The Role of Endoscopy as an Endpoint for Adult Registration Trials

William J. Sandborn, MD

Professor of Clinical Medicine
Chief, Division of Gastroenterology
Director, UCSD IBD Center
University of California San Diego
La Jolla, California
History of Equipment Evolution

- 1955 - Rigid proctosigmoidoscopy with cotton swab test of friability
- 1970’s - Fiberoptic endoscopy
  - Flexible sigmoidoscopy
  - Colonoscopy
- 1990’s - Video endoscopy
- 2000’s - Video capture
- 2010’s – Video capture compressed and transmitted via the internet in real- / near-real time
How Much Colon Should be Examined?

- Distal colon
  - Initially, rigid proctosigmoidoscopy could only reach the distal colon
  - Subsequently, flexible sigmoidoscopy can be performed without oral bowel preparation and without sedation
  - Rationale is that ulcerative colitis is a continuous disease that always involves the rectum, and that the distal colon disease activity is reflective of proximal colon activity – no evidence that this is not true

- Total colon
  - Colonoscopy (requires full bowel preparation, sedation, and costs more)
  - ? grade the entire colon or grade by 5 segments (rectum, sigmoid, descending, transverse, cecum/ascending)
  - Very limited experience with colonoscopy assessment of disease activity in clinical trials
History of Instrument Evolution

- 1964 - Baron
- 1987 - Mayo/Sutherland (UCDAI) composite instruments with endoscopy subscore
  - Limitations – not validated, no operating manuals, no training recommendations
- 2012 - UCEIS (Travis)
- 2012 - UCCIS
## Baron Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal: mat mucosal, ramifying vascular pattern clearly visible throughout, no spontaneous bleeding, no bleeding to light touch</td>
</tr>
<tr>
<td>1</td>
<td>Abnormal but not hemorrhagic: appearances between “0” and “2”</td>
</tr>
<tr>
<td>2</td>
<td>Moderately hemorrhagic: bleeding to light touch, but no spontaneous bleeding seen ahead of instrument on initial inspection</td>
</tr>
<tr>
<td>3</td>
<td>Severely hemorrhagic: spontaneous bleeding seen ahead of instrument at initial inspection, and bleeds to light touch</td>
</tr>
</tbody>
</table>

Mayo Scoring System for Assessment of UC Activity

Four components
a. Stool frequency
b. Rectal bleeding
c. Findings of 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)
d. Physicians global assessment

Used for FDA approval of Asacol and Remicade

Sutherland Index (UCDAI) (0-12 points)

12 point index with 4 components

a. Stool frequency (0-3)
b. Rectal bleeding (0-3)
c. Mucosal appearance (0-3)*
   - 0 = Normal
   - 1 = Mild friability
   - 2 = Moderate friability
   - 3 = Exudation, spontaneous hemorrhage
d. Physicians global rating (0-3)

Used for FDA approval of Rowasa and Lialda

* Modified in Lialda trials so that friability is a score of ≥ 2 points

Ulcerative Colitis Endoscopic Index of Severity (UCEIS)

- Validated instrument
- Developed from a library of flexible sigmoidoscopy videos using different combinations of descriptors predicting the overall assessment of severity using VAS
- Three descriptors
  - Vascular pattern (normal – 1, patchy obliteration – 2, obliterated – 3)
  - Bleeding (none – 1, mucosal – 2, luminal mild – 3, luminal moderate or severe – 4)
  - Erosions and ulcers (none – 1, erosions – 2, superficial ulcer – 3, deep ulcer – 4)
- The score from each of the descriptors are added to calculate the UCEIS score
- The UCEIS score accounts for 90% of the overall assessment of endoscopic severity as judged by VAS (pR²=0.90)

Predicted Mean Overall Assessment of Severity for Each Level of Each Descriptor

Vascular Pattern
Mucosal oedema
Mucosal surface
Mucosal erythema
Mucopus
Bleeding
Incidental friability
Contact friability
Erosions & Ulcers
Extent of Erosions & Ulcers

95% CI of mean severity evaluation

Predicted Mean Assessment of Severity (UCEIS) Compared with Reported Mean Assessment of Severity (VAS)

![Graph showing the comparison between predicted and reported mean severity evaluations.]

Ulcerative Colitis Colonoscopic Index of Severity (UCCIS)

- Validated instrument
- Developed from a library of colonoscopy videos (with 5 segments of colon scored) using different combinations of descriptors to predict the global or segmental assessment of endoscopic severity (GAES or SAES) or VAS
- Four descriptors
  - Vascular pattern (normal – 0, partially visible – 1, complete loss – 2)
  - Granularity (normal – 0, fine – 1, course - 2)
  - Ulceration (normal – 0, erosions – 1, shallow – 2, deep – 3, diffuse > 30% deep - 4)
  - Bleeding/friability (normal – 0, friable – 1, spontaneous bleeding – 2)
- The UCCIS score is $3.1 \times \text{vascular pattern} + 3.6 \times \text{granularity} + 3.5 \times \text{ulceration} + 2.5 \times \text{bleeding/friability}$
- The UCCIS score accounts for 74-81% of the variance in the GAES score and 80-85% of the variance in the VAS score
- Results were similar for GAES and SAES

History of Endpoint Evolution

• Improvement - change by 1 point on endoscopy subscore, remission = score of 0 points

