#UC2019

MUCOSAL HEALING AND STEROID-FREE REMISSION IN ULCERATIVE COLITIS:

What Is the Role of Current and Emerging Treatments?

MONDAY, OCTOBER 28, 2019

6:00 AM to 7:30 AM

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#UC2019

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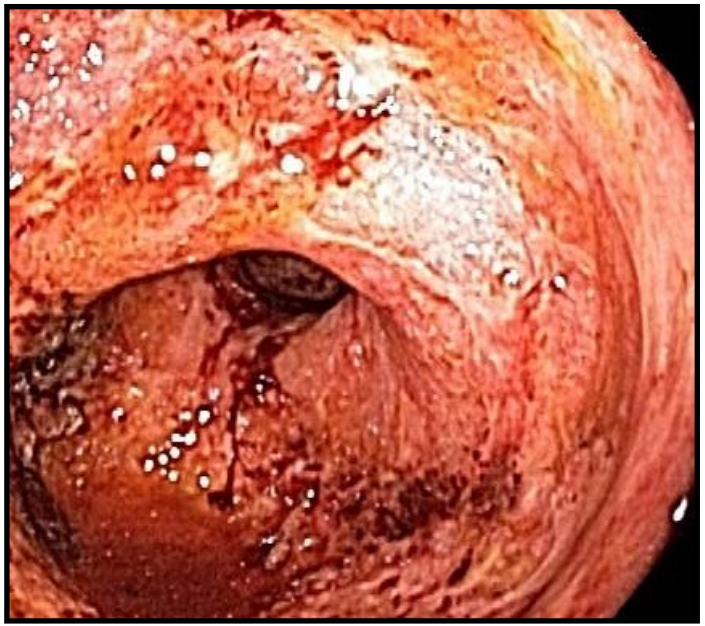
LEARNING OBJECTIVE 1

Apply approaches to achieve mucosal healing in patients with ulcerative colitis.

Case 1: Meet Kris

Kris is a 28-year-old woman who was referred to you by her PCP

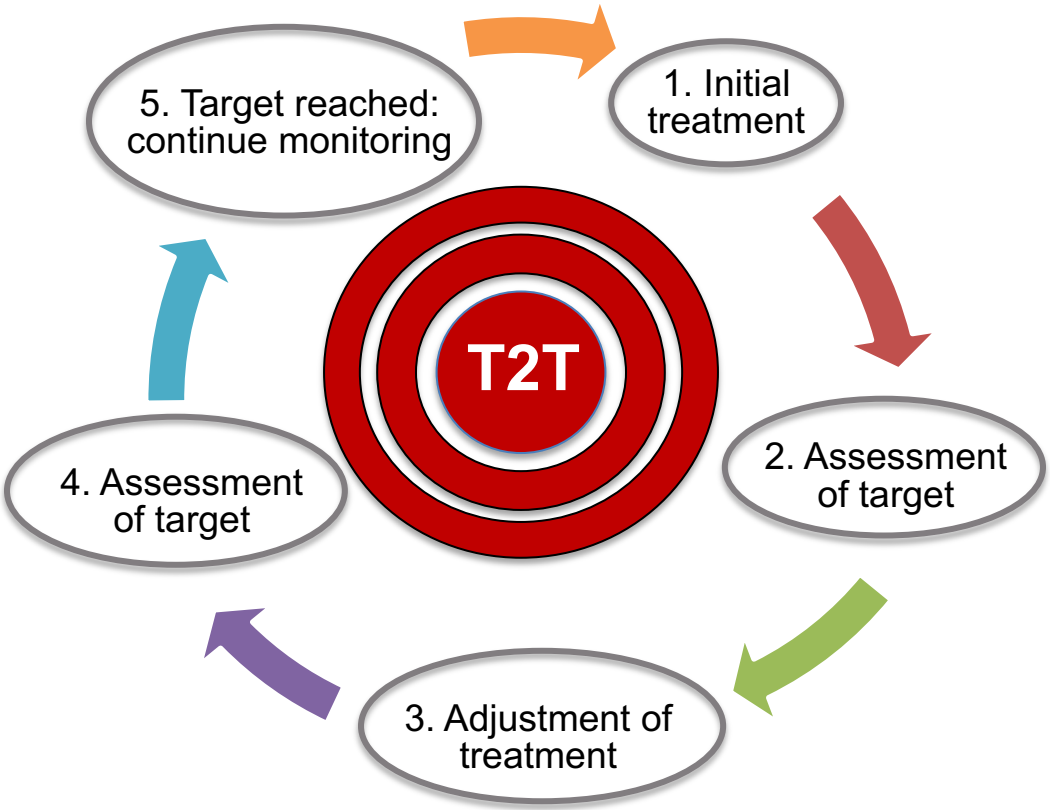
- Family history: mother with life-long "stomach issues"
- 12 bloody stools/d with urgency and tenesmus
- Hgb 10 g/dL; Albumin 3.2
- Negative for *Clostridioides difficile*
- Endoscopic findings: extensive colitis, deep ulcers



Historical Treatment Strategies Are Flawed

- Need to “earn” the next step in therapy by being sick
- Do not factor PROGNOSIS in treatment choices
- Do not account for combination or de-escalation

Treat to Target (T2T) Is a Rationale-Based Approach to Treatment Selection Using Systematic Adjustments

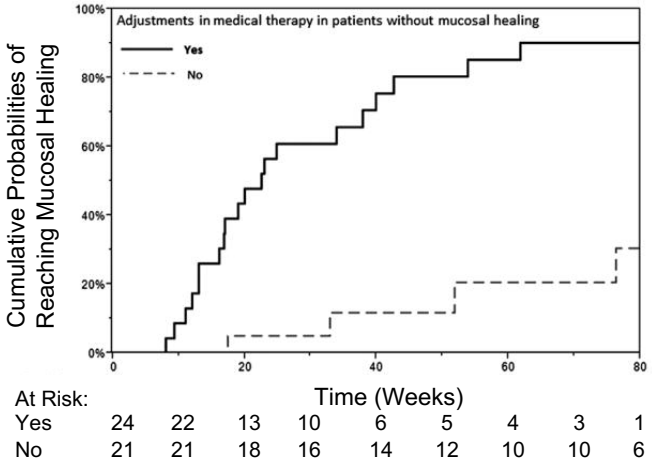


Real-World T2T Is Possible

Retrospective analysis of patients undergoing colonoscopy for UC:
1. Treated to target of mucosal healing: dose adjustments in therapy
2. Not treated to target of mucosal healing: no change in therapy

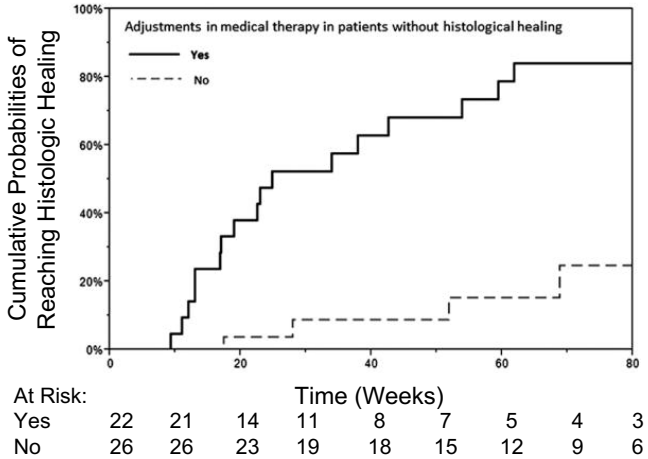
Mucosal Healing

Adjustments in medical therapy in patients without mucosal healing



Histologic Healing

Adjustments in medical therapy in patients without histologic healing



Bouguen G, et al. *Inflamm Bowel Dis.* 2014;20(2):231-239.

