The Role of Surgery for Ulcerative Colitis in the Era Of Modern Immunosuppression

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Epidemiology of Ulcerative Colitis

- Ulcerative colitis:
  - Incidence: 7-15/100,000 per year
  - Prevalence: 150-250/100,000
  - F=M ratio
  - Age: frequency greatest 20-40 years of age
    - Second peak in elderly

- Standard surgical therapy:
  - Total proctocolectomy with J-pouch.
  - Variations on this theme.
  - End-ileostomy

Colectomy rates and modern therapy

- What do we compare to?
- What defines “modern immunotherapy?”
- How do we gauge influence of off-label use of new drugs in shifting trends in treatment?
Current Theories of the Pathogenesis of IBD

Genetic Predisposition

IBD

Immunologic Abnormalities

Environmental Factors
Treating IBD: Goals of Management

- Induce remission
- Maintain remission
  - Most patients require maintenance therapies
  - Need effective and safe long-term therapies
- Enhance quality of life
- Avoid adverse events
  - Complications of the disease, including surgery
  - Safety issues associated with therapy
Drug Therapies for IBD

Aminosalicylates
- Sulfasalazine
- Mesalamine
- Olsalazine
- Balsalazide

Corticosteroids
- Prednisone/
- Prednisolone
- Budesonide

Immunomodulators
- 6MP/Azathioprine
- Cyclosporine
- Anti-TNF
- Tacralimus

Antibiotics
- Metronidazole
- Quinolones
- Rifaximin
- Other

Supportive Agents
- Antidiarrheal
- Bile sequestrants
- Bulk formers
- Antidepressants
- Pain management
- Anti-spasmodics
Medical Therapeutic Pyramid

- Biologics
- Immunomodulators
- Non-biologics
- Corticosteroids
- Aminosalicylates

Moderate to severe disease
Surgery vs. long term medical maintenance: moderate and severe UC

Questions:

- What is the evidence for medical maintenance vs. surgery?
- What is the definition of “long-term?”
- Are certain immunomodulators better than others?
- What are the short and long term risks?
- Are there any quality of life data?
- If surgery is the “last resort,” how do we decide when to quit?
Medical Maintenance Therapy: moderate and severe UC

- **First Line Drugs**
  - Azathioprine/6-mercaptopurine
  - Infliximab

- **Second Line Drugs**
  - CSA
  - Mycophenolate
  - Tacrolimus

- **Corticosteroids are not an option for long-term maintenance.**

Very little data for these!
Cumulative Relapse Rates in Patients with UC and CD*

*Between diagnosis and follow-up (mean, 16.2 months).

Need for Surgery

- 74% for Crohn's Disease
- 25% for Ulcerative Colitis

Surgery
Natural Course of UC: Pancolitis

*Based on a multivariate analysis.

## Colectomy Rates with solely aminosalicylates: 10 years

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colectomy Rates at 10 years</td>
<td>28%</td>
<td>49%</td>
<td>64%</td>
</tr>
</tbody>
</table>
Colectomy rates with high dose steroids: 3 month data*

**A. Gustavsson et al. Am J Gastroenterology;102, 2007.**

**1975-1982 data**
Colectomy rates with high dose steroids: 20 year data*


**1975-1982 data
6-MP/Azathiaprine

- Used for maintenance therapy in moderate and severe UC.
- Requires 6-8 weeks or longer to take effect, so not useful for induction therapy alone.
- Is most often used in combination with CSA, steroid, or infliximab at induction for maintenance in moderate to severe UC.
## UC: 6-MP/AZA Maintenance

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Drug Dose</th>
<th>Length of Rx</th>
<th>Response 6-MP/AZA</th>
<th>Response Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jewell (1974)</td>
<td>80</td>
<td>AZA 1.5-2.5 mg/kg/d</td>
<td>11 mo</td>
<td>40%</td>
<td>23%</td>
<td>.18</td>
</tr>
<tr>
<td>Hawthorne (1992)</td>
<td>67</td>
<td>AZA NR</td>
<td>1 yr</td>
<td>64%</td>
<td>41%</td>
<td>.039</td>
</tr>
<tr>
<td>Sood (2003)</td>
<td>25</td>
<td>AZA 2.5 mg/kg/d</td>
<td>18 mo</td>
<td>42%</td>
<td>62%</td>
<td>NS</td>
</tr>
</tbody>
</table>
Colectomy avoidance rates with CSA induction ± AZA therapy*

