Deep Remission

Top-Down Treatment Strategies and Real-World Data in Patients with UC:
An Interactive and Innovative Case Series

Sunday, May 7, 2017

6:00 PM – 6:30 PM Buffet; 6:30 PM – 8:00 PM Presentation
Sheraton Grand, Chicago Ballroom 8-10

This program is not affiliated with Digestive Disease Week®.

#UCcase2017

Provided by:
CME Outfitters

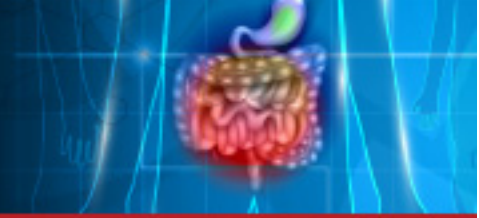
Maria T. Abreu, MD (Moderator)

Director, Crohn's & Colitis Center
Martin Kalser Chair in Gastroenterology
Professor of Medicine
Professor of Microbiology & Immunology
University of Miami Miller School of Medicine
Miami, FL

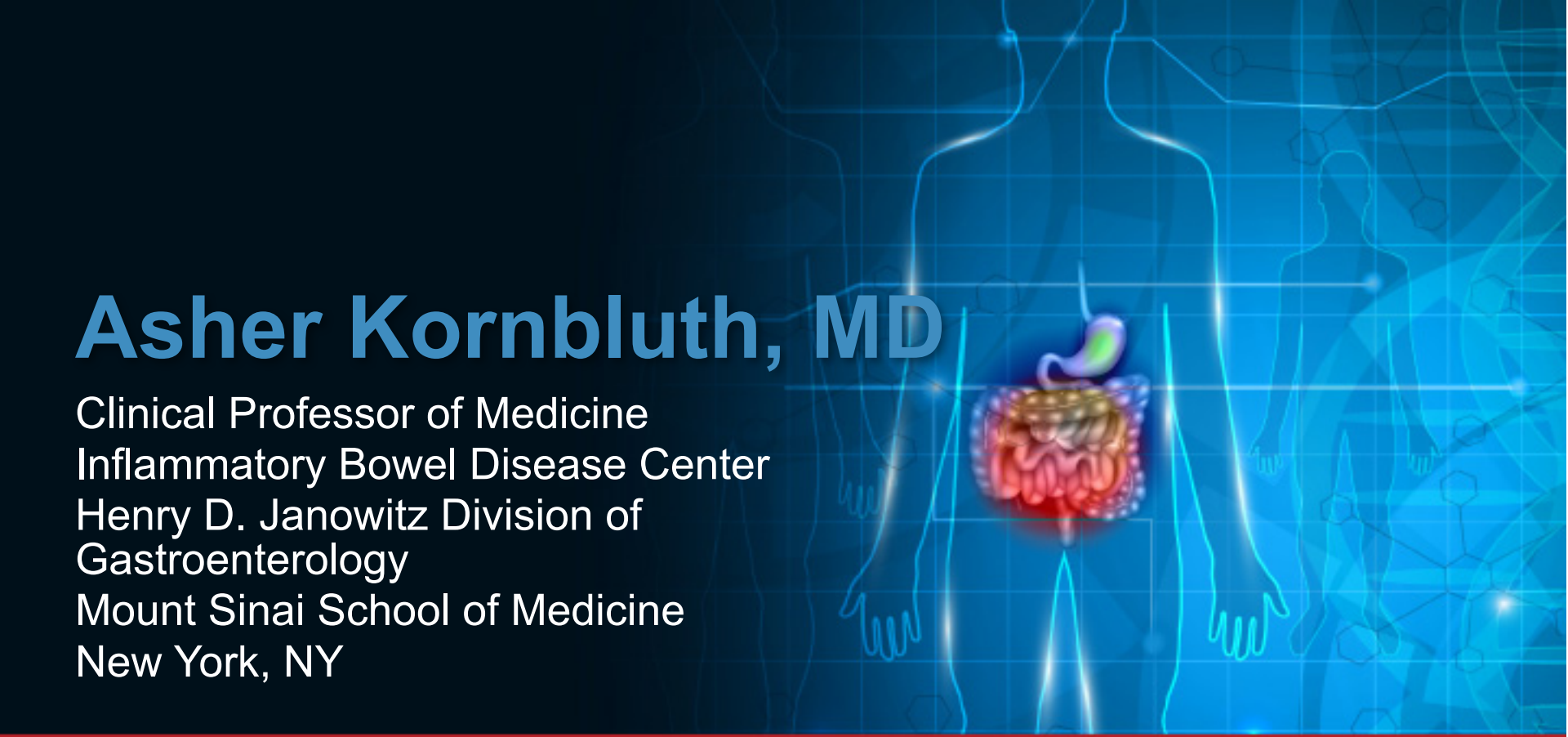
#UCcase2017

Maria T. Abreu, MD

Disclosures



- ***Speakers Bureau:*** AbbVie Inc.; Imedex
- ***Consultant:*** Eli Lilly & Company; Focus Medical Communications; Janssen Pharmaceuticals, Inc.; Pfizer Inc.; Premetheus Laboratories Inc.; Takeda Pharmaceuticals U.S.A., Inc.; Theravance Biopharma US, Inc.; UCB, Inc.
- ***Advisory Board:*** AbbVie Inc.; Boehringer Ingelheim Pharmaceuticals, Inc.; Celgene Corporation; Roche Pharmaceuticals; Shire



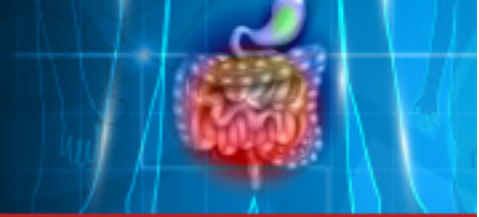
Asher Kornbluth, MD

Clinical Professor of Medicine
Inflammatory Bowel Disease Center
Henry D. Janowitz Division of Gastroenterology
Mount Sinai School of Medicine
New York, NY

#UCcase2017

Arthur A. Kornbluth, MD

Disclosures



- ***Research/Grants:*** AbbVie Inc.; Bristol Myers Squibb Company; Janssen Pharmaceuticals, Inc.
- ***Speakers Bureau:*** AbbVie Inc.; Janssen Pharmaceuticals, Inc.; Millennium Pharmaceuticals, Inc./Takeda Pharmaceutical Company Limited; Prometheus Laboratories, Inc.; Santarus, Inc./Salix Pharmaceuticals
- ***Advisory Board:*** AbbVie Inc.; Janssen Pharmaceuticals, Inc.; Millennium Pharmaceuticals, Inc./Takeda Pharmaceutical Company Limited; Prometheus Laboratories Inc.

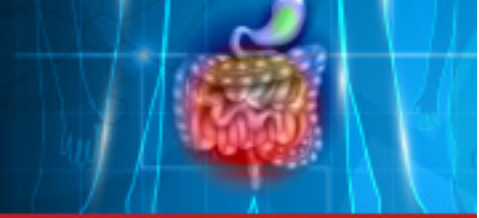
Miguel Regueiro, MD, FACP, FACG, AGAF

Professor of Medicine, Professor of Clinical & Translational Science
University of Pittsburgh School of Medicine
Associate Chief, Education
Division of Gastroenterology, Hepatology, & Nutrition
Clinical Medical Director of Inflammatory Bowel Disease
Senior Medical Lead of Specialty Medical Homes
University of Pittsburgh Medical Center
Pittsburgh, PA

#UCcase2017

Miguel Regueiro, MD, FACP, FACG, AGAF

Disclosures



- ***Consultant:*** AbbVie Inc.; Janssen Pharmaceuticals, Inc.; Pfizer Inc.; Takeda Pharmaceuticals U.S.A., Inc.; UCB, Inc.

Learning Objective 1

Differentiate between disease activity and disease severity to drive treatment decisions in patients with ulcerative colitis (UC).

#UCcase2017

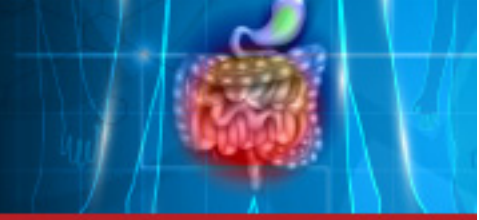
Learning Objective 2

Apply the unique risk/benefit profiles of different biologic therapies when making treatment decisions based on individual prognosis and severity of disease.

Learning Objective 3

Utilize data from real-world studies on the use and effectiveness of biologic therapy for UC to initiate early, effective treatment for patients with UC.

Case 1



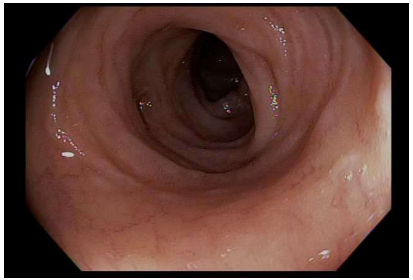
- 21 year-old young man with ulcerative colitis diagnosed last year
- He needed steroids at presentation and again 6 months later
- He is on mesalamine 4.8gm a day but often forgets to take it
- He is now flaring with 6 bowel movements (BMs) a day with blood, 2 at night and leaving class because of urgency

Case 1 (cont):

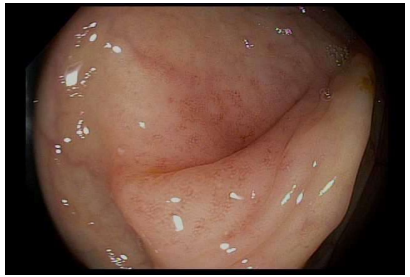
- His colonoscopy shows Mayo 2 to splenic flexure and a cecal patch
- *C. diff* is negative
- He starts prednisone 40 mg
- 2 weeks later he is down to 4 BM a day and less urgency
- EBV IgG is negative

EBV, Epstein-Barr virus

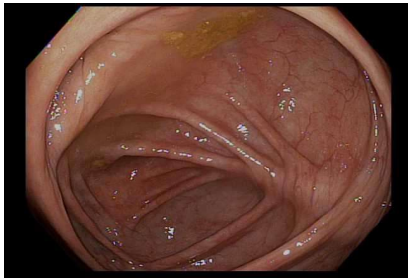
Colonoscopy Pictures



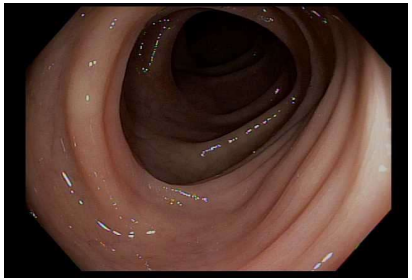
Terminal Ileum



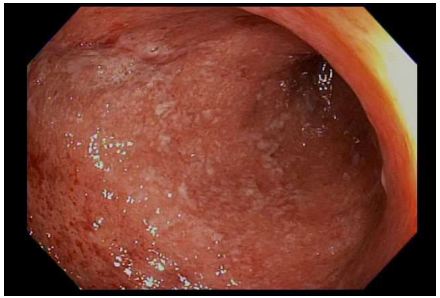
Cecum



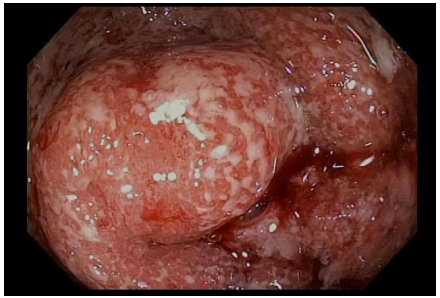
Ascending Colon



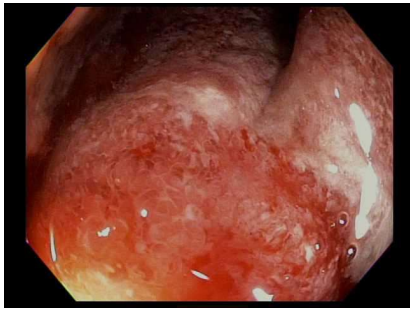
Transverse Colon



Descending Colon



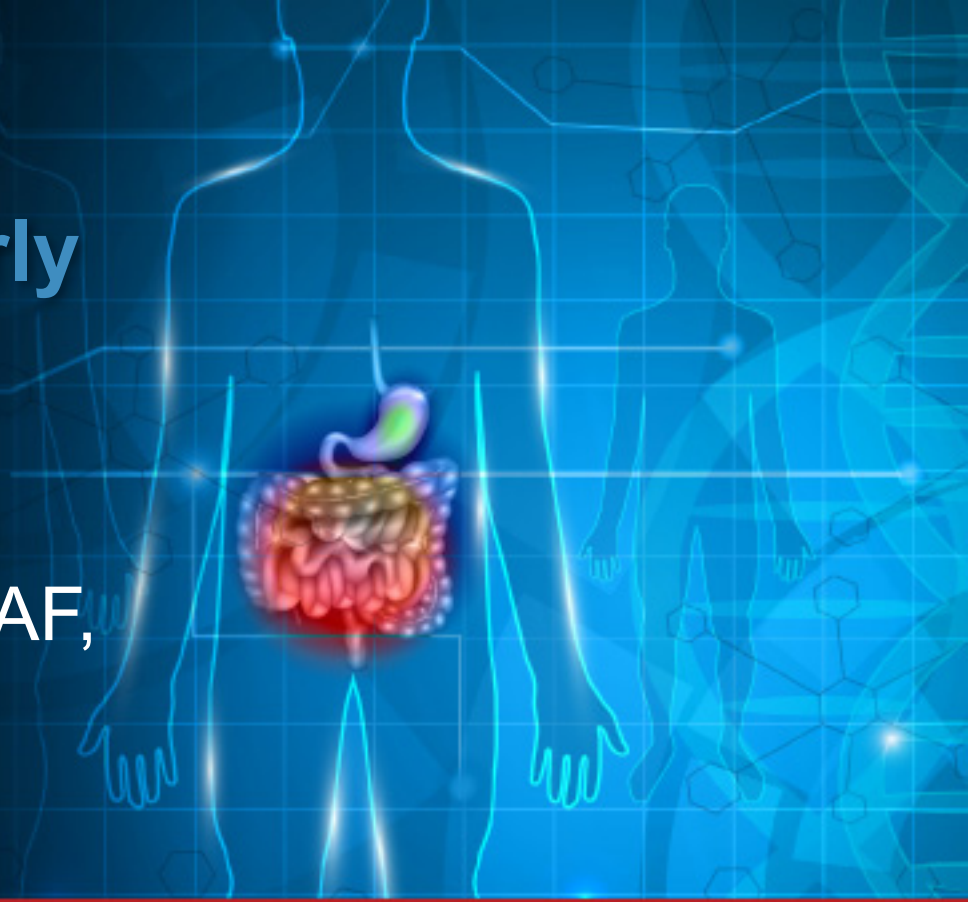
Sigmoid Colon



Rectum

Disease Activity vs. Disease Severity: Early Implementation of Biologic Therapy to Optimize Outcomes

Miguel Regueiro, MD, AGAF, FACG, FACP



AGA Ulcerative Colitis (UC) Care Pathway

- Risk assessment of UC
  - Inflammation
  - Comorbidities
  - Colectomy risk
- Initial therapy
- Exacerbation treatment options
- Clinical Decision Support tool

Dassopoulos T, et al. *Gastroenterology*. 2015;149(1):238-245.

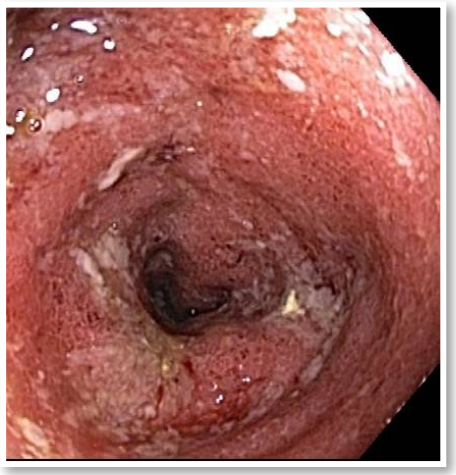
AGA Clinical Pathway for Ulcerative Colitis: Characterizing Colectomy Risk (Disease Severity)

Low Risk		High Risk
> 40 years	Age of diagnosis	< 40 years
Limited	Anatomic involvement	Extensive
Elevated	CRP and ESR at diagnosis	High
No	Steroids required	Yes
Mild	Ulcers	Deep
No	*C difficile* infection	Yes
No	History of hospitalization	Yes
No	CMV infection	Yes

Dassopoulos T, et al. *Gastroenterology*. 2015;149(1):238-245.

