“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
Bruce Sands, MD FACG
Jean-Frederic Colombel, MD

David Rubin, MD FACG
Brian Feagan, MD FACG
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)

Variable no.	Variable description	Multiplier	Total
1	No. of liquid or soft stools (each day for 7 days)	x 2	
2	Abdominal pain, sum of seven daily ratings (0 = none, 1 = mild, 2 = moderate, 3 = severe)	x 5	
3	General well-being, sum of seven daily ratings (0 = generally well, 1 = slightly under par, 2 = poor, 3 = very poor, 4 = terrible)	x 7	
4	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])	x 20	

Best WR et al. *Gastroenterology.* 1976;70:439-444.

Crohn's Disease Activity Index (CDAI) (cont'd)

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

Best WR et al. *Gastroenterology.* 1976;70:439-444.

Crohn's Disease Activity Index (CDAI) Scoring

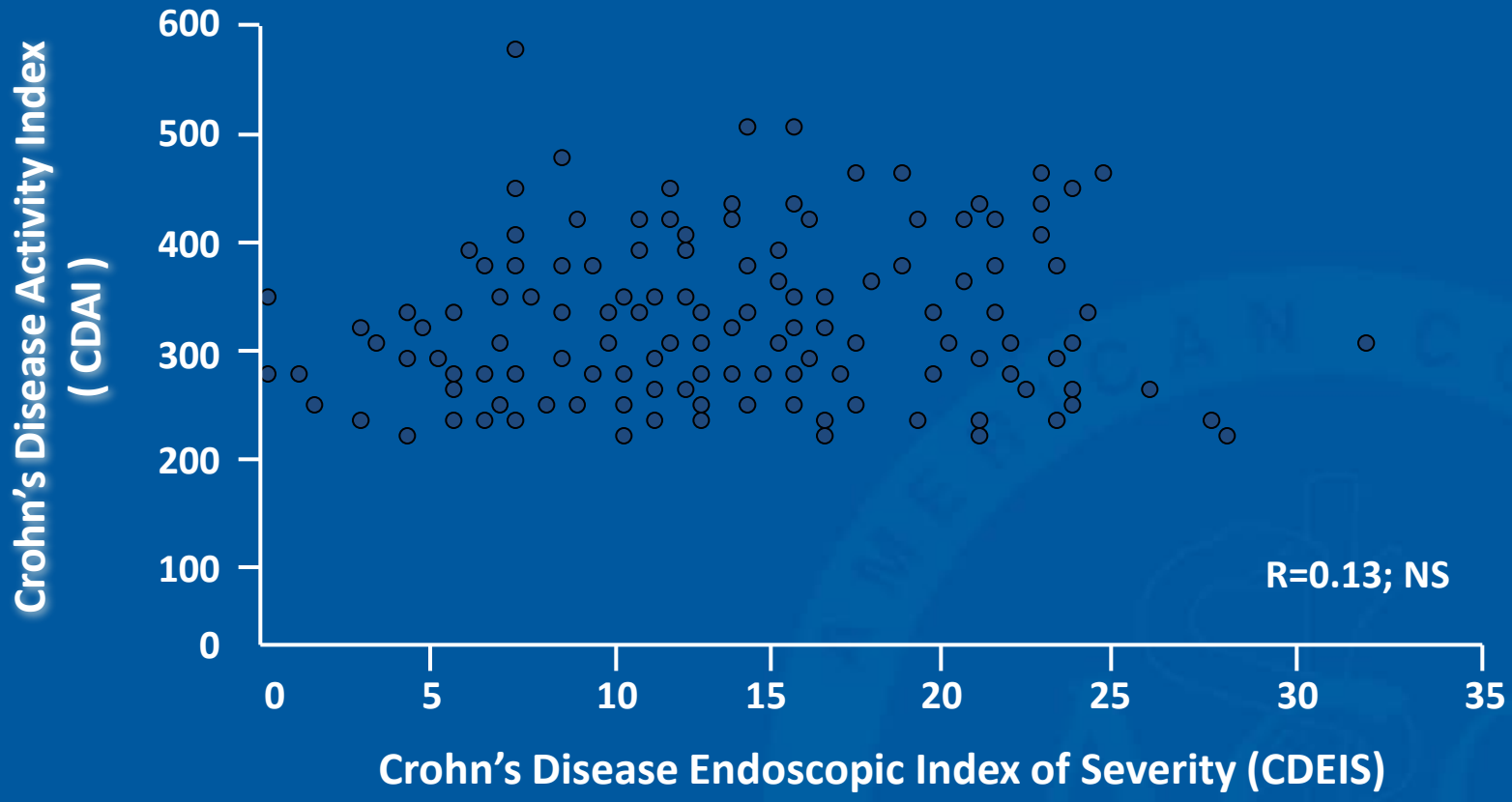
- **Remission** **<150**
- **Moderate activity** **200 – 450**
- **Severe activity** **>450**
- **Maximum score** **600**

Best WR et al. *Gastroenterology.* 1976;70:439.

