Dropping our Defenses: Infections in the Setting of Immunosuppressive Therapy

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Objectives

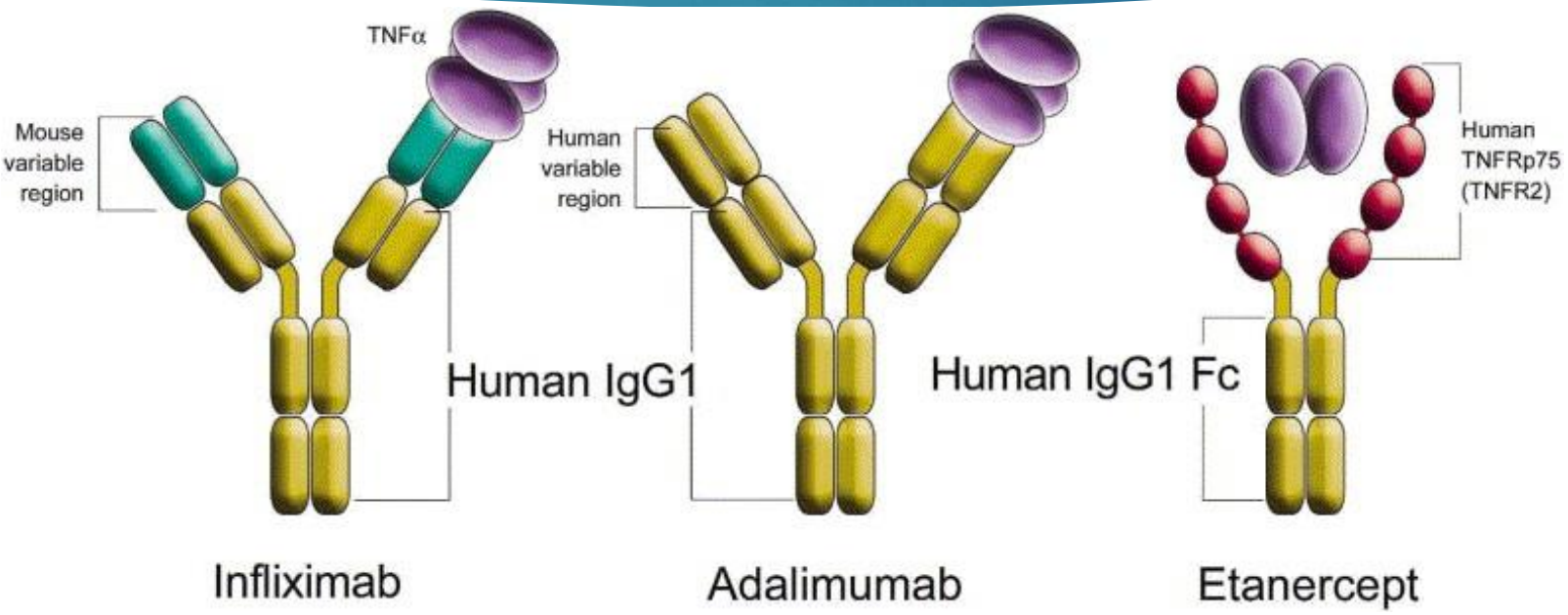
- Identify infections associated with TNF-inhibitor and/or glucocorticoids
- Choose the appropriate pre-treatment infectious disease testing
- Recommend pre-treatment prophylaxis and/or vaccines

Warning: Mostly RA data used

Background

- TNF-α = pro-inflammatory cytokine
  - Key role in chronic immune mediated disease (e.g. RA)
- Synthesized by activated macrophages & T-cells
  - PP cleaved into soluble TNF-α → trimeric → binds TNFR1/2
- Functions:
  - Releases inflammatory cytokines
  - Macrophage & phagosome activation
  - Neutrophil & macrophage recruitment
  - Granuloma formation & maintenance

Background



- MOA: block TNF -TNFR interaction
  - Infliximab – strong binding to mono/trimeric TNF, transmembrane TNF, no LT-α binding
  - Etanercept – weaker binding of trimeric TNF, transmembrane TNF, binds LT-α

Anderson PJ. 2005.