*Actis, G et al. BMC Gastroenterology 2007;7:13
The influence of AZA on colectomy rates in CSA induced remission*

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=34)</th>
<th>+ AZA (n=15)</th>
<th>-AZA (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colectomy &gt;1 year</td>
<td>39%</td>
<td>20%</td>
<td>53%</td>
</tr>
<tr>
<td>Colectomy &gt;3 years</td>
<td>62%</td>
<td>44%</td>
<td>85%</td>
</tr>
<tr>
<td>Colectomy &gt;7 years</td>
<td>65%</td>
<td>40%</td>
<td>90%</td>
</tr>
</tbody>
</table>

*Actis, G et al. BMC Gastroenterology 2007;7:13
Cyclosporine

- No controlled trials of oral CSA in UC.
- Only 4 controlled trials of IV CSA (severe UC).
- No long-term data.
Cyclosporine (CSA) for Severe Steroid Refractory UC (Short term data)

N=20
Dose = 4 mg/kg IV
Duration = 14 d
p<0.001

CSA vs Corticosteroids for Severe UC (Short term data)

- CSA vs Corticosteroids
- N=30
- Methylprednisolone dose 40 mg/d
- CSA dose 4 mg/kg IV
- Duration 8 d
- p=NS

Impact of CSA on Colectomy

- Of 604 patients studied in 42 trials, overall colectomy rate of 30% (182/604).
- Mean number of patients with long term response after discontinuation: 39% (237/604).
- CSA for long-term maintenance in UC is not recommended.
Impact of therapy on colectomy rate in moderate/severe colitis at 10 years

- All treatments: 40-50%
- Aminosalicylates: 49-54%
- Steroids: 52-60%
- 6-MP/Azathiaprine: 40%
- CSA: No long term data
- Inflixamab???
Infliximab: Indications in UC

- An antibody that binds to TNF to block inflammatory response/cascade and also induces apoptosis.
- First reported use in 2001 for salvage of steroid refractory UC.
- Off-label use of drug stimulated interest in concept of “salvage” in UC.
Key Actions Attributed to TNF

- Proinflammatory cytokines
- Chemokines
- Macrophages
  - Adhesion molecules
  - Increased inflammation
- Endothelium
  - Adhesion molecules
  - Increased cell infiltration
- Liver
  - Acute phase response
  - Increased CRP in serum
- Fibroblasts
  - Metalloproteinase synthesis
  - Collagen production
  - Tissue remodeling
- Epithelium
  - Ion transport
  - Permeability
  - Compromised barrier function
Infliximab effect on symptoms in steroid resistant UC*

*G. Dhaens Gastroenterology 2005;128
## Infliximab data in steroid dependent severe UC

<table>
<thead>
<tr>
<th>Study</th>
<th># of pts</th>
<th>Follow-up times</th>
<th>Colectomy rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaser 2001</td>
<td>6</td>
<td>6 mo</td>
<td>30%</td>
</tr>
<tr>
<td>Gornet 2003</td>
<td>30</td>
<td>12 mo</td>
<td>33%</td>
</tr>
<tr>
<td>Kohn 2004</td>
<td>13</td>
<td>24 mo</td>
<td>23%</td>
</tr>
</tbody>
</table>
Controlled Trials and Infliximab in UC

- Probert et al 2005 (mod/severe steroid resistant)
  - Remission rates at 6 weeks: 39% infliximab vs 30% with placebo. NS.

