Adverse Events From Biologic Agents in IBD

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Case
28-year-old with Refractory Disease

- 28-year-old male comes to office for 2nd opinion with 3 year history of Crohn’s ileocolitis.

- He has abdominal pain and diarrhea (6-7x/day) with urgency and 5# wt loss. He has been on 2.5 mg/kg/day of azathioprine and 4 grams of mesalamine for over a year.

- He is a non-smoker.

- No previous h/o surgery.

- On exam he looks thin, afebrile. Tender to palpation in RLQ. HR is 100
  - Labs: WBC= 10k, Hgb 11, Plt 600, CRP 20
  - Stool studies negative.

28-year-old with Refractory Disease (Part B)

- Colonoscopy is performed and shows severe ulceration in the right colon and ileum.

- CTE: 8 cm segment in distal ileum with inflammation and some narrowing.
Before We Review the Risks of Biologics......

It is important to review the risks of under-treatment of IBD

They say "always trust your gut".
Have you met my gut? You don't want to trust that bastard.

Most Crohn’s Disease Patients Will Require Surgery

The Natural History of Progressive CD: Opportunities for Disease Modification

In other words, IBD is a....

A chronic and progressive destructive disease of the intestines
Weighing the Risks and Benefits of Biologics

**Pros**
- Control Inflammation
- Maintenance of remission
- Improved function and QOL
- Early promotion of mucosal healing to prevent complications
- Prevent Surgery

**Cons**
- Short-Term Side Effects
- Long-Term Toxicity
- Cost

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**Anti-TNF Agents: Adverse Events**

- Immunogenicity
- Injection site reactions
- Infections including bacterial, viral, fungal and granulomatous (TB, histo, Listeria, etc.)
- Lymphoproliferative disorders
- Autoimmunity

- Psoriasiform lesions
- Demyelinating disorders (?)
- Worsen or de novo congestive heart failure
- Hepatotoxicity (rare)
### Adverse Events Associated with anti-TNF Treatment

<table>
<thead>
<tr>
<th>Event</th>
<th>Estimated Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop therapy due to adverse event</td>
<td>10%</td>
</tr>
<tr>
<td>Infusion or injection site reactions</td>
<td>3%-20%</td>
</tr>
<tr>
<td>Drug related lupus-like reaction</td>
<td>1%</td>
</tr>
<tr>
<td>Serious infections</td>
<td>3%</td>
</tr>
<tr>
<td>Skin</td>
<td>1-20%</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>0.05% (5/10,000)</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma (combo)</td>
<td>0.06% (6/10,000)</td>
</tr>
<tr>
<td>Multiple sclerosis, heart failure, serious liver injury</td>
<td>Case reports only</td>
</tr>
</tbody>
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**Risk:** Lymphoma
Risk of Developing Non-Hodgkin’s Lymphoma

Patient with Crohn’s disease (without immune suppression)

Estimated annual risk = 2 per 10,000 treated patients

Patient with Crohn’s disease receiving Anti-TNF monotherapy

Estimated annual risk = 4 per 10,000 treated patients
Putting Risk in Perspective

Anti-TNF and NHL

- Absolute risk is not known because there is not sufficient numbers of patients with IBD on an anti-TNF that have NOT been exposed to an immunomodulator
  - Meta-analysis estimates rate of NHL in CD patients treated with an anti-TNF to be 4-6 per 10,000 treated over a course of a year

Siegel, C, Review Article: explaining risks of inflammatory bowel disease therapy to patients. Aliment Pharmacol Ther 2011;33:25-32
Incidence Rates of Lymphoproliferative Disorders