Background

- Glucocorticoids
  - Around since 1940s → very common
  - Treat acute/chronic inflammation
  - **PO**, INH, topical, injection
- Natural role is whole-body homeostasis, esp. stress
- MOA: inhibit initial inflammatory response, promote resolution via GR
  - Broad response → affects nearly every cell
- May augment immune response in certain scenarios (Frank et al., 2010)

Coutinho AE, Chapman KE. 2011.

Anti-TNF Antibody Therapy in Rheumatoid Arthritis and the Risk of Serious Infections and Malignancies

Bongartz et al.

JAMA, May 17, 2006—Vol 295, No. 19 2275

- Pool results of RCTs for adverse events
- EMBASE, MEDLINE, Cochrane until 2005
  - Unpublished trials from abstract & manufacturer
  - Infliximab and adalimumab
- 9 trials → 5014 pts with RA
  - 126 SI in active Tx vs. 26 in control arm

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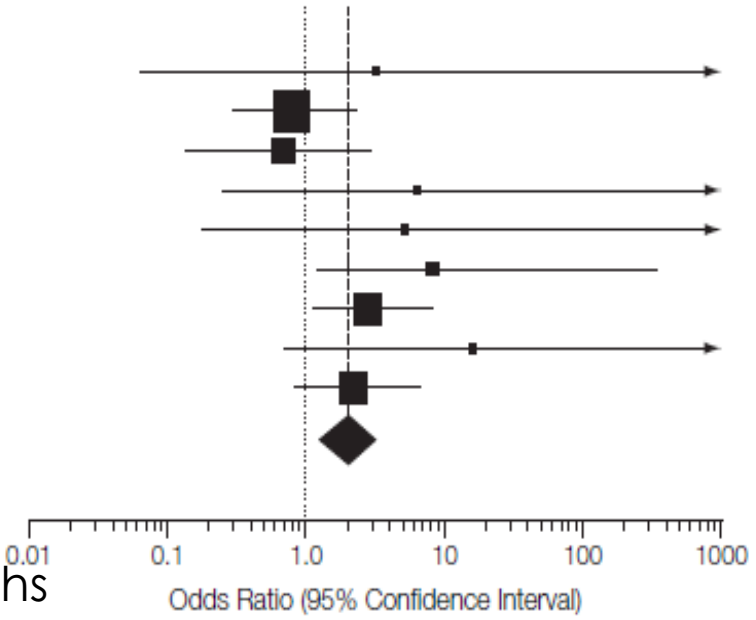
Source	Serious Infections, No./Total: Anti-TNF	Serious Infections, No./Total: Placebo	Odds Ratio (95% Confidence Interval)
Maini et al,[32] 1998	2/87	0/14	3.13 (0.06-Infinity)
Lipsky et al,[9] 2000	21/342	7/86	0.76 (0.30-2.18)
Furst et al,[8] 2003	4/318	6/318	0.66 (0.14-2.83)
Van de Putte et al,[10] 2003	4/214	0/70	6.33 (0.30-Infinity)
Weinblatt et al,[11] 2003	3/209	0/62	4.93 (0.19-Infinity)
Keystone et al,[6] 2004	16/419	1/200	7.90 (1.21-332.96)
St Clair et al,[7] 2004	40/749	6/291	2.68 (1.11-7.81)
Van de Putte et al,[33] 2004	11/434	0/110	15.34 (0.71-Infinity)
Westhovens et al,[34] 2004	25/721	6/361	2.13 (0.84-6.39)
Total	**126/3493**	**26/1512**	**2.01 (1.31-3.09)**

Test for overall effect:
Mantel-Haenszel $\chi^2 = 9.1$; $P = .002$



NNH = 59 (95% CI, 39-125) within 3-12 months

TNF Infection Risk

- Risk is highest in the first 6 months
  - Galloway et al. (2011) used observational data
  - HR for SI 1.8 (95% CI 1.3, 2.6) vs. 0.9 (95% CI 0.6, 1.3 at 24-36 mos.)
  - Healthy user effect vs. improved disease course vs. lower steroids
- Certain risks may be biologic dependent
  - *Listeria* and IFN (Bodro & Paterson. 2015)
  - TB = 3-4x the risk with IFN/ADA vs. ETN (Dixon et al. 2010)

Which Infections - TNF?

- Black box warning for TB
- Histoplasmosis
  - Unlike TB, not typically reactivation (Vail et al. 2002)
- Intracellular organisms
  - Listeria, Legionella
- Viral
  - Zoster, (?HBV/HCV)
- Other: visceral leishmaniasis, PJP, Aspergillus, Coccidioides

Murdaca et al. 2015.

