



Feidhmeannacht na Seirbhíse Sláinte  
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# **Tumour Necrosis Factor- $\alpha$ (TNF- $\alpha$ ) antagonists and Tuberculosis**

**A briefing paper from the Latent TB Infection Subgroup of the National TB  
Advisory Committee**

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## **Executive summary**

There is concern that new groups of drugs called TNF- $\alpha$  antagonists, which are being used effectively to modify the immune system response in the treatment of a number of immune-mediated diseases, may be associated with a risk of developing TB infection and clinically active TB disease. This briefing paper aims to review the issues around TNF- $\alpha$  antagonists and tuberculosis.

TNF- $\alpha$  is a cytokine produced by immune system cells which regulates cellular activity and promotes inflammation. In health, it has appropriate and beneficial roles in responding to infection and tumours. However, TNF- $\alpha$  has also been implicated in the development of a number of diseases wherein the immune system response is neither appropriate nor beneficial, notably rheumatoid arthritis and inflammatory bowel disease.

TNF- $\alpha$  antagonists are a group of new drugs which block TNF- $\alpha$  activity. Members of this group include Infliximab, Etanercept and Adalimumab. Although these agents work in slightly different ways, they have been shown to be effective in the management of a number of immune-mediated diseases including rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, Crohn's disease, ankylosing spondylitis and psoriasis.

Following infection with Mycobacterium Tuberculosis, TNF- $\alpha$  plays an important role in the immune system response, including control of persistent infection and containment of mycobacteria in granulomata in latent TB infection. There is laboratory evidence from animal models demonstrating that TNF- $\alpha$  activity blockade can lead to TB infection, breakdown of granulomata and to clinically active TB disease.

In humans, published studies of these agents, based on post-marketing surveillance of adverse drug reactions, have shown them to be consistently associated with a risk of developing clinically active TB disease. Temporal association has been demonstrated. These published studies have estimated the risk of developing clinically active TB disease in patients treated with TNF- $\alpha$  antagonists to be between approximately 4 to 20 times greater than the risk among similar patients not treated with these agents. This may represent either new TB infection or reactivation of latent TB infection. However, measurement of this potential increase in risk poses a number of methodological challenges. Patients for whom TNF- $\alpha$  antagonists are indicated may have a greater risk of developing clinically active TB disease than the general population independent of their administration of on account of increasing age and changes rendered to the immune system by their disease and co-medications. Since the development of clinically active TB disease with TNF- $\alpha$  antagonists is a rare outcome of treatment, it is difficult to discern any possible increase in risk with statistical confidence. Moreover, there are methodological limitations with the studies published to date.

However, there is biological plausibility to the hypothesis that treatment with these agents poses a risk of developing clinically active TB disease, and the evidence available from human studies is consistent in this regard. The possibility of increased risk of TB associated with these agents has important implications for patients and for the general population. The TB cases described occurred in patients with co-morbid

immune-mediated disease and have been severe, frequently extra-pulmonary, and associated with a high case-fatality ratio. There is also a risk that persistence of TNF- $\alpha$  antagonists after their discontinuation may make TB difficult to treat. A precautionary approach is appropriate: the manufacturers advise that TB is a possible adverse effect of treatment with these agents, and recommendations to manage this risk have been published by a number of sources.

While the evidence-base for recommendation is weak, there is consensus that clinically active TB disease should be excluded in patients to undergo treatment with TNF- $\alpha$  antagonists. While there is agreement that patients should be screened for latent TB infection, the optimum interpretation of tuberculin skin testing in this setting is disputed, and complicated by the issues of BCG vaccination and co-existent immunosuppressant conditions and therapy. Patients with latent TB infection should be treated for TB, but the priority given to various regimens varies and there is recognition of the need to balance potential harms and benefits. Finally, the timing of safe commencement TNF- $\alpha$  antagonists after initiation of anti-tuberculous treatment remains uncertain. Nevertheless, the publication of national guidelines in this area by one country has been shown to be associated with a reduction in the rate of TB in patients treated with TNF- $\alpha$  antagonists.

In Ireland Infliximab, Etanercept and Adalimumab are all authorized for use, and in the last 5 years, the Irish Medicines Board has received reports of 8 cases of TB associated with Infliximab, 1 case associated with Etanercept, and 1 case associated with both drugs.

In conclusion, TNF- $\alpha$  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 increased 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- $\alpha$  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- $\alpha$  antagonists in an Irish setting:**

1. Prior to commencing TNF- $\alpha$  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, immuno-competence etc), physical examination, chest radiograph and Mantoux test.