Case 2

- 34 year old female recently quit cigarette smoking with 2 months of symptoms
- 10-15 bloody BM's, rectal urgency, tenesmus
- Hgb 10.8, stool complaints/*C.diff* negative
- Colonoscopy shows moderately active pan-ulcerative colitis



Definition of Mucosal Healing

- “Restoration of normal mucosal appearance by endoscopy of a previously inflamed region and the complete absence of ulceration, and macroscopic and histological signs of inflammation.”

Feagan BG, et al. *Inflamm Bowel Dis*. 2012;18:152–160.

Ulcerative Colitis: Treat to Mucosal Healing or Symptoms?

- Better correlation of symptoms to mucosal inflammation in UC than CD
  - Rectum is involved
  - Most pts have bleeding, diarrhea, tenesmus
- Difficulty with UC management when there is incomplete mucosal healing
  - Decrease in mucosal inflammation often leads to decrease in symptoms

Evolving Clinical Endpoints in UC: Sustained Deep Remission

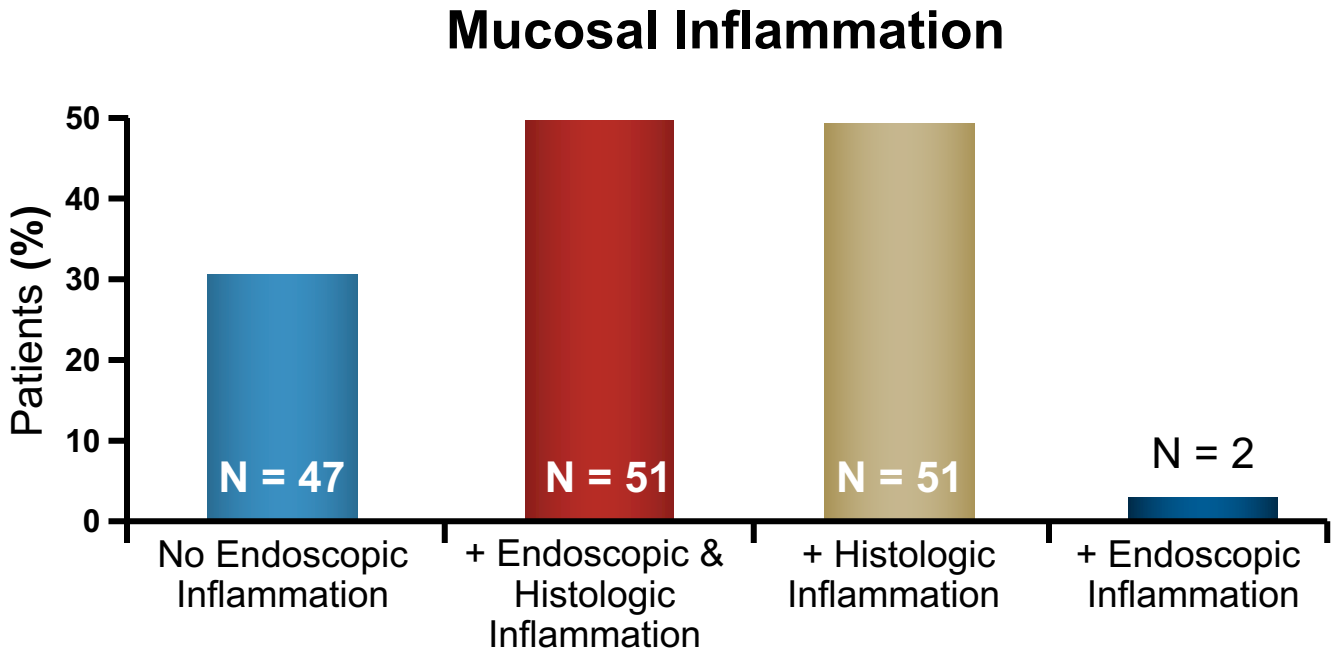
Goal	Clinical Parameters	Outcomes
Response	Improved symptoms	Improved quality of life
Remission	No symptoms Normal labs	Decreased hospitalization
Deep remission	Normal endoscopy Mucosal healing	Avoidance of surgery Minimal/no disability

SUSTAINED DISEASE CONTROL

Challenges to Current Clinical Endpoints in UC

- Symptoms may be nonspecific
  - Do not correlate to endoscopic findings of "healing" in clinical trials
  - Do not delineate extent of disease
  - Patients live with active disease!
- Endoscopy is invasive, expensive
- Symptoms may lag behind the development of active inflammation

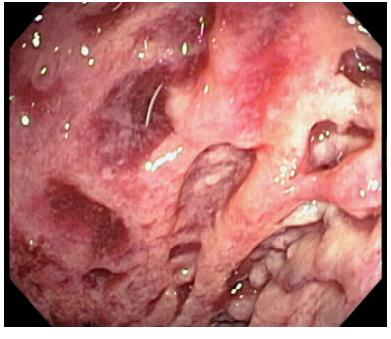
The Majority of IBD Patients in Clinical Remission Have Mucosal Inflammation



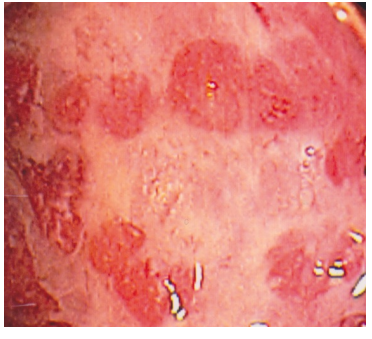
Baars JE, et al. *Inflamm Bowel Dis*. 2012;18(9):1634-1640.

Predictors of Colectomy in Severe Colitis: Poor Prognostic Endoscopic features

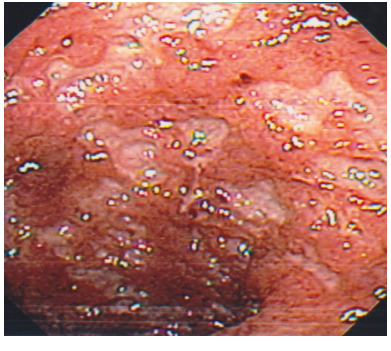
Deep Ulcers



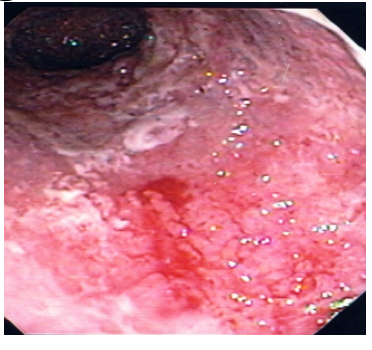
Extensive Loss of Mucosal Layer



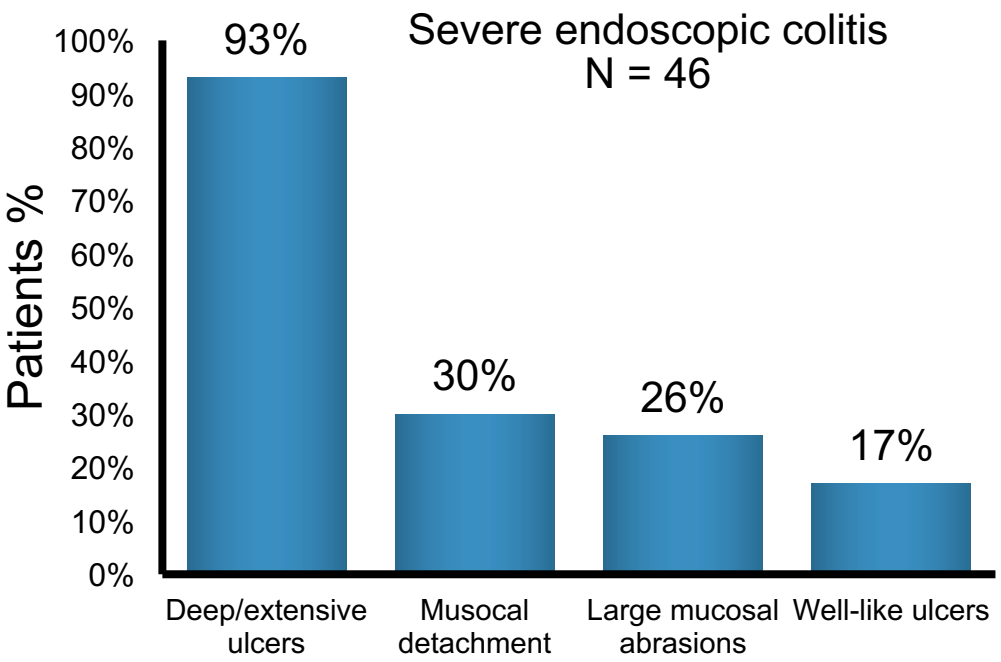
Well-like Ulcers



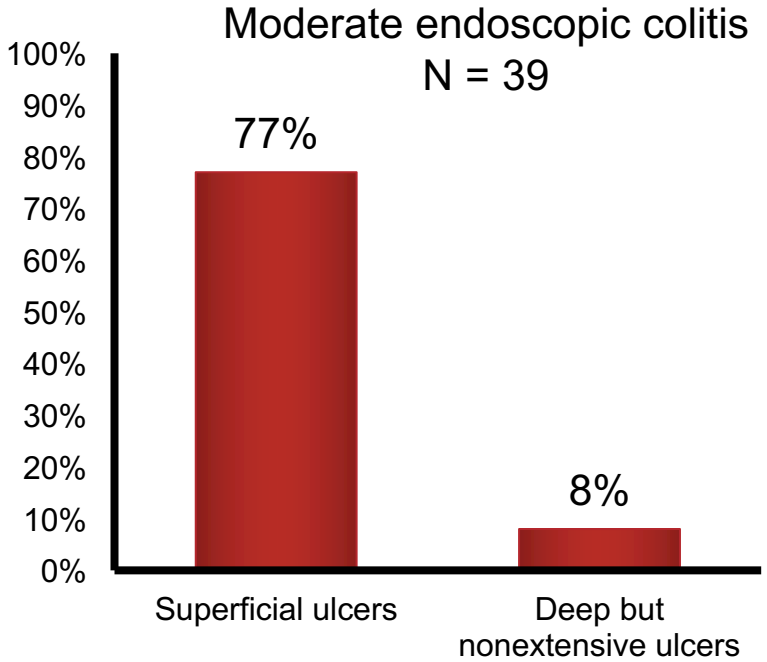
Large Mucosal Abrasions



Endoscopic Severity of Disease Correlates With Colectomy



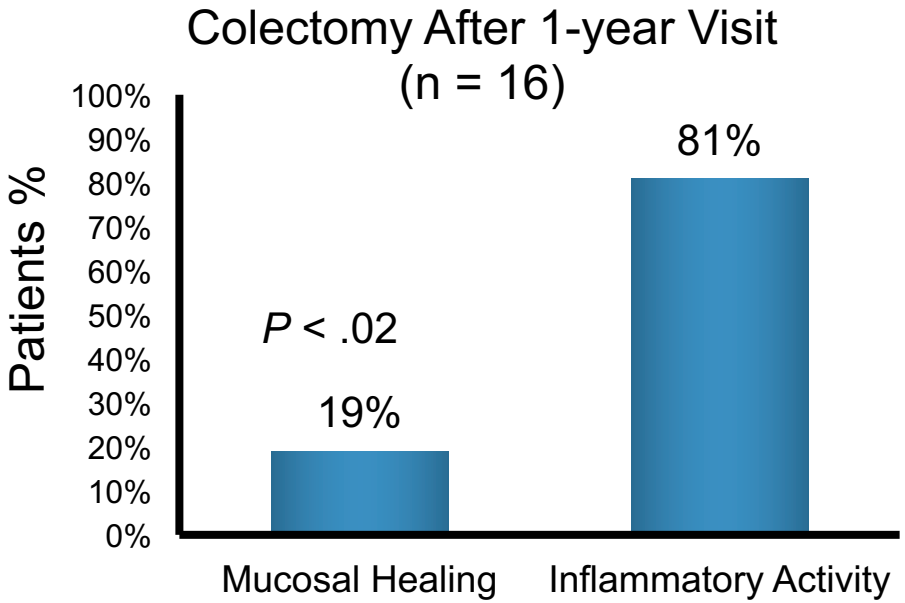
74% underwent colectomy



23% underwent colectomy

Carbonnel F, et al. *Dig Dis Sci*. 1994;39:1550-1557.

Mucosal Healing at 1-Year Is Associated With Lower Rate of Colectomy Independent of Symptoms

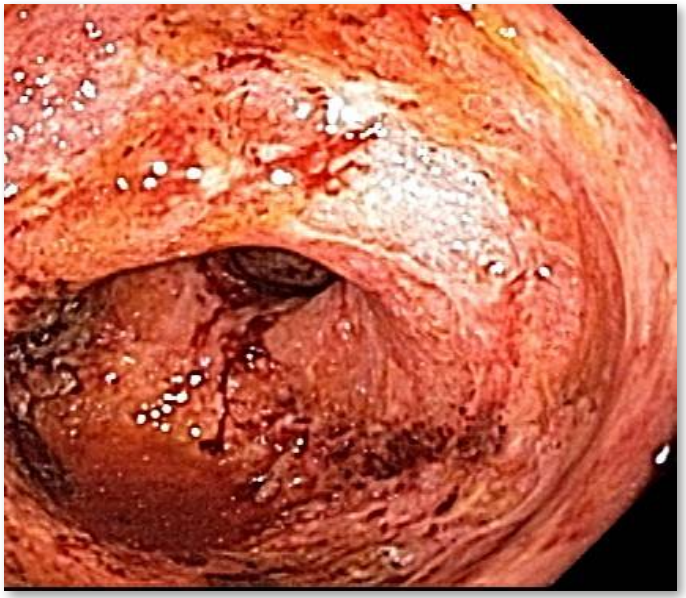


	Risk of colectomy after 1 yr. visit	95% CI
Mucosal healing after 1 year of treatment	0.22	0.06-0.79

Frøslie KF, et al. *Gastroenterology*. 2007;133:412-422.

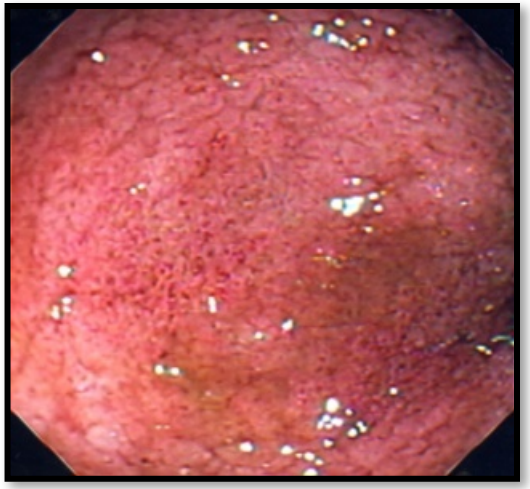
Back to Case 2 – Next Steps

- Despite prednisone and mesalamine, the patient's symptoms progress
- Severe n/v on azathioprine – now severe pan-UC



Back to the Case

- Patient on infliximab; has occasional diarrhea, no bleeding and feels well
- Repeat colonoscopy: significant improvement but slight mucosal and histologic inflammation, is this ok????



Treat-to-Target: The Ins and Outs of Mucosal Healing

Asher Kornbluth, MD

#UCcase2017

Why Should We Incorporate Mucosal Healing Into Our Practices?

Historical Management Strategies for IBD Are Flawed

- Not disease-modifying: prior medical therapies have limited durable effect
- Decisions are based on symptom control or are made after development of complications
- Adjustments to management are delayed and allow progression of disease
  - Symptoms occur after activation of disease

Why Should We Be Moving Toward Endoscopic Endpoints for Management of IBD?

