unless an adequate treatment course can be verified).

For patients with TB risk factors who have a normal chest x-ray and negative IGRA, addition of a Mantoux test may improve sensitivity. We advise against "blind" treatment of LTBI, but these patients must be followed very closely during TNFα inhibitor treatment and any symptoms suggestive of TB, such as unexplained cough, fever or weight loss, should be promptly and aggressively investigated. If TB is suspected, TNFα inhibitor therapy should be withheld and only restarted if TB can be confidently excluded.

Summary of our recommended screening protocol



LTBI = latent tuberculosis infection. * Tuberculosis (TB) risk factors are history of birth or residence in a TB-endemic area, history of contact with active tuberculosis, or prior personal history of tuberculosis. † Low-risk group = Australian-born, younger than 50 years, with no TB risk factors. ‡ Indeterminate results: consider repeat test in 2 weeks if not immunosuppressed, or discuss with infectious diseases specialist. § If TB risk factors, maintain heightened vigilance for signs and symptoms of TB infection during tumour necrosis factor inhibitor therapy. Consider performing a Mantoux test as well to increase sensitivity. ◆

In some cases, an indeterminate result occurs because of a low or absent positive control response (or alternatively, a high background interferon γ response in the nil control).[22] For patients with TB risk factors and an indeterminate result who are not on immunosuppression, the test can be repeated in 2 weeks. If it remains indeterminate (or the patient is on immunosuppression), referral to an infectious diseases or respiratory medicine specialist is advised (Dr David Leslie, Director, Victorian Mycobacterium Reference Laboratory, Victorian Infectious Diseases Reference Laboratory, Melbourne, Vic, personal communication).

Compared with Mantoux testing, this approach incorporating an IGRA is more convenient for patients, does not require a trained tuberculin skin tester and, as a consequence, ought to improve adherence to LTBI screening by clinicians. The greater specificity of IGRAs may mean that fewer patients will be unnecessarily treated for LTBI with isoniazid (with attendant risks of hepatotoxicity). The disadvantage is that, if the IGRA is less sensitive than Mantoux testing, patients with LTBI infection will be missed.

Alternative IGRA testing approaches

Some clinicians advocate performing a Mantoux test in addition to an IGRA and chest x-ray, the rationale being that patients with LTBI who have a negative IGRA result may be detected by the Mantoux test and vice versa. This may be a reasonable approach, but adds to the complexity and inconvenience of the screening process; it may be an option in people with TB risk factors and a negative IGRA result.

The use of a lower positive cut-off in the QFT-G test (analogous to applying a lower cut-off of 5 mm for the Mantoux test in immunocompromised patients) is untested and not recommended.

Treatment of latent tuberculosis infection

Treatment of LTBI generally consists of treatment with isoniazid for a minimum of 9 months. Whether to start the TNFα inhibitor

therapy before treatment of LTBI is complete should be discussed with an infectious diseases or respiratory medicine specialist, and will depend upon how urgently TNFα inhibitor treatment is required. For some patients, the decision to not use a TNFα inhibitor may be appropriate, even if the patient is treated for LTBI.

Active tuberculosis

Any patient suspected to have active TB on the basis of symptoms or chest x-ray changes before starting TNFα inhibitor treatment should be promptly referred to an infectious diseases or respiratory medicine specialist, and use of the TNFα inhibitor should be deferred. The possibility that the patient's underlying condition is actually TB and not Crohn's disease also needs to be considered, given the overlap in clinical features between Crohn's disease and some forms of gastrointestinal TB.

If the patient becomes unwell on TNFα inhibitor therapy, the possibility of TB should be considered, even if LTBI treatment has been given or LTBI screening tests are negative. TB often presents with disseminated or extrapulmonary disease in this group of patients, and symptoms may be non-specific and include fever, weight loss and cough.[23]

Conclusion

In immunosuppressed patients, such as those planned for treatment with TNFα inhibitors, the Mantoux test performs poorly when used for screening for LTBI.[11] In these patients, basing decisions about isoniazid treatment of LTBI on clinical risk factors alone runs the risk of over-treatment, with attendant problems such as hepatotoxicity. A screening approach that incorporates an IGRA offers greater specificity and convenience than Mantoux testing. Assessment of the sensitivity of IGRAs is hampered by the lack of a gold standard for diagnosis of LTBI, and further information about sensitivity in immunosuppressed patients is needed. Nevertheless, in addition to their other advantages over Mantoux testing, the improved clinician compliance that should result from use of IGRAs is a strong argument for adopting these tests to screen for LTBI in these patients.

Note that these guidelines are designed for an Australian population, and may not be applicable in other populations, such as those with a higher prevalence of TB.

As more information becomes available about the use of IGRAs and screening of LTBI, these recommendations may change.

Competing interests

None identified.

Author details

Arun Gupta, MB BS, Research Fellow, Department of Colorectal Medicine and Genetics
Alan C Street, MB BS, FRACP, Deputy Director, Victorian Infectious Diseases Service
Finlay A Macrae, MB BS, MD, FRACP, Director, Department of Colorectal Medicine and Genetics
Royal Melbourne Hospital, Melbourne, VIC.
Correspondence: arun.gupta@mh.org.au

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(Received 13 Sep 2007, accepted 19 Dec 2007) ❑