



SCREENING FOR LATENT TUBERCULOSIS INFECTION (LTBI) PRIOR TO USE OF BIOLOGICAL AGENTS IN AUSTRALIA*

* DISCLAIMER

This guideline is to be read in conjunction with UPDATED RECOMMENDATIONS FOR THE USE OF BIOLOGICAL AGENTS FOR THE TREATMENT OF RHEUMATIC DISEASES
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INTRODUCTION

The utilisation of biological agents in Australia which includes the tumour necrosis factor (TNF) inhibitors has both changed and challenged the management of rheumatic diseases particularly rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA).

Rheumatologists remain the largest group of Australian medical practitioners prescribing these therapies since their subsidisation on the Pharmaceutical Benefits Scheme (PBS) from July 2003 onwards. We are in the unique position of providing a user perspective aided by, and subject to, continuing change with updated rheumatology literature.

TNF INHIBITORS AND TUBERCULOSIS RISK

The cytokine TNF not only has a major role in the pathogenesis of some rheumatic diseases, psoriasis and inflammatory bowel disease, but also plays an integral role in defence against infection, particularly those resulting from mycobacterium including *M. tuberculosis* causing tuberculosis infection (TBI).

An increased susceptibility to active tuberculosis infection (TBI) or reactivation of latent TBI (LTBI) has been reported for all TNF inhibitors. Those currently available in Australia are etanercept (Enbrel) a human TNF soluble receptor fusion protein, adalimumab (Humira) a human monoclonal antibody and infliximab (Remicade) a chimeric human / mouse monoclonal antibody. From February 2010 golimumab (Simponi) a human antibody has also been available on a Product Familiarisation Program by the Australian distributor. Using data from the British Society for Rheumatology Biologics Register the rate of TB in patients treated with TNF was 3-4 fold higher in patients receiving Infliximab and adalimumab compared to etanercept which may be in part due to differences in monoclonal antibody versus soluble receptor TNF inhibitor actions. However, as no head to head comparisons among TNF inhibitors have been carried out to date, there is no definitive data on relative incidence of reactivation of latent to active TBI.

The risk of reactivation of TB depends on the underlying rate of latent infection or previous TB infection in the population. There are also high risk groups for TB infection including injecting drug users, those with HIV infection, a history of working or living in TB high risk settings such as prison, and finally people on immunosuppressive medications particularly corticosteroids, as occurs in many of our patients with rheumatic diseases.

Tuberculosis affects one third of the world population and even if patients not from an endemic high prevalence area, people now have the opportunity to travel to these areas. In the USA, the background rate of TB in patients with RA who had not received a TNF inhibitor was 6.2 cases per 100,000. The Australian background rate is slightly less. LTBI is by definition asymptomatic but is capable of rapid evolution to disease after a long latency although only 10% of people with LTBI normally go on to active TBI. Treatment of LTBI cases before TNF inhibitor commencement decreases the incidence of active TBI development by more than 80%.

This was well demonstrated with early infliximab use for RA overseas. The crude world rate of TBI in RA patients receiving infliximab was 47.6 / 100,000 (2001) which subsequently fell with LTBI screening programs to 24.4 / 100,000.

The following guideline has been developed to reduce the risk of active TBI in Australian rheumatic disease patients receiving TNF inhibitors. There will be initial discussion on the screening modalities available for LTBI, and why Australian guidelines differ slightly from overseas guidelines.

SCREENING MODALITIES FOR LTBI

Prospective screening with 3 of 4 modalities for all patients starting TNF inhibitors should be considered.

1. A case history TB risk factor assessment with physical examination **AND**
2. Chest radiograph (CXR) **AND**
3. Two-step tuberculin skin test (TST) **OR**
Interferon gamma release assay (IGRA) such as QuantiFERON-TB Gold (QFT-G) blood test (Cellestis, Melbourne, Vic).