Comparison of Treatment Strategies (CALM): Study Design

CALM: A Prospective, Multicenter, Open-label Randomized Study of Treatment Strategies

N = 244

Randomization 1:1

N = 122

Clinical Management
Driven by CDAI, prednisone use

- CDAI decrease < 100 points compared to baseline or CDAI ≥ 200
- Prednisone use a week prior to visit

- **No Treatment**
- **ADA 160/80 mg 40 mg EOW**
- **ADA 40 mg EW**
- **ADA 40 mg EW + AZA 2.5 mg/kg/day**

N = 122

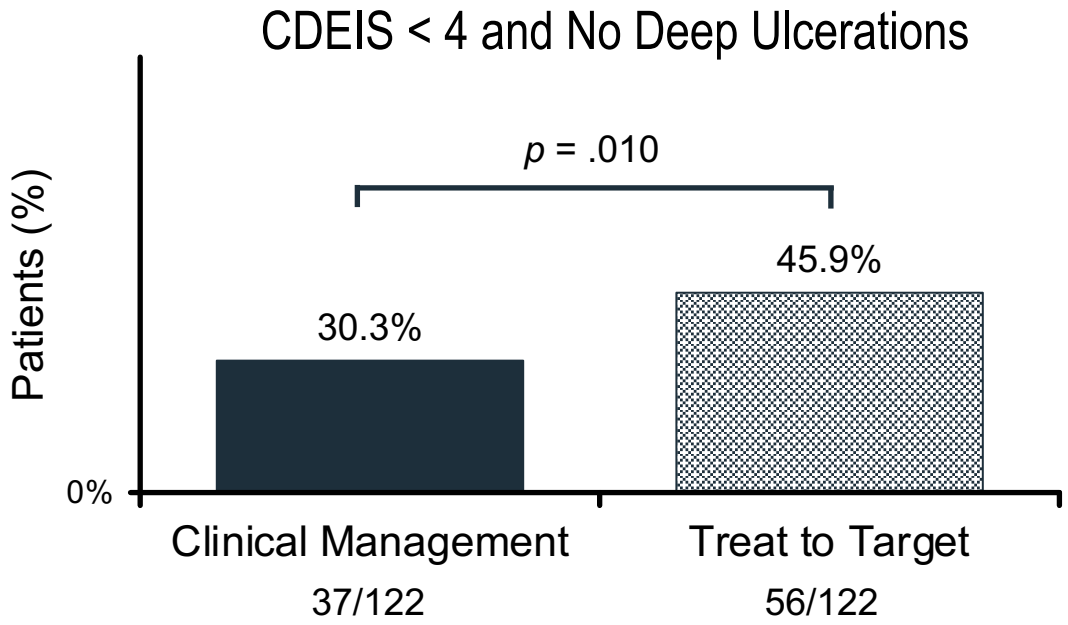
Treat to Target
Driven by CDAI, FC, CRP, prednisone use

- CDAI ≥ 150
- CRP ≥ 5 mg/L
- FC ≥ 250 µg/g
- Prednisone use a week prior to visit

ADA = adalimumab; AZA = azathioprine;
CDAI = Crohn's Disease Activity Index;
EW = every week; EOW = every other week;
FC = fecal calprotectin.

Colombel JF, et al. *Lancet*. 2017;390:2779-2789.

Comparison of Treatment Strategies (CALM): Primary Endpoint at Week 48



T2T leads to superior endoscopic and deep remission outcomes

CDEIS = Crohn's Disease Endoscopic Index of Severity.

Colombel JF, et al. *Lancet*. 2017;390:2779-2789.

The Keys to T2T in Inflammatory Bowel Disease (IBD)

- Willing patient
- Informed provider
- Reliable disease activity measure
- Available treatment options
- Monitoring strategies after target(s) reached
- It also works for de-escalation

Treatments Are Aimed at Observations and Theories (Not the Cause of the Disease)

Immune Modification

- Steroids
- Thiopurines/MTX
- Anti-TNFα therapies
- Anti-integrin therapies
- Anti–IL-12/23

Surgery

- Resection of fibrostenosis
- Resection in fulminant disease

Microbiota Manipulation

- Antibiotics
- Prebiotics
- Probiotics
- Fecal transplantation
- Bacterial derived proteins
- Diet?

Updated Goals of Management for UC

- Make diagnosis quickly and accurately
- Clarify disease type and severity
- Achieve normal bowel function
- Induce remission rapidly – defined by both patient-reported outcomes and objective markers
  - 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- and disease-related complications
  - Reduce costs of care

Rubin DT, et al. *Am J Gastroenterol*. 2019;114(3):384-413. Peyrin-Biroulet L, et al. *Am J Gastroenterol*. 2015;110(9):1324-1338.

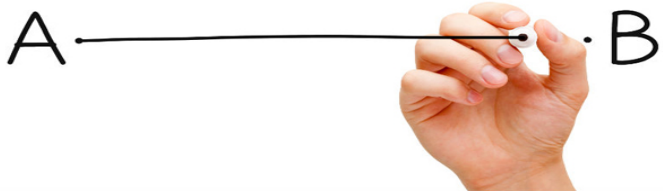
Evolving Principles of IBD 2019

- Incorporate elements of prognosis into diagnosis and medical decision-making
- Moving beyond “one size fits all” to “smart therapy for the right patient”
- Precision medicine − optimization of treatments instead of “guesswork”
- Monitoring disease activity to achieve deeper remission and to anticipate flares

Rubin DT, et al. *Am J Gastroenterol*. 2019;114(3):384-413.

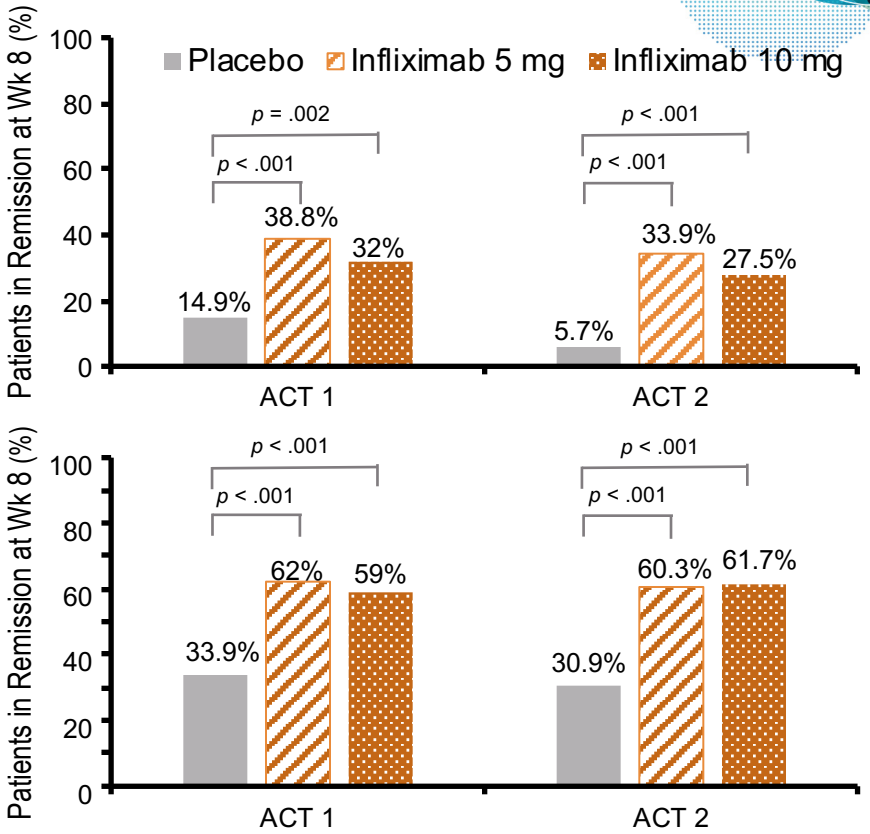
Why don’t we achieve preferred outcomes for everyone?

