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Current treatment targets in IBD

Jeffrey Jacobs, MD

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Disclosures

- None

What Are Our Treatment Goals in IBD?

- Ultimately, we want patients to feel better, restore quality of life, and avoid disability.
- The primary goal of IBD treatment is deep remission: resolution of both symptoms and inflammation, which in turn prevents disease progression and improves long-term outcomes.
  - What does symptom control mean?
  - What definition do we use for control of inflammation?
  - What other targets are there?

Selecting Therapeutic Targets in IBD (STRIDE-II): Treat-to-Target (T2T) Approach

- A T2T approach is a collaborative approach between the physician and the patient.
- It involves identifying an appropriate target, selecting initial therapy according to the risk of disease progression, measuring baseline characteristics of disease, monitoring progress, and optimizing therapy to reach the agreed goal.

Treatment Targets in IBD

- Clinical response and remission
- Endoscopic response and remission
- Biomarker normalization
- Absence of disability and normalization of quality of life
- Adjunct goals: histologic healing (UC) and transmural healing (CD)

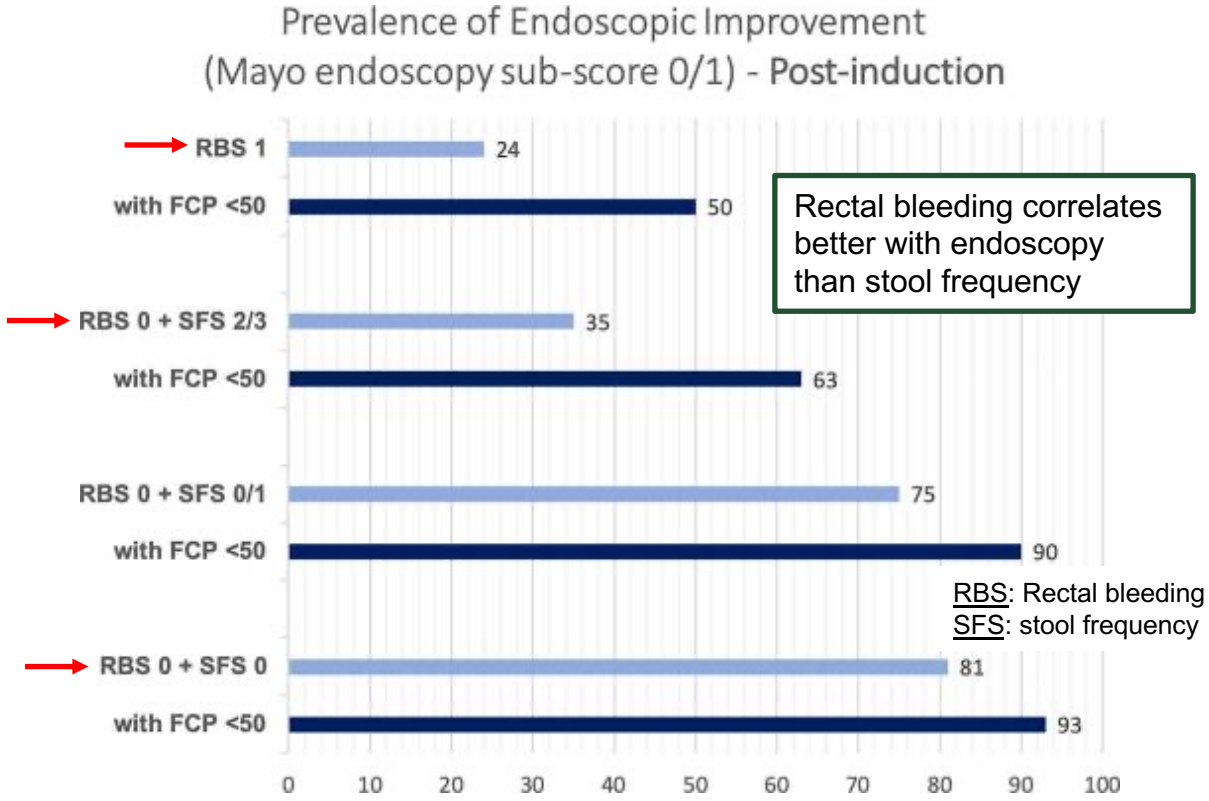
Definitions:

- Deep remission: clinical and endoscopic remission
- Mucosal healing: endoscopic and histologic healing

Symptoms Correlate Moderately Well With Endoscopic Improvement in Ulcerative Colitis

- Clinical treatment targets in UC:
  - Resolution of rectal bleeding
  - Normalization of stool frequency

