Inflammatory Bowel Disease: Complications and Risks from Immunomodulators and Biologics

Edward V. Loftus, Jr., M.D.
Professor of Medicine
Mayo Clinic
Rochester, Minnesota, USA
### Loftus Disclosures (last 12 months)

<table>
<thead>
<tr>
<th>Research support</th>
<th>Consultant</th>
</tr>
</thead>
<tbody>
<tr>
<td>• AbbVie*</td>
<td>• AbbVie*</td>
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<tr>
<td>• UCB*</td>
<td>• UCB*</td>
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<td>• Genentech</td>
<td>• Janssen*</td>
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<td>• Janssen*</td>
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<td>• Pfizer</td>
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<td>• Takeda*</td>
<td>• Mesoblast</td>
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<tr>
<td>• Robarts Clinical Trials</td>
<td>• Salix</td>
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<td>• Seres Therapeutics</td>
<td>• Bristol-Myers Squibb</td>
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<td>• Receptos</td>
<td>• CVS Caremark</td>
</tr>
<tr>
<td>• Gilead</td>
<td>* Company manufactures a drug discussed in this presentation</td>
</tr>
<tr>
<td>• MedImmune</td>
<td></td>
</tr>
</tbody>
</table>
The Difficulty in Assessing Causality in Adverse Events

Direct

Drug → Adverse Effect

Indirect

Confounder

Underlying Disease
Disease Severity
Other Drugs
Infection Definitions

• Opportunistic infection
  • Infection by an organism which has limited pathogenic capacity in ordinary circumstances

• Serious infection
  • Infection resulting in need for intravenous therapy or hospitalization, or which results in disability or death

• Not all opportunistic infections are serious and not all serious infections are opportunistic
Immunosuppression in IBD

• Not all IBD patients are immunosuppressed
• Most important factors
  • Increased age
  • Malnutrition
  • Comorbidities (e.g., COPD, DM)
  • Medications: steroids, immunosuppressives, biologics
  • Hospitalization
• Interplay of these factors results in variable amounts of immunosuppression with same medications
• No clinical test available to measure “immunity”
Risk of Hospitalization for Serious Infection After Starting Medication for IBD (n=2,323 Pairs Matched on Propensity Score)


- Incidence rates:
  - Anti-TNF: 10.9 per 100 PY
  - AZA/6MP: 9.6 per 100 PY

- Adjusted hazard ratio: 1.1 (0.8-1.5)

Conclusion: Anti-TNF agents NOT associated with increased risk of hospitalization due to serious infection relative to non-biologics

Grijalva CG et al, JAMA 2011;306:2331-9
Infections and Mortality in the TREAT Registry: 15,000 Patient-Years of Experience

**Multivariate Analysis**

- **Mortality**
  - IFX
  - AZA
  - 6-MP
  - MTX
  - Steroids
  - *P* < 0.001

- **Serious infections**
  - IFX
  - AZA
  - 6-MP
  - MTX
  - Steroids
  - *P* = 0.006
  - *P* = 0.002

AZA = azathioprine; IFX = infliximab; MTX = methotrexate.
Opportunistic Infections with Anti-TNF Agents in IBD: Meta-Analysis of RCT’s

• 39 OI’s in 4135 patients on anti-TNF (0.9%)
  • 8 active TB (0.2%)
  • 6 oral/esophageal candidiasis (0.15%)
  • 6 herpes zoster (0.15%)
  • 2 varicella zoster (0.05%)
  • 8 herpes simplex (0.2%)

• 9 OI’s in 2919 patients on placebo (0.3)

• RR, 2.05 (95% CI, 1.1 – 3.9)

• In other words, anti-TNF use doubles the risk of opportunistic infection
Oral Steroids and Serious Infections in Patients with Elderly-Onset IBD

- Quebec provincial healthcare database, ‘96-’09
- 3522 IBD pts (diagnosed >66 yrs) followed mean of 4 years: 564 serious infections
  - Incidence of serious infection: 3.7 per 100 PY
- Incidence rate of serious infection 2.3 times higher in those on steroids last 6 months
  - 2.8 times higher in those on steroids last 45 days
- In other words, steroids double to triple rate of serious infections in the elderly

## Mayo Case-Control Study of Opportunistic Infections in IBD

<table>
<thead>
<tr>
<th>Number of 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

- Corticosteroids alone: 16, 27, 2.2 (1.0-4.9)
- 6MP/AZA alone: 20, 31, 3.4 (1.5-7.5)
- IFX alone: 3, 2, 11.1 (0.8-148)
- AZA/6MP + steroids: 16, 6, 17.5 (4.5-68)
- AZA/6MP + IFX: 1, 5, 1.6 (0.1-19)
- AZA/6MP + IFX + steroids: 5, 0, 1.1 (1.0-1.2)

