“Feasibility of Mucosal Healing as a Clinically Significant Endpoint in Inflammatory Bowel Disease”

American College of Gastroenterology
and
U.S. Food & Drug Administration
Workshop
October 31, 2011
ACG-FDA Joint IBD Workshop

Moderators:
Stephen Hanauer, MD FACG  Zana Handy-Marks, MD MHP

Panel Members:
William Sandborn, MD FACG  David Rubin, MD FACG
Bruce Sands, MD FACG  Brian Feagan, MD FACG
Jean-Frederic Colombel, MD  J-P Achkar, MD FACG
Robert Fiorentino, MD
The CDAI

- Developed for NCCDS Study
- Logistic regression analysis: independent predictors of physician global ratings
- Scores 0 - ~ 600
- Validated extensively (reliable, responsive)
- Gold Standard for clinical trials
- 70-100 point change is meaningful
- <150 = remission
**Crohn’s Disease Activity Index (CDAI)**

<table>
<thead>
<tr>
<th>Variable no.</th>
<th>Variable description</th>
<th>Multiplier</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No. of liquid or soft stools (each day for 7 days)</td>
<td>x 2</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Abdominal pain, sum of seven daily ratings (0 = none, 1 = mild, 2 = moderate, 3 = severe)</td>
<td>x 5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>General well-being, sum of seven daily ratings (0 = generally well, 1 = slightly under par, 2 = poor, 3 = very poor, 4 = terrible)</td>
<td>x 7</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Number of listed complications (arthritis or arthralgia; iritis or uveitis; erythema nodosum, pyoderma gangrenosum, or aphthous stomatitis; anal fissure, fistula, or abscess; other fistula; fever over 37.8°C [100°F])</td>
<td>x 20</td>
<td></td>
</tr>
</tbody>
</table>

## Crohn’s Disease Activity Index (CDAI) (cont’d)

<table>
<thead>
<tr>
<th>Variable no.</th>
<th>Variable description</th>
<th>Multiplier</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Use of diphenoxylate or loperamide for diarrhea</td>
<td>x 30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0 = no, 1 = yes)</td>
<td></td>
<td>0-600</td>
</tr>
<tr>
<td>6</td>
<td>Abdominal mass</td>
<td>x 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0 = no, 2 = questionable, 5 = definite)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Hematocrit (males: 47-Hct [%], females: 42-Hct [%])</td>
<td>x 6</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Body weight (1-weight/standard weight) x 100</td>
<td>x 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(add or subtract according to sign)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Crohn’s Disease Activity Index (CDAI) Scoring

- Remission <150
- Moderate activity 200 – 450
- Severe activity >450
- Maximum score 600

### The Crohn’s Disease Activity Index

**Problem:** The patient has Irritable Bowel Syndrome

<table>
<thead>
<tr>
<th>Condition</th>
<th>Value</th>
<th>Calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquid stools - 3x7 days = 21x2</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain - 2x7 = 14 = 5</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Well being - avg 3/d = 21x7</td>
<td>147</td>
<td></td>
</tr>
<tr>
<td>Taking loperamide</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td><strong>Total = 289 CDAI</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Indicates mild-moderate CD
Relationship Between Clinical Symptoms and Endoscopic Indices at Presentation of Acute CD

Crohn’s Disease Activity Index (CDAI)

Crohn’s Disease Endoscopic Index of Severity (CDEIS)

$R=0.13; \text{ NS}$

Measuring Disease Activity in UC Clinical Trials

Instruments for Measuring Disease Activity

**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

**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

**DAI or Mayo Score**

**Stool Frequency**
- 0 = Normal
- 1 = 1-2 Stools > Normal for individual
- 2 = 3-4 Stools > Normal for individual
- 3 = 5 or more stools > Normal for individual

**Rectal Bleeding**
- 0 = No bleeding
- 1 = Streaks of blood with less than ½ of stools
- 2 = Obvious blood in stool
- 3 = Passage of blood alone

**Endoscopy**
- 0 = Normal
- 1 = Erythema, decreased MVP, mild friability
- 2 = Marked erythema, absent MVP, friability, erosions
- 3 = Spontaneous bleeding, ulceration

**Physician Global Assessment**
- 0 = Normal
- 1 = Mild
- 2 = Moderate
- 3 = Severe

**Total score 0-12**
ACG-FDA

IBD Workshop Questions

1. Is mucosal healing meaningful as a primary endpoint in IBD treatment trials?

2. Is the histopathological evaluation an important component of assessing mucosal healing?

3. If symptomatic clinical remission is achieved, how important is mucosal healing?

4. Are there potential alternatives to endoscopic assessment of mucosal healing?
Is mucosal healing meaningful as a primary endpoint in IBD treatment trials?

