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

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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 Adalimumab 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>
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<tbody>
<tr>
<td>≥ 10</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>

www.cdc.gov

Infection Risks in Observational Studies

<table>
<thead>
<tr>
<th></th>
<th>Steroids</th>
<th>Thiopurines</th>
<th>Anti-TNF</th>
</tr>
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<tbody>
<tr>
<td>Serious</td>
<td>2.2</td>
<td>0.8</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>(1.5 – 3.3)</td>
<td>(0.5 – 1.2)</td>
<td>(0.6 – 1.5)</td>
</tr>
</tbody>
</table>

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>
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<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 Adalimumab?

<table>
<thead>
<tr>
<th>As of April 15, 2007</th>
<th>RA</th>
<th>PsA</th>
<th>AS</th>
<th>JIA</th>
<th>PI</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 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 infliximab. Treatment for latent infection should be initiated prior to treatment with infliximab."
- "... Closely monitor patients for the development of signs and symptoms of infection during and after treatment with infliximab, 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 infliximab…”
- UMB IBD Program Approach
  - Annual PPD or Quantiferon gold testing in all patients on biologic

http://www.renicade.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 infliximab 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 Adalimumab
  - Stopped Adalimumab 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; budesonide 9 mg per day started
- Does not respond to 4 months of AZA at 3 mg/kg and budesonide

Before and after treatment with Natalizumab
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

PML Case Overview

- As of 6/30/12
  - 104,300 patients have received Natalizumab in post-marketing setting
- As of 10/3/12
  - 298 cases of confirmed PML
  - One confirmed case of PML in a Natalizumab-treated CD patient

https://medinfo.elan.com

PML Incidence

<table>
<thead>
<tr>
<th>Total # patients exposed to Nataliz.</th>
<th>Total # of Nataliz. patients exposed to PML, (US)</th>
<th>Total # of Nataliz. patients exposed to PML, (EEA)</th>
<th>Total # of Nataliz. patients exposed to PML, (ROW)</th>
</tr>
</thead>
<tbody>
<tr>
<td>104,300</td>
<td>56,612</td>
<td>35,371</td>
<td>8,275</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 Natalizumab-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
Natalizumab PML Risk Estimates by Treatment Epoch

Risk Stratification and Monitoring Prior to and After Initiation of Natalizumab

- “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 Natalizumab
  - Incidence of PML related to exposure to JC virus, concurrent IS, and duration of exposure to Natalizumab
  - Risk of PML as high as 1/91 if JCV +, prior IS use and more than 2 years exposure to Natalizumab
- 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