Clinical response: reduction of bleeding and diarrhea by at least 50%

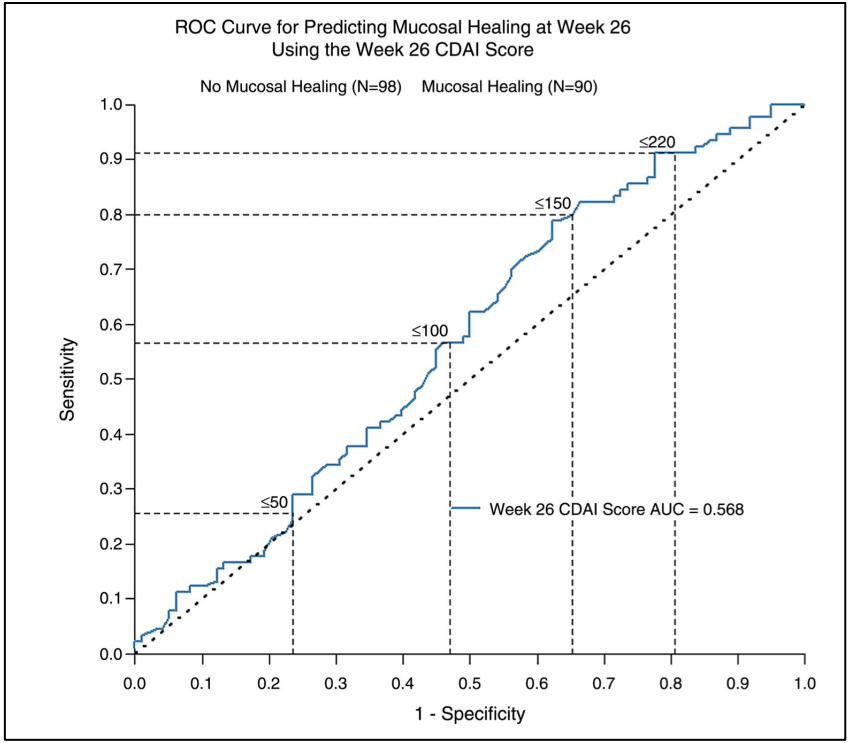


Dulai et al. *Am J Gastro*. 2020.

Alternatively, Symptoms Correlate Poorly With Endoscopic Disease Activity in Crohn's Disease

- Clinical treatment targets in Crohn's disease nonetheless remain a primary treatment target:
  - Resolution of abdominal pain
  - Normalization of stool frequency
  - Clinical response: reduction of pain and diarrhea by at least 50%

Post-hoc analysis of SONIC trial demonstrated 50% of patients in clinical remission had residual active inflammation; 20% with mucosal healing had persistent symptoms.



Peyrin-Biroulet et al. *Gut*. 2014.

Symptom Control is Important but Not the Only Target

- Endoscopic remission predicts sustained clinical remission and is associated with a reduced risk of complications:
  - Surgery
  - Colectomy
  - Colorectal cancer
  - Disease flares
  - Hospitalizations

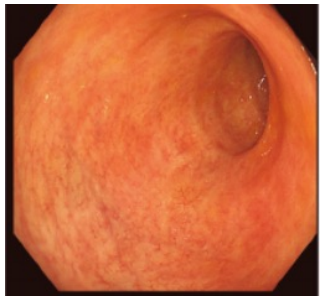
Turner et al. STRIDE-II. *Gastro*. 2021.

Endoscopic Targets in IBD

Ulcerative colitis

- Mayo endo score ≤1*
- Mayo endo score 0 is associated with better outcomes

*Mayo 1: erythema, decreased vascular pattern, mild friability



Crohn's disease

- Endoscopic response: >50% reduction in SES-CD
- Endoscopic remission: SES-CD ≤2 and no ulceration
- Resolution of inflammation on cross-sectional imaging if not reachable endoscopically

	SES-CD values			
Variable	0	1	2	3
Ulcers	None	Aphthous ulcers (Diameter 0.1-0.5 cm)	Large ulcers (Diameter 0.5-2 cm)	Very large ulcers (Diameter >2 cm)
Ulcerated surface	None	<10%	10-30%	>30%
Affected surface	Unaffected segment	<50%	50-75%	>75%
Stenosis	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Chen et al. *Therap Adv Gastroenterol*. 2020; Turner et al. STRIDE-II. *Gastro*. 2021.

What Endoscopic Target Is Good Enough?

- Not all patients will achieve endoscopic remission, especially those with a longer time since diagnosis
- Resolution of severe endoscopic lesions or large ulcers should remain a target
- Dose optimization is a relatively low risk modification to treat ongoing inflammation
- Whether to change therapy altogether based on an endoscopic result depends on patient goals and risk tolerance, disease history and complications, and prior medication use

Biomarkers Are Intermediate Targets

Biomarker goals:

1. Normalization of CRP
2. Normalization of calprotectin (100-250 µg/g)

CALM trial: Crohn's patients with adalimumab dose adjustment based on CDAI or calpro or CRP had higher rates of endoscopic healing compared to dose change based on CDAI alone (46% vs. 30%).