The British Thoracic Society recommends:

- asking about TB risk factors
 - performing a chest radiograph
- BUT NOT A Mantoux (TST) because of its reduced sensitivity in a setting of immunosuppression including corticosteroid use.

Treatment of LTBI is considered for selected patients with TB risk factors even if the chest radiograph is normal (in addition to those with chest radiograph changes or past history of TBI).

The Centres of Disease Control (USA) recommends:

- Asking about TB risk factors
 - Mantoux TST testing of cases with TB risk factors
- OR alternatively an Interferon Gamma Release Assay (IGRA) for selected populations including immunosuppressed cases.
BUT a chest radiograph is performed **ONLY** if treatment of LTBI is planned, to exclude active TBI.

Treatment of LTBI may be considered in patients with a negative Mantoux TST test if there are convincing TB risk factors on case history.

An algorithm for LTBI screening for Australian rheumatic disease patients commencing TNF inhibitors recommends:

2. Chest radiograph (CXR) **AND**
3. Two-step tuberculin skin test (TST) **OR**
1. A case history TB risk factor assessment with physical examination **AND**

Interferon gamma release assay (IGRA) such as QuantiFERON-TB Gold (QFT-G) blood test (Cellestis, Melbourne, Vic).

The scored case history risk assessment involving ten questions is easy to perform and remains the most important modality.

Patients are then recommended to have either a two step TST or IGRA depending on availability, convenience, if on immuno-modulators past BCG vaccination or non tuberculosis mycobacteria infection (NTM). Both tests can have false negatives.

Finally all patients have a chest x-ray to assess evidence of past or current possible TB infection (e.g. calcified nodular lesions, apical fibrosis, pleural scarring).

Any positive high risk modality response as per the algorithm should usually be considered for LTBI treatment. If there are multiple positive moderate risk modality responses, LTBI treatment needs to be considered on a case by case basis which includes the not inconsiderable hepatotoxicity risk with isoniazid use for LTBI. "Blind" treatment of LTBI is not recommended.

The majority of cases with reactivation of LTBI to active TBI occur within 12 weeks of onset of TNF inhibitor use and over 50% have extra pulmonary TB site infection. If a patient becomes unwell with fever and weight loss on TNF inhibitor treatment, the possibility of TBI should be considered even if initial LTBI screening tests were negative.

Patients with LTBI are usually recommended to commence isoniazid (5mg/kg/d, maximum <300mg/d) with pyridoxine (25mg/d) for 6-9 months or rifampicin (10mg/kg/d maximum, <600mg/d) for four months. There is general consensus that TNF inhibitor therapy can be commenced concurrently 1-2 months after beginning prophylaxis.