- Seeing is believing
- Symptoms are nonspecific
  - Irritable bowel syndrome, infection, obstruction
- Endoscopic mucosal healing is associated with improved short- and long-term outcomes
  - Durable remission
  - Reduced rates of hospitalization and surgery
  - Possibly less cancer/dysplasia (evidence is for histology)

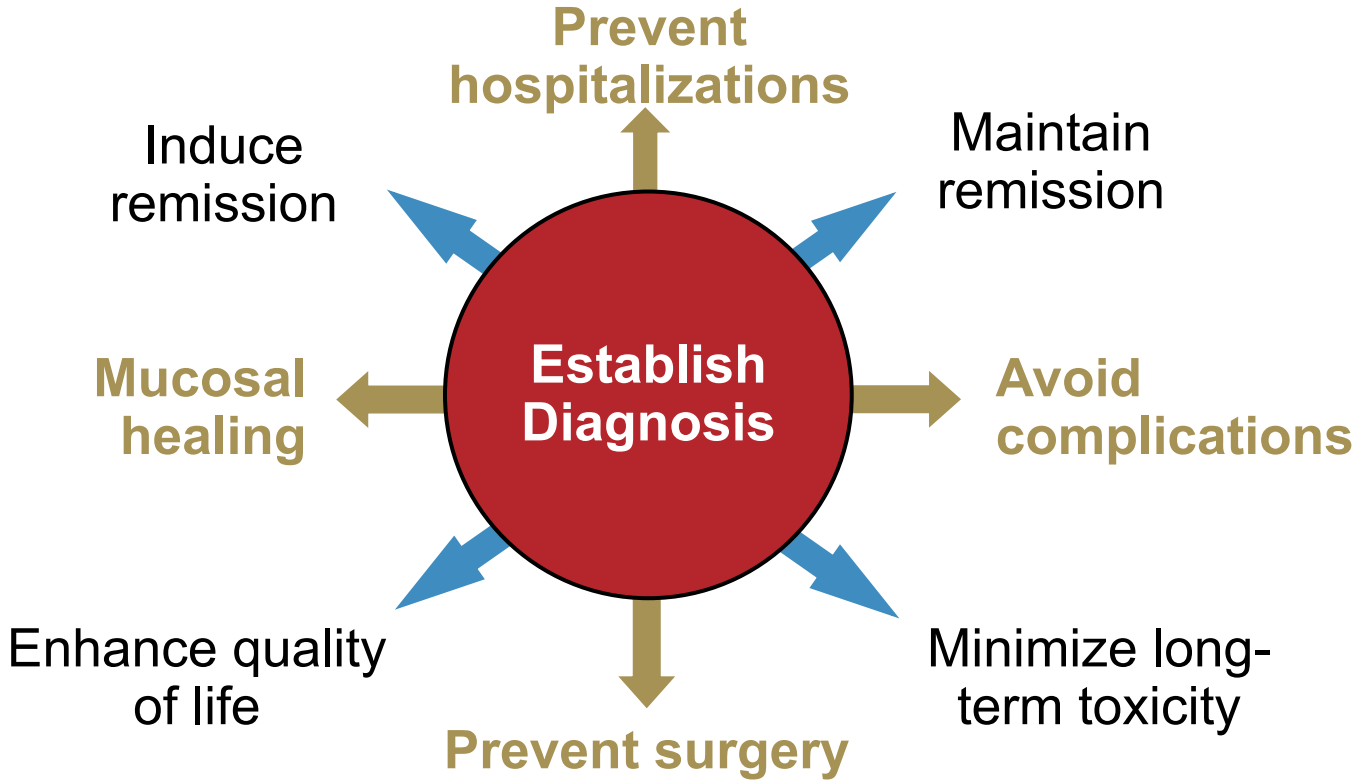
Rubin DT. *Clin Gastroenterol Hepatol*. 2011;9:456-457.; Rutter M, et al. *Gastoenterology*. 2004;126(2):451-459.; Baert F, et al. *Gastroenterology*. 2010;138(2):463-468.

Treat to Target Rheumatology: Are We Ready to Apply it to IBD?

- Shared decision-making between rheumatoid arthritis (RA) patient and MD
- Primary goal: maximize HQROL
  - Control symptoms
  - Prevent progressive structural damage
  - Normalize function and social participation
- Abrogation of inflammation is the most important way to achieve goals
- Treat-to-target by measuring disease activity and adjusting therapy accordingly optimizes outcomes in RA

Smolen JS, et al. *Ann Rheum Dis*. 2010;69(4):631-637.

Goals of Therapy for UC



Kornbluth A, et al. *Am J Gastroenterol*. 2010;105(3):501-523.

Medical Management of Ulcerative Colitis

Miguel Regueiro, MD, FACP, FACG, AGAF

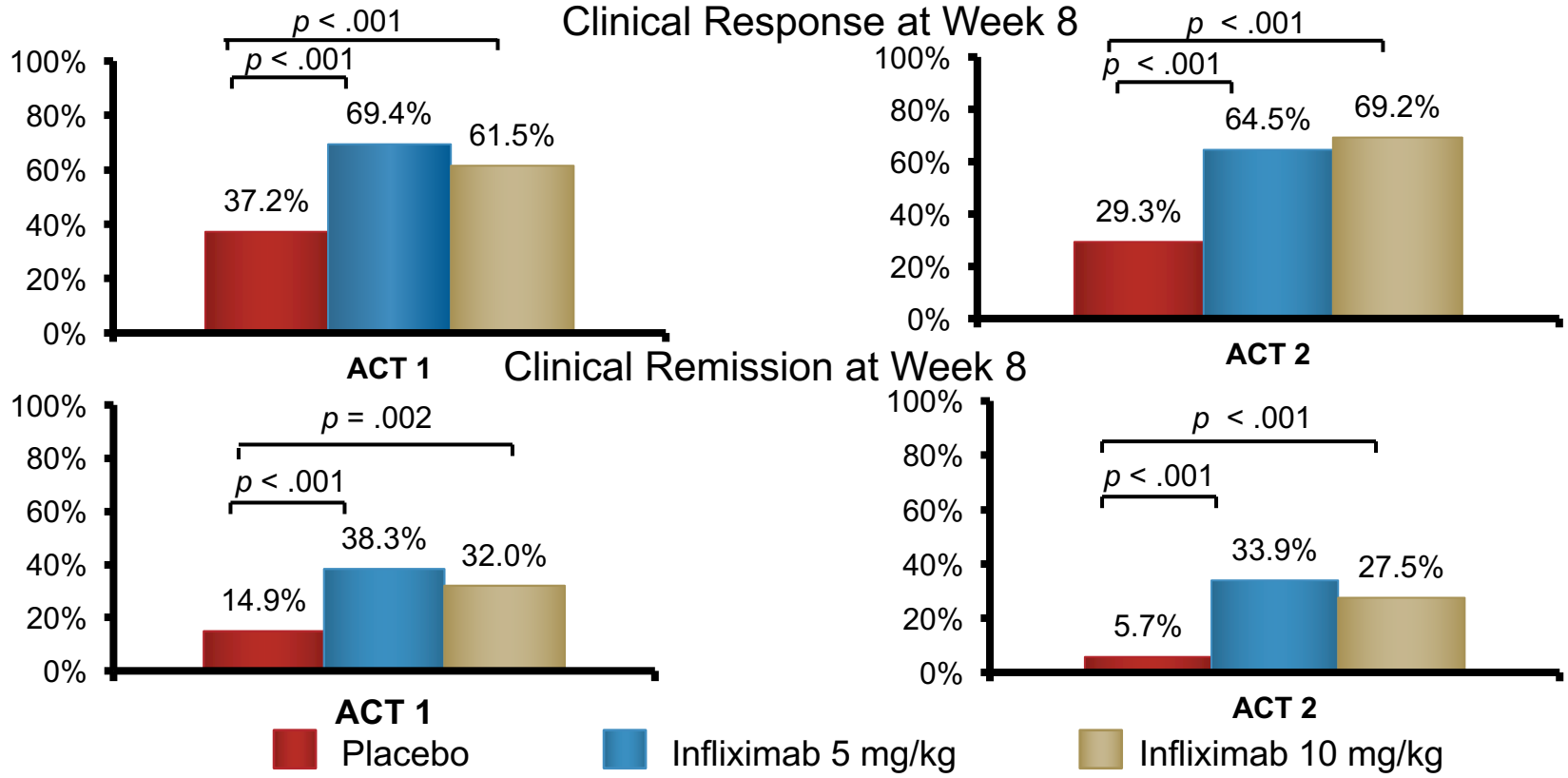
#UCcase2017

Approved Biologic Agents for UC

	Mechanism	Induction of Clinical Response and Remission	Warnings/Precautions
Infliximab	Anti-TNF	ACT-1[1]	Serious infections, opportunistic infections, melanoma risk (annual skin exam recommended). Need to test for TB and HBV prior to initiation of therapy. *(See prescribing information for full listing)*
Adalimumab	Anti-TNF	ULTRA-1[2]	
Golimumab	Anti-TNF	PURSUIT-SC[3]	
Vedolizumab	Selective α4β7 integrin antagonist	GEMINI-I[4]	Nasopharyngitis, upper respiratory and nasal infections, headache, nausea *(See prescribing information for full listing)*

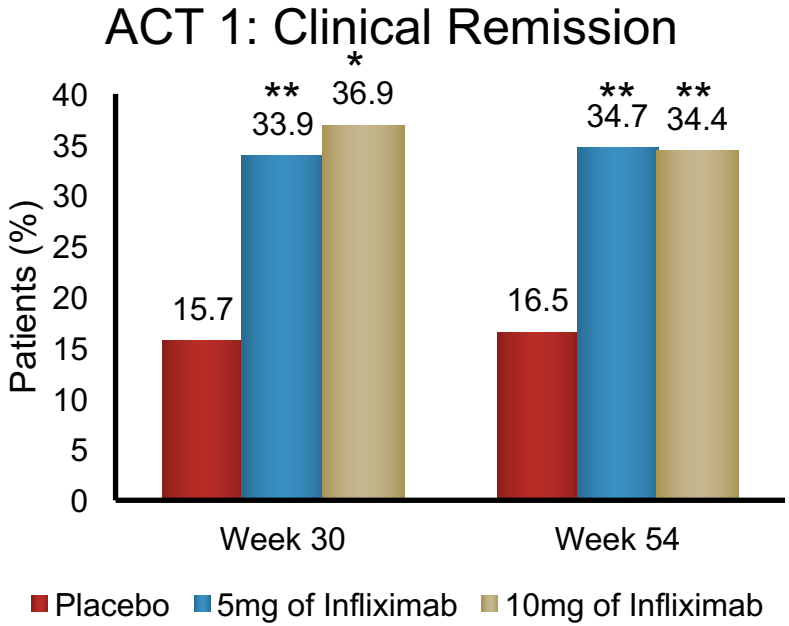
[1]Rutgeerts P, et al. *N Engl J Med.* 2005;353(23):2462-2476; [2]Sandborn WJ, et al. *Gastroenterology*. 2012;142(2):257-265.; [3]Sandborn WJ, et al. *Gastroenterology.* 2014;146(1):96-109; [4]Feagan BG, et al. *N Engl J Med*. 2013;369(8):699-710.

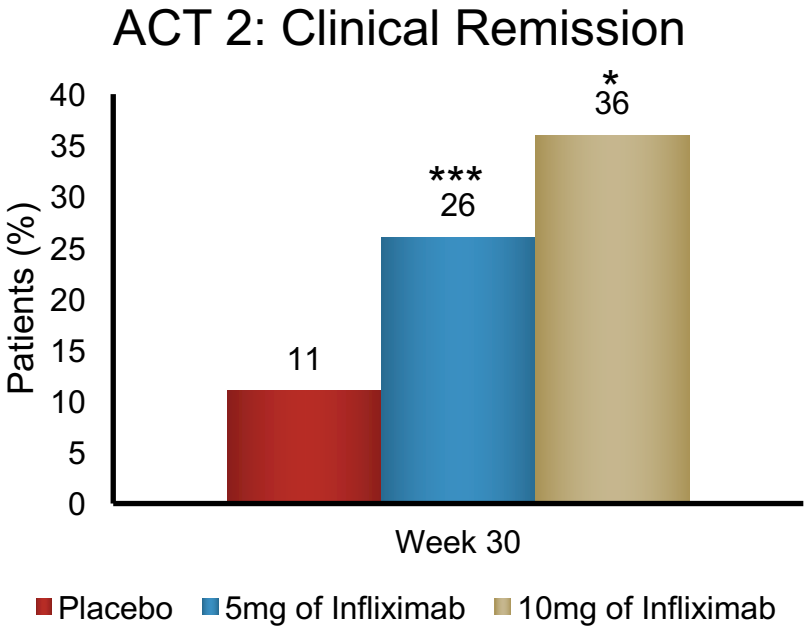
Infliximab for Moderate to Severe UC: ACT 1 & 2



Rutgeerts P, et al. *N Engl J Med.* 2005;353:2462-2479.

