Rheumatoid arthritis

- 1% of US population
- Substantial disability
  - 50% lost work in 10 years
- Premature mortality by 5-10 years.
Summary of FDA-imposed Boxed Warnings about Infections with TNF Antagonists

- Increased risk of serious infections that may lead to hospitalization or death
- Increased risk of active TB or reactivation
- Risk of invasive fungal infections
  - (including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis)
- Risk of bacterial and viral infection with opportunistic pathogens

Clin Ther 2011 Jun
**Therapies that Increase the Risk of TB Progression**

<table>
<thead>
<tr>
<th>Antibodies</th>
<th>Trade Name</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>etanercept</td>
<td>Anti TNF receptor</td>
<td>Enbrel®</td>
</tr>
<tr>
<td>Infliximab</td>
<td>TNF-α inhibitor</td>
<td>Remicade®</td>
</tr>
<tr>
<td>adalimumab</td>
<td>TNF-α inhibitor</td>
<td>Humira®</td>
</tr>
<tr>
<td>certolizumab</td>
<td>TNF-α inhibitor</td>
<td>Cimzia®</td>
</tr>
<tr>
<td>golimumab</td>
<td>TNF-α inhibitor</td>
<td>Simponi®</td>
</tr>
<tr>
<td>abatacept</td>
<td>Anti-CTLA4</td>
<td>Orecnia®</td>
</tr>
<tr>
<td>tocilizumab</td>
<td>Anti-IL-6</td>
<td>Actmera®</td>
</tr>
<tr>
<td>Leflunamide</td>
<td>steroid</td>
<td></td>
</tr>
</tbody>
</table>

**Therapies that Potentially Increase the Risk of TB Progression**

<table>
<thead>
<tr>
<th>Antibodies</th>
<th>Trade Name</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>anakinra</td>
<td>Anti-IL1</td>
<td>Kineret®</td>
</tr>
<tr>
<td>Methotrexate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cyclosporine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Extracellular molecular targets in rheumatoid arthritis (RA)

*Image: A diagram illustrating extracellular molecular targets in rheumatoid arthritis (RA).*

*Image: A child with rheumatoid arthritis (RA) using a walker.*
FDA Approved Indication for Anti-TNF Therapy

- Rheumatoid arthritis
- Psoriatic arthritis
- Psoriasis
- Juvenile idiopathic arthritis
- Ankylosing spondylitis
- Ulcerative colitis
- Chron's disease

Worldwide Best Selling Drugs 2010

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brands</th>
<th>Indications</th>
<th>$ billion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Lipitor</td>
<td>Cholesterol</td>
<td>11.8</td>
</tr>
<tr>
<td>Clopidrogel</td>
<td>Plavix</td>
<td>Atherosclerosis</td>
<td>9.4</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Remicade</td>
<td>Rheumatoid, etc.</td>
<td>8.0</td>
</tr>
<tr>
<td>Flut/Salmeterol</td>
<td>Advair</td>
<td>Asthma, COPD</td>
<td>7.96</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Enbrel</td>
<td>Rheumatoid, etc</td>
<td>7.4</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Avastin</td>
<td>Cancer</td>
<td>6.8</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Abilify</td>
<td>Depression, Bipolar</td>
<td>6.8</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Rituxan</td>
<td>NHL, CLL, RA</td>
<td>6.7</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Humira</td>
<td>Rheumatoid, etc</td>
<td>6.5</td>
</tr>
</tbody>
</table>
Radiography of right elbow shows extensive osteolytic bony lesions.

Arthroscopic view of elbow joint; severe inflammatory changes in hypertrophic synovium observed.

Histologic exam of synovial tissue; inflammation w/ granuloma composed of epitheloid and giant cells.