- We are too late
- Therapies don’t work: guesswork (no predictive biomarkers)
- Therapies are not optimized in clinical practice
- We are treating the wrong problem
- Wrong endpoints: symptom improvement is “enough”



Symptoms Are Not a Reliable Indicator of Mucosal Healing in UC

- Meta-analysis of nine studies found pooled prevalence of irritable bowel syndrome symptoms at 31.0% [95% CI: 21.0-43.0%] in UC patients 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]



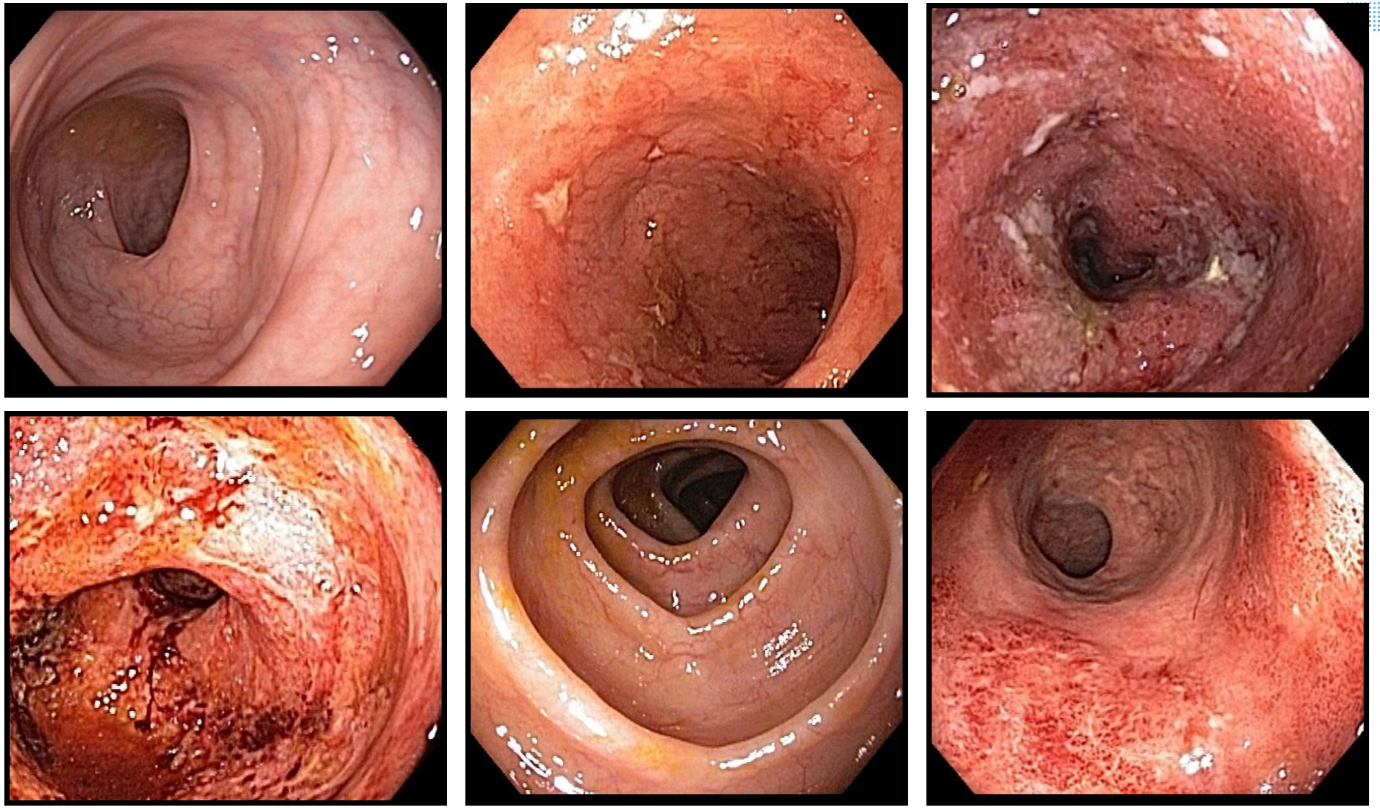
1. Halpin SJ, Ford AC. *Am J Gastroenterol.* 2012;107:1474-1482.
2. Rutgeerts P, et al. *N Engl J Med.* 2005;353:2462-2476.

The Evolution of the Definition of "Mucosal Healing"

- "Mucosal healing" is proposed as a composite of both endoscopy and histology
- In UC, endoscopic healing can be defined as[1]:
  - Return to normal vascular pattern
  - Absence of friability or ulcerations
  - Normal or near-normal mucosal appearance, originally defined as with "slight hyperemia or slight granularity"[2]
- Histology: absence of intra-epithelial neutrophils[3] (or < 5% neutrophils)
- Histo-endoscopic mucosal healing[4]: a novel, pre-specified endpoint that requires both histological and endoscopic improvement

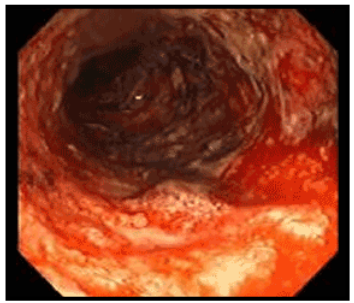
1. Pineton de Chambrun G, et al. *Nat Rev Gastroenterol Hepatol*. 2010;7:15-29. 2. Truelove SC, et al. *Br Med J*. 1955;2:1041-1048.
3. Rubin DT, et al. *Am J Gastroenterol.* 2019;114(3):384-413. 4. Sands BE, et al. *N Engl J Med*. 2019;381(13):1201-1214.

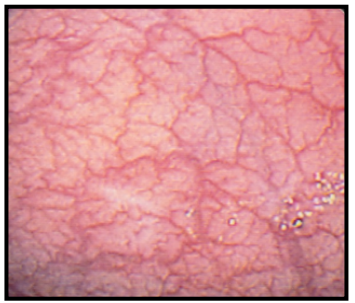
Variations of Endoscopic Appearance of UC

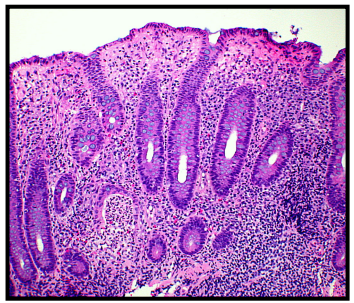


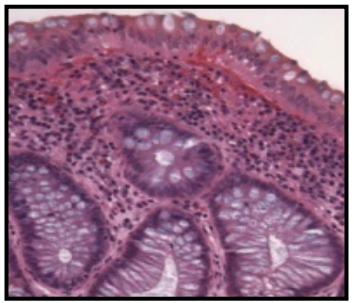
What About Histology?

