Ulcerative Colitis Therapy

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GI for GP’s Jasper AB

Faculty Disclosure

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Objectives

- Goals of therapy in UC
- Review common therapies
- Review side effects
- Review biologic therapy
  - What options
  - When its used
  - Contraindications

Ulcerative Colitis

- Chronic inflammatory bowel disease – only affects the colon (starts “burn up”)
  - proctitis,
  - proctosigmoiditis,
  - l-sided,
  - pancolitis
- Severity:
  - mild,
  - moderate,
  - severe
  - fulminant

Anatomy of Large Intestine

- Normal or inactive disease
- Mild disease (erythema, shallow ulceration, mild tenderness)
- Moderate disease (sharpened erythema, deep ulceration, moderate tenderness)
- Severe disease (spontaneous bleeding, perforation)
What are the goals of therapy?

1. Induce and maintain remission
   - Steroid-free remission
2. Prevent complications
3. Improve QOL
4. Avoid surgery
5. Mucosal healing
**Treatment of IBD**

**TWO PHASES:**
- **INDUCTION** of Remission
  - 5-ASA
  - Corticosteroids
  - MTX
  - Anti-TNF
  - Surgery
- **MAINTENANCE** of Remission
  - 5-ASA
  - Imuran/6-MP, MTX
  - Anti-TNF

**IBD Treatment Pyramid**

- Surgery
- Biologic Therapy
- AZA/6-MP
- MTX
- Prednisone
- Budesonide
- 5-ASA
- Antibiotics

**Aminosalicylates (5-ASA)**

**TWO TYPES:**
- Sulfasalazine: sulfapyridine + mesalamine
- Mesalamine: mesalamine + mesalamine
  - Pentasa, Asacol, Salofalk, MMX
  - Different release characteristics...
Side Effects – 5-ASA

**Sulfasalazine**
- Anorexia
- N/V
- Neutropenia, agranulocytosis
- Hemolysis
- Macrocytosis (folate deficiency)
- Reversible male infertility
- Plus mesalamine SE

**Mesalamine**
- Headache
- Drug fever, rash
- Paradoxical exacerbation of diarrhea
- Pancreatitis
- Hepatitis
- Pericarditis
- Nephritis

SOAP note:
- **S**tudies have shown...
- **O**bserved side effects...
- **A**ctions to take...
- **P**atient education...

**Generally well tolerated**

5-ASA in Ulcerative Colitis

- **Mainstay of treatment** in mild-moderate UC
- Effective for induction & maintenance
- No need more than daily or BID therapy
- Combination oral & rectal therapy improves remission rates

Glucocorticoids for Ulcerative Colitis

**VERY EFFECTIVE FOR INDUCTION OF REMISSION:**
- Prednisone 40-60mg/day plus taper
  - Effective for inducing remission
- Budesonide - **Not effective**

**FOR IN-PATIENTS:**
- Solumedrol (methylprednisone) 20-30mg IV BID
Side Effects - Prednisone

• Sleep & mood disturbance
• Acne, alopecia
• Striae, central obesity
• Hirsutism
• Adrenal suppression
• Proximal myopathy
• Glucose intolerance
• Hypertension
• Weight gain

• Glaucoma
• Cataracts
• Infection
• Pseudotumor cerebri
• Edema
• Impaired wound healing
• Growth retardation
• Osteopenia/osteoporosis
• Avascular necrosis

Immunosuppressives

• Azathioprine – 2.5 mg/kg/d
• 6-mercaptopurine – 1.5 mg/kg/d
• (Methotrexate – 15-25mg/week (PO/SC))

AZA/6-MP – Crohn’s Disease & UC

• Azathioprine 2.5mg/kg/d
• 6-mercaptopurine 1.5mg/kg/d
• Not effective in inducing remission
• 70% effective in maintaining remission
• Need to follow bloodwork (CBC, liver enzymes for side effects)
Side Effects – AZA/6-MP

- Nausea
- Drug fever
- Rash
- Arthralgias
- Leukopenia
- Thrombocytopenia
- Bone marrow suppression
- Pancreatitis
- Hepatitis
- Infection
- Lymphoma

Anti-TNF: Biologic Therapy

- Anti-TNF α
  - Infliximab (Remicade®)
  - Adalimumab (Humira®)
  - Certolizumab
  - Golimumab (Simponi®) (New)

Why anti-TNF?