Presented by William Sandborn, MD FACG
Is mucosal healing meaningful as a primary endpoint in IBD

William J. Sandborn MD
Professor of Clinical Medicine
Chief, Division of Gastroenterology
Director, UCSD IBD Center
UC San Diego Health System
La Jolla, California
What’s Wrong with Using Clinical Endpoints Rather Than Mucosal Healing?

• Crohn’s disease
  – Clinical endpoints don’t correlate with endoscopic findings
  – Patients treated to clinical endpoints often have progression of their disease – from luminal inflammatory disease to complications of stricture, fistula, and abscess that require surgery
  – Disease progression and operations frequently result in disability

• Ulcerative colitis
  – Patients with COMPLETE clinical remission and COMPLETE mucosal healing (score of 0) have a good prognosis
  – Clinicians and patients usually don’t escalate therapy for mild residual symptoms
Crohn’s Disease Symptoms (CDAI) versus Crohn’s Disease Endoscopic Findings (CDEIS)

CDAI = Crohn’s Disease Activity Index; CDEIS = Crohn’s Disease Endoscopic Index of Severity.


Correlation of CDAI vs CDEIS at D₀ (n = 142)

R = 0.13 ; NS
Correlations Between hsCRP, IL-6, Fecal Markers, CDAI, and Endoscopic Activity in Crohn’s Disease (N=164)

<table>
<thead>
<tr>
<th></th>
<th>IL-6</th>
<th>Calprotectin</th>
<th>Lactoferrin</th>
<th>CDAI</th>
<th>SES-CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsCRP</td>
<td>0.65</td>
<td>0.47</td>
<td>0.52</td>
<td>0.16</td>
<td>0.46</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.45</td>
<td></td>
<td>0.55</td>
<td>0.15</td>
<td>0.43</td>
</tr>
<tr>
<td>Calprotectin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactoferrin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDAI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.15</td>
</tr>
</tbody>
</table>

Correlation coefficients highlighted in red were significant (P < 0.05).

When stratified by extent, correlation coefficients were highest for colonic disease.

hs-CRP = high-sensitivity C-reactive protein; IL-6 = interleukin 6; CDAI = Crohn’s Disease Activity Index; SES-CD = Simple Endoscopic Score for Crohn’s Disease.

Immunosuppressive versus Anti-TNF Antibody versus Combination Therapy for Active Crohn’s Disease

Mucosal Healing at Week 26

- **IS + placebo**
  - 18/109
  - Proportion of Patients (%) 16%

- **Anti-TNF + placebo**
  - 28/93
  - Proportion of Patients (%) 30%

- **Anti-TNF + AZA**
  - 47/107
  - Proportion of Patients (%) 44%

- *P* = 0.023
- *P* = 0.055
- *P* < 0.001

**IS** = immunosuppressive; **Anti-TNF** = Anti-tumor necrosis factor monoclonal antibody.

**Immunosuppressive versus Anti-TNF Antibody versus Combination Therapy for Active Crohn’s Disease: Corticosteroid-Free Clinical Remission at Week 26 by Baseline Endoscopy Status**

<table>
<thead>
<tr>
<th>Lesions (n=325)</th>
<th>No Lesions (n=93)</th>
<th>No Endoscopy or UTD* (n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IS + placebo (n=170)</td>
<td>Anti-TNF + placebo (n=169)</td>
<td>Anti-TNF + IS (n=169)</td>
</tr>
<tr>
<td><strong>Proportion of Patients (%)</strong></td>
<td><strong>Proportion of Patients (%)</strong></td>
<td><strong>Proportion of Patients (%)</strong></td>
</tr>
<tr>
<td>30.4</td>
<td>61.3</td>
<td>21.4</td>
</tr>
<tr>
<td>68/111</td>
<td>40.7</td>
<td>12/30</td>
</tr>
<tr>
<td>50.5</td>
<td>33.3</td>
<td>38.2</td>
</tr>
<tr>
<td>35/115</td>
<td>11/27</td>
<td>6/28</td>
</tr>
</tbody>
</table>

