Opportunistic Infections Related to Immune Suppressant and Biologic Drug Therapy in IBD

Raymond Cross, M.D., M.S., AGAF
Associate Professor of Medicine
Director of the Inflammatory Bowel Disease Program
University of Maryland School of Medicine
Co-Director, Digestive Health Center
University of Maryland Medical Center
11/9/12
Case #1

- 39 year old WM trauma orthopedist with obstructing ileal Crohn’s disease with upper tract involvement
- He presented ~two years ago with severe abdominal pain
  - Ex lap revealed a jejunal stricture
  - Resection of 20 cm of jejunum with primary anastomosis
  - Ileocolonoscopy revealed aphthous ileitis.
Case #1 (cont.)

- Post operatively, started on Humira 40 mg eow
  - Annual negative TST
  - Hep B vaccination in medical school
- 6 months after surgery, capsule endoscopy performed
  - Large, irregular, “rake like” ulcers from D2-D4
  - Small erosions between D2-D4 and jejunal anastomosis
  - Irregular ulcerations present proximal to the anastomosis
- TPMT activity 20.6
- Azathioprine started at 2.5 mg/kg per day
- Repeat capsule performed one year later was normal.
Case #1 (cont.)

• Medications continued
• At annual employee health physical, TST was + with 10 mm of induration
# Interpretation of TST

<table>
<thead>
<tr>
<th>TST reaction size (mm)</th>
<th>Situation in which reaction is considered positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥5</td>
<td>HIV infection</td>
</tr>
<tr>
<td></td>
<td>Close contact with active TB</td>
</tr>
<tr>
<td></td>
<td>Abnormal CXR with changes c/w old TB</td>
</tr>
<tr>
<td></td>
<td>Immunosuppressed individuals</td>
</tr>
<tr>
<td>≥10</td>
<td>Conditions that increase risk of reactivation</td>
</tr>
<tr>
<td></td>
<td>Less than 4 years of age</td>
</tr>
<tr>
<td></td>
<td>Foreign born from countries with high prevalence</td>
</tr>
<tr>
<td></td>
<td>High risk workers</td>
</tr>
<tr>
<td>≥15</td>
<td>Healthy people with low likelihood of true TB infection</td>
</tr>
</tbody>
</table>
# Infection Risks in Observational Studies

<table>
<thead>
<tr>
<th></th>
<th>Steroids</th>
<th>Narcotics</th>
<th>IFX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious</td>
<td>1.97</td>
<td>2.07</td>
<td>1.48</td>
</tr>
<tr>
<td></td>
<td>(1.42 – 2.73)</td>
<td>(1.52 – 2.82)</td>
<td>(1.09 – 2.00)</td>
</tr>
</tbody>
</table>

*Multivariable Cox proportional hazards regression model and medication exposure in the prior 6-mo CRF data collection period*

Lichtenstein, G et al. DDW 2010
Combined Use of Immunosuppressive Drugs Increase Risk of Opportunistic Infections

<table>
<thead>
<tr>
<th>Number of Immunosuppressant Medications</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Reference</td>
</tr>
<tr>
<td>1</td>
<td>2.9 (1.5-5.3)</td>
</tr>
<tr>
<td>2 or more</td>
<td>14.5 (4.9-43)</td>
</tr>
</tbody>
</table>

Toruner, M et al. Gastroenterology 2008
Risk of TB in Patients with Moderate to Severe CD

• Claims data from CD and control patients in the US with private insurance (2002-2005)
  – CD n=22,310
  – Control n=111,550
• Monotherapy with steroids, IS, or anti-TNF
  – HR TB 2.7 (1.0-7.3)
• Two or three drugs
  – HR TB 7.4 (2.1-26.3)

How common is TB in Patients Treated with Humira?

<table>
<thead>
<tr>
<th>As of April 15, 2007</th>
<th>RA</th>
<th>PsA</th>
<th>AS</th>
<th>JIA</th>
<th>Ps</th>
<th>CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>12,345</td>
<td>837</td>
<td>1,641</td>
<td>171</td>
<td>1,819</td>
<td>2,228</td>
</tr>
<tr>
<td>Exposure (PY)</td>
<td>18,284</td>
<td>998</td>
<td>1,255</td>
<td>398</td>
<td>2,425</td>
<td>2,374</td>
</tr>
<tr>
<td>TB (events/100 patient years)</td>
<td>0.29</td>
<td>0.30</td>
<td>0</td>
<td>0</td>
<td>0.12</td>
<td>0.13</td>
</tr>
</tbody>
</table>

How common is TB in patient treated with IFX?