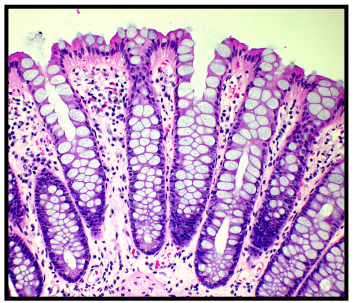
INFLAMED → **CHRONIC, QUIESCENT** → **?** → **NORMAL**





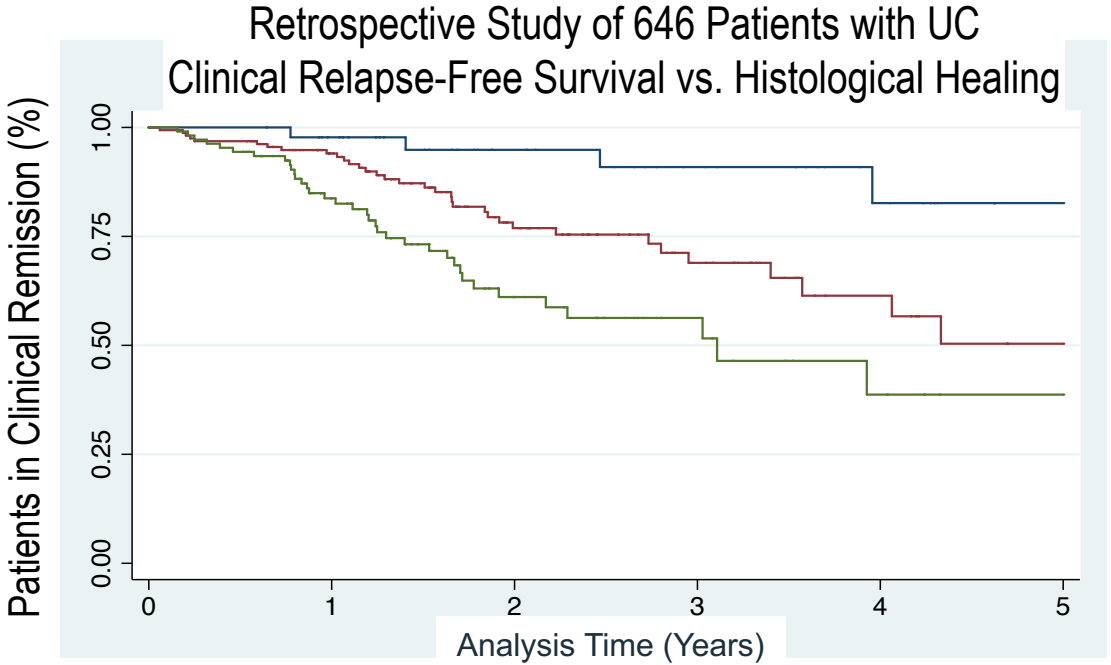






Schroeder KW, et al. *N Engl J Med.* 1987;317(26):1625-1629.

Histological Normalization in Patients with UC



Complete Histological Remission

Histological Quiescence

Histological Inflammation

25% patients had clinical relapse in median 1.3 years

Clinical relapse-free survival: 91% at 1 year, 68% at 3 years, 53% at 5 years

Christensen B, et al. *Clin Gastroenterol Hepatol*. 2017;15:1557-1564.

LEARNING OBJECTIVE 2

Evaluate the efficacy of current and emerging UC treatments in achieving mucosal healing and steroid-free remission.

Case 2: Meet Matt

Matt is a 26-year-old man with 3 years of left-sided UC presenting to you with a flare

- Treated intermittently with 5-aminosalicylic acid (5-ASA) and steroids
- Struggles with adherence
- Extension of disease to pancolitis

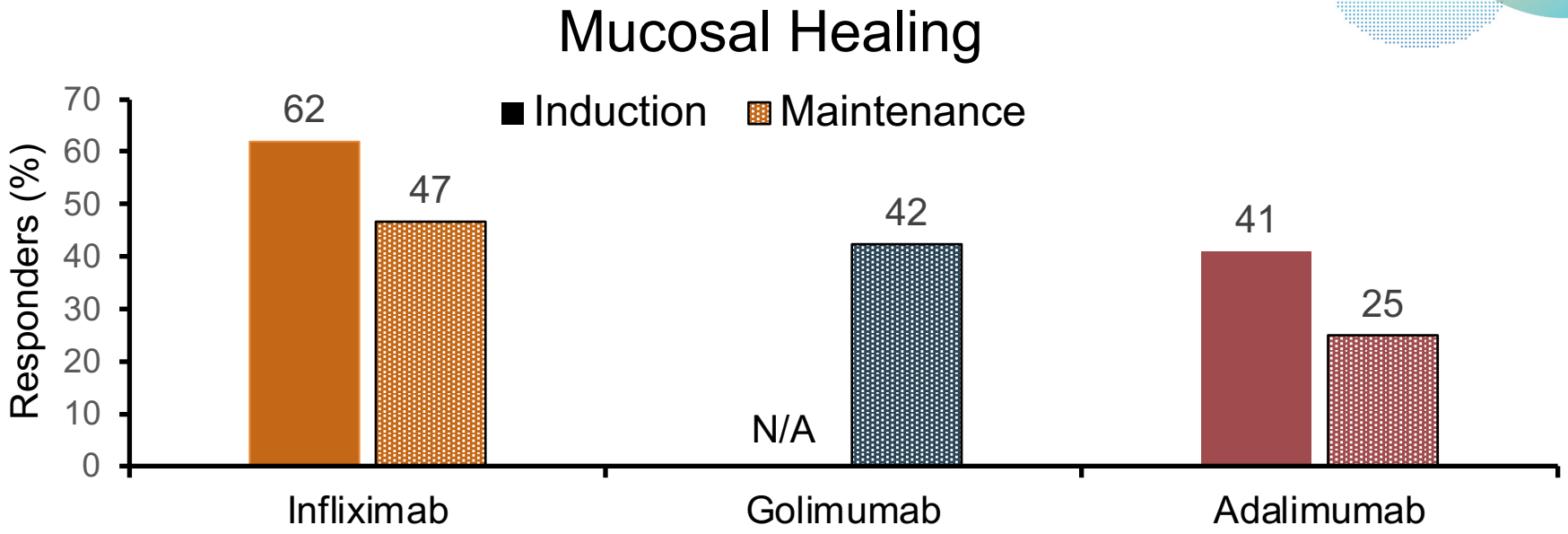
Therapies Approved by the FDA for Moderate-to-Severe UC

	Mechanism	Induction of Clinical Response and Remission	Adverse Events*
Infliximab	Anti-TNF	ACT[1]	Serious infections, opportunistic infections. Need to test for tuberculosis (TB) and hepatitis B virus (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]	Serious infections, opportunistic infections. Need to test for TB and HBV prior to initiation of therapy. (Increased risk of herpes zoster)
Ustekinumab	Anti-IL-12/23	UNIFI[6]	Nasopharyngitis

*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;376:1723-1736. 6. Sands BE, et al. N Engl J Med 2019 381(13):1201-1214.

