**Biologics: Too Risky**

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Why Anti-TNF Therapy?

- CD patients have long-term risk of intestinal resection (80%) and permanent ileostomy (10%)
- To reverse these unfavorable figures, consider the early use of aggressive therapy
  - Aim to bring patients into deep and sustained remission
- Some CD patients present at diagnosis with localized and uncomplicated (no perforation, no stricture) disease
  - Early and prolonged use of immunosuppressive therapy, with its associated risks is questionable
  - Spontaneous evolution of the disease could be benign

Jess T et al. Changes in clinical characteristics, course, and prognosis of inflammatory bowel disease during the last 5 decades: a population-based study from Copenhagen, Denmark. Inflamm Bowel Dis. 2007;13:481-489.
Risks of anti-TNF Therapy

- Infection
- Malignancy
- Other
  - Infusion reactions
  - Autoimmune complications
  - Dermatologic complications
  - Neurologic complications
  - Liver complications

Risks for Infections

“Doc- these are the most common side effects of biologic medications and I’m worried”
Anti-TNFα and Infections

• In RA – clear association of anti-TNFs and increased risk of infections
  • Meta-analysis of 9 trials with anti-TNFs – OR of 2.01 for serious infection
  • Cochrane review – ↑ risk of serious infections with certolizumab (OR 2.82) and infliximab (OR 1.97)
    • No increased risk in patients w IBD – RA patients older with more co-morbid disease

• Older patients with IBD (>65 years) on anti-TNFs have increased risk of serious infections (11% vs 2.6% in younger patients)

Cottone M et al. Advanced age is an independent risk factor for severe infections and mortality in patients given anti-tumor necrosis factor therapy for IBD. Clin Gastroenterol Hepatol 2011;9:30-5.

Anti-TNFα and Infections

• Crohn’s TREAT registry
  • 6723 patients w CD (3420 treated w infliximab) treated for mean of 5.2 years
    • ↑ risk of serious infections with corticosteroid therapy
    • ↑ risk of serious infections with infliximab
      • Study did not look at concommitant immunomodulator or corticosteroid therapy

• Largest single center experience in Belgium
  • 1400 CD patients followed for median of 5 years
    • No difference in rate of serious infections between infliximab group and no infliximab group

• Largest population-based cohort study in Canada – 10,662 patients
  • Event rate of serious bacterial infection was 4.28 per 1000 patient years
    • But not significantly increased compared w patients on corticosteroids or immunomodulators

Rare Infections associated with anti-TNF α

- Tuberculosis
  - Therefore we screen for latent TB
  - TST – low sensitivity in immune-compromised patients
  - Interferon gamma release assay (IGRA)
    - Improved specificity and sensitivity but higher cost
  - Test before immunosuppression
- Other granulomatous infections
  - Listeria monocyto genes
  - Nocardiosis
- Clostridium Difficile
  - Corticosteroids associated with 3x increased risk for C diff
  - No increased risk with infliximab
- Bacterial Infections
  - Streptococcus pneumonia, Legionella, Salmonella


Rare Infections associated with anti-TNF α Fungal Infections

- Pneumocystis carinii
  - Consider PCP prophylaxis in all patients on triple therapy
- Granulomatous fungal infections
  - Histoplasmosis
  - Coccidiomycosis
  - Watch out for patients living in endemic areas
- Cryptococcus neoformans
- Aspergilosis
- Systemic candidiasis
- Cryptosporidal infections

Rare Infections associated with anti-TNF α Viral Infections

- **Hepatitis B**
  - Immunosuppression can lead to reactivation of latent hepatitis B
  - Can occur as early as after the second infusion or as late as 2 years after the start of therapy
  - 2/3 of patients with HBV reactivation developed hepatic failure
  - Screen for Hep B
  - Vaccinate if not immune; monitor titers and consider booster
  - In chronic HbSAg+ carriers, prophylaxis with nucleotide/nucleoside analogues prior to starting immunosuppression