Infliximab for Maintenance of Moderate to Severe UC: ACT 1 & 2

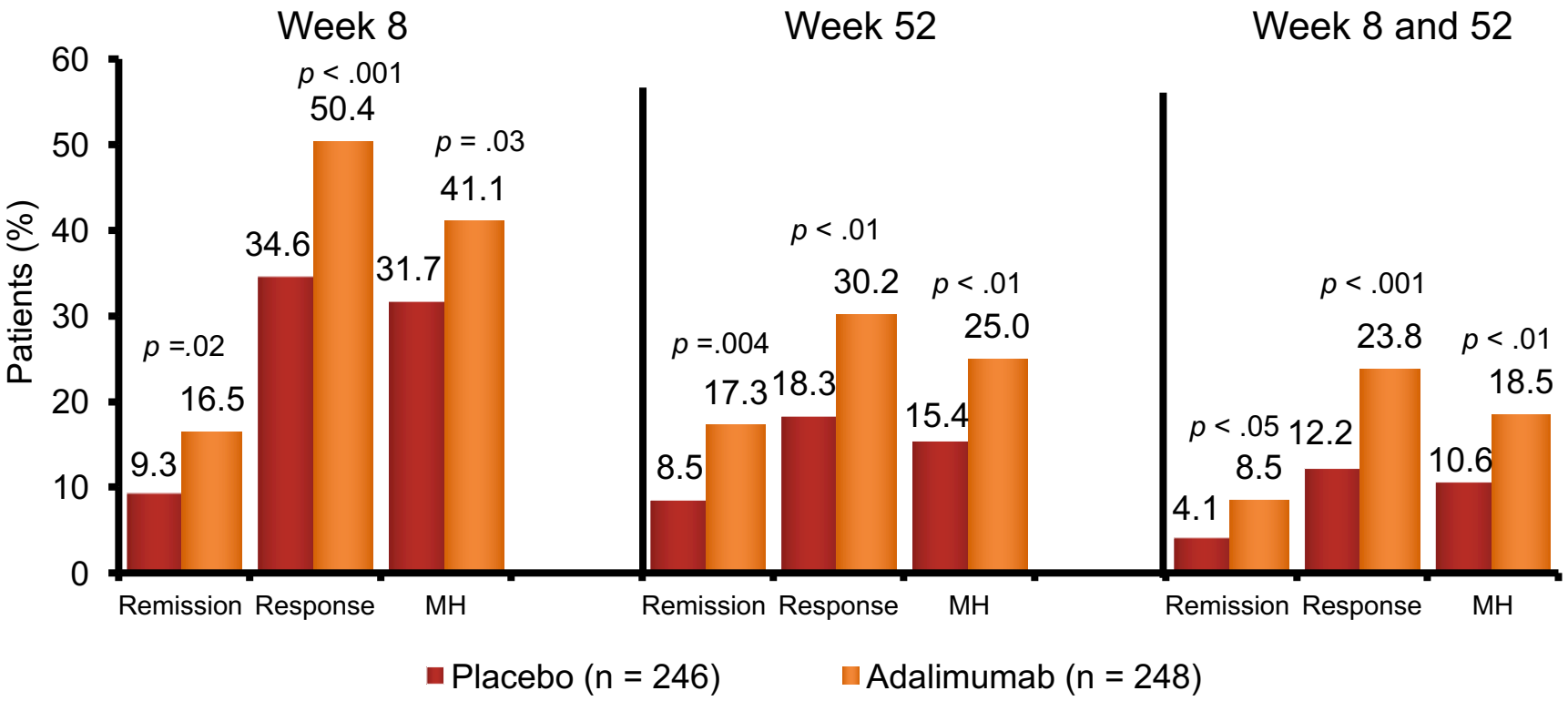




*p < .001 vs. placebo (PBO) ; **p = .001 vs. PBO; ***p = .003 vs. PBO

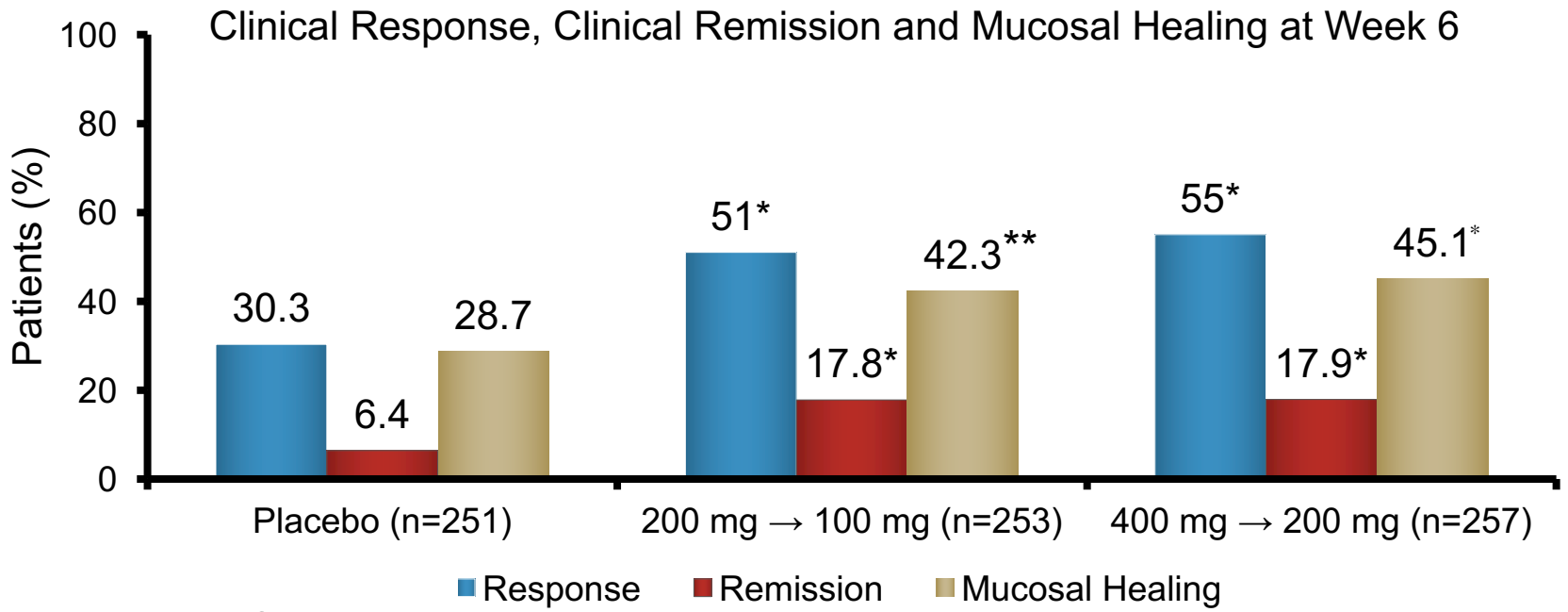
Rutgeerts P, et al. *N Engl J Med.* 2005;353:2462-2479.

Adalimumab in UC: ULTRA 2 Week 8 and 52 Results



Sandborn WJ, et al. *Gastroenterology*. 2012;142:257-265.

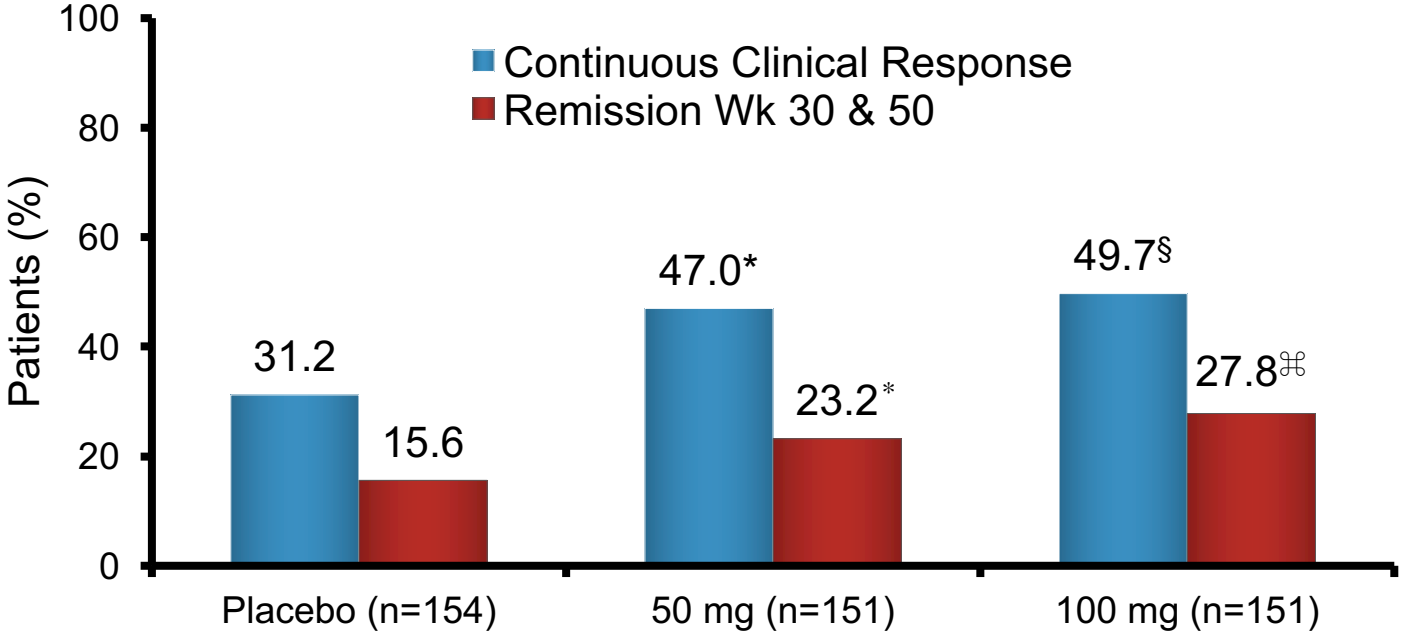
PURSUIT: Golimumab for the Induction of Moderate to Severe UC



*p < .0001 vs. PBO
p = .0014 vs. PBO

Sandborn WJ, et al. *Gastroenterology*. 2014;146:85–95.

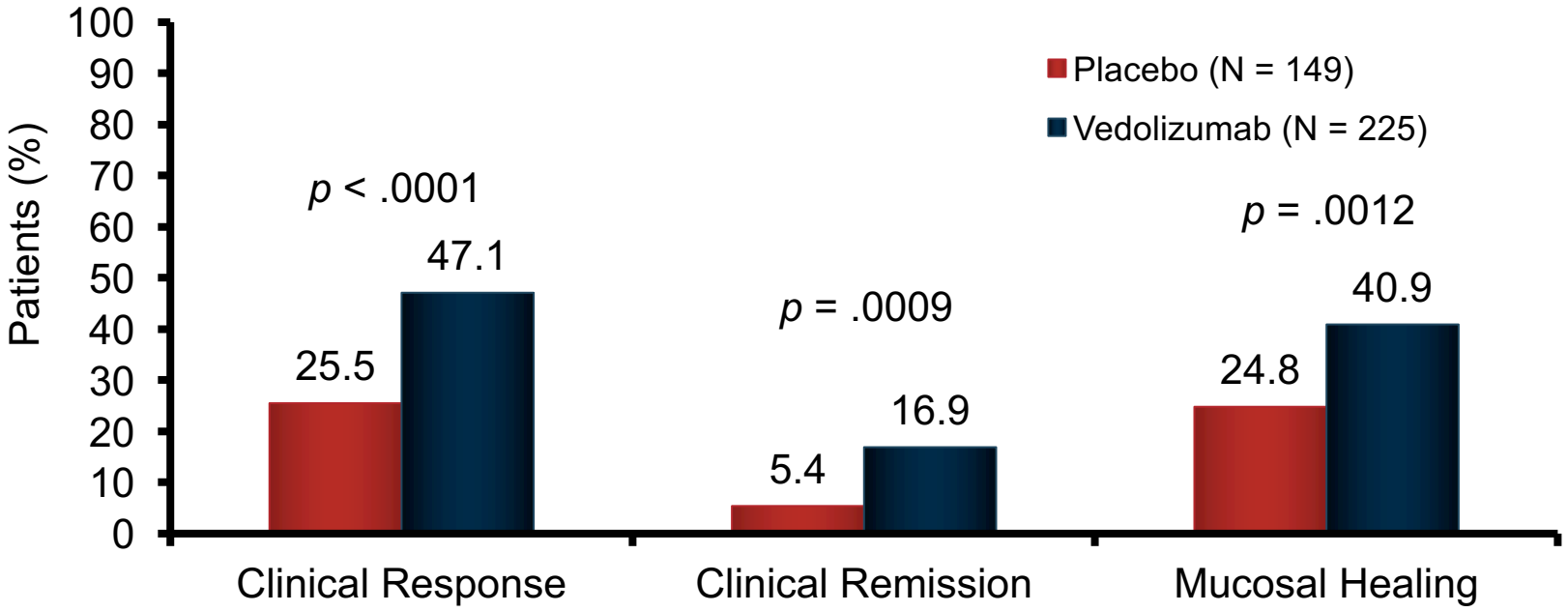
PURSUIT: Golimumab for the Maintenance of Moderate to Severe UC



*p = .01 vs placebo
§p < .001 vs. placebo
⌘p =.004 vs. placebo

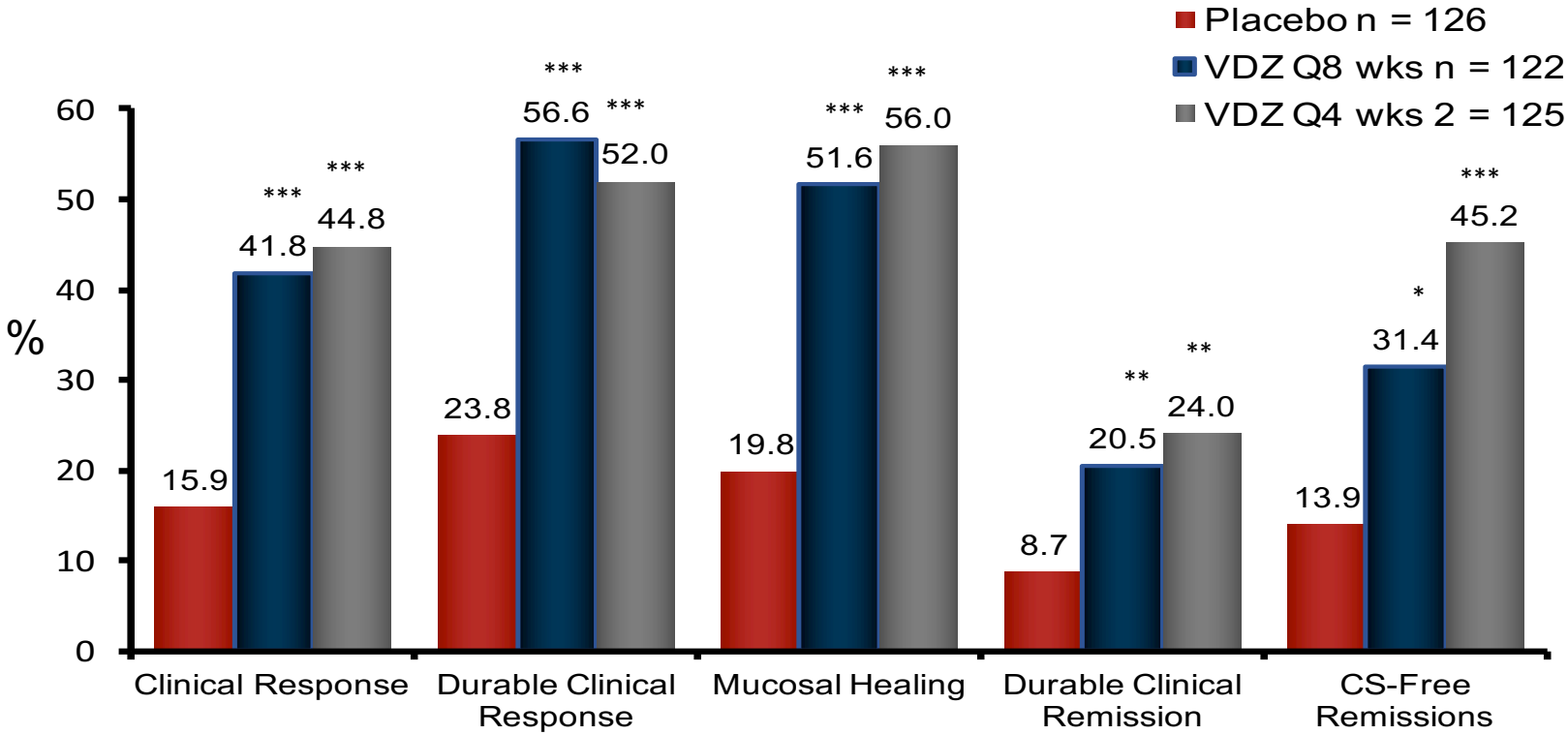
Sandborn WJ, et al. *Gastroenterology*. 2014;146:96-109.

GEMINI I:Vedolizumab in UC
Efficacy at week 6



Feagan BG, et al. *N Engl J Med.* 2013;369:699-710.