- Pts with UC have high levels of TNF-α in the colon mucosa, produced by lamina propria mononuclear cells
- TNF-α key player in the inflammatory cascade
- Shut it off and decrease inflammation
Anti-TNFα (available in Canada)

- **Infliximab** (intravenous)
  - Chimeric monoclonal antibody to soluble and membrane-bound TNFα
- **Adalimumab** (subcutaneous)
  - Human monoclonal antibody to soluble TNFα but not to lymphotoxin
- **Golimumab** (subcutaneous)
  - IgG1 monoclonal antibody against TNF
  - Subcutaneous administration
  - AKA: CNTO 14B
  - Binds membrane bound and soluble TNF

Who we use it on?

- Outpatients failing other therapies
- Fulminant/severe not responding to steroids
  - Oxford rule

“Oxford Rule”
In-patient Severe/Fulminant Colitis

- **Day 3**
  - 8 BM/day or 3-8 BM/day and CRP > 45
  - 85% chance of colectomy

- **Day 7**
  - > 3 BM/day or visible blood
  - 60% chance of continuing Sx and 40% of requiring colectomy

(Gut 1996; 38: 905-910)
Evidence for Infliximab in Steroid-Refactory UC (Jarnerot)

None of the pts in endoscopic remission at 3 months had a colectomy; versus 50% who were not in remission (p=0.02)

Infliximab – Ulcerative Colitis Outpatients

• ACT I&II (NEJM 2005; 353:2462)
  – Outpatient trial
    • 2 – DR, RCT of 364 pts with mod-severe UC (Mayo 6-12; with endo score 2+) randomized to placebo, 5, 10 mg/kg at 0, 2, 6 & q8wk
    • DEFINITIONS:
      • Response: decrease Mayo 3 (at least 50%) with bleeding decreasing by 1+ (absolute score 0-1)
      • Remission: Mayo ≤ 2, endo score 0-1
      • Mucosal healing: Absolute score 0-1

ACT I&II – Clinical Response 8 wks

69% better with infliximab vs placebo
37% (steroid+/-aza)
ACT I&II – Remission 8 weeks

38% REMISSION with infliximab vs placebo 15% (steroid+/-aza)

ACT I&II – Mucosal Healing 8 wks

ACT I&II – Sustained Remission
Side Effects – Anti-TNF

- **Infusion reactions** (fever, headache, nausea, flushing, dyspnea, anaphylaxis)
- **Serum sickness** (myalgia, arthralgia, facial edema, urticaria)
- **Infection** – URTI, UTI, abscess
- **Re-activation of TB**
- **CNS** – optic neuritis, MS
- **Malignancy** – lymphoma, hepatosplenic T-cell lymphoma
- **CHF** – contraindicated in heart failure

Why we test for TB prior to starting anti-TNF

- Macrophages activated by TB need TNF-α which is needed to form granuloma and trap the TB bug and contain the infection

Anti-TNF Summary

- Anti-TNF therapy are useful for induction and maintenance of remission in both Crohn’s Disease and UC
- No stopping rules
- Often used in combination therapy
Surgery in Ulcerative Colitis

• “Cure” for UC
• Indications:
  1. Refractory to medical therapy
  2. Toxic megacolon/fulminant
  3. Malignancy or dysplasia
  4. Patient preference

Goals of therapy

1. Induce and maintain remission
   — Steroid-free remission
2. Prevent complications
3. Improve QOL
4. Avoid surgery
5. Mucosal healing

Questions??????
What is Golimumab?