- 2.1. Interferon- $\gamma$  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- $\alpha$  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- $\alpha$  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- $\alpha$  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- $\alpha$  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- $\alpha$  antagonist treatment and discussion of individual preferences.
  - 6.1. Initiation of TNF- $\alpha$  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- $\alpha$  antagonists in the setting of clinically active TB disease requires particularly careful assessment; where possible, it is recommended that TNF- $\alpha$  antagonists be postponed until curative treatment has been satisfactorily completed; in some cases, clinicians and patients may prefer to avoid TNF- $\alpha$  antagonists completely in this scenario.
  - 6.3. The risk associated with commencement or re-commencement of TNF- $\alpha$  antagonists in the setting of LTBI also requires careful assessment; again, where possible, it is recommended that TNF- $\alpha$  antagonists be postponed until LTBI treatment has been satisfactorily completed. However, clinicians and patients may, on balancing risks and benefits, prefer to initiate TNF- $\alpha$  antagonists during treatment for LTBI; while no specific duration of LTBI treatment prior to initiation of TNF- $\alpha$  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- $\alpha$  antagonists.

7. Clinically active TB disease may still arise in patients treated with TNF- $\alpha$  antagonists despite a negative initial assessment or LTBI treatment. Therefore, it is recommended that with a high index of clinical suspicion for development of TB is exercised in the setting of any clinical deterioration while patients are undergoing TNF- $\alpha$  blockade.
8. Cooperation between clinicians initiating TNF- $\alpha$  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- $\alpha$  antagonists to the Irish Medicines Board.

## **1. Introduction**

The immune system plays a central role in the maintenance of health and in the development of disease. Advances in the understanding of its functioning at a molecular level have identified opportunities to modify the immune system response and, as a result, a number of promising new drugs have been developed. However, while these drugs exert their therapeutic effect through modification of pathways involved in disease, they may also alter pathways involved in health, and thereby lead to undesirable side effects. Tumour Necrosis Factor- $\alpha$  (TNF- $\alpha$ ) antagonists are a case in point: while these drugs have been shown to be valuable in treating a number of diseases mediated by the immune system, they have also been implicated in the development of infection, most notably Tuberculosis (TB).

This briefing paper aims to review the issues around TNF- $\alpha$  antagonists and tuberculosis. TNF- $\alpha$  and the drugs which modify its effects will be described; current understanding of TNF- $\alpha$ 's role in TB infection will be discussed; studies describing the risk of TB with TNF- $\alpha$  antagonists will be appraised; and international guidelines for the management of this risk will be reviewed. Finally, evidence-informed recommendations for the use of TNF- $\alpha$  antagonists in Ireland will be proposed.

## **2. TNF- $\alpha$ in health and disease**

Cytokines are a large family of low-molecular-weight soluble proteins involved in regulating cellular activity, particularly (but by no means exclusively) within the immune system.<sup>1</sup> Cytokines lack immunological memory, and are therefore a component of the innate immune system response. The cytokine family includes Interleukins, Interferons, Colony Stimulating Factors and TNF- $\alpha$ . Macrophages, T cells, B cells, Mast cells and Natural Killer cells all produce TNF- $\alpha$ . Its major activity is the promotion of inflammation.<sup>2</sup> TNF- $\alpha$  is found in soluble or membrane-associated forms. Its effects are mediated through binding to either of two cellular receptors: Tumour Necrosis Factor Receptor-1 (TNFR-1) binds soluble TNF- $\alpha$ ; TNFR-2 binds membrane-associated TNF- $\alpha$ .<sup>3</sup>

In health, TNF- $\alpha$  has appropriate and beneficial roles in response to infection and tumours. However, it has also been implicated in the development of a number of diseases wherein the immune system response is neither appropriate nor beneficial, notably rheumatoid arthritis and inflammatory bowel disease.<sup>4 5</sup>

### 3. TNF- $\alpha$ antagonists

Study of the mechanisms of TNF- $\alpha$  action and its role in immune-mediated disease has led to the development of a several agents that block its effect. Collectively these drugs are known as TNF- $\alpha$  antagonists, TNF- $\alpha$  blockers or anti-TNF- $\alpha$  drugs.

Two agents have been most extensively studied: Infliximab and Etanercept.<sup>3</sup> Infliximab is derived from combined human-mouse antibodies against TNF- $\alpha$ . It binds with the soluble and membrane-associated forms of TNF- $\alpha$ , thereby inactivating the molecule and mediating lysis of immune system cells (macrophages and monocytes) with the membrane-associated form. It does not have activity against other cytokines. It has a longer half-life relative to other agents in this group. Etanercept is derived from human antibodies attached to a portion of the human TNFR. Unlike Infliximab, it does not bind as well to membrane-associated forms of TNF- $\alpha$ : this is an important distinction in the mechanisms of action of the two agents. It binds to soluble forms of the molecule and is also active in binding and inactivating another related cytokine, Lymphotoxin  $\alpha$ . Adalimumab, a recombinant monoclonal antibody, is a newer agent with activity similar to Infliximab, and other TNF- $\alpha$  antagonists such as CDP870 (a PEGylated agent) are under study.<sup>3</sup>

