Policy 6.4  
Active Surveillance for Tuberculosis prior to anti-TNF alpha Treatment

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Related WA TB Control Program Policies
1.1 Diagnosis of tuberculosis – Laboratory
1.2 Diagnosis of tuberculosis – Clinical
2.1 Medical treatment of tuberculosis (adults)
2.2 Case management of tuberculosis
3.1 Diagnosis of latent tuberculosis infection
3.2 Treatment of latent tuberculosis infection
4.1 Tuberculosis (active and latent) in children
4.2 Management of tuberculosis in prisoners and immigration detainees
4.3 Tuberculosis (active and latent) in pregnant women
4.4 Tuberculosis and HIV
5.1 BCG Vaccination
6.1 Contact tracing for tuberculosis
6.2 Active surveillance for tuberculosis in recent migrants
6.3 Active surveillance for tuberculosis in health care workers
6.4 Active surveillance for tuberculosis prior to anti-TNF alpha treatment
7.1 Notification of tuberculosis and enhanced surveillance data
8.1 Diagnosis and management of Hansen’s disease
9.1 Management of confidential information for the WA Tuberculosis Control Program
9.2 Client record management policy for the WA Tuberculosis Control Program
9.3 Fees and charges associated with tuberculosis and leprosy treatment

Document Control

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1.0 Introduction

Tumour necrosis factor alpha (TNFα) antagonist therapy is being used increasingly in the specialties of rheumatology, dermatology and gastroenterology for disorders such as rheumatoid arthritis, psoriasis and inflammatory bowel disease. The TNFα antagonist agents currently available in Australia are:

i) Etanercept (Enbrel),
ii) Adalimumab (Humira),
iii) Infliximab (Remicade),
iv) Certolizumab (Cimizia), and
v) Golimumab (Simponi).

TNFα antagonist therapy has been associated with an increased susceptibility to active tuberculosis and reactivation of latent tuberculosis disease. Tuberculosis, either active or latent disease, is not a contraindication to TNFα antagonist therapy. Patients with active TB should be referred promptly for treatment of their disease, and patients who are at risk of reactivation of TB disease while on TNFα antagonist therapy should be identified prior to the commencement of therapy for consideration of preventive TB therapy.

2.0 Role of TNFα

Tumour necrosis factor alpha (TNFα) has an important role in the immune response to *M. tuberculosis* infection. The release of TNFα in response to mycobacterial infection increases the ability of macrophages to phagocytose and kill mycobacteria, and TNFα production is a requirement for the formation of granulomas, which wall off mycobacteria and prevents their dissemination (Gardam & al, 2003; Wolfe & al, 2004) The presence of granulomatous lesions is protective to the host and limits tissue damage. Any inhibition of this process therefore has the potential to increase the susceptibility of patients to *M. tuberculosis*.

While TNFα production seems to be required for an effective immune response, excessive production seems to increase host tissue sensitivity to the cytokine and cause necrotising reactions and damage to tissues and organs (Gardam & al, 2003). TNFα mediates systemic inflammation, which manifests clinically as cachexia.

3.0 Tuberculosis and TNFα antagonist therapy

Patients treated with TNFα antagonists have an increased risk of reactivation of latent tuberculosis infection (LTBI) and anti TNFα therapy may increase the susceptibility for acquisition of primary TB (Keane, Gershon, Wise, & al, 2001). The use of TNFα antagonist therapy also increases the risk of reactivation of Hepatitis B infection (Carroll & Forgione,
and has been associated with candidiasis, histoplasmosis, aspergillosis and listeriosis (Perlmutter & al, 2009).

Active tuberculosis may develop soon after the initiation of treatment with TNFα antagonist therapy with the median time to onset being about 3 months (Keane & al, 2001). Most patients who develop TB associated with TNFα antagonist therapy have reactivation disease. Given the key role of TNFα in the immune response to tuberculosis, patients receiving TNFα antagonist therapy are probably also susceptible to disease after primary infection and exogenous re-infection with *M. tuberculosis*.

Patients who develop tuberculosis associated with TNFα antagonist therapy have a higher proportion of extrapulmonary and disseminated forms of TB compared to the non-immunosuppressed population (Keane & al, 2001). A review of 70 cases of tuberculosis that developed after the initiation of treatment with infliximab by Keane et al (2001) showed that the majority of the patients (56%) had extrapulmonary tuberculosis, and 24% had disseminated disease compared to the non-immunosuppressed population where 18% manifested as extrapulmonary disease, and disseminated disease accounted for less than 2%. This difference in presentation of TB may contribute to delays in investigating and diagnosing TB in patients undergoing TNFα antagonist therapy, as well as increased morbidity and mortality from TB.