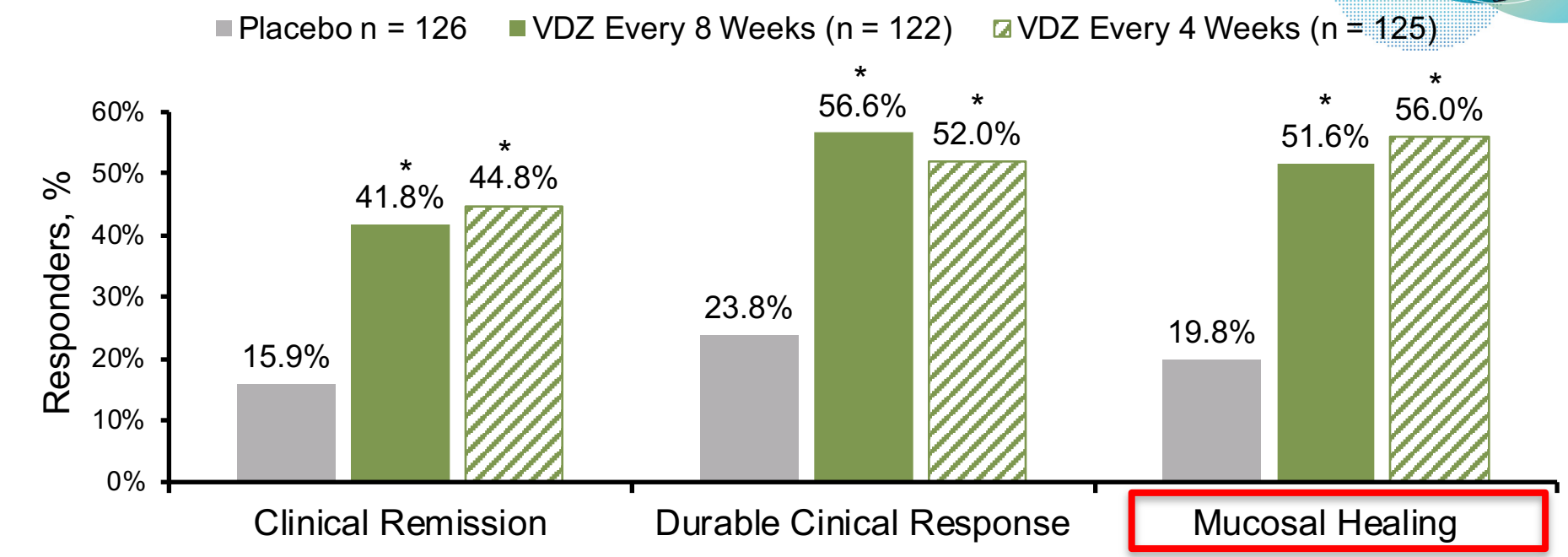
Anti-TNF Therapy: Overall Efficacy



Data presented from different trials and cannot be directly compared

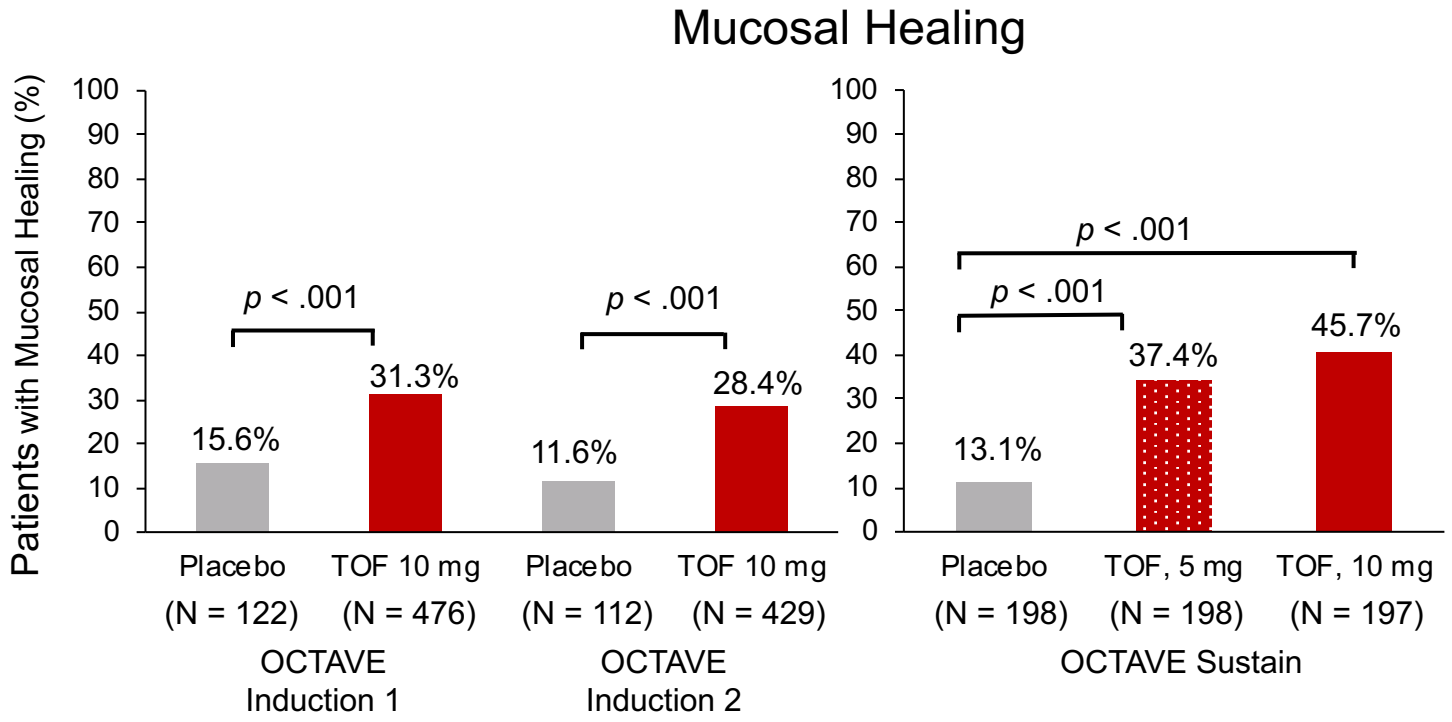
Rutgeerts P, et al. *N Engl J Med.* 2005;353(23):2462-2476; Sandborn WJ, et al. *Gastroenterology.* 2012;142(2):257-265 e251-253; Sandborn WJ, et al. *Gastroenterology.* 2014;146(1):96-109.

Vedolizumab: Maintenance in UC at Week 52 (GEMINI I)



Durable clinical response = clinical response (reduction in Mayo score of at least 3 points + > 30% decrease from baseline + at least 1 point decrease in rectal bleeding) at weeks 6 and 52.
Clinical remission = Mayo score of 2 or lower and no subscore higher than 1.
Endoscopic healing = Mayo endoscopic subscore of 0 or 1.
*$p < .001$.
Feagan BG, et al. *N Engl J Med*. 2013;369:699-710.

