Infectious and Malignancy Risks with Immunomodulator and Biologic Therapies

Brian Behm MD
Associate Professor of Medicine
Director, Inflammatory Bowel Disease Program
University of Virginia

Infections in patients with IBD

- How often and with what medications?
- Does combination therapy increase risk?
- Vaccinations
• 59M Crohn’s disease

• Clinical remission on azathioprine 200mg/d
  – Saw PCP for annual exam
  – Discussed vaccines including zoster vaccine
  – Can zoster vaccine be administered on AZA?

How often do infections occur on immunosuppressive medications?

<table>
<thead>
<tr>
<th></th>
<th>MTX</th>
<th>MTX + infliximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>58.7%</td>
<td>61.9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>AZA</th>
<th>Infliximab</th>
<th>AZA + IFX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious infections</td>
<td>5%</td>
<td>2.5%</td>
<td>3.4%</td>
</tr>
</tbody>
</table>

Feagan BG. Gastroenterology 2014;146:681
Colombel N. N Eng J Med 2010; 362:1383
Dulai PS. Clin Gastroenterol Hepatol 2014;12:1443
Life-threatening infections on anti-TNF therapy

• Risk of death from sepsis = 4/1000 pt/yr

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th># Deaths from sepsis attributed to infliximab</th>
<th># of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ljung et al. Gut 2004</td>
<td>Population Based Cohort</td>
<td>1</td>
<td>191</td>
</tr>
<tr>
<td>Senderer et al. Gastroesoph 2004</td>
<td>Single-Center Cohort</td>
<td>0</td>
<td>92</td>
</tr>
<tr>
<td>Colombel et al. Gastroenterology 2004</td>
<td>Single-Center Cohort</td>
<td>5</td>
<td>500</td>
</tr>
<tr>
<td>Sands et al. NEJM 2004</td>
<td>Randomized Controlled Trial</td>
<td>2</td>
<td>282</td>
</tr>
<tr>
<td>Hannauer et al. Lancet 2002</td>
<td>Randomized Controlled Trial</td>
<td>1</td>
<td>573</td>
</tr>
<tr>
<td>Rutgeerts et al. Gastroenterology 1999</td>
<td>Randomized Controlled Trial</td>
<td>0</td>
<td>73</td>
</tr>
</tbody>
</table>

Siegel CA. Clin Gastroenterol Hepatol 2006;4:1017

Who is at highest risk of severe infection (sepsis) related to anti-TNF?

• Older
  – Average age = 63 (systematic review); 65 (Mayo)
• Multiple co-morbidities
• Concomitant medications
• Long-standing disease

Young “healthy” patients seem to have much less risk

Siegel CA. Clin Gastroenterol Hepatol 2006;4:1017
Colombel JF. Gastroenterology 2004;126:19
Toruner M. Gastroenterology 2008;134:929
Opportunistic infections with one or more immunosuppressants

• Opportunistic infections

<table>
<thead>
<tr>
<th>Prednisone, 6MP/AZA, Infliximab</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 medication</td>
<td>2.9 (1.5–5.3)</td>
</tr>
<tr>
<td>2 or 3 medications</td>
<td>14.5 (4.9–43)</td>
</tr>
</tbody>
</table>

Risk of OI greatest in patients > 50

Opportunistic infections: Mayo Clinic experience

<table>
<thead>
<tr>
<th>Number of IS meds</th>
<th>Cases</th>
<th>Controls</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>38</td>
<td>129</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>1</td>
<td>38</td>
<td>59</td>
<td>2.9 (1.5-5.3)</td>
</tr>
<tr>
<td>2 or 3</td>
<td>24</td>
<td>12</td>
<td>14.5 (4.9-43)</td>
</tr>
</tbody>
</table>

Specific combinations

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZA/6MP + steroids</td>
<td>16</td>
<td>6</td>
<td>17.5 (4.5-68)</td>
</tr>
<tr>
<td>AZA/6MP + IFX</td>
<td>1</td>
<td>5</td>
<td>1.6 (0.1-19)</td>
</tr>
<tr>
<td>AZA/6MP + IFX + steroids</td>
<td>5</td>
<td>0</td>
<td>infinite</td>
</tr>
<tr>
<td>Number of IS meds</td>
<td>Cases</td>
<td>Controls</td>
<td>OR</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------</td>
<td>----------</td>
<td>------------------</td>
</tr>
<tr>
<td>0</td>
<td>38</td>
<td>129</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>1</td>
<td>38</td>
<td>59</td>
<td>2.9 (1.5-5.3)</td>
</tr>
<tr>
<td>2 or 3</td>
<td>24</td>
<td>12</td>
<td>14.5 (4.9-43)</td>
</tr>
</tbody>
</table>