TNF- $\alpha$  antagonists have shown effectiveness in the treatment of a number of immune-mediated diseases, in particular rheumatoid arthritis,<sup>6-10</sup> psoriatic arthritis juvenile, idiopathic arthritis, Crohn's disease,<sup>11-14</sup> ankylosing spondylitis,<sup>15</sup> and psoriasis.<sup>16</sup>

#### **4. TNF- $\alpha$ in TB infection**

Infection with *Mycobacterium Tuberculosis* (M. Tb.) evokes a complex immune system response, which is usually effective in containing the organism through granuloma formation, but frequently fails to eradicate infection.<sup>17</sup> Evidence from mouse models of infection with M. Tb. illustrates that TNF- $\alpha$  plays a crucial role in protection against TB infection and the development of clinically active TB. It promotes phagocytosis and killing of mycobacteria by macrophages, recruitment and accumulation of immune cells at the site of infection and granuloma formation.<sup>18</sup> In latent TB infection (LTBI), TNF- $\alpha$  is also important in controlling persistent infection and in containing organisms within granulomas. Again, using mouse models, it has been illustrated that treatment with antibodies to inhibit TNF- $\alpha$  can lead to failure to control persistent infection with granuloma breakdown and release of mycobacteria leading to clinically active TB disease.<sup>18</sup> Lymphotoxin  $\alpha$ , a cytokine closely related to TNF- $\alpha$ , which is inhibited by Etanercept, has also been shown to be important in the control of persistent infection through granuloma formation.<sup>18</sup>

## 5. TNF- $\alpha$ antagonists and risk of TB

Given the role of TNF- $\alpha$  in protection against infection, there is concern that TNF- $\alpha$  antagonists may increase the risk of TB infection and clinically active disease. Although there were some reports of infections, including tuberculosis, amongst participants treated with TNF- $\alpha$  antagonists in randomised controlled trials of effectiveness, the evidence was not strong or consistent enough between studies to preclude licensing. However, subsequent to licensing, there have been reports of tuberculosis associated with TNF- $\alpha$  antagonists from a number of sources.

In 2001, Keane et al analysed reports of tuberculosis to the spontaneous adverse drug event reporting system of the Food and Drug Administration in the United States of America. Seventy cases of tuberculosis were reported following treatment with Infliximab from licensing in 1998, most cases occurring in close temporal relationship with the initiation of treatment. Over half of the reported cases had extra pulmonary disease, and one quarter had disseminated disease; 12 patients died subsequent to the report of tuberculosis, and at least 4 of these deaths were directly attributable to tuberculosis. Other opportunistic infections were also reported including listeriosis, Pneumocystis Carnii Pneumonia (PCP), histoplasmosis, aspergillosis and severe candida. The estimated rate of tuberculosis among patients with rheumatoid arthritis treated with Infliximab within the previous year was 24.4 cases per 100,000, which was compared in the analysis to an estimated background rate among patients with rheumatoid arthritis in the United States of 6.2 cases per 100,000 per year (95% confidence interval 0.6-34.0). The design of this study does not allow a conclusion of causality to be drawn; estimation of the incidence of TB in the Infliximab treated population may be biased as it is drawn from a passive reporting system, and this rate falls within the 95% confidence interval of the estimated incidence in patients with rheumatoid arthritis. However, given the temporality of the association, the biological plausibility, and the significance of the finding, the hypothesis has justifiably drawn further attention.

Following licensing of Infliximab and Etanercept in Spain, the Spanish Society of Rheumatology established a registry of all patients treated with these agents in 2000, named BIOBADASER.<sup>19</sup> This was a passive reporting system of unmeasured completeness; however it used clear definitions for a case of TB occurring in a patient treated with a TNF- $\alpha$  antagonist. The rate of TB cases reported to BIOBADASER was compared with the rate in the same period for the general population (based on data from the National Network of Epidemiological Surveillance) and patients with rheumatoid arthritis (based on a prospective cohort study of a sample of 788 Spanish patients). Since its establishment, BIOBADASER received reports of infections in 118 of 1540 patients registered; 17 of these patients had TB, 65% of which had extra pulmonary disease. The incidence of clinically active TB disease in patients treated with TNF- $\alpha$  antagonists was estimated at 1893 and 1113 per 100,000 in 2000 and 2001 respectively. The risk of clinically active TB disease in patients treated with TNF- $\alpha$  antagonists was greater than the general population and patients with rheumatoid arthritis not treated with TNF- $\alpha$  antagonists in similar periods: relative risk compared to the general population 90.1 (95% Confidence Interval (CI) 58.8-146.0) in 2000 and 53.0 (95% CI 34.5-89.0) in 2001; relative risk compared to patients with rheumatoid arthritis not treated with TNF- $\alpha$  antagonists 19.9 (95% CI 16.2-24.8) in 2000 and 11.7 (95% CI 9.5-14.6) in 2001. In this study patients with rheumatoid arthritis not treated with TNF- $\alpha$  antagonists had a greater risk of TB than

the general population: relative risk 4.1 (95% CI 2.6-6.8). Again, the design of this study means that measurement of risk associated with TNF- $\alpha$  antagonists is subject to error. However, the increase in risk was statistically significant, and the consistency with the study by Keane et al adds weight to the hypothesis that these agents cause clinically active TB disease either through increasing the risk of primary infection or leading to reactivation of LTBI.<sup>20</sup> It should be noted that the estimate of risk in the Spanish study may not be generalised to populations with a lower incidence of TB.

