TUMOR NECROSIS FACTOR-ALPHA (TNF-ALPHA) ANTAGONISTS AND THE INCREASED RISK OF TUBERCULOSIS

What is tumor necrosis factor-alpha (TNF-alpha)?

- A potent cytokine that is an important mediator of the body's response to infection
- Promotes inflammation and tissue destruction in rheumatic/immune mediated diseases
- Plays a central role in the initial host response to infection and granuloma formation

What are TNF-alpha antagonists?

- Medications that work to oppose the tissue's destructive effects of TNF-alpha
- They are used to treat diseases such as rheumatoid arthritis, Crohn's disease, psoriatic arthritis, juvenile rheumatoid arthritis and ankylosing spondylitis.
- TNF-alpha antagonists often provide an impressive improvement (in treated diseases).

Which TNF-alpha antagonists are used in the U.S.?

Drug	Indications
infliximab (Remicade®)	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's Disease, ulcerative colitis
adalimumab (Humira®)	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's Disease
certolizumab pegol (Cimzia®)	Rheumatoid arthritis, Crohn's Disease
etanercept (Enbrel®)	Rheumatoid arthritis, psoriatic arthritis, psoriasis, sarcoidosis
golimumab (Simponi®)	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis

Why do they increase the risk of TB?

- Granuloma formation is crucial to the host's ability to contain and control TB infection.
- In tuberculosis, these drugs inhibit macrophage activation, recruitment of inflammatory cells, granuloma formation, and maintenance of the granuloma integrity.
- Antibodies against TNF-alpha cause increased susceptibility to M. tuberculosis in mouse models. Patients treated with TNF–alpha antagonists have an increased risk of tuberculosis.

Epidemiological data indicate that the risk of active TB is greatest with Infliximab

- **TB rates of 53.8/100,000 with Infliximab and 28.3/100,000 with Etanercept vs. US rate of 5/100,000 (Wallis, et al. Clin Inf Dis 2004; 39: 1254-56).**
- **Possible increased risk of reactivation of latent tuberculosis infection (LTBI) with Infliximab than Entercept (Wolfe, Arthritis and Rheumatism 2004; 50: 372-379).**
- **Risk of new infections progressing directly to active disease appears to be similar for both drugs. (Wallis, The Lancet 2008; 8: 601-611).**

What can be done to decrease the risk of TB when using these agents?

- Carefully screen all candidates prior to prescribing TNF-alpha antagonists
  - Identify risk factors for TB exposure
  - Screen for evidence of LTBI, and exclude active TB
- Educate patients about the risk of opportunistic infections, especially TB
- Instruct patients to report symptoms of an infectious disease:
  - Fever, malaise, cough, local or generalized pain
- Consult a physician knowledgeable about the risk of infections in patients receiving these and other immunosuppression regimens.
- Be aware that the onset of TB may be subtle, but disease can escalate and disseminate quickly.
  - A routine chest radiograph may appear normal; miliary infiltrates may only be visible on chest CT.

What does CDC recommend before starting?

- **Screen for TB risk factors**
- **Test for LTBI and TB disease**
- **Treat LTBI and TB disease according to published guidelines**
- **Treat those with TB risk factors for LTBI even if TST or IGRA negative**

Revised December 2011

TUMOR NECROSIS FACTOR-ALPHA (TNF-ALPHA) ANTAGONISTS AND THE INCREASED RISK OF TUBERCULOSIS *CONTINUED*

What additional recommendations are there?

- An interferon gamma release assay (IGRA) QuantiFEROn-Gold Intube or the TSpot TB can be used to screen perspective TNF-alpha antagonist recipients.
  - See MMWR 2010: 59 (RR-5); 1-25 for guidelines
- Two step TST testing at baseline has not been specifically recommended by CDC; although recent case reports and post-licensure surveillance in Spain note improved accuracy (Gomez-Reino (2007) Arthritis and Rheumatism 57(5):576-761).
- Repeat testing periodically for TB infection even if TST or IGRA is initially negative.
- Starting TNF-alpha antagonist therapy may improve immune response.
- Some patients may acquire tuberculosis infection after TNF-alpha therapy is initiated (Fuchs, Clin Rheum 2008).

When can TNF-alpha antagonists be started after a diagnosis of latent TB infection?

- Treatment for LTBI (e.g. Isoniazid for nine months) should start BEFORE TNF-alpha antagonist treatment is initiated.
- CDC recommends considering postponing TNF-alpha antagonist treatment until completion of LTBI treatment (MMWR 2004: 53 (RR-30)).
- More recent publications suggest delaying TNF-alpha antagonist treatment until one month after the start of LTBI treatment (Furst, Annals of the Rheumatic Diseases, 66 (Suppl 3): ii2-22).

What if a patient who is on one of these agents develops signs or symptoms of an infectious disease?

- Evaluate thoroughly for both routine and opportunistic infectious disease processes.
  - If a plain radiograph is normal in a patient with cough, shortness of breath or unexplained fever, a chest CT should be strongly considered.
  - Collect sputum for mycobacterial smear and culture as well as for other opportunistic pathogens including fungi.
- Stop the TNF-alpha antagonist therapy until a diagnosis is made.
  - Most TB experts prefer that TB be treated until it is under control, cultures are negative, and patients are tolerating their TB medicines prior to reintroducing the TNF-alpha antagonist.

This publication was supported by the Cooperative Agreement Number U52PS004087-01 from the Centers for Disease Control and Prevention. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention.

What is the typical course of TB in patients taking these agents?

- TB progresses rapidly in TNF-alpha antagonist recipients.
  - Median duration of onset was 12 weeks after initiating TNF-alpha antagonist treatment in the initial 57 patients reported.
  - TB is much more likely to be extrapulmonary and disseminated.
  - In the initial 70 reports to the FDA Adverse Reporting System, 56% of the TB cases were extrapulmonary and 24% were disseminated disease (Keane, NEJM 345 (15) 1098).
  - For patients not receiving TNF-alpha antagonists extrapulmonary is reported in only 15-20% and disseminated in 1-2% of TB cases reported annually (CDC Surveillance Reports 2009).
- TB is more likely to result in death.
  - 12/17patients (70%) died (Keane).
    - <5% of TB cases reportedly annually are diagnosed at death or died during treatment (CDC Surveillance Reports 2009).

Are there concerns other than the risk of TB?

- Yes, other opportunistic infections have also been reported including viral, bacterial, fungal and protozoal infection.
- The increased risk of fungal infections seems to be of extra concern.
- Immune Reconstitution Inflammatory Syndrome (IRIS) reactions may occur with improvement in immune function when the TNF-alpha antagonist is stopped and TB therapy started.
  - IRIS reactions may be especially severe.
  - IRIS reaction may improve with reinstitution of the TNF-alpha antagonist (Wallis, CID 2009, 48:1429), steroid, or anti-inflammatory agents.

How should patients taking these agents be monitored?

- All TNF-alpha antagonist recipients should be monitored carefully for any signs or symptoms of infectious disease.
- Pursue TB diagnosis as the potential cause of any febrile or respiratory illness (CDC 2005).

HEARTLAND
NATIONAL TB CENTER
A PARTNERSHIP OF UT HEALTH NORTHEAST AND TCID

Produced by Heartland National TB Center. Consultation to healthcare providers at 1-800-TEX-LUNG, www.HeartlandNTBC.org
This product produced with funds awarded by the Centers for Disease Control & Prevention (CDC).