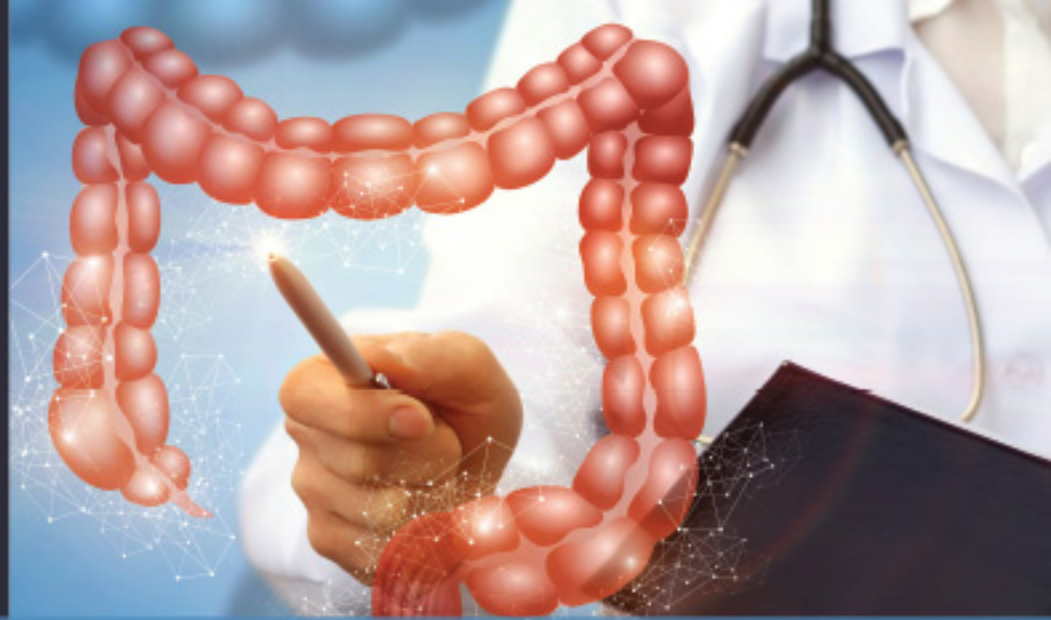
Stopping Ulcerative Colitis Progression in its Tract:



Combining the Latest Evidence and Engaging Teaching Tools to Improve Patient Outcomes

Provided by: CME Outfitters

This program is not affiliated with Digestive Disease Week®.

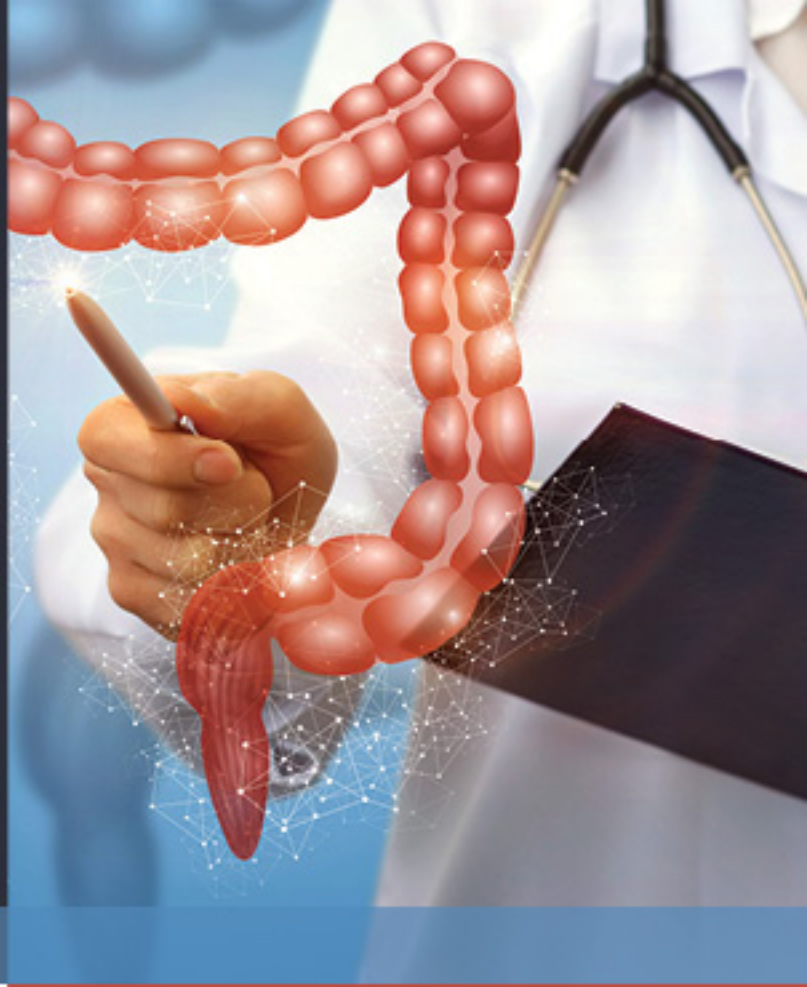
Supported by an educational grant from Takeda Pharmaceuticals U.S.A., Inc.

Learning Objectives

1. Examine the rationale for the use of early, effective treatment in altering the progressive course of ulcerative colitis (UC).
2. Utilize the AGA UC Care Pathway to guide personalized biologic therapy to halt disease progression in UC.
3. Incorporate disease activity monitoring strategies, including objective measures of disease improvement, to facilitate optimal management of moderate to severe UC.

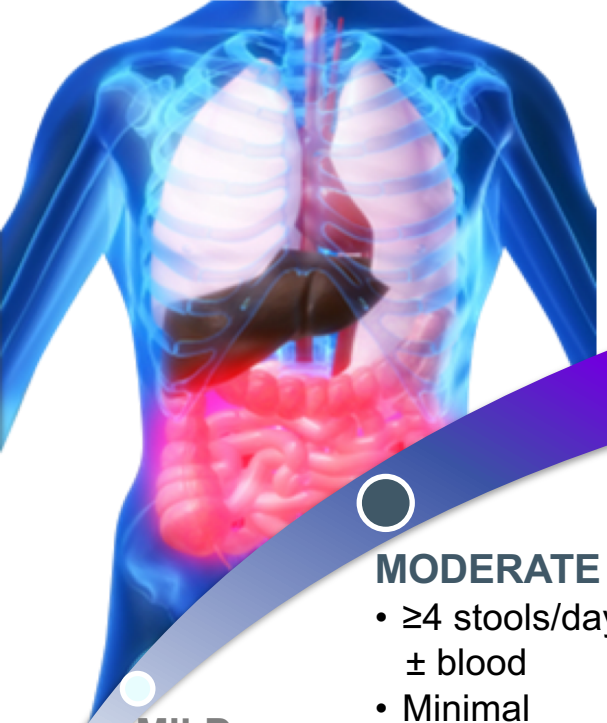
Learning Objective 1

Examine the rationale for the use of early, effective treatment in altering the progression course of ulcerative colitis (UC).



#stopUC

Classification of UC Severity



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

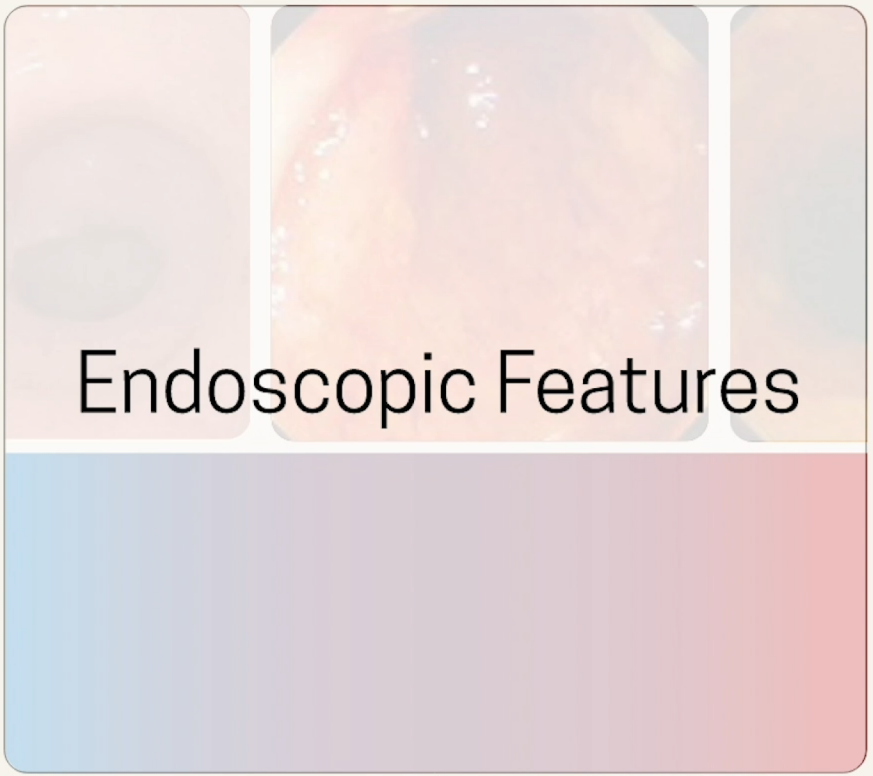
MODERATE
- ≥4 stools/day ± blood
- Minimal signs of toxicity

SEVERE
- >6 bloody stools/day
- Fever
- Tachycardia
- Anemia or ↑ ESR

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

Truelove SC, Witts LJ. *Br Med J.* 1955;2:1041.; Kornbluth A, Sachar DB. *Am J Gastroenterol*. 2010;105:501.