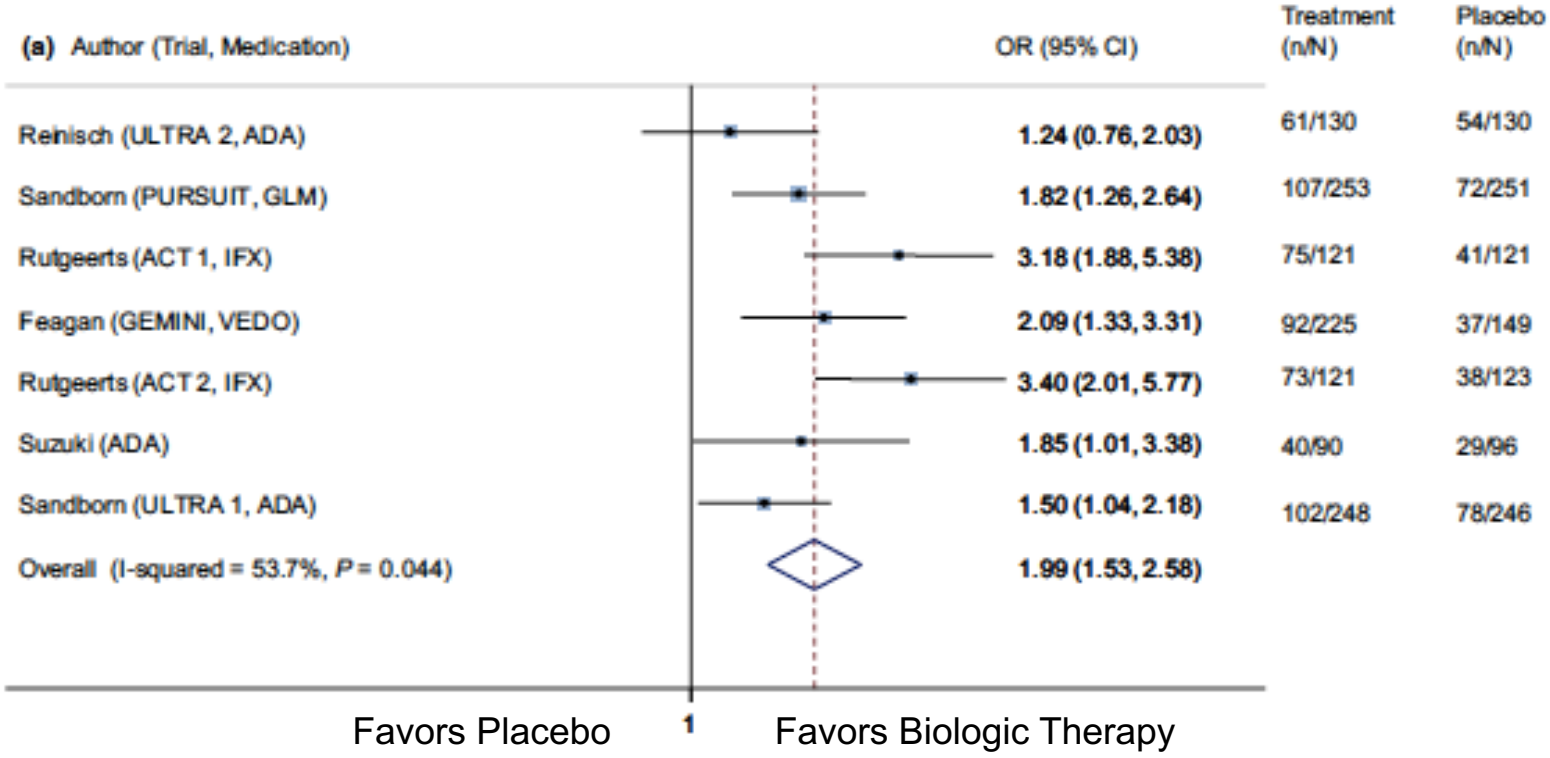
GEMINI I: Vedolizumab in UC Primary and Secondary Outcomes Through 52 Weeks, Maintenance ITT Population



*$p < .05$ **$p < .01$ ***$p < .001$

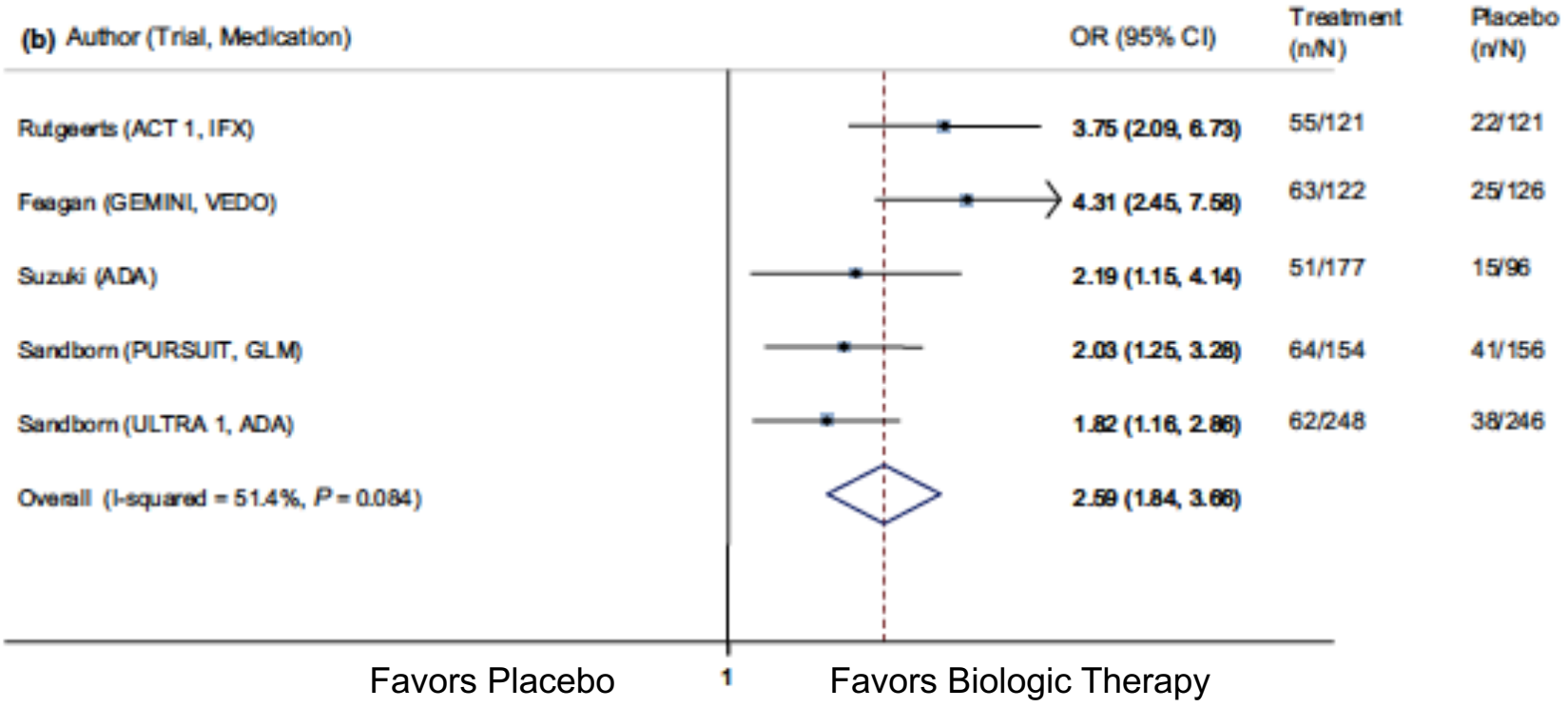
Feagan BG, et al. *N Engl J Med.* 2013;369:699-710.

Effectiveness of Biologics in Attaining Mucosal Healing in UC: Induction Trials



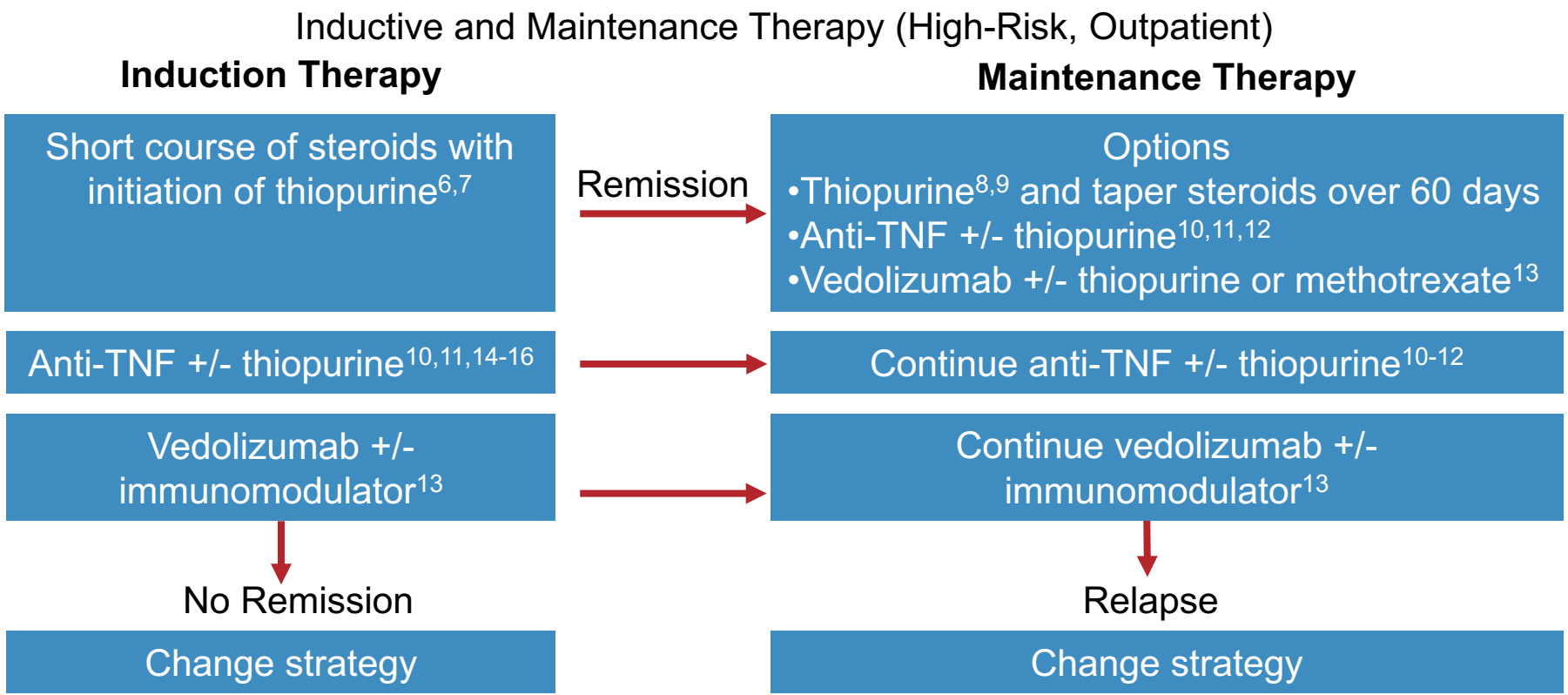
Cholapranee A, et al. *Aliment Pharmacol Ther*. 2017.45(10):1291-1302.

Effectiveness of Biologics in Attaining Mucosal Healing in UC: Maintenance Trials



Cholapranee A, et al. *Aliment Pharmacol Ther*. 2017.45(10):1291-1302.

Induction and Maintenance Therapy in High Risk UC Patients



Dassopoulos T, et al. *Gastroenterology.* 2015;149(1):238-245. See supplemental listing for additional references.

Summary

- Anti-TNFs and vedolizumab are effective for induction and maintenance of remission in patients with moderate to severe UC.
- Anti-TNFs and vedolizumab are effective for mucosal healing in patients with moderate to severe UC.
- Earlier use of biologics in moderate to severe UC may improve outcomes.
- Surgery is not a failure of treatment; it is sometimes a necessary component of the treatment of UC.

Biologics in Clinical Practice: Real-World Experience

Asher Kornbluth, MD

#UCcase2017

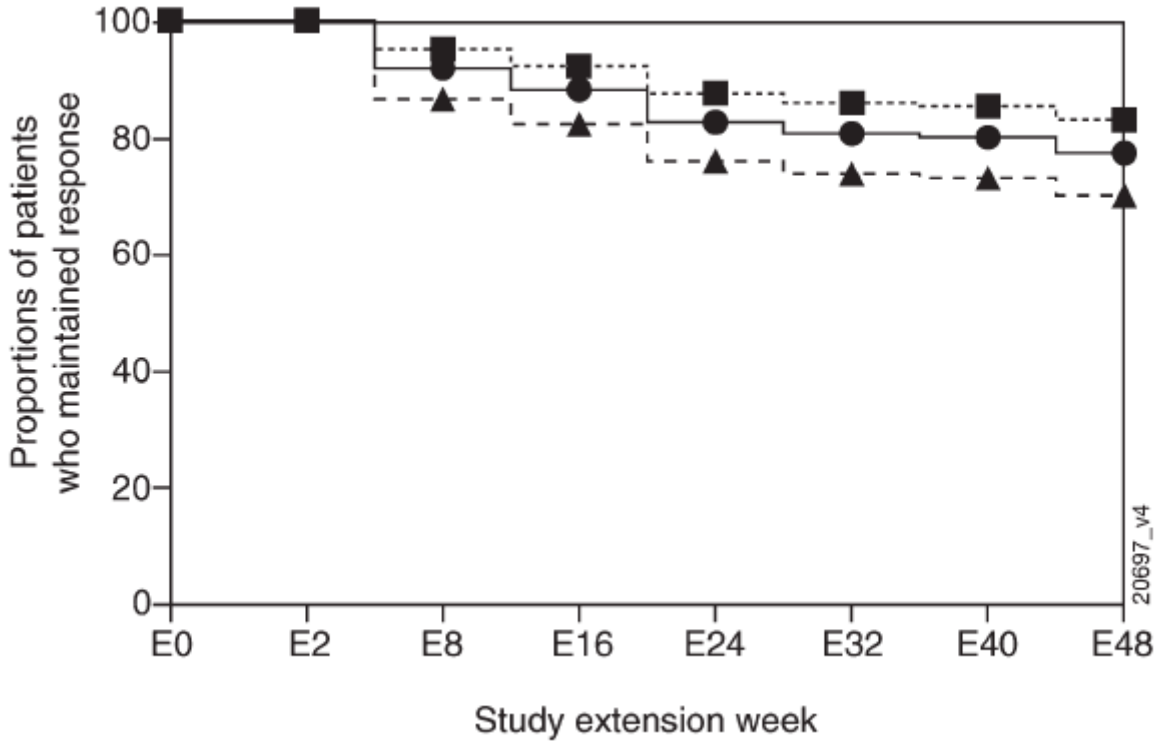
Predictors of IBD-Related ED Visits, Hospitalizations, and High Costs

Predictor variables	IBD-related hospitalizations		ED visits		High charges (>$30,000)	
	OR	95% CI	OR	95% CI	OR	95% CI
On corticosteroids	1.80	1.25–2.61	1.54	1.09–2.17	1.89	1.29–2.79
On narcotics	1.72	1.16–2.56	1.89	1.30–2.75	1.90	1.27–2.86
Minimum Hgb (per g/dL)	0.88	0.01–0.95	0.90	0.83–0.97	0.89	0.81–0.97
Total IBD-related hospitalizations	1.65	1.36–2.02	1.31	1.10–1.57	1.31	1.09–1.59
Psychiatric illness	1.60	1.08–2.36	1.61	1.11–2.32	1.49	0.97–2.24
Total OP encounters	0.80	0.70–0.91				
Age (per year)			0.987	0.978–0.997		
Diagnosis of CD			1.48	1.04–2.11		
Maximum CRP (per mg/L)					1.03	1.00–1.06

Limsrivilai J, et al. *Clin Gastroenterol Hepatol*. 2017;15(3):385-392.