**Neuromeningeal TB**

Tuberculosis Associated with Infliximab, A Tumor Necrosis Factor α-Neutralizing Agent

- FDA approved infliximab in 1998
- All reports of TB after infliximab as of May 29, 2001
- 70 reported cases of TB for a median of 12 weeks
- Majority or 36% had extrapulmonary TB
- 24% had disseminated disease
  - Forms of TB that are associated with marked immunosuppression

**Conclusions**

- Active TB may develop soon after the initiation of treatment with infliximab. Before prescribing the drug, physicians should screen patients for latent TB infection.
Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR) BMJ 2009

**Characteristics of Tuberculosis Related to TNF Antagonist Therapies**

- Reactivation rather than new cases of TB
- Risk for TB is 1.6–25 times depending on the clinical settings
  - 4x in the US
  - Greater in endemic area
- Occur in close proximity to treatment initiation
- Reactivation of latent infection shows rapid progression

*Eur Respir J 2010, 36: 1185*
Lesson

Monoclonal antibody has higher incidence of TB compare to receptor antagonist (Etanercept)

---

Risk of tuberculosis is higher with anti-tumor necrosis factor monoclone antibody therapy than with soluble tumor necrosis factor receptor therapy: The three-year prospective French research axed on tolerance of biotherapies registry.

---

Risk of active tuberculosis in different studies in patients suffering from rheumatic diseases treated with TNF antagonists

<table>
<thead>
<tr>
<th>Country</th>
<th>Adalimumab</th>
<th>Infliximab</th>
<th>Etanercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>56/100,000</td>
<td>38/100,000</td>
<td>37/100,000</td>
</tr>
<tr>
<td>Spain</td>
<td>176</td>
<td>183</td>
<td>114</td>
</tr>
<tr>
<td>France</td>
<td>235</td>
<td>187</td>
<td>9</td>
</tr>
<tr>
<td>Canada</td>
<td>RR 1.6</td>
<td>RR 1.2</td>
<td></td>
</tr>
<tr>
<td>Portugal</td>
<td>4/575 patient</td>
<td>8/456 patient</td>
<td>17/83 patient</td>
</tr>
</tbody>
</table>

Eur Respir J 2010
TNF has a central role in the initial host response to infection

- In TB, TNF results in macrophage activation, formation and maintenance of granuloma
- Mice lacking the gene for TNF or TNFR1, or treated with an anti-TNF, fail to contain the infection after challenge with M. tuberculosis
- Treatment of chronically TB-infected mice with an anti-TNF resulted in:
  - Ten-fold increased bacillary load,
  - Compromised granuloma structure, and
  - Shortened survival

How tumor necrosis factor blockers interfere with tuberculosis immunity

- TNF-blockers have been shown to diminish interferon (IFN)-γ effects; stimulate apoptosis of key immune cells
  - Including monocytes, CD4+ T helper cells and M. tb reactive CD8+ T cells
- Anti-TNF therapy increased regulatory T cell (Treg) function, which has been linked with susceptibility to TB

References:
Lancet Infect Dis 2008
Clinical and Experimental Immunology 2010
Clinical and Experimental Immunology, 161: 1–9
Clinical Infectious Diseases 2005; 41:S199–203
WHAT DO WE DO TO PREVENT TB INFECTION IN PATIENT BEFORE ANTI-TNF TREATMENT?

Preventive Measures

- All persons initiating anti-TNF should be screened for latent tuberculosis infection using tuberculin skin test or interferon-gamma release assay
  - Periodically during therapy
  - FDA labeling
- Package inserts recommend TST before initiating TNFi
  - etanercept, infliximab, adalimumab, certolizumab, golimumab, abatacept, tocilizumab or ustekinumab

Tuberculosis infection in rheumatic patients with infliximab therapy: experience with 157 patients

- Done in Fortaleza (Brazil), a region where tuberculosis is endemic 58 cases/100,000
- The cutoff for a + skin test was >5 mm
- 157 patients: 13.4% were diagnosed with LTBI, and 3 patients developed active TB

Conclusion: Risk of TB is 21 times compare to general population
**LESSON**

PPD is not reliable for diagnosis because of attenuated response to PPD in patient with rheumatoid arthritis.