- Calprotectin <150 µg/g is associated with endoscopic healing after induction
  - 100-250 µg/g is a gray zone; even levels up to 600 µg/g do not always signal significant inflammation
  - No single optimal cut-off for calprotectin exists; levels above 250 µg/g should be investigated
- Calprotectin has poor correlation with ileal Crohn's disease (r=0.44)
- CRP has poor sensitivity; in one study half of patients with CRP <3 mg/dl had active endoscopic disease

Colombel et al. *Lancet*. 2017; Turner et al. STRIDE-II. *Gastro*. 2021.

Long Term Goal: Patient Well-Being and Restoration of Quality of Life

- Health related well-being correlates modestly with inflammatory burden
  - Fatigue
  - Disability
  - Sexual health
  - Depression and anxiety
  - Food related QoL
  - Body image
  - Sleep

Turner et al. STRIDE-II. *Gastro*. 2021.

Combining Targets Improves Outcomes

Deep remission is the ultimate goal: both clinical and endoscopic remission

Long-term follow up of patients in CALM trial

Variable	HR (95% CI)
Deep remission	0.23 (0.09–0.32)
Endoscopic remission	0.46 (0.31–0.60)
Clinical remission	0.64 (0.34–0.61)

Risk of disease progression: new internal fistula/abscess, stricture, perianal fistula/abscess, CD hospitalization, or CD surgery since end of CALM

Ungaro et al. *Gastro*. 2020.

IBD Medications Take Time

Table 4. Time (Mean Number of Weeks) Required for Achieving the Goal After Starting Treatment for CD (n = 39) and UC (n = 36), Based on the Delphi-like Process and the Systematic Review of the Evidence

	Clinical response	Clinical remission	Norm of CRP/ESR	Decrease of FC[a]	EH
		Crohn's disease			
Oral steroids/EEN	2	4	5	8	13
Budesonide	3	6	8	10	15
Thiopurines	11	15	15	17	24
Methotrexate	9	14	14	15	24
Anti-TNF	2–4	4–6	9	11	17
Vedolizumab	11	17	15	17	24
Ustekinumab	7	13	11	14	19
		Ulcerative colitis			
Oral 5-ASA	4	8	8	10	13
Oral Steroids	2	2	5	8	11
Locally active steroids[b]	3	8	8	9	13
Thiopurines	11	15	15	15	20
Adalimumab	6	11	10	12	14
Infliximab	5	10	9	11	13
Vedolizumab	9	14	14	15	18
Tofacitinib	6	11	9	11	14

Clinical assessment:

- Assess clinical response every 3 months until remission
  - Every 6-12 months after symptom resolution

Endoscopic assessment:

- UC: 3-6 months after start of therapy
- CD: 6-9 months after start of therapy

Note. Given the paucity of high-quality scientific data, the data in this table should be considered merely as a rough estimate of experts' opinion.
Turner et al. STRIDE-II. *Gastro*. 2021.

Supporting a T2T Approach to Achieve Mucosal Healing

- A retrospective analysis of patients with CD demonstrated that repeat endoscopic procedure <26 weeks from previous and adjustment of therapy when mucosal healing was not achieved were predictive of achieving mucosal healing

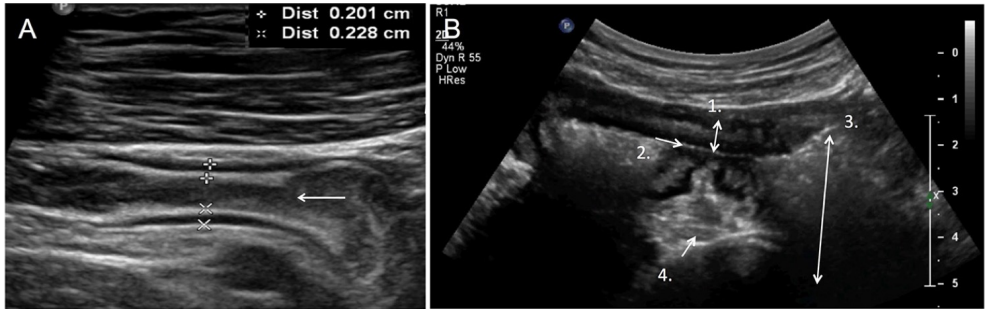
Table 3. Factors Associated With MH During the Follow-up Period After Referral by Univariate Analysis (Log-Rank Test) and by Multivariate Analysis (Cox Model)

