Optimal Management of Moderate to Severe Ulcerative Colitis

Hans Herfarth, MD, PhD
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina
Case 1

• Therapies with Colazal and Apriso without significant effect and recurrent need for prednisone.
• 6-MP start approximately in 5/2011
• 6/2011 pancreatitis, thought to be associated with 6-MP.
• 11/2011 recurrent pancreatitis (off 6-MP)
• 12/2011 first presentation to IBD Clinic: just off prednisone taper, 4.8 g Asacol, 4-6 bloody bowel movements daily

Labs:
HGB 12.1 g/dl, CRP 1.5 mg/dl, C. diff negative.
Steroid Therapy in IBD – Olmsted County

All patients with IBD 1970 - 1993

<table>
<thead>
<tr>
<th></th>
<th>CD n= 173</th>
<th>UC n=185</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid therapy</td>
<td>43 % (74)</td>
<td>34 % (63)</td>
</tr>
<tr>
<td>Therapeutic response*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td>58 % (43)</td>
<td>54 % (34)</td>
</tr>
<tr>
<td>Partial response</td>
<td>26 % (19)</td>
<td>30 % (19)</td>
</tr>
<tr>
<td>No response</td>
<td>16 % (12)</td>
<td>16 % (10)</td>
</tr>
</tbody>
</table>

*30 days after initiating steroid therapy

Faubion et al 2001
Steroid Therapy in IBD - 1-year Outcome
Olmsted County

CD
- Prolonged response (n=31)
- Steroid dependent (n=14)
- Surgery (n=18)

UC
- Prolonged response (n=31)
- Steroid dependent (n=14)
- Surgery (n=18)

Faubion et al 2001
Algorithm for Induction and Maintenance of Remission in Ulcerative Colitis

Flare with mild to moderate activity
5-ASA +/- local therapy

Flare with moderate-severe activity
Oral/iv steroids +/- oral 5-ASA

Recurrence after steroid induction; Steroid dependent/refractory course

Immunomodulator for induction and maintenance of remission:
Azathioprin, 6-MP
Infliximab or Humira

Infliximab, Cyclosporin or Tacrolimus

Remission

Continued activity

Surgery
Colectomy and ileoanal pouch procedure

Remission

Continued activity

Maintenance therapy 5-ASA

Remission

severe activity
Cochrane Analysis: Azathioprine versus Placebo: Failure to Maintain Remission

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>AZA n/N</th>
<th>Placebo n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight %</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hawthorne 1992</td>
<td>12/33</td>
<td>20/34</td>
<td></td>
<td>26.1 %</td>
<td>0.62 [ 0.36, 1.05 ]</td>
</tr>
<tr>
<td>Jewell 1974</td>
<td>24/40</td>
<td>31/40</td>
<td></td>
<td>41.1 %</td>
<td>0.77 [ 0.57, 1.05 ]</td>
</tr>
<tr>
<td>Sood 2000</td>
<td>11/25</td>
<td>15/25</td>
<td></td>
<td>19.9 %</td>
<td>0.73 [ 0.42, 1.27 ]</td>
</tr>
<tr>
<td>Sood 2002</td>
<td>4/17</td>
<td>10/18</td>
<td></td>
<td>12.9 %</td>
<td>0.42 [ 0.16, 1.10 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>115</strong></td>
<td><strong>117</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.68 [ 0.54, 0.86 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 51 (AZA), 76 (Placebo)
Heterogeneity: Chi² = 1.85, df = 3 (P = 0.60); I² =0.0%
Test for overall effect: Z = 3.16 (P = 0.0016)
Test for subgroup differences: Not applicable

Number needed to treat (NNT): 5
Infliximab in Patients with Ulcerative Colitis: Clinical Remission ACT-1 and ACT-2 trial

Infliximab in Patients with Ulcerative Colitis: Clinical Remission ACT-1 and ACT-2 trial