The Crohn's Disease Activity Index

Liquid stools- 3x7 days=21x2	=42
Abdominal pain-2x7=14=5	=70
Well being-avg 3/d=21x7	=147
Taking loperamide	=30
PROBLEM: THE PATIENT HAS IRRITABLE BOWEL SYNDROME	**TOTAL =289 CDAI** **Indicates mild-moderate CD**

Relationship Between Clinical Symptoms and Endoscopic Indices at Presentation of Acute CD



Modigliani R et al. *Gastroenterology.* 1990;98:811.

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

D'Haens G, et al. *Gastroenterology*. 2007;132:763-786.

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

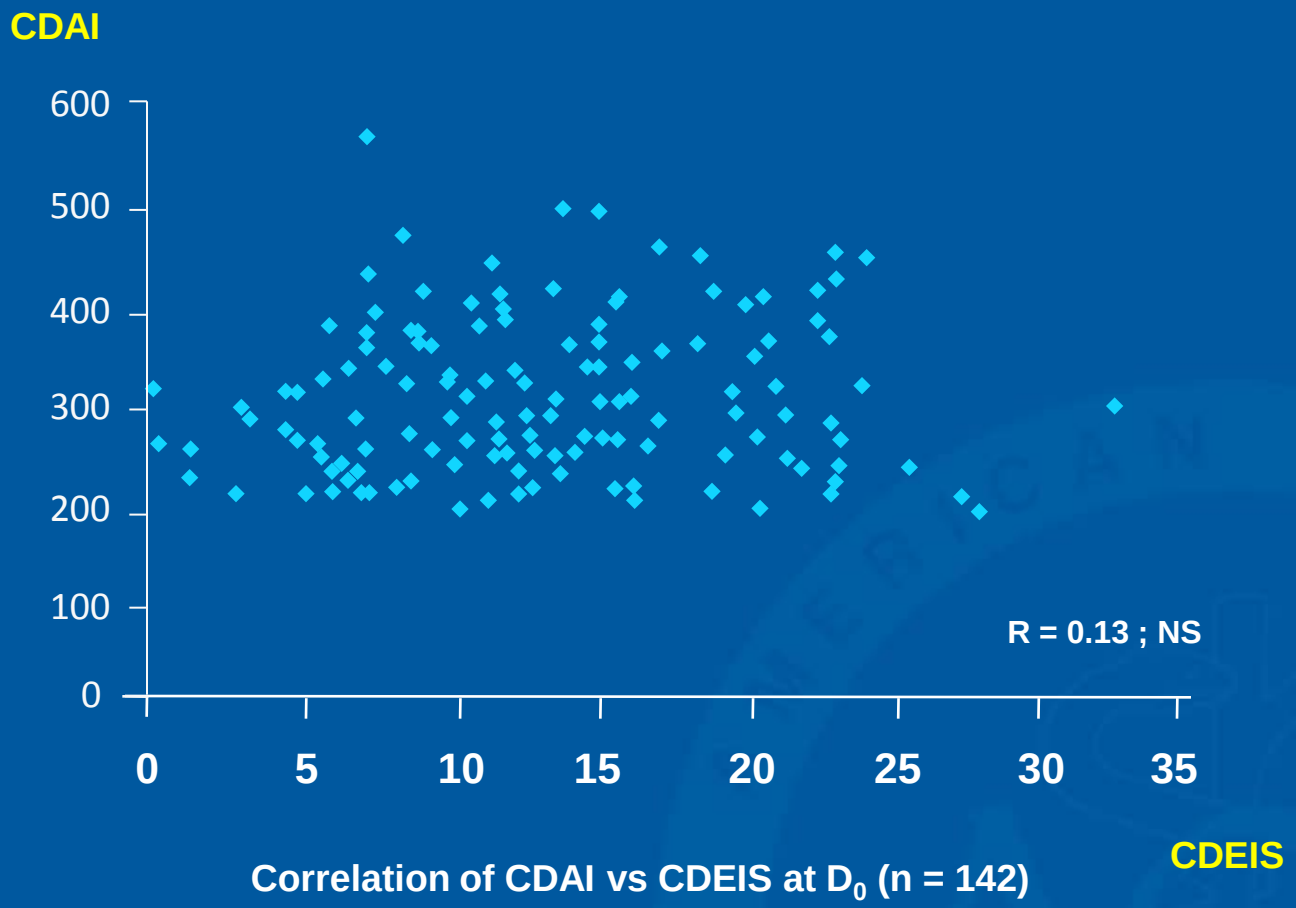
Is mucosal healing meaningful as a primary endpoint in IBD

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.
Modigliani R, et al. *Gastroenterology*. 1990;98:811-818.