Disease Progression



AGA Clinical Pathway for Ulcerative Colitis: Characterizing Colectomy Risk

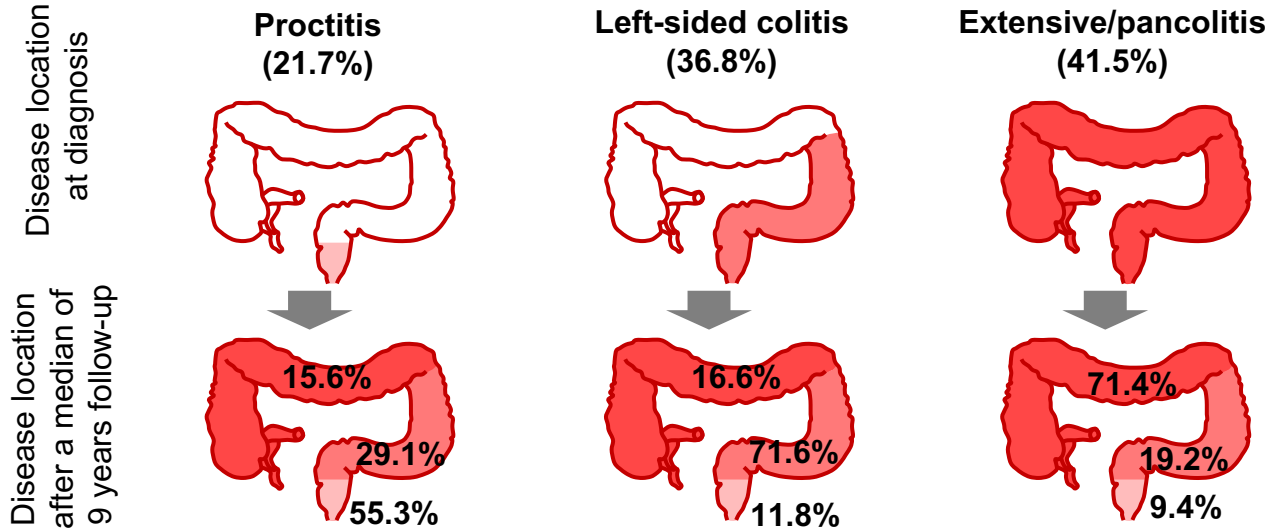
Low Risk		Mod-High Risk
> 40 years	Age of diagnosis	< 40 years
Limited	Anatomic involvement	Extensive
Elevated	CRP, ESR, FCP levels	High
No	Steroid required	Yes
Mild	Ulcers	Deep
No	*C. difficile* infection	Yes
No	History of hospitalization	Yes
No	CMV infection	Yes

Sandborn WJ. *Gastroenterology*. 2014;147:702-705.

Ulcerative Colitis Is a Progressive Disease: How Do We Measure Progression — Proximal Extension?

Swiss IBD cohort study: Evolution of disease extent over a median disease duration of 9 years, from 2006 (N = 918)

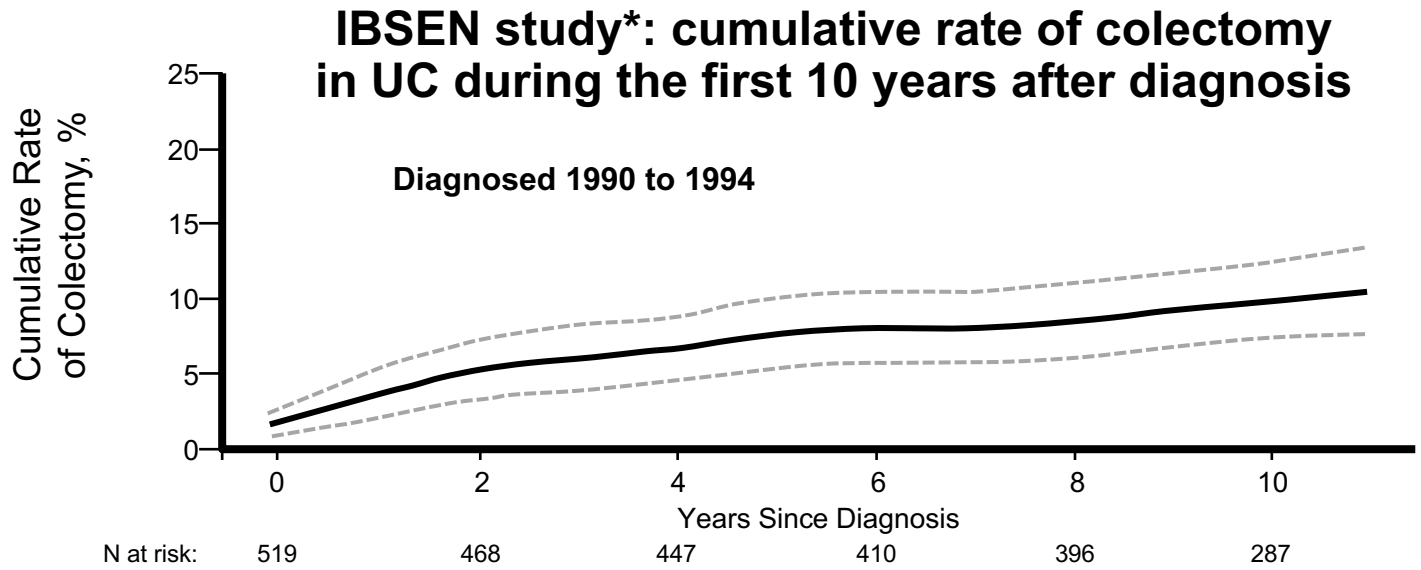
Disease duration at study inclusion: Median 6 years, IQR 2-13 years, Range 0-46 years



~15% of UC patients experienced proximal disease extension over 9 years

Safroneeva E, et al. *Aliment Pharmacol Ther*. 2015;42:540-548.

Ulcerative Colitis Is a Progressive Disease: How Do We Measure Progression — Colectomy?



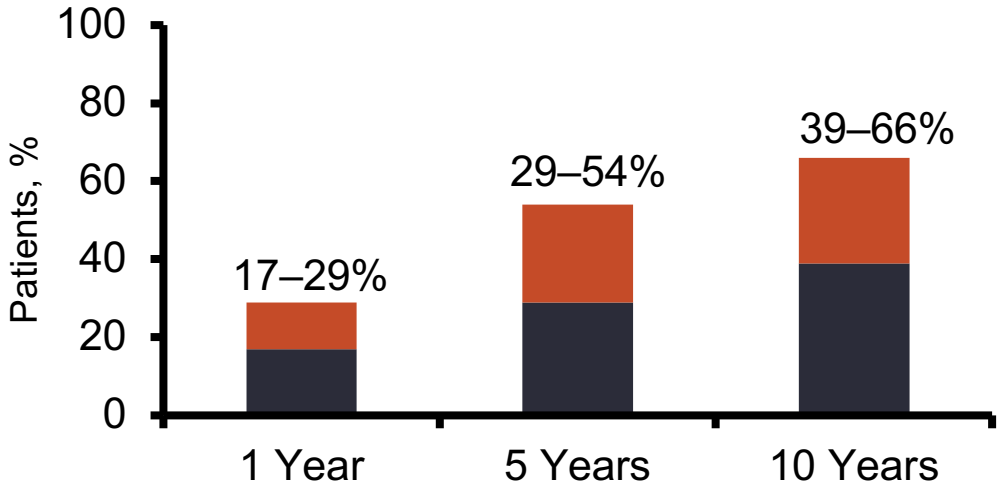
~10% of patients with UC required colectomy over 10 years

*From 1990 to 1994, patients with inflammatory bowel disease were enrolled in South-Eastern Norway and systematically followed-up for up to 10 years after diagnosis.

Solberg IC, et al. *Scand J Gastroenterol.* 2009;44:431-440.

Ulcerative Colitis Is a Progressive Disease: How Do We Measure Progression — Hospitalization?

Cumulative probabilities of hospitalization in patients with UC

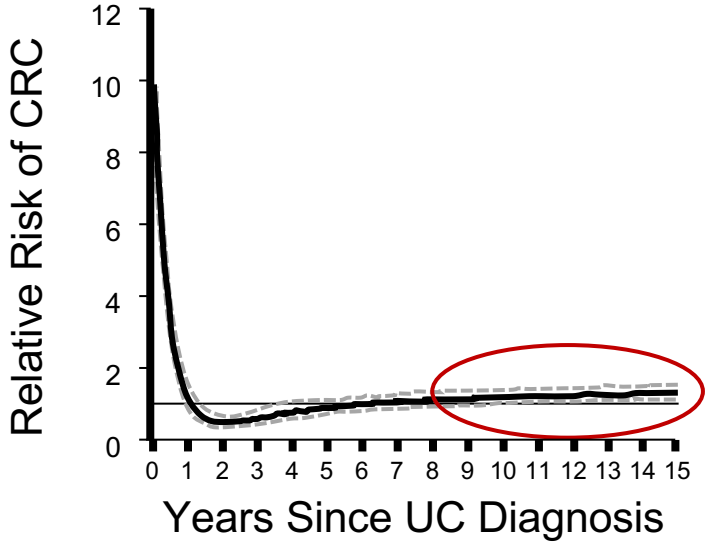


~50% of patients with UC required hospitalization at some point during disease course

Fumery M, et al. *Clin Gastroenterol Hepatol.* 2017;15:665-674.

Ulcerative Colitis Is a Progressive Disease: How Do We Measure Progression — Colorectal Cancer?

Risk of colorectal cancer in a nationwide cohort of Danish patients with UC > 30 yrs (N = 32,911)

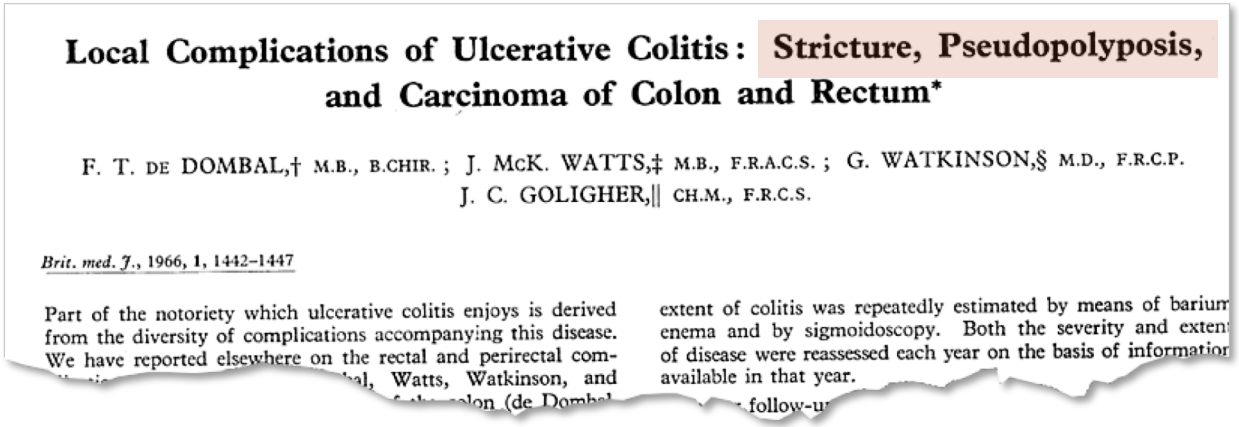


Relative risk adjusted for sex, age, calendar time.
Dotted lines indicated 95% confidence intervals.