In 2004, Wolfe et al reported the results of two studies in a paper examining the risk of TB in patients treated with TNF- $\alpha$  antagonists.<sup>21</sup> In the first study, 10,782 patients with rheumatoid arthritis were surveyed in 1998 to measure their lifetime prevalence of TB infection, and then entered into a prospective cohort study to measure the incidence of TB over an 18 month period. This study took place at a time prior to the widespread use of TNF- $\alpha$  antagonists. In the second study, 6460 patients who received Infliximab (although not necessarily during the period of follow up) were entered into a prospective cohort study to investigate the safety of the agent. Lifetime prevalence and incidence of TB were established by self-report: patients reporting a positive tuberculin test or a diagnosis of TB underwent a validation process prior to classification as a case of TB, including documentation of diagnosis in study two. In the first study (prior to routine use of Infliximab) the lifetime prevalence of clinically active TB disease was 696 (95% CI 547-872) per 100,000; and the incidence of TB disease was 6.2 (95% CI 1.6-34.4) per 100,000 patients in 16,173 patient-years of follow up. In the second study (TNF- $\alpha$  antagonists in routine use), the incidence of clinically active TB disease in those patients who received Infliximab was 52.5 (95% CI 14.3-134.4) per 100,000 patient-years. The risk of TB was greater in patients diagnosed with rheumatoid arthritis and treated with Infliximab than in patients diagnosed with rheumatoid arthritis followed up at a time when TNF- $\alpha$  antagonists were not in regular use. Again, the design of this study is not ideal for measurement of the relative risk of tuberculosis associated with TNF- $\alpha$  antagonists; in particular the estimated incidence in the first study is subject to error. In addition, there were relatively few cases of TB occurring in both studies, and the interval estimates (95% CI) for the rates overlap indicating that the difference in rates may be a chance finding. However, it is consistent with other studies in indicating an association between treatment with TNF- $\alpha$  antagonists and increased risk of developing TB.<sup>19 20</sup> The study also included follow up on over 2,000 patients treated with Etanercept, in whom no cases of TB were detected.

Reports of TB following Etanercept to the spontaneous adverse drug event reporting system of the Food and Drug Administration in the United States of America from its licensing in 1998 through to 2004 were described by Mohan et al in 2004.<sup>22</sup> There were 25 reported cases of TB disease in patients treated with the drug, over half of which had extra-pulmonary disease; two deaths occurred, which included one death from disseminated tuberculosis and one death from tuberculous meningitis. The rate of reporting of TB disease in patients receiving Etanercept in the United States was 10 per 100,000 patient-years of exposure. This study has similar limitations to that undertaken by Keane et al.<sup>20</sup> It cannot be concluded that Etanercept causes TB disease, however, there is temporal association, and the hypothesis is supported by biologically illustrated mechanisms. In conjunction with the study by Wolfe et al,<sup>21</sup> and in comparison with the studies of the risk associated with Infliximab,<sup>19-21</sup> it has been suggested that Etanercept may be associated with a lower magnitude of risk than

Infliximab. Appraising this possibility, Keane proposed a number of mechanisms for this observed difference: doses of the agents differ, as do their duration of action; Infliximab may have more potent effects on protective aspects of the immune system response to TB infection; Infliximab may be more frequently co-administered with other immunosuppressant drugs which confound its effect on risk of TB disease; the observation may be due to preferential use of Infliximab in countries with higher prevalence of TB infection and disease.<sup>23</sup>

In 2004, the Centers for Disease Control and Prevention published a description of 12 cases of TB associated with TNF- $\alpha$  antagonist treatment and noted that the US Food and Drug Administration had determined tuberculosis to be a possible side effect of Infliximab, Etanercept and Adalimumab.<sup>24</sup> Treatment with TNF- $\alpha$  antagonists for Crohn's disease has also been reported to be associated with TB disease.<sup>25</sup>