Toruner et al. Gastro 2008;134:929
Best Recommendations for Management of Opportunistic Infections in IBD

- Multidisciplinary task force
- Developed statements, then systematic reviews, then further refining of statements online, then in-person meeting to develop consensus

Rahier JF et al, J Crohns Colitis 2014;8:443-68
Viral Infections in Immunosuppressed IBD

- Herpes simplex
- Varicella zoster
  - Varicella
  - Zoster
- Cytomegalovirus
- Epstein-Barr Virus
- Human papillomavirus
- John Cunningham (JC) virus
- Hepatitis B and C

Rahier JF et al, J Crohns Colitis 2014
Dave M/Loftus EV Jr et al, Inflamm Bowel Dis 2014;20:196-212
Cytomegalovirus Colitis in IBD

• Classic case: immunosuppressed patient with steroid-refractory disease
  • Ulcers usually present

• Need biopsies, ask for immunohistochemistry

• CMV viremia present in only 30%

Courtesy of Dr. Jeffrey McCurdy
CMV: Impact of Treatment & Density

Antiviral therapy lowers colectomy rate, especially in those with higher CMV inclusion density.

Anti-Viral Therapy & Risk of Colectomy: Systematic Review and Meta-Analysis

Includes only studies of steroid-refractory disease

Conclusion: There IS a role for anti-viral therapy in CMV-positive patients with steroid-refractory IBD

Shukla T/Singh S/McCurdy JD et al., Inflamm Bowel Dis 2015;21:2718-25
CMV Colitis Treatment

• Antiviral therapy for patients with high-density CMV and steroid-refractory disease
  • For low-density CMV, focus on IBD therapy, because CMV is “innocent bystander”

• In patients with isolated CMV colitis, consider holding immunosuppression while treating

• For patients with viremia, immunosuppression must be held

Rahier JF et al, J Crohns Colitis 2014
Jones/McCurdy et al, Inflamm Bowel Dis 2015
Risk of Herpes Zoster Is Increased in IBD

• Case control study, GPRD 1988-1997
  • 7823 (Crohn’s), 11,930 (UC), and 79,563 (control)

• Incidence of HZV is about 1.5x higher in IBD

• Risk increases with immunosuppression
  • Corticosteroids OR 1.5 (1.1 – 2.2)
  • AZA/6MP OR 3.1 (1.7 – 5.6)

Gupta, Lautenbach, and Lewis. Gastroenterology 2006
Therapy-Related Herpes Zoster Risk in IBD Patients

- Combined major US databases to assess anti-TNF initiation on herpes zoster (HZ) risk
  - n=236,531; 10,717 with IBD

- No significant difference between anti-TNF and non-biologics (6-MP/AZA/steroids)

Bacterial Infections More Common With Immunosuppression

- Tuberculosis
- Other mycobacterial infections
- Listeriosis
- Pneumococcal infections
- Legionellosis
- Clostridium difficile infection

Rahier JF et al, J Crohns Colitis 2014
Dave M/Loftus EV Jr et al, Inflamm Bowel Dis 2014;20:196-212
Baseline TB Testing Prior to Immune Suppression

- Testing for latent tuberculosis Quantiferon vs TST

- QuantiFERON Gold is consistent despite immunosuppression or BCG status
- Lower false positive
- Single office visit
- Cost effective
- Recommended by CDC!

Disease activity may play a big role in indeterminate results of Quant-Gold

If Tuberculosis Screening Test is Positive...

- Quantiferon Gold positive or skin test ≥ 5mm
- Chest X-Ray
- Work with ID experts
- Before initiating anti-TNF, ideally treat for 6 months with INH, but not always practical – 2 months acceptable (sometimes concurrent needed with close follow)
  - INH 300mg PO qd x 6 months
  - INH + Rifampicin x 3 months (higher hepatitis risk)
  - +/- pyridoxine 50mg PO qd

Rahier JF et al, J Crohns Colitis 2014;8:443-68.
Increased Risk of Invasive Pneumococcal Disease in IBD Patients: Denmark, 1977-2013

- Over 74,000 IBD patients, over 1.4 M controls
- Risk highest in 1st 6 months after diagnosis (more than 3-fold)
- Then stabilized at lower level—>2-fold for CD
- Risk was increased for up to 4 years BEFORE IBD diagnosis
- Limited impact of meds on risk