According to thiopurine exposure
Grouped by age at entry in cohort

Risk of Lymphoma Associated with TNFs

<table>
<thead>
<tr>
<th>1st Author</th>
<th>Setting</th>
<th>Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siegel CGH 2009</td>
<td>Meta-Analysis of RCT</td>
<td>3.23</td>
<td>1.5 – 6.9</td>
</tr>
<tr>
<td>Herrinton AJG 2011</td>
<td>Registry (Kaiser-Permanente)</td>
<td>4.4</td>
<td>3.4 – 5.4</td>
</tr>
<tr>
<td>Anderson 2014</td>
<td>Registry (Denmark)</td>
<td>0.90</td>
<td>0.42 – 1.91</td>
</tr>
<tr>
<td>Kopylov 2015</td>
<td>Health insurance Database (Quebec)</td>
<td>3.1 (Combo)</td>
<td>0.72 – 13.48</td>
</tr>
<tr>
<td>Kopylov 2015</td>
<td>Health insurance Database (Quebec)</td>
<td>1.57 (Mono)</td>
<td>0.16 – 14.94</td>
</tr>
</tbody>
</table>
Rate of Malignancy in TNF Exposed IBD Pts

- Nationwide Danish Registry including 56,146 pts (4553 pts exposed to TNFs)
  - 489,433 person-years of follow-up
- No increased risk of cancer (OR 1.07; 95%CI 0.85 – 1.36)

Increased Risk for Malignancy with Combination vs Mono Therapy

- Pooled analysis of ADA controlled trials
- Pts receiving monotherapy at no greater risk for NMSC or other cancers
- Those on combo had 4.59 (2.51-7.70) for NMSC and 3.04 (1.66-5.10) for other cancers when compared to SEER data
- Combo vs mono NMSC 3.46 (1.08-11.06) and 2.82 (1.07-7.44) all others
- These data suggest cancer risk driven by thiopurine and not anti-TNF,
Hepatosplenic T-cell Lymphoma Risk in IBD

HSTCL: Rare form of lymphoma
- 200 reports in the literature
- Post-organ transplant

Inflammatory bowel disease:
- N=36 total
  - AZA alone: N=16
  - Anti-TNF: N=20
    - N=20: infliximab, all with current or prior AZA
    - N=4: adalimumab, all with prior infliximab

All patients who received AZA
  - All but 1 patient had >2 years of AZA use

Of 31 pts of known gender, only 2 were female

27 of the 30 pts of known age were <35 years old, most <22 years

Risks: Cancer
Malignancy and Biologic Use

• N=14,590 pts from 49 trials

• No association between biologic use and an increased risk of malignancy
  • OR 0.90 (CI 0.54 – 1.50)

The Risk of Developing Cancer in Patients With IBD: Does Infliximab Contribute to Risk?

Methods:

Results:
• Over the 15 yr period, out of 56.6 million people, 3,973,484 pts (6.9%) developed cancer (non-IBD population: cancer rate 6.9% n=3,904,520/56,198,035).

• However, the rate of cancer amongst IBD population was significantly higher at 11.5% (n=42,571/368,716, P<0.001)
Anti-TNFs Do not Increase Risk of Recurrent Cancer

Two meta-analyses presented to understand risk of combined cancer recurrence in individuals with inflammatory conditions:

- >11,000 persons with a history of cancer and immune mediated baseline condition
- Stratified according to disease type and cancer type
- Median interval of IS use: 6 years

Risk: Skin Manifestations
### Incidence of Dermatologic Consequences in IBD Patients on Anti-TNFs

<table>
<thead>
<tr>
<th>Dermatologic Consequences</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous Infections</td>
<td>11.6</td>
</tr>
<tr>
<td>Psoriasiform Eruption</td>
<td>10.1</td>
</tr>
<tr>
<td>Skin Cancer</td>
<td>0.9</td>
</tr>
<tr>
<td>Eczema</td>
<td>2.2</td>
</tr>
<tr>
<td>Immune Mediated</td>
<td>0.9</td>
</tr>
</tbody>
</table>

#### Risk: Skin Cancer
Rates of BCC and SCC in IBD pts Exposed to Thiopurines

<table>
<thead>
<tr>
<th>Thiopurine therapy</th>
<th>&lt;50 years</th>
<th>50-65 years</th>
<th>&gt;65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuing</td>
<td>0.66</td>
<td>1.96</td>
<td>4.04</td>
</tr>
<tr>
<td>Discontinued</td>
<td>0.38</td>
<td>5.70</td>
<td>0.84</td>
</tr>
<tr>
<td>Never received</td>
<td>0.00</td>
<td>0.60</td>
<td>6.70</td>
</tr>
</tbody>
</table>