In conclusion, there is biological plausibility supporting the hypothesis that TNF- $\alpha$  antagonists cause clinically active TB disease either through reactivation of LTBI, or increasing the risk of primary infection. Rheumatoid arthritis is associated with an immunosuppressed state, and many of the traditional agents used in the management of this condition (for example steroids and cytotoxic drugs) are immunosuppressive.<sup>23</sup> These conditions also apply to other diseases for which TNF- $\alpha$  antagonists are administered, rendering patients at increased risk of TB infection and clinically active disease independent of these agents, although evidence in support of this risk is contradictory.<sup>19,21</sup> There is evidence from animal models that inhibition of TNF- $\alpha$  causes TB disease.<sup>18</sup> The epidemiological studies that have been described above all have limitations in measuring the risk of TB associated with TNF- $\alpha$  antagonist treatment which preclude a conclusion of causality from being drawn; however, there is consistency between studies, and the observed difference in risk between Infliximab and Etanercept could be interpreted as a dose-response effect. The possibility of increased risk of TB associated with these agents has important implications for patients and for the general population. The TB cases described occurred in patients with co-morbid immune-mediated disease and have been severe, frequently extra-pulmonary, and associated with a high case-fatality ratio. There is also a risk that persistence of TNF- $\alpha$  antagonists after their discontinuation may make TB difficult to treat.<sup>23</sup> A precautionary approach is appropriate: the manufacturers advise that TB is a possible adverse effect of treatment with these agents ([www.emea.eu.int](http://www.emea.eu.int)), and recommendation to manage this risk have been published by a number of sources. Such an approach is also warranted from the public health perspective given that cases of clinically active TB disease in the community are an important source of secondary spread and therefore pose a threat to the overall control of TB in the population.

## 6. International guidelines for TNF- $\alpha$ antagonists and risk of TB

Recommendations on management of the risk of TB associated with TNF- $\alpha$  antagonist have been published by a number of individual authors and organisations. These are now presented.

### *Unites States*

The Centers for Disease Control and Prevention made recommendations for the screening, diagnosis and treatment of LTBI and TB in patients receiving or to receive TNF- $\alpha$  antagonists in 2004, which are set out in Box 1.<sup>24</sup>

#### Box 1: Centers for Disease Control and Prevention Recommendations

- “Screen patients for risk factors for *Mycobacterium tuberculosis* and test them for infection before initiating immunosuppressive therapies, including TNF-antagonists. Risk factors include birth in a country where TB is prevalent or history of any of the following: residence in a congregate setting (e.g., jail or prison, homeless shelter, or chronic-care facility), a positive tuberculin skin test (TST) result, substance abuse (i.e., injection or non-injection), health-care employment in settings with TB patients, and chest radiographic findings consistent with previous TB.
- Diagnosis and treatment of LTBI and TB disease should be in accordance with published guidelines.
- In patients who are immunocompromised (e.g., because of therapy or other medical conditions), interpret a TST induration of >5mm as a positive result and evidence of *M. tuberculosis* infection.
- Interpret a TST induration of <5mm as a negative result but not an exclusion for *M. tuberculosis* infection. Results from control-antigen skin testing (e.g., *Candida*) do not alter the interpretation of a negative TST result.
- Test to exclude TB disease before starting treatment for LTBI.
- Start treatment for LTBI before commencing TNF-blocking agents, preferably with 9 months of daily isoniazid.
- Consider treating for LTBI in patients who have negative TST results but whose epidemiologic and clinical circumstances suggest a probability of LTBI.
- Pursue TB disease as a potential cause of febrile or respiratory illness in immunocompromised patients, including those receiving TNF- $\alpha$  blocking agents.
- Consider postponing TNF- $\alpha$  antagonist therapy until the conclusion of treatment for LTBI or TB disease.”

Source: CDC.<sup>24</sup>

### *Spain*

The Spanish Health Authorities and the Spanish Society of Rheumatology issued recommendations for management of TB risk in Rheumatoid Arthritis patients undergoing treatment with TNF- $\alpha$  antagonist.<sup>19</sup> Treatment with nine months of isoniazid is advised for any patients fulfilling the following criteria:

- “History of untreated or partially treated TB, or exposure to an active case of TB
- Chest radiograph showing residual changes indicative of prior TB infection
- Reaction of >5mm in diameter on PPD skin testing or on 2 step testing procedure (when initial PPD result is < 5mm in diameter), with interval of 7-10 days between steps.”<sup>19</sup>

### *France*

A cooperative group including specialists from the disciplines of infectious diseases, pneumology, gastroenterology, and rheumatology proposed guidelines for the diagnosis and treatment of latent and active tuberculosis in patients with rheumatoid arthritis treated with TNF- $\alpha$  antagonist: these guidelines were validated by the French agency for healthcare product safety.<sup>26</sup> Latent TB infection and patients at risk are defined by the following criteria:

- TB treated before 1970, including at least 2 months rifampicin/pyrazinamide, or not treated for at least 6 months.
- Weal larger than 10mm or in response to intradermal tuberculin test done more than 10 years since BCG vaccination, with no history of correct treatment for active TB.
- Residual radiographic tuberculous lesions over 1cm<sup>2</sup> in size with no certainty that eradicated treatment was received.

