

Canada Future Directions in IBD



Clinical Approaches to the Management of Fibrosis

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Disclosures

Florian Rieder, MD: Advisory Board – Allergan, AbbVie, Boehringer Ingelheim, Celgene, Gilead, Gossamer, Merck, Pfizer, Prometheus Therapeutics, Receptos, Samsung, Takeda, Techlab, UCB; Consulting – Allergan, AbbVie, Agomab, BMS, Boehringer Ingelheim, Celgene, Falk Pharma, Galapagos, Galmed, Gossamer, Gilead, Genentech, Helmsley, Janssen, Koutif, Mestag, Merck, Morphic, Origo, Pfizer, Pliant, Prometheus Therapeutics, Receptos, RedX, Samsung, Surrozzan, Takeda, Theravance, Thetis, UCB, 89Bio; Research Support – Helmsley Charitable Trust, Crohn's & Colitis Foundation, Boehringer Ingelheim, Cleveland Clinic Foundation, ECCO, Genentech, German Research Foundation, Pliant, Morphic, Celgene, UCB, Kenneth Rainin Foundation, National Institutes of Health

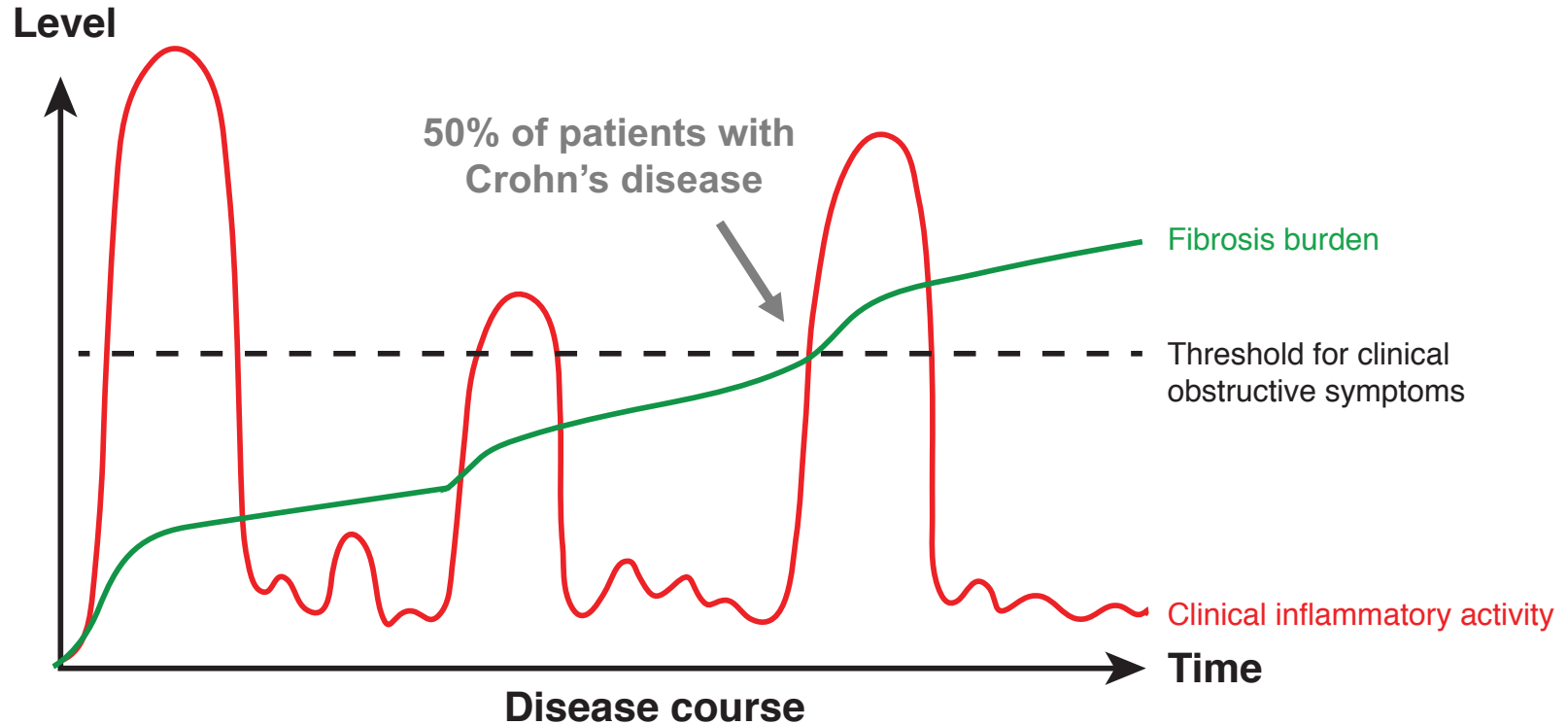
Learning Objectives

- Understand diagnosis of stricturing Crohn's disease and modalities to differentiate fibrosis from inflammation, including intestinal ultrasound
- Delineate the medical, endoscopic, and surgical management of stricturing Crohn's disease
- Discuss novel clinical trial endpoints for stricturing Crohn's disease

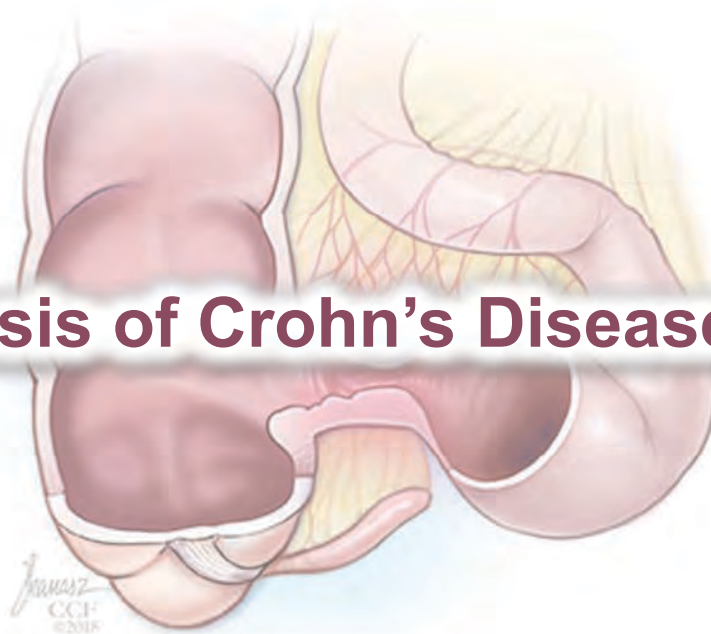
Case

- 32-year-old male
- Ileal Crohn's disease diagnosed 10 years ago, on long-term 5-ASA with minimal symptoms
- Presents acutely with abdominal pain, nausea, abdominal distension, constipation
- Increased bowel sounds on abdominal exam, no guarding
- CT – inflamed and edematous TI, dilated small bowel loops to 3 cm with a 4 cm stenosis in the TI; no penetrating complications
- Colonoscopy – patchy colonic disease and impassable stenosis in TI to adult colonoscope

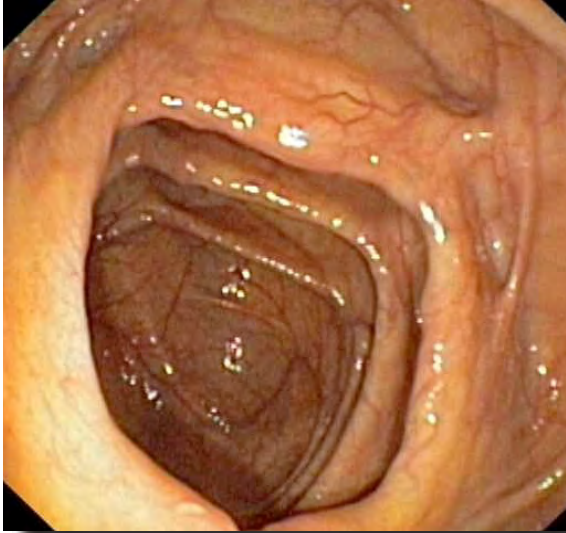
Natural History of Strictureing Crohn's Disease



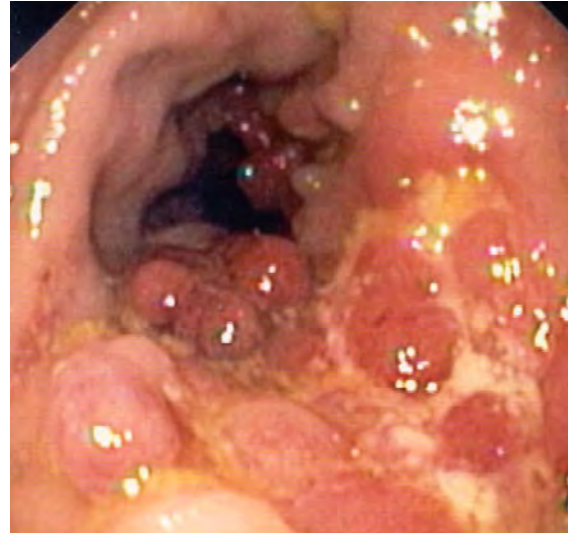
Diagnosis of Crohn's Disease Stenosis



What Is a Stenosis on Endoscopy?