Correlations Between hsCRP, IL-6, Fecal Markers, CDAI, and Endoscopic Activity in Crohn's Disease (N=164)

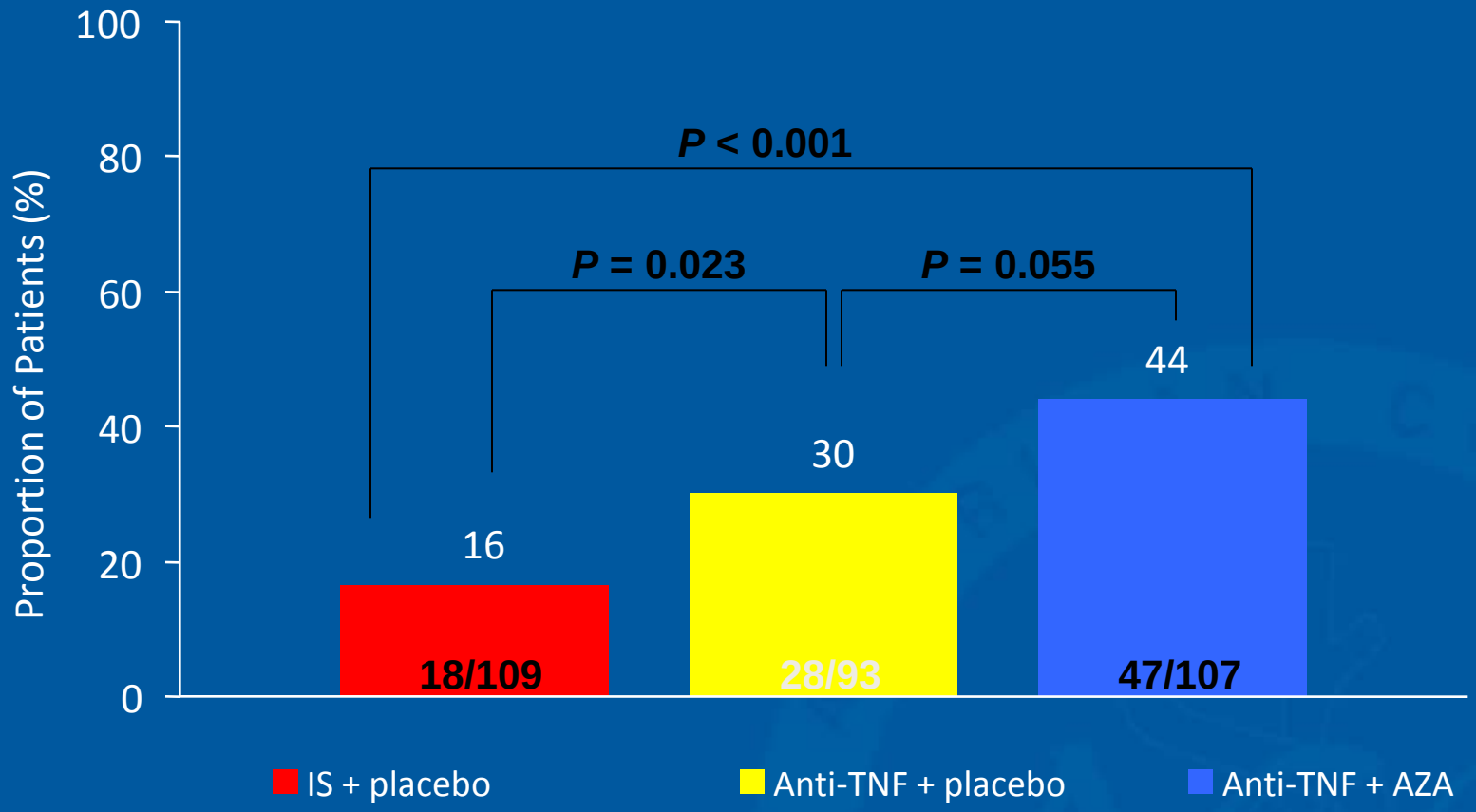
	IL-6	Calprotectin	Lactoferrin	CDAI	SES-CD
hsCRP	**0.65**	**0.47**	**0.52**	0.16	**0.46**
IL-6		**0.45**	**0.55**	0.15	**0.43**
Calprotectin			**0.76**	**0.23**	**0.45**
Lactoferrin				**0.19**	**0.48**
CDAI					0.15

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.

Jones JL, et al. *Clin Gastroenterol Hepatol*. 2008;6:1218-1224.