Kantso B et al, Am J Gastroenterol 2015;110:1582-7
## Burden of CDI in IBD

<table>
<thead>
<tr>
<th>Author</th>
<th>Years</th>
<th>Population</th>
<th>Rate of CDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodemann¹</td>
<td>1998-2004</td>
<td>Referral center</td>
<td>UC: 1.8 → 5.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CD: 1.0 → 2.2%</td>
</tr>
<tr>
<td>Issa²</td>
<td>2004-2005</td>
<td>Referral center</td>
<td>All IBD: 1.8 → 4.6%</td>
</tr>
<tr>
<td>Ananthakrishnan³</td>
<td>1998-2004</td>
<td>NIS discharge database</td>
<td>UC: 2.4 → 3.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CD: 0.8 → 1.2%</td>
</tr>
<tr>
<td>Nguyen⁴</td>
<td>1998-2004</td>
<td>NIS discharge database</td>
<td>UC: 2.7 → 5.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CD: 0.9 → 1.1%</td>
</tr>
<tr>
<td>Ricciardi⁵</td>
<td>1993-2003</td>
<td>NIS discharge database</td>
<td>UC: 1.7 → 3.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CD: 0.9 → 1.3%</td>
</tr>
<tr>
<td>Ananthakrishnan⁶</td>
<td>1998-2007</td>
<td>NIS discharge database</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CD: 0.8 → 1.5%</td>
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</tbody>
</table>

¹Rodemann JF et al, Clin Gastroenterol Hepatol 2007  
²Issa M et al, Clin Gastroenterol Hepatol 2007  
³Anathakrishnan AN et al, Gut 2008  
⁴Nguyen GC et al, Am J Gastroenterol 2008  
⁵Ricciardi R et al, Dis Colon Rectum 2009  
⁶Anathakrishnan AN et al, Inflamm Bowel Dis 2011
# Clinical Outcome in IBD

<table>
<thead>
<tr>
<th>Reference</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Issa¹</td>
<td>63% required hospitalization, 20% had colectomy</td>
</tr>
<tr>
<td>Ananthakrishnan²</td>
<td>↑ mortality (OR 4.7 [2.9-7.9]), hospital stay (OR 3), charges ($11.4K), TPN use (OR 1.9) vs. IBD</td>
</tr>
</tbody>
</table>
| Nguyen³ | ↑ mortality vs. UC: OR 3.8 (2.8-5.1)  
↑ hospital stay/charges (46/46%, 65/63%) vs. UC/CD |
| Ricciardi⁴ | ↑ mortality over time in UC: 5.3% → 8.5%  
Operative mortality 26% in UC |
| Ananthakrishnan⁵ | Mortality vs. IBD: OR 2.4 (1.5-3.7) → 3.4 (2.7-4.3)  
Colectomy vs. IBD: OR 1.4 (0.8-2.4) → 2.5 (1.9-3.3) |
| Jodorkovsky⁶ | 2-fold ↑ hospitalization and colectomy at 1y vs. UC |
| Jen⁷ | ↑ in-hospital mortality vs. IBD: OR 6.3 (5.7-7.0)  
↑ hospital stay vs. IBD: 28 days |

¹Issa M et al, Clin Gastroenterol Hepatol 2007  
²Ananthakrishnan AN et al, Gut 2008  
³Nguyen GC et al, Am J Gastroenterol 2008  
⁴Ricciardi R et al, Dis Colon Rectum 2009  
⁵Ananthakrishnan AN et al, Inflamm Bowel Dis 2011  
⁶Jodorkovsky D et al, Dig Dis Sci 2010  
⁷Jen M-H et al, Aliment Pharmacol Ther 2011
CDI Risk Factors: IBD

- UC (vs. CD)
- Colonic disease\(^1,2\)
- Extent of colonic disease (left-sided / extensive vs. distal)\(^3\)
- Active disease (vs. remission)\(^4\)
- Comorbidities\(^2\)
- Hospitalization\(^5,6\) and abx use\(^5,7\) may be less of a factor than in gen population

\(^1\)Issa M et al, Clin Gastroenterol Hepatol 2007  
\(^2\)Nguyen GC et al, Am J Gastroenterol 2008  
\(^3\)Powell N et al, Gut 2008  
\(^4\)Pascarella F et al, J Pediatr 2009  
\(^5\)Bossuyt P et al, J Crohns Coliits 2009  
\(^6\)Clayton EM et al, Am J Gastroenterol 2009  
\(^7\)Goodhand JR et al, Aliment Pharmacol Ther 2011
Risk Factors: IBD

• IBD meds
  • Maintenance IM ± anti-TNF: OR 2.6 (1.3-5.1)\(^1\)
  • IFX: no increased risk vs. IM\(^2\)
  • Corticosteroids vs. IM\(^2\)
    • Any: RR 3.4 (1.9-6.1)
    • Monotherapy: RR 2.7 (1.5-4.6)

