Immune Modulating Agents and the Potential Infection Aftermath

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Objectives

- What are DMARD agents?
- What are anti-TNF biologic agents?
- What are potential infectious complications with initiation of these drugs?
- Appropriate pre-screening prior to initiation of these agents
- Take home highlights
DMARD Agents

- **Disease Modifying anti-Rheumatic Drug**
  - Medications aside from steroids that are used to slow disease progression in rheumatoid arthritis and other autoimmune conditions
- **DMARDs include anti-TNF agents**
- **The “others”**
  - Azathioprine
  - Methotrexate
  - Sulfasalazine
  - Cyclosporine
  - Hydroxychloroquine
  - 6-MP
Tumor Necrosis Factor

- TNF, cachexin, cachectin and formerly known as TNFα
- A cytokine that can stimulate acute phase reactions
  - Fever, apoptotic cell death, cachexia, inflammation, production of IL-1 and IL-6
- Due to promotion of the inflammatory response, certain conditions benefit from agents which block this cytokine
  - RA, ankylosing spondylitis, psoriasis, inflammatory bowel disease, hidradenitis
Focus - Biologic Drugs

- Enbrel (etanercept)
- Humira (adalimumab)
- Orencia (abatacept)
- Remicade (infliximab)
- Rituxan (rituximab)
- Cimzia (certolizumab)
- Simponi (golimumab)
- Tysabri (natalizumab)
Boxed Warnings

• Patients treated with _______ are at increased risk for developing serious infections which may lead to hospitalization or death
  ○ “Routine” bacterial and viral infections
  ○ Listeria and Legionella
  ○ Active TB, reactivation of latent TB
  ○ Invasive fungal infections including histoplasmosis, coccidiodomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis
  ○ Hepatitis C

• All patients should be screened for TB prior to the initiation of these agents
Greatest risk?

- Patients on additional DMARDs along with the initiation of their anti-TNF therapies
  - Most patients on combination therapy
- Increased dose-dependent risk with concurrent use of steroids
- In general, most infection complications are seen within the first 6 months of initiating anti-TNF biologics
Sample Case #1

- ER doc: “I’ve got this guy with cellulitis. It’s pretty bad.”
- Mia: (Yawwwwn...looking at clock). Ok, is he sick? Did you get cultures? Has he been given any antibiotics?
- ER doc: “Gave him Vanco and Zosyn. Vitals are stable. Cultures pending. He also has a h/o diabetes. That’s probably why this is bad. Oh and he has some kind of inflammatory bowel disease.”
Most Commonly...

- Complicated bacterial pneumonias and skin/soft tissue infections
- Often polymicrobial, usually require hospitalization, prolonged IV antibiotics
By the numbers...

- 16,000K+ Patients (1998-2007)
  - 10,484 RA, 2323 IBD, 3215 psoriasis/arthropathy
- 1172 ‘serious’ infections identified
  - 53% were either pneumonia or skin/soft tissue
- Patients on infliximab (Remicaid) at greater risk
- HOWEVER – overall conclusion is that anti-TNF agents alone did not predispose patients to greater infection risk.
- Those patients on combined therapies, however, at greater risk overall
Listeria and Legionella?

- **9/7/2011:**
  - FDA issued a new Black Box warning across the entire anti-TNF class
  - 1999-2010 FAERS database search
    - 80 case reports of Legionella pneumonia, 14 deaths
    - 26 case reports of Listeria (sepsis, meningitis, bacteremia, endophthalmitis), 7 deaths
  - Majority of patients were on additional DMARD agents
Herpes Simplex

- Patients with herpes simplex on anti-TNF agents at increased risk for:
  - More frequent outbreaks
  - More severe outbreaks

- Consideration for suppressive antiviral therapies depending on severity and frequency of flares
Shingles

- Patients treated with anti-TNF agents have a substantially increased risk of the incidence of shingles
  - 61% higher than the general population
- ~10x more likely to have a severe infection requiring hospitalization
- Hold anti-TNF agents during acute stages
Vaccination?

- For patients over the age of 50yo intending to begin anti-TNF therapies:
  - Recommendation to give live attenuated Zostavax at least 14 days and preferably 1 month prior to the initiation of therapy
- Low-dose methotrexate, azathioprine, 6-MP
  - Not a contraindication for co-administration of Zostavax
Sample Case #2

- Consult: A 56yo man with a h/o chronic hepatitis C and psoriatic arthritis is being evaluated for appropriate pre-testing prior to the initiation of Enbrel therapy
- What now?
Pre-initiation screening

- Routine TB testing
- Review of Hep C status, check viral load
- Check LFTs/hepatic function panel
  - Patients with LOW viral load and normal LFTs prior to the initiation of therapy appear to be safe to initiate anti-TNF biologics with close monitoring
Co-infection? HIV?

- HIV patients on appropriate HAART with stable CD4 counts and viral loads are safe for consideration of anti-TNF treatments
- HIV/Hep C co-infection – ok to initiate anti-TNF treatments where indicated if HIV/Hep C both well suppressed and patients are closely monitored
Other Viruses?