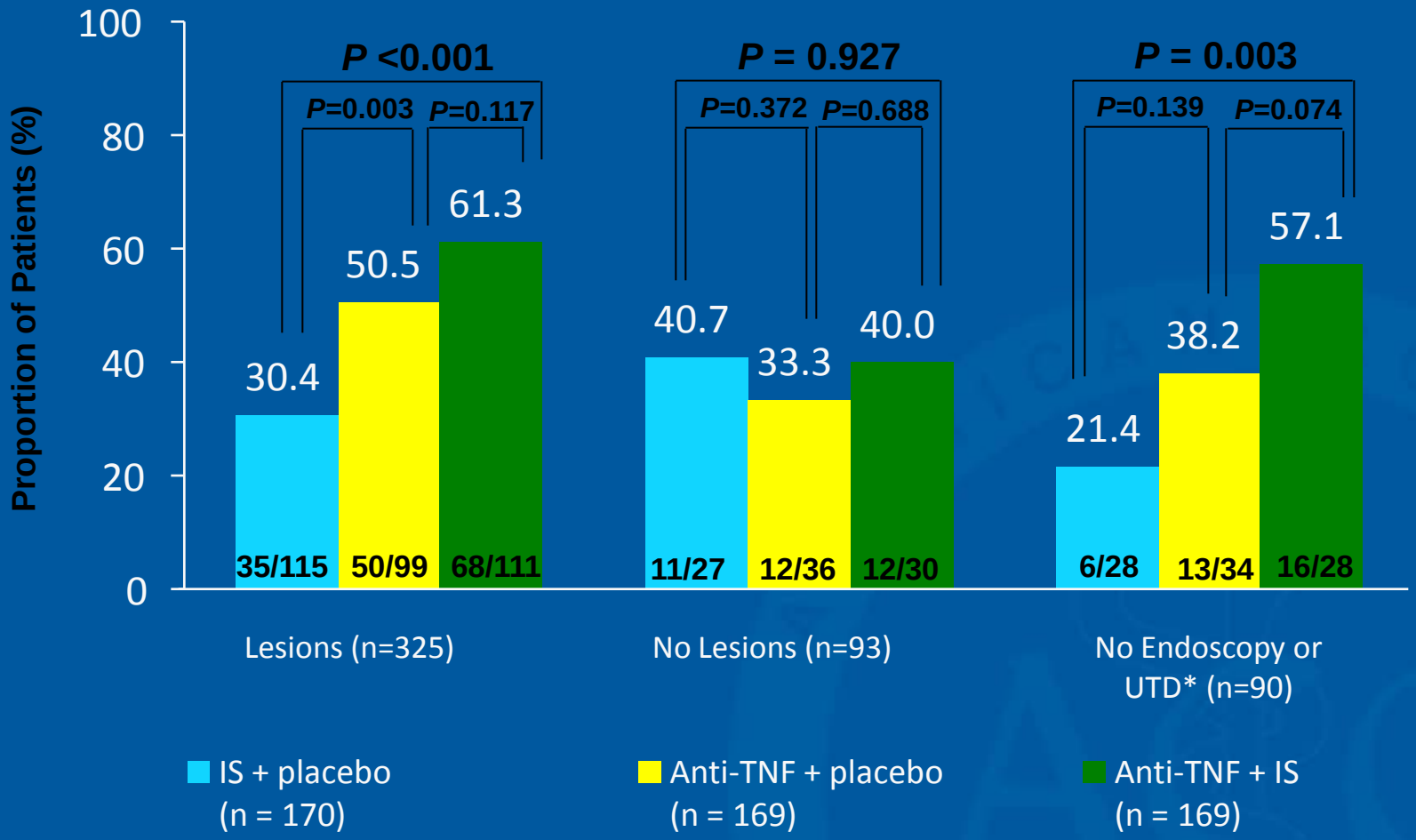
Immunosuppressive versus Anti-TNF Antibody versus Combination Therapy for Active Crohn's Disease
Mucosal Healing at Week 26



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

Colombel JF, Sandborn WJ, et al. New England Journal of Medicine 2010.

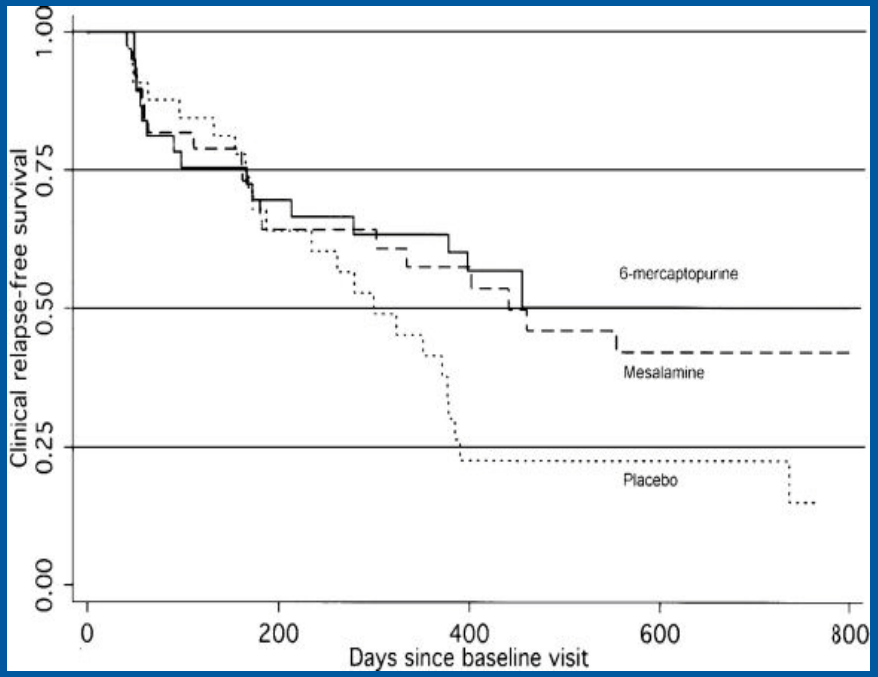
Immunosuppressive versus Anti-TNF Antibody versus Combination Therapy for Active Crohn's Disease: Corticosteroid-Free Clinical Remission at Week 26 by Baseline Endoscopy Status