**Legend:**
- IS = immunosuppressive
- Anti-TNF = anti-tumor necrosis factor monoclonal antibody
- *Unable to determine.

6-Mercaptopurine and Mesalamine for Prevention of Post-Operative Recurrence of Crohn’s Disease

Hanauer Gastroenterology 2004
What are the other causes of symptoms in patients with Crohn’s disease

• Disease complications
  – Strictures
  – Fistulas
  – Abscesses
• Complications of surgical resection
  – Bile acid diarrhea
  – Steatorrhea
  – Small bowel bacterial overgrowth
• Irritable bowel syndrome
• Infection
  – Clostridium difficile
  – Cytomegalovirus
• Depression
Overall, aiming for deep remission (DR) is managing disease beyond symptom control

- In patients with **no bowel damage or disability**, DR is resolution of one or more objective measures of inflammation (endoscopy, biomarkers, imaging) AND **resolution** of symptoms
  
  • To treat symptoms in patients whose symptoms are due to active inflammatory Crohn’s disease
  
  • To prevent damage and disability

- In patients with **existing bowel damage and disability**, DR is resolution of one or more objective measures of inflammation (endoscopy, biomarkers, imaging) AND **improvement** of symptoms if possible
  
  • To treat the component of symptoms that are due to active inflammatory Crohn’s disease in patients who have multi-factorial symptoms that are partially due to co-morbidities from irreversible bowel damage
  
  • To prevent further damage and disability, and reverse damage if possible
Association Between Week 8 Mayo Endoscopy Subscore and Corticosteroid-Free Symptomatic Remission at Week 30 During Anti-TNF Antibody Therapy

<table>
<thead>
<tr>
<th>Week 8 Mayo endoscopy Subscore</th>
<th>Corticosteroid-free symptomatic Remission, n/n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>30/65 (46)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>1</td>
<td>35/102 (34)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>8/71 (11)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2/31 (6.5)</td>
<td></td>
</tr>
</tbody>
</table>

Colombel JF. Gastroenterology 2011
Implications for Future Clinical Trials in IBD

- Limit enrollment of patients in clinical trials to those with documented objective evidence of inflammation (biomarkers, endoscopy, imaging)
- In Phase II - do dose find to determine the doses necessary to normalize inflammation
- In Phase III – evaluate deep remission
- In Phase IV – evaluate prevention of bowel damage and disability
Is the histopathological evaluation an important component of assessing mucosal healing?

Presented by David Rubin, MD FACG
Is the histopathological evaluation an important component of mucosal healing in IBD?

David T. Rubin, MD, FACG, AGAF, FACP
Associate Professor of Medicine
Co-Director, Inflammatory Bowel Disease Center
University of Chicago Medical Center
Why Should we Consider Histopathology as a Marker of Mucosal Healing in IBD?

• IBDs (Crohn’s disease and ulcerative colitis) are diseases of mucosal inflammation
• Histology is necessary (but not always sufficient) for accurate diagnosis of IBD
• Histologic degree of inflammation is associated with some clinical endpoints of interest
  – Time to relapse\(^1\)
  – Risk of neoplasia\(^2\)

Assumptions Regarding Histology in IBD

- Biopsies provides more objective evidence of disease activity
- Histologic quiescence represents more stable disease control (deeper remission)
- Histology is more predictive of disease outcomes than other historic markers (activity indices, symptoms, endoscopic scores)

What is needed in order to adapt histopathology as a mucosal healing endpoint in clinical trials?