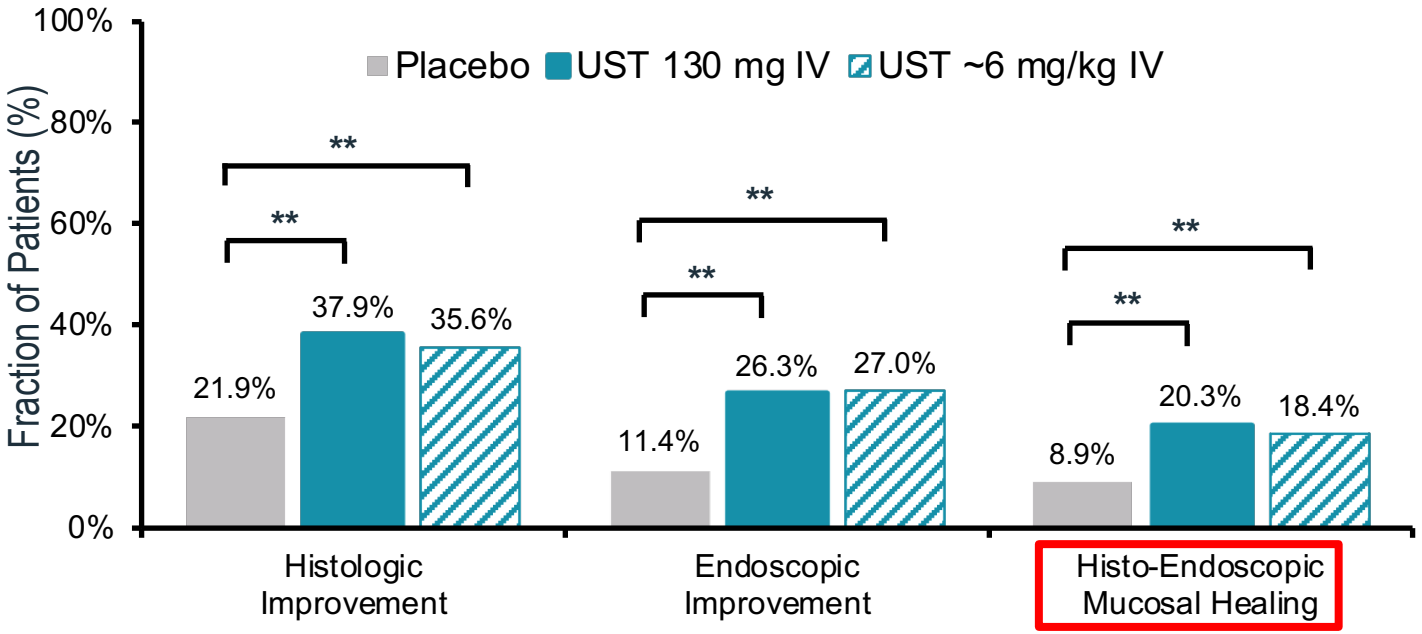
Tofacitinib: Maintenance in UC at Week 52 (OCTAVE)



TOF = tofacitinib
Endoscopic healing = Mayo endoscopic subscore of 0 or 1..

Sandborn W, et al. *N Engl J Med*. 2017;376(18):1723-1736.

Ustekinumab Induction in UC: Week 8 (UNIFI)

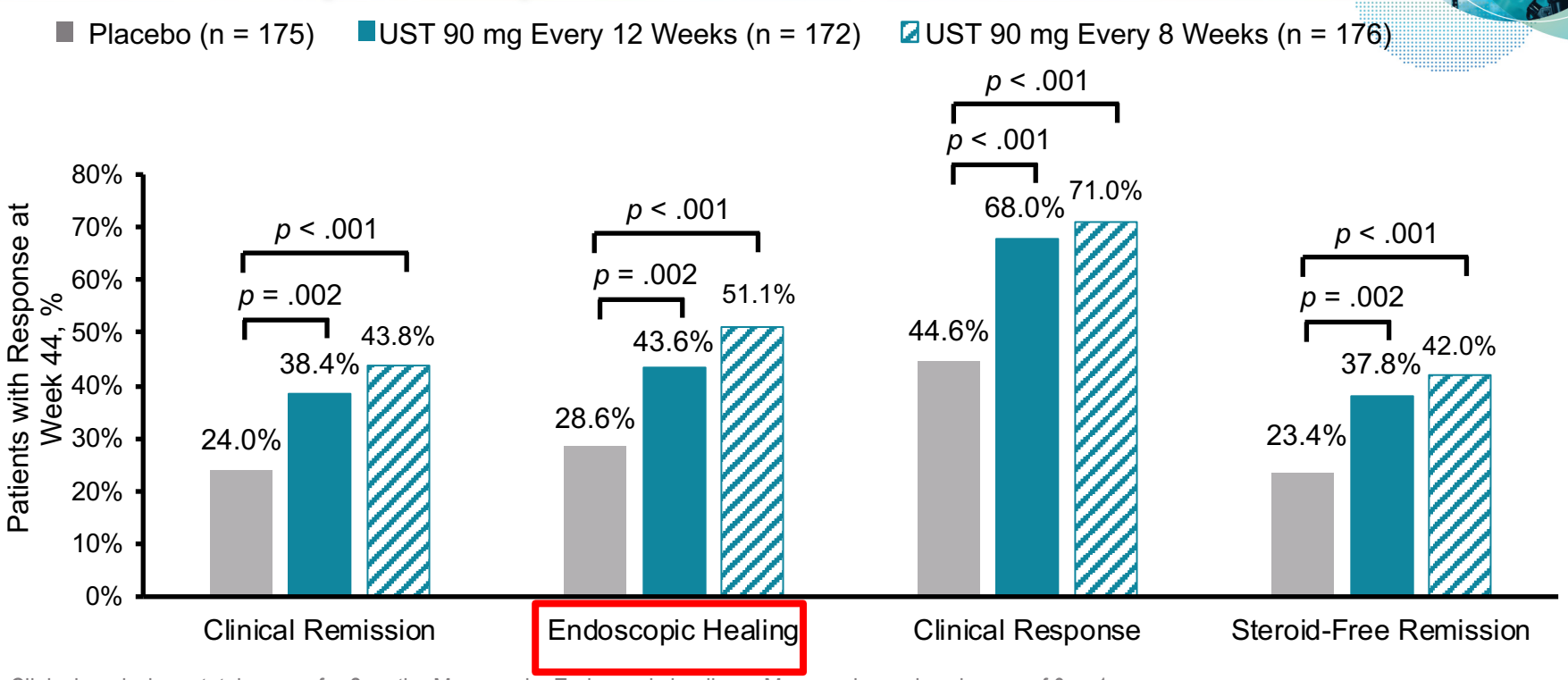


- Phase III, randomized, controlled trial; N = 397; UST week 8 responders randomized from UNIFI induction
- UC diagnosis ~6 years, biopsy failure (~51%): anti-TNF (~51%), anti-TNF + VDZ (~17%)
- Histologic improvement is significantly associated with endoscopic improvement at induction weeks 8 and 16

Histologic: 0 to < 5% neutrophils in epithelium, no crypt destruction, and no erosions, ulcerations, or granulations.
Endoscopic healing = Mayo endoscopic subscore of 0 or 1.
**$p < .001$.