- **Hepatitis C**
  - No data to suggest reactivation or exacerbation of HCV

- **CMV**
  - Unclear if anti-TNF agents pose a specific risk

- **Varicella Zoster Virus – Shingles/ disseminated varicella infection**
  - Increased risk with IBD
  - Even greater risk with immunosuppression
  - Vaccinate

- **HIV**
  - No adverse impact of anti-TNF on the course of HIV

- **HPV**
  - Increased incidence of HPV warts/condylomata in patients on immunosuppressants
  - No data to suggest a specific association with biologics
  - Vaccinate

Educate and vaccinate for prevention

• IBD patients can mount a response to the vaccine
  • May be diminished in patients on combination therapy
• Vaccinate prior to initiation of immunosuppressive agents if possible
• IBD disease activity will not be affected by vaccinations
• As the gastroenterologist, take responsibility because the PCP is often not sure what to do when the patient is on immunosuppression

Risk of cancer from biologics

One of the biggest obstacles to overcome – the fear of cancer
Risk of Lymphoma with anti-TNF therapy

- Driven by the use of concomitant thiopurine therapy

<table>
<thead>
<tr>
<th>Incidence Rate (per 10,000 PYF)</th>
<th>SIR</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td><strong>Current Thiopurine Without Anti-TNF Exposure</strong></td>
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<tr>
<td>Herrinton et al, 2011</td>
<td>4.1</td>
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<td>CESAME</td>
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<td>6.5</td>
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<td>Khan et al, 2013</td>
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<td>7.5</td>
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<td><strong>Current Thiopurine with Previous Anti-TNF Exposure</strong></td>
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<td>15.1</td>
<td>5.3</td>
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<td><strong>Current Anti-TNF Therapy with Current Thiopurine Therapy</strong></td>
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<tr>
<td>Dulai et al, 2014</td>
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</tr>
<tr>
<td>TREAT</td>
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<td>2.0</td>
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<td>Siegel et al, 2009</td>
<td>6.1</td>
<td>3.2</td>
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Risk of Hepatosplenic T cell lymphoma

- Aggressive subtype of lymphoma
- High fatality rate
- Pooled data of published literature and the US FDA AERS
  - 36 cases of HSTCL (34 males)
    - Thiopurine therapy alone (n = 16)
    - Thiopurine + anti-TNF agent (n = 20)
- Risk of HSTCL highest in patients on thiopurine monotherapy and combination therapy with an anti-TNF agent and thiopurines.
- Risk seems to be exposure and patient (age and gender) dependent
  - Highest risk: Men < 35 years exposed to long-term (>2 years) thiopurines


Risk of Non-Melanoma Skin Cancer
(Basal cell cancer and Squamous cell cancer)

- Nested case-control retrospective cohort analysis of 742 patients with IBD with NMSC matched to 4 patients with IBD without NMSC
  - recent (<90 days) and persistent (>365 days) use of biological monotherapy increased the risk of NMSC 2-fold to 3-fold
  - 3-fold to 4-fold increase in risk seen with thiopurine monotherapy
  - 5-fold to 6-fold increase in risk seen with combination therapy
- Another similar study showed the risk of NMSC with biologics to be limited to only those patients with persistent (>365 days) use of biologics.
  - Use of an immunomodulator, alone or in combination with a biologic, carried a higher risk for NMSC than biologic therapy alone.


Risk of Melanoma

- Patients with IBD are at a higher baseline risk for the development of melanoma skin cancer
- Nested case-control study
  - Risk of melanoma was increased with biologics
  - Patients undergoing long-term therapy with anti-TNF agents were at higher risk than those not exposed to long-term therapy
  - No increase with immunomodulators
- CESAME - risk of melanoma not increased in patients with IBD who were receiving thiopurines or anti-TNF treatment
  - Less than 10% of patients were prescribed non-thiopurine medications

Risk Factors for malignancy with biologics

• Non modifiable risk factors
  • Young males
  • Older age
  • Disease duration and subtype (more inflammation means greater risk)

