TB - TNF Blockers

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One of the most exciting advances in the therapy of RA was the demonstration of clinical efficacy of a monoclonal anti-TNF antibody. Proof of concept was obtained by administration of the mouse-human chimeric monoclonal antibody cA2 (now known as infliximab) to patients with RA resulting in rapid and impressive improvement in pain, swelling, and general sense of well-being.
What is TNF

- Tumor necrosis factor-alpha is one of the most important cytokines involved in inflammatory response through its entanglement in the cascade of inflammatory reactions. TNF blockers bind to tumor necrosis factor-alpha, rendering it inactive, and interfering with inflammatory activity, ultimately decreasing inflammatory damage
History

- Inhibitors of tumor necrosis factor-alpha (TNF-alpha) represent important treatment advances in a number of inflammatory conditions, including rheumatoid arthritis, the seronegative spondyloarthropathies, and inflammatory bowel disease and inflammatory skin conditions.
Advantage

• TNF-alpha inhibitors offer a targeted strategy that contrasts with the nonspecific immunosuppressive agents traditionally used to treat most inflammatory diseases.
• The mechanism of action of these antibodies is only beginning to be understood. It is likely to be multifactorial since TNF is involved in a number of processes
Advantages

• They work in the majority of patients with RA (for example)

• Onset in general much faster than agents such as Methotrexate

• They can be combined with other agents
Examples

- **Etanercept (Enbrel)** A soluble p75 TNF-alpha receptor fusion protein
- **Infliximab (Remicade)** A chimeric (mouse/human) anti-TNF-alpha antibody
- **Adalimumab (Humira)** A fully human monoclonal anti-TNF-alpha antibody
- **Certolizumab pegol (Cimzia)** An antigen-binding fragment (Fab') of a humanized monoclonal antibody coupled to polyethylene glycol
- **Golimumab (Simponi)** A human anti-TNF-alpha monoclonal antibody
Availability

- Entanercept or Enbrel was the first agent available 1998
- Infliximab or Remicade became available 1999
- Adalimumab or Humira came to market 2002
Adverse effects of targeted TNF-alpha inhibition

- Mycobacterial infection, particularly tuberculosis
- Other infections (bacterial, viral, and fungal)
- Injection site reactions
- Infusion reactions
- Induction autoimmunity
- Demyelinating disease
- Heart failure
- Malignancy
- Skin conditions
Therapeutic differences

- **Infliximab** and **adalimumab** both have a broader clinical spectrum of activity than **etanercept**. The former medications are effective in many cases of IBD and sarcoidosis as well as RA, psoriatic arthritis, and the seronegative spondyloarthropathies. In contrast, etanercept does not appear to be effective in IBD or in sarcoidosis.
• **RISK OF TB** Tumor necrosis factor-alpha (TNF-alpha) inhibitors increase the risk of reactivation of latent TB infection.

• This risk is greater for the anti-TNF antibodies **infliximab** and **adalimumab** than for **etanercept**
The importance of tumor necrosis factor-alpha (TNF-alpha) in protection against mycobacterial infections, has been studied in animal models.

Mycobacteria are not killed readily by host defense mechanisms, but instead are sequestered within granulomas, which are comprised of a central core of macrophages, multinucleated giant cells, and necrotic debris surrounded by macrophages and lymphocytes.
TNF and granuloma

- TNF-alpha is required for the orderly recruitment of these cells and for continued maintenance of the granuloma structure
TB manifestations

• TB occurring in association with TNF-alpha inhibitors has a higher likelihood of involving extrapulmonary sites and of being disseminated at presentation compared with other TB cases.
• B,H is a 27 year old male with long standing history of IBD
• Symptoms first began 2 to 3 years earlier when he experienced diarrhea and rectal bleeding
• Colonoscopy revealed proctitis up to 10 cm
• Treated with 5-ASA enemas with good initial response but then relapsed
• One year later a second colonoscopy performed most of colon now involved with superficial ulcers and granular mucosa.
• Transverse distal and ascending colon relatively spared TI spared R colon biopsy chronic active colitis with cryptitis but no granulomas
• Diagnosed with patchy colitis most c/w Crohn’s treated with po 5-ASA
Patient continued to have diarrhea and rectal bleeding despite Asacol at therapeutic doses.

Saw a second GI specialist and started on Entocort 9 mg daily.

No improvement prompted a third colonoscopy (20 months).

This revealed a continuous colitis from dentate line to splenic flexure with miniature ulcerations, granularity, edema, and erythema ending abruptly at the splenic flexure.