Rutgeerts et al. 2005

\[ *p \leq 0.001 \text{ vs placebo} \]
\[ +p \leq 0.003 \text{ vs placebo} \]

Infliximab in Patients with Ulcerative Colitis: Clinical Remission ACT-1 and ACT-2 trial

Rutgeerts et al. 2005

\[ *p \leq 0.001 \text{ vs placebo} \]
\[ +p \leq 0.003 \text{ vs placebo} \]
Adalimumab (ADA) for Induction and Maintenance of Clinical Remission (ULTRA 2)

Placebo week 8  ADA week 8  Placebo week 52  Ada week 52

- Remission
- Response
- Mucosal Healing

Delta: 7.2%; p<0.05
Delta: 8.8%; p<0.005

n=494

Infliximab, Azathioprine or Combination – UC SUCCESS Trial: Week 16 Results

Patients naïve to anti-TNF and AZA or >3 months stop of AZA before trial

Patients (%)

Remission: Steroid-free + Mayo <2, Mucosal Healing: endoscopy 0 or 1

Panaccione et al ECCO and DDW 2011
Infliximab in Patients with Ulcerative Colitis on Steroids: Clinical Remission and Off Steroids ACT-1 and ACT-2

Steroids at study entry: ACT-1: 222 patients (61%); ACT-2: 186 patients (51%)
Median daily corticosteroid dose: 20 mg

**Clinical Remission and off steroids**

<table>
<thead>
<tr>
<th>Week</th>
<th>ACT-1 Placebo</th>
<th>ACT-1 5mg/kg IFX</th>
<th>ACT-1 10 mg/kg IFX</th>
<th>ACT-2 Placebo</th>
<th>ACT-2 5mg/kg IFX</th>
<th>ACT-2 10 mg/kg IFX</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>10%</td>
<td>24%</td>
<td>19%</td>
<td>3%</td>
<td>18%</td>
<td>27%</td>
</tr>
<tr>
<td>54</td>
<td>9%</td>
<td>26%</td>
<td>16%</td>
<td>3%</td>
<td>18%</td>
<td>27%</td>
</tr>
</tbody>
</table>

*p ≤ 0.05 vs placebo

Rutgeerts et al. 2005
Adalimumab (ADA) for Induction and Maintenance of Clinical Remission (ULTRA 2) – Prior anti-TNF Exposure

n=494

<table>
<thead>
<tr>
<th>Prior anti-TNF</th>
<th>Remission Week 8</th>
<th>Remission Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>6.9%</td>
<td>3.0%</td>
</tr>
<tr>
<td>ADA</td>
<td>9.2%</td>
<td>11.4%</td>
</tr>
<tr>
<td>p&lt;0.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11.0%</td>
<td>10.2%</td>
</tr>
<tr>
<td>p&lt;0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>21.3%</td>
<td></td>
</tr>
<tr>
<td>p&lt;0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.0%</td>
<td>11.4%</td>
</tr>
<tr>
<td>p&lt;0.03</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NNT: Number needed to treat

NNT 11

NNT 14

We have 4 therapeutic possibilities for UC patients with the need for additional immunosuppression: azathioprine/6-MP, infliximab, adalimumab or infliximab + azathioprine/6-MP.

It is difficult to compare efficacies of all 3 agents due to different trial designs and study endpoints.

Need for better understanding of therapeutic mechanisms of anti-TNF therapy.

Need for comparative clinical effectiveness studies.
Case 2

64 yo male, treated with varying doses of steroids from 10/06-12/06. Therapy with oral steroids and iv steroids failed. Transfer to UNC. 20 bloody bowel movements daily. Low grade fever.

PMHx: Ulcerative colitis, first diagnosed in 2000 (pancolitis), 2 flares 2002 and 2005, Maintenance therapy with 5-ASA until 10/06.

Physical examination: temp 37.8 ºC, HF 90, bloated abdomen, soft, no rebound tenderness.