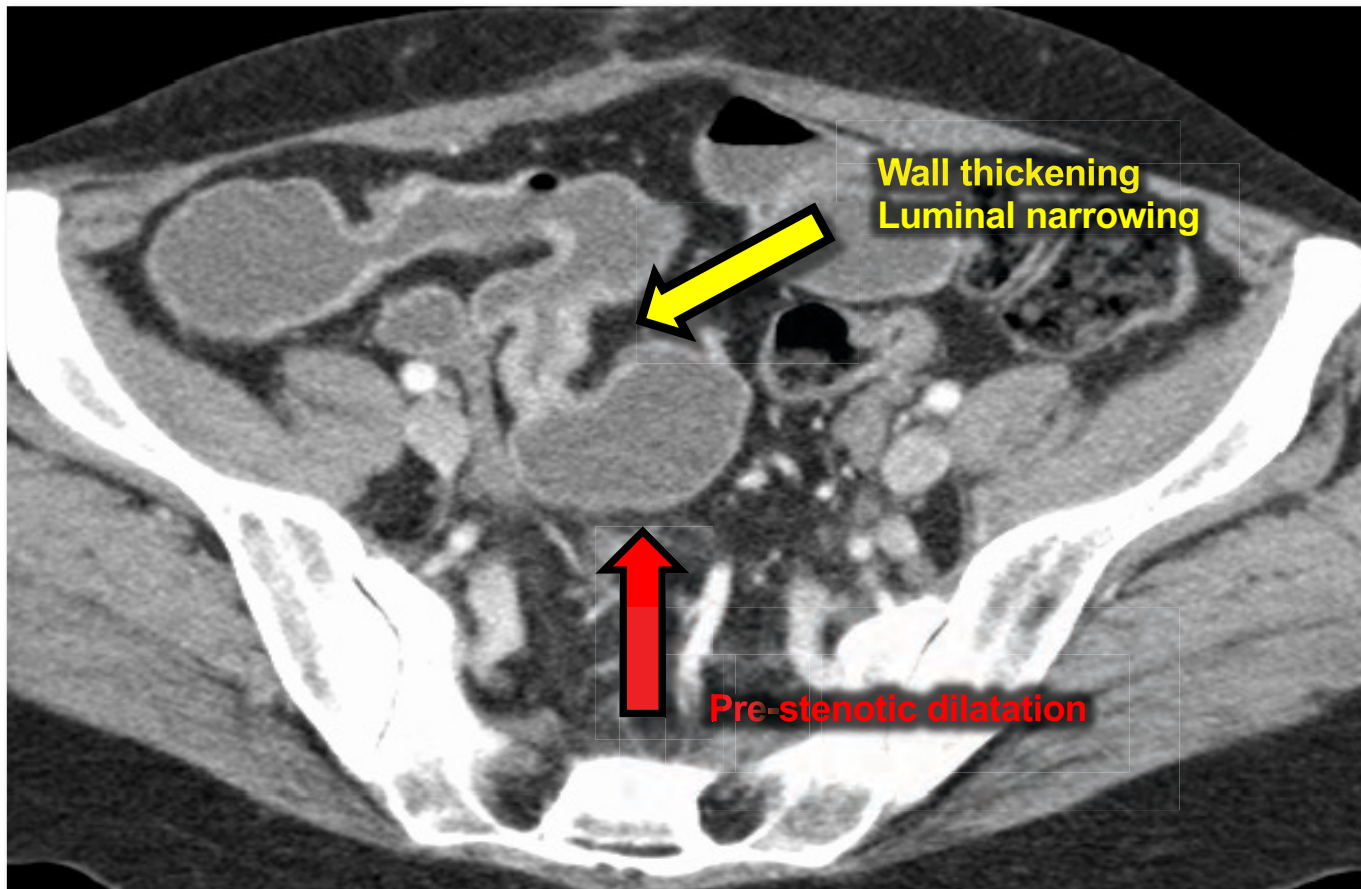
NORMAL COLON



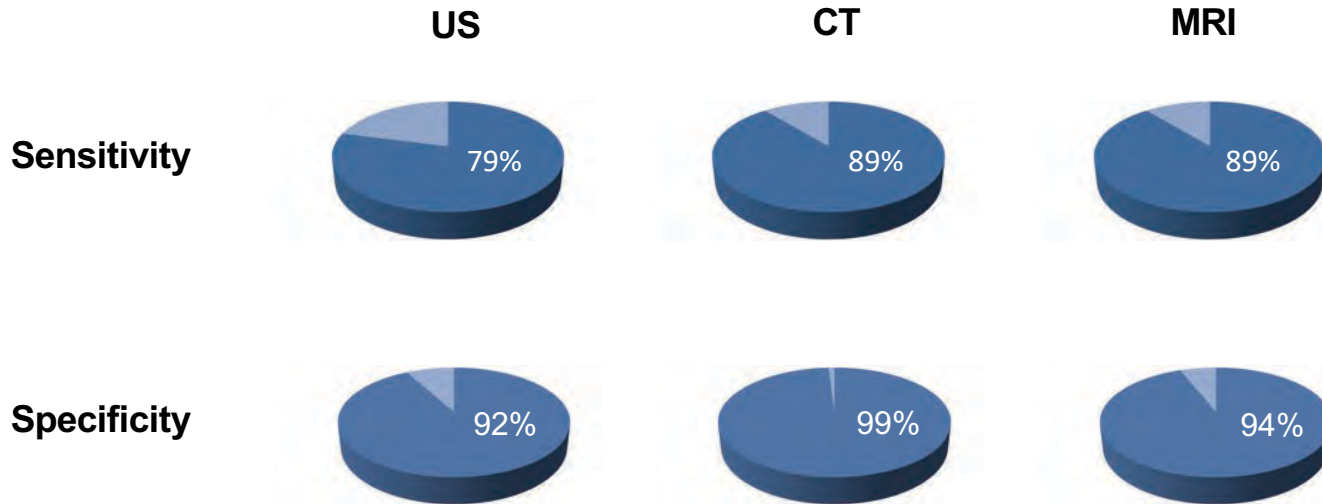
CROHN'S DISEASE STENOSIS

“Luminal narrowing impossible or difficult to pass
with an adult endoscope”

Strictureing Crohn's Disease – CT Enterography



Accuracy of Cross-sectional Imaging for Diagnosis of Stenosis



Intestinal Ultrasound in CD strictures

Strength

- Inexpensive
- Non-invasive
- No preparation
- No sedation
- Easy to do longitudinally
- Real time peristalsis

Limitations

- Challenging at higher BMI
- Concerns about operator dependence
- Impractical for evaluation of the entire bowel
- Methods need to be standardized

Intestinal Ultrasound in CD strictures

Strength

- Inexpensive
- Non-invasive
- No preparation
- No sedation
- Easy to do longitudinally
- Real time peristalsis

Limitations

- Challenging at high
- Concerns about op
- Impractical for eva
- Methods need to b

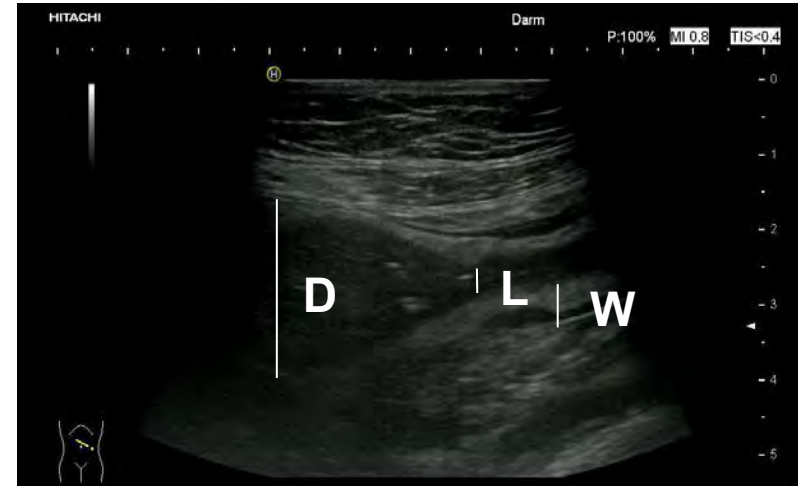


Dr. Lu
International expert
in IUS

Intestinal Ultrasound for Diagnosis of CD strictures

Consensus Criteria for Diagnosis

- Localized luminal narrowing < 1 cm
- Bowel wall thickening > 3 mm
- Pre-stricture dilation > 3 cm (perhaps 2.5 cm)
- **Motility abnormalities**