**Cases of NMSC (n)**
- 9: 13590
- 3: 7624
- 0: 15736
- 6: 2319
- 3: 1530
- 3: 4968
- 3: 743
- 3: 526
- 2: 2383

**Patient-years**
- <50 years: 393
- 50-65 years: 15736
- >65 years: 2383

Risk of Skin Cancer Based on Treatment

- Combination therapy has been associated with an increased risk of skin cancer
  - (OR 5.85, CI 3.2 – 10.8)
Melanoma in Patients with IBD

Risk of 2nd NMSC is not Increased with Biologic Treatment
Risk: Psoriasis

Psoriasis associated with Anti-TNF therapy

- Described with all the anti-TNF: class effect
- Described in patients receiving treatment for diverse indications (RA, IBD, psoriasis, psoriatic arthritis, ankylosing spondylitis)
- Often leads to therapy discontinuation
- First IBD case reported in 2004 in a CD patient treated with infliximab

Increasingly recognised side-effect of anti-TNF therapy in the IBD literature
When you see this – think anti-TNF Mediated Psoriasis

- Several phenotypes:
  - Palmoplantar pustular psoriasis: form most commonly associated with anti-TNF therapy (even in patients treated for plaque psoriasis)

....or this......anti-TNF Psoriasis

- Several phenotypes:
  - Inverse psoriasis (type of psoriasis in plaques)
Risk of Anti-TNF Induced Psoriasis

- Risk is low (1.7%) overall or 0.5% per patient year
- Risk elevated in Females (HR 1.9) and Smokers (HR 2.1)
- Location:
  - Palmoplantar – 38%
  - Scalp - 33%
  - Trunk – 18%
  - Flexures – 21%
  - Facial – 10%

- Topical steroids or combination therapy was effective in 2/3 of pts
- Re-occurred in > 50% when changed to another TNF
- Not associated with elevated drug levels or antibodies

Demyelinating Disease with Anti-TNF

- Increased risk in IBD population (even before biologic era)
- Estimated risk:
  - 0.2 cases per 1000 pt yrs for infliximab
  - 1 case per 1000 pt yrs for adalimumab

### Table 2B
Characteristics of Neurologic Complications Reported with Anti-TNF-α Agents
Based on FDA Adverse Event Reporting System (Adapted from Ref. 43)

<table>
<thead>
<tr>
<th>Pattern of Neurological Involvement in Patients with Neurological Complications Due to Anti-TNF-α Agents</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>'Demyelination'</td>
<td>136 (32)</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>71 (16.7)</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>33 (7.8)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>141 (33.2)</td>
</tr>
<tr>
<td>Leukoencephalopathy</td>
<td>17 (4)</td>
</tr>
<tr>
<td>Transverse myelitis</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Chronic inflammatory demyelinating polyneuropathy</td>
<td>10 (2.3)</td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td>Posterior reversible encephalopathy syndrome</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

Singh S, et al. IBD 2013;19:864
Risk: Infections

Meta-Analysis of Biologic Clinical Trials

N=14,590 pts from 49 trials

- Rate of any infection was moderately increased OR 1.19 (CI 1.10-1.29)
- Significant increased Risk of opportunistic OR 1.90 (CI 1.21 – 3.01)
- Rate of serious infection was not increased OR 0.89 (0.71-1.12)
Infections and Mortality in the TREAT Registry: 15,000 Patient-Years of Experience

Multivariate Analysis

Adjusted Odds Ratio

0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5

Mortality

Serious infections

IFX = infliximab
AZA = azathioprine
6-MP = 6-mercaptopurine
MTX = methotrexate

P = .001
P = .006
P = .002

Risk Factors for Serious Infections in Patients Receiving Infliximab and Other IBD Therapies: TREAT™ Registry Data

Factors Associated with SAEs

Age and Rate of SAEs with Treatment

Adjusted Hazard Ratios (95% CI)

Rates of AEs and Serious Infections Are Stable Over Time with anti-TNF Therapy

• Methods
  • Population based cohort: Olmsted County, US
  • Medical record review – CD patients (1970-2010)
  • Data recorded anti-TNF therapy use
  • Assessed hospitalizations, surgeries, AEs, and serious infections

