Dropping our Defenses: Infections in the Setting of Immunosuppressive Therapy

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Disclosures

- Educational grant money
  - UBC-Pfizer
  - UBC-Sunovion

- Advisory Board
  - Merck

- Speaker fees
  - Astellas
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)
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- Unpublished trials from abstract & manufacturer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
## Anti-TNF Antibody Therapy in Rheumatoid Arthritis and the Risk of Serious Infections and Malignancies

Bongartz et al.  

### Pool results of RCTs for adverse events

- EMBASE, MEDLINE, Cochrane until 2005

### Table: Serious Infections, No./Total

<table>
<thead>
<tr>
<th>Source</th>
<th>Anti-TNF</th>
<th>Placebo</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maini et al, 1998</td>
<td>2/87</td>
<td>0/14</td>
<td>3.13 (0.06-Infinity)</td>
</tr>
<tr>
<td>Lipsky et al, 2000</td>
<td>21/342</td>
<td>7/86</td>
<td>0.76 (0.30-2.18)</td>
</tr>
<tr>
<td>Furst et al, 2003</td>
<td>4/318</td>
<td>6/318</td>
<td>0.66 (0.14-2.83)</td>
</tr>
<tr>
<td>Van de Putte et al, 2003</td>
<td>4/214</td>
<td>0/70</td>
<td>6.33 (0.30-Infinity)</td>
</tr>
<tr>
<td>Weinblatt et al, 2003</td>
<td>3/209</td>
<td>0/62</td>
<td>4.93 (0.19-Infinity)</td>
</tr>
<tr>
<td>Keystone et al, 2004</td>
<td>16/419</td>
<td>1/200</td>
<td>7.90 (1.21-332.96)</td>
</tr>
<tr>
<td>St Clair et al, 2004</td>
<td>40/749</td>
<td>6/291</td>
<td>2.68 (1.11-7.81)</td>
</tr>
<tr>
<td>Van de Putte et al, 2004</td>
<td>11/434</td>
<td>0/110</td>
<td>15.34 (0.71-Infinity)</td>
</tr>
<tr>
<td>Westhovens et al, 2004</td>
<td>25/721</td>
<td>6/361</td>
<td>2.13 (0.84-6.39)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>126/3493</strong></td>
<td><strong>26/1512</strong></td>
<td><strong>2.01 (1.31-3.09)</strong></td>
</tr>
</tbody>
</table>

### Graph: Odds Ratio (95% Confidence Interval)

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


- 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.
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

<table>
<thead>
<tr>
<th></th>
<th>HBV sAg</th>
<th>HBV sAb</th>
<th>HBV cAb</th>
<th>HBV DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>“Inactive”</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Past infection</td>
<td>-</td>
<td>±</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Occult</td>
<td>-</td>
<td>±</td>
<td>±</td>
<td>+</td>
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</table>
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.
Pre-Rx Recommendations

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

Di Bisceglie et al. 2015.
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?
References