Chemoprophylaxis (to be commenced at least 3 weeks prior to commencing TNF- $\alpha$  antagonist) is advised for patients who fulfil these criteria. Three regimens are proposed: rifampicin and pyrazinamide for 2 months; rifampicin and isoniazid for 3 months; or isoniazid alone for 9 months. Treatment with rifampicin and pyrazinamide is suggested on the grounds of control of resistant organisms, especially in Asian and African immigrants. Gastric aspiration is advised in cases where LTBI is suspected, and curative treatment should be administered if *Mycobacterium tuberculosis* organisms are identified. Curative treatment including rifampicin, pyrazinamide, isoniazid and ethambutol is advised as indicated, and resumption of TNF- $\alpha$  antagonist is generally not advised. However, if the clinical benefit from resumption of TNF- $\alpha$  antagonist is anticipated to be large, it should be commenced no sooner than 2 months after discontinuation of curative treatment, ensuring that there is no clinical, radiological or microbiological evidence of residual disease.

### *United Kingdom*

The British Thoracic Society Standards of Care Committee recently published guidelines for assessing risk and managing *Mycobacterium tuberculosis* infection and disease in patients due to start anti-TNF- $\alpha$  treatment.<sup>27</sup> While the guidance is based on published evidence, most of the recommendations are informed by non-analytical studies or expert opinion, or by extrapolated evidence from lower quality cohort or case-control studies. Assessment for clinically active TB disease and LTBI prior to TNF- $\alpha$  antagonist treatment is advised. Curative treatment is advised for patients diagnosed with clinically active TB disease. It is recommended that patients with abnormal chest X-rays, but with previously adequate treatment, initiate TNF- $\alpha$  antagonist treatment as indicated with close follow up. Treatment for LTBI is advised for patients with abnormal chest X-rays who have not previously had adequate treatment, but for whom clinically active TB disease is excluded. The guidance for patients without clinically active TB disease, and with normal chest X-rays highlights the possible unreliability of tuberculin skin testing in this patient group.<sup>28</sup> For patients who have not been previously treated with immunosuppressive therapy, it is recommended that they undergo tuberculin skin testing to assess for LTBI. However, the authors determine that patients who are on immunosuppressive therapy are not assessable by tuberculin skin test and recommend an individual risk-benefit assessment instead: if the risk of developing clinically active TB disease is greater than the risk from LTBI treatment, then patients should initiate anti-tuberculous treatment in advance of commencing TNF- $\alpha$  antagonists; if the risk from LTBI

treatment is greater, then TNF- $\alpha$  antagonist treatment should be commenced, and the patients should be followed closely for the development of clinically active TB disease. To undertake this risk-benefit assessment, risk of developing clinically active TB disease from TNF- $\alpha$  antagonist treatment is estimated by multiplying by a factor of 5 the annual risk of TB disease based on age, place of birth, duration of residence in England and Wales and ethnicity (ranging from 3/100,000 to 593/100,000). The risk of hepatitis from treatment of LTBI is estimated at 278/100,000 with isoniazid alone for 6 months and 1,766/100,000 with rifampicin/isoniazid combination for 3 months.

The British Society for Rheumatology issued guidelines for prescribing TNF- $\alpha$  antagonists in adults with rheumatoid arthritis in 2001, which were updated in 2005, and include advice on managing the risk of tuberculosis.<sup>29</sup> They recommend that all patients to be treated with these agents be screened in line with guidelines from the British Thoracic Society on managing TB infection in patients due to start TNF- $\alpha$  antagonist. The British Society for Rheumatology makes similar recommendations in their guidelines for TNF- $\alpha$  antagonist therapy in patients with psoriatic arthritis.<sup>30</sup>

#### *Other opinions*

In an editorial on the issue, Keane makes a number of suggestions on the approach to managing the risk of TB in patients to be treated with TNF- $\alpha$  antagonist.<sup>23</sup>

- TNF- $\alpha$  antagonist should not be used until active TB has been excluded or completely treated.
- Patients should be tested for LTBI.
- LTBI should be diagnosed if a tuberculin skin test is positive and the chest radiograph is normal.
- A patient with a negative tuberculin skin test should be considered with suspicion, because, in this patient group, it may be a result of immunosuppressant conditions or therapy.
- Childhood BCG should be ignored in interpretation of LTBI screening.
- Treatment with TNF- $\alpha$  antagonist should be delayed until LTBI treatment is completed.
- Treatment of LTBI with isoniazid, even in low prevalence countries, should be strongly considered.

#### *Issues arising from review of guidelines*

Internationally, a number of individuals and professional organisations have issued advice around management of the risk of TB associated with TNF- $\alpha$  antagonist therapy. While this is evidence that the issue is considered a priority, it is also apparent that “one-size does not fit all”, in that there are differences in opinion on how the problem should best be approached. The evidence-base for recommendation is weak, and there can be differences of opinion in how it should best be interpreted. The risk of TB associated with treatment may also vary between countries, on account of differences in LTBI prevalence, TB incidence, policy and practice around BCG use, and local issues around TB such as the occurrence of drug resistance. There is consensus that, in patients to undergo treatment, active TB is excluded. While there is agreement that patients should be screened for LTBI, the interpretation of tuberculin skin testing in this setting is disputed, and complicated by the issues of BCG vaccination and immunosuppressant conditions and therapy. Patients with LTBI

should be treated, but the priority given to various regimens varies and there is recognition of the need to balance potential harms and benefits. Finally, the optimum timing of commencement of TNF- $\alpha$  antagonists after initiation of anti-tuberculous treatment remains undetermined.