Subgroups of patients with UC were at increased risk for colorectal cancer

Jess T, et al. *Gastroenterology*. 2012;143:375-381.

Ulcerative Colitis Is a Progressive Disease: How Do We Measure Progression — Bowel Damage?



Local Complications of Ulcerative Colitis: Stricture, Pseudopolyposis, and Carcinoma of Colon and Rectum*

F. T. DE DOMBAL,† M.B., B.CHIR.; J. McK. WATTS,‡ M.B., F.R.A.C.S.; G. WATKINSON,§ M.D., F.R.C.P.
J. C. GOLIGHER,‖ CH.M., F.R.C.S.

Brit. med. J., 1966, **1**, 1442–1447

Part of the notoriety which ulcerative colitis enjoys is derived from the diversity of complications accompanying this disease. We have reported elsewhere on the rectal and perirectal com-

…al, Watts, Watkinson, and …olon (de Dombal …

extent of colitis was repeatedly estimated by means of barium enema and by sigmoidoscopy. Both the severity and extent of disease were reassessed each year on the basis of information available in that year.

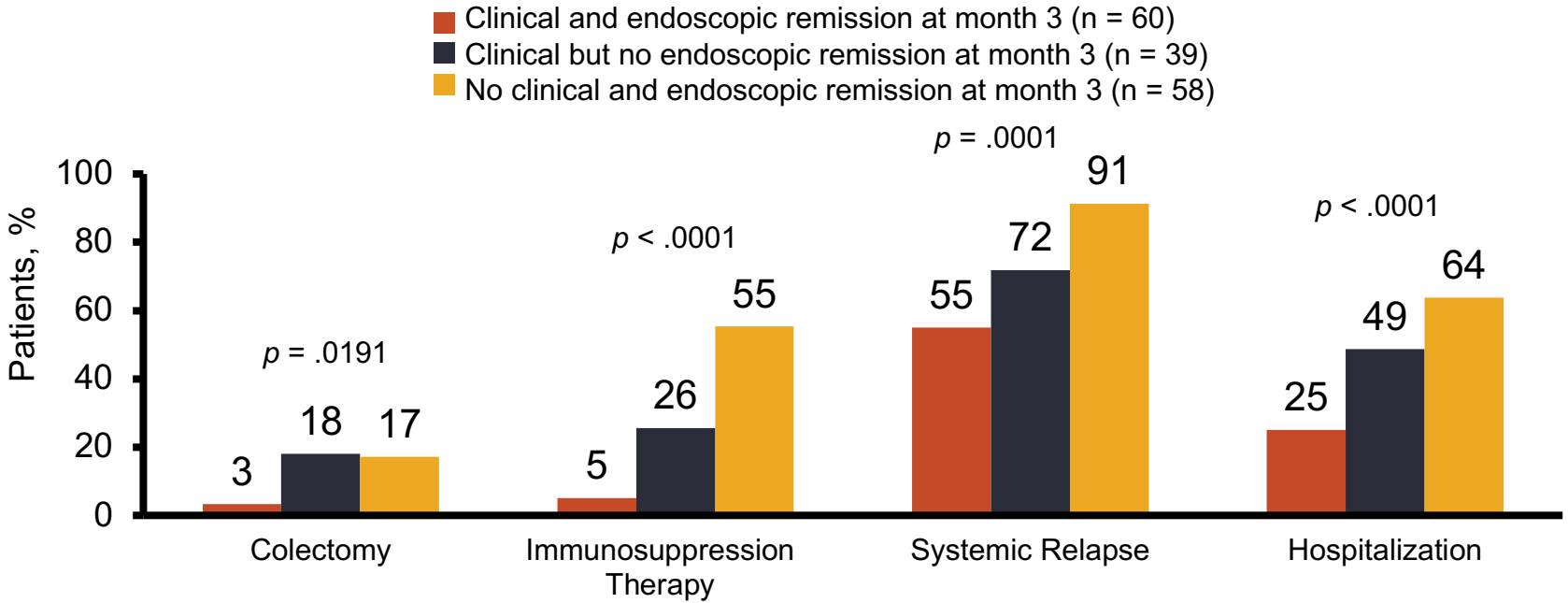
… follow-u…

Other damage		
Dysmotility	Anorectal dysfunction	Impaired permeability

Torres J, et al. *Inflamm Bowel Dis*. 2012;18:1356-1363.

Early, Lasting Clinical and Endoscopic Remission Predicts Better Long-term Outcomes in UC

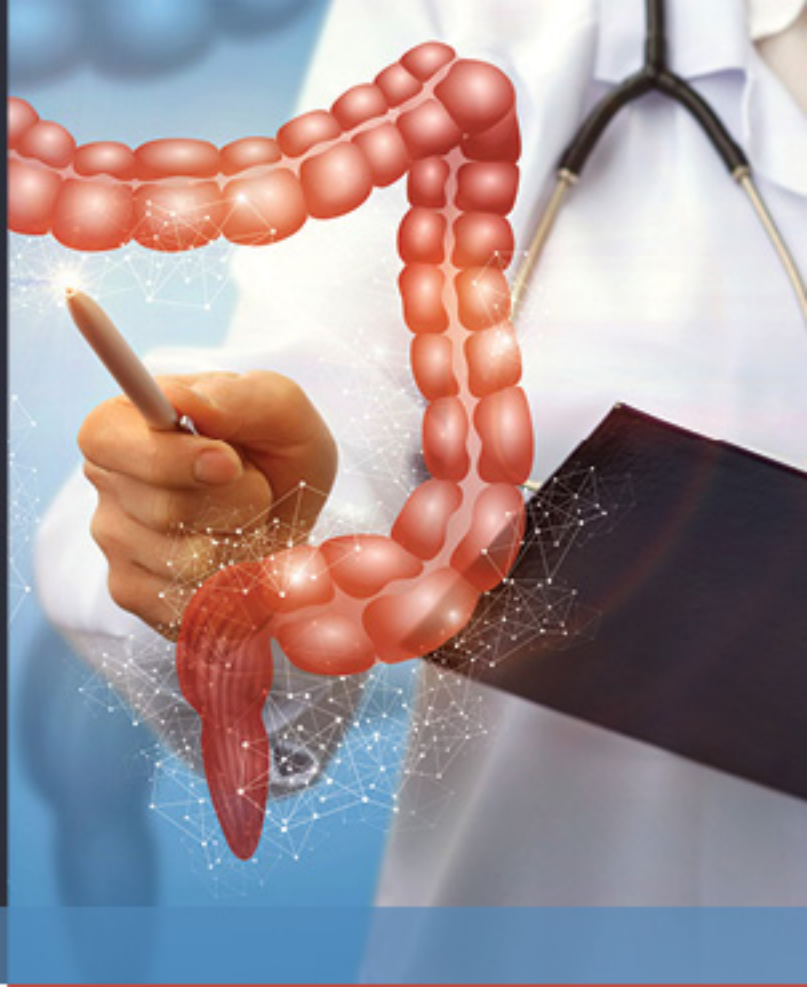
Outcome at 5-year follow-up according to early response to steroids



N = 157 patients with moderate-to-severe newly diagnosed UC; 5-year follow-up after first course of steroids; classified according to remission at 3 months; mean follow-up 51 (4−60) months.

Ardizzone S, et al. *Clin Gastroenterol Hepatol*. 2011;9:483-489.e3.

Symptoms Don’t Often Correlate with Endoscopic Findings



#stopUC

DTR

BRITISH MEDICAL JOURNAL

LONDON SATURDAY JUNE 9 1956

BIOPSY STUDIES IN ULCERATIVE COLITIS

BY

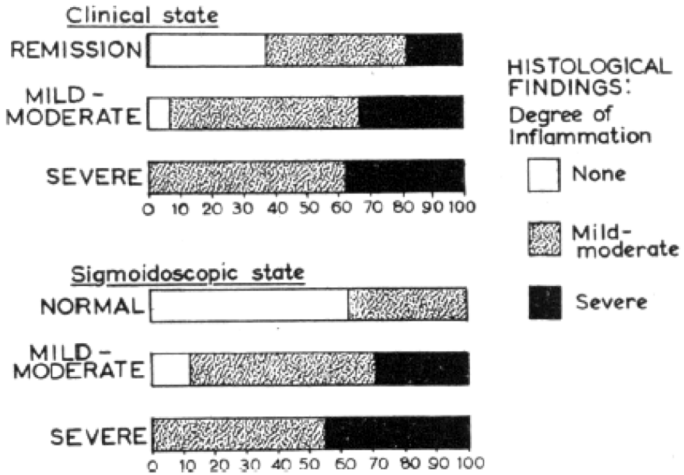
S. C. TRUELOVE, M.D., M.R.C.P., and W. C. D. RICHARDS, M.B., B.S.

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.

