



Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive



Tumour Necrosis Factor- α (TNF- α) antagonists and Tuberculosis

**Recommendations for the Management of the risk of TB associated with the use of
TNF- α antagonists in an Irish setting**

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TNF- α antagonists offer great promise to patients suffering a number of immune-mediated diseases, and have been used safely in many patients worldwide. However, it is plausible that these agents may carry a risk of reactivation of LTBI or of new TB infection. Concern is supported by the finding of a possible increase risk of TB in peer-reviewed publications from a number of countries: while the design of these studies does not allow causality to be concluded, the consistency of the studies and the temporal association with the agents, together with the gravity of the consequence for individual patients and for the wider community suggest that a precautionary approach is appropriate. Manufacturers of TNF- α antagonists have indicated that TB is a possible side effect of treatment, and a number of guidelines for management of this risk have been issued by professional organizations and individuals.

The following recommendations are made for management of the risk of TB associated with the use of TNF- α antagonists in an Irish setting:

1. Prior to commencing TNF- α antagonist, patients should be thoroughly assessed for clinically active TB disease, including clinical history, physical examination, and chest radiograph. If clinically active TB disease is diagnosed, it should be treated as per existing guidelines.
2. Patients without clinically active TB disease should be screened for LTBI with clinical history, assessment of risk factors (for example time spent living in a high incidence country, immunocompetence etc), physical examination, chest radiograph and Mantoux test.
 - 2.1. Interferon- γ immunodiagnosis may be a useful adjunct in screening wherein it is available.
3. It is recommended that patients whose chest radiograph shows evidence of clinically active TB disease should receive curative treatment per existing guidelines.
4. Patients without radiographic evidence of TB, but with a positive Mantoux should be classified as a case of LTBI.
 - 4.1. For the purpose of LTBI screening prior to commencing TNF- α antagonists, 2 TU Mantoux testing is recommended. While reactions over 10mm should be interpreted as indicating TB infection, this cut off may not be reliable for some patients being considered for treatment with TNF- α antagonists, since their disease and co-medications may lead to anergy. Therefore, the use of a 5mm cut-off may be more useful for patients who are considered to be immunocompromised. It is recognized that on the basis of individual risk-assessment, clinicians may prefer to use an even more conservative cut-off for individual patients. Although a negative Mantoux test reduces the probability of LTBI, a high clinical suspicion for LTBI should be maintained, since the reaction to tuberculin may be complicated by anergy.

- 4.2. It is recommended that the interpretation of Mantoux testing in the context of testing for LTBI prior to commencement of a TNF- α antagonist should not usually take account of the patient's BCG history.
5. It is recommended that patients diagnosed with LTBI should be treated. Options for treatment include at least 9 months of isoniazid, which is associated with a lower risk of hepatitis, or 4 months of rifampicin +/- isoniazid, associated with a higher risk of hepatitis but offers the advantage of shorter duration which may promote successful completion of treatment for some patients. Pyridoxine may also be used in combination with these regimens.
6. Optimal timing of initiation of TNF- α antagonists is challenging and in the absence of high-quality evidence to support specific recommendation in this regard, decisions on the treatment of individual patients need to be made collaboratively by patients and clinicians following a careful assessment of the risks of TB disease and the benefits of TNF- α antagonist treatment and discussion of individual preferences.
 - 6.1. Initiation of TNF- α antagonists prior to commencement of treatment of clinically active TB disease or LTBI should be avoided.
 - 6.2. The risk associated with commencement or re-commencement of TNF- α antagonists in the setting of clinically active TB disease requires particularly careful assessment; where possible, it is recommended that TNF- α antagonists be postponed until curative treatment has been satisfactorily completed; in some cases, clinicians and patients may prefer to avoid TNF- α antagonists completely in this scenario.
 - 6.3. The risk associated with commencement or re-commencement of TNF- α antagonists in the setting of LTBI also requires careful assessment; again, where possible, it is recommended that TNF- α antagonists be postponed until LTBI treatment has been satisfactorily completed. However, clinicians and patients may, on balancing risks and benefits, prefer to initiate TNF- α antagonists during treatment for LTBI; while no specific duration of LTBI treatment prior to initiation of TNF- α antagonists can be recommended on the basis of currently available evidence, where possible, a longer duration of satisfactory LTBI treatment is suggested as good practice in managing the risk of initiation of TNF- α antagonists.
7. Clinically active TB disease may still arise in patients treated with TNF- α antagonists despite a negative initial assessment or LTBI treatment. Therefore, it is recommended that a high index of clinical suspicion for development of TB is exercised in the setting of any clinical deterioration while patients are undergoing TNF- α blockade.
8. Cooperation between clinicians initiating TNF- α antagonists and clinicians with expertise in TB is recommended in the assessment and management of patients.
9. Clinicians are encouraged to report all adverse drug events associated with the use of TNF- α antagonists to the Irish Medicines Board.

It is suggested that these national recommendations provide a framework for the drafting of guidelines for use by individual professional societies, units and clinicians on the use of TNF- α antagonists in clinical guidance; it is recognized that such guidelines may have broader concerns than the management of the risk of TB (e.g. surveillance for other side

effects) and may wish to include local good practice advice, however, guidelines should be made cognisant of these recommendations. An algorithm summarizing these recommendations is provided below.

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Appendix 1: Algorithm for TB assessment prior to TNF- α of antagonists