• 2005 - Mucosal healing definition in infliximab trials –
  ▪ Inclusion criteria
    – Endoscopic evidence of moderate or severe UC (endoscopy score \( \geq 2 \)) and total Mayo score of 6-12
  ▪ Mucosal healing definition - endoscopy sub-score 0 or 1

• 2007 - Modified Sutherland (UCDAI) in MMX mesalamine trials
  ▪ Mucosal appearance
    – 0 = Normal or inactive disease
    – 1 = Mild disease (erythema, decreased vascular pattern, minimal granularity)
    – 2 = Moderate disease (marked erythema, friability, granularity, absent vascular pattern, bleeding minimal trauma, no ulcerations)
    – 3 = Severe disease (ulcerations, spontaneous bleeding)

• 2007 - IOIBD Position paper on UC endpoints

MUCOSAL HEALING AND TIME TO COLECTOMY IN INFLIXIMAB-TREATED PATIENTS

History of Central Reading Evolution

• Site investigator reading
• Site investigator reading with still photo capture for documentation
• Delayed central reading of videos for quality assurance
• Real-time or near real-time central reading of videos via internet to determine patient eligibility +/- reading of endpoint
Can Fecal Calprotectin and/or CRP Replace Endoscopy?

• Fecal calprotectin
  ▪ The median (interquartile range [IQR]) fecal calprotectin level was 465 (61-1128) µg/g
  ▪ Using ROC statistics, a fecal calprotectin >250 µg/g gave a sensitivity of 71.0% and a specificity of 100.0% (PPV 100.0%, NPV 47.1%) for active mucosal disease activity (Mayo >0)

• CRP
  ▪ Elevated in 50-60% of patients with moderate to severe UC and 20% of patients with mild to moderate UC

D’Haens G. Inflammatory Bowel Diseases 2012 (epub)
Why Endoscopy Rather Than Clinical Symptoms?

• Endoscopy is not a biomarker, endoscopy is physical (visual) examination of the colon
• Analogies
  ▪ Psoriasis – physical (visual) examination showing presence and severity of typical skin lesions
  ▪ Rheumatoid arthritis – physical examination showing swollen and tender joints + biomarkers
• Clinical symptoms are a surrogate for endoscopy findings, not the other way around
What are the Problems with Clinical Symptoms?

- Missing data
- What is a stool?
- How do you measure rectal bleeding?
- What is urgency?
- Recall versus diary?
- Paper diary versus IVRS versus electronic versus web-based diary?
- 3 day versus 7 day diary?
- Worst findings of day versus average findings of day?
- Worst daily score versus average daily score?
- Round mean sub-scores to the closest integer then add sub-scores versus add mean sub-scores then round to the closest integer?
- Impact of language, translation, education, and cultural context
What are the Problems with Endoscopy?

• In the past
  ▪ Poor definition of descriptors
  ▪ No validated instruments which define which combinations of descriptors best predict VAS
  ▪ High inter-observer variability
  ▪ Lack of standardized approach to investigator training
  ▪ Incentive for investigators to up-code endoscopy score to ensure that the patient qualifies for a trial
  ▪ Inability to centrally read endoscopy in real time
  ▪ Lack of standardization regarding endpoints
  ▪ Cut points for clinically meaningful change and for remission using validated instruments have not yet been defined

• In the present
  ▪ Reproducible descriptors have been identified
  ▪ Validated instruments exist that predict 85-90% of the variability in VAS
  ▪ Real time central reading now feasible
  ▪ Still need to determine cut-points for new validated instruments and then standardize endoscopic endpoints
  ▪ High quality “cinematography” by the site is necessary
Clinical Symptoms Versus Endoscopy: Which has the Most Potential to be Standardized and Minimize Bias?

• Challenges with measuring clinical symptoms are formidable
• Although substantial challenges with endoscopy exist, there is great potential for improved standardization with video capture, central reading, use of descriptors that are proven to be reproducible, and use of instruments that have been validated and well characterized
There is Already a Precedent for Endoscopy as the Primary Endpoint for Ulcerative Colitis Trials that Led to Regulatory Approval

• Maintenance of remission
  ▪ Asacol
  ▪ Lialda
Delayed-Release Oral Mesalamine: Maintenance of Endoscopic Remission of UC

- **Treatment Success**
  - Placebo: 48%
  - Mesalamine 0.8 g: 63%
  - Mesalamine 1.6 g: 70%

† “Maintenance of endoscopic remission at 6 months” (score of 0 out of 3 on sigmoidoscopic scale)
‡ P = .05
§ P = .005

Once Daily MMX mesalamine 2.4 g for Maintenance of Endoscopic Remission in Ulcerative Colitis

Where Do We Go From Here?

• The status quo should change, but probably gradually
• In the near term
  ▪ Central reading of endoscopy to verify that patients meet entry criteria for clinical trial
  ▪ Possibly central reading of endoscopy to score endpoints
  ▪ Possibly continued use of Mayo endoscopy sub-score, with friability = score of 2
  ▪ Use UCEIS (and/or possibly UCCIS) as exploratory endpoint(s)
• In intermediate term
  ▪ Determine cut-points for UCEIS for active disease versus remission, and minimum clinically important difference in score to develop entry criteria, and response and remission definitions
  ▪ Apply these criteria and endpoints to future clinical trials and/or existing video libraries of clinical trials with drugs of known efficacy
• In the longer term
  ▪ Transition to primary endpoint for UC trials from clinical or composite endpoint to endoscopic endpoint