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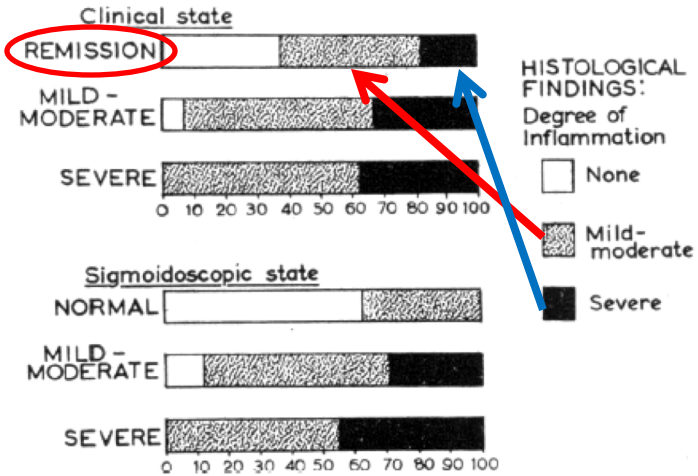

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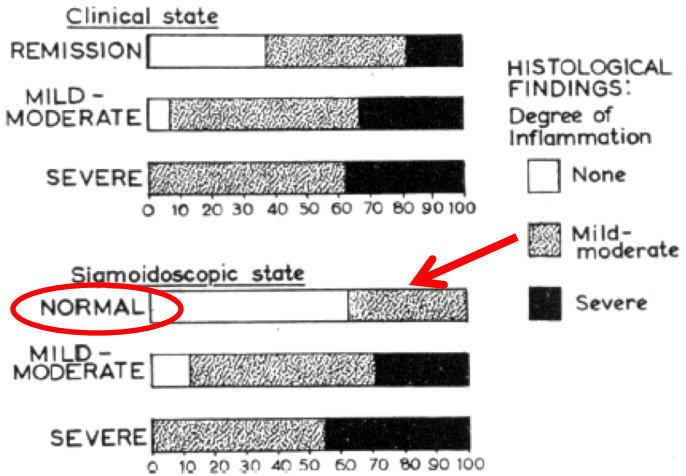
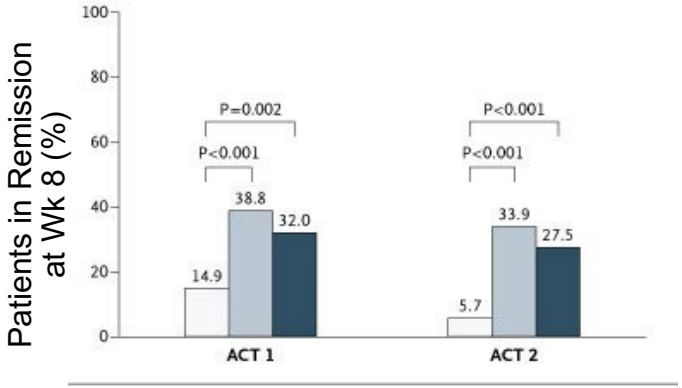
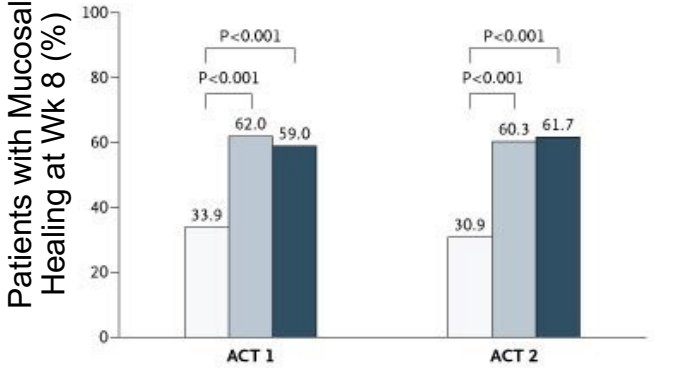


Graph showing relationships between clinical state, sigmoidoscopic appearance, and histological appearance in ulcerative colitis.

Symptoms are Not a Reliable Indicator of Mucosal Healing in UC

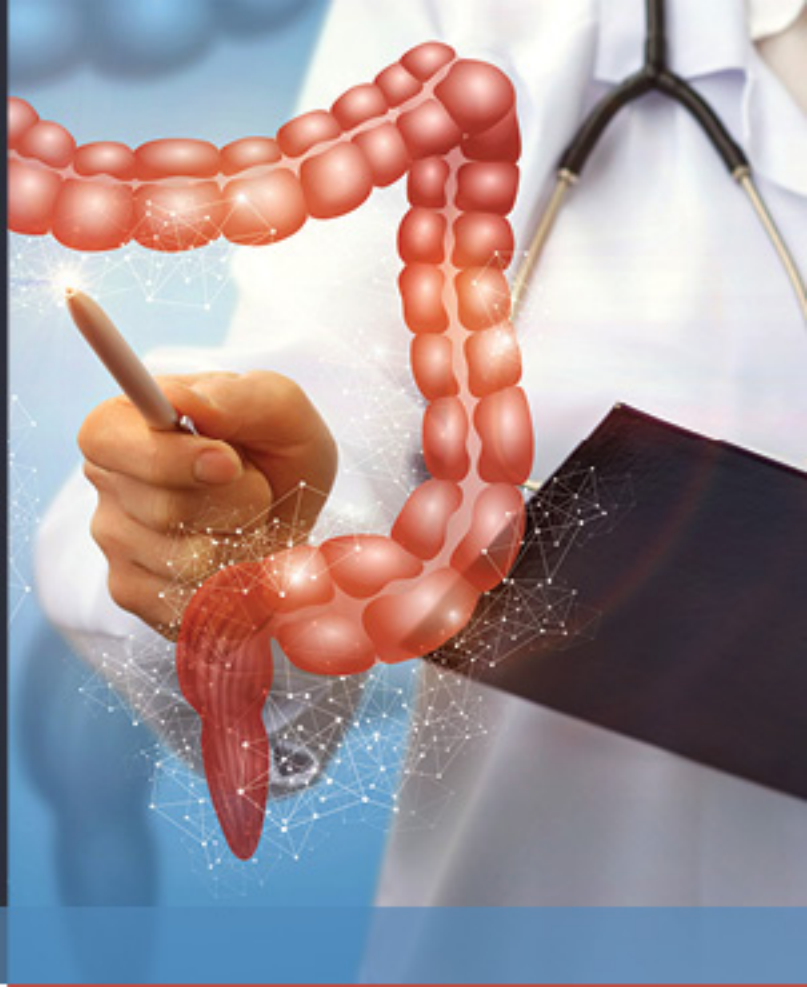
- Meta-analysis of 13 studies found pooled prevalence of IBS at 36% [95% CI: 30.0-48.0%] in UC in remission[1]
- In ACT 1 and 2, at week 8 after infliximab induction, nearly twice as many patients had mucosal healing as had clinical remission[2]





[1]Halpin SJ, Ford AC. *Am J Gastroenterol.* 2012;107:1474-82.
[2]Rutgeerts P, et al. *N Engl J Med.* 2005;353:2462-76.

What Do We Know about Measuring and Understanding Outcomes in Mucosal Healing?



#stopUC

The Roadmap to Incorporation of Mucosal Healing as an Endpoint in IBD

- Define mucosal healing (MH)
- Demonstrate that MH is associated with better short-term and longer-term outcomes
- Understand which therapies can be achieve MH
- Develop strategies to achieve MH after initiation of therapy
- Perform prospective studies to show that MH is a viable, safe, and cost effective target of treatment

How is Mucosal Healing Defined in UC?

- Return to normal vascular pattern[1]
- Absence of friability or ulcerations[1]
- Normal or near normal mucosal appearance, originally defined as with “slight hyperemia or slight granularity”[2]
- Histology
  - Geboes Score
  - Nancy Histology Index
  - Robarts Histology Index

1. Pineton de Chambrun G, et al. *Nat Rev Gastroenterol Hepatol*. 2010;7(1):15-29.; 2. Truelove SC, et al. *Br Med J*. 1955;2:1041-1048.

Endoscopic Indices of Severity in Ulcerative Colitis

Descriptor (Score most severe lesions)	Likert scale anchor points
Vascular pattern	Normal (0)
Bleeding	Patchy obliteration (1)
	Obliterated (2)
	None (0)
	Mucosal (1)
Erosions and ulcers	None (0)
	Erosions (1)
	Superficial ulcer (2)
	Deep ulcer (3)

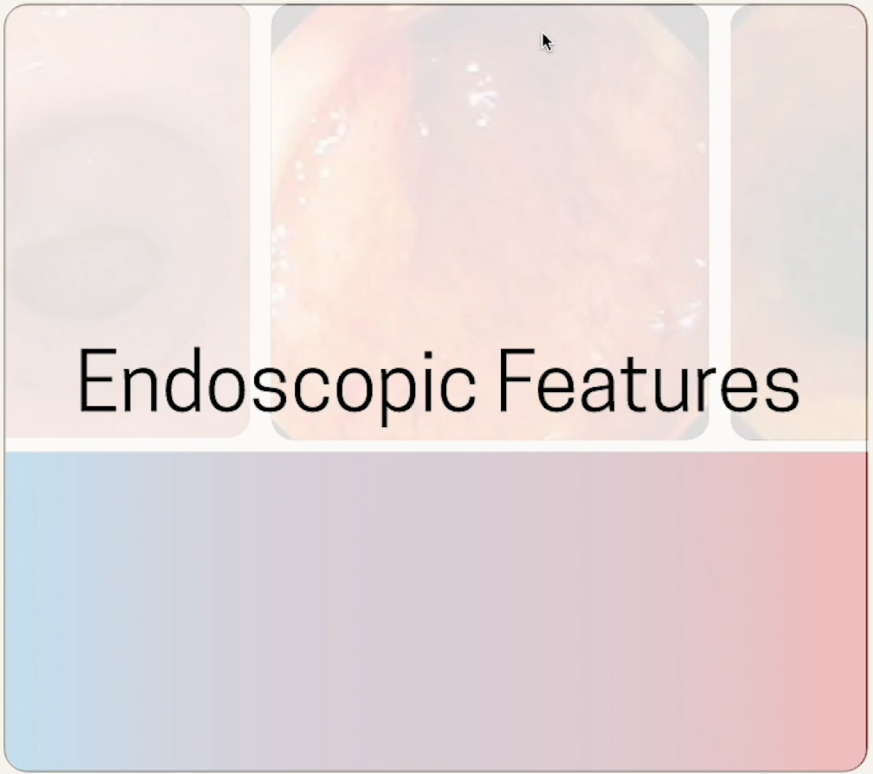
Travis SPL, et al. *Gastroenterology*. 2013; 145:987-95.