Biopsy revealed chronic colitis severe with cryptitis.
B,H

- Patient begun on prednisone 40 with a nice response but with taper relapsed
- Imuran begun but did not tolerate secondary to abdominal symptoms
- Remicade (Infliximab) begun after a nI CXR obtained but no PPD as he was born in India and clinical impression was PPD would be positive as he had BCG
- After third dose of Remicade he experienced fever, night sweats, chills fatigue and a 30 lb weight loss
The Diagnosis

- Admitted to an OSH and had bronchoscopy, VATS, PPD and sputum collection
Therapy

- Patient initially started on an expanded regimen of 6 drugs and there was early worsening of CXR and he developed additional R supraclavicular adenopathy
Subsequent Course

- All specimens save for stool and urine grew including multiple sputums, as he was pan sensitive reduced to 4 drugs only
Errors

- Significance of BCG immunization
- Should he have been placed on INH regardless of PPD (he had been on steroids)
- This case predates the IGRAs but was within the time frame that we knew the TNF blockers associated with increased risk of TB
77 year old Trinidadian female with long standing history of RA and severe sideroblastic anemia

RA history sero negative and a long standing history R hip pain. Aspiration with neg culture and patient switched from MTX Arava to Remicade Arava

Patient first presented to ER OH with systemic symptoms sent home with antibiotics for CAP about three month after Remicade begun

Patient found down in her home with slurred speech

When brought to ER at yet another hospital patient stated she had been in her USOH until 3 weeks earlier when she experienced fatigue NS chills and cough
Hospital Course

- Admitted treated with Levofloxacin for CAP (LLL)
- Subsequent course ruled in for MI, flash pulmonary edema
- Continued to have high spiking fevers CT revealed multiple small nodules
- Patient required intubation
- Sputum positive for AFB
- Started on medication
• Multiple issues related to toxicity.

• History obtained from chart ten years earlier had 6 months of INH

• No additional therapy offered prior to institution of Remicade (Infliximab)
Errors

• Was 6 months sufficient?
• What was the documentation?
• What about the fact that it was ten years ago?
• Had MD in addition to her RA and immunosuppressive therapy?
• 40 year old male born in Guatemala with severe and deforming psoriasis (skin only) dating back more than ten years

• Five years ago started on Enbrel miraculously cured his psoriasis

• 5 years into therapy develops fever cough weight loss
CT
Diagnosis made

- Diagnosis suspected and made by sputum analysis
- Patient with recurrent high spiking fevers on TB meds
- Eventually hospitalized and medication reintroduced one at a time
- Severe febrile reactions to isoniazid
- PS Completed a 9 - 12 month course of meds without INH
Treatment

• Dermatologist unwilling to start back on Humira
• Patient developed severe psoriatic disease entire lower leg arms ears scalp with bleeding and scaling
• Eventually prevailed on dermatologist to restart Humira.
Errors

- High risk for TB infection
- Born in country with fairly high incidence TB
- Most likely reflects reactivation
- Long induction
- ? Reflects patients overall health and lack of co morbidities or other toxic medications
- ? Reflects Enbrel
• Long standing history of RA
• Followed at B and W and in 2007 started on Remicade
• Pretreated with 7 months of Isoniazid
• Developed miliary TB shortly after therapy with Remicade
Hospital Course

- Received IRZE
- Developed renal failure secondary to Rifampin
- Started on Streptomycin
- Developed vestibulopathy secondary to Strep
- Found to be INH resistant
- Complicated course received E/Quinolone and PZA
Given 7 months of INH

Was INH resistance the result of monodrug treatment for disease

Was INH resistance simply bad luck

No history of prior treatment
AERS database
The Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) is a database that was established for post marketing surveillance of adverse drug events.

Using this database from 1998 to 2002, investigators found that among patients in the United States treated with infliximab etanercept, estimated rates of TB were 54 and 28 per 100,000 patients who started therapy during the study period, respectively.

These rates are substantially higher than the overall rates of TB in the United States during the same period (5.2 to 6.8 cases per 100,000)
The Spanish Society of Rheumatology Database on Biologic Products (BIOBADASER), surveillance project, to assess the safety of TNF-alpha inhibitors in patients with rheumatic disease.

Investigators compared the TB infection rate among 1540 patients who had received either infliximab (86 percent) or etanercept to none. 17 cases of TB, all of which were among patients taking infliximab. The calculated incidence of TB cases associated with the use of infliximab 1900 per 100,000 patients in the year 2000 and 1100 per 100,000 patients in 2001. By comparison, the baseline incidence in Spain in 2000 was 21 cases per 100,000 inhabitants. Extrapulmonary disease occurred in 11 of the 17 cases. Six patients developed disseminated or hepatosplenic disease, and five had disease involving the nervous system.
Given the risk of reactivation of latent TB infection (LTBI) in patients receiving TNF-alpha inhibitors, it is crucial to screen all patients for LTBI prior to starting a TNF-alpha inhibitor. Screening is recommended by the United States Centers for Disease Control and Prevention. Patients with evidence of LTBI should initiate LTBI therapy prior to starting a TNF-alpha inhibitor. Appropriate screening includes a full medical history, physical examination, tuberculin skin test (TST) or interferon-gamma release assay (IGRA), and a chest radiograph in those with a positive TST or IGRA or a history or physical exam suggestive of TB. Although routine testing with both TST and IGRA is not recommended, it is reasonable under certain circumstances, which are discussed separately.
Summary

TNF blockers are associated with an increased risk of TB disease often disseminated

With proper screening this should be preventable

Not clear optimum time course prior to initiation of agents

One might think some overlap wise if not preferable

Efficacy of screening was demonstrated in the Spanish registry of BIOBADASER, investigated impact of mandated recommendations implemented in 2002. They noted a 74 percent reduction in TB case rates following the introduction of screening and treatment in patients with rheumatoid arthritis treated with infliximab. However, the remaining risk still appeared to be higher than that of the general population.