#### 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?

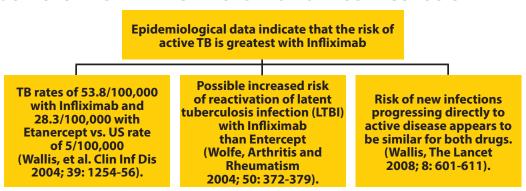
- Medications that work to oppose the tissue's destructive effects of TNF-alpha
- They are used to treat diseases such as rheumatoid arthritis, Crohn's disease, psoriatic arthritis, juvenile rheumatoid arthritis and ankylosing spondylitis.
- TNF-alpha antagonists often provide an impressive improvement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

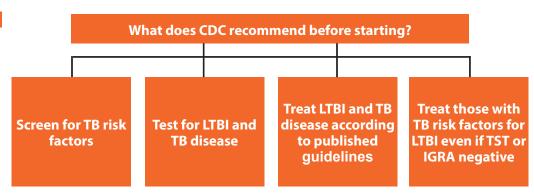
#### Why do they increase the risk of TB?

- 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.



#### 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.



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#### 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.

#### 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).