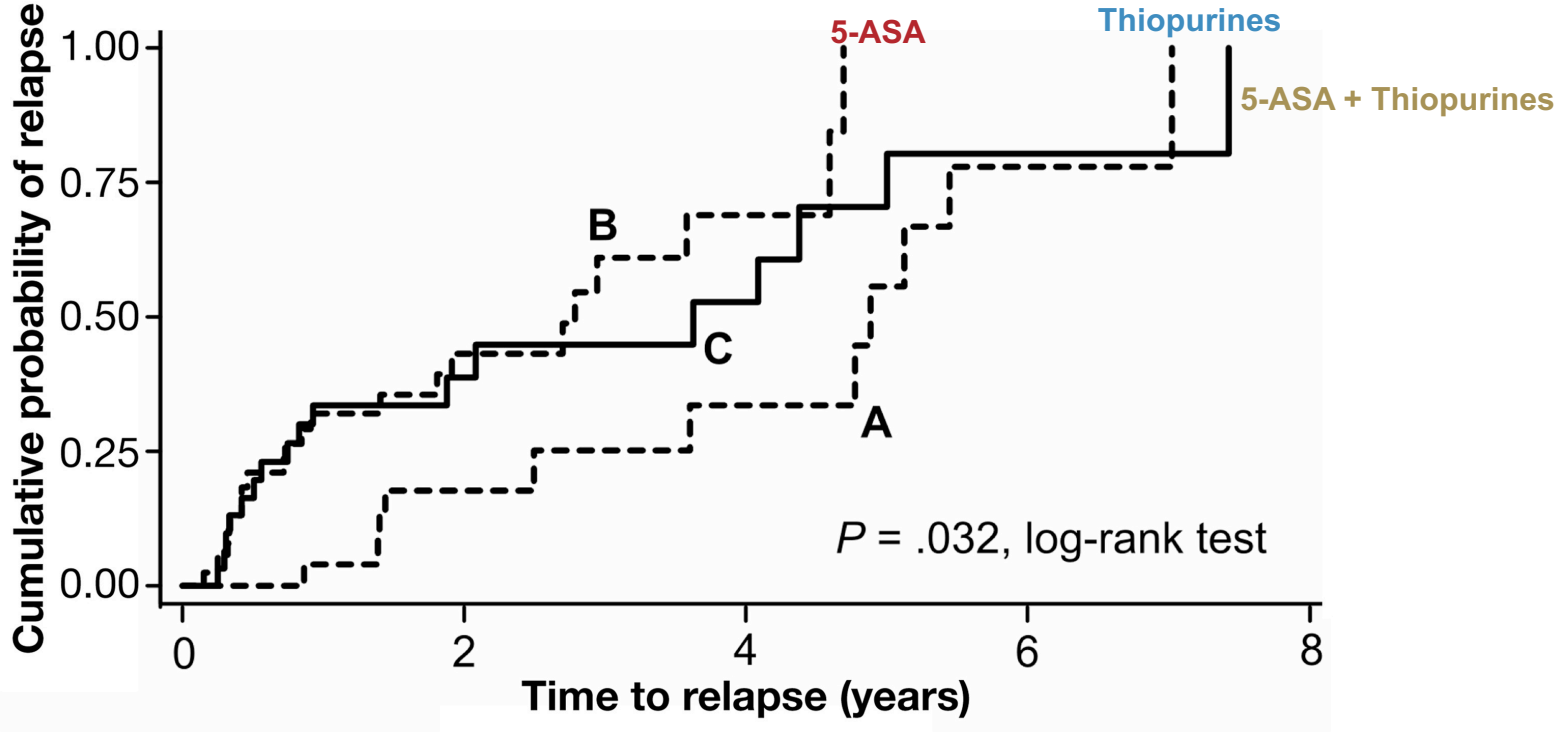
Anti-TNF Blockers

ACT 1 and 2: Open Label Infliximab Extension Studies in UC (N = 229)



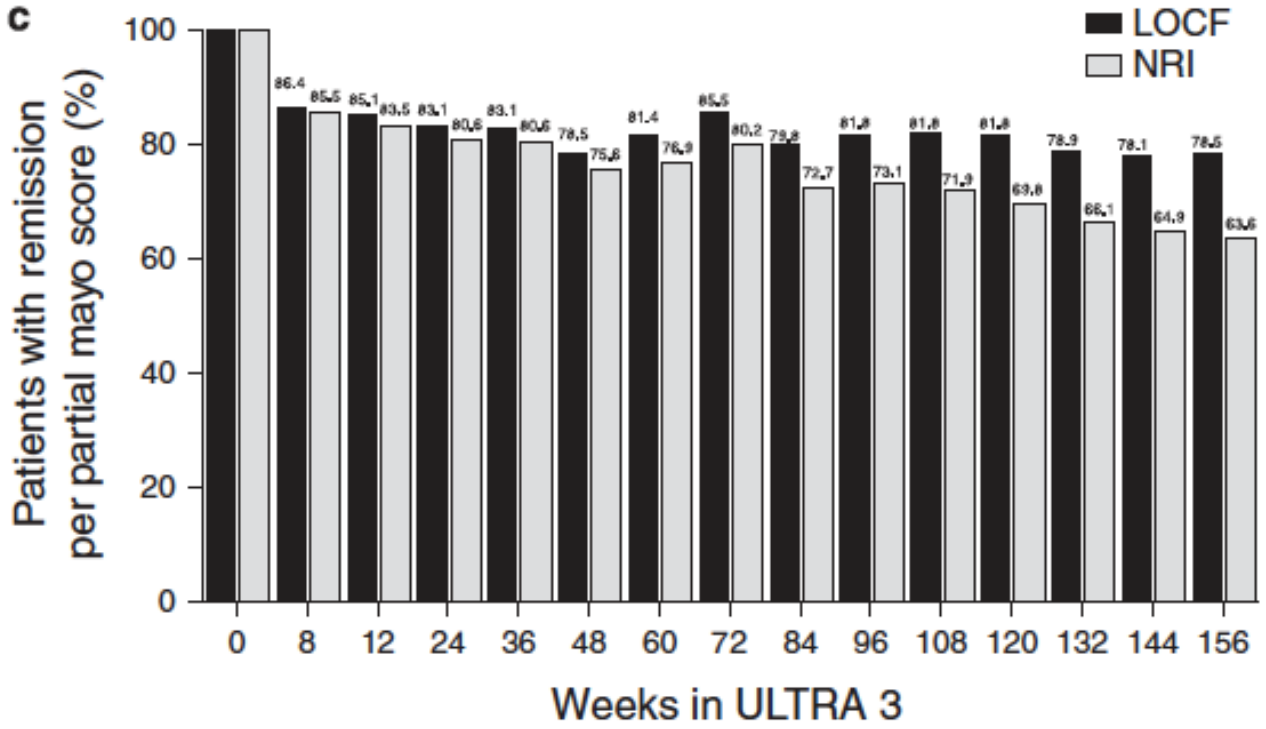
Reinisch W, et al. *Inflamm Bowel Dis*. 2012;18(2):201-211.

Relapse Risk After Infliximab Discontinuation and Continued Use of 5-ASA or Thiopurines (N=193)



Fiorino G, et al. *Clin Gastroenterol Hepatol.* 2016;14(10):1426-1432.

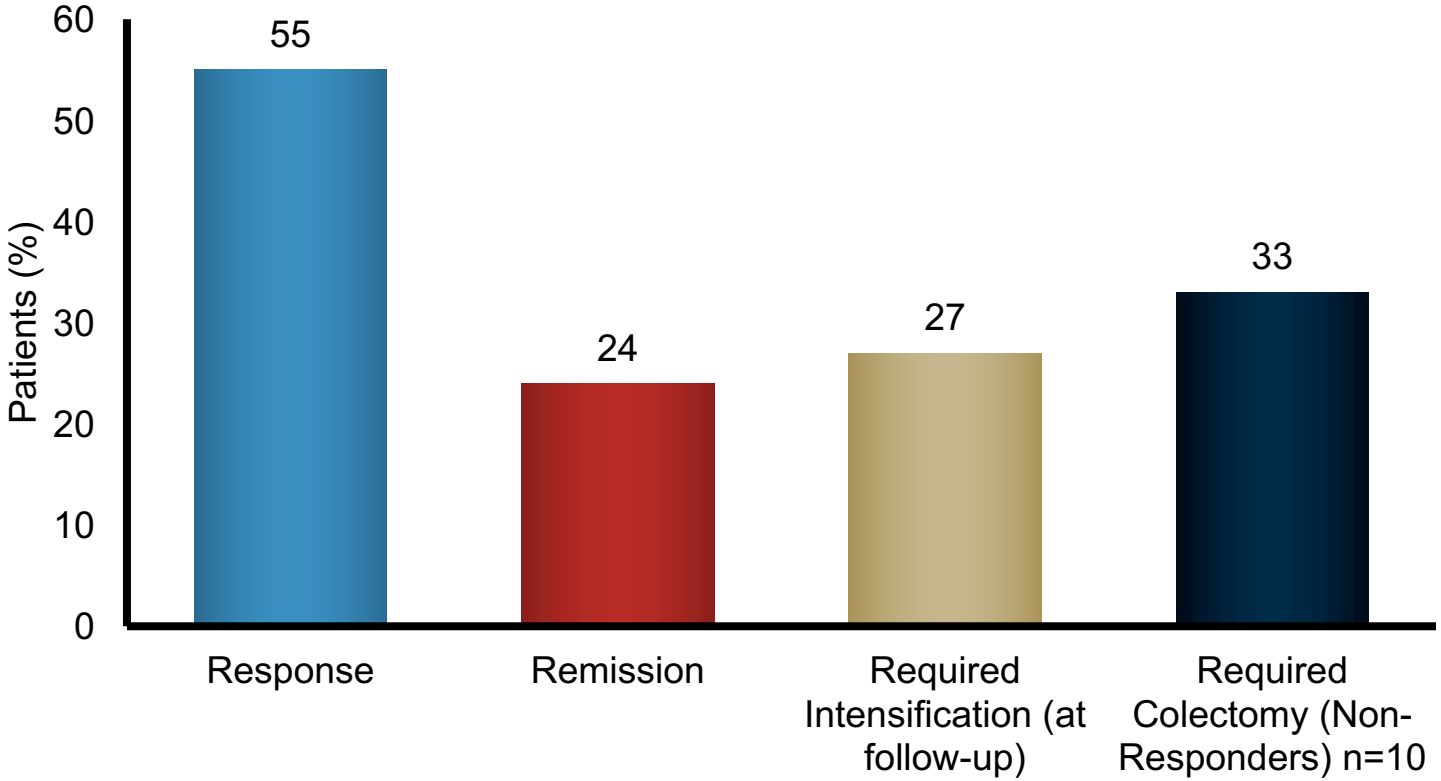
Open Label Adalimumab Maintenance of Remission in UC for 3 years



LOCF, last observation carried forward; NRI, nonresponder imputation

Colombel JF, et al. *Am J Gastroenterol*. 2014;109:1771-1780.

Real-World Effectiveness of Golimumab in UC



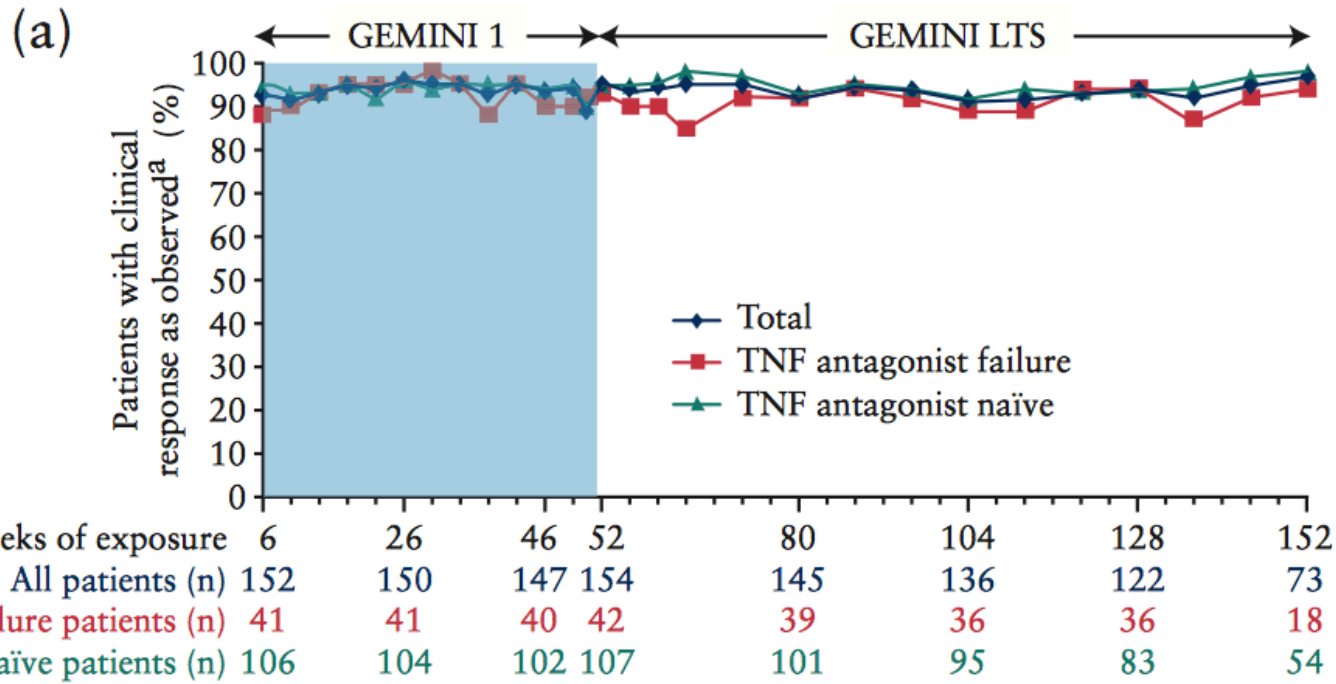
N = 33 Patients followed to 14 weeks 3/10 non-responders needed a colectomy

Bosca-Watts MM, et al. *World J Gastroenterol*. 2016;22(47):10432-10439.

Vedolizumab

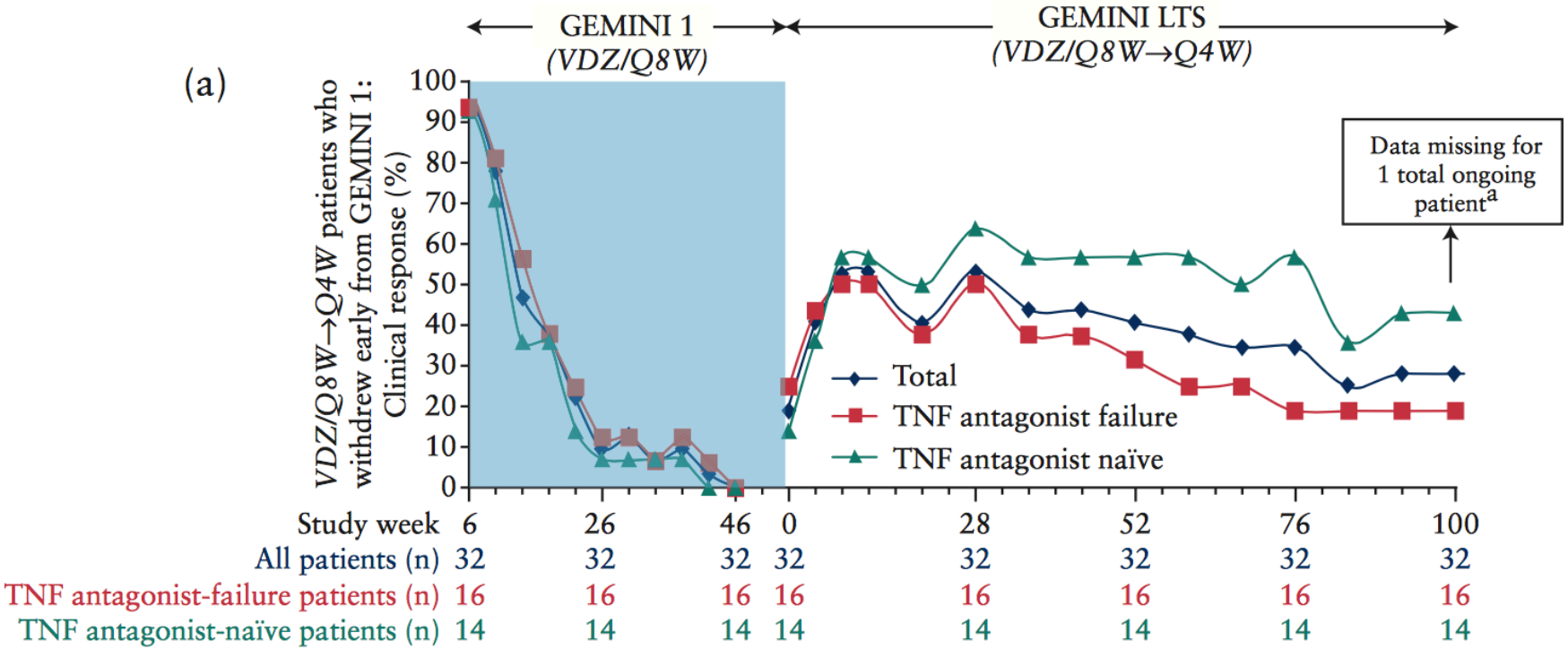
#UCcase2017

Vedolizumab 3-Year Real World Efficacy Data



Loftus EV, et al. *J Crohns Colitis.* 2017;11(4):400-411.

Proportion of Patients Who Experience Maintenance Dose Escalation in Real World Clinical Practice



Loftus EV, et al. *J Crohns Colitis.* 2017;11(4):400-411.

SMART Goals

- Mucosal healing is an important clinical endpoint, as patients can be in clinical remission and still have evidence of active disease
- Treatment strategies for UC should extend beyond symptomatic remission and promote mucosal healing
- Real-world data indicates that biologics are an important component in promoting mucosal healing in UC and have varying degrees of efficacy in achieving clinical remission, clinical response, and sustained remission

Thank You!

Don’t forget to turn in your forms so you can collect your credit.