Role of Fecal Calprotectin (FCP) in IBD

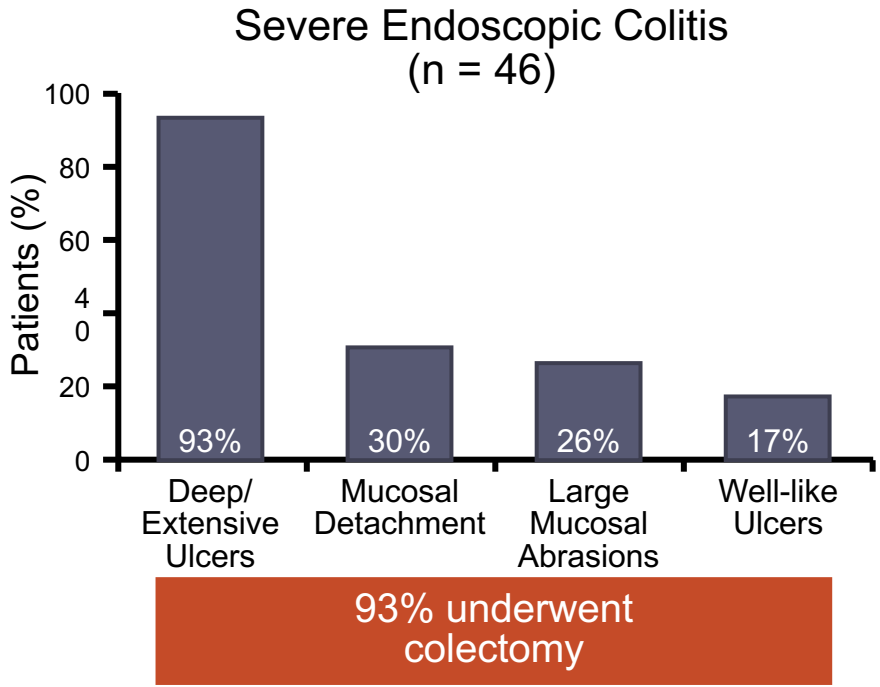
- Diagnostic
- Assessing disease activity and response to treatment
- Prognostic
- Research

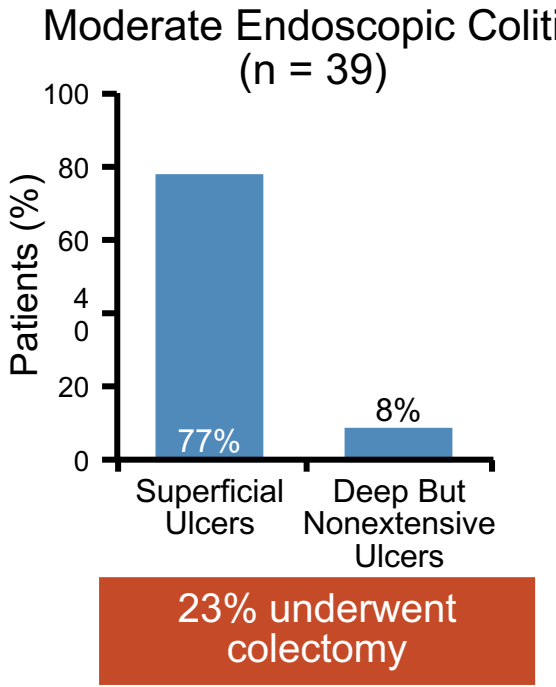
Walsham NE, et al. *Clin Exp Gastroentrol.* 2016;9:21-29.

Disease Progression



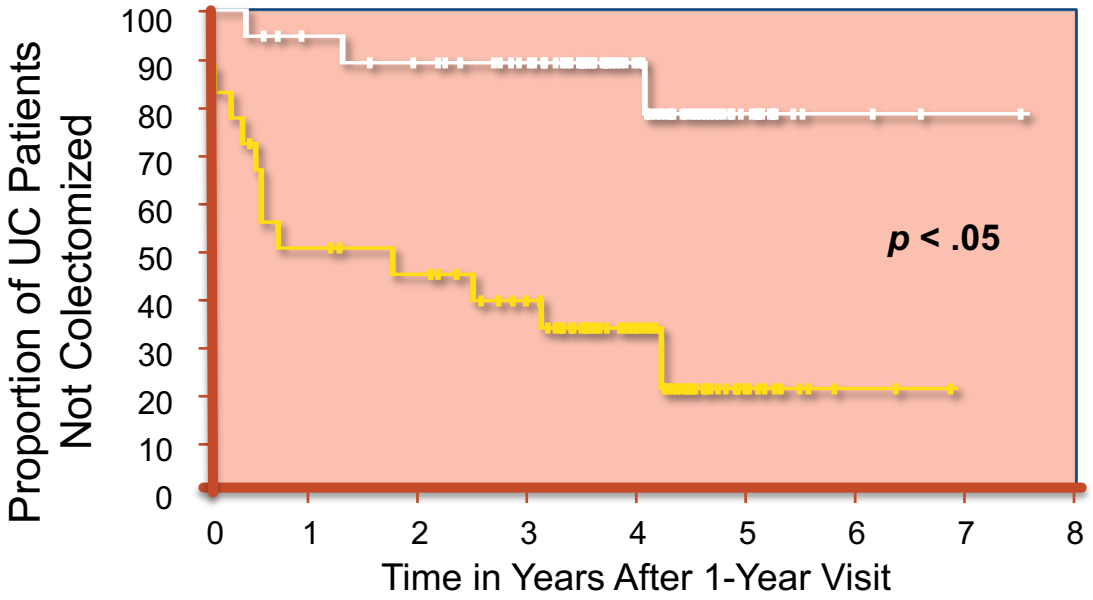
Severity of Endoscopic Disease in UC Correlates With Colectomy





Carbonnel F, et al. *Dig Dis Sci.* 1994;39(7):1550-1557.

Mucosal Healing at Year 1 Associated with Risk of Subsequent Colectomy in UC



Patients without endoscopic activity at 1-year visit

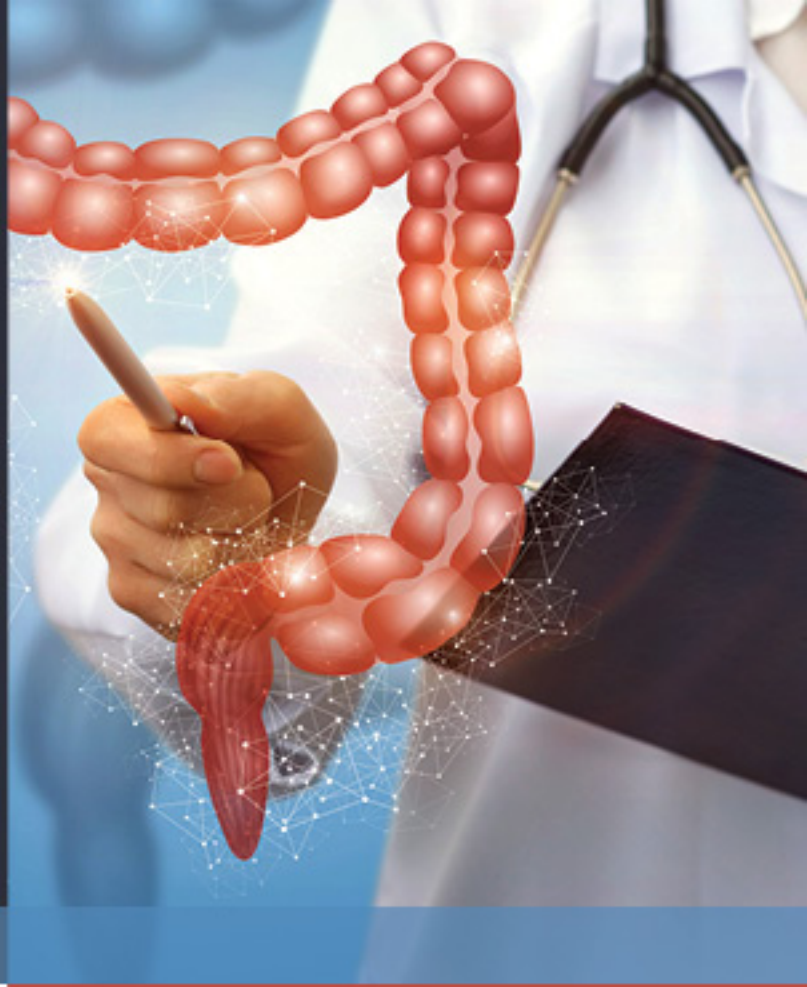
Patients with endoscopic activity at 1-year visit

Patients with compromised mucosa 1 year after diagnosis showed a trend toward more surgeries.

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

Learning Objective 2

Utilize the AGA UC Care Pathway to guide personalized biologic therapy to halt disease progression in UC.



Movement to Objective Measures of Control and Chronic Care Model of IBD

Goal	Clinical Parameters	Outcomes
Response	Improved symptoms	Improved QoL
Remission	No symptoms Normal labs	Decreased hospitalization
Deep remission	Normal endoscopy Mucosal healing	Appropriate timing of surgery Minimal or no disability

SUSTAINED DISEASE CONTROL

Updated Goals of Management for IBD in 2018

- Clarify disease **type** and **severity**
- Induce remission rapidly – defined by both **patient-reported outcomes** and objective markers
  - Ulcerative colitis: absence of rectal bleeding and diarrhea/altered bowel habits
- Maintain steroid-free remission
- Change the natural history of IBD
  - Avoid hospitalization and surgery
  - Avoid drug-related and disease-related complications
  - Reduce costs of care

Rubin DT, et al. *Am J Gastroenterol Suppl*. 2016;3:4-7.
Peyrin-Biroulet L, et al. *Am J Gastroenterol*. 2015;110(9):1324-38.

Why Don't We Achieve Preferred Outcomes in Everyone?

- We are too late
- Therapies don't work
- Therapies are not optimized
- We are treating the wrong problem
- Symptom improvement is NOT "enough"