While it is impossible to test the effectiveness of recommendations in this area using the gold standard of a randomized controlled trial, evaluation of the impact of guidelines on the incidence of TB disease in patients treated with TNF- $\alpha$  antagonists can be useful in providing direction. To this end, the Spanish group responsible for the BIOBADASER registry have undertaken an uncontrolled before and after study of the impact of their national guidelines on the rate of reports of TB among patients treated with TNF- $\alpha$  antagonists.<sup>31</sup> Following the publications of national guidelines,<sup>19</sup> the incidence of active TB in patients with rheumatoid arthritis treated with TNF- $\alpha$  antagonists fell by 74%. No serious side-effects were reported amongst those patients treated with isoniazid. While these results are useful, the methodology does not take into account other factors which may have resulted in a reduction in the incidence of TB in this group such as secular trends, reporting practices, patient selection practices and other aspects of clinical care outside the guidelines. The findings may not be generalised to other countries with lower rates of TB and different practices regarding BCG.

## **7. Situation in Ireland**

Infliximab, Etanercept and Adalimumab are all authorized for use in Ireland. In the last 5 years, the Irish Medicines Board have received a small number of reports of suspected cases of TB associated with TNF- $\alpha$  antagonists.<sup>32</sup>

## 8. Recommendations

TNF- $\alpha$  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 increased 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- $\alpha$  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- $\alpha$  antagonists in an Irish setting:

1. Prior to commencing TNF- $\alpha$  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, immuno-competence etc), physical examination, chest radiograph and Mantoux test.
  - 2.1. Interferon- $\gamma$  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- $\alpha$  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- $\alpha$  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- $\alpha$  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- $\alpha$  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- $\alpha$  antagonist treatment and discussion of individual preferences.
  - 6.1. Initiation of TNF- $\alpha$  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- $\alpha$  antagonists in the setting of clinically active TB disease requires particularly careful assessment; where possible, it is recommended that TNF- $\alpha$  antagonists be postponed until curative treatment has been satisfactorily completed; in some cases, clinicians and patients may prefer to avoid TNF- $\alpha$  antagonists completely in this scenario.
  - 6.3. The risk associated with commencement or re-commencement of TNF- $\alpha$  antagonists in the setting of LTBI also requires careful assessment; again, where possible, it is recommended that TNF- $\alpha$  antagonists be postponed until LTBI treatment has been satisfactorily completed. However, clinicians and patients may, on balancing risks and benefits, prefer to initiate TNF- $\alpha$  antagonists during treatment for LTBI; while no specific duration of LTBI treatment prior to initiation of TNF- $\alpha$  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- $\alpha$  antagonists.
7. Clinically active TB disease may still arise in patients treated with TNF- $\alpha$  antagonists despite a negative initial assessment or LTBI treatment. Therefore, it is recommended that with a high index of clinical suspicion for development of TB is exercised in the setting of any clinical deterioration while patients are undergoing TNF- $\alpha$  blockade.
8. Cooperation between clinicians initiating TNF- $\alpha$  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- $\alpha$  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- $\alpha$  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 included in Appendix 1.