\(^1\)Issa M et al, Clin Gastroenterol Hepatol 2007
\(^2\)Schneeweiss S et al, Aliment Pharmacol Ther 2009
FMT for Recurrent C. diff Infection in IBD Patients at Mayo: Long-Term Follow-Up (n=38)

- 27% Crohn’s, 73% UC
- Median IBD duration, 4 yrs (0.15-41)
- Median of 3 CDI episodes (2-15)
- Median of 4 failed CDI rx (2-14)
- 42% on biologics, 36% IMM
- After FMT, 37% had transient worsening
- 38% noted overall improvement
- 25% needed IBD rx escalation
- 3 pts had recurrent CDI

Khanna S et al, Gastroenterology 2015 Supplement (DDW 2015 poster)
FMT for Recurrent *Clostridium difficile* Infection in Immunocompromised Patients

• Multicenter retrospective analysis of 80 pts with recurrent CDI who were immunosuppressed
  • Included 36 pts with IBD on IMMs or biologics

• Efficacy in IBD population:
  • 86% had resolution of CDI with first FMT
  • Overall cure rate (including 2\textsuperscript{nd} FMT), 94%

• Safety: SAE in 15% within 12 wks post-FMT
  • 2 deaths, including one witnessed aspiration while sedated for scope to administer FMT
  • SAE rate for IBD patients similar (11%)

• 5 IBD pts (14%) had disease flare post-FMT, and 3 UC pts underwent colectomy

**Clostridium difficile Infections in IBD**

- Up to 33% of IBD patients will get *C. diff* infection\(^1\)

- Risk factors:
  - Pre-existing colonic inflammation
  - Severe underlying IBD
  - Immunosuppression
  - Do not need antibiotics as risk factor

- Colonization rate in false-positive testing result unknown

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**Treatment of CDI recurrences\(^1\)**

- **First recurrence:**
  - Same regimen as initial episode
  - If severe, vancomycin should be used

- **Second recurrence:**
  - Pulsed vancomycin regimen

- **3+ recurrences:**
  - Fecal microbiota transplant (FMT) should be considered\(^2\)

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Special Situation: Can Immunosuppression Be Given in the Setting of Abscess?

• Short answer: yes, if abscess is controlled by drain (or if small and on antibiotics)

• In fact, IMM/biologic therapy in this setting REDUCES risk of abscess recurrence!

<table>
<thead>
<tr>
<th>Pharmacologic Therapy* at Abscess Resolution (n=95)</th>
<th>Recurrence (n=25)</th>
<th>Hazard Ratio for Abscess Reoccurrence (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No therapy (n=13)</td>
<td>13</td>
<td>1.00 (reference)</td>
<td>Overall &lt; 0.01</td>
</tr>
<tr>
<td>Immunomodulator monotherapy (n=44)</td>
<td>10</td>
<td>0.42 (0.17 - 1.03)</td>
<td>0.059</td>
</tr>
<tr>
<td>Any anti-TNF therapy (n=38)</td>
<td>2</td>
<td>0.10 (0.02 - 0.36)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Nguyen DL et al, Clin Gastroenterol Hepatol 2012;10:400-4
Fungal Infections More Common in Immunosuppressed Patients

- Histoplasmosis
- Coccidioidomycosis
- Candidiasis
- Aspergillosis
- Pneumocystosis
Geographic Distribution of Histoplasmosis and Coccidioidomycosis in Older Americans, 1999-2008: Medicare Sample

Histoplasmosis

Coccidioidomycosis

Cases per 100,000 person-years

**Pneumocystis jirovecii** Pneumonia (PJP) in Non-HIV-Infected Patients

- Incidence increasing
- Mortality rate 30% – 60%
- Risk factors include corticosteroids (CS), other immunosuppressants (IS), preexisting lung disease
- PJP chemoprophylaxis is effective

Reid AB, Chen SC. Curr Opin Infect Dis 2011;24:534-44
PJP & Inflammatory Bowel Disease (IBD)

• Possible increased risk of PJP in IBD patients

• Incidence not clearly defined

• Crude incidence: 10.6 per 100,000 person-years, increasing to 32 per 100,000 person-years in patients on IMM

• ECCO recommendations for PJP prophylaxis
  - 3 Immunomodulators
  - Consideration with double therapy (if one = calcineurin inhibitor)
  - No consensus with single or double therapy (w/o calcineurin inhibitor)

Rahier JF et al. J Crohns Colitis 2014
PJP in IBD: Olmsted County, Minnesota

- 937 IBD patients 1970-2010, followed through Feb 2016
  - All IBD cases validated through medical record review
  - IBD cases crossed against 2 microbiology databases for PJP
  - 16,066 person-years of follow-up (median 14.8 years)