- Case reports suggesting increased incidence in:
  - Varicella
  - HIV
  - Cytomegalovirus (CMV)
  - Ebstein-Barr virus (EBV)
  - Human Papillomavirus (HPV)
Sample Case #3

- A 45yo woman with a h/o RA on weekly methotrexate is being evaluated for initiation of Humira
- TB screening is recommended for all patients and she undergoes QuantiFERON TB gold testing and tests POSITIVE
- What now?
Time from onset of last anti TNF treatment and first symptoms of tuberculosis according to the last anti TNF received
TB Screening

- Mantoux PPD TST
- QuantiFERON TB gold
  - Indeterminate testing is due to TEST FAILURE
  - Positive result is the same interpretation as a positive TST
- What if both tests are done and one is positive, one is negative?
POSITIVE Quantiferon TB

- All positive testing should be followed by a CXR for possible active tuberculosis
- Patients with positive CXR should be referred for induced sputum sampling and/or bronchoscopy as appropriate
- Patients with negative CXR may begin treatment for LTBI
  - 6-9mo of INH
  - 4mo of rifampin
Anti-TNF Start?

- When is it “safe” to initiate Humira?
- What if you patient was QuantiFERON negative and 1 year after initiation of Humira her testing is repeated and is now POSITIVE?
- What if patient develops active TB while on Humira?
Fungal Infections

- **Black Box warning September 2008**
  - “Ask your doctor if you live in an area or may have traveled to an area where certain fungal infections are present.”

- Antibody testing?

- If acquired during treatment, required to be reported to the FAERS
Histoplasmosis

- Histoplasmosis – most common
  - “Ohio River Valley”
  - Kentucky, Minnesota, Illinois, Mississippi, Indiana, Michigan, Pennsylvania
- Disease primary infects the lungs, however can be disseminated or cutaneous
- Typical infection features flu-like symptoms 3-17 days after exposure
  - Soil, decaying bat guano, bird droppings
Fungal Infections cont’d.

- Initial Black Box warning summarized 240 cases of histoplasmosis in patients on Humira, Enbrel, and Remicade
- Most troubling – 21 patients were asymptomatic until their disease was fulminant
  - Antifungal therapy was delayed and anti-TNF therapies continued
  - 12/21 patients died
Histoplasmosis cont’d.
Histoplasmosis cont’d.

- Mayo clinic review of RA patients who contracted histoplasmosis 1998-2009
- 26 total patients – most on combination tx
  - 15 of these patients had anti-TNF agents as a part of their therapy
  - All completed at least 6 months of treatment
  - 4 were restarted on anti-TNF agents
    - Histoplasmosis reoccurred in 1 case
Blastomycosis

- **Blastomycosis**
  - Louisiana, Michigan, Mississippi, Minnesota, Wisconsin

- **Numerous presentations**
  - Typical presentation has flu-like illness, progressive pulmonary infection, bone involvement, skin lesions
  - 40% of immunocompromised hosts will have CNS involvement, brain abscesses, meningitis
Blastomycosis cont’d.

Area where Blastomycosis is found
Coccidioidomycosis

- Coccidioidomycosis
  - SW United States (California/Arizona), Mexico, Central and South America
  - “San Joaquin Valley Fever”
- Less than 5% of patients develop disease
  - Usually immunocompromised hosts
Coccidioidomycosis cont’d.

Areas of prevalence approach 50-70% in Southern California, Arizona, Texas
Fungal Infections cont’d.

- Consider endemic fungal infections in all anti-TNF patients who develop pneumonia
- Patients who live in or travel to endemic areas should be counseled about risk of infection and activities to avoid
- Anti-TNF agents should be held as soon as fungal infections are suspected and appropriate treatment initiated pending further w/u
- Low threshold for bronchoscopy in these cases
A 48yo woman with a h/o relapsing, remitting MS x 7 years presents to the ER with a c/o blurred vision, weakness, and unusual movements in her dominant hand

Last IV treatment for MS 3 weeks prior to presentation

Concerned about and MS flare in spite of treatment, w/u includes an MRI
Unique Consideration

- **Tysabri (natalizumab) 2004**
  - Exact mechanism is unknown
  - Binds integrins on leukocyte cell walls, preventing migration into inflamed parenchymal tissue
  - Indicated for patients with relapsing forms of MS which have failed other therapies
  - Unique correlation with use of this medication and Progressive Multifocal Leukoencephalopathy caused by reactivation of the JC virus
Tysabri cont’d.

- All patients about to begin Tysabri should have JC virus antibody testing
- Greatest risk in patients who are JC+ (nearly 50% of our healthy population) and who have had >12mo of Tysabri infusions
- Prognosis very poor
Tysabri cont’d.

- As of February 29, 2009
  - 212 cases of PML in 99,571 patients treated with Tysabri
  - Patients negative for JC virus antibodies prior to treatment had an incidence of 0.09 cases/1000 patients
  - Patients positive for JC, who had been on other immune modulators, and who had at 24+ months of Tysabri infusion had a risk of 11.1 cases/1000 patients
Treatment

- There is no known cure
- Cidofovir, interleuken treatments have been explored
- Cytarabine (ara-C), a chemotherapy drug has been used in non-AIDS PML patients
  - Some slowing of disease progression
- In June 2010 – Mefloquine (antimalarial) was successfully used in a single case
  - Resulted in remission of active disease, elimination of JC virus, prevention of further neurologic deterioration.
Take Home Highlights

- Anti-TNF agents *alone* do not necessarily increase the rate of all-cause infection
- The greatest risk for all-cause infection is within the first 6 months of initiating the agent
- Screen for TB prior to the initiation of treatment
- Consider screening for endemic fungi
- Consider Zostavax in patients over the age of 50yo prior to the initiation of anti-TNF agents
- Screen all Tysabri patients for JC virus antibody prior to treatment
- When in doubt, STOP biologics in the setting of acute infections and begin appropriate antibiotic and antiviral therapies
References

References