#UCcase2017

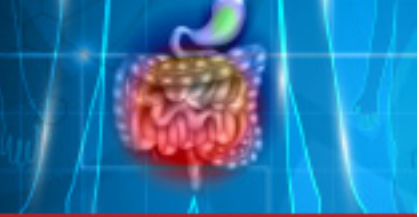
Supplement List of References

1. D'Haens G. *Gastroenterology.* 2007;132:763-786.
2. Rao SS, et al. *Gut.*1988;29:342-245.
3. Truelove SC, et al. 1955;2:1041-1048.
4. Annese V, et al. *J Crohns Colitis.* 2013;7:982-1018.
5. Bitton A, et al. *Am J Gastroenterol*. 2012;107:170-194.
6. Sandborn WJ, et al. *Gastroenterology.* 2012;143:1218-1226. e1-2.
7. Lennard-Jones JE, et al. *Gut*. 1962;3:207-210.
8. Dignass A, et al. *J Crohns Colitis*. 2012;6:991-1030.
9. Khan KJ, et al. *Am J Gastroenterol.* 2011;106:630-642.
10. Sandborn WJ, et al. *Gastroenterology.* 2012;142-257-265 e1-3.
11. Rutgeerts P, et al. *N Engl J Med*. 2005;353:2462-2476.
12. Sandborn WJ, et al. *Gastroenterology*. 2014;146:96-109 e1.
13. Feagan BG, et al. *N Engl J Med.*2013;369-699-710.
14. Panaccione R, et al. *Gastroenterology*. 2014;146:392-400 e3.
15. Reinisch W, et al. *Gut*. 2011;60;780-787.
16. Sandborn WJ, et al. *Gastroenterology*. 2014;146:85-95; quiz e14-15.

Resource Slides

#UCcase2017

Symptoms Assessed by Mayo Score Criteria (Clinical Trials)



Stool frequency

- Normal number of stools
- 1 to 2 stools per day more than normal
- 3 to 4 stools more than normal
- ≥5 stools more than normal

Rectal bleeding

- No blood seen
- Streaks of blood with stool less than half the time
- Obvious blood with stool most of the time
- Blood alone passes

Classification of UC Severity

MILD
- <4 stools/day ± blood
- Normal ESR
- No signs of toxicity

MODERATE
- ≥4 stools/day ± blood
- Minimal signs of toxicity

SEVERE
- >6 bloody stools/day
- Evidence of toxicity:
  - Fever
  - Tachycardia
  - Anemia
  - ↑ ESR

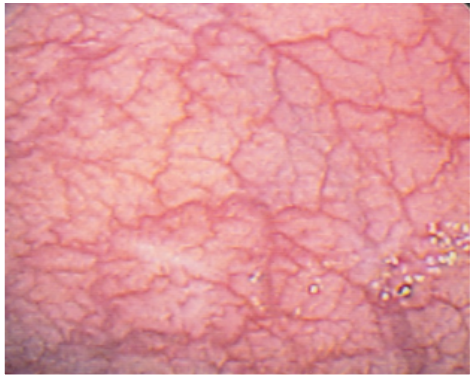
FULMINANT
- >10 stools/day
- Continuous bleeding
- Toxicity
- Abdominal tenderness/distension
- Transfusion requirement
- Colonic dilation on x-ray

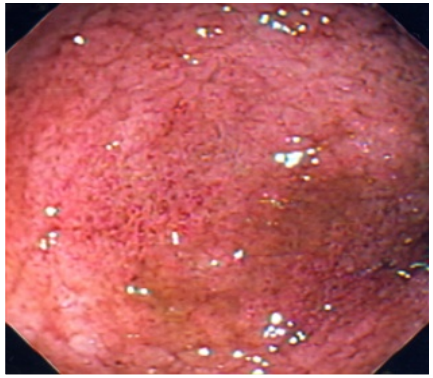
ESR, erythrocyte sedimentation rate

Kornbluth A, et al. *Am J Gastroenterol*. 2010;105(3):501-523.

Endoscopic Severity of Disease

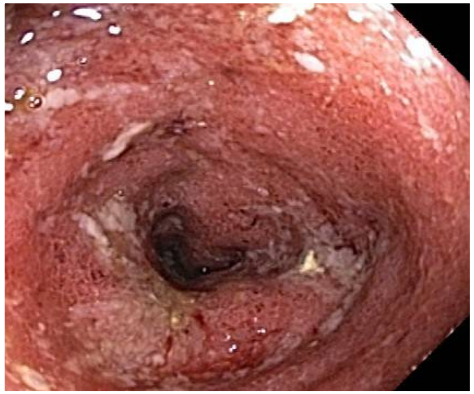
Normal

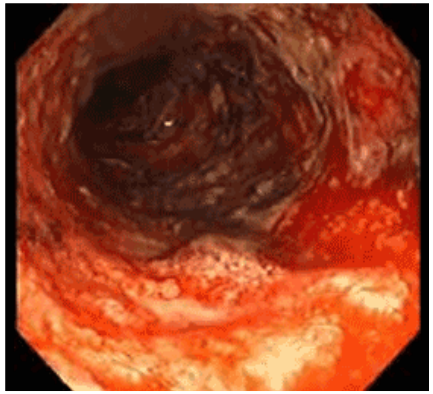




Mild

Moderate





Severe

What We Know—Healing the Mucosa in UC Patients is Associated With:

- Improved quality of life
- Reduction in hospitalization
- Decreased colectomies
- Decrease in dysplasia and colorectal cancer

Interpreting Discordance of Clinical Remission and Mucosal Healing

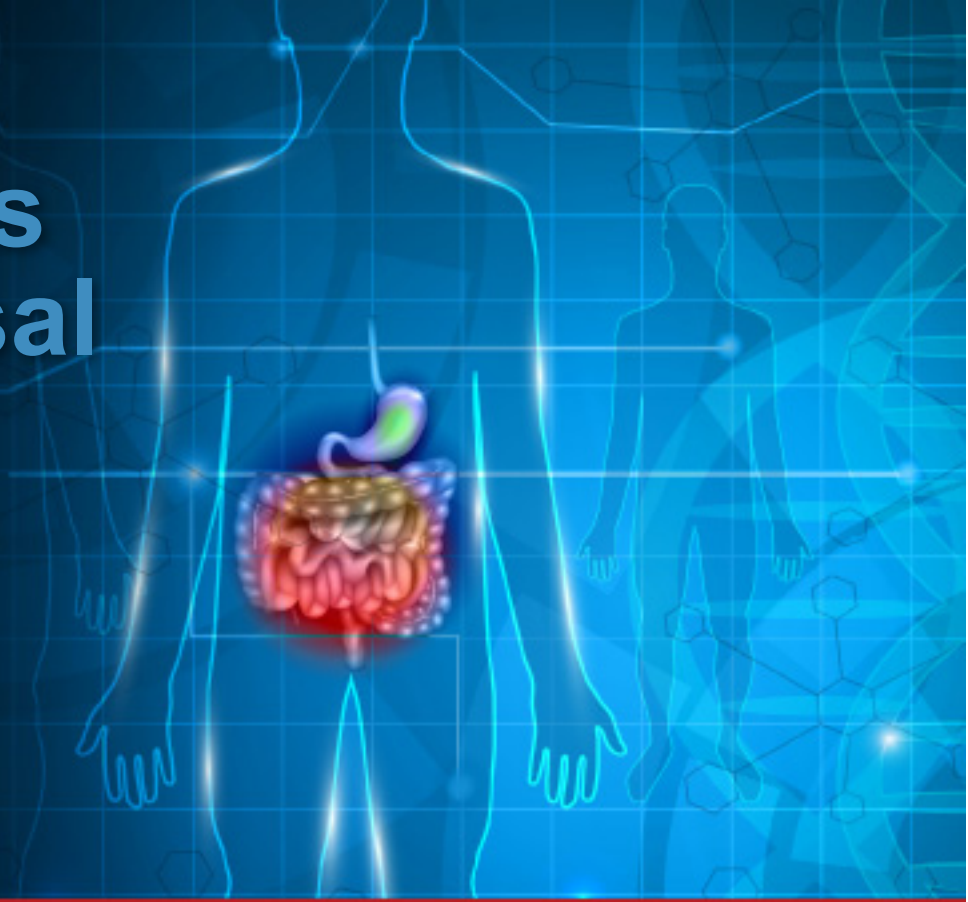
	MH+	MH-
Clinical Remission +	"True remission" (deep remission)	• Placebo response? • Other pharmacologic effect? • Lag time between MH and symptoms?
Clinical Remission -	• Other conditions driving symptoms (eg, irritable bowel syndrome) • Irreversible disease complications driving symptoms (eg, fibrosis, "lead pipe" rectosigmoid)	True lack of response

Sandborn W, et al. Available at http://gi.org/wp-content/uploads/2012/02/FDA-ACG-IBDWorkshopOct2011.pdf. Accessed March 20, 2017.

Evolved Goals of Management of IBD

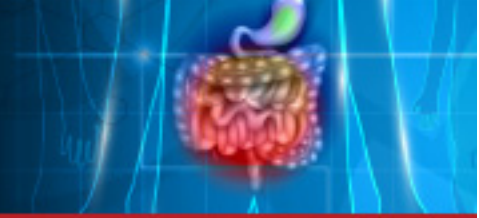
- Early and accurate diagnosis
- Rapid induction of clinical remission
- Stable, sustained maintenance of remission
  - Steroid-free
  - Recognition of the value of a healed mucosa (deep remission)
- Modified natural history and long-term outcomes of the disease
  - Reduce hospitalization
  - Avoid surgery or repeat surgery
  - Eliminate disability

Novel Techniques to Assess Mucosal Healing: Radiology and Biomarkers



#UCcase2017

Surrogate Markers for Mucosal Healing



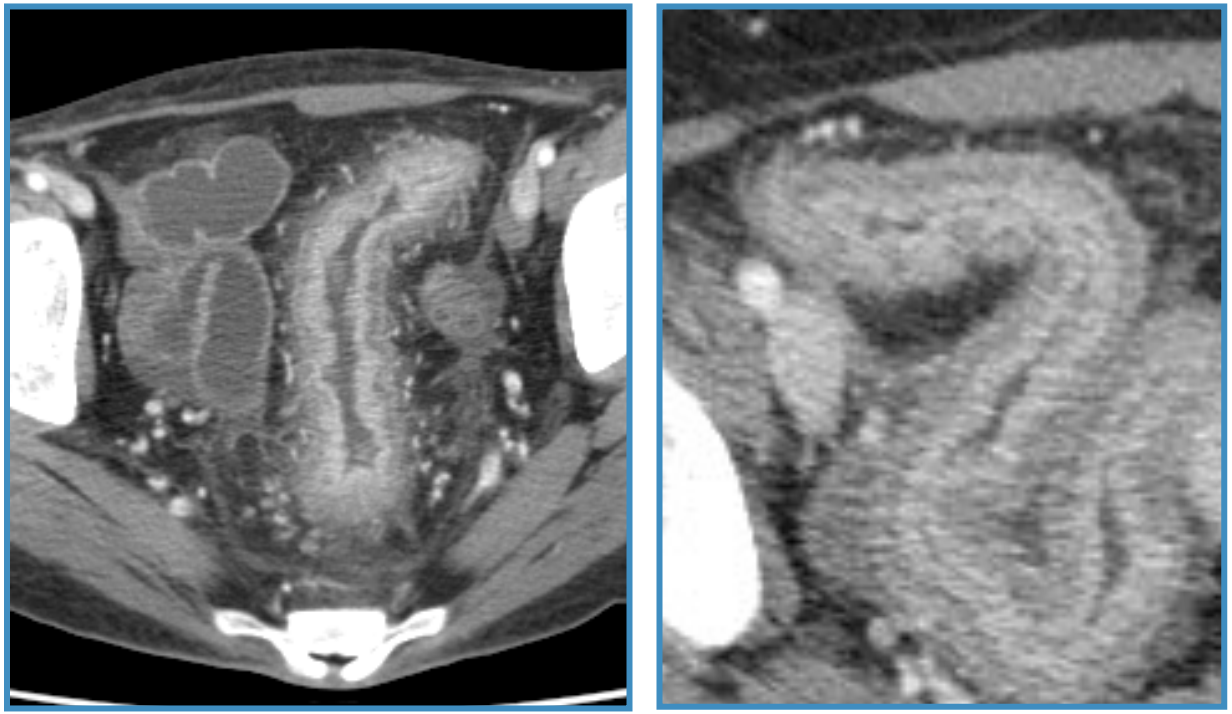
- Radiology
- Capsule endoscopy
- Serologic markers
- Fecal markers

Radiographic Mucosal Healing

- Is healing of the superficial mucosa “too little” and “too partial?”
- Is radiographic transmural healing BETTER than endoscopy?
- Modalities include CT, MRI, ultrasound, PET-CT, and scintigraphy (SPECT)
- Diagnostic accuracy about the same across modalities

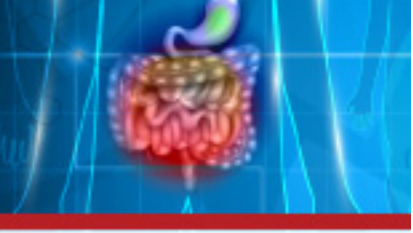
Daperno M, et al. *J Crohns Colitis.* 2011;5:484.; Horsthuis K et al. *Radiology.* 2008;247:64.

Significantly Active Disease Is Easier Than Assessing for Mucosal Healing



Courtesy of E. Loftus, Jr., MD.

Summary: Surrogate Markers for Mucosal Healing



- Most data available for MRI, fecal calprotectin, and CRP as surrogate markers for mucosal healing in Crohn's disease
- More accurate in distinguishing severely active disease (from less active or remission)
- Fecal calprotectin may be more accurate to distinguish mildly active from "healed" mucosa
- Likely a combination of markers (index) will yield the highest accuracy

Corticosteroids

- Fast-acting[1]
- Oral steroid ± 5-ASA for moderate to severe active IBD
- Rectal or IV delivery if necessary
- Given only to achieve remission — not appropriate for maintenance due to risk of serious side effects:[2,3]
- Adrenal suppression and metabolic disturbances, including diabetes

[1]Crohn's & Colitis Foundation of America. Available at http://www.ccfa.org/corticosteroids-2013.pdf. Accessed March 23, 2017.; [2]Present DH. *Inflamm Bowel Dis*. 2000;6(1):48-57.; [3]Rutgeerts PJ. *Aliment Pharmacol Ther.* 2001;15(10):1515-1525.

Immunomodulators

- Thiopurines: Azathioprine* and 6-mercaptopurine*
  - Used to maintain remission in UC of any severity[1,2]
  - Slow onset of action (6–12 weeks), often given with corticosteroid or combination anti-TNF; SAEs include pancreatitis, bone marrow suppression
- Methotrexate*:
  - Not proven effective in UC[1]
  - Absolutely contraindicated in pregnancy; SAEs include bone marrow suppression, acute and chronic liver toxicity, serious infection[3]
- Cyclosporine*:
  - IV for acute, severe, steroid-refractory UC[4]

*, azathioprine, 6-mercaptopurine, methotrexate, and cyclosporine not FDA-approved for moderate-to-severe ulcerative colitis

1 Kornbluth A, et al. *Am J Gastroenterol*. 2010;105(3):501-523; 2 Lichtenstein GR, et al. *Am J Gastroenterol*. 2009;104(2): 465-483; 3 Methotrexate injection USP [package insert]. Drugs@FDA Website. 2011. 4 Campbell S, et al. *Eur J Gastroenterol Hepatol*. 2005;17(1):79-84.