---

**Tuberculin Skin Testing vs. Interferon Gamma Receptor Assay (IGRA)**

- Skin test has a low sensitivity in patients with rheumatoid arthritis
- >50% of the IGRA positive patients are actually missed by the skin test

**Recommendations:** favor the use of IGRA over tuberculin skin in the treatment with anti-TNF
  - Most apparent in immunocompromised individuals

---

**Summary of Tuberculin Skin Testing and Tuberculosis History in a Subset of Patients treated with Infliximab**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST performed</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>47</td>
</tr>
<tr>
<td>Negative result</td>
<td>34</td>
</tr>
<tr>
<td>Positive result</td>
<td>12</td>
</tr>
<tr>
<td>Unknown result</td>
<td>1</td>
</tr>
<tr>
<td>No</td>
<td>6</td>
</tr>
</tbody>
</table>

Ann Intern Med. 2007

---

**WHAT IS THE ROLE OF CHEST X-RAY?**

(American College of Rheumatology Guidelines 2012)

- CXR is indicated when there is a + TST or IGRA
  - Negative – treat for LTBI
- If positive CXR, follow up w/sputum exam
  - Sputum positive – treat for active TB
  - Sputum negative – treat for LTBI
Can Patients With a Past History of Treated Latent or Active TB Infection Receive TNF Inhibitors?

- **YES**
- However, previously treated patients can be re-infected
- *Should be monitored for potential re-infection, especially when exposure risk is present (e.g., those residing in endemic areas)*

In Patient with LTBI: When To Start TNF Inhibitor Therapy After Isoniazid Initiation?
Recommendation: 2012 ACR Guidelines

- Pretreatment screening lower the risk of TB disease by 85%
- INH had to be given before the first dose of the anti-TNF drug
- A delay of 4 weeks is advocated to ensure the initial safety of INH

Are patients with a history of TB, at increased risk for TB reactivation when they receive TNF antagonist therapies?

- Patients who have completed appropriate TB therapy do not appear to have an increased risk of TB when TNF antagonist therapy is started
Preventive Chemotherapy

- Type and duration of preventive therapy for persons treated with TNF antagonists
  - No clinical trial
- Recommended preventive chemotherapy – as per TB specialist

What is the optimal duration of anti-TB chemotherapy for patients who developed TB in relation to TNF antagonist therapies?

- There is no evidence that the duration of anti-TB treatment needs to be prolonged
- Could be dramatically reduced by 9 months isoniazid preventive therapy

Risk of tuberculosis in patients treated with TNF antagonists due to incomplete prevention of reactivation of latent infection

- Spanish Society of Rheumatology
- Rate 172 per 100,000
- 7 times higher when recommendations were not followed
- Success rate: isoniazid preventive therapy is 80%
**Worldwide Best Selling Drugs 2010**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brands</th>
<th>Indications</th>
<th>$ billion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Lipitor</td>
<td>Cholesterol</td>
<td>11.8</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Plavix</td>
<td>Atherosclerosis</td>
<td>9.4</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Remicade</td>
<td>RA, etc</td>
<td>8.0</td>
</tr>
<tr>
<td>Flut/Salmetrol</td>
<td>Advair</td>
<td>Asthma, COPD</td>
<td>7.96</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Enbrel</td>
<td>RA etc</td>
<td>7.4</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Avastin</td>
<td>Cancer</td>
<td>6.8</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Abilify</td>
<td>Depression, Bipolar</td>
<td>6.8</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Rituxan</td>
<td>NHL, CLL, RA</td>
<td>6.7</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Humira</td>
<td>RA etc</td>
<td>6.5</td>
</tr>
</tbody>
</table>

---

**INT J TUBERC LUNG DIS 2008**

The Union estimating the market for tuberculosis drugs in industrialized and developing nations
N. R. Schwalbe,** Global Alliance for TB Drug Development, NY

- TB is 2nd only to HIV as the leading infectious killer of adults worldwide
- 1/3 of the world’s population is infected, and TB killed ~1.6 million people worldwide in 2005

RESULTS: global market for first-line TB drugs; final ranges were US$261–316 million
THANK YOU