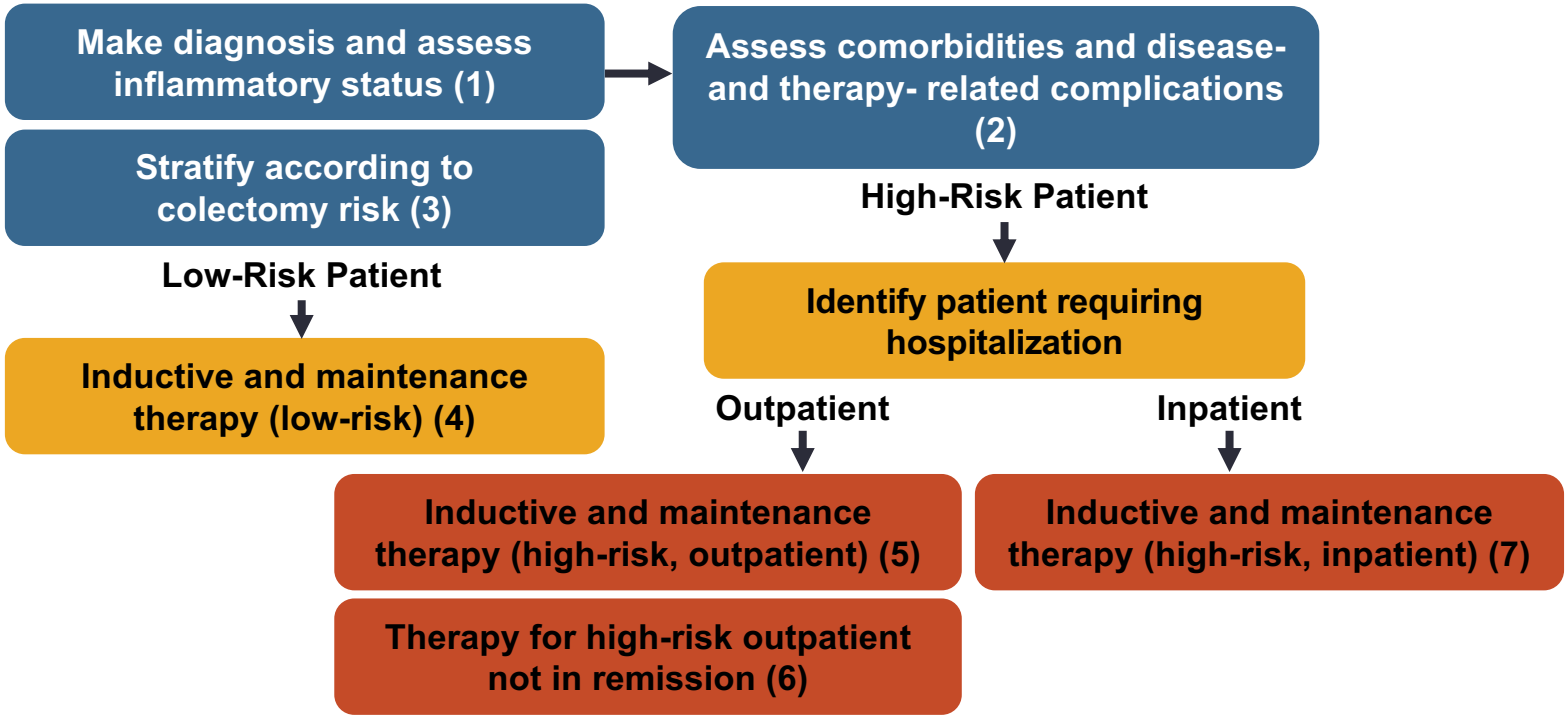
Errors of commission vs Errors of omission

AGA Ulcerative Colitis (UC) Care Pathway

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

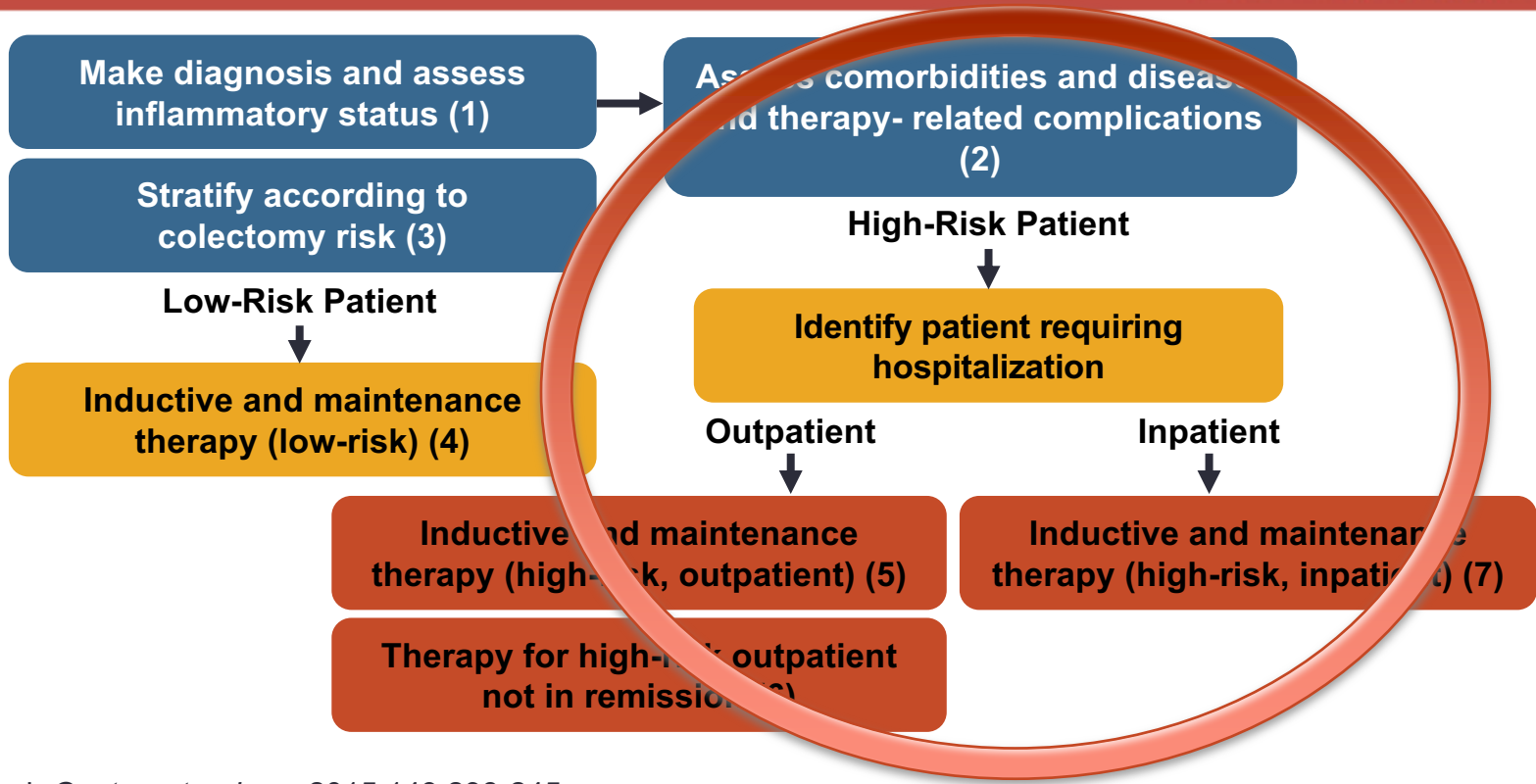
Dassopoulos T, et al. *Gastroenterology*. 2015;149(1):238-245.

Ulcerative Colitis Care Pathway



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

Ulcerative Colitis Care Pathway



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

When to Introduce Biologics in Patients with UC

- Steroid refractory UC
- Steroid dependent UC
- Immunomodulator refractory UC patient
- Immunomodulator intolerant UC patient
- Clinical predictors of a poor outcome at diagnosis?

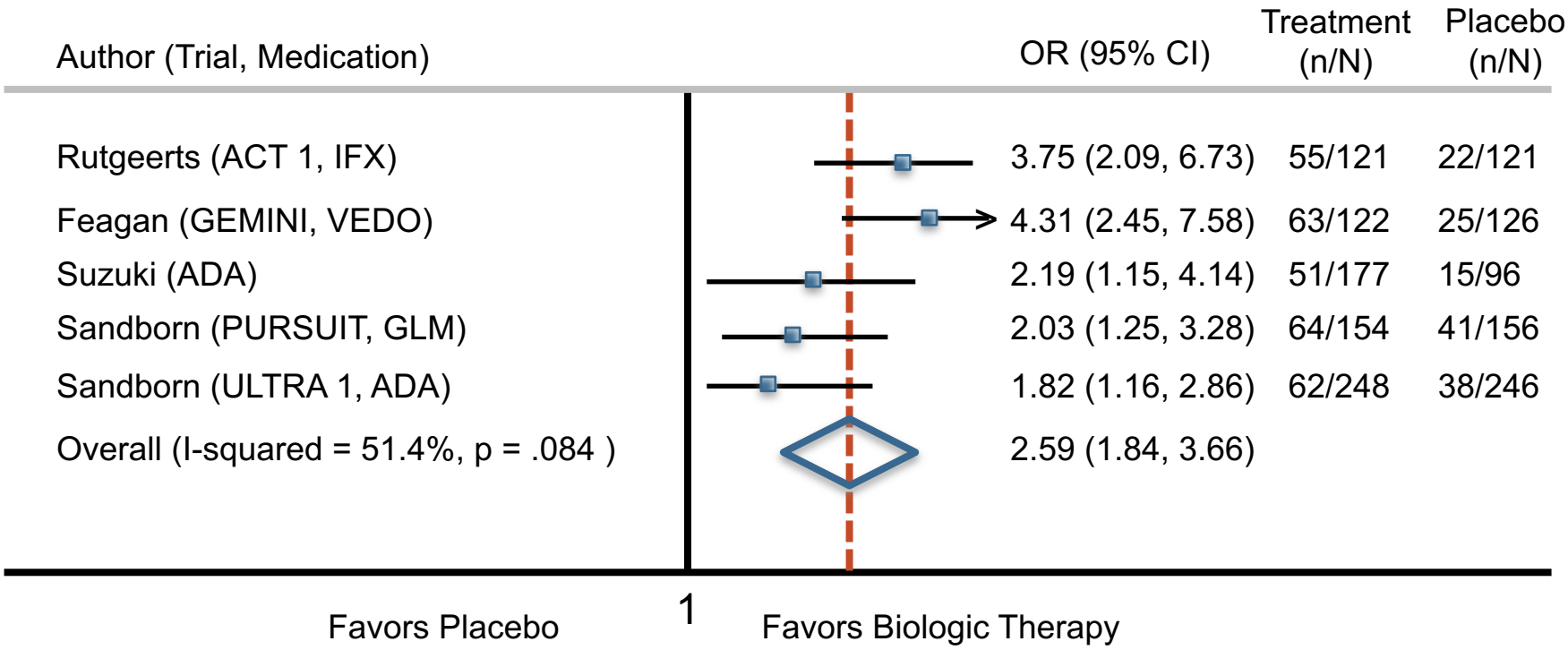
Approved Therapies for Moderate to Severe Ulcerative Colitis

	Mechanism	Induction of Clinical Response and Remission	Adverse Events*
Infliximab	Anti-TNF	ACT[1]	Serious infections, opportunistic infections. Need to test for TB and HBV prior to initiation of therapy.
Adalimumab	Anti-TNF	ULTRA[2]	
Golimumab	Anti-TNF	PURSUIT-SC[3]	
Vedolizumab	Selective α4β7 integrin antagonist	GEMINI[4]	Nasopharyngitis
Tofacitinib	JAK-inhibitor	OCTAVE Induction[5]	Monitor lipids. Increased risk of Herpes zoster.

