Which Endpoint of Therapy Should We Use in Clinical Practice?

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Disclosure
Research, Advisory and/or Honorarium

- Abbott
- Astra-Zeneca
- Axcan
- Centocor
- Elan
- Millenium Pharmaceuticals
- Otsuka America
- Procter & Gamble
- Prometheus Laboratories
- Salix
- Synta Pharmaceuticals
- Schering-Plough
- Shire
- Smith Kline Beecham
- UCB
- Wyeth
Which Endpoint in Clinical Practice is Appropriate?

- Adequate Nutrition
- Normal QOL
- Avoid Hospitalizations
- Avoid Surgeries
- Clinical Remission
- Steroid Free
- Endoscopic Mucosal Healing
- Maintaining Remission

Natural History of IBD

- Ulcerative Colitis
- Crohn’s Disease
UC: Natural History

Disease Severity at Presentation

- **Mild Activity**: < 4 stools daily
  - No systemic disturbance
  - ESR: Nl

- **Moderate Activity**: > 4 stools daily
  - Minimal systemic effects

- **Severe Activity**: > 6 stools daily
  - Bloody stools
  - Fever
  - Tachycardia
  - Anemia
  - ESR > 30 mm/hr

Hendriksen C, Kreiner S, Binder V. Gut 1985;26:158-163

UC Natural History

Disease course one year after diagnosis

- **No Symptoms**: (50%)
- **Low Activity**: (30%)
- **Moderate-High Activity**: (20%)
- **Colectomy Rate (%)**:
  - 0% at year 0
  - 10% at year 5
  - 23% at year 10
  - 31% at year 15
  - 40% at year 20
Natural Course of Ulcerative Colitis

UC: Natural History*

* Percent of patients with disease activity, in remission, or having colectomy performed each year after diagnosis


Natural Course of Ulcerative Colitis

Proctitis

Left-Sided

Pan-colitis

Altering the Natural Course of IBD

Mucosal healing

Disease modification

↓ Risk of surgery
↓ Risk of Hospitalization

Mucosal Healing

- Definition

- Rates amongst agents
Ulcerative Colitis: Mucosal Healing in Clinical Trials

<table>
<thead>
<tr>
<th>Instrument</th>
<th>UC Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Truelove and Witts Severity Index</td>
<td>Cortisone</td>
</tr>
<tr>
<td>St Mark’s Index (Powell-Tuck Index)</td>
<td>Prednisolone</td>
</tr>
<tr>
<td>Clinical Activity Index (Rachmilewitz index)</td>
<td>Coated mesalamine</td>
</tr>
<tr>
<td>Mayo score</td>
<td>Delayed-release oral mesalamine</td>
</tr>
<tr>
<td>Sutherland Index</td>
<td>Rectal 5-ASA enema</td>
</tr>
<tr>
<td>Physician global assessment (PGA) scale</td>
<td>Oral controlled-release mesalamine</td>
</tr>
<tr>
<td>Improvement of individual symptom scores</td>
<td>Balsalazide</td>
</tr>
<tr>
<td>Lichtiger score (Modified Truelove and Witts Severity Index)</td>
<td>Cyclosporine, visilizumab</td>
</tr>
<tr>
<td>Modified Mayo score</td>
<td>Infliximab</td>
</tr>
<tr>
<td>Composite clinical and endoscopic end point</td>
<td>MLN-02</td>
</tr>
</tbody>
</table>
Difference in UC Clinical Trials: Definitions and Assessment

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>Definition of Mucosal Healing</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Truelove and Witts(^1)</td>
<td>Cortisone</td>
<td>Near-normal defined as slight hyperemia or slight granularity noted as the only abnormal findings</td>
<td>Baseline and week 6</td>
</tr>
<tr>
<td>Kozarek(^2)</td>
<td>Methotrexate</td>
<td>Not defined</td>
<td>Baseline and week 6</td>
</tr>
<tr>
<td>ASCEND I and II(^3)</td>
<td>Delayed-release mesalamine</td>
<td>Endoscopy subscore of 0 or 1</td>
<td>3 and 6 weeks</td>
</tr>
<tr>
<td>Lichtenstein et al(^4)</td>
<td>Delayed release mesalamine</td>
<td>Modified score of ≤1 (with no mucosal friability)</td>
<td>8 weeks</td>
</tr>
<tr>
<td>ACT 1 and 2(^5)</td>
<td>Infliximab</td>
<td>Absolute subscore for endoscopy of 0 or 1</td>
<td>8 weeks</td>
</tr>
</tbody>
</table>

\(^1\) Asacol®
\(^2\) Lialda™


UC: Mucosal Healing in ASCEND I and II Trials

Mucosal healing defined as endoscopy subscore of 0 or 1.