Comparison of Real-World Outcomes of Adalimumab and Infliximab in UC

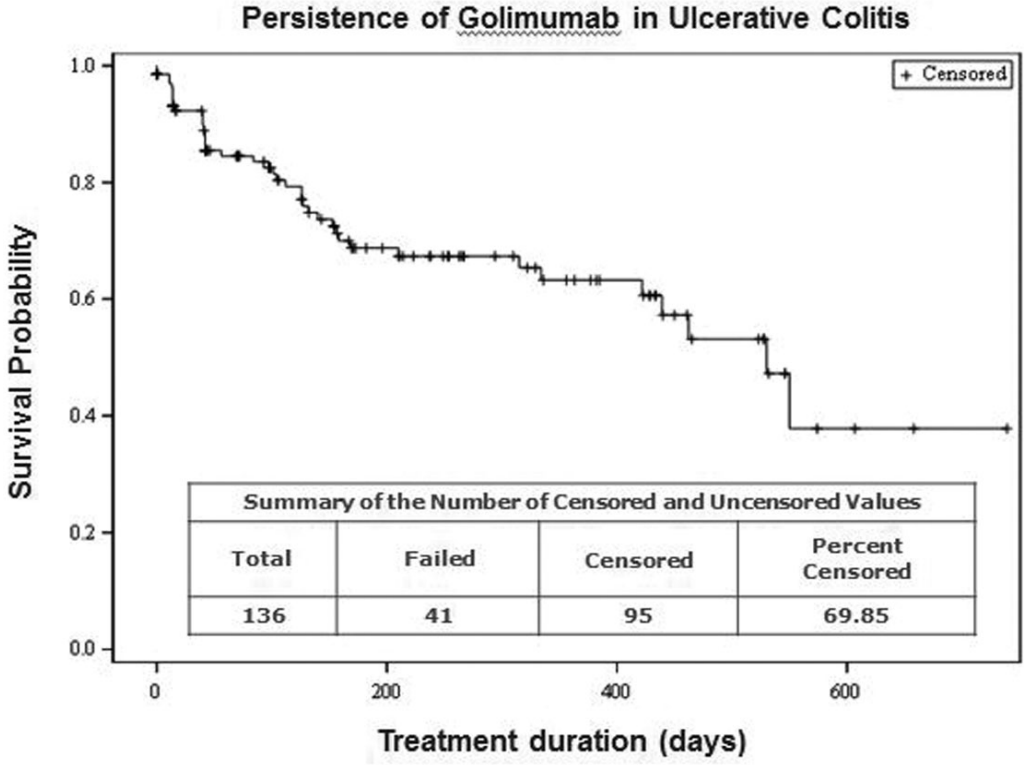
Adalimumab, n = 380
Infliximab, n = 424
No prior anti-TNF therapy, history of Crohn's disease, or colectomy

	Follow-up week[1]	Adalimumab[2]	Infliximab[2]	P-value (Log-rank)[3]
Probability of achieving remission	8 weeks	10.7%	8.2%	0.2240
	12 weeks	21.2%	18.3%	0.3180
	16 weeks	30.3%	28.2%	0.4947
	20 weeks	41.0%	38.3%	0.4253
	24 weeks	45.3%	44.3%	0.6721
Probability of no rectal bleeding	8 weeks	11.3%	10.0%	0.5415
	12 weeks	19.8%	18.5%	0.6203
	16 weeks	28.9%	27.4%	0.6225
	20 weeks	40.8%	39.4%	0.6556
	24 weeks	45.2%	45.1%	0.8767
Probability of normal stool count	8 weeks	7.0%	6.1%	0.6437
	12 weeks	12.8%	13.2%	0.8863
	16 weeks	20.3%	19.8%	0.8695
	20 weeks	27.8%	28.1%	0.9342
	24 weeks	32.6%	33.0%	0.9107
Probability of Normal PGA score	8 weeks	4.7%	4.3%	0.7682
	12 weeks	11.3%	10.7%	0.8097
	16 weeks	17.7%	17.4%	0.9417
	20 weeks	25.3%	25.3%	0.9935
	24 weeks	30.6%	29.6%	0.8136

[1]Weeks after index date; [2]Probability of achieving parameter to each of the assessment points after the index date; [3]The log-rank tests for the homogeneity of the results from the index date to each of the assessment points after the index date. PGA, physician's global assessment.

Sandborn WJ, et al. *Curr Med Res Opin*. 2016;32(&):1233-1241.

Persistence with Golimumab Therapy in Responders



N = 136
72% anti-TNF naïve
63% remained on therapy after 1 year
3.6% required dose optimization

Bressler B, et al. *J Crohns Colitis*. 2016;10(Suppl 1):S396.

Proportion of Patients Who Experience Maintenance Dose Escalation (DE) in Real-World Clinical Practice

	180-day Analysis		210-day Analysis	
	VDZ (n = 101)	IFX (n = 228)	VDZ (n = 96)	IFX (n = 213)
Dose Escalation	4.0%	21.5%	5.2%	25.8%
With Prior Biologic Treatment				
	VDZ (n = 71)	IFX (n = 27)	VDZ (n = 68)	IFX (n = 24)
Dose Escalation	5.6%	25.9%	5.9%	29.2%
Without Prior Biologic Treatment				
	VDZ (n = 30)	IFX (n = 201)	VDZ (n = 28)	IFX (n = 189)
Dose Escalation	0%	20.9%	3.6%	25.4%

$p < .05$ for all.

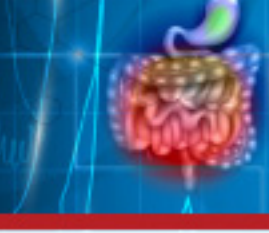
DE = Received ≥2 maintenance infusions with a higher dose or within a shortened interval of 7-52 days

DE (sensitivity analysis) = Interval of 7-45 days

Khalid JM, et al. *Am J Gastroenterol*. 2016;111(suppl 1):S316.

Thiopurines

Risk of Lymphoma Associated with Immunomodulators



- 20,802 IBD patients
- 35% thiopurines and 4.8% anti-TNF
- 1 Hodgkin disease, 16 Non-Hodgkin Lymphomas (NHL)
- Compared to expected number in FANCIM registry
  - SIR IBD vs. Controls = 2.07 (1.2-3.3) for NHL
- Among 16 NHL, 3 naïve to immunomodulators
- 7 of 11 patients where were tested for Epstein-Barr virus were POSITIVE

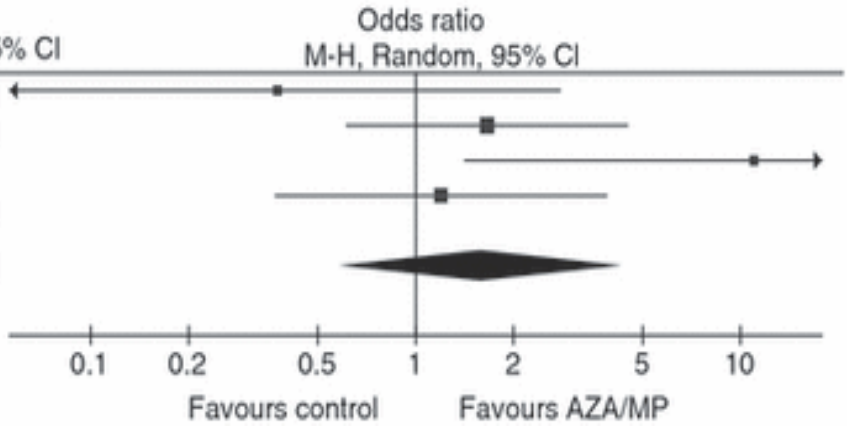
Beaugerie L. *Gastroenterology.* 2008;134(4, Suppl 1):A116-A-117.

Efficacy of Thiopurines for Induction of Remission in UC

Study or subgroup	AZA/MP Events	AZA/MP Total	Control Events	Control Total	Weight	Odds ratio M-H, Random, 95% CI
Caprilli 1975	6	10	8	10	17.0%	0.38 [0.05, 2.77]
Jewell 1974	31	40	27	40	35.4%	1.66 [0.61, 4.48]
Mate 2000	11	14	2	8	16.5%	11.00 [1.42, 85.20]
Sood 2000	17	25	16	25	31.1%	1.20 [0.37, 3.86]
Total (95% CI)		89		83	100.0%	1.59 [0.59, 4.29]
Total events	65		53			

Heterogeneity: $\tau^2 = 0.47$; $\chi^2 = 5.66$, df = 3 ($P = 0.13$); $I^2 = 47\%$

Test for overall effect: $Z = 0.91$ ($P = 0.36$)



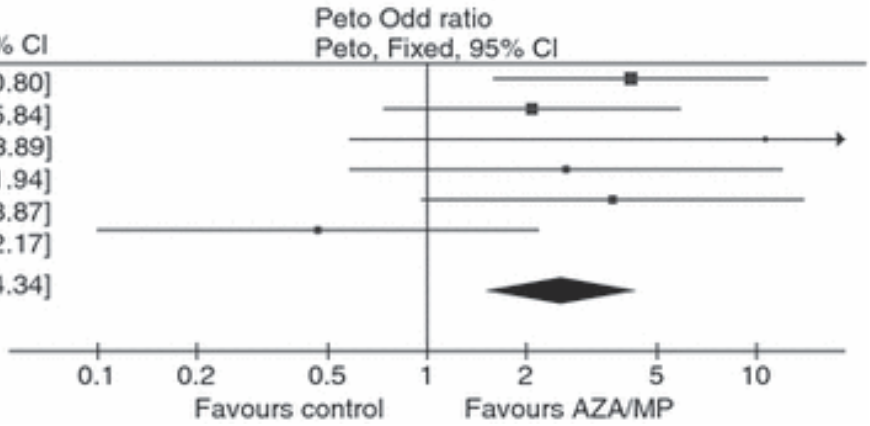
Gisbert JP, et al. *Aliment Pharmacol Ther*. 2009;30(2):126-137.

Efficacy of Thiopurines for Maintenance of Remission in UC

Study or subgroup	AZA/MP Events	AZA/MP Total	Control Events	Control Total	Weight	Peto Odd ratio Peto, Fixed, 95% CI
Ardizzone 2006	19	36	7	36	30.7%	4.16 [1.60, 10.80]
Jewell 1974	16	31	9	27	26.2%	2.08 [0.74, 5.84]
Mate 2000	7	11	0	2	3.3%	10.63 [0.58, 193.89]
Sood 2000	14	17	10	16	12.3%	2.64 [0.58, 11.94]
Sood 2002	13	17	8	18	15.7%	3.66 [0.96, 13.87]
Sood 2003	5	12	8	13	11.8%	0.47 [0.10, 2.17]
Total (95% CI)		124		112	100.0%	2.56 [1.51, 4.34]
Total events	74		42			

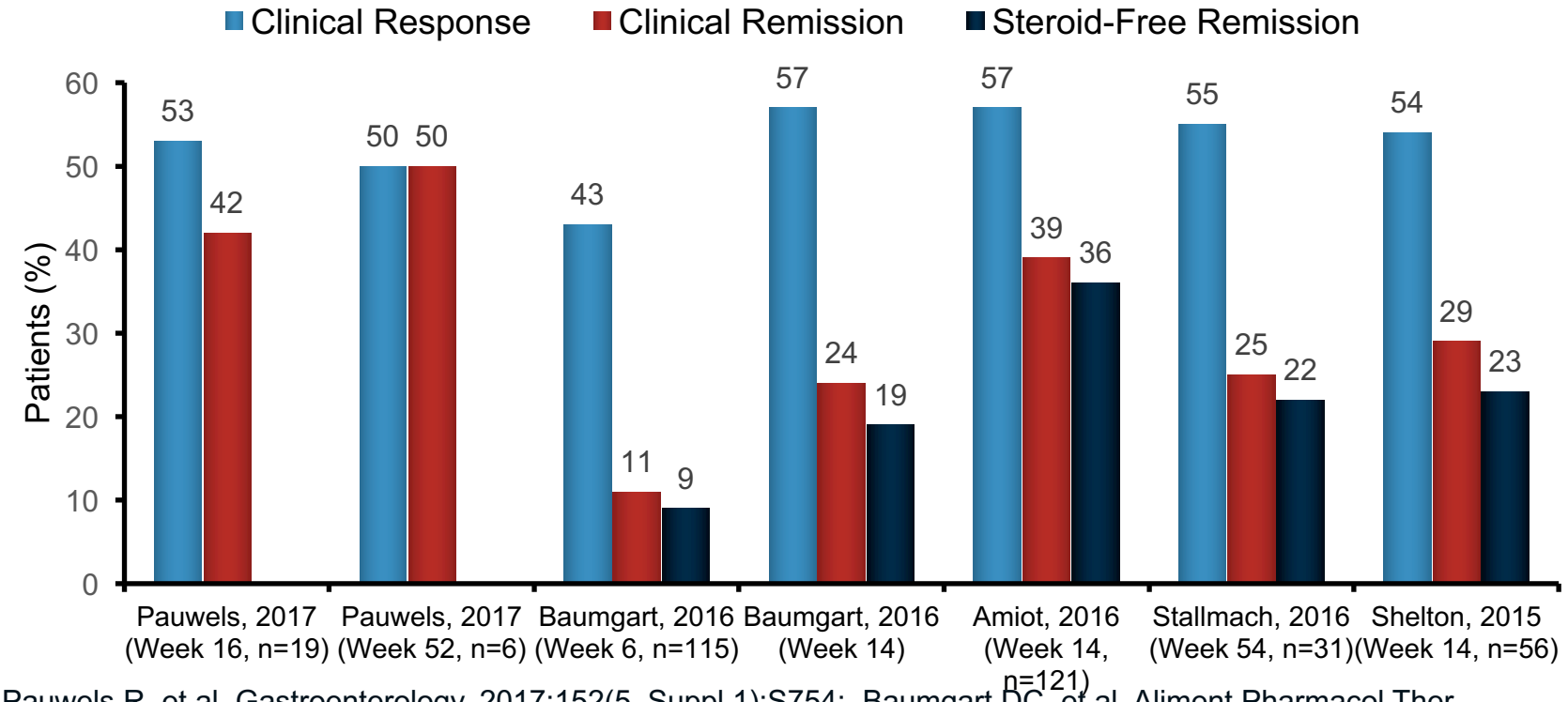
Heterogeneity: $\chi^2 = 7.06$, df = 5 ($P = 0.22$); $I^2 = 29\%$

Test for overall effect: $Z = 3.48$ ($P = 0.0005$)



Gisbert JP, et al. *Aliment Pharmacol Ther*. 2009;30(2):126-137.

Real-World Efficacy of Vedolizumab



Pauwels R, et al. Gastroenterology. 2017;152(5, Suppl 1):S754; Baumgart DC, et al. Aliment Pharmacol Ther. 2016;43(10):1090-1102; Amiot A, et al. Clin Gastroenterol Hepatol. 2016;14(11):1593-1601; Stallmach A, et al. Aliment Pharmacol Ther. 2016;44(11-12):1199-1212. Shelton E, et al. Inflamm Bowel Dis. 2015;21(12):2879-2885.

Effectiveness Outcomes in Patients with UC and Cumulative Vedolizumab Exposure for Up to 248 Weeks

Cumulative VDZ exposure (wks)	GEMINI OLE study wk	Combined VDZ, observed cases*			Combined VDZ, non-responder imputation†		
		N	Clinical response, n (%)	Clinical remission, n (%)	N	Clinical response, n (%)	Clinical remission, n (%)
52	0	154	146 (95)	135 (88)	154	146 (95)	135 (88)
80	28	145	134 (92)	127 (88)	154	134 (87)	127 (82)
104	52	136	124 (91)	120 (88)	154	124 (81)	120 (78)
128	76	127	119 (94)	117 (92)	154	119 (77)	117 (76)
152	100	118	114 (97)	110 (93)	154	114 (74)	110 (71)
200	148	108	104 (96)	100 (93)	154	104 (68)	100 (65)
248	196	63	62 (98)	57 (90)	154	62 (40)	57 (37)

*Number of patients in clinical response or remission (n) over number of observed cases (N) at study visit

†Patients without available data (for reasons including discontinuation and patients ongoing in the study who have not yet reached specified assessment time points) were included as non-responders

Clinical response was defined as a decrease in PMS of ≥2 points and ≥25% change from baseline, with either an accompanying decrease in rectal bleeding subscore of ≥1 point from baseline or an absolute rectal bleeding subscore of ≤1 point. Clinical remission was defined as a PMS of ≤2 with no individual subscore >1

OLE, open-label extension; PMS, partial Mayo Score; UC, ulcerative colitis; VDZ, vedolizumab; wk, week

Loftus EV, et al. *J Crohns Colitis*. 2017;11(suppl 1):S182-S183. doi:10.1093/ecco-jcc/jjx002.334