The association between systemic glucocorticoid therapy and the risk of infection in patients with rheumatoid arthritis: systematic review and meta-analyses

Dixon et al. *Arthritis Research & Therapy* 2011, **13**:R139

- 21 RCTs and 42 observational studies
  - Not exclusively SI → any infections
- RCTs: RR infection 0.97 (0.69, 1.36)
- Observational: RR 1.67 (1.49, 1.87)
  - Case-control RR 1.95 (1.61, 2.36) vs. cohort 1.55 (1.35, 1.79)
  - Dose-response relationship
  - <5 mg/d RR 1.37 (1.18, 1.58) vs. 5-10 mg/d RR 1.93 (1.67, 2.23)
- Differences due to **GC exposure duration**, study heterogeneity, inconsistent reporting/definitions

Which infections - steroids?

- Serious bacterial infections
- PJP
  - Yale & Limper (1996) – 91% of non-HIV PJP had steroids w/i 1 mo. of diagnosis (med 30 mg/d)
- *Strongyloides stercoralis*
  - Risk of hyperinfection & disseminated disease
  - Mortality 63% (Buonfrate et al. 2013)
- TB
- Zoster
- HBV
- Dose & duration effect, possibly disease effect

Youssef et al. 2016.

Screening

1. R/O current active infection
2. TB assessment
   - **History**, CXR, +/- TST/IGRA
3. Varicella status
4. HBV, HCV status
   - HbsAg, HBV cAb, DNA – immune, carrier, resolved infection
   - HCV Ab/RNA + fibrosis measurement
5. Strongyloides screening
   - Ab, stool, empiric Rx

N.B. No histoplasma screening

Screening

- Other good preventative measures
- General vaccination status
  - Pneumococcal vaccine
  - Influenza
  - Zoster
- Sun protection
- Food and water safety
- Mosquito protection
- Travel safety

Pre-Rx Recommendations

- Treat active infections prior to starting therapy

1. TB
   - If latent TB is found, initiate LTBI therapy first
   - INH + pyridoxine x 9 mos. is gold standard
   - No minimal duration (suggest 1 month)
2. Histoplasmosis = patient education
3. PJP
   - Consider on a case-by-case basis
   - Steroid dose >20 mg/d? 16? Combo IS? Three weeks+?
   - TMP-SMX SS daily, DS TIW (+alternatives)

Pre-Rx Recommendations

4. Zoster
   - Live vaccine licensed in Canada for >50 y.o.
   - Protection wanes ~5 years (Schmader et al. 2012)
- Best to review pre-IS
   - Need 4 wk vaccine washout if high IS anticipated
- Post-IS, need 3+ mo. IS washout period
- Low-dose IS not a contraindication
   - Prednisone <20 mg/d, short course (<14 d), topical/INH
   - ≤ MTX 0.4 mg/kg/week, ≤ AZA 3.0 mg/kg/day, ≤ 6-MP 1.5 mg/kg/day

Canadian Immunization Guide.

Association Between Vaccination for Herpes Zoster and Risk of Herpes Zoster Infection Among Older Patients With Selected Immune-Mediated Diseases

Zhang et al. JAMA, July 4, 2012—Vol 308, No. 1 43

- Retrospective cohort: 463,541 Medicare pts ≥60 y.o.
  - RA, PsA/P, AS, or IBD between 2006-2009
- 551 patients on anti-TNF
  - No zoster, meningitis/encephalitis within 42 d of vaccine
  - RR for HZ 0.61 (95% CI, 0.52-0.71) over a median of 2 y of f/u

- Canadian Immunization Manual: consider on case-by-case basis for those on anti-TNF

Pre-Rx Recommendations

5. Influenza, pneumococcal vaccine
   - Expect reasonable seroconversion rates (RA – Hua et al. 2014; IBD – Launay et al. 2015)
   - Immunity wanes rapidly over time
6. HBV