2.4 g/d delayed-release mesalamine\(^6\) (400 mg tablet) (n=209)
4.8 g/d (800 mg delayed-release mesalamine tablet) (n=182)

* P<0.05
\(^6\) Asacol®

UC: Mucosal Healing With Delayed Release Mesalamine

Mucosal healing defined as modified score of ≤1 (with no mucosal friability).

<table>
<thead>
<tr>
<th>Week 8</th>
<th>2.4 g/day given QD (n=84)</th>
<th>4.8 g/day given QD (n=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placbo (n=86)</td>
<td>46.5</td>
<td>69.0*</td>
</tr>
<tr>
<td>Delayed Release Mesalamine**</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Corticosteroids and Mucosal Healing in UC

Near-normal defined as slight hyperemia or slight granularity noted as the only abnormal findings.

- Cortisone 50 to >100 mg/day (n=63)
- Control (n=57)

Sigmoidoscopic Appearances

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Normal or near normal</th>
<th>Improved</th>
<th>No change or worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisone</td>
<td>30</td>
<td>30</td>
<td>48</td>
</tr>
<tr>
<td>Control</td>
<td>11</td>
<td>11</td>
<td>68</td>
</tr>
</tbody>
</table>


Methotrexate and Mucosal Healing in UC

- Corticosteroids, variable doses (n=17)
- Sulfasalazine or metronidazole (n=14)
- Failed previous AZA/6-MP therapy (n=10)

Methotrexate IM 25 mg q week

21 patients with refractory IBD (7 with UC)

- Clinical improvement* 71% (5/7)
- Endoscopic remission 0% (0/7)
- Histologic remission 0% (0/7)

*Mean decrease in chronic ulcerative colitis activity index from 13.3 to 6.3 (P=0.007).

UC: Mucosal Healing in ACT-1 and ACT-2 Trials


Mucosal healing defined as absolute subscore for endoscopy of 0 or 1.

*P<0.001 vs placebo
†P=0.009 vs placebo

Does Mucosal Healing Matter?
Recent Evidence
Histologic Findings of Basal Plasmacytosis Predict Shorter Time to Relapse in UC

Mucosal Healing with Conventional Therapy* Reduces Colectomy Rate in UC

* Oral 5-ASA, topical 5-ASA, sulfasalazine, antibiotics, corticosteroids, azathioprine, and/or metronidazole

Reprinted from Gastroenterology 120, Bitton A et al, Clinical, biological, and histologic parameters as predictors of relapse in ulcerative colitis, 13-20. Copyright (2001), with permission from the American Gastroenterological Association.

Proportion of Patients with Colectomy Through 54 Weeks

ACT 1 & ACT 2

$n=36/244$

$n=46/484$


Severity of Colonic Inflammation Increases CRC Risk

$P<0.001$

$P=0.001$

OR=5.13

OR=2.54

$*$ Odds ratio is for a 1-unit increase in score.

Inflammatory Activity Increases Risk of Dysplasia-CRC in UC


Mean inflammatory activity = 2.0 for cases vs 1.6 for controls (P=0.013)

* Adjusted for family history of CRC, smoking status, 5-ASA, and immunomodulator use.

Endoscopic Indices Correlate With Clinical Symptoms in UC

66 UC patients evaluated with invasive indices (St. Mark’s Index, UCDAI) and noninvasive indices (SCCAI, Seo Index)

Correlations between indices measured

Endoscopy items contributed little additional information to noninvasive indices

Endoscopy items correlated with stool frequency and stool blood

Does Mucosal Healing Matter?
Recent Evidence

<table>
<thead>
<tr>
<th>Active sx(s)</th>
<th>Inactive sx(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>?</td>
</tr>
<tr>
<td>No</td>
<td>? Other Disorders (? IBS)</td>
</tr>
</tbody>
</table>

Conclusions

- Definition of mucosal healing differs between clinical trials
- Mucosal healing has been observed with various agents:
  - In UC: with mesalamine, steroids, and infliximab
- Mucosal healing has been shown to correlate with reduced future colectomy in UC
- Both endoscopic and histologic inflammation have been found to be independent predictors of CRC in UC
- Endoscopic indices correlate with clinical symptoms in UC
- Mucosal healing is a goal of therapy
Practice Guides

