Tuberculosis and Biologic Therapies: Risk and Prevention

Kevin L. Winthrop, MD, MPH
Associate Professor, Divisions of Infectious Diseases, Public Health and Preventive Medicine Oregon Health & Science University
Portland, OR
Disclosures

- Research funding from Pfizer, Oxford Immunotech
- Scientific consultant work for Genentech, Pfizer, Abbott, UCB
- Data safety monitoring boards for RCTs conducted by UCB, Roche, Abbott, Astellas, Merck-Serono, Janssen

IMID Biologic Therapies

- TNF-α inhibition
  - Infliximab, adalimumab, golimumab, certolizumab (monoclonal antibodies)
  - Etanercept (soluble p75 receptor)

- Other
  - CD4 co-stimulation modulator: abatacept
  - B-cell (CD20+) antibody: rituximab
  - Anti-IL-6 receptor antibody: tocilizumab
  - Anti- IL12/IL23 antibody: ustekinumab

- JAK 1/3 inhibitor: tofacitinib
Global TB Epidemiology

Estimated new TB cases (all forms) per 100,000 population:
- 0-24
- 25-49
- 50-99
- 100-299
- ≥300
- No estimate

FIGURE 2. Number and rate* of tuberculosis (TB) cases among U.S.-born and foreign-born persons, by year reported — United States, National Tuberculosis Surveillance System, 2000–2012†

No. of TB cases among U.S.-born persons
No. of TB cases among foreign-born persons
TB rate among U.S.-born persons
TB rate among foreign-born persons

* Per 100,000 population.
† Data current as of February 15, 2013. Data for 2012 are provisional.
TB Pathogenesis

- Transmitted by inhalation (or ingestion) of *M. tuberculosis* bacilli
  - Alveolar macrophage
  - Bacilli replication
  - Brief hematogenous dissemination
- Cytokine and cellular activation
- Immune system attempts to limit spread of infection
  - Granuloma formation around bacilli
  - Intracellular killing of bacilli

Prednisone and Tuberculosis

- *Jick et al. Arthritis Rheum 2006*
- General Practice Research Database, UK
- TB cases 1990-2001 and controls†
- Current glucocorticoid use *OR 4.9 (2.9-8.3)*
  - ≤15mg/day *OR 2.8 (1.0-7.9)
  - >15mg/day *OR 7.7 (2.8-21.4)

*Adjusted for smoking, BMI, lung disease, diabetes, anti-rheumatic therapy, other TB risk factors
†Controls matched for age, sex, residence, time clinically followed
More TB Risk with Monoclonals?

- Drug mechanisms differ
- Greater TNF-α binding
  - Transmembrane and soluble TNF-α
  - Forms stable complex
- Longer half-life
- Apoptosis of monocytes and T lymphocytes
- Interferon-gamma down-regulation
- Differential granuloma penetration
Interferon-\(\gamma\) Downregulation

Saliu et al. JID 2006

Granuloma Penetration

Plessner HL et al JID 2007
Granuloma Penetration

- Acute TB infection (mouse)
  - Large bacillary load and death
  - No difference between anti-TNFs
- Chronic TB infection (mouse)
  - Monoclonal antibodies = death (1 month)
  - Etanercept = 60% alive at 6 months
  - Lung path: etanercept with less penetration of granulomas

Plessner et al JID 2007

Downregulation of CD8⁺ Cells

Interferon-gamma Release Assays (IGRAs)

- **T-SPOT. TB 96**
- Oxford Immunotec

Relative Sensitivity of IGRA

- Case-control study, Peru
- 80% BCG use in both groups
- High prednisone use among RA group

<table>
<thead>
<tr>
<th></th>
<th>RA (n = 101)</th>
<th>Controls (n = 93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST+</td>
<td>27 (27%)a</td>
<td>61 (66%)</td>
</tr>
<tr>
<td>QFT-IT+</td>
<td>45 (45%)</td>
<td>55 (59%)</td>
</tr>
</tbody>
</table>

N=317 TST OR QFT positive, all received INH. No TB
N=5 cases TB, all screened negative at baseline

Figure 1. Overlap of screening test results and rates of positivity from the tuberculin skin test (TST) and an interferon-γ release assay (IGRA). The Quantiferon-TB Gold In-Tube (QFT-GIT) test for the detection of latent tuberculosis infection in all patients (A), bacillus Calmette-Guérin (BCG)-vaccinated patients (B), and non-BCG-vaccinated patients (C).

TB risk factors include: a history of contact to a case of active TB; birth or extended living in regions where TB is prevalent (crude incidence >20/100,000 per year); history of working or living in jails, prisons, healthcare facilities providing care to TB patients, or homeless shelters; or history of intravenous drug use.

Immunosuppression includes poorly controlled rheumatoid arthritis or other inflammatory immune-mediated disease, current use of biologic or non-biologic disease modifying therapies, or current use of corticosteroids, and other conditions.

In regions of BCG use (or individuals with BCG history), consider a dual strategy of using both commercially available IGRA (QuantiFERON-TB In Tube® and T. Spot.TB®) in lieu of the TST.

For patients with risk factors and immunosuppressed in whom false negative results are more likely, consider repeat screening with one or both tools.

TB: tuberculosis; IGRA: interferon-gamma release assay; TST: tuberculin skin test.
LTBI Treatment

- Begin treatment before starting anti-TNF therapy
  - 9 months isoniazid (INH) preferred
  - 4 months rifampin is alternative
- Start INH 1 month prior to anti-TNF initiation
  - 83% reduction in INF-associated cases in Spain\(^1\)
  - Ensure INH compliance and tolerance
- Liver function testing
  - Many patients taking methotrexate

New Therapy Option

- **INH and Rifapentine**
  - 3 months, once weekly (directly observed?)