Lab: WBC 5.4, Hgb 9.5, Potassium 3.2, ESR 90.
Clinical Course

**Histology**: compatible with ulcerative colitis.

**Microbiology**: C. diff. negative, CMV PCR plasma and biopsy negative.

**Radiology**: No colonic dilation.

**Surgical consult**: Close observation, no immediate need for operation.

**Therapy**:

NPO

Start cyclosporine 2 mg/kg/day trough level (day 2): 230 ng/ml.

Ciprofloxacin 500 mg bid, metronidazole 500 mg tid, parenteral nutrition.
**Cyclosporine A - optimal dose in the treatment of severe, steroid refractory colitis**

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Cyclosporine (mg/kg/day)</th>
<th>Mean cyclosporine blood level (ng/ml)</th>
<th>Mean time to response days (range)</th>
<th>Response after 8 days</th>
<th>Colectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>4</td>
<td>332 ± 43</td>
<td>4 (1-7)</td>
<td>32/38 (84%)</td>
<td>5/38 (13%)</td>
</tr>
<tr>
<td>35</td>
<td>2</td>
<td>237 ± 33</td>
<td>4 (1-8)</td>
<td>32/35 (86%)</td>
<td>3/35 (9%)</td>
</tr>
</tbody>
</table>

Van Assche et al. 2003
Cyclosporin in severe colitis - long term single center experience (Mount Sinai, New York)

**1987-1994**

- **75 patients**
- Cyclosporin 4 mg/kg bw
- Mean level 512
- 16 pat. colectomy (21%)
- 59 pat. discharge (79%)
- 6-MP as needed
- 6 months
  - 42 pat. Remission (56%)
- 34 pat. Remission (45%)
  - Follow-up mean 14.7 years

**1995-2005**

- **69 patients**
- Cyclosporin 4 mg/kg bw
- Mean level 376
- 14 pat. colectomy (20%)
- 55 pat. discharge (80%)
- 6-MP as needed
- 2 weeks after discharge
- 40 pat. Remission (73%)
- 37 pat. Remission (54%)
  - Follow-up mean 8.6 years

Lichtiger et al. ACG 2006
**Moderate – Severe Steroid Refractory Ulcerative Colitis – Infliximab Therapy**

- 44 patients moderately - severe ulcerative colitis not responding to i.v. steroids* (after 6-8 days)

24 patients infliximab 5 mg/kg bw

20 patients placebo

**Outcome after 90 days**

![Bar chart showing outcomes for operated and not operated patients](chart.png)

- Infliximab: 29% operated, 67% not operated
- Placebo: 33% operated, 33% not operated

* 4 mg betamethasone bid

Janerot et al. 20005
Cyclosporine A or Infliximab for Steroid Refractory UC

111 Pat.
Randomization after 5 days iv. steroids

55 Pat CyA
2 mg/kg/day i.v. then switch to oral
Start of azathioprine day 7

Response day 7: 84%
Treatment failure 60%
Colectomy until day 98: 10 patients

56 Pat. IFX 5 mg/kg b.w.
Week 0, 2, and 6, then q 8 weeks

Response day 7: 86%
Treatment failure 54%
Colectomy until day 98: 13 patients

Laharie et al. DDW 2010
Day 3 after start cyclosporine A
Surgery:

Total abdominal colectomy with end ileostomy. Intraoperative findings: Severe pancolitis and perforation at the rectosigmoid junction.

Pathology:

Focal severe chronic active colitis with mucosal ulceration and pseudopolyp formation, consistent with clinical history of ulcerative colitis.

- Transmural fissures with associated acute and chronic inflammation and purulent serositis, consistent with perforation
KUB if suspicion of toxic megacolon, unprepped flexible sigmoidoscopy to determine diagnosis and severity of disease

Exclude CMV
Exclude Clostridium difficile

IV steroids plus IV antibiotics 5-7 days

No response or partial response

OR

IV Cyclosporine

OR

IV Infliximab ? Humira?