- 3 cases of PJP
  - All males
  - All over age of 62 years
  - 2 had underlying lung disease
  - 2 on infliximab

PJP in IBD: Olmsted County

- Overall incidence of PJP 0.01 per 100 person-years
  - Steroids: 0.18 per 100 PY
  - Immunosuppressives: 0.13 per 100 PY
  - Biologics: 0.30 per 100 PY
- Double therapy 0.6 per 100 PY
- Triple therapy 0 per 100 PY
- Conclusion: routine PJP prophylaxis may not be warranted; consider in older patients with comorbidities on double or triple therapy

# Suggestions for Managing IBD Therapy in the Setting of Infection*

<table>
<thead>
<tr>
<th></th>
<th>VIRAL</th>
<th>BACTERIAL</th>
<th>FUNGAL</th>
<th>C. diff</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EBV, HSV, CMV, HIV, HepB, HepC, HPV, VZV</td>
<td>Strep/Staph Mycobact</td>
<td>Histoplasm Coccidio</td>
<td></td>
</tr>
<tr>
<td>Thiopurine</td>
<td>Stop</td>
<td>Stop + Rx then individualize</td>
<td>Stop + Rx then Restart when cleared</td>
<td>Continue</td>
</tr>
<tr>
<td></td>
<td>May need to stop + Rx virus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Individualize as to who to restart 6MP/AZA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>Continue</td>
<td>Stop + Rx then individualize</td>
<td>Stop + Rx then Restart when cleared</td>
<td>Continue</td>
</tr>
<tr>
<td></td>
<td>Prob ok to continue, except active Hep B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Integrins</td>
<td>Continue</td>
<td>Continue</td>
<td>Continue</td>
<td>Continue</td>
</tr>
</tbody>
</table>

*in addition to treating the underlying infection
Vedolizumab Safety

• Integrated safety analysis of GEMINI trials: rates of serious adverse events not significantly higher with vedolizumab compared to placebo
  • Rates of serious infections not significantly higher with vedo vs. placebo
  • No cases of PML
  • Risk factors for serious infections
    • Prior anti-TNF failure and opioid analgesic use in UC
    • Younger age, steroid use and opioid analgesic use in CD
  • No black boxed warnings for infection or cancer
  • Perioperative use before abdominal operations may be associated with higher rates of infection (53% vs 33% on anti-TNF vs 28% on non-biologics)

Colombel JF et al, Gut 2016 online early
Lightner AL et al, J Crohns Colitis 2016 online early
Serious Infections with Ustekinumab—PSOLAR Safety Registry of Psoriasis

- Self-reported IBD cases within a psoriasis safety registry PSOLAR (n = 276)
  - Overall prevalence of self-reported IBD was 2.3%
  - Rate of serious infections was more than 2x higher in IBD (3.8 vs 1.6 per 100 PY)
  - Rate of serious infection with UST was only 1.3 per 100 PY, vs. 5.75/100 with IFX, 4.3 with other biologics

Baseline Risk of Lymphoma in IBD

• Most population-based studies, including the very large GPRD study, do not demonstrate an increased baseline risk of lymphoma among IBD patients

• If there is an increased baseline risk it is relatively small

• Referral-based or hospital-based studies need to be viewed with caution due to biases

• We need to stratify such analyses by disease severity/activity
Epstein-Barr Virus-Positive Lymphomas

- Sign of immunosuppression in Western world (e.g., PTLD)
- Case reports of EBV-positive lymphomas in IBD patients on AZA or 6-MP
- Some have regressed after discontinuation of AZA

The overall number of IBD patients seen was similar between these two time frames.

Dayharsh GA et al. Gastroenterology. 2002
Thiopurines and Lymphoma Risk: CESAME

Overall incidence rates of LPD among current thiopurine users = 9 per 10,000
• Hazard ratio thiopurine exposed vs naïve = 5.3 (2.0-13.9)

- 18/23 (78%) diagnosed with lymphoma were over 50 yrs old
- 10/18 (65%) current thiopurine use (range 1-10 yrs)

Risk factors for LPD:
• older age (OR 1.06 per 1-year increase)
• duration of IBD (OR 1.04 per 1-year increase)
• continued thiopurine therapy (OR 5.28)
Incidence Lymphoma Among UC Patients Stratified By Thiopurine Exposure, Veterans Administration Database

Lymphoma Incidence Stratified By Duration of Thiopurine Exposure, VA Database

Recently Updated Meta-Analysis of Lymphoma Risk Among IBD Patients on Thiopurines

- Pooled RR in referral-based studies: 9.16
- Pooled RR in pop-based studies: 2.43

Kotlyar DS et al, Clin Gastroenterol Hepatol 2014 (online early)
Meta-analysis Of Lymphoma Rate Associated With Anti-TNF Agents