- Mucosal healing is a desired endpoint for therapy in UC
- Mucosal healing has been observed with various agents:
  - In UC: with mesalamine, steroids, and infliximab
- Mucosal healing has been shown to correlate with reduced future colectomy in UC
- Both endoscopic and histologic inflammation have been found to be independent predictors of CRC in UC
- Endoscopic indices correlate with clinical symptoms in UC
- Mucosal healing is a goal of therapy

Disease Activity Indices in Clinical Practice

Active Disease

Inactive Disease
Operating Properties of the CDAI

- Developed in 1975
- Composite score: 8 subjective & objective criteria
- Maximum score 600
  - Higher the score, the more severe the disease
- “Remission” generally defined as a CDAI ≤ 150
- Minimally Clinical Important Difference = ~50 points
- “Response” generally defined as a reduction in the score by at least 70-100 points

Evidence Based Medicine

- Trial Design
  - Comparison across trials are always dubious at best given different entry criteria, patient populations and endpoints.
  - Crohn’s Disease
    - CDAI
      - Response
        - Decrease in the CDAI of 50, 70, 100, or 150 points
        - Decrease of 70–100 points and a 25% improvement from baseline
      - Remission
        - CDAI ≤ 150 points
        - CDAI < 150 points and decrease by ≥50–100 points
        - CDAI < 150 points and steroid free
        - CDAI ≤ 150 points and IL10D ≤ 180–190 points
      - Maintenance of remission
        - Baseline CDAI of <150 points with relapse defined as a rise in the CDAI score to a value >150, with an increase of at least 50–60 points over baseline

- Ulcerative Colitis
  - Different indices
CDAI: Which Variables Matter?

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Multiplier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of liquid stools</td>
<td>Sum of 7 days</td>
<td>X2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Sum of 7 days ratings</td>
<td>X5</td>
</tr>
<tr>
<td>General well being</td>
<td>Sum of 7 days ratings</td>
<td>X7</td>
</tr>
<tr>
<td>Extraintestinal complications</td>
<td>Number of listed complications</td>
<td>X20</td>
</tr>
<tr>
<td>Antidiarrheal drugs</td>
<td>Use in previous 7 days</td>
<td>X30</td>
</tr>
<tr>
<td>Abdominal mass</td>
<td>Use in previous 7 days</td>
<td>X10</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Expected - observed Hct Males: 47 - observed Females: 42 - observed</td>
<td>X6</td>
</tr>
<tr>
<td>Body weight</td>
<td>Ideal/observed ratio [1 - (ideal/observed)] X 100</td>
<td>X1 (NOT &lt; -10)</td>
</tr>
</tbody>
</table>

Operating Properties of the CDAI

- Developed in 1975
- Composite score: 8 subjective & objective criteria
- Maximum score 600
  - Higher the score, the more severe the disease
- “Remission” generally defined as a CDAI ≤ 150
- Minimally Clinical Important Difference = ~50 points
- “Response” generally defined as a reduction in the score by at least 70-100 points
Administration and Scoring the CDAI is Highly Variable

- Medline search to identify authors of articles published from 1976 to 1997 in which the CDAI was used
  - 208 authors identified
  - 100 valid questionnaires obtained
- Survey identified considerable variation in the administration and scoring
- Authors disagreed on the following parameters:
  - Definition of “liquid or very soft stools”
  - Recording of number of stools
  - Recording of pain rating
  - Scoring of extraintestinal manifestations and fistulas
  - Recording of fever, scoring for opiates, standard for weight

Variations in Recording the CDAI

- Number of bowel movements:
  - Instructed to keep a running total 51%
  - By recall before going to sleep 23%
  - No specific instructions given 22%
- Fever
  - Do not require patients to possess a thermometer 38%
  - Tell to check when they ‘feel’ may be running a fever 37%
  - Advocate routine monitoring 20%
- Abdominal pain:
  - Graded on a spectrum of no pain to ‘worst’ 57%
  - Rated on interference with daily activities 23%
  - No or minimal instruction 9%

Total CDAI = 289
Indicates Mild-to-Moderate CD

- Liquid stools
  - 3 X 7 days = 21 X 2 = 42

- Abdominal pain
  - 2 X 7 = 14 X 5 = 70

- Well being
  - Avg. 3/day = 21 x 7 = 147

- Taking loperamide
  - = 30

Patient Has Irritable Bowel Syndrome
Limitations of the CDAI

- Interobserver variability
- ‘general well being’ and ‘abdominal pain’ scores are subjective
- Calculation of CDAI is based on a diary filled by the patient for 7 days before evaluation
- CDAI is not accurate in patients with fistulizing and stenosing behavior
- It is not useful in patients with previous extensive ileo-colonic resections or stoma