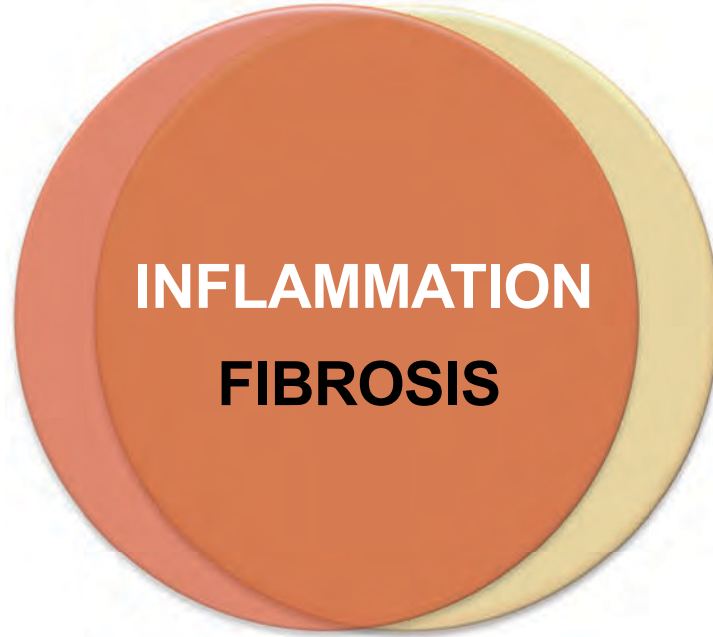
Strictureing Crohn's Disease



INFLAMMATION

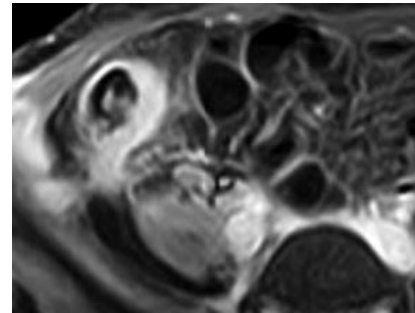
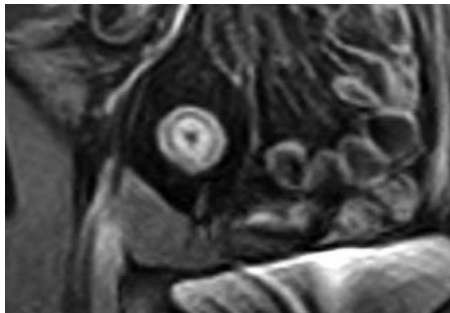
FIBROSIS

Strictureing Crohn's Disease



MRI Features and Histologic Substrate

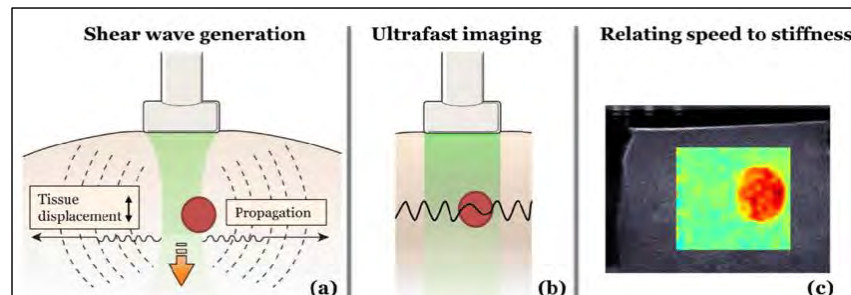
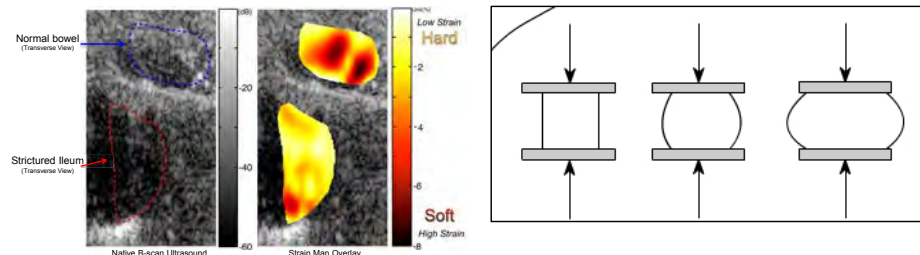
	Inflammation	Fibrosis
Wall thickness	X	X
T2 hypersignal	X	X
Delayed hyperenhancement	X	
Layered enhancement	X	
Comb sign	X	X
Fistula	X	X



US Elasticity Imaging

Mechanical Stiffness with Ultrasound

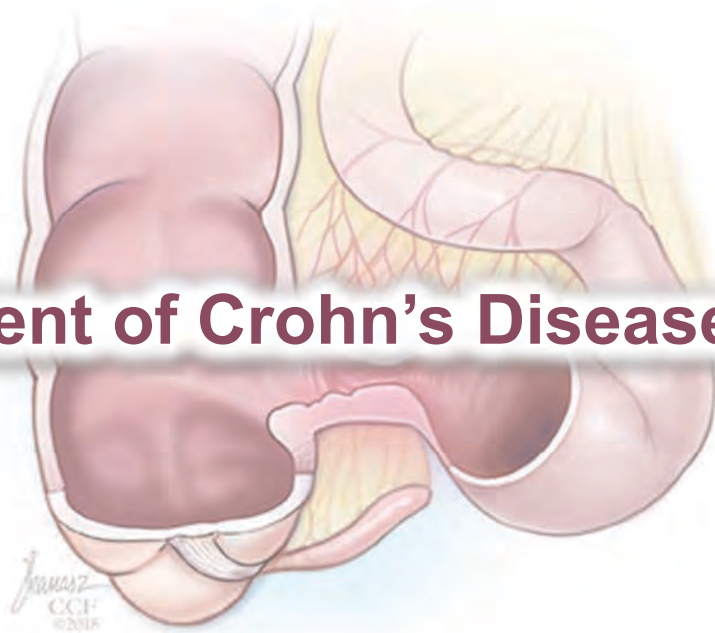
- Strain during bowel compression = strain elastography
 - Stiffer tissues compress less
 - Softer tissues compress more
- Shear Wave Velocity
 - Sound waves travel faster through stiff tissue



Diagnosis of a Small Bowel Stricture

- Symptoms alone are not appropriate to diagnose a stricture and are not required
- Disconnect between symptoms and stricture severity exists
- Cross sectional imaging alone OR ileocolonoscopy alone are sufficient to diagnose a small bowel stricture
- MRe is the preferred diagnostic modality. US is a critical tool, due to no radiation, ease of use and availability
- No imaging technique can currently distinguish the inflammatory from the fibrotic component of a small bowel stricture

Treatment of Crohn's Disease Stenosis



Adalimumab in Stricturing Crohn's Disease: CREOLE

CREOLE: Multicenter, observational, open-label study
(N=97)

Population: Patients with Crohn's disease with single/multiple small bowel strictures (endoscopic or radiological)

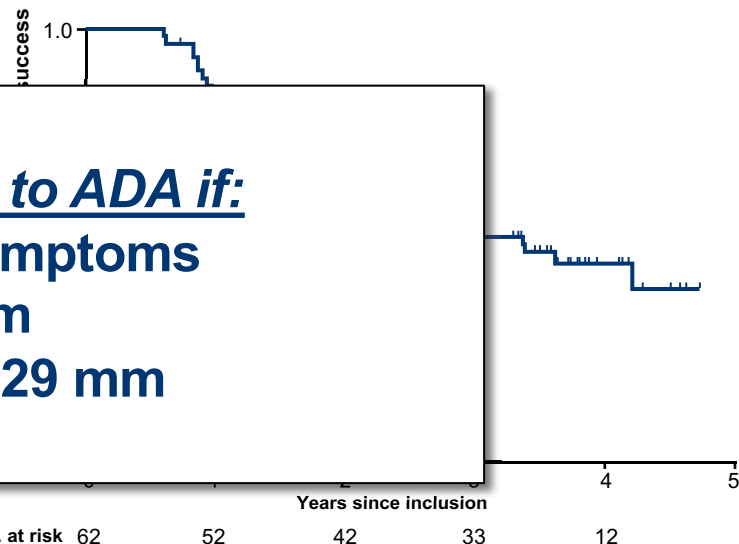
Intervention: Steroid taper

Comparator: ADA

Primary outcome: Surgery, or ADA withdrawal

Limitations: obstructive, the authors' clinical experience

CREOLE: Time to failure after successful response to ADA (n=62)



Patients respond better to ADA if:
Shorter duration of symptoms
Stricture <12 cm
Proximal dilatation <29 mm

- At week 24, 64% of patients had achieved success
- ≈30% of whole cohort had prolonged success at 4 years
- ≈50% of whole cohort was free of surgery at 4 years

Adalimumab in Structuring Crohn's Disease: STRIDENT

STRIDENT: Phase 4, single-center, open-label RCT (N=77)

Population: Patients with Crohn's disease with intestinal stricture(s) identified on MRI or ileocolonoscopy

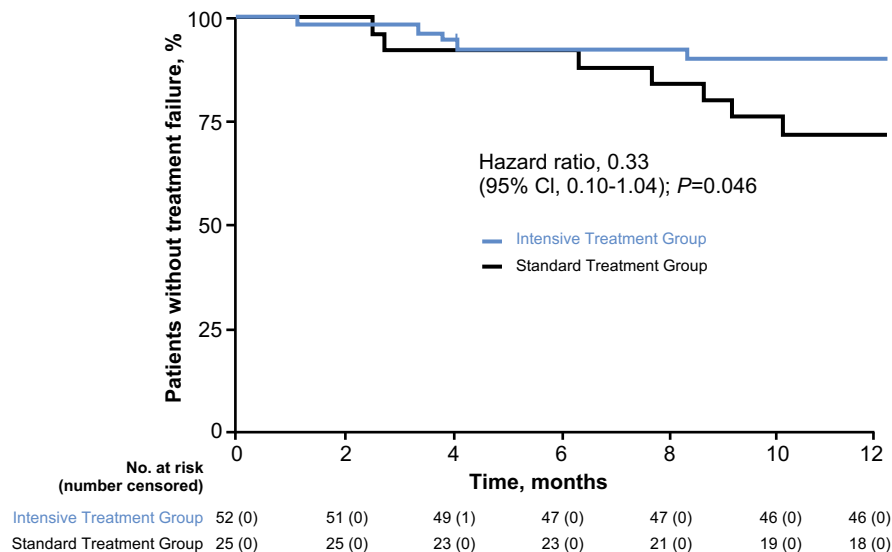
Intervention: High-dose ADA induction / escalation + dose-optimized thiopurine

Comparator: Standard ADA monotherapy

Primary outcome: Improvement in obstructive symptoms

Limitations: Single-center, open-label study; obstructive symptoms graded by a 5-point Likert scale

STRIDENT: Time to treatment failure over 12 months



At 12 months, 79% of patients receiving ADA + thiopurine and 64% of patients receiving ADA achieved improvement in obstructive symptoms ($P=0.17$)

CI = confidence interval.