OR

Colectomy

No or partial response

Consult with surgeon!!!
Potential Future Therapeutic Directions and Options for Moderate-Severe Ulcerative Colitis
Infliximab Concentration and Clinical Outcome – ACT1 and ACT2 Study

Infliximab Concentration and Clinical Outcome – ACT1 and ACT2 Study

Infliximab 5 mg/kg bodyweight week 0, 2, 6, IFX level week 8

Proportion of Patients in Remission (%)

Clinical Remission week 8

1st Quartile 2nd Quartile 3rd Quartile 4th Quartile

- 0 < 21.3
- 21.3-33.0
- 33.0-47.9
- 47.9

Week 8

p = 0.05

Clinical Remission Week 30

1st Quartile 2nd Quartile 3rd Quartile 4th Quartile

- 0 < 1.4
- 1.4-3.6
- 3.6-6.8
- 6.8

Week 30

p = 0.0001

Clinical Remission Week 54

1st Quartile 2nd Quartile 3rd Quartile 4th Quartile

- 0 < 1.4
- 1.4-3.6
- 3.6-8.1
- > 8.1

Week 54

p = 0.007

Prediction of Colectomy Week 8 – 54 Based on Mucosal Inflammation in Week 8 - ACT-1 and ACT-2 trial

Infliximab therapy
n=466
38 colectomies (8.2%)
Vedolizumab (VDZ) – Clinical Response, Remission and Mucosal Healing Week 6

Patients (%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo</th>
<th>VDZ</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Response</td>
<td>25.5%</td>
<td>47.1%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Clinical Remission</td>
<td>5.4%</td>
<td>16.9%</td>
<td>&lt;0.0009</td>
</tr>
<tr>
<td>Mucosal Healing</td>
<td>24.8%</td>
<td>40.9%</td>
<td>&lt;0.0012</td>
</tr>
</tbody>
</table>

n=374

Vedolizumab (VDZ) – Clinical Remission, Corticosteroid-free Remission and Mucosal Healing Week 52

Clinical Remission

- Placebo: 15.9%
- VDZ q 4 week: 44.8%
- VDZ q 8 week: 41.8%

CS-Free Remission

- Placebo: 13.9%
- VDZ q 4 week: 31.4%
- VDZ q 8 week: 45.2%

Mucosal Healing

- Placebo: 19.8%
- VDZ q 4 week: 56.0%
- VDZ q 8 week: 51.6%

*P < 0.0012

Vedolizumab (VDZ) – Clinical Response and Remission Week 6 Depending on Prior anti-TNF Exposure

Tofacitinib (oral Janus Kinase Inhibitor) – Induction of Clinical and Endoscopic Remission Week 8

Endoscopic remission: Score 0.

n=194

Methotrexate (MTX) and Ulcerative Colitis

### 17 Reports MTX and UC

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative placebo controlled trial</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Prospective open label studies</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Retrospective case series or single center experience reports</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Meeting abstracts</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Herfarth et al. 2010
Clinical Studies MTX in UC

Comparison of Methotrexate vs Placebo in Steroid-Refractory Ulcerative Colitis (METEOR)

Randomized, double blind, prospective trial investigating the efficacy of Methotrexate in induction and maintenance of steroid free remission in ulcerative colitis (MEthotrexate Response In Treatment of UC - MERIT-UC)
54 patients, 2500 pig worm eggs (in Gatorade) or Placebo q 2 weeks for 12 weeks.

Trichuris suis Therapy for Active Ulcerative Colitis: A Randomized Controlled Trial

Summers et al. 2005

p<0.04
• Need for further optimization of anti-TNF therapy

• Exciting pipeline (Biologics, small molecules, immunomodulation with “ecological” approach)

• Given multiple therapeutic choices, need for individualization of therapeutic intervention

→ Predictive modeling of therapy algorithms e.g. with genotyping/phenotyping of individual patient