8905 patients representing 20,602 patient-years
13 Non-Hodgkin lymphomas (mean age 52, 62% male)
10/13 exposed to immunomodulators (IM), 2/13 not reported

<table>
<thead>
<tr>
<th></th>
<th>NHL rate per 10,000</th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEER all ages</td>
<td>1.9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IM alone</td>
<td>3.6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anti-TNF vs. SEER</td>
<td>6.1</td>
<td>3.23</td>
<td>1.5-6.9</td>
</tr>
<tr>
<td>Anti-TNF vs. IM alone</td>
<td>6.1</td>
<td>1.7</td>
<td>0.5-7.1</td>
</tr>
</tbody>
</table>

Not significantly different

# TREAT Registry: Malignancies

Over 6000 Patients, Over 30,000 Person-Years of Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>Infliximab patients</th>
<th>Non-infliximab patients</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cancer*</td>
<td>0.64</td>
<td>0.71</td>
<td>0.88</td>
<td>0.66-1.19</td>
</tr>
<tr>
<td>Lymphoma*</td>
<td>0.05</td>
<td>0.05</td>
<td>0.98</td>
<td>0.34-2.82</td>
</tr>
<tr>
<td>Non-melanoma skin cancer</td>
<td>0.16</td>
<td>0.18</td>
<td>0.89</td>
<td>0.45-1.74</td>
</tr>
<tr>
<td>Solid tumors</td>
<td>0.42</td>
<td>0.45</td>
<td>0.92</td>
<td>0.66-1.28</td>
</tr>
</tbody>
</table>

*Incidence per 100 patient-years

TREAT: Predictors of Malignancy

- Multivariate Cox proportional hazards regression analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age per 10 years</td>
<td>1.59 (1.42-1.78)</td>
</tr>
<tr>
<td>Duration per 10 years</td>
<td>1.64 (1.11-2.42)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>1.38 (1.01-1.89)</td>
</tr>
<tr>
<td>Immunosuppressive use</td>
<td>1.43 (0.92-2.21)</td>
</tr>
<tr>
<td>Infliximab monotherapy</td>
<td>0.59 (0.28-1.22)</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>1.22 (0.81-1.86)</td>
</tr>
</tbody>
</table>

Overall Risk of Cancer in IBD with Anti-TNF Agents: Denmark, 1999-2012

Rate Ratios for incident Overall Cancer Among 56,146 Patients With Inflammatory Bowel Disease Exposed and Unexposed to TNF-a Antagonists*

<table>
<thead>
<tr>
<th>TNF-a Antagonist Exposure</th>
<th>Exposed</th>
<th>Unexposed</th>
<th>Rate Ratio (95%(1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Person-years</td>
<td>Cases</td>
<td>Person-years</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-------------</td>
<td>-------</td>
<td>-------------</td>
</tr>
<tr>
<td>Total</td>
<td>18,440</td>
<td>81</td>
<td>469,874</td>
</tr>
<tr>
<td>Female</td>
<td>10,665</td>
<td>43</td>
<td>258,706</td>
</tr>
<tr>
<td>Male</td>
<td>7,776</td>
<td>38</td>
<td>211,168</td>
</tr>
</tbody>
</table>

Adjusted for age, calendar year, disease duration, baseline propensity scores, use of 5-ASAs/sulphasalazine, local/systemic corticosteroids, methotrexate/cyclosporine/cyclophosphamide, and azathioprine.

- 4,553 exposed; 51,593 unexposed
- After adjusting for use of azathioprine, risk disappears

Cancer Risk: ADA Monotherapy vs Combination Therapy

- Cancers excluding NMSC

- NMSC only

Osterman MT et al, Gastroenterology 2014;45:941-9
Hepatosplenic T-Cell Lymphoma Following Infliximab and Thiopurines

- May 2006: black-boxed warning amended to include lymphoma risk
- As of 10/07: 13 cases in adolescents or young adults who received infliximab in combination with AZA or 6MP
- Aggressive course, mostly fatal
- All but one were males
- Is it the infliximab, the thiopurine, or the combination?