Schulberg, et al. *Lancet Gastroenterol Hepatol.* 2022.

Medical Therapy for Stricturing Crohn's Disease – Global Consensus

- Appropriate **A**
■ Uncertain
■ Inappropriate

**Naïve
stricture**

Patient with <i>naïve</i> fibrostenosing CD				
	Bio-naïve and symptomatic	Bio-naïve and asymptomatic	Anti-TNF-experienced and symptomatic	Anti-TNF-experienced and asymptomatic
5-ASA	1 [1,1]	1 [1,2]	1 [1,1]	1 [1,1]
Corticosteroids	7.5 [6,8,8]	2 [1,7,4]	5 [2,2,7]	3 [1,4,3]
Thiopurines	2 [2,3]	3 [2,4]	2.5 [2,6]	2.5 [2,5]
Anti-TNF agents	8 [6,6,8]	7.5 [7,9]	2 [1,3]	2 [1,3]
Immunomodulators and anti-TNF agent	7.5 [5,8]	8 [5,7,8,3]	3 [2,4,3]	3.5 [2,5]
Vedolizumab	4 [3,7,6]	5 [4,6,3]	3 [2,5]	3 [2,5]
Immunomodulator and vedolizumab	4 [3,7,6]	4 [4,6,3]	4 [3,5]	4 [2,5]
Ustekinumab	6.5 [6,7,9]	6.5 [5,8]	7 [6,8]	7 [5,3,8]
Immunomodulator and ustekinumab	5 [4,6,3]	5.5 [4,7]	6 [3,7,8]	5.5 [4,8]
Methotrexate	2 [2,3]	3 [2,7,4]	3 [2,5]	3 [1,3,3]
Calcineurin-inhibitors	2 [1,3,4]	2 [2,3]	2 [1,3,2]	2 [1,2]

B

**Anastomotic
stricture**

Patient with <i>anastomotic</i> fibrostenosing CD				
	Bio-naïve and symptomatic	Bio-naïve and asymptomatic	Anti-TNF-experienced and symptomatic	Anti-TNF-experienced and asymptomatic
5-ASA	1 [1,1]	1 [1,1]	1 [1,1]	1 [1,1]
Corticosteroids	8 [6,3,9]	2.5 [1,5]	7 [4,3,8,7]	2 [1,5]
Thiopurines	3 [2,4]	3 [2,4,7]	2.5 [2,4,7]	3 [2,5]
Anti-TNF agents	8 [6,6,9]	7.5 [6,8,7]	2 [1,3,3,7]	3 [1,4]
Immunomodulators and anti-TNF agent	8 [5,7,8]	7 [5,7,8]	3.5 [1,7,5]	3 [1,7,4]
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Medical Therapy for Stricturing Crohn's Disease – Global Consensus

		Patient with <i>naïve</i> fibrostenosing CD			
		Bio-naïve and	Bio-naïve and	Anti-TNF-experienced	Anti-TNF-experienced asymptomatic
Naïve	<p>Naïve/anastomotic and symptomatic/asymptomatic strictures and <u>non-bio-IR</u></p> <ul style="list-style-type: none"> • First: Anti-TNF +/- immunomodulator • Second: Ustekinumab • Corticosteroids only if symptomatic 				1 [1,1]
					3 [1,4,3]
					2.5 [2,5]
					2 [1,3]
					3.5 [2,5]
					3 [2,5]
					4 [2,5]
					7 [5,3,8]
					5.5 [4,8]
					3 [1,3,3]
Anastomotic	<p>Naïve/anastomotic and symptomatic/asymptomatic strictures and <u>bio-IR</u></p> <ul style="list-style-type: none"> • First: Ustekinumab • Corticosteroids only if symptomatic 				2 [1,2]
					1 [1,1]
					2 [1,5]
					3 [2,5]
					3 [1,4]
					3 [1,7,4]
					3 [2,5,3]
					3.5 [1.7,5.3]
					7 [5,8]
					7 [3,7,8]
			3 [2,5]		
	Calcineurin-inhibitors	2 [1,2]	2 [1,2]	2 [1,2]	2 [1,2]

Medical Therapy for Stricturing Crohn's Disease – Global Consensus

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■ Uncertain
■ Inappropriate

**Naïve
stricture**

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Calcineurin-inhibitors	2 [1,3,4]	2 [2,3]	2 [1,3,2]	2 [1,2]
Endoscopic balloon dilation	8 [7,7,8,3]	5.5 [4,7]	8 [7,7,9]	7 [5,4,8]
Surgery	7 [7,8]	4.5 [3,7,6]	8 [8,9]	5 [4,6]

B

**Anastomotic
stricture**

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Corticosteroids	8 [6,3,9]	2.5 [1,5]	7 [4,3,8,7]	2 [1,5]
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Surgery	8 [8,8]	4 [2,5,3]	8 [8,8]	5 [2,7,5,3]

Risankizumab in Patients with Luminal Stenosis

Post-hoc analysis of Phase 3 registration program (ADVANCE, MOTIVATE, FORTIFY) n= 337 / 1419

Population: Patients with moderate to severe Crohn's disease with stenosis at baseline (SES-CD narrowing subscore > 0)

Intervention: Risankizumab 600 / 1200 mg IV then 160 / 320 mg SQ

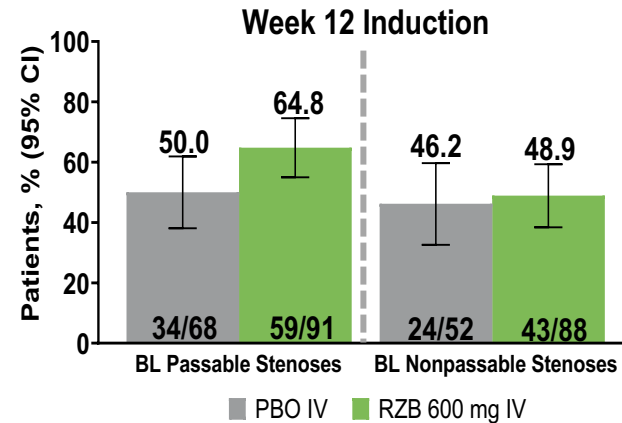
Comparator: Placebo

Primary outcome: Reduction in baseline stenosis, Resolution of baseline stenosis

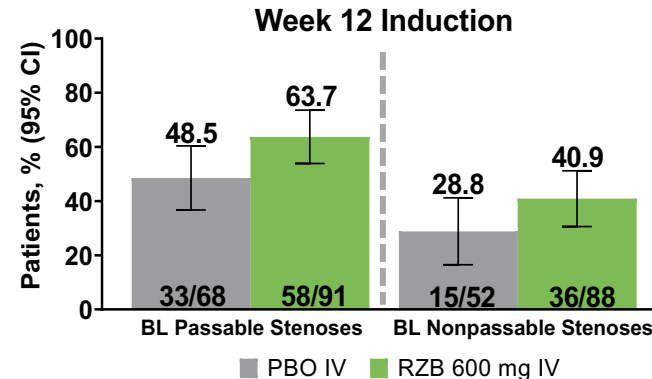
Limitations: Post-hoc analysis, no imaging available

Numerical improvement in endpoints with risankizumab compared to placebo

Reduction in baseline stenosis



Resolution of baseline stenosis



Upadacitinib in CD Patients with Luminal Stenosis

Post-hoc analysis of Phase 3 registration program (U-EXCEL, U-EXCEED, U-ENDURE) n= 274 / 1021

Population: Patients with moderate to severe Crohn's disease with stenosis at baseline (SES-CD narrowing subscore > 0)