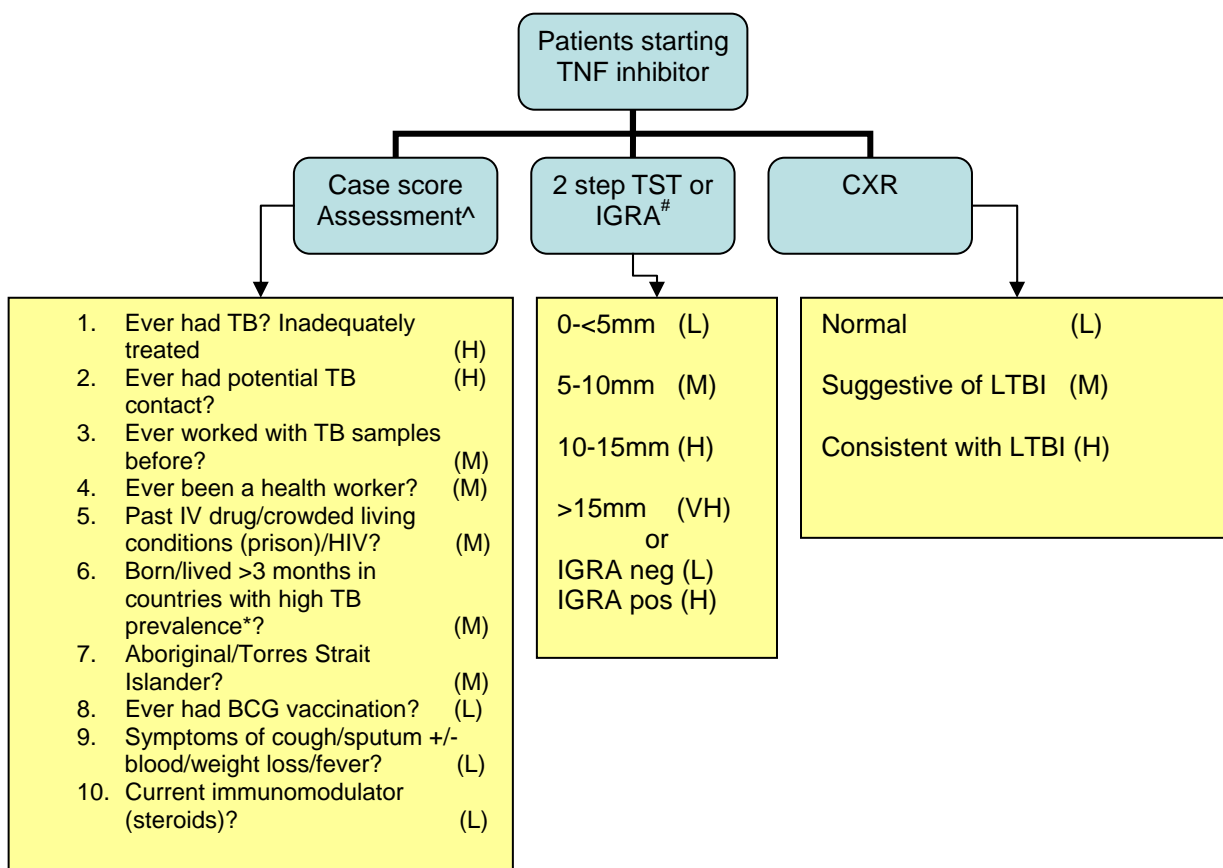
Patients with active TB (versus latent) infection should cease their TNF inhibitor, minimise use of other immunomodulators and be referred to the local TB expert be it an infectious diseases or respiratory physician for full anti tuberculosis drug therapies and follow up. When pronounced 'cured', TNF or other biological therapy can be reconsidered. There is no ready answer to patients going back to high risk TB prevalence countries. One may need to retreat versus repeating LTBI tests.

With respect to other biological therapies for rheumatic diseases there has been no evidence of increased susceptibility or incidence of TB. However most of these patients have been screened or have previously received TNF inhibitors and thus pre-screened for possible LTBI.

The rheumatologist should always be vigilant for the occurrence of TB in any of his or her patients on biological agents.

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Figure 1. ALGORITHM for LTBI screening for patients commencing TNF inhibitors. Each modality assesses whether patients are at low (L), moderate (M) or high (H) risk. Any high risk modality response should be referred to the local TB expert for consideration LTBI treatment. Consider LTBI therapy if multiple moderate risk modalities. Adapted from Perera LC, Tymms KE, Dorai Raj AK et al. IMJ 2006: 36(Suppl 2):A29



^Each question stratifies a patient into a risk category. Patient is classed as the highest category they have obtained. If patient answered yes to more than one moderate risk category question, they are still classed as moderate risk

*high TB prevalence countries include India, Pakistan, Bangladesh, China, Philippines, Indonesia, Ethiopia, Nigeria, South Africa, Congo

#The Interferon Gamma Release Assay (IGRA) test QuantiFERON-TB Gold has been suggested as an alternative to 2 step TST to eliminate TST false negatives for those with rheumatic diseases on immuno-modulators. Consider IGRA also for false positives from possible past BCG or atypical mycobacteria infection.

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