Sterling T et al. NEJM 2011

<table>
<thead>
<tr>
<th>Population and Study Group</th>
<th>No. of Subjects</th>
<th>Subjects with Tuberculosis</th>
<th>Difference in Cumulative Rate</th>
<th>Upper Limit of 95% CI for Difference in Cumulative Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified intention-to-treat analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid only</td>
<td>3745</td>
<td>15</td>
<td>0.16</td>
<td>0.43</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>3086</td>
<td>7</td>
<td>0.07</td>
<td>0.19</td>
</tr>
<tr>
<td>Per protocol analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid only</td>
<td>2585</td>
<td>8</td>
<td>0.11</td>
<td>0.32</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>3273</td>
<td>4</td>
<td>0.05</td>
<td>0.13</td>
</tr>
</tbody>
</table>

* Combination therapy consisted of 3 months of directly observed once-weekly therapy with rifapentine (900 mg) plus isoniazid (300 mg). Isoniazid-only therapy consisted of 9 months of self-administered daily isoniazid (300 mg). Data are shown for a period up to 33 months after study enrollment.
† The difference is the rate in the combination-therapy group minus the rate in the isoniazid-only group.


Other Biologics

- **Rituximab**
  - EIN Survey found 3 TB/5 NTM cases with rituximab. All on prednisone

- **Abatacept**
  - Clinical trial program, 7 TB cases reported (rate 60/100,000)

- **Tocilizumab**
  - Clinical development program, 10 TB cases (rate 100/100,000).
  - Post-marketing surveillance in Japan, 4 cases (rate 220/100,000)
Pre-clinical Data

- **Rituximab**
  - B cell importance to granuloma/survival in murine models of TB*

- **Abatacept**
  - Murine chronic TB not affected by abatacept*
  - Mortality, T cell, B cell, INF-γ production in lung, and bacillary load

- **Tocilizumab**
  - Murine chronic TB not affected by tocilizumab


Tofacitinib in RA

- **Tuberculosis rate = 173/100,000**
  - Most cases at 10mg BID dose
  - All cases screened negative prior to trial entry

- **Mechanism?**
  - Macrophage control of TB
  - Interferon signalling?

Winthrop et al abstract, American College of Rheumatology (ACR), Washington DC, Nov 2012
LTBI Treatment during Tofacitinib

- 209 patients diagnosed with LTBI
  - All treated INH X 9 months during trial
  - No cases of TB
  - No hepatotoxicity noted
- INH is therapy of choice
  - Drug-drug interaction with Rifampin
Table 2. Crude incidence rates of tuberculosis and nontuberculous mycobacterial disease (NTM) among the general population and rheumatoid arthritis patients, Kaiser Permanente Northern California, 2000-2008.

<table>
<thead>
<tr>
<th></th>
<th>Crude incidence rate (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tuberculosis</td>
</tr>
<tr>
<td><strong>General KPNC population</strong></td>
<td>2.8 (2.6-3.0)</td>
</tr>
<tr>
<td><strong>General KPNC population, ≥50 years old</strong></td>
<td>5.2 (4.7-5.8)</td>
</tr>
<tr>
<td><strong>Unexposed RA population</strong></td>
<td>8.7 (5.3-13.2)</td>
</tr>
<tr>
<td><strong>RA Anti-TNF users</strong></td>
<td>56 (24-111)</td>
</tr>
</tbody>
</table>

* rate per 100,000 patient years (95% confidence interval)
**Unexposed to anti-TNF therapy

1. General KPNC population: 774 Tuberculosis and 1145 NTM cases in 27,668,456 person-years;
2. General KPNC population, ≥50 years old: 396 Tuberculosis cases/7,615,385 person-years, 897 NTM cases/7,601,695 person-years;
3. Unexposed RA population: 19 Tuberculosis and 42 NTM cases in 219,205 person-years;
4. RA Anti-TNF users: 8 Tuberculosis and 15 NTM cases in 14,286 person-years.
Acknowledgments

• Friends and collaborators within:
  – CDC
  – ACR
  – EULAR
  – OHSU
  – KPNC
  – UAB

Zoster risk with anti-TNF

<table>
<thead>
<tr>
<th>Exposures</th>
<th>Events</th>
<th>Person-years</th>
<th>Crude incidence rate</th>
<th>Adj. Hazard ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid Arthritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non biologic DMARD</td>
<td>90</td>
<td>7,100</td>
<td>12.7 (10.3, 15.6)</td>
<td>Reference</td>
</tr>
<tr>
<td>New users of TNF antagonists</td>
<td>266</td>
<td>22,019</td>
<td>12.1 (10.7, 13.6)</td>
<td>1.00 (0.77, 1.29)</td>
</tr>
<tr>
<td>Baseline glucocorticoid use (prednisone equivalents)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td>0-5 mg/day</td>
<td></td>
<td></td>
<td></td>
<td>1.19 (0.92, 1.54)</td>
</tr>
<tr>
<td>5-10 mg/day</td>
<td></td>
<td></td>
<td></td>
<td>0.99 (0.72, 1.35)</td>
</tr>
<tr>
<td>&gt;10 mg/day</td>
<td></td>
<td></td>
<td></td>
<td>1.87 (1.37, 2.57)</td>
</tr>
</tbody>
</table>

RA = TNF new users (n= 24,383); non-biologic DMARD new users (n=11,830)

Winthrop KL et al. JAMA 2013