Intervention: Ustekinumab 45 mg PO then Ustekinumab 30 mg or 15 mg PO

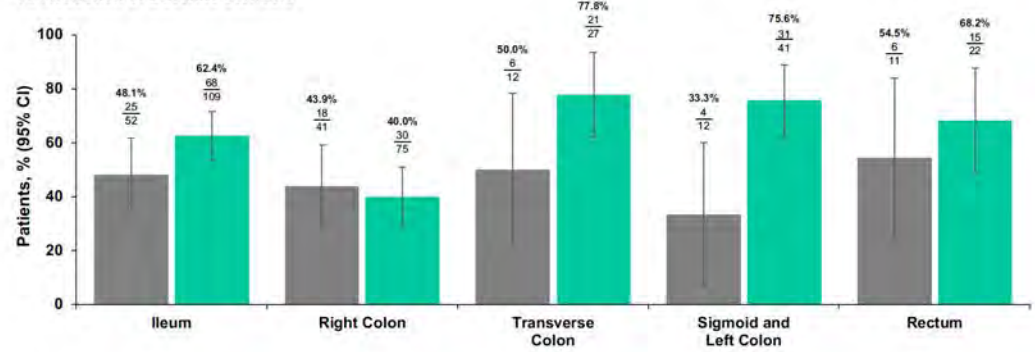
Comparator: Placebo

Primary outcome: Reduction in baseline stenosis, Resolution of baseline stenosis

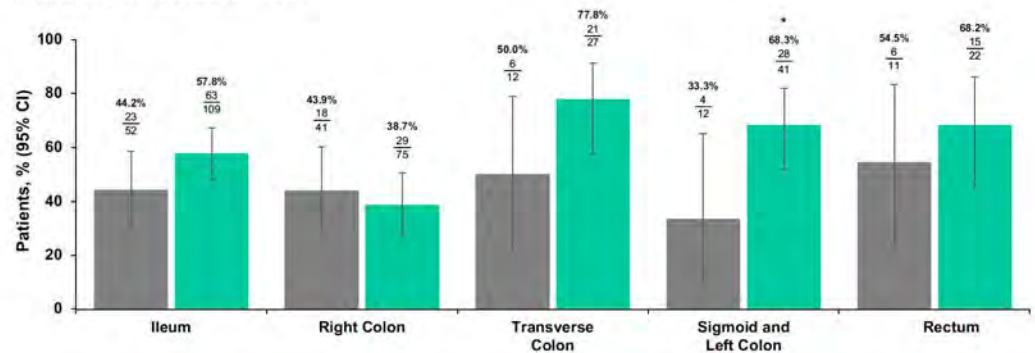
Limitations: Post-hoc analysis, no imaging available

Numerical improvement in endpoints with ustekinumab compared to placebo

A. Reduction of Baseline Stenosis^a



B. Resolution of Baseline Stenosis^b



Week 12

■ PBO ■ UPA 45 mg

Indications for Endoscopic Balloon Dilatation

- Symptomatic ileocolonic or colonic strictures
- Isolated anastomotic strictures preferred
- Upper GI strictures, if technically feasible
- Ulcerated stenosis/inflamed stenosis is not a contraindication

Cross-sectional imaging is important to exclude penetrating complications, length, and angulation

Endoscopic Balloon Dilatation

Systematic review: n=1463 with n=3213 dilatations

Dilation	Median %	95% CI
Technical success	89	87–91
Clinical efficacy	81	75–85

- **Stricture <5 cm associated with surgery-free outcome**
- **Each 1 cm increase = 8% increase in hazard for surgery**
- **Active disease NOT associated with increased risk**

Symptoms	35.9 (4.8–56.9)	62.1 (27.6–80.2)	75.9 (31.0–91.6)
Re-dilatation	36.5 (24.6–45.9)	51.8 (36.0–63.6)	73.5 (56.8–83.8)
Surgery	17.5 (11.8–22.9)	30.1 (17.4–40.9)	42.9 (23.7–57.4)

*Perforation, bleeding, dilation-related surgery.
Bettenworth, et al. *Inflamm Bowel Dis*. 2017.

Technical Parameters for Endoscopic Balloon Dilatation of Fibrostenosing CD

Cross-sectional imaging prior to intervention

Maximal stricture length 5 cm

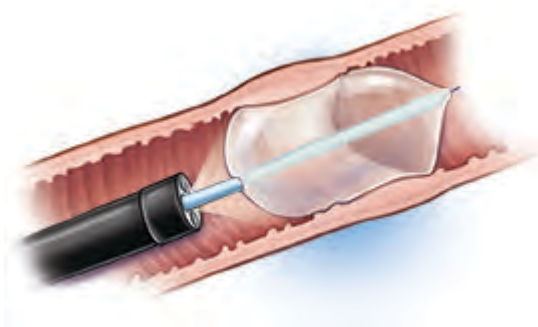
Luminal diameter influences initial balloon size

Escalation of anti-inflammatory therapy after dilation in case of active inflammation

Balloon insufflation time 60-90 sec

Contraindications to dilation

- Deep ulcers
- Malignant alterations
- Associated penetrating complications



Maximum of 3 steps for graduated dilation

Time to re-assessment after dilation

- Symptoms
- Endoscopic appearance
- Imaging appearance

15-18 mm is adequate luminal diameter at end of dilation therapy

Endoscopic Dilatation Is Superior to Intestinal Stent Placement

ProtDilat Study: Multicenter, open-label, randomized study (N=80)

Population: Patients with Crohn's disease with no more than 2 symptomatic, "pre-dominantly fibrotic" small bowel strictures (endoscopic or radiological) <10 cm

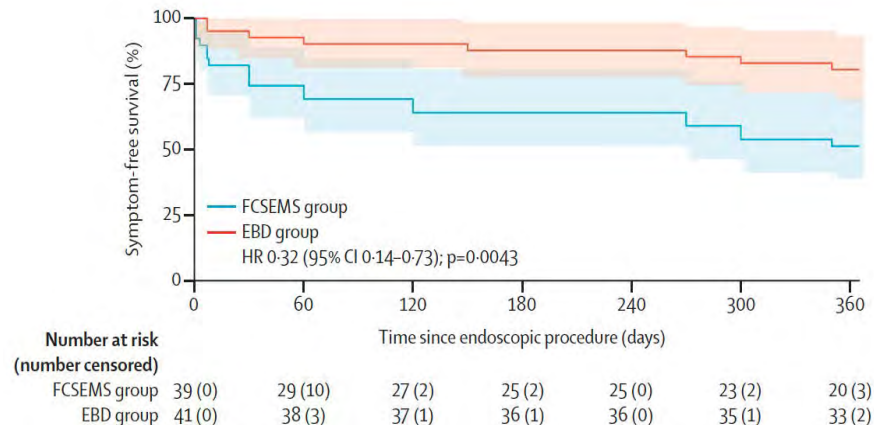
Intervention: Fully covered self-expanding metal stent (FCSEMS)

Comparator: Endoscopic balloon dilation (EBD)

Primary outcome: Proportion of patients free of a new therapeutic intervention (EBD, FCSEMS, or surgery) due to symptomatic recurrence at 1 year of follow-up

Limitations: Not blinded, early trial termination, mainly short strictures (median 30 mm), high rate of stent migration, no central reading for imaging

ProtDilat: Symptom-free survival over 12 months



80% in EBD group and 51% in FCSEMS group were free of new therapeutic intervention at 1 year (ITT, $P=0.0061$)