Sands BE, et al. *N Engl J Med* 2019 381(13):1201-1214.

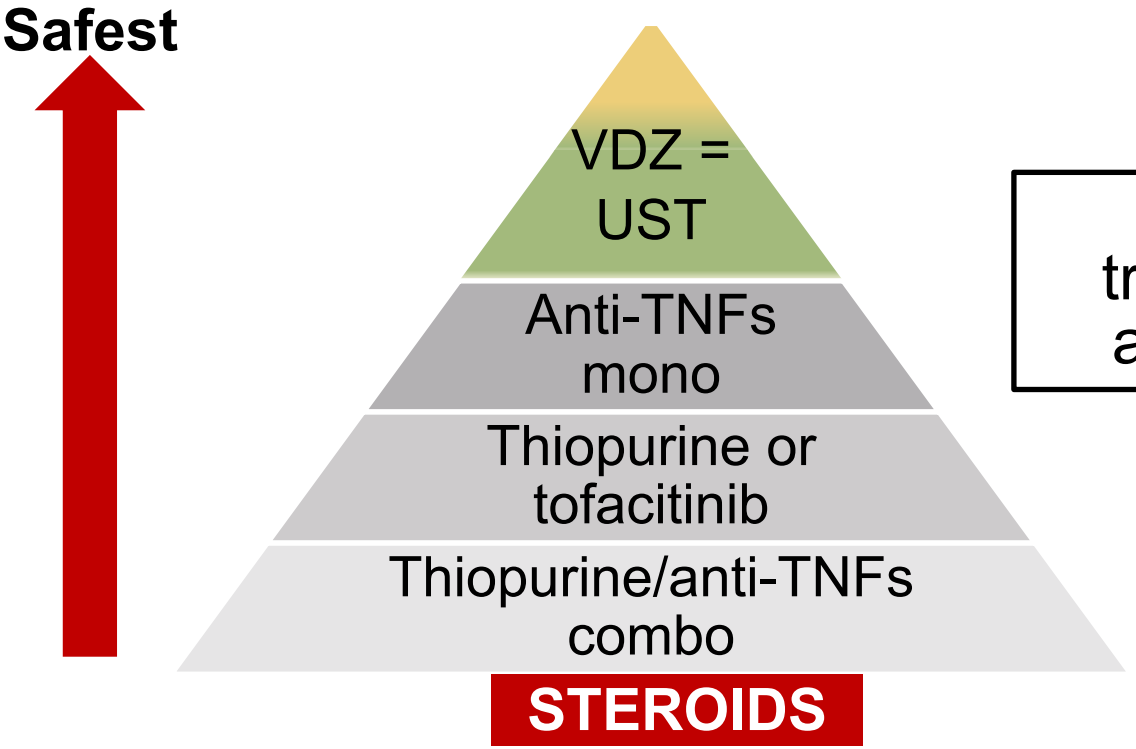
Ustekinumab Maintenance in UC: Week 44 (UNIFI)



Clinical remission = total score of ≤ 2 on the Mayo scale. Endoscopic healing = Mayo endoscopic subscore of 0 or 1.
Clinical response = decrease in the total Mayo score of at least 30% and of at least 3 points from baseline.

Sands BE, et al. *N Engl J Med* 2019 381(13):1201-1214.

Safety Pyramid of Current IBD Medications



Inadequate treatment is an adverse event

VDZ = vedolizumab; UST = ustekinumab

Click B, Regueiro M. *Inflamm Bowel Dis*. 2019;25(5):831-842.

Suggestions for Sequencing Therapy for Moderate-Severe UC

- Age > 65:
  - Vedolizumab
  - Ustekinumab
- Inpatient
  - Infliximab
  - Cyclosporine (induction followed by vedolizumab, ustekinumab (no data), or azathioprine maintenance)
  - Tofacitinib (no data)
- Significant cancer history, lymphoma
  - Vedolizumab
  - Ustekinumab
- Pregnancy
  - Anti-TNF
  - Azathioprine
  - Vedolizumab
  - Ustekinumab
- Steroid responsive mild-moderate disease
  - Thiopurine
- Extraintestinal manifestations such as arthritis:
  - Anti-TNF
  - Tofacitinib
  - Ustekinumab
- Previous anti-TNF failure
  - Tofacitinib
  - Vedolizumab
  - Ustekinumab

Rubin DT, et al. *Am J Gastroenterol.* 2019;114(3):384-413.
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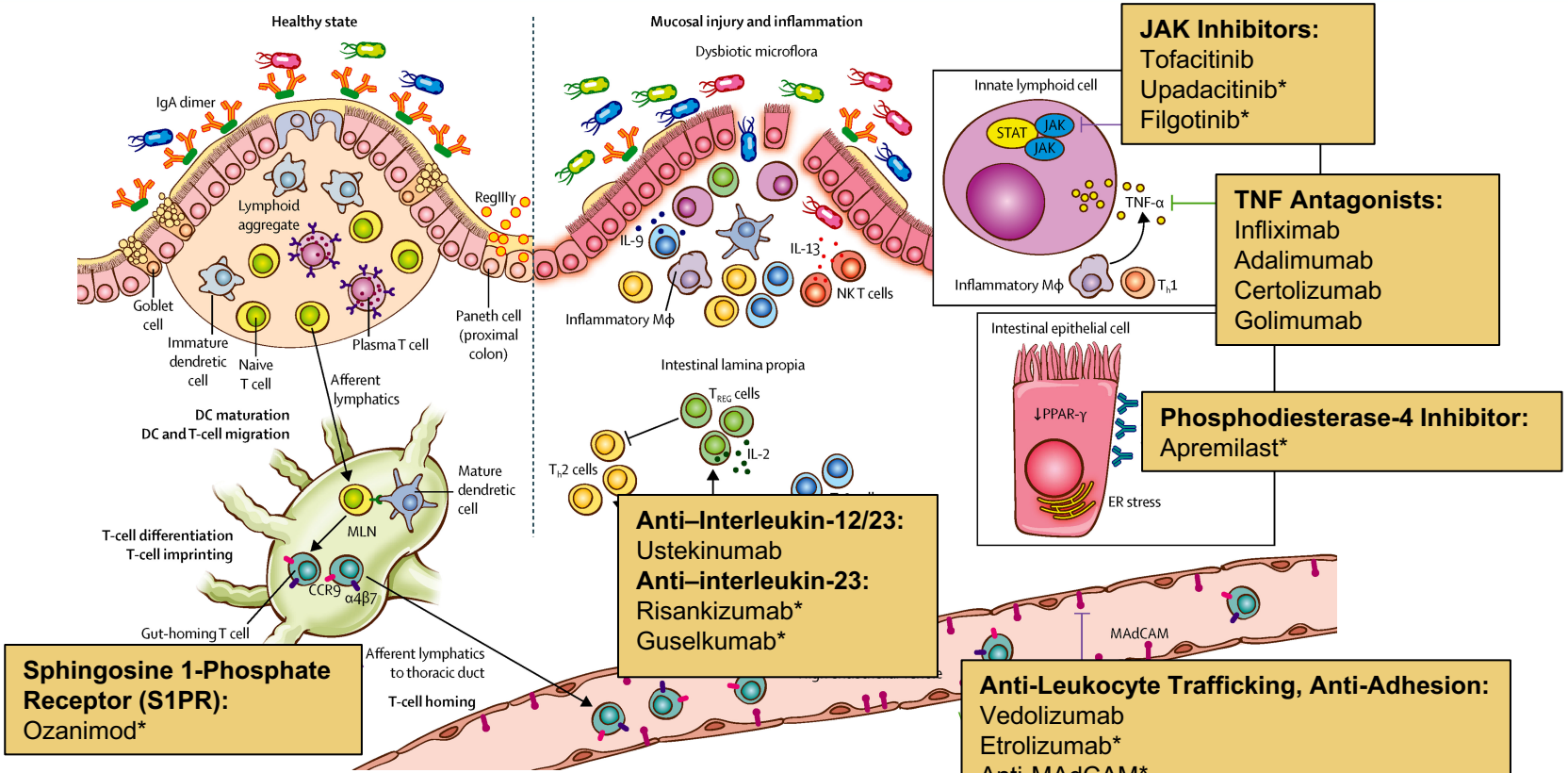
Emerging Therapies