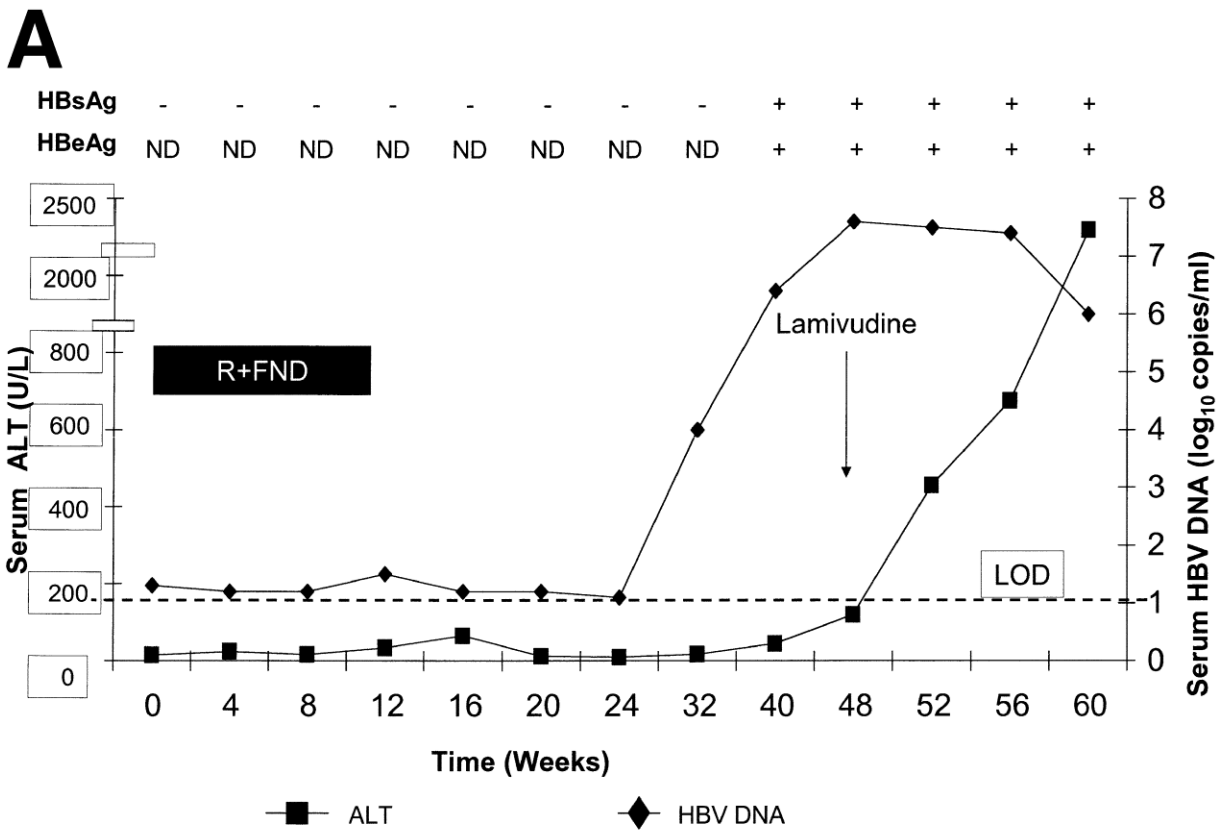
	HBV sAg	HBV sAb	HBV cAb	HBV DNA
Chronic	+		+	+++
"Inactive"	+		+	±
Past infection	-	±	+	
Occult	-	±	±	+

Pre-Rx Recommendations

- Determine risk of reactivation
  - Highest risk if HBV sAg+ (38%) vs. HBV sAg-, cAb+ (5%)
  - Higher risk with prednisone >20 mg/day
  - Moderate risk with TNF
    - Infliximab >> ETN
- Recommendations are for antiviral therapy if HBV sAg+
  - HBV cAb+ is dilemma

Di Bisceglie et al. 2015.

Pre-Rx Recommendations



Hui et al. 2006.

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- Recommendations are for antiviral therapy if HBV sAg+
  - HBV cAb+ is dilemma
  - Treat all vs. monitor? If monitor, how frequent?
    - Recent paper suggested monitoring for TNF/steroids

Di Bisceglie et al. 2015.

Pre-Rx Recommendations

7. HCV
   - RCT with ETN + IFN/RBV for patients with HCV (Zein et al. 2005.)
   - No RCT data in patients with RA/IBD = no formal recommendations (Brunasso et al. 2011.)
   - Avoid if acute HCV or CP class B, C (ACR)
   - ?Treat patients on therapy
8. Strongyloides (empiric or after screening)
   - Ivermectin

Questions?

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