97% of FCSEMS migrated after a median of 2 days

Endoscopic Dilation vs Surgery

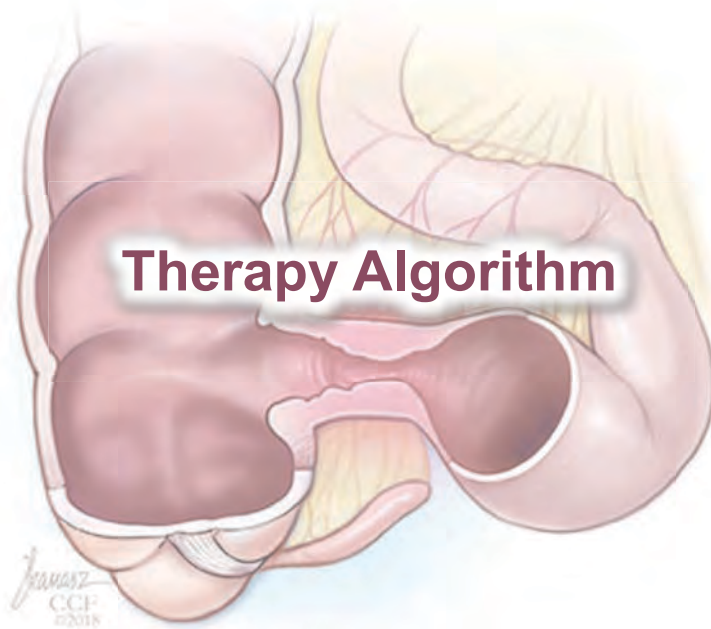
Favors endoscopic dilation

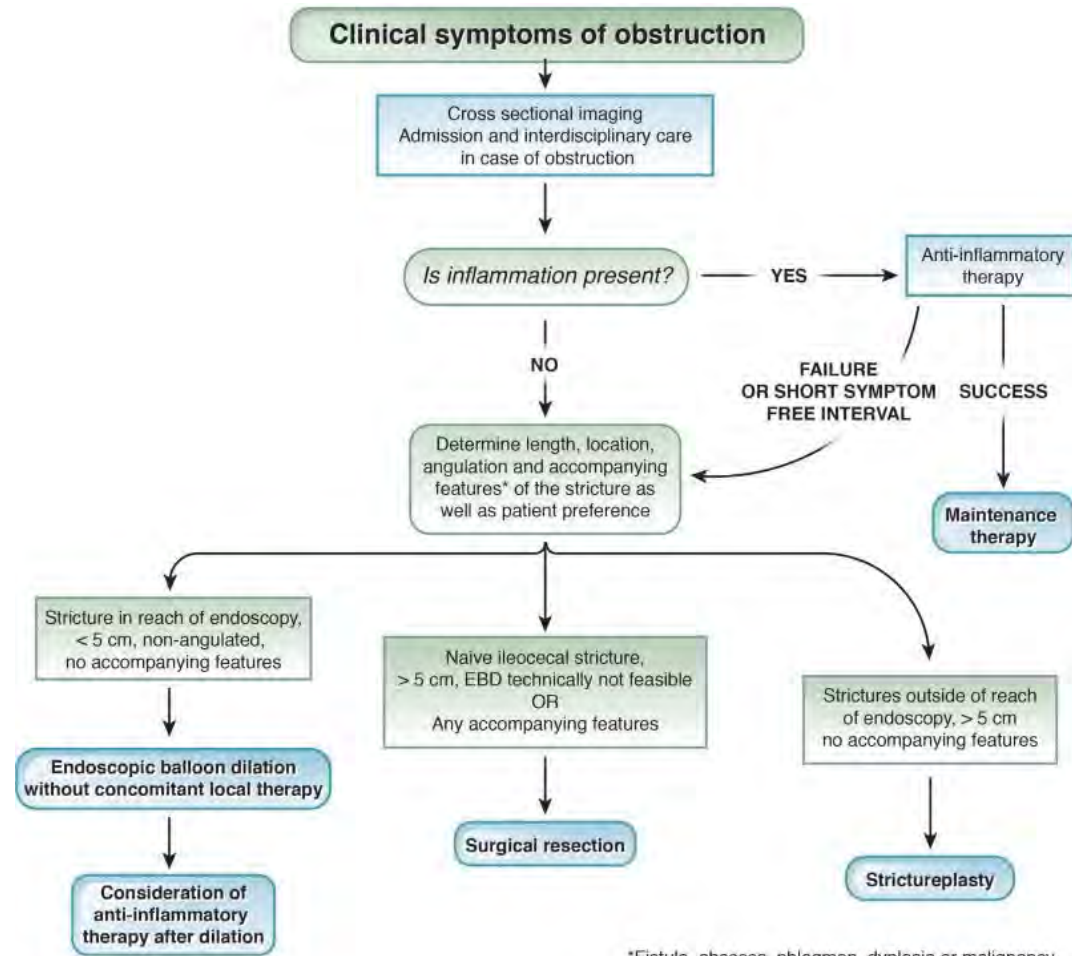
- Anastomotic stricture
- Short stenosis (<4-5 cm)
- Long interval to previous surgery/dilation
- Intermittent obstructive episodes

Favors strictureplasty/resection

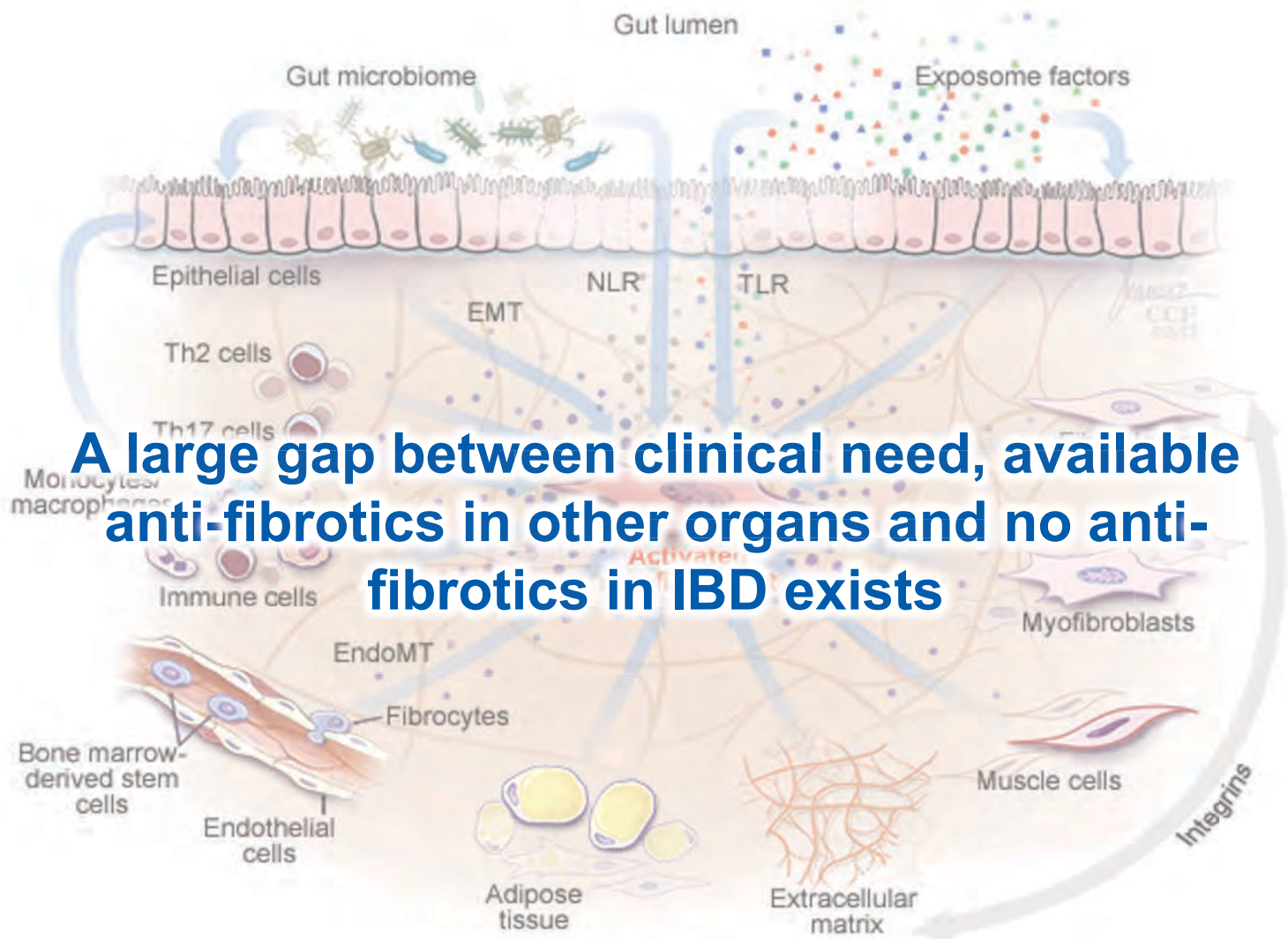
- Dilation technically difficult
- Long or multiple strictures
- Early recurrence after dilation
- Abscess/fistula/phlegmon
- Dysplasia/malignancy
- Long-standing or significant pre-stenotic dilation

Therapy Algorithm



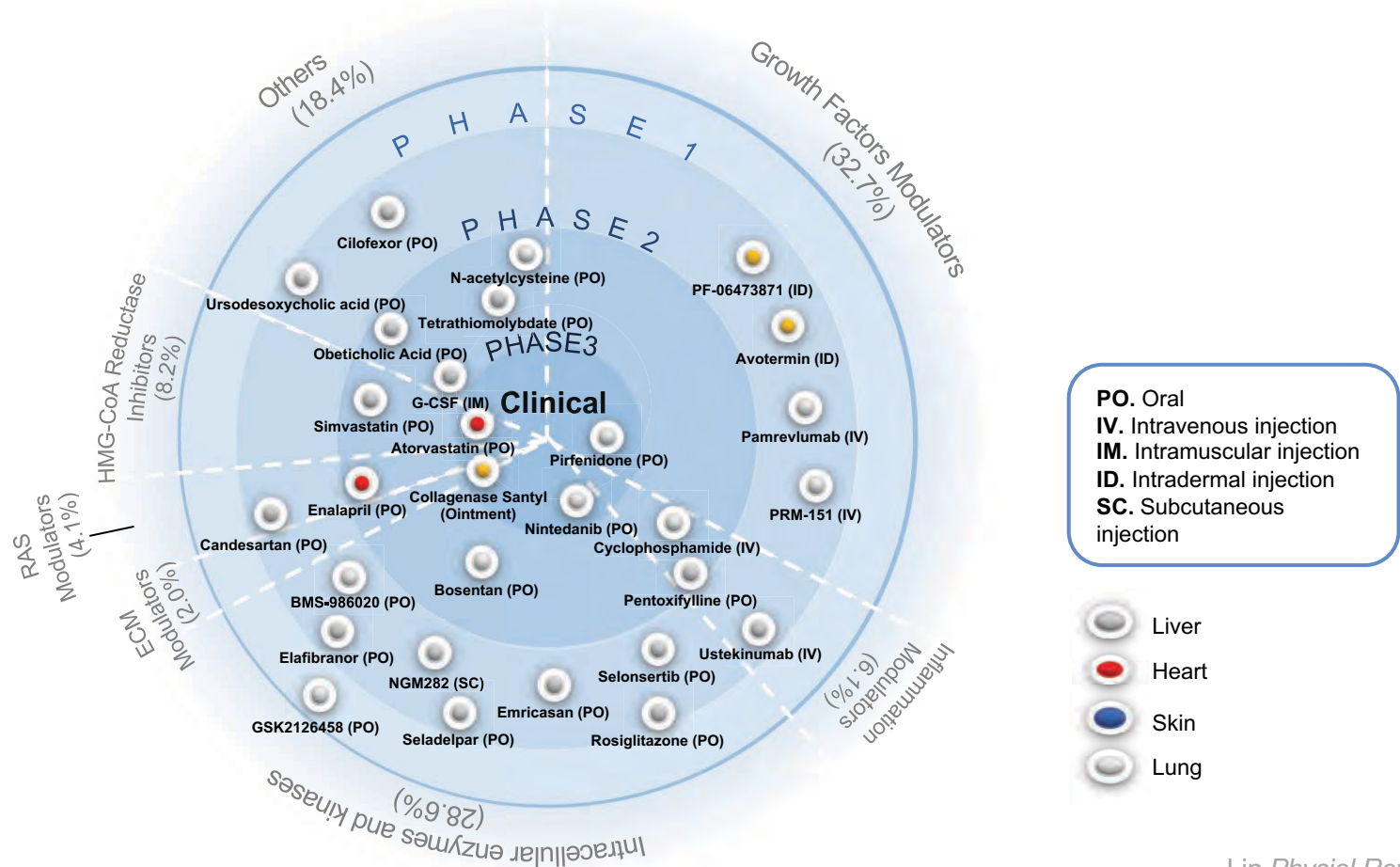


*Fistula, abscess, phlegmon, dysplasia or malignancy



A large gap between clinical need, available anti-fibrotics in other organs and no anti-fibrotics in IBD exists