Updated Assessment of HSTCL Risk

• 36 cases of IBD pts with HSTCL
  • 20 on thiopurine plus anti-TNF
  • 16 on thiopurine alone

• For combo rx pts, 95% were males, median age 27 years (range 12-58)

• Median duration thiopurine exposure, 5.5 years (1-13.5)

• Estimated risk of HSTCL on combo rx: 1 in 22,000

• Estimated risk of HSTCL on combo rx in young men: 1 in 3,534

Kotlyar DS et al, Clin Gastroenterol Hepatol 2011;9:36-41
Risk of Lymphoma with Anti-TNF Agents: Summary

• There may be a small but real risk of lymphoma in IBD patients receiving anti-TNF therapy
  – This risk remains unquantified
  – Confounded by concomitant meds especially thiopurines

• Larger studies or meta-analysis needed to answer this question

• Absolute risk of lymphoma seems small

• Benefits appear to outweigh risks
Risk of Melanoma in IBD Patients

Non-Melanoma Skin Cancer Risk and IBD Therapies

Peyrin-Biroulet et al. Gastroenterology, 2011
Risk of Skin Cancers in IBD patients and Therapy Exposure

- Retrospective cohort and nested case-control studies using administrative data from the LifeLink Health Plan Claims Database
- 1997-2009
- N=108,579 patients with IBD, matched to 4 individuals without IBD

### Table 5. Multivariate Analyses of Medication Use and Skin Cancer Outcomes in Patients With IBD, Overall and by CD or UC

<table>
<thead>
<tr>
<th>Medication</th>
<th>Melanoma</th>
<th>NMSC</th>
<th>Melanoma</th>
<th>NMSC</th>
<th>Melanoma</th>
<th>NMSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-ASA</td>
<td>1.06 (0.77–1.45)</td>
<td>0.99 (0.92–1.08)</td>
<td>0.98 (0.63–1.53)</td>
<td>1.01 (0.90–1.13)</td>
<td>1.22 (0.76–1.96)</td>
<td>0.99 (0.89–1.11)</td>
</tr>
<tr>
<td>Biologic</td>
<td>1.88 (1.08–3.29)</td>
<td>1.14 (0.95–1.36)</td>
<td>1.94 (1.03–3.68)</td>
<td>1.16 (0.95–1.41)</td>
<td>1.73 (0.53–5.63)</td>
<td>1.06 (0.69–1.64)</td>
</tr>
<tr>
<td>Thiopurine</td>
<td>1.10 (0.72–1.67)</td>
<td>1.85 (1.66–2.05)</td>
<td>0.92 (0.53–1.59)</td>
<td>1.99 (1.73–2.27)</td>
<td>1.31 (0.66–2.60)</td>
<td>1.63 (1.36–1.94)</td>
</tr>
</tbody>
</table>

## Cervical Cancer Studies In IBD

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Setting</th>
<th>IBD cases (CD)</th>
<th>Outcome</th>
<th>Dz</th>
<th>Measur e</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connel 1994</td>
<td>Cohort registry</td>
<td>Tertiary center</td>
<td>755(450)</td>
<td>Carcinoma</td>
<td>IBD</td>
<td>SIR</td>
<td>4 (2/0.5) P=0.09</td>
</tr>
<tr>
<td>Bhatia 2006</td>
<td>Case-control</td>
<td>Tertiary center</td>
<td>116 (64)</td>
<td>Dysplasia</td>
<td>IBD</td>
<td>%</td>
<td>18% vs 5% (P=0.004)</td>
</tr>
<tr>
<td>Kane 2008</td>
<td>Case-control</td>
<td>Tertiary center</td>
<td>40(32)</td>
<td>Dysplasia</td>
<td>IBD</td>
<td>%</td>
<td>42% vs7% (P&lt;0.001)</td>
</tr>
<tr>
<td>Huftless 2008</td>
<td>Nested case-control</td>
<td>Population-based</td>
<td>1165</td>
<td>Carcinoma</td>
<td>IBD</td>
<td>OR</td>
<td>(1.45 95% CI 0.74-2.84)</td>
</tr>
<tr>
<td>Singh 2009</td>
<td>Nested case-control</td>
<td>Population-based</td>
<td>595(292)</td>
<td>Cervical abnormality</td>
<td>IBD</td>
<td>OR</td>
<td>(1.41 95% CI 1.09-1.81)</td>
</tr>
<tr>
<td>Lees 2009</td>
<td>Case-control</td>
<td>Tertiary center</td>
<td>362(184)</td>
<td>Dysplasia on pap smears</td>
<td>IBD</td>
<td>%</td>
<td>(LGD 10.5% vs 7.7% HGD 9.0% vs 6.9% (P = 0.37)</td>
</tr>
<tr>
<td>Rungø 2013</td>
<td>Matched-cohort</td>
<td>Population-based</td>
<td>30,008(9,466)</td>
<td>Dysplasia or cancer</td>
<td>CD</td>
<td>Hazard ratio</td>
<td>(1.51; 95% CI: 1.08 2.13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>UC</td>
<td>Hazard ratio</td>
<td>(0.78; 95% CI: 0.57-1.08)</td>
</tr>
</tbody>
</table>