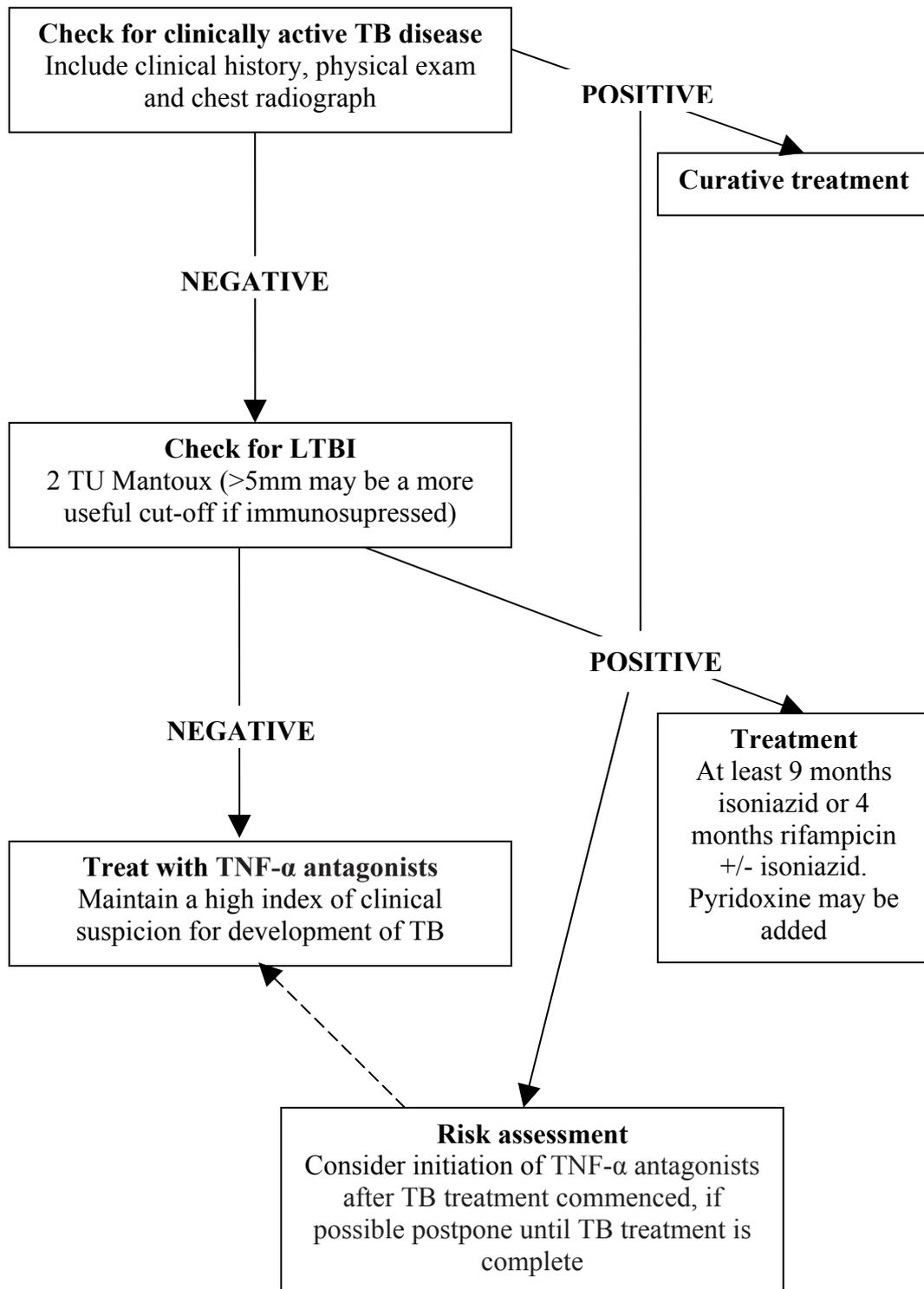
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**Appendix 1: Algorithm for TB assessment prior to TNF- $\alpha$  of antagonists**



## **Appendix 2: Response to consultation**

In December 2005, the National TB Advisory Committee at the Health Protection Surveillance Centre circulated this report for consultation to key stakeholders.

In total, seven responses were received to this document.

Two responses agreed with the conclusions and recommendations of the document.

Two responses concerned Mantoux screening prior to initiation of these agents: one expressed a preference for the use of 10TU tuberculin; one expressed preference for a 5mm cut-off. The preferences expressed in both these responses concern the possibility for reduced sensitivity of the 2TU/10mm cut-off screening test arising from the potential for anergy associated with the chronic disease states and immunosuppressive treatments prevalent in the population in which tumour necrosis factor- $\alpha$  antagonists may be used.

One response highlighted the potential harm that may arise from delaying commencement of tumour necrosis factor- $\alpha$  antagonists wherein LTBI is suspected; however the evidence base for formulation of recommendation on optimal time to commencement of tumour necrosis factor- $\alpha$  antagonists wherein LTBI is suspected is poor. The same response also highlighted the potential for variation in the risk of TB between tumour necrosis factor- $\alpha$  antagonists; however it would be difficult to interpret the evidence base on this subject as robust enough to inform commercially sensitive recommendation and, moreover, agent-specific recommendations did not emerge from review of international guidelines in this area.

One response advised greater specification of factors that might be reviewed as part of an individual patients LTBI risk assessment.

Two responses received from consultant rheumatologists advised a tripartite meeting between the National TB Advisory Committee members, authors of Irish Society for Rheumatology guidelines on the use of tumour necrosis factor- $\alpha$  antagonists in Ireland, and Dr Joe Keane to agree a joint position.

Finally, the Irish Medicines Board (IMB) provided some helpful corrections and technical amendments to the document. It is suggested that the document recommend reporting of tumour necrosis factor- $\alpha$  antagonists associated adverse reactions to the IMB. Consideration could also be given to surveillance needs from a health protection perspective.

A workshop was held on 3<sup>rd</sup> of May 2007 by teleconference with members of the LTBI Subcommittee of the National TB Advisory Committee, representatives of the Irish Society for Rheumatology (including authors of their guidelines) and Dr Joe Keane to review and agree the final recommendations.