Therapeutic Strategies to Target Fibrosis in Other Organs



Catch 22

No anti-fibrotic



No endpoints

An expert consensus to standardise definitions, diagnosis and treatment targets for anti-fibrotic stricture therapies in Crohn's disease

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A. Dignass⁹ | G. Rogler¹⁰ | S. A. Taylor¹¹ | J. Stoker¹² | J. Rimola¹³ | M. E. Baker¹ |
J. G. Fletcher¹⁴ | J. Panes¹³ | W. J. Sandborn^{4,15} | B. G. Feagan⁴ | V. Jairath⁴

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Summary

Background: Fibrotic stricture is a common complication of Crohn's disease (CD) affecting approximately half of all patients. No specific anti-fibrotic therapies are available; however, several therapies are currently under evaluation. Drug development for the indication of stricturing CD is hampered by a lack of standardised definitions, diagnostic modalities, clinical trial eligibility criteria, endpoints and treatment targets in stricturing CD.

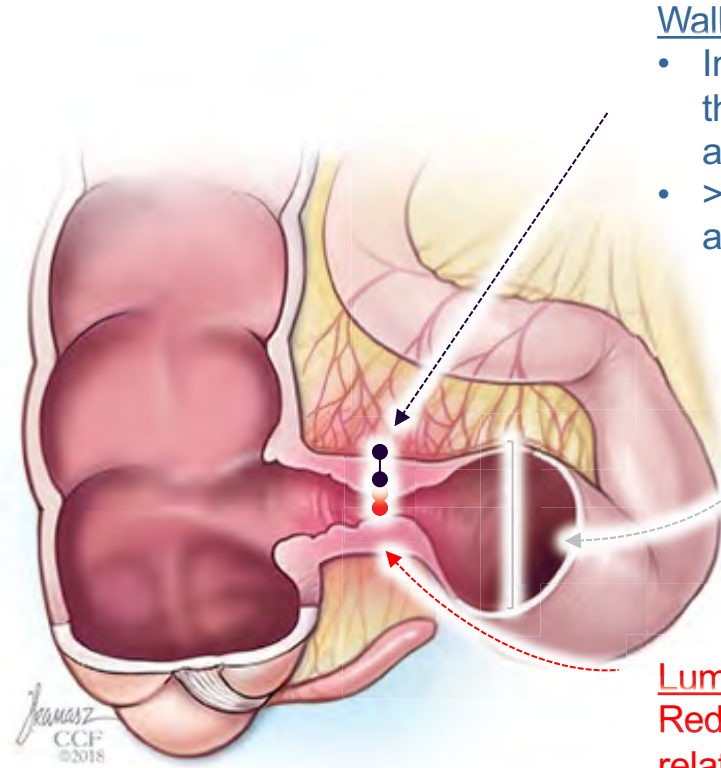
Aim: To standardise definitions, diagnosis and treatment targets for anti-fibrotic stricture therapies in Chron's disease.

Methods: An interdisciplinary expert panel consisting of 15 gastroenterologists and radiologists was assembled. Using modified RAND/University of California Los Angeles appropriateness methodology, 109 candidate items derived from systematic review and expert opinion focusing on small intestinal strictures were anonymously rated as inappropriate, uncertain or appropriate. Survey results were discussed as a group before a second and third round of voting.

Results: Fibrotic strictures are defined by the combination of luminal narrowing, wall thickening and pre-stenotic dilation. Definitions of anastomotic (at site of prior intestinal resection with anastomosis) and naïve small bowel strictures were similar; however, there was uncertainty regarding wall thickness in anastomotic strictures. Magnetic resonance imaging is considered the optimal technique to define fibrotic strictures and assess response to therapy. Symptomatic strictures are defined by abdominal distension, cramping, dietary restrictions, nausea, vomiting, abdominal pain and post-prandial abdominal pain. Need for intervention (endoscopic balloon dilation or surgery) within 24-48 weeks is considered the appropriate endpoint in pharmacological trials.

Conclusions: Consensus criteria for diagnosis and response to therapy in stricturing Crohn's disease should inform both clinical practice and trial design.

What Is a Stenosis on Cross-sectional Imaging?



Wall thickness

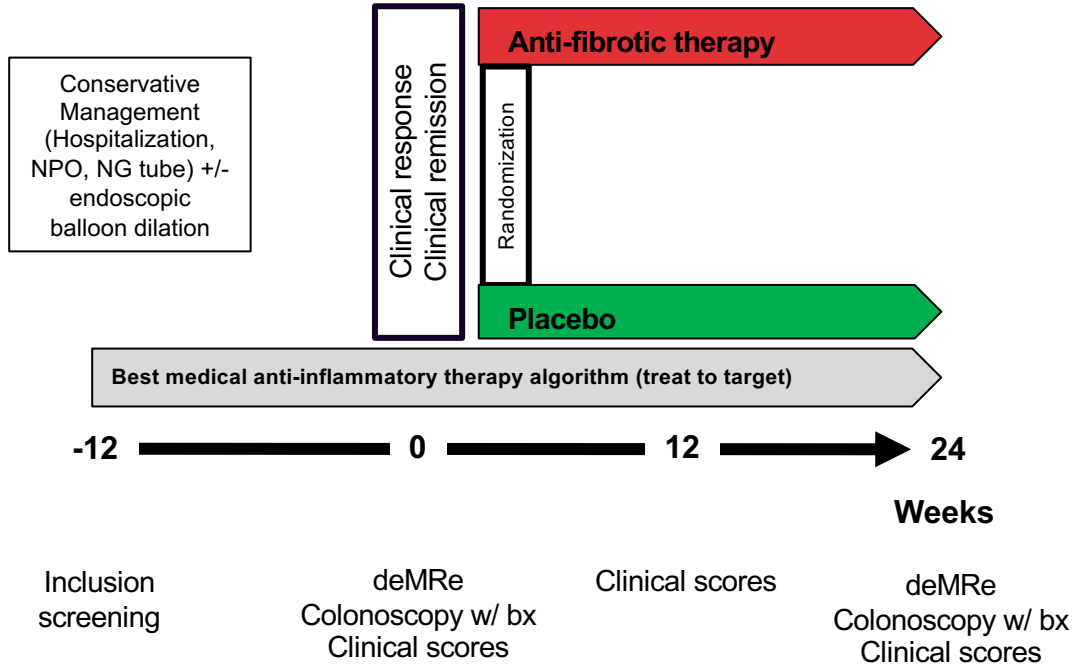
- Increase of 25% in maximally thickened area relative to normal adjacent bowel (naïve)
- >3 mm in maximally thickened area (anastomotic)

Pre-stenotic dilation
≥30 mm

Luminal diameter

Reduction by at least 50% measured relative to normal adjacent bowel

CONSTRUCT Study Group: Potential phase II proof of concept study design

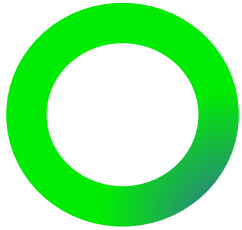


HELMSLEY

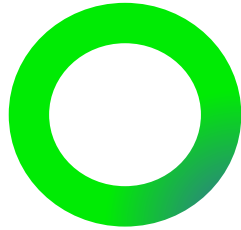
expMRe: experimental MR enterography; CSP: Colonoscopy; FC: Fecal Calprotectin; CRP: C-reactive protein
Clinical scores: Crohn's disease stricture score, Crohn's disease activity index