- TREAT registry
  - 3401 patients received IFX (16,129 patient years)
  - 3 cases of TB
  - 0.02 cases/100 patient years compared to 0.009/100 patient years in patients not treated with IFX

Lichtenstein, G., et al. DDW 2010
How do you Monitor Patients for TB while on Anti TNF Therapy?

- ".... Patients frequently presented with disseminated or extrapulmonary disease [TB]. Patients should be tested for latent TB before and during treatment with REMICADE®. Treatment for latent infection should be initiated prior to treatment with REMICADE®".

- ".... Closely monitor patients for the development of signs and symptoms of infection during and after treatment with REMICADE®, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy".

- "Risk of infection may be higher in patients greater than 65 years of age, pediatric patients, patients with co-morbid conditions and/or patients taking concomitant immunosuppressant therapy. In clinical trials, other serious infections observed in patients treated with REMICADE®....".

- **UMB IBD Program Approach**
  - Annual PPD or Quantiferon gold testing in all patients on biologic

http://www.remicade.com/hcp/crohns-disease/safety
How Useful is TST Screening before Anti TNF Therapy?

- 82 consecutive patients about to start IFX
- TST placed on all; control panel in 69
- 0/82 had a + TST
- 20/69 responded to control panel
  - 83% of patients on steroids and/or IS for more than 30 days anergic compared to 43% not administered those meds (p < 0.002)

QuantiFERON-TB Gold In-Tub Assay

• Measure T cell release of IFN-gamma following stimulation by antigens unique to M. TB
• Cannot distinguish between latent and active infection
  – Not affected by BCG vaccination or non TB Mycobacterial infections
• High specificity and sensitivity
  – Less sensitive in setting of immune suppression
    • Indeterminate result more likely in this situation
    • Test should be repeated to exclude technical or lab flaws
• CDC recommends use of QFT-GIT in all situations in which PPD is recommended

QFT-GIT vs. PPD

• PPD and QFT-GIT performed in 212 patients
  – 81% had IBD and were on IS
  – 71% vaccinated with BCG

• 18% of IBD patients and 43% of controls were PPD+
  – Vaccinated controls 52% vs. Vaccinated IBD 23%

• 8% of IBD patients vs. 9% of controls + for QFT-GIT test

• Agreement between tests significantly higher in controls

How would you manage the +TST?

- Hold anti TNF for 3-4 weeks
  - Restart without load
- Begin INH and pyridoxine for 9 months
- Refer to infectious diseases
- Monitor LFT’s closely on both INH and AZA
Summary for Case #1

• Patients on anti TNF therapy should undergo testing for latent TB before initiating therapy
• Patients on chronic anti TNF therapy should be assessed for exposure to TB at follow up assessments
• Periodic assessment for latent TB should be done with TST or QFT GIT
• Patients with latent TB should be treated with INH and pyridoxine for 9 months
  – Anti TNF should be held while INH is initiated
Case #2

- 30 year old WF with penetrating ileocolonic Crohn’s disease with upper tract involvement
- Diagnosed at age 23 and underwent combination of small bowel resection (50 cm) and stricturoplasty x 4 three years after diagnosis
- Postoperatively maintained on Remicade but lost response and developed lupus-like symptoms
Case #2 (cont.)

- Minimal response to high dose steroids
- Underwent anastomotic resection and additional small bowel resection (5 strictures)
- Post op AZA 100 mg daily and Humira
  - Stopped Humira secondary to high co-pay with resolution of urticaria and joint pain
- Colonoscopy showed moderate recurrence at the anastomosis
  - AZA increased to 162.5 mg per day
- Diarrhea worsens; Entocort 9 mg per day started
- Does not respond to 4 months of AZA at 3 mg/kg and Entocort
Before and after treatment with Tysabri
PML