Crohn’s Disease activity in Clinical Practice

<table>
<thead>
<tr>
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<tbody>
<tr>
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</tr>
<tr>
<td>Antidiarrheal drugs</td>
</tr>
<tr>
<td>Abdominal mass</td>
</tr>
<tr>
<td>Hematocrit</td>
</tr>
<tr>
<td>Body weight</td>
</tr>
</tbody>
</table>

1.) If still with active sxs then mucosal evaluation

2.) If not still with active sxs then NO mucosal evaluation
In Ulcerative Colitis
Do We Need Disease Activity Indices?

Take your pick...
Ulcerative Colitis Activity Assessment

<table>
<thead>
<tr>
<th>Stools (#/day)</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Fulminant</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4</td>
<td>&gt; 6</td>
<td>&gt; 10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood in stool</th>
<th>Intermittent</th>
<th>Frequent</th>
<th>Continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature (C)</td>
<td>Normal</td>
<td>&gt; 37.5</td>
<td>&gt; 37.5</td>
</tr>
<tr>
<td>Pulse</td>
<td>Normal</td>
<td>&gt; 90</td>
<td>&gt; 90</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Normal</td>
<td>&lt; 75% of normal</td>
<td>Transfusion required</td>
</tr>
<tr>
<td>ESR</td>
<td>&lt; 30</td>
<td>&gt; 30</td>
<td>&gt; 30</td>
</tr>
</tbody>
</table>


Clinical Trial Efficacy Endpoints in UC

Based on Clinical and Biochemical Disease Activity
- Truelove and Witts Severity Index (TWSI)
- Powell-Tuck Index
- Clinical Activity Index (CAI)
- Activity Index (AI, or Seo Index)
- Physician Global Assessment
- Lichtiger Index (mTWSI)
- Investigators Global Evaluation
- Simple Clinical Colitis Activity Index (SCCAI)
- Improvement Based on Individual Symptom Scores
- Ulcerative Colitis Clinical Score (UCCS)
- Patient Defined Remission

Instruments for Measuring Disease Activity
- Ulcerative Colitis Activity Assessment
- Composite Clinical & Endoscopic Disease Activity
  - Mayo Score (DAI)
  - Sutherland Index (DAI, UCDAI)

Based on Endoscopic Disease Activity
- Truelove and Witts Sigmoidoscopic Assessment
- Baron Score
- Powell-Tuck Sigmoidoscopic Assessment
- Rachmilewitz Endoscopic Index
- Sigmoidoscopic Index
- Sigmoidoscopic Inflammation Grade Score
- Mayo Score Flexible Proctosigmoidoscopy Assessment
- Sutherland Mucosal Appearance Assessment
- Modified Baron Score
Primary Endpoints in UC Clinical Trials Differ

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary Endpoint</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCEND-II</td>
<td>Treatment success at Week 6</td>
<td>Improvement in baseline PGA score &amp; improvement in ≥ 1 other clinical assessment &amp; no worsening in any other clinical assessment (ie, rectal bleeding, stool frequency, endoscopy score and patient’s functional assessment)</td>
</tr>
<tr>
<td>MATRx1²</td>
<td>Remission at Week 8</td>
<td>UCDAI ≥ 1 with rectal bleeding &amp; stool frequency of 0 &amp; ≥ 1 point reduction in sigmoidoscopy from baseline</td>
</tr>
<tr>
<td>ACT-1 and ACT-2³</td>
<td>Clinical response at Week 8</td>
<td>↓ from baseline in total Mayo score of ≥ 3 pts &amp; ≥ 30%, with accompanying ↓ in rectal bleeding subscore ≥ 1 point or an absolute subscore for rectal bleeding of 0 or 1</td>
</tr>
</tbody>
</table>

PGA = physician’s global assessment; UCDAI = Ulcerative Colitis Disease Activity Index.

**Results of Primary Endpoints for ASCEND, MATRx1, and ACT 1 Trials**

**ASCEND I and II**
- Overall Improvement at 6 Weeks:
  - 2.4 g Mesalamine: 58%
  - 4.8 g Mesalamine: 72%*

**MATRx1**
- Remission at 8 Weeks:
  - Placebo: 13%
  - 2.4 g 5-ASA MMx: 34%1
  - 4.8 g 5-ASA MMx: 29%2

**ACT 1**
- Clinical Response at 8 Weeks:
  - Placebo: 37%
  - 5 mg/kg Infliximab: 69%3
  - 10 mg/kg Infliximab: 62%3

*P<.05; 1P<.01; 2P<.001.