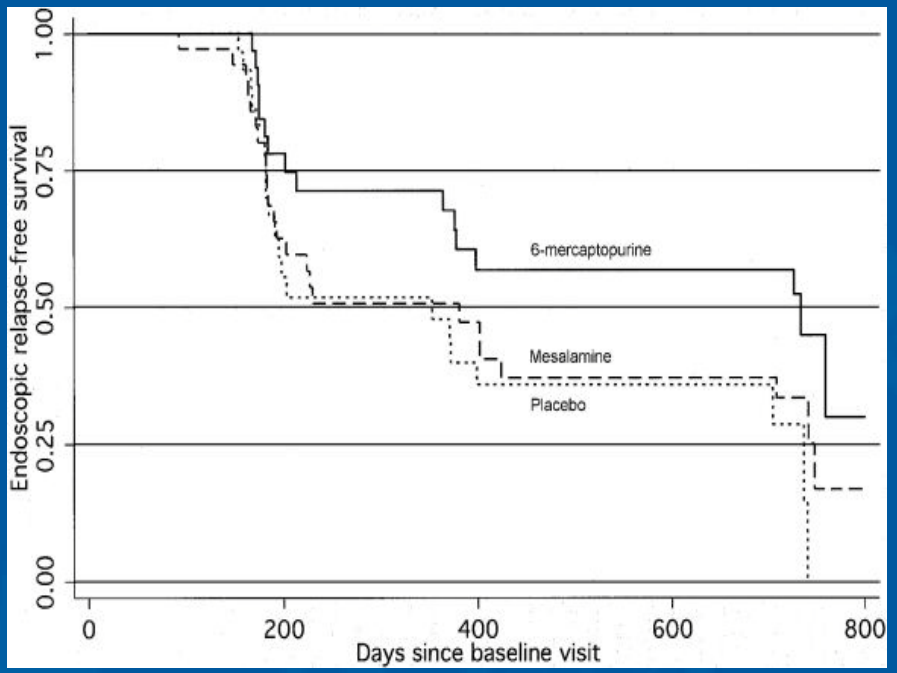


IS = immunosuppressive; Anti-TNF = anti-tumor necrosis factor monoclonal antibody. *Unable to determine.

Colombel JF, Sandborn WJ, et al. New England Journal of Medicine 2010.

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

Working definition of deep remission

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 patient 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 and Corticosteroid-Free Symptomatic Remission at Week 30 During Anti-TNF Antibody Therapy

Week 8 Mayo endoscopy Subscore	Corticosteroid-free symptomatic Remission, n/n (%)	P value
0	30/65 (46)	<.0001
1	35/102 (34)	
2	8/71 (11)	
3	2/31 (6.5)	

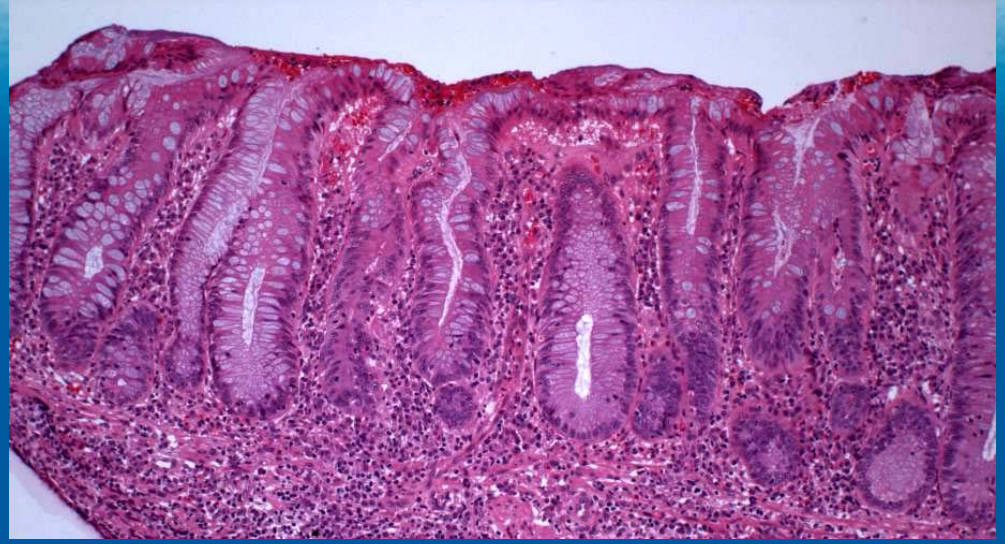
Colombel JF. Gastroenterology 2011

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?

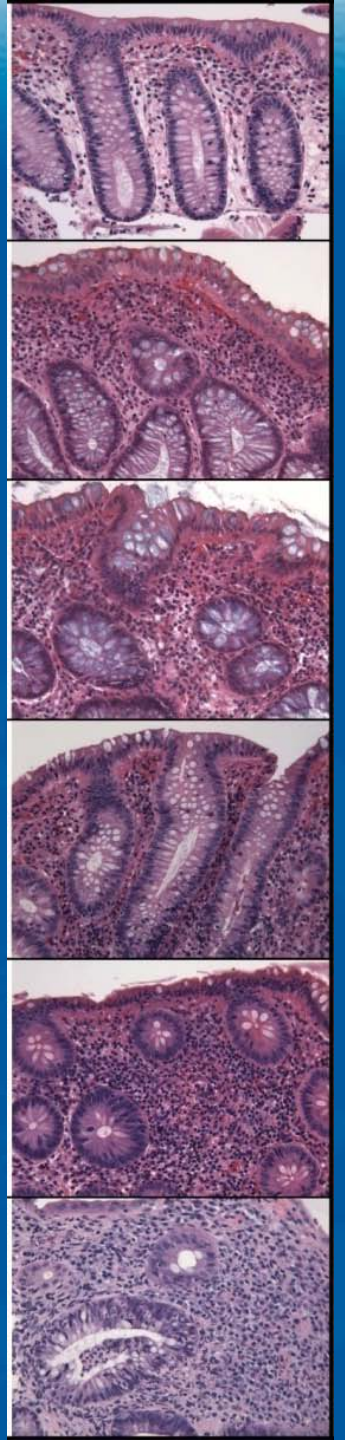
David T. Rubin, MD, FACG, AGAF, FACP
Associate Professor of Medicine
Co-Director, Inflammatory Bowel Disease Center
University of Chicago Medical Center