O/E ratio=Observed-Expected ratio; HR= Hazard ratio; OR=adjusted Odds ratio; LGD Low-grade-dysplasia; HGD=High-grade dysplasia. Numbers in bold are significant results.
No Risk of Solid Tumors with anti-TNF Therapy

Rheumatoid arthritis
- 13,000 patients, ½ on biologics

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancers</td>
<td>1.0 (0.8-1.2)</td>
</tr>
<tr>
<td>All solid tumors</td>
<td>1.0 (0.8-1.2)</td>
</tr>
<tr>
<td>Colon</td>
<td>0.8 (0.3-1.7)</td>
</tr>
<tr>
<td>Lung</td>
<td>1.1 (0.7-1.8)</td>
</tr>
<tr>
<td>Breast</td>
<td>0.9 (0.5-1.3)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.5 (0.1-2.6)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2.3 (0.9-5.4)</td>
</tr>
<tr>
<td>Non-melanoma</td>
<td>1.5 (1.2-1.8)</td>
</tr>
</tbody>
</table>

Inflammatory bowel disease
- limited data

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Associated risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population based</td>
<td>SIR 0.7 (0.2-1.7)</td>
</tr>
<tr>
<td>651 patients</td>
<td></td>
</tr>
<tr>
<td>Single center</td>
<td>OR 0.97 (0.56-1.65)</td>
</tr>
<tr>
<td>734 patients</td>
<td></td>
</tr>
</tbody>
</table>

No clear evidence that anti-TNF is associated with (non-skin) solid tumors

Wolfe, Arthritis and Rheumatism 2007;56:2886.
Drug Interaction Between Thiopurines and Anti-TNF?

- Infliximab may cause transient increase in 6TGN metabolites in first few weeks, with transient leukopenia, which normalizes.

- No effect of adalimumab on thiopurine metabolites over 12 weeks in 12 patients.

Wong DR et al, J Crohns Colitis 2013 Online early
Adverse Events with Anti-TNF Therapies

- Neurologic
- Cardiac
- Hepatic
- Rheumatologic
- Infusion reactions
- Injection site reactions
  - Usually minor
Other Neurologic Side Effects Reported with Anti-TNF Therapy

• Guillain-Barre syndrome
• Peripheral neuropathy
• Aseptic meningoencephalitis
• Leukoencephalopathy
• Transverse myelitis
• Chronic inflammatory demyelinating polyneuropathy
• Progressive multifocal leukoencephalopathy
• Posterior reversible encephalopathy syndrome

Congestive Heart Failure and Anti-TNF Therapy

• Etanercept trials to treat CHF were negative
• Infliximab trial of CHF: highest mortality rate in IFX 10 mg/kg arm
• Adalimumab: event rate of CHF <0.26 per 1000 p-y
• Use with caution in patients with CHF or reduced LVEF
• IFX contraindicated at doses >5mg/kg in NYHA Class III/IV
• Consider ECHO ± Cards consult in those with suspected CHF

Hepatotoxicity with Anti-TNF

- Most commonly described with infliximab but has been described with all
  - PI contains warning
  - Hepatocellular > cholestatic injury, often with autoimmune characteristics
  - Slowly improves after drug cessation
  - Rare cases of hepatic failure/liver transplant

Lupus-Like Reactions with Anti-TNF

- Most are women
- Virtually all have arthritis/arthralgias
- Rash is common
- Serositis
- ANA positive
- Anti-ds-DNA often positive
- Don’t forget to check anti-histone

- Treatment is anti-TNF cessation
- Sometimes steroids needed, rarely hydroxychloroquine
- Recurrence with a 2nd anti-TNF is relatively low
- One study from U of C suggested cumulative 5-yr incidence over 10% in women on anti-TNF

Subramanian S et al, Inflamm Bowel Dis 2011;17:99-104.
**Infliximab Infusion Reactions**

- **Acute infusion reactions**
  - Associated with antibodies to infliximab
  - Mild reactions treated with acetaminophen, diphenhydramine and slowing of infusion rate
  - Severe reactions require cessation, steroids, or epinephrine

- **Delayed hypersensitivity reactions**
  - Not necessarily associated with ATI
  - Arthralgias 1 to 5 days after infusion
  - Sometimes require steroids
  - More common on monotherapy episodic
Natalizumab: Adverse Events Beyond PML

• Headache
• Infusion reactions, generally mild
• Hepatotoxicity
  • Rare but severe cholestatic liver injury reported
Conclusions

• A wide variety of infections (viral, bacterial, fungal) can occur in IBD patients
  • Risk factors include age, degree of colitis, and meds (steroids, IMM, anti-TNFs)
  • Risk for infection qualitatively lower with vedolizumab and ustekinumab

• Be vigilant for infection—most are successfully treated