* = *See prescribing information for full listing of warnings, precautions and adverse events*

[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. [5]Sandborn WJ et al. *N Engl J Med*. 2017;376:1723-36.

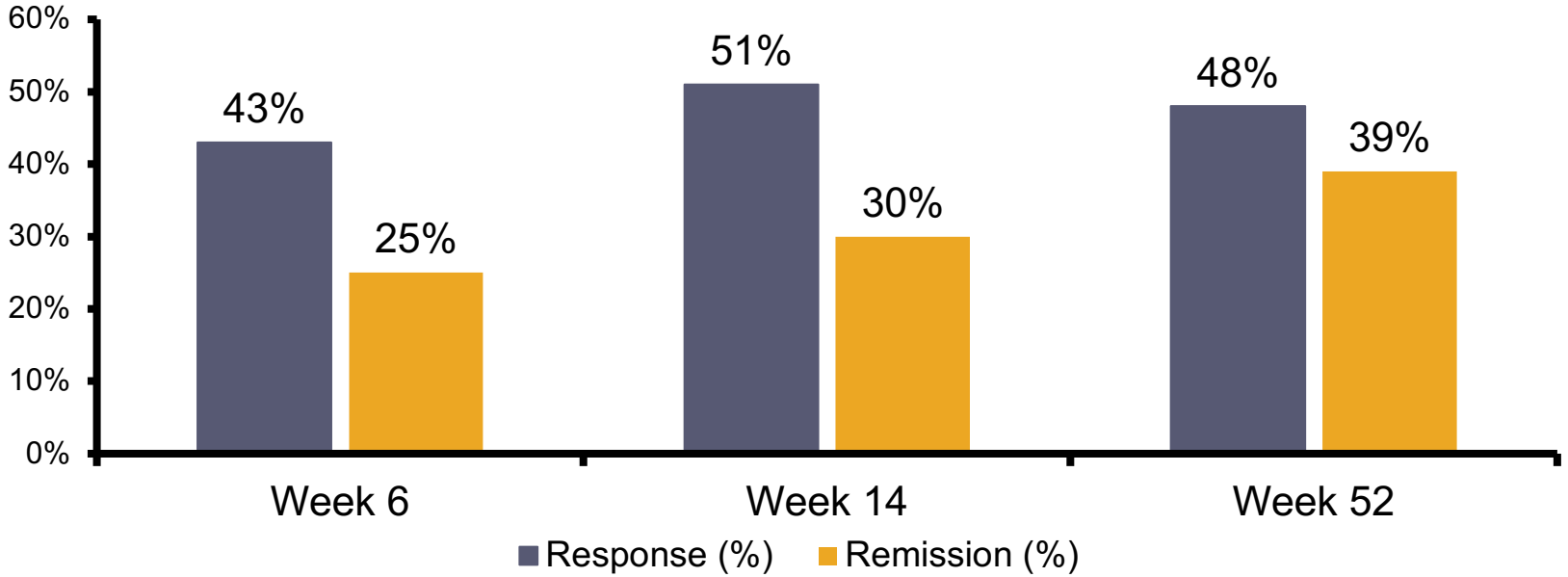
Effectiveness of Biologics in Attaining Mucosal Healing in UC: Maintenance Trials



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

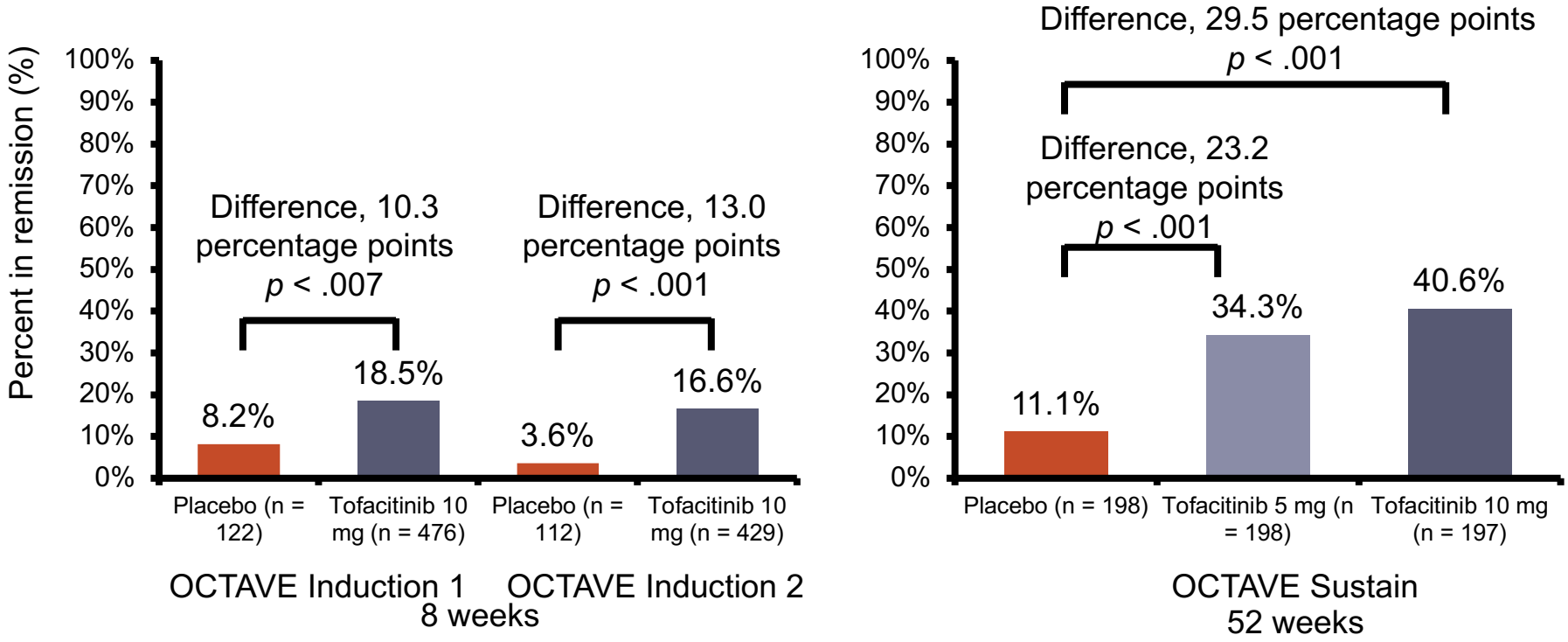
Real World Effectiveness of Vedolizumab in UC

- Pooled analysis, 9 studies, 571 UC patients
- Adverse effects were minor and occurred in 30.6% of the patients



Engel T, et al. *J Crohn's Colitis*, 2018. 24: 245-257.

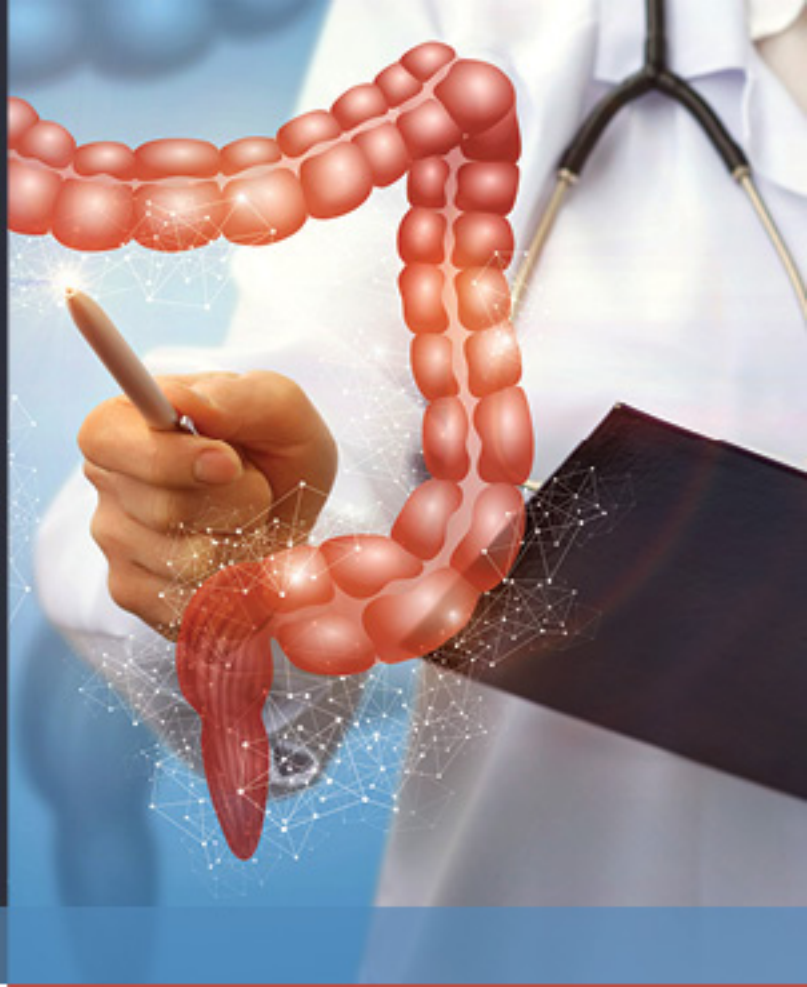
Tofacitinib: Remission in Ulcerative Colitis



Sandborn WJ et al. *N Engl J Med*. 2017;376:1723-36.