THE UNIVERSITY OF CHICAGO MEDICAL CENTER

Inflammatory Bowel Disease Center

Why Should we Consider Histopathology as a Marker of Mucosal Healing in IBD?

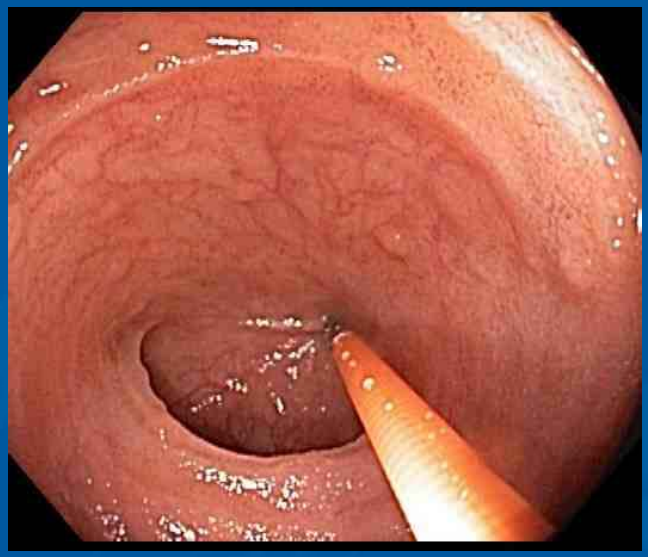
- IBDs (Crohn's disease and ulcerative colitis) are diseases of mucosal inflammation
- Histology is necessary (but not always sufficient) for accurate diagnosis of IBD
- Histologic degree of inflammation is associated with some clinical endpoints of interest
  - Time to relapse[1]
  - Risk of neoplasia[2]



1. Riley et al. Gut. 1991;32:174-178.
2. Rutter et al. Gastroenterology. 2004;126:451-459.

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)



1. Sipponen, et al. *Ailment Pharmacol Ther.* 2008 Nov 15;28(10): 1221-9.
2. Osada T, et al. *J Gastroenterol Hepatol.* 2008 Dec;23 Suppl 2:S262-7.
3. Lok KH, et. al. *J Dig dis.* 2008 Nov;9(4):219-24.

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

BRITISH MEDICAL JOURNAL

LONDON SATURDAY JUNE 9 1956

BIOPSY STUDIES IN ULCERATIVE COLITIS

BY

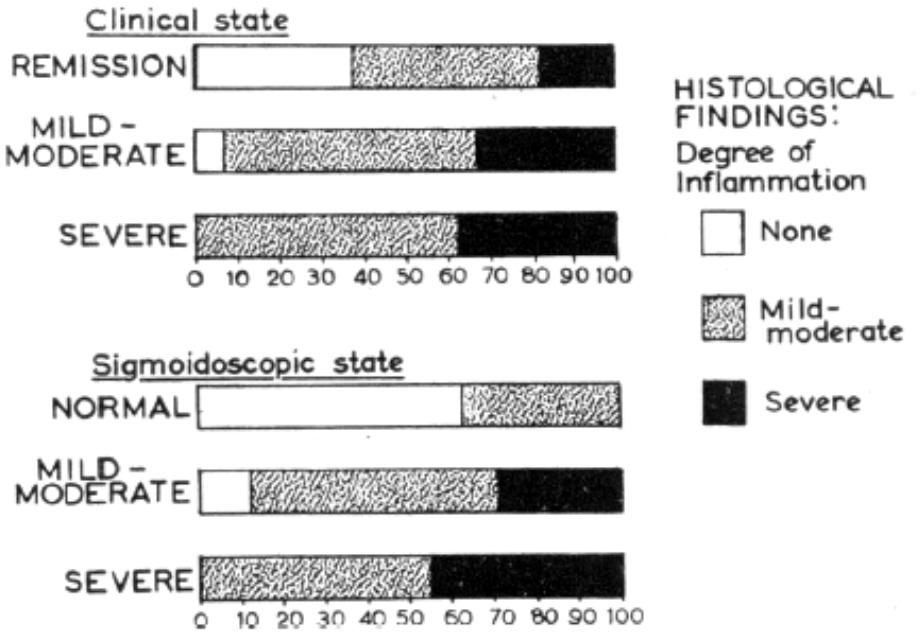
S. C. TRUELOVE, M.D., M.R.C.P., and W. C. D. RICHARDS, M.B., B.S.