**Specific combinations**

<table>
<thead>
<tr>
<th>Combination</th>
<th>Cases</th>
<th>Controls</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZA/6MP + steroids</td>
<td>16</td>
<td>6</td>
<td>17.5 (4.5-68)</td>
</tr>
<tr>
<td>AZA/6MP + IFX</td>
<td>1</td>
<td>5</td>
<td>1.6 (0.1-19)</td>
</tr>
<tr>
<td>AZA/6MP + IFX + steroids</td>
<td>5</td>
<td>0</td>
<td>infinite</td>
</tr>
</tbody>
</table>

Toruner M Gastroenterology 2008;134:929
Integrin inhibitors

- Natalizumab - risk of PML (progressive multifocal leukoencephalopathy)
  - Estimated risk: 1/500
  - 1/100 in highest risk pts

- Vedolizumab-
  - Clinical trials - no increase in serious infections
  - PML risk uncertain but likely lower


Vaccination recommendations for immunosuppressed IBD patients

- Annual influenza vaccination in IBD patients

- Pneumococcal vaccination in IBD patients, repeat 5 years later

- Consider vaccinating IBD patients at diagnosis before immunosuppressed
**Vaccinations- when to give**

- IBD patients on thiopurine alone had a normal response to pneumococcal and influenza vaccinations.

- Combination anti-TNF + immunomodulator had poor response to pneumococcal and influenza vaccination.

**2013 IDSA Guidelines: vaccination of the immunosuppressed patient**

- How long to wait to start immune suppression after live virus vaccine?
  - At least 4 weeks.

  - **NEVER** give live influenza, MMR, or yellow fever if immune suppressed.

- Household contacts
  - CAN receive: MMR, rotavirus, Varicella/Zoster, yellow fever, oral typhoid.
  - **CANNOT** receive: live influenza, live polio.

References:
Melmed GY Gastroenterology 2007;132:A-68.
Lu, Am J Gastroenterol 2009; 104:444.

Rubin, LG Clin Infect Dis 2014:58:e44.
2013 IDSA Guidelines: Herpes Zoster vaccination

- Differentiate “low-level” from “high-level” immune suppression
  - Low-level = prednisone ≤ 20mg/kg/day, AZA ≤ 3.0mg/kg, 6MP ≤ 1.5mg/kg, MTX ≤ 0.4mg/kg/wk
  - High-level = prednisone > 20mg, higher doses AZA/6MP, MTX or ANY anti-TNF biologic

- Zoster vaccine
  - NO for high-level
  - YES for low-level (if > 50 years old, younger if history of varicella)

Rubin, LG Clin Infect Dis 2014:58:e44

Infections- bottom line

- We can’t prevent them all
  - Serious infection - 3-5% immunomodulator and anti-TNF therapies
  - Increased risk in older patients
  - Opportunistic infections- rare, increased with 2 or 3 immunosuppressant

- We can minimize risk of serious infections through patient selection and vaccination

- Live vaccines contraindicated in patients on anti-TNF
- Zoster vaccine may be given to patients on “low-dose” immunomodulator
Malignancy in patients with IBD

- What is the patient’s baseline risk?
  - Lymphoma
  - Skin cancer

- How much is the medication going to increase this risk?

