

# **Rheumatoid Arthritis and the Role of Tumor Necrosis Factor Inhibitors: Clinical Aspects**

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# Indications

- Rheumatoid arthritis
- Psoriatic arthritis
- Ankylosing spondylitis
- Inflammatory bowel disease such as Crohn's disease
- Psoriasis
- Used off-label for a number of other conditions such as SLE, IIM

# TNF in RA

- Reduce the symptoms and signs of disease
- Slow the progression of the disease and limit tissue destruction (joints in RA,; bowel in Crohn's disease)
- Indicated for patients with moderate to severe and active disease
- Have been used in RA and AS at disease outset if markers of severe progression present (high number of active swollen joints, high ESR/C-rp); positive RF/antiCCP ab.
- Have improved outcomes in patients with RA: less joint damage, better function, less CVD,

# Combination Therapy with Anti-TNF Agents

- Routinely used together with methotrexate (in doses of about 7.5-25 mg/wk)
- Also routinely used in combination with other disease modifying anti-rheumatic drugs (DMARDs): azathioprine, sulfasalazine, hydroxychloroquine, leflunomide)
- No studies of combinations of systemically administered antiTNF agents

- No known significant pharmacodynamic or pharmacokinetic interactions between anti-TNF agents and conventional DMARDs
- However, heightened risk of infection when used with glucocorticosteroids and chemotherapeutic immunosuppressants, and anakinra (IL1ra).  
Unknown but possibly no increased risk for infection preceding or following rituximab use.

# Adverse Effects of anti-TNF Agents

- Hematologic (usually self-limited thrombocytopenia or leukopenia)
- Demyelinating disease
- Hepatitis B reactivation
- Herpes simplex virus infection
- Hypersensitivity
- ?Malignancy
- Infection

# RA and Infections

- Baseline risk for infections is increased ca 2-fold, irrespective of therapy compared to the general population
- All labeling for available anti-TNF agents warns of possible infection risks; various studies suggest risk either not increased to increased.
- Approximately 2-fold increased risk of infection with anti TNF agents has been described; up to 4x increased in first 6 months of use (Curtis et al, Arthritis Rheum 2007; Bongartz et al JAMA 2006)
- Risk of infection dose dependent (Westhovens et al, Arthritis Rheum 2006; Bongartz et al JAMA 2006)
- Risk may be related to genomic and pharmacodynamic factors, such as TNF-alpha polymorphisms

# Opportunistic Infections and anti-TNF agents in RA

The overall risk of opportunistic infections has not been adequately addressed.

- TB most concerning; awareness and screening has decreased this risk in more recent years since introduction of anti-TNF therapies in 1998.
- Others include atypical mycobacterial infections, salmonellosis, listeriosis, invasive and endemic fungal disease: coccidioidomycosis, histoplasmosis, aspergillosis legionellosis, parasitic disease such as toxoplasma; CMV, VZV, HSV

- Overall rate of granulomatous infections\*  
(infliximab) 129/100,000 (639/197,000)  
(etanercept) 60/100,000
- Median time to onset of infection:  
infliximab: 40 days; etanercept 236 days

\*Wallis RS, Broder M, Wong J, Beenhower D. Granulomatous infections due to tumor necrosis factor blockade: correction. *Clin Infect Dis.* 39, 1254-5 (2004).

Wallis RS, Broder M, Wong J, Beenhower D. Granulomatous infections associated with tumor necrosis factor antagonists. *Clin Infect Dis.* 38, 1261-5 (2004).

# Histoplasmosis

- Over 40 cases associated with anti-TNF therapy have been reported to MedWatch
- Infection usually presents from 1 to 6 months after starting anti-TNF therapy
- Symptoms may mimic the underlying inflammatory disease (for example, worsening of joint swelling)
- Patients can present with an acute and fulminant course with fever, malaise, cough, dyspnea, interstitial pneumonitis

# Pre anti-TNF screening

- Complete H&P
- Clinical and/or laboratory/X-ray screening for conditions which may contraindicate use of anti-TNF agents if not controlled:
  - TB by PPD, Chest X-ray (for every patient)
  - Hepatitis with cirrhosis (no consensus about screening)
  - Significant congestive heart failure
  - Acute infections; chronic infections such as SBE and OM
- Chronic or latent infections in asymptomatic host without a clinical history of specific infection:
  - No consensus regarding serologic screening, even in endemic areas (examples: coccidioidomycosis, histoplasmosis)

# Infection in RA: Prevention

## Specific Measures: WHAT

- **Indicated:** Routine vaccinations with inactivated vaccine or toxoid
  - diphtheria, tetanus, and pertussis
  - hepatitis A and B
  - influenza
  - haemophilus influenzae type b
  - inactivated polio
- **Contraindicated:** Live-attenuated vaccines such as measles, mumps, rubella, varicella, rotavirus, FluMist, HSV