Novel Targets and Therapies in UC



*Not approved by the U.S. Food and Drug Administration (FDA) for the treatment of UC.

Ungaro R, et al. *Lancet.* 2017;389:1756-1770.

Other Treatments of Interest for IBD

- Fecal microbiota transplantation
  - Four randomized trials in UC
  - Non-standardized, FDA issues, not recommended
- Dietary interventions
  - NIH-funded collaborative effort in CD
    - Mediterranean Diet vs. Specific Carbohydrate Diet

LEARNING OBJECTIVE 3

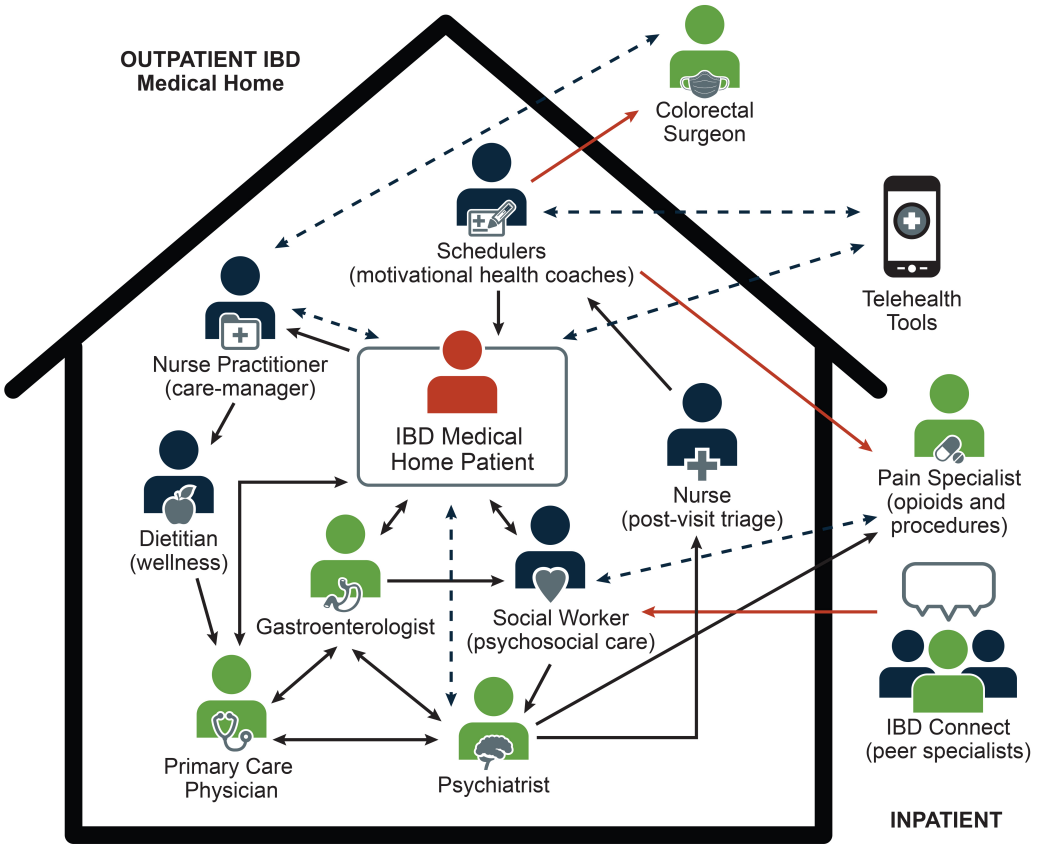
Implement strategies to monitor patients with UC for endoscopic and histologic disease activity in order to guide therapy.

Case 3: Meet Theresa

Theresa is a 50-year-old woman with UC in clinical remission

- Comorbidities: obesity and psoriasis
- Diagnosed with UC in her 20s, stable clinical remission (denies symptoms) for 20+ years
- Current medications: azathioprine and 5-ASA
- Colonoscopy shows endoscopic (Mayo 2) activity

IBD Medical Home: Team-based, GI-Point of Care, Patient-Centered, Coordinated Care



Let’s go back to our cases…

Case 1: Meet Kris

Kris is a 28-year-old woman who was referred to you by her PCP

- Family history: mother with life-long "stomach issues"
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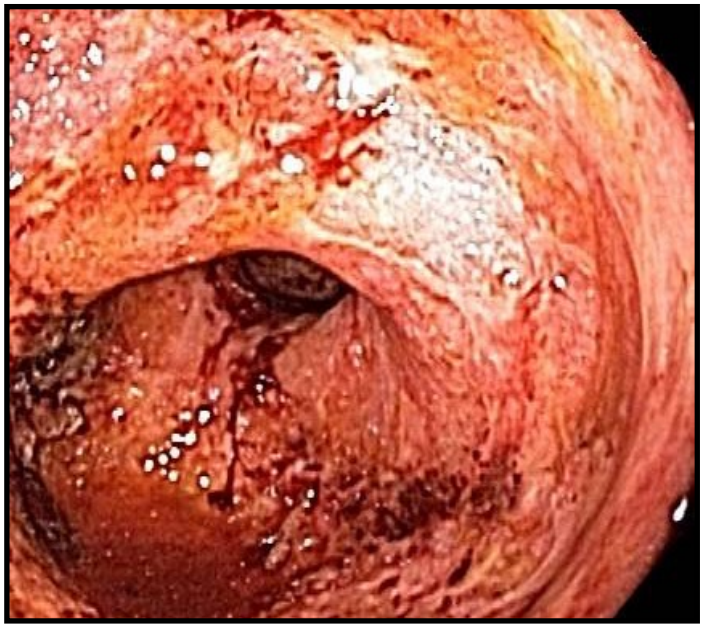
- Hgb 10 g/dL; Albumin 3.2
- Negative for *Clostridioides difficile*
- Endoscopic findings: extensive colitis, deep ulcers



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- Colonoscopy shows endoscopic (Mayo 2) activity

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Newly approved treatment options in UC promise to achieve histo-endoscopic mucosal healing
- Use validated objective endpoints of disease control
- Adjust therapies serially until endpoints are achieved (T2T)
- Monitor disease activity to achieve deeper remission and to anticipate flares

QUESTIONS & ANSWERS

THANK YOU!

Don’t forget to complete the evaluation and collect your credit.