• Severe demyelinating disease of the CNS caused by reactivation of polyomavirus JC (JC virus)
  – Up to 86% of adults have antibodies to JC virus
  – Latent in kidneys and lymphoid organs
  – Reactivates in context of immune suppression
• Presents with subacute neurologic deficits
  – Altered mental status, motor deficits, limb and/or gait ataxia, and visual symptoms
• Seizures in 18%

Diagnosis of PML

Diagnosis based on:
1) Clinical signs and symptoms
2) MRI findings (see right)
3) Evidence of JC viral DNA in CSF or brain tissue
Progressive Multifocal Leukoencephalopathy after Natalizumab Therapy for Crohn’s Disease

Gert Van Assche, M.D., Ph.D., Marc Van Ranst, M.D., Ph.D., Raf Sciot, M.D., Ph.D., Bénédicte Dubois, M.D., Ph.D., Séverine Vermeire, M.D., Ph.D., Maja Noman, M.D., Jannick Verbeeck, M.Sc., Karel Geboes, M.D., Ph.D., Wim Robberecht, M.D., Ph.D., and Paul Rutgeerts, M.D., Ph.D.
PML Case Overview

• As of 6/30/12
  – 104,300 patients have received Tysabri in post-marketing setting

• As of 10/3/12
  – 298 cases of confirmed PML
  – One confirmed case of PML in a Tysabri-treated CD patient

https://medinfo.elan.com
## PML Incidence

<table>
<thead>
<tr>
<th>Total # patients exposed to Tysabri</th>
<th>Total # of Tysabri patients dx with PML</th>
<th>Total # of MS and CD patients exposed to Tysabri</th>
<th>Total # of Tysabri patients dx with PML (US)</th>
<th>Total # of MS patients exposed to Tysabri (EEA)</th>
<th>Total # of Tysabri patients dx with PML (EEA)</th>
<th>Total # of MS patients exposed to Tysabri (ROW)</th>
<th>Total # of Tysabri patients dx with PML (ROW)</th>
</tr>
</thead>
<tbody>
<tr>
<td>104,300</td>
<td>298</td>
<td>56,612</td>
<td>105</td>
<td>39,371</td>
<td>176</td>
<td>8,275</td>
<td>17</td>
</tr>
</tbody>
</table>

EEA=European Economic area; ROW=rest of world

**Overall risk of PML** 2.71/1,000 patients (95% CI 2.41-3.04/1,000)

**Overall risk of PML (US)** 1.85/1,000 patients
Outcomes of Patients with Tysabri-associated PML

• As of 10/3/2012
  – 63/298 patients with PML have died (21%)
  – In 58 patients alive with 6 months of follow up data
    • 10% had mild disability
    • 50% had moderate disability
    • 40% had severe disability
Tysabri PML Risk Estimates by Treatment Epoch

Incidence per 1,000 patients

Post Marketing 1-12 Inf 13-24 Inf 25-36 Inf 37-48 Inf 49-60 Inf

3.04 2.71 2.41 2.27 2.29 2.76
0.82 0.62 0.45 1.51 1.82 1.49
2.05 1.49

0 0.5 1 1.5 2 2.5 3 3.5
Estimated Incidence of PML Stratified by Risk Factor

<table>
<thead>
<tr>
<th>Tysabri Exposure</th>
<th>Anti JCV Antibody Positive</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>No Prior IS Use</td>
</tr>
<tr>
<td>1-24 months</td>
<td>&lt;1/1,000</td>
</tr>
<tr>
<td>25-48 months</td>
<td>4/1,000</td>
</tr>
</tbody>
</table>

If JCV negative 0.9/10,000
Risk Stratification and Monitoring Prior to and After Initiation of Tysabri

“Consideration should be given for anti-JCV antibody status prior to treatment or during treatment if antibody status is unknown....patients with a negative anti-JCV antibody test result should be retested every 6 months.”
Summary for Case #2

• PML is a rare opportunistic infection associated with immune suppression

• ~2 cases of PML per 1,000 patients treated with Tysabri
  – Incidence of PML related to exposure to JC virus, concurrent IS, and duration of exposure to Tysabri
  – Risk of PML as high as 1/91 if JCV +, prior IS use and more than 2 years exposure to Tysabri

• Monitoring of JCV Ab status while on therapy is recommended
  – Some patients have few therapeutic options available
  – Risks of withdrawal of drug vs. risk of continuation of treatment should be discussed before testing