### 4.0 Active surveillance

The risk of TB disease can be decreased by appropriate screening of patients for TB infection prior to the commencement of TNFα antagonist therapy. Before initiating treatment with a TNFα antagonist, an assessment of the risk of tuberculosis should be done.

#### 4.1 Assessing risk factors for TB

Certain subgroups of patients who have been offered TNFα antagonist therapy are more at risk of TB infection or reactivation. These are:

1. A contact of active TB.
2. Persons born, or who have lived for at least 3 months, in countries that have a high incidence of active TB defined as >50/100 000 per year (e.g. Africa, Asia). Country specific rates are available from WHO Tuberculosis country profiles.
4. Elderly patients (date of birth prior to 1940) born in a low prevalence country (e.g. Australia) in which rates of TB were higher in the past.
5. Certain occupational or residential settings e.g. health care workers
4.2 Screening procedure for TB

4.2.1 Exclude active TB

A history should be taken to exclude a history of prior TB or symptoms of current active TB. All patients should have a chest x-ray if one has not been performed in the two months prior to starting the TNFα antagonist. Further examination and investigation for active TB should be directed by the history (refer to the WA TB Control Program policy 1.2 Diagnosis of Tuberculosis – Clinical).

4.2.2 Exclude latent TB infection (LTBI)

The assessment of a patient for TB infection involves:

- Taking a good history to assess risk of TB infection and exclude active TB disease;
- A latent TB screening test if indicated; and
- A recent chest x-ray. The chest x-ray, while primarily to exclude active TB, can also show evidence of TB infection (e.g. calcified nodular lesions, apical fibrosis, pleural scarring).

4.2.2.1 Who to test for LTBI?

While the Australian Rheumatology Association and other guidelines (Gupta, Street, & Macrae, 2008) recommend a test for LTBI in all patients starting TNFα antagonist therapy, this is contrary to the general principal of targeted screening (see the WA TB Control Program policy 3.1 Diagnosis of LTBI). The American Thoracic Society (2011) recommends that a screening test for LTBI be done only if there is an identifiable risk for LTBI. In subjects with a low pre-test probability for LTBI, the screening tests will have a low positive predictive value, and therefore be at risk of being falsely positive.

Therefore, contrary to the above and other published guidelines, the WA Tuberculosis Control Program recommends in patients who are to receive a TNFα antagonist, undergo a TST or IGRA test only if they satisfy the following 3 criteria:

1. The patient is at risk of having TB infection

A patient history should be taken to assess for risk factors of TB infection. A patient is considered to be at risk if he/she answers positive to any of the following:

- Ever has TB? If yes, was the treatment adequate or inadequate?
- Ever had contact with TB?
- Ever worked with TB samples?
- Ever been a health care worker?
- Past IV drug use or HIV?
• Persons born, or who have lived for > 3 months, in countries that have a high incidence of active TB defined as >50/100 000 per year (e.g. Africa, Asia). For country based tuberculosis incidence refer to the WHO website http://www.who.int/tb/country/data/profiles/en/index.html (World Health Organisation 2011)
• Aboriginal or Torres Strait Islander?
• Any symptoms of cough/sputum/haemoptysis/weight loss/fever to indicate active infection?
• Current medications including an immunosuppressant?

At the very least the result of the TST or IGRA should be interpreted in the light of the assessment of risk factor and pre-test probability for LTBI; AND

2. The result of the test will be acted on.

If the test is positive, treatment for LTBI can be given (i.e. no major contra-indication) and, is either likely to be accepted by the patient or the TNFα antagonist won’t be given if the test is positive. A test for LTBI should not be done in anticipation of the possibility of future TNFα antagonist therapy e.g. at the initial assessment of a rheumatologic condition as routine screening; AND

3. There is no history of past treatment for TB.

If a patient has been treated in the past for TB, the test in this circumstance is likely to remain positive, and the management is not influenced by the test result (see section 5.2 below).

4.2.2.2 Which test for LTBI?

Either TST or QIFN can be used, but the WA TB Control Program recommends that, in this group of patients, QIFN is preferable. This is because QIFN has an in-built positive control that will reduce the chance of false results due to anergy. In these patients with autoimmune conditions and having received immunosuppressant therapy, anergy is more common. A negative TST due to this is indistinguishable from a genuinely negative TST, whereas a QIFN test will tend to be indeterminant in a strongly anergic patient.

5.0 Treatment

Any patient with symptoms or signs of active TB or who has a positive or indeterminant test for latent TB infection, should be referred to a physician experienced in the management of TB for assessment, investigation and treatment.
5.1 Active TB

The majority of cases with reactivation of LTBI to active tuberculosis occur within 12 weeks of onset of TNFα antagonist therapy and over 50% have extra pulmonary TB site infection (British Thoracic Society Standards of Care Committee, 2005). If a patient becomes unwell with fever and weight loss on TNFα antagonist therapy, the possibility of active TB should be considered even if initial LTBI screening tests were negative or treatment for LTBI has been given.