• Clinically validated technique and scoring system
  – Reproducibility of results by investigators of various experience

• Correlation with disease activity

• Association with outcome measures
  – Short term
  – Long term

• Safety
BIOPSY STUDIES IN ULCERATIVE COLITIS

BY


Assistant Physician, Nuffield Department of Clinical Medicine
Graduate Assistant, Department of Pathology
(From the Radcliffe Infirmary, Oxford)

[WITH SPECIAL PLATE]

---

Graph showing relationships between clinical state, sigmoidoscopic appearance, and histological appearance in ulcerative colitis.
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[WITH SPECIAL PLATE]

Graph showing relationships between clinical state, sigmoidoscopic appearance, and histological appearance in ulcerative colitis.
Challenges to the Use of Histopathology to Assess Mucosal Healing in IBD

- Patchiness of disease activity (CD and UC)
- Represents a small surface area of mucosa
- Requires endoscopist “judgment” for sampling
  - In worst disease, tend to biopsy areas that are less involved
  - In milder disease, tend to biopsy areas that are more involved
- Requires multiple people and levels of expertise for processing and interpretation

Where would you biopsy?
When would you biopsy?
Challenges to Histopathology as an Endpoint in Clinical Trials in IBD - 1

- Endoscopist choice: How many biopsies? Where are they obtained? When are they obtained? How are they labeled?
- Technician handling: how many are placed in paraffin for review?
- Pathologist expertise: Do pathologists agree with severity?
Challenges to Histopathology as an Endpoint in Clinical Trials in IBD - 2

• Little evidence of histopathology as a clinical trial endpoint -
  – where to start?
  – which scale to use?
• Will central readers be required?
• Cost (high)
• Risk of complications (low)

If symptomatic clinical remission is achieved, how important is mucosal healing?

Presented by Bruce Sands, MD FACG
If symptomatic clinical remission is achieved, how important is mucosal healing?

Bruce E. Sands, MD, MS
Chief of the Dr. Henry D. Janowitz Division of Gastroenterology
Dr. Burrill B. Crohn Professor of Medicine
Mount Sinai School of Medicine
New York, NY
Why is symptomatic clinical remission important in IBD?

• It is what matters most to the patient in the here and now

• In CD, more than in UC, heterogeneity of symptoms may necessitate composite instruments to measure symptoms
Mucosal healing: added value beyond clinical remission?

• Support for biologic plausibility of clinical remission
• Increased specificity of clinical remission
• Surrogate marker for longer term outcomes
## Interpreting discordance of clinical remission and mucosal healing

<table>
<thead>
<tr>
<th>Clinical Remission</th>
<th>MH +</th>
<th>MH -</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>“True remission”</td>
<td>•Clinical remission driven by placebo response?</td>
</tr>
<tr>
<td>-</td>
<td>•Other conditions driving symptoms, e.g., bile salt diarrhea, irritable bowel syndrome</td>
<td>True lack of response</td>
</tr>
<tr>
<td></td>
<td>•Irreversible disease complications driving symptoms, e.g., stricture or fistula</td>
<td>•Clinical remission driven by pharmacologic effects other than direct effect on inflammation?</td>
</tr>
</tbody>
</table>
Mucosal healing as a surrogate for longer term outcomes

Associated with

• Better quality of life
• Fewer hospitalizations
• Fewer surgeries
• Longer time to clinical relapse
• Reduction in dysplasia/cancer
Does the importance of mucosal healing differ between CD and UC?

- MH is the mucosal aspect of a mucosal disease in UC
- MH is the mucosal aspect of a transmural disease in CD
- Ease of accessibility to mucosa in UC as compared to CD
- Need to minimize placebo response greater in CD than UC
How could both symptomatic clinical remission and MH be accounted for in clinical trials?

- Symptomatic clinical remission and MH may occur at discrepant timepoints
- Timing of MH may vary by drug
- Symptoms can be measured frequently (daily); MH cannot
- Therefore, not ideal to combine MH and symptomatic clinical remission into a single composite measure to be applied to all studies
- Would mucosal healing need to be incorporated into pivotal trials? For all subjects, or a subset? Or in a stand-alone study to address a specific designation?
Are there potential alternatives to endoscopic assessment of mucosal healing?

Presented by Brian Feagan, MD FACG
Surrogates for Mucosal Healing
(Endoscopy is not an ideal surrogate measure!)

- Candidates include CRP, fecal leukocyte markers, imaging (MRE, CT, US)

- CRP: clinically useful, non-parametric distribution, large variances, non-production

- Calprotectin, FLF: differential expression by disease and anatomical location, role in predicting relapse

- Imaging: not ideal either cost, time, availability

- Ionizing radiation for CT, operator dependence for US, MRE probably most promising
Questions?

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