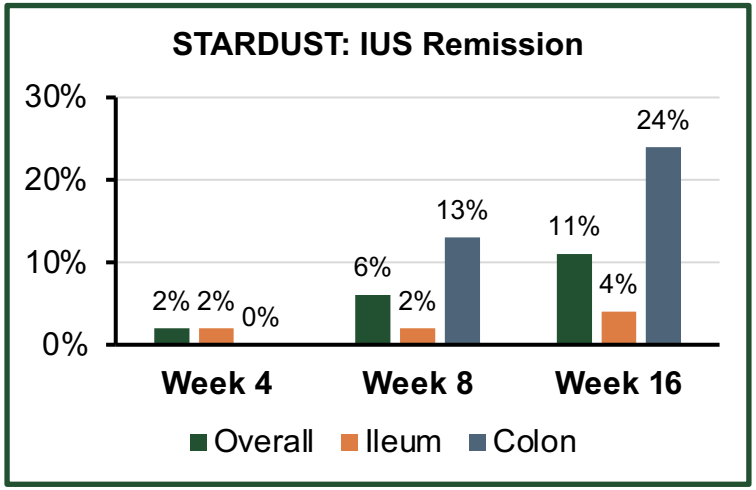
	Univariate analysis		Multivariate analysis	
Baseline factors	*P*	HR (95% CI)	*P*	HR (95% CI)
Time between endoscopic procedures, <26 wk	.039	2.08 (1.02–4.3)	.019	2.35 (1.15–4.97)
Use of TNF antagonists during follow-up evaluation	.54			
Use of azathioprine, 6-mercaptopurine, or methotrexate during follow-up evaluation	.51			
Use of combination therapy during follow-up evaluation	.56			
Adjustment of medical therapy when there was no MH	.0006	3.97 (1.7–10.7)	.0003	4.28 (1.9–11.5)

Bouguen et al. *CGH*. 2014.

Transmural Healing Is the Ultimate Goal in Crohn's Disease but Also Not a Formal Treatment Target Yet

- Transmural healing:
  - Defined as normal bowel wall thickness, and often normal vascularization or enhancement and absence of inflammatory mesenteric fat
  - Requires imaging – CT or MR enterography or intestinal ultrasound
  - Endoscopic healing is often not predictive of transmural healing





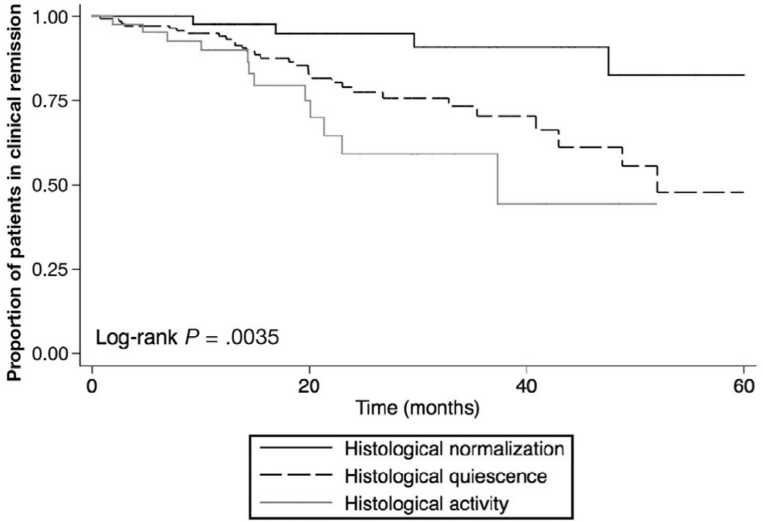
STARDUST substudy:

- STARDUST: T2T trial comparing ustekinumab dose intensification based on wk 16 colonoscopy vs standard of care
- A clinical meaningful % of patients achieved transmural healing

Kucharzik et al. *JCC*. Abstract DOP10. 2020; Bryan RV et al. *Gut*. 2017.

Histologic Healing Is a Deeper Form of Remission but Not a Treatment Target (Yet)

- Histologic activity even with clinical/endoscopic remission increases the risk of clinical relapse
- Histologic healing is associated with a reduced risk of IBD complications including colorectal cancer



Histologic healing is an adjunct target in UC

- Difficult to achieve
- Lack of standardized reporting
- Insufficient evidence to recommend immunosuppression intensification to achieve this goal

Christensen et al. *CGH*. 2017.

Summary

- The primary treatment targets in IBD are combined clinical and endoscopic remission
- Regular assessment is needed to achieve this goal and reduce the risk of disease progression
- Biomarkers are intermediate goals and useful for monitoring
- Future targets will include transmural healing (CD) and histologic healing (UC)