- IgG1 monoclonal antibody against TNF
- Subcutaneous administration
  - (also tested IV – data not published)
- AKA: CNTO 148
- Binds membrane bound and soluble TNF

Golimumab for UC

- INDUCTION (PURSUIT-SC)
  - Combined with Phase 2 dose-finding study 1064 pts
  - 4 dosing groups: 100/50, 200/100, 400/200, placebo
- P: 774 pts with mod-severe UC (Mayo 6-12, endo 2+)
  - TNF-naive
- I: 200/100, 400/200 at wks 0, 2
- C: placebo
- O: Wk 6 clinical response
  - 2ndary: clinical remission, mucosal healing, IBDQ

Golimumab - Induction

![Graph showing clinical response](Gastro 2013; June E-pub)
Golimumab Induction - Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>200/100</th>
<th>400/200</th>
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<tbody>
<tr>
<td></td>
<td>N=256</td>
<td>N=257</td>
<td>N=258</td>
</tr>
<tr>
<td>Clinical Remission</td>
<td>6.3%</td>
<td>18.7%</td>
<td>17.8%</td>
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<tr>
<td></td>
<td>P&lt;0.0001</td>
<td>P&lt;0.0001</td>
<td>P&lt;0.0001</td>
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<tr>
<td>Mucosal Healing</td>
<td>28.5%</td>
<td>43.2%</td>
<td>45.3%</td>
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<tr>
<td></td>
<td>P=0.0005</td>
<td>P&lt;0.0001</td>
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<tr>
<td>Change in IBDQ</td>
<td>14.6</td>
<td>27.4</td>
<td>27.0</td>
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<tr>
<td></td>
<td>P&lt;0.0001</td>
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Gastro 2013; June E-pub

Golimumab for UC

• MAINTENANCE
• P: 464 pts who responded to Induction Golimumab
• I: 50 or 100mg q4wks
• C: placebo
• O: Wk 54 clinical response
  – 2ndary: clinical remission, mucosal healing at wk 30 & 54

Gastro 2013; June E-pub

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Gastro 2013; June E-pub
Golimumab Maintenance - 2ndary Outcomes

<table>
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<th>Placebo N=156</th>
<th>200/100 N=153</th>
<th>400/200 N=154</th>
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<tbody>
<tr>
<td>Clinical Remission at Wk 30</td>
<td>22.4%</td>
<td>35.9%</td>
<td>40.9%</td>
</tr>
<tr>
<td></td>
<td>P=0.009</td>
<td>P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Clinical Remission at Wk 54</td>
<td>22.4%</td>
<td>33.3%</td>
<td>34.4%</td>
</tr>
<tr>
<td></td>
<td>P=0.071</td>
<td>P=0.01</td>
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<tr>
<td>Steroid Use at Baseline</td>
<td>87</td>
<td>79</td>
<td>83</td>
</tr>
<tr>
<td>Steroid free at Wk 54</td>
<td>20.7%</td>
<td>38.0%</td>
<td>31.3%</td>
</tr>
<tr>
<td></td>
<td>P=0.031</td>
<td>P=0.112</td>
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Gastro 2013; June E-pub

Golimumab Maintenance – Adverse Reactions

• SAE: 7.7%, 8.4%, 14.3% (P, 50, 100)
• Serious infections: 1.9%, 3.2%, 3.2%
• 4 pts developed active TB
• 3 deaths: sepsis, TB, cardiac failure (all in 100mg group)

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Golimumab Dosing

• Ulcerative colitis:
• U.S. labeling: SubQ: Induction: 200 mg at week 0, then 100 mg at week 2, followed by maintenance therapy of 100 mg every 4 weeks
• Canadian labeling: SubQ: Induction: 200 mg at week 0, then 100 mg at week 2, followed by maintenance therapy of 50 mg every 4 weeks (maintenance dose may be increased to 100 mg every 4 weeks if needed)

Uptodate.com