- 24M Crohn’s- ileal, perianal
  - Inadequate response to steroids
  - Discussion of anti-TNF therapy – combination or monotherapy

- Patient concern re: cancer (lymphoma)
Risk of lymphoma with thiopurine therapy

- Meta-analysis
  - 18 studies
  - SIR 5.71 (3.7-10.1) current
  - SIR 1.42 (0.86-2.34) former

Kotlyar DS Clin Gastroenterol Hepatol 2014;epub

CESAME – Lymphoma risk

<table>
<thead>
<tr>
<th>At cohort entry</th>
<th>N</th>
<th># Lymphomas</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never exposed to thiopurines</td>
<td>10,810</td>
<td>6</td>
<td>Reference</td>
</tr>
<tr>
<td>On therapy with thiopurines</td>
<td>5,867</td>
<td>16</td>
<td>5.3 (2.0 – 13.9)</td>
</tr>
<tr>
<td>Previously discontinued thiopurines</td>
<td>2,809</td>
<td>2</td>
<td>1.0 (0.2 – 5.1)</td>
</tr>
</tbody>
</table>

Beaugerie L. Lancet 2009:374-1617
Lymphoma risk with anti-TNF therapy

- Meta-analysis 8905 patients
- NHL rate – 6.1 per 10,000 p-y of exposure

<table>
<thead>
<tr>
<th>Combination</th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF vs SEER</td>
<td>3.2</td>
<td>1.5 – 6.9</td>
</tr>
<tr>
<td>Anti-TNF vs IMM alone from Kandiel</td>
<td>1.7</td>
<td>0.5 – 7.1</td>
</tr>
</tbody>
</table>


Combination therapy - lymphoma

- Retrospective cohort (Kaiser)
- 16023 pts with IBD – 43 lymphoma (10 pts on immunosuppression)
  - Thiopurine SIR 1.4 (1.2-2.7)
  - Anti-TNF monotherapy did not increase risk (1 pt)

<table>
<thead>
<tr>
<th>Combination therapy</th>
<th># (abs)</th>
<th>SIR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current thiopurine + TNF</td>
<td>2</td>
<td>10.2</td>
<td>1.2 – 36.9</td>
</tr>
<tr>
<td>Current thiopurine + TNF</td>
<td>1</td>
<td>6.6</td>
<td>4.4 – 8.8</td>
</tr>
<tr>
<td>Current thiopurine + TNF</td>
<td>1</td>
<td>5.0</td>
<td>0.1 - 28.0</td>
</tr>
</tbody>
</table>

Herrinton LJ Am J Gastroenterol 2011;106:2146
Beaugerie L. Lancet 2009;374:1617
Osterman M. Gastroenterology 2014
Hepatosplenic T-Cell Lymphoma

- IBD patients reported to FDA AERS
  - Young males – median age 22.5
  - Long-term thiopurine (median 6 yr)
    - Thiopurine alone 17
    - Anti-TNF alone 1
    - Combination therapy 23

Kotlyar DS Clin Gastroenterol Hepatol 2011;9:36

Beaugerie L. Lancet 2009;374:1617

Hepatosplenic T-cell lymphoma

- CESAME cohort – 0 cases from 26,640 person-years (16,659 current, 9,981 prior exposure; 44% male)
Lymphoma risk in the elderly: thiopurines

- Thiopurine therapy
  - Continuing
  - Discontinued
  - Never received

<table>
<thead>
<tr>
<th>Cases of LD</th>
<th>5</th>
<th>0</th>
<th>0</th>
<th>6</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>1</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence rate (per 1000 patient-years)</td>
<td>0.37</td>
<td>0</td>
<td>0</td>
<td>2.58</td>
<td>0.66</td>
<td>0.40</td>
<td>1.88</td>
<td>1.68</td>
<td>5.41</td>
</tr>
</tbody>
</table>

Incidences rates of lymphoproliferative disorders according to thiopurine exposure grouped by age at entry in the cohort

Is vedolizumab associated with increased risk of lymphoma?

- Mechanistically- seems unlikely
- One case B-cell lymphoma in clinical trials
Lymphoma- bottom line

• Does immunosuppressive therapy increase the risk of lymphoma?
  – Thiopurines – yes, but risk may resolve after discontinuation
  – Anti-TNF – Possibly
  – Combination – Yes and possibly more than thiopurine alone

• Do the benefits outweigh the risks?
  – In most scenarios, yes
  – Older patients, young males

Crohn’s is associated with increased risk of skin cancer at baseline

• Non-melanoma (NMSC)
  – SIR 2.4 (1.4-3.9)

• Melanoma
  – SIR 1.52 (1.15-1.98)
Past and current thiopurine exposure increases the risk for NMSC

Do thiopurines increase the risk of melanoma?