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.

BRITISH MEDICAL JOURNAL

LONDON SATURDAY JUNE 9 1956

BIOPSY STUDIES IN ULCERATIVE COLITIS

BY

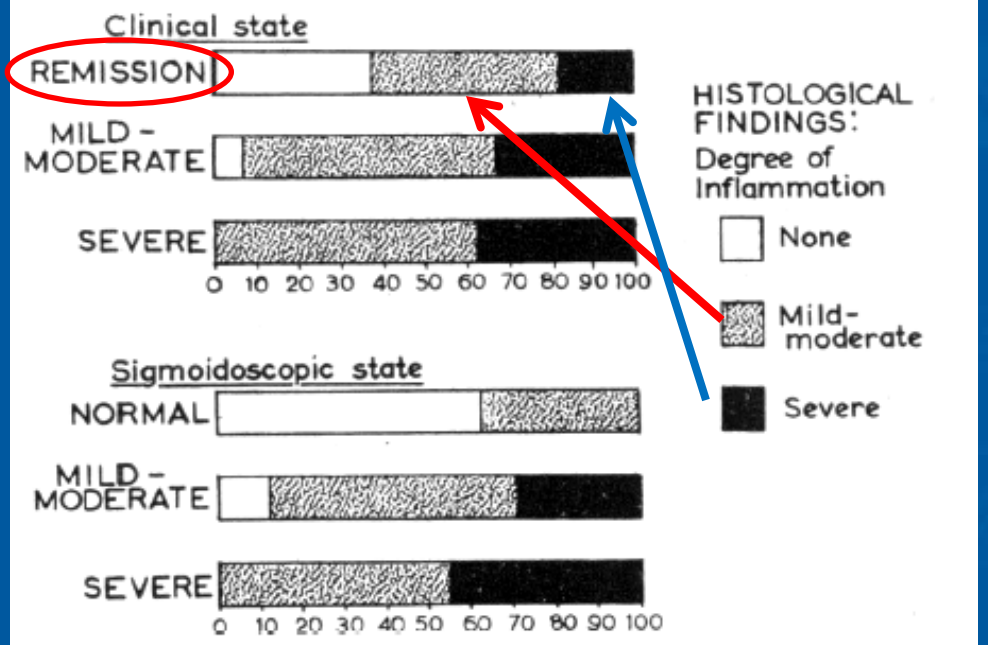
S. C. TRUELOVE, M.D., M.R.C.P., and W. C. D. RICHARDS, M.B., B.S.

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.

BRITISH MEDICAL JOURNAL

LONDON SATURDAY JUNE 9 1956

BIOPSY STUDIES IN ULCERATIVE COLITIS

BY

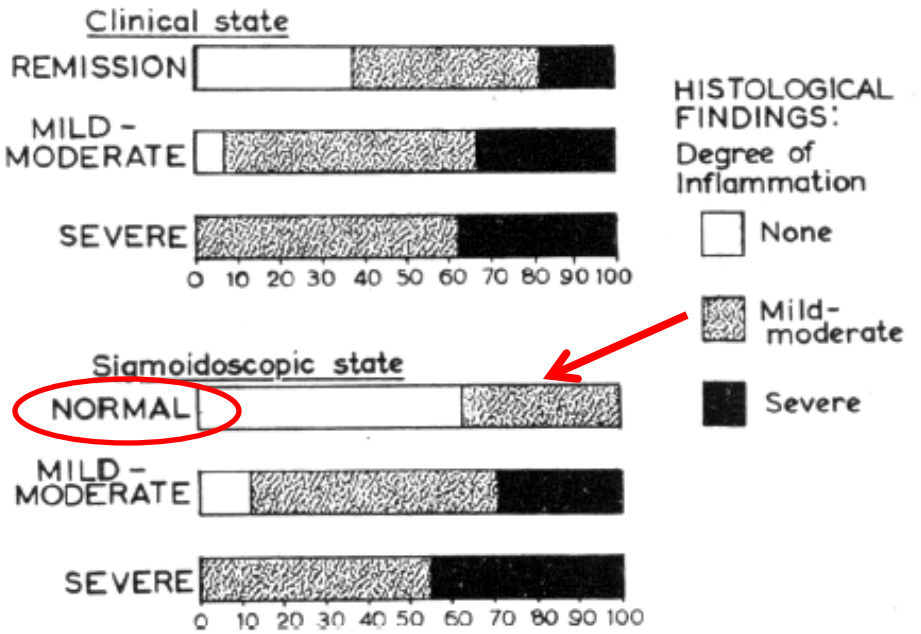
S. C. TRUELOVE, M.D., M.R.C.P., and W. C. D. RICHARDS, M.B., B.S.