• Modifiable risk factors
  • Smoking cessation
  • Sun protection strategies
  • Vitamin D deficiency repletion
  • Immunosuppressant use

What else does our patient need to be aware of with Biologic Agents

The VERY rare events
Infusion Reactions

• Acute – within 24 hours of infusion – about 3-5% of patients
  • Mild: flushing, dizziness, diaphoresis, nausea, palpitations
  • Moderate: chest pain, HTN, hypotension, fever, urticaria, dyspnea, chills, rash
  • Severe: HTN, hypotension, significant dyspnea, bronchospasm, stridor, rigors

  • Prevention – non-episodic dosing, concomitant immunomodulator therapy
  • Treatment – reduce rate, acetaminophen, antihistamine, systemic steroid


Infusion Reactions

• Delayed – 5 to 7 days after an infusion – about 1-3% of patients
  • Serum sickness-like reaction
  • Likely result from antibody formation
  • Risk factors – episodic dosing, delays in routine infusion schedule, lack of concomitant immunomodulator

  • Symptoms – joint pains, rash, arthritis, myalgias, jaw pain, fatigue, headaches, edema, sore throat, fever
  • Must differentiate from a viral syndrome, drug induced lupus, and EIM
  • Treatment – acetaminophen, may need short course of steroids
  • Re-infuse if ATI are minimal or absent

Autoimmune complications

- Development of autoantibodies (ANA, anti-dsDNA, anti-cardiolipin and antihistone antibodies)
- Drug induced Lupus – rare despite above
  - Polyarthralgias, myalgias, serositis, fever, fatigue, rash
  - Need to stop anti-TNF, may need to start steroids
  - If decision to continue anti-TNF made with patient, then try a second anti-TNF
- Vasculitis – most are cutaneous leukocytoclastic vasculitis
  - Palpable purpura
  - Need to stop anti-TNF, may need to start steroids
- Joint Inflammation
  - Consider changing to a different anti-TNF, steroids, or immunomodulator therapy

Dermatologic Complications

- Psoriasis
  - Can occur at anytime of anti-TNF therapy
  - Class effect
  - Consult dermatology – steroids, emollients, UV light
  - May need to stop anti-TNF – takes about 3 months for the psoriasis to resolve
- Eczema
  - More common in men, smokers, history of atopy
  - Most respond to topical therapy
  - Severe cases – may need to stop anti-TNF
- Rare Stevens Johnson syndrome
Neurologic Complications

• Demyelinating disorder
  • Usually early on in the treatment
  • Symptoms – nonspecific
    • confusion, ataxia, dysesthesia, visual disturbances, gait disturbances, parathesias
  • If suspected, stop anti-TNF – in most cases, symptoms should improve

Liver Complications

• DILI
  • May be a class effect
• Autoimmune hepatitis
  • May be a class effect
• Recommend episodic monitoring of LFTs to identify early rise
Does our patient REALLY need the anti-TNF?

- The risk of over-treating patients can be reduced with the use of clinical predictors at diagnosis regarding the subsequent course of IBD

<table>
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<th>Clinical risk factor</th>
<th>Our patient</th>
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<td>Age of onset &lt;40</td>
<td>yes</td>
</tr>
<tr>
<td>Smoker</td>
<td>yes</td>
</tr>
<tr>
<td>Perianal lesion at diagnosis</td>
<td>no</td>
</tr>
<tr>
<td>Required steroids for first flare</td>
<td>yes</td>
</tr>
<tr>
<td>Terminal ileal, ileo-colonic disease</td>
<td>yes</td>
</tr>
<tr>
<td>Severe endoscopic lesions</td>
<td>moderate</td>
</tr>
<tr>
<td>Stricturing, penetrating behavior</td>
<td>no</td>
</tr>
</tbody>
</table>

- Our patient is high risk for aggressive Crohn’s disease and should consider stronger therapy
  - Vaccinate him
  - Counsel to stop smoking
  - Sun protection strategies
  - Replete vitamin D
  - If planning on concomitant therapy, counsel on risks of thiopurines, monitor duration on therapy