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**Various Definitions of Clinical Remission Used in Recent UC Clinical Trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Definition of Remission Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCEND-II1</td>
<td>Complete resolution (score=0) of stool frequency, rectal bleeding, sigmoidoscopy findings, patient functional assessment, and PGA at Week 6</td>
</tr>
<tr>
<td>MATRx12</td>
<td>UCDAI ≤ 1 with rectal bleeding and stool frequency of 0 and ≥ 1 point reduction in sigmoidoscopy from baseline at Week 8</td>
</tr>
<tr>
<td>ACT-1 and ACT-23</td>
<td>Mayo score ≤ 2 with no individual subscores &gt; 1 at Week 8</td>
</tr>
</tbody>
</table>

PGA = physician’s global assessment; UCDAI = Ulcerative Colitis Disease Activity Index.

**Clinical Remission Rates Vary Depending on the Definition of Remission**

**Analysis of ASCEND Data (mild and moderate population)**
**Using Different Definitions of Remission**

- Complete Resolution (score = 0) of stool frequency, rectal bleeding, sigmoidoscopy findings, patient functional assessment, & PGA: 22%
- UCDAI score ≤ 1 & rectal bleeding & stool frequency subscores of 0 & ≥ 1 point ↓ in sigmoidoscopy score from baseline: 28%
- UCDAI score ≤ 2, no individual subscore > 1: 50%

PGA = physician’s global assessment; UCDAI = Ulcerative Colitis Disease Activity Index.
Katz S, Kane S, et al. Gastroenterology. 2006;130(suppl 2);A-482.

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**Clinical Trial Designs for UC: Conclusions**

- Clinical trial design must apply to individual patient's scenario.
- There is no current standard/accepted efficacy endpoint for UC.
  - Endpoints differ among clinical trials in UC.
- Clinical relevance of endoscopic remission vs clinical remission is uncertain.
- Remission rates vary depending on definition used.
  - Physicians should be aware of definitions of remission being utilized when comparing clinical efficacy.
**The Mayo Score**

Components of the Mayo Score

- **Stool Frequency**  
  0 = Normal  
  1 = 1-2 stools/day more than normal  
  2 = 3-4 stools/day more than normal  
  3 = >4 stools/day more than normal

- **Rectal bleeding**  
  0 = None  
  1 = Visible blood with stool less than half the time  
  2 = Visible blood with stool half of the time or more  
  3 = Passing blood alone

- **Mucosal appearance at endoscopy**  
  0 = Normal or inactive disease  
  1 = Mild disease (erythema, decreased vascular pattern, mild friability  
  2 = Moderate disease (marked erythema, absent vascular pattern, friability,  
  erosions)  
  3 = Severe disease (spontaneous bleeding, ulceration)

- **Physician rating of disease activity**  
  0 = Normal  
  1 = Mild  
  2 = Moderate  
  3 = Severe

---

**Be Objective and Consider All Explanations**

- **DON’T** overestimate your history taking abilities, they are often wrong
- **Use** labs, colonoscopy, and radiology studies to determine if patients have active disease- and thus to determine if patients should start steroids, azathioprine, infliximab, or go to surgery
- **DON’T** forget about steatorrhea, bile salt diarrhea, small bowel bacterial overgrowth, and IBS
Ulcerative Colitis

The Clinicians Assessment of The Mayo Score

Components of the Mayo Score

- **Stool Frequency**: 0 = Normal
- **Rectal bleeding**\(\uparrow\): 0 = None
- **Mucosal appearance at endoscopy**\(\uparrow\): 0 = Normal or inactive disease
- **Physician rating of disease activity**: 0 = Normal
Take Home Messages

• Appropriately administer topical, oral, and parenteral therapy to maximize patient outcomes
  ▪ 5-ASA, corticosteroids, immune modulators, biologic agents
• Select optimal therapy for appropriate disease activity and disease distribution
• In patients with “aggressive” disease (e.g., steroid-dependent, steroid-refractory) use appropriate “aggressive” therapy
  ▪ Immunosuppressants (CyA, 6-MP/AZA, MTX)
  ▪ Anti-TNF Therapy (Infliximab, Adalimumab or Certolizumab Pegol)