Assistant Physician, Nuffield Department of Clinical Medicine

Graduate Assistant, Department of Pathology

(From the Radcliffe Infirmary, Oxford)

[WITH SPECIAL PLATE]



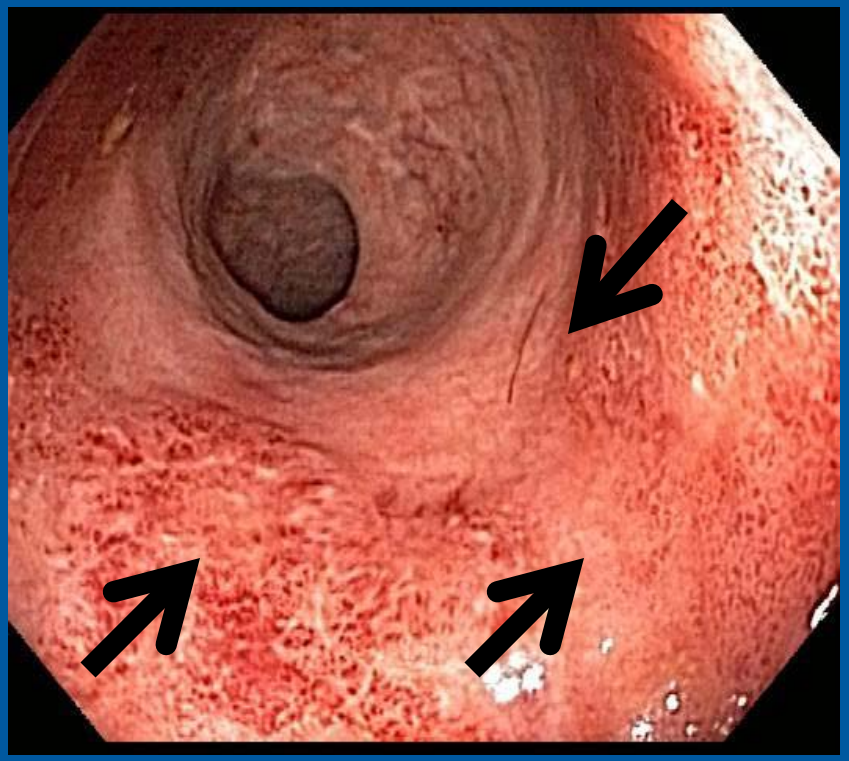
Graph showing relationships between clinical state, sigmoidoscopic appearance, and histological appearance in ulcerative colitis.

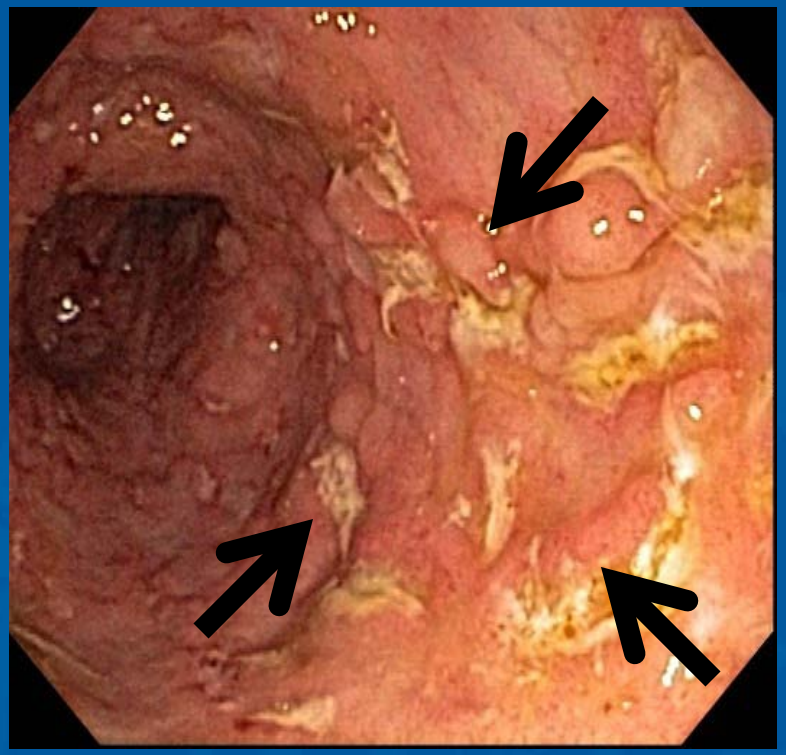
Challenges to the Use of Histopathology to Assess Mucosal Healing in IBD

- 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

1. Kim B, et al. *Am J Gastroenterol.* 1999 Nov;94(11):3258-62.
2. BernsteinCN, et. al. *Gastrointest Endosc.* 1995 Sep;42(3):232-7.

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?

De Lange, et al. *BMC Gastroenterology*; 2004; Vol. 4;9-10,

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)

1. Osada T, et al. *J Gastroenterol Hepatol.* 2008 Dec;23 Suppl 2:S262-7.
2. Terheggen G, et. al. *Endoscopy. 2008* Aug;40(8):656-63.

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

	MH +	MH -
Clinical Remission +	"True remission"	•Clinical remission driven by placebo response? •Clinical remission driven by pharmacologic effects other than direct effect on inflammation?
Clinical Remission -	•Other conditions driving symptoms, e.g., bile salt diarrhea, irritable bowel syndrome •Irreversible disease complications driving symptoms, e.g., stricture or fistula	True lack of response

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?

Brad Conway

Vice President, Public Policy

American College of Gastroenterology

301.263.9000

bconway@acg.gi.org