Learning Objective 3

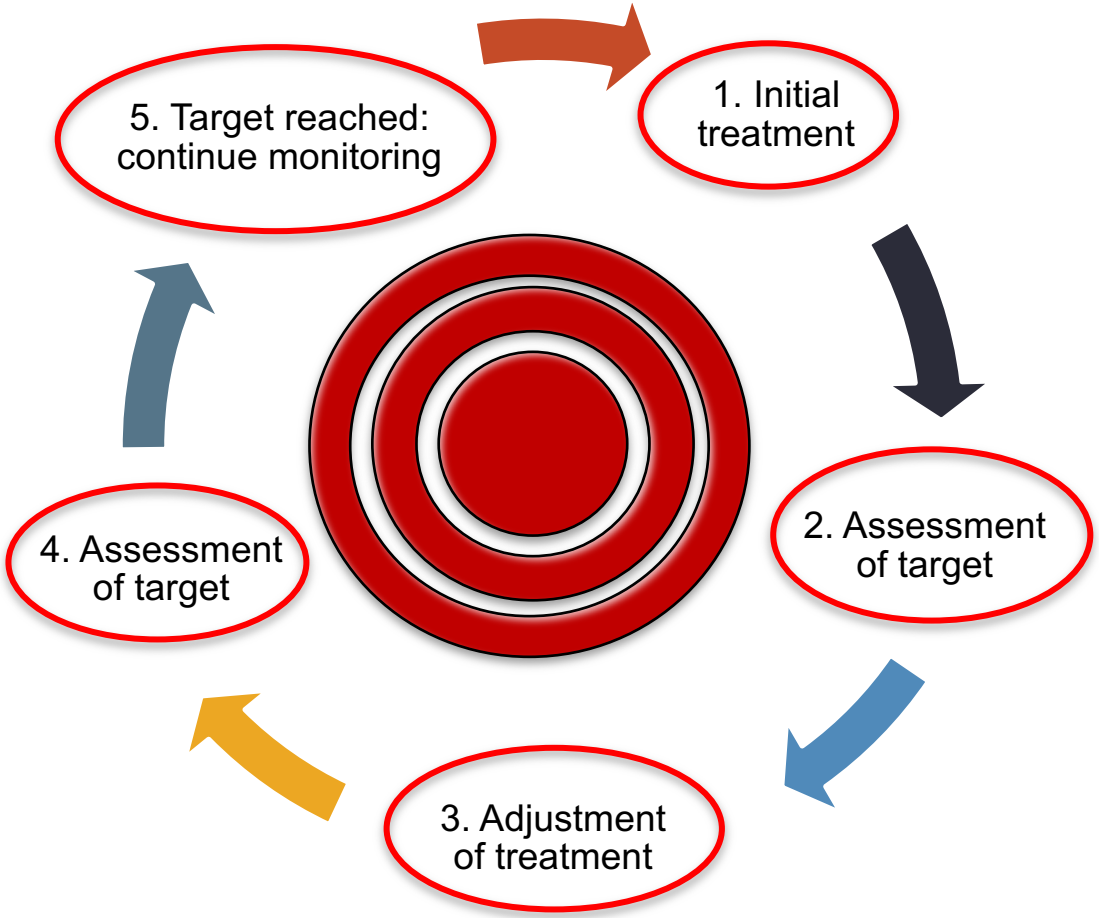
Incorporate disease activity monitoring strategies, including objective measures of disease improvement, to facilitate optimal management of UC.



How to Choose Therapy in UC?

- Severity/prognosis
- Effectiveness
- Safety
- Convenience
- Insurance/coverage

Treating to Achieve a Target Goal



So What Should the Targets Be?

Selecting **T**herapeutic Ta**R**gets in **I**nflammatory Bowel **D**isease **E**ndpoints

- Methods: 28 IBD specialists developed recommendations based on a systematic literature review and expert opinion
- Results: 12 recommendations for UC and CD.
- UC Target:
  - PRO: Resolution of rectal bleeding and diarrhea/altered bowel habit and
  - Endoscopic remission: Mayo endoscopic subscore of 0-1. Histological remission is an adjunctive goal.
- Biomarker remission (normal CRP and calprotectin) was considered an adjunctive target.

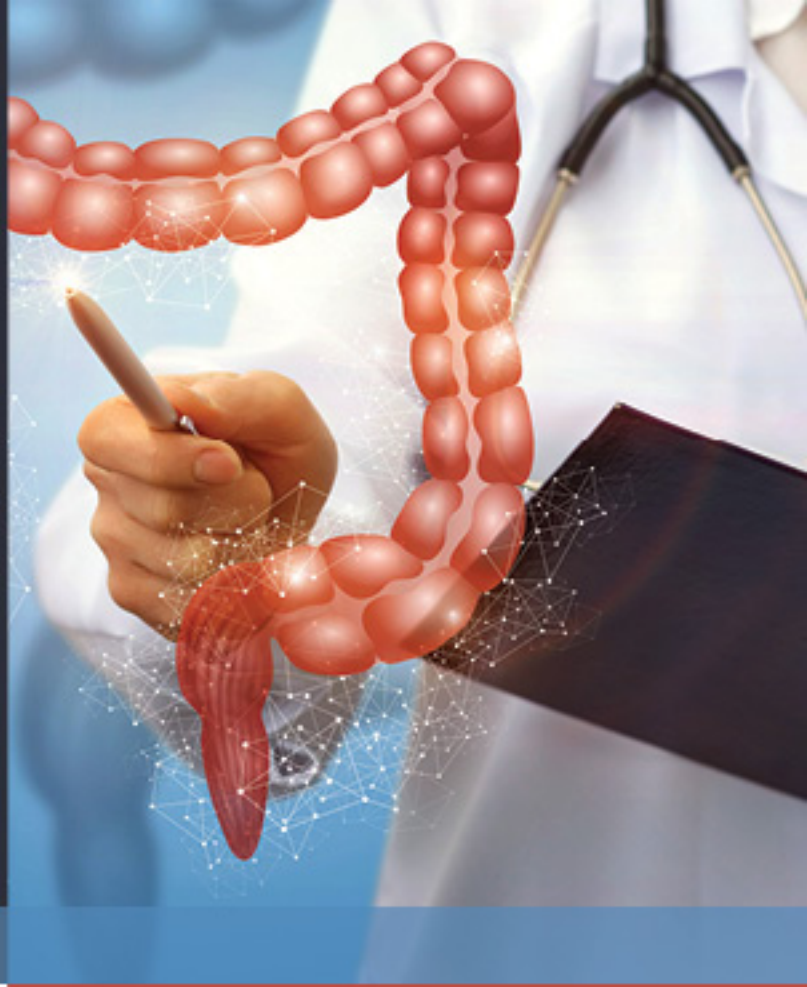
Peyrin-Biroulet, et al. *Am J Gastroenterol*. 2015; 110:1324–38.

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

1. Integrate the assessment of prognosis in your active UC patients at the time of diagnosis or relapse.
2. Identify specific targets for treatment to improve outcomes in your high-risk UC patients.
3. Use the data on efficacy and safety in decision-making for UC patient treatments.
4. Assess number of UC patients who achieve steroid-free deep remission over time.
5. Adjust therapy to achieve composite endpoints of symptomatic and objective disease control.

Questions & Answers



Downloadable Resources

Presentation slides, the course guide booklet, and the credit request/evaluation form will be available for download at:

www.CMEOutfitters.com/stopUCResources

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In order to receive credit, please complete the evaluation/credit request form found on your table and turn them in to the CME Outfitters staff on your way out of the ballroom.

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Claim ABIM MOC Credit

3 Things to Do

1. Actively participate in the meeting by **responding to ARS** and/or **asking the faculty questions**

   (It's ok if you miss answering a question or get them wrong, you can still claim MOC)

2. Complete the evaluation form found on your tables

   (For live stream participants, follow the credit claim link)

3. Be sure to fill in your **ABIM ID number** and **DOB** (MM/DD) on the evaluation, so we can submit your credit to ABIM.

ABIM CME MOC ACCREDITED

Quality Payment Program (QPP)

How to Claim this Activity as a QPP Improvement Activity

- **Actively participate** by responding to ARS and/or asking the faculty questions
- **Complete the 2 forms** found on your table:
  - Evaluation form found on your table
  - The Quality Payment Program Improvement Activity form
- Over the next 90 days, **actively work to incorporate improvements** in your clinical practice from this presentation
- **Complete the follow-up survey** from CME Outfitters in approximately 3 months

CME Outfitters will send you confirmation of your participation to submit to CMS attesting to your completion of a QPP Improvement Activity.

Visit the New Gastroenterology Digital Hub

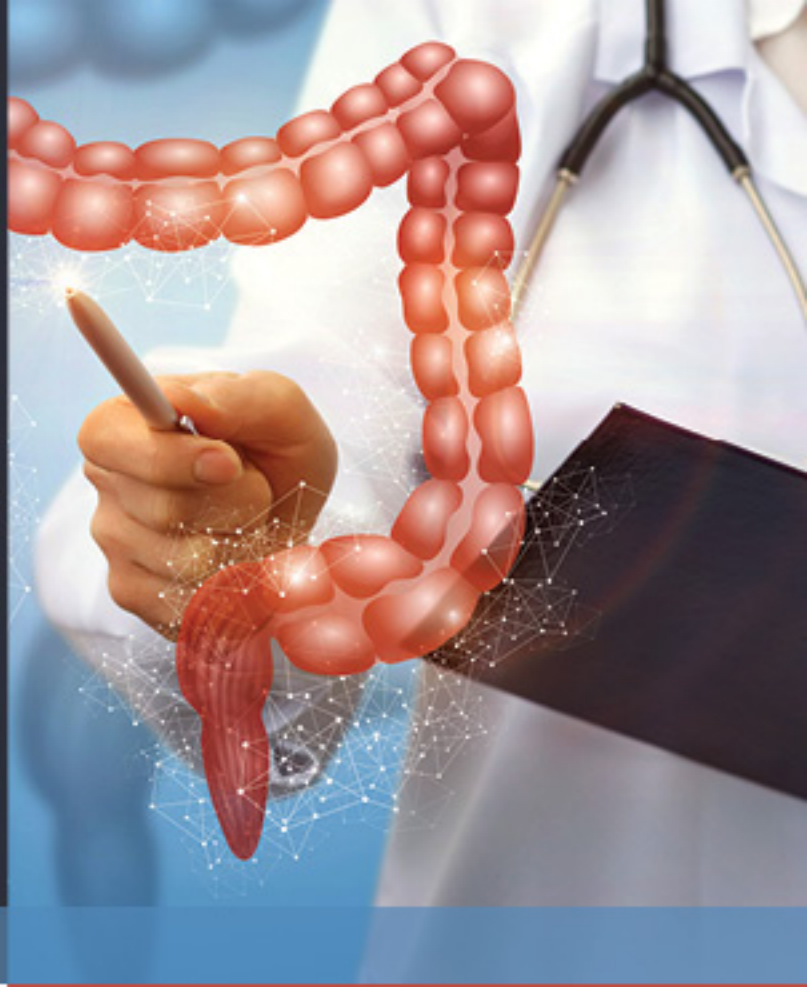
Find free CE activities & resources necessary to optimize your approach to clinical care, as well as prior authorization (PA) activities & resources that will help the entire care team immediately improve the PA process to ensure consistent approvals that minimize administrative time & streamlines communications with payers.

Visit the Hub Today!

www.cmeoutfitters.com/gastrohub

Thank You!

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



#stopUC