Patients with active TB detected after the commencement of TNFα antagonist therapy should cease their therapy, minimise their use of other immunosuppressants and be referred for TB treatment. Pulmonary and extra-pulmonary TB diagnosed either before or after commencement of TNFα antagonist therapy should receive standard chemotherapy for tuberculosis (see the WA TB Control Program policy 2.1 Medical treatment of tuberculosis). While ideally it would be preferable to delay TNFα antagonist therapy until completion of the full course of anti-TB treatment, TNFα antagonist therapy should not be given until at least 2 months after anti-TB treatment provided the patient is compliant with therapy, drug susceptibilities are known and there is good evidence of response to TB treatment (British Thoracic Society Standards of Care Committee, 2005).

5.2 Previous TB treatment

Patients who give a history of previous treatment for TB should be appropriately investigated for the presence of active TB disease. Once active disease has been ruled out, patients who give a good history of previous adequate treatment for tuberculosis are able to start TNFα antagonist therapy, but should be monitored closely and investigated promptly with a chest x-ray and sputum cultures if respiratory symptoms develop (British Thoracic Society Standards of Care Committee, 2005). Every effort should be made to obtain independent documentation of the prior treatment to assess its adequacy.

A test for LTBI should not be performed in patients previously treated for TB, as the test is likely to remain positive, even if the treatment was adequate. Giving routine treatment for LTBI e.g. isoniazid monotherapy in this circumstance is not recommended, because if the prior treatment was adequate there is no LTBI to treat, and if it was inadequate, the TB infection has a high risk of being drug resistant.

If prior TB treatment is considered inadequate but there is no current evidence of active TB, assessment for further treatment prior to the start of TNFα antagonist therapy should be made by a physician experienced in TB.

5.3 Latent TB

Patients with latent TB infection should be given treatment to prevent active disease (called preventive treatment) before TNFα antagonist therapy is commenced. Preventive therapy can decrease the incidence of active TB development by more than 80% (Tymms,
2009) though complete prevention is not possible (Sichletidis & al, 2006). For example, preventive therapy with 6 months of isoniazid may give protection as low as 60% (British Thoracic Society Standards of Care Committee, 2005).

Active TB infection must be excluded before preventive therapy is started.

Standard preventive therapy for LTBI should be given to patients who are to receive TNFα antagonists, as detailed in the WA TB Control Program policy 3.2 Treatment of latent tuberculosis infection.

TNFα antagonists can be started in patients with LTBI once the patient is established on preventive therapy without difficulty, and does not need to be delayed until the preventive therapy is completed. A patient is established on preventive therapy once they have demonstrated steady compliance, have not manifest any early side effects and have had at least one follow up liver function test that is satisfactory. This usually takes 2 – 4 weeks.

6.0 Exposure to active TB while on TNFα antagonists

Patients exposed to an infectious case of TB whilst taking a TNFα antagonist should be managed as per usual contact tracing protocol (see the WA TB Control Program policy 6.1 Contact Tracing for Tuberculosis). However, the decision to test for LTBI or give preventive therapy should be made in the light of the patient's immunosuppression. For example, in a high-risk exposure empiric preventive therapy irrespective of LTBI test results could be considered, as in HIV infected individuals.

7.0 TB re-infection after preventive therapy, while on TNFα antagonists

Re-infection after prior treatment for active or latent TB is documented, though rare. A patient taking a TNFα antagonist is potentially at higher risk of re-infection because of the immunosuppression, and, if reinfected, is again at increased risk of activation and dissemination because of the TNFα antagonist. There is currently no way to test for re-infection as the TST or QIFN are likely to positive from the first infection. Thus, if a patient that has formerly been treated for TB and is taking a TNFα antagonist is subsequently identified as a contact of TB, consideration should be given to empiric preventive therapy, with the decision being based on the clinical circumstances of the contact.

8.0 Conclusion

Tumour necrosis factor alpha (TNFα) antagonist therapy is being used increasingly in the specialities of rheumatology, dermatology and gastroenterology for disorders such as rheumatoid arthritis, psoriasis and inflammatory bowel disease. Patients treated with TNFα antagonists have an increased risk of reactivation of latent tuberculosis infection (LTBI) and incidence of tuberculosis. Close cooperation between clinicians prescribing anti-TNF-a and specialists in the management of TB is essential.
9.0 Works Cited


Endorsing Authority

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**Feedback or comments related to this policy should be addressed to the Medical Director, WA TB Control Program Justin.Waring@health.wa.gov.au**