- Jarnerot et al 2005 (severe steroid dependent)
  - Infliximab: 7/24 (29%) required colectomy at 3 months.
  - Placebo: 14/2 (66%) required colectomy p=.017.
Infliximab for Induction and Maintenance Therapy for Ulcerative Colitis

Paul Rutgeerts, M.D., Ph.D., William J. Sandborn, M.D., Brian G. Feagan, M.D., Walter Reinisch, M.D., Allan Olson, M.D., Jewel Johans, Ph.D., Suzanne Travers, M.D., Daniel Rachmilewitz, M.D., Stephen B. Hanauer, M.D., Gary R. Lichtenstein, M.D., Willem J.S. de Villiers, M.D., Ph.D., Daniel Present, M.D., Bruce E. Sands, M.D. and Jean Frédéric Colombel, M.D.

N Engl J Med
Volume 353;23:2462-2476
December 8, 2005
Results of two randomized, placebo-controlled trials of infliximab in patients who had active UC despite conventional therapy.

Infliximab was more effective than placebo in achieving and maintaining clinical response and remission.

Patients with moderate-to-severe active UC were treated with infliximab at weeks 0, 2, and 6 and every eight weeks thereafter were more likely to have a clinical response at weeks 8, 30, and 54 than were those receiving placebo.
## Response to Infliximab in UC

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Infliximab 5mg/kg</th>
<th>Placebo</th>
<th>Infliximab 5mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 8</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response (%)</td>
<td>37.2</td>
<td>69.4&lt;sup&gt;1&lt;/sup&gt;</td>
<td>29.3</td>
<td>64.5&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Remission (%)</td>
<td>14.9</td>
<td>38.8&lt;sup&gt;1&lt;/sup&gt;</td>
<td>5.7</td>
<td>33.9&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mucosal healing (%)</td>
<td>33.9</td>
<td>62&lt;sup&gt;1&lt;/sup&gt;</td>
<td>30.9</td>
<td>60.3&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Week 30</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response (%)</td>
<td>29.8</td>
<td>52.1&lt;sup&gt;1&lt;/sup&gt;</td>
<td>26</td>
<td>47.1&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Remission (%)</td>
<td>15.7</td>
<td>33.9&lt;sup&gt;3&lt;/sup&gt;</td>
<td>10.6</td>
<td>25.6&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Remission and discontinued CS (%)</td>
<td>10.1</td>
<td>24.3&lt;sup&gt;6&lt;/sup&gt;</td>
<td>3.3</td>
<td>18.3&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mucosal healing (%)</td>
<td>24.8</td>
<td>50.4&lt;sup&gt;1&lt;/sup&gt;</td>
<td>30.1</td>
<td>46.3&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Week 52</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response (%)</td>
<td>19.8</td>
<td>45.5&lt;sup&gt;1&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Remission (%)</td>
<td>16.5</td>
<td>34.7&lt;sup&gt;3&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Remission and discontinued CS (%)</td>
<td>8.9</td>
<td>25.7&lt;sup&gt;1&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mucosal healing (%)</td>
<td>18.2</td>
<td>45.5&lt;sup&gt;9&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Impact of therapy on colectomy rate in moderate/severe UC ≤ 1 year

- All treatments: 20%
- Aminosalicylates: No data
- Steroids: 20%
- 6-MP/Azathiaprine: 20%
- CSA: >30%
- Infliximab: 23-33%
Conclusions: Predictors for Colectomy in UC

- Distribution of disease (pancolitis).
- Severity of disease.
- Length of time from first presentation.
- Medications?
  - Type of medication does not seem to make an appreciable difference in colectomy rate, but may help in other ways.
  - Some medications are more tolerable than others.
Conclusions

- Colectomy is not a primary endpoint in any of these short-term studies, therefore CR are difficult to deduce.
- No clarity yet on drug-drug interactions and possible synergy.
- No data on Quality of Life.
- No data on the long-term effects of exposure to new agents.
- Azathiaprine is still most likely to produce reduce colectomy rates, long-term.
Conclusions

- There is not enough short or long-term data on modern immunotherapy to conclude that it is protective against colectomy.
- Other benefits may be realized, not discussed here.
- Colectomy rates are related to severity, disease distribution, and time.
- Length of time to colectomy may be increasing, but overall rates may not change.
- We may be able to alter the course of the disease, but not the biology and final outcome.