• Results
  • 424 patients (50.7% women, 29.4 years old [IQR 20.9-46.6])
    • 33 with AE or serious infection
    • Cumulative probability: 10% at 90 days, 21.6% at 1 year

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Total (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td>3</td>
</tr>
<tr>
<td>Skin and soft tissue infections</td>
<td>4</td>
</tr>
<tr>
<td>Intra-abdominal abscess</td>
<td>1</td>
</tr>
<tr>
<td>Pneumocystis jiroveci pneumonia</td>
<td>1</td>
</tr>
<tr>
<td>E. coli bacteremia</td>
<td>1</td>
</tr>
<tr>
<td>C. difficile toxic megacolon</td>
<td>1</td>
</tr>
</tbody>
</table>

Cumulative Probability of AE or Serious Infection after anti-TNF Initiation

<table>
<thead>
<tr>
<th>Cumulative Probability of First AE or Serious Infection</th>
<th>0</th>
<th>20</th>
<th>40</th>
<th>60</th>
<th>80</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>21.6%</td>
<td>25.5%</td>
<td>30.5%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AE, adverse event; IQR, interquartile range

Opportunistic Infections

• Bacterial
  • Tuberculosis
  • Atypical mycobacterial
  • Listeriosis

• Invasive Fungal
  • Histoplasmosis
  • Coccidioidomycosis
  • Candidiasis
  • Aspergillosis
  • Pneumocystosis


Histoplasmosis

Geographic Distribution of Histoplasmosis, 1999-2008: Medicare Sample

Minimizing Toxicity for Anti-TNF Therapy

- Rule out evidence for TB prior to initiation
  - If immunocompromised, PPD and Quantiferon may be negative
- Rule out active infection prior to initiation
  - Abscess, C. difficile, CMV
- Check serology for Hepatitis B
- Vaccination for age-appropriate disease
  - Influenza, HAV, HBV, Pavax
- Assess for signs/symptoms of:
  - Uncontrolled heart failure
  - Demyelinating disorders
  - Skin cancers/suspicious moles

Vedolizumab
Vedolizumab Safety

• ~3000 patients treated in clinical trials, including ~1000 treated for ≥2 years
  • Nasopharyngitis, URI, sinusitis and UTIs most commonly reported in clinical trials
    • Infections/patient year: 0.85 vedolizumab, 0.7 placebo
    • Serious infections/patient year: 0.07 vedolizumab, 0.06 placebo
  • Infusion reactions are infrequent
    • 4% of patients in clinical trials developed an infusion reaction c/w 3% of patients treated with placebo
    • Vedolizumab discontinued in < 1% of patients in clinical trials due to infusion reactions
  • Abnormal liver function tests seen rarely
  • No cases of progressive multifocal leukoencephalopathy (PML) seen to date

Vedolizumab Safety in Clinical Trials

• N= 2830 (4811 pt years)
  • Infection rate was 63.5/100 PY vs. 82.9 / 100 PY in placebo
    • URI accounted for > 50%
  • Malignancy rate 0.1 /100 PY
Real World Data on Vedolizumab Safety – US Victory Consortium Results

- Multicenter Retrospective Cohort Study
  - Moderate to Severe CD only
  - N=212
  - Serious Infections occurred in 21 pts (13 / 100 PYF)
  - Serious Adverse Events occurred in 17 (10 / 100 PYF)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Event per 100 PYF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteric Infection</td>
<td>5</td>
</tr>
<tr>
<td>URI</td>
<td>4.4</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>3.1</td>
</tr>
<tr>
<td>UTI</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Conclusion / Take Home Points

- Need to frame the discussion in context with the risk of disease progression
- Risk of Lymphoma is low ~ 6/10,000 patients for those on combo
- Risks of infection with TNFs low – highest risk groups are the elderly, those on concomitant steroids or narcotics
- Other potential risks including drug induced psoriasis, MS, etc are uncommon
- Some of the risks can be mitigated by performing indicated pretesting including TB, HBV, etc., administering appropriate vaccines, and correctly selecting the appropriate patients.