- Thiopurines were not associated with increased risk
  - Nested case-control
  - 108,579 IBD patients
  - OR: 1.10 (95% CI, 0.72-1.67)
Risk of NMSC in IBD patients exposed to anti-TNF

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Risk estimate</th>
<th>Biologics increase the risk of NMSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long CGH 2010</td>
<td>IFX/ ADA in CD</td>
<td>Recent use (≤90 days): OR 2.07 (95% CI 1.28-3.33) Persistent use (&gt;365 days): OR 2.18 (95% CI 1.07-4.46)</td>
</tr>
<tr>
<td>Long Gastro 2012</td>
<td>IFX/ ADA/ CZP in IBD</td>
<td>Any use OR 1.14 (95% CI 0.95-1.36)</td>
</tr>
<tr>
<td>Burmester Ann Rheum Dis 2013</td>
<td>ADA in CD</td>
<td>SIR 2.29 (95% CI 1.44-3.47)</td>
</tr>
</tbody>
</table>

What about combination therapy?

<table>
<thead>
<tr>
<th>Medication</th>
<th>NMSC cases (n = 1895) n (%)</th>
<th>Controls (n = 8914) n (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No immunosuppressant</td>
<td>1587 (83.8)</td>
<td>8290 (93.0)</td>
<td>Referent</td>
</tr>
<tr>
<td>Any thiopurine alone</td>
<td>265 (14.0)</td>
<td>484 (5.4)</td>
<td>2.72 (2.27-3.26)</td>
</tr>
<tr>
<td>Any biologic alone</td>
<td>74 (3.9)</td>
<td>181 (2.0)</td>
<td>1.14 (0.95-1.36)</td>
</tr>
<tr>
<td>Combined thiopurine and biologic</td>
<td>31 (1.6)</td>
<td>40 (0.5)</td>
<td>3.89 (2.33-6.46)</td>
</tr>
</tbody>
</table>

Combined use of thiopurines and biologics >1 year was associated with the greatest increased NMSC risk
Combination therapy with adalimumab / IMM is associated with increased risk of NMSC

- Pooled adalimumab RCT data
  - 5-fold increased risk NMSC

Melanoma risk in IBD patients exposed to anti-TNF agents

- Uncertain
- Meta-analysis
  - Pooled RR: 1.08 (95% CI: 0.59-1.96)
Skin cancer: bottom line

- Thiopurines associated with increased risk of skin cancer
  - 2-fold increased risk of NMSC
    - persists after drug withdrawal
  - Probably no increased risk of melanoma

- Anti-TNF
  - Uncertain whether risk of NMSC or melanoma are increased
  - Combination therapy may increase risk NMSC more than thiopurine

- Vedolizumab- uncertain but mechanistically unlikely

How to incorporate this into clinical practice?

- Spend time discussing risk/benefit
  - Identify those at increased risk from disease
  - Identify those at increased risk from medication

- Discuss using absolute risk rather than relative risk
- Discuss the risk of doing nothing
Crohn’s disease: Risk stratification

• Clinical risk factors for aggressive CD
  – Younger age of onset
  – Ileal or ileocolonic involvement
  – Penetrating / perianal disease
  – Corticosteroids early
  – Smoking

• Endoscopic risk factors
  – Severe endoscopic lesions at index colonoscopy

Beaugerie L. Gastroenterology 2006;130:650
Arnott ID. Am J Gastroenterol 2004;99:2376
Ezoses J. Gastroenterology 1996;110:424
Allez et al. Am J Gastroenterol 2002;97:147

Value of a Short Term Therapeutic Trial

• Define whether patient will respond to therapy
• Entails less risk
• Only continue therapy if there is documented benefit
Summary

- Infections- vaccinate early
  - Zoster vaccine not anti-TNF, okay for IMM
- Older patients most likely to have infectious and malignant complications
  - Consider alternatives to thiopurine in elderly
- Consider monotherapy (or thiopurine withdrawal) in young males starting anti-TNF

TREAT registry data- infection

- 6,273 patients
- Mean follow up 5.2 years
- Risk of serious infection
  - More severe disease activity (HR 2.24)
  - Narcotic use (HR 1.98)
  - Prednisone use (HR 1.57)
  - Infliximab (HR 1.43)

Lichtenstein GR Am J Gastroenterol 2012;107:1409
Thiopurines and NMSC

Relationship of Age and Outcome with Azathioprine Therapy