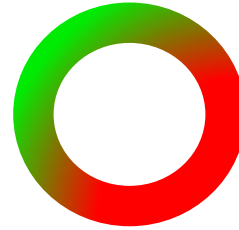
STAR Consortium Development Program



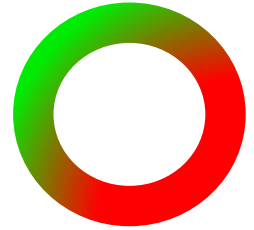
Patient reported outcome tool



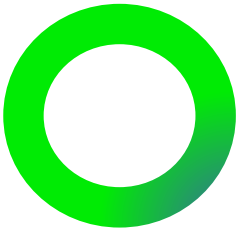
CT stricture index



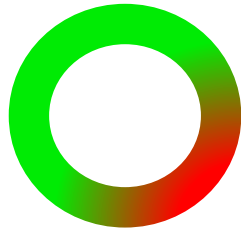
IUS index



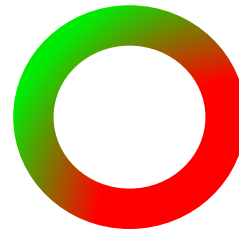
AI radiology



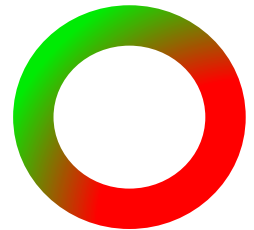
MR stricture index



Stricture histopathology index



NextGen trial population



STAR 2.0 Biomarker Program

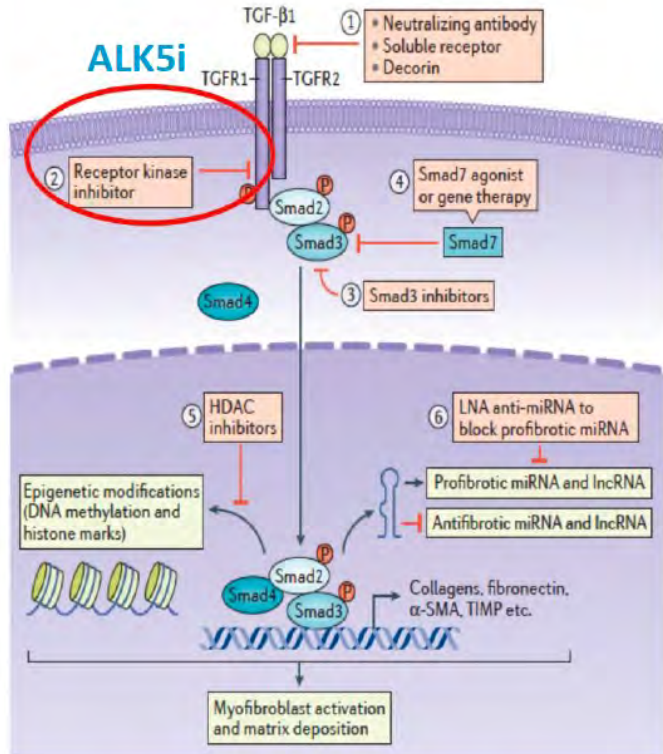
Summary

- Control of inflammation is the first step in therapy
- Anti-TNFs do not cause strictures
- Endoscopic dilation is indicated for strictures <5 cm, but perform imaging to exclude fistula, abscess, phlegmon
- Serial dilation +/- escalation of medical therapy is feasible, depending on patient preferences and symptom-free interval
- Perform resection in case of fistula, abscess, phlegmon, or malignancy
- Clinical trials with anti-fibrotic medications are starting

Summary

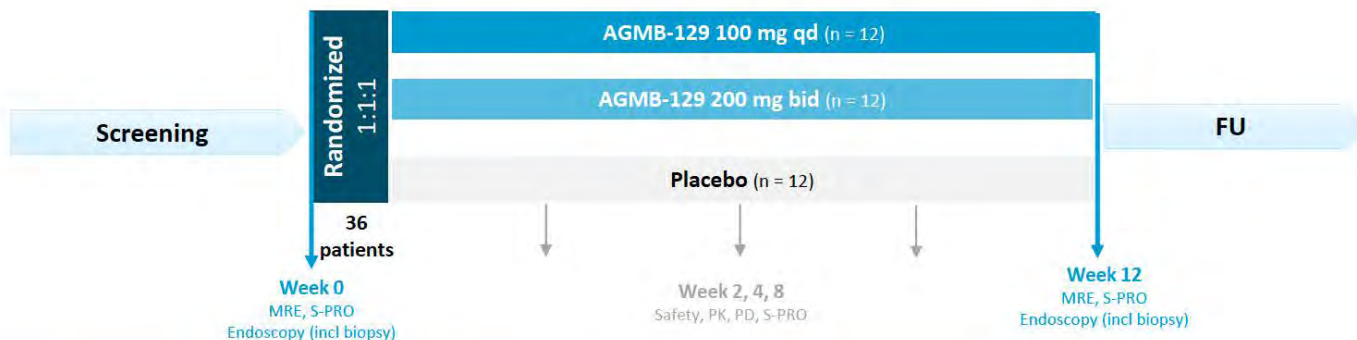
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GI Restricted ALK5 Inhibition as a Novel Therapeutic Target in Strictureing Crohn's Disease



- TGF-β1 is a highly validated target in fibrosis
- The intracellular receptor kinase ALK5 is required for TGF-β1 signaling
- Systemic inhibition is hampered by concern for cardiotoxicity, cancer risk and immune activation
- AGMB-129 is a GI restricted ALK5 inhibitor with exposure limited to the target tissue

Phase 2a Study in Stricturing Crohn's Disease with Non-Critical Symptoms



Patient Population

- Ileal or ileocolonic CD
- Up to 2 ileal stricture(s) which should be noncritical naive or anastomotic, with the most distal stricture (passable or non-passable) located in the (neo)-terminal ileum within reach of an endoscope and confirmed by MRE according to the following criteria:
 - localized luminal narrowing (luminal $\leq 50\%$ relative to normal adjacent bowel); AND
 - wall thickening ($\geq 25\%$ relative to adjacent bowel)
- Presence of tolerable obstructive symptoms (e.g., abdominal pain after eating, dietary restrictions), but not expected to require hospitalization, EBD, surgical resection, or additional therapy during the study. Participants should have sufficient food intake, even with diet modification
- Stable background treatment for CD and able to stay on the current treatment for the duration of the trial

Objectives

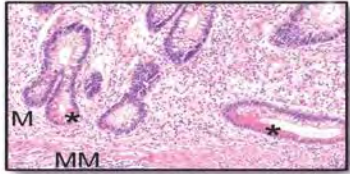
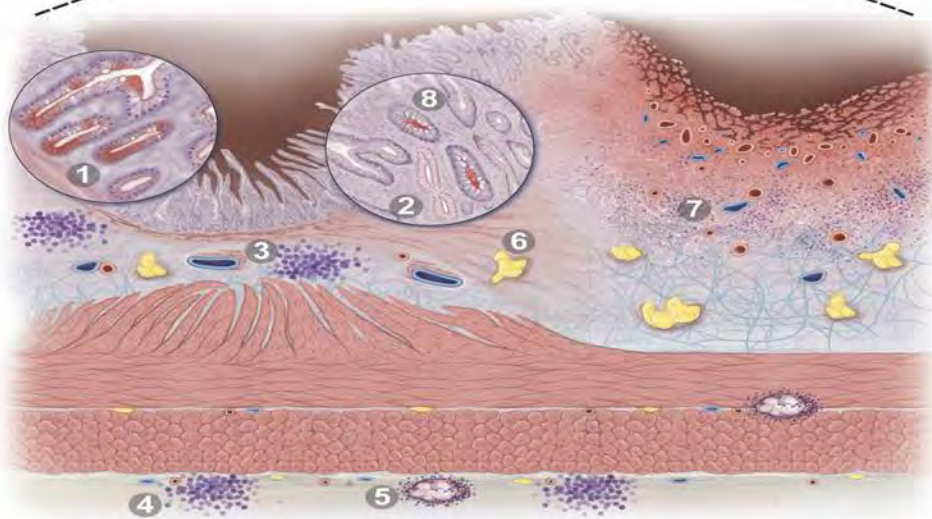
- To evaluate the safety of AGMB-129 in patients with fibrostenotic Crohn's disease, compared to placebo
- To evaluate the local (ileal) & systemic **pharmacokinetics and target engagement** of AGMB-129
- To evaluate the effect of AGMB-129 on signs and symptoms of inflammation
- To explore the clinical efficacy of AGMB-129, including on symptoms (s-PRO) and imaging (MRE)

What Is the Treatment Goal for This Patient?

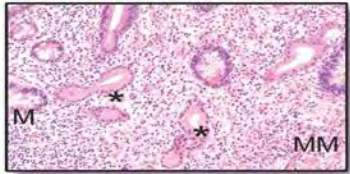
- Achieve remission
 - Normalization of symptoms
 - Return to normal diet
 - Endoscopic and radiologic improvement
- Avoidance of surgery
- Spare small intestinal loss

A New Gold Standard

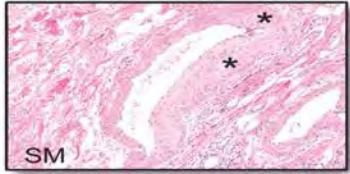
Stricture Histopathology



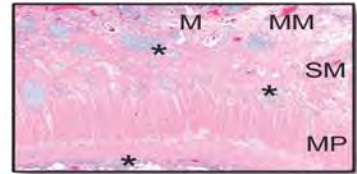
1. Paneth cell hyperplasia



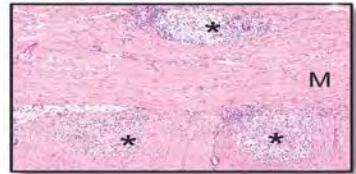
2. Pyloric gland metaplasia



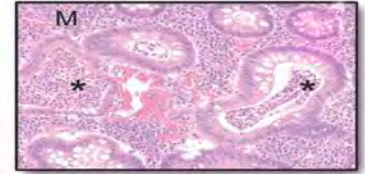
3. Fibromuscular hyperplasia



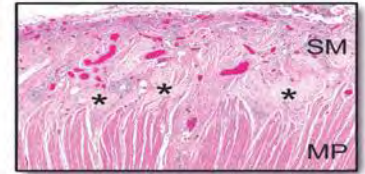
4. Transmural inflammation



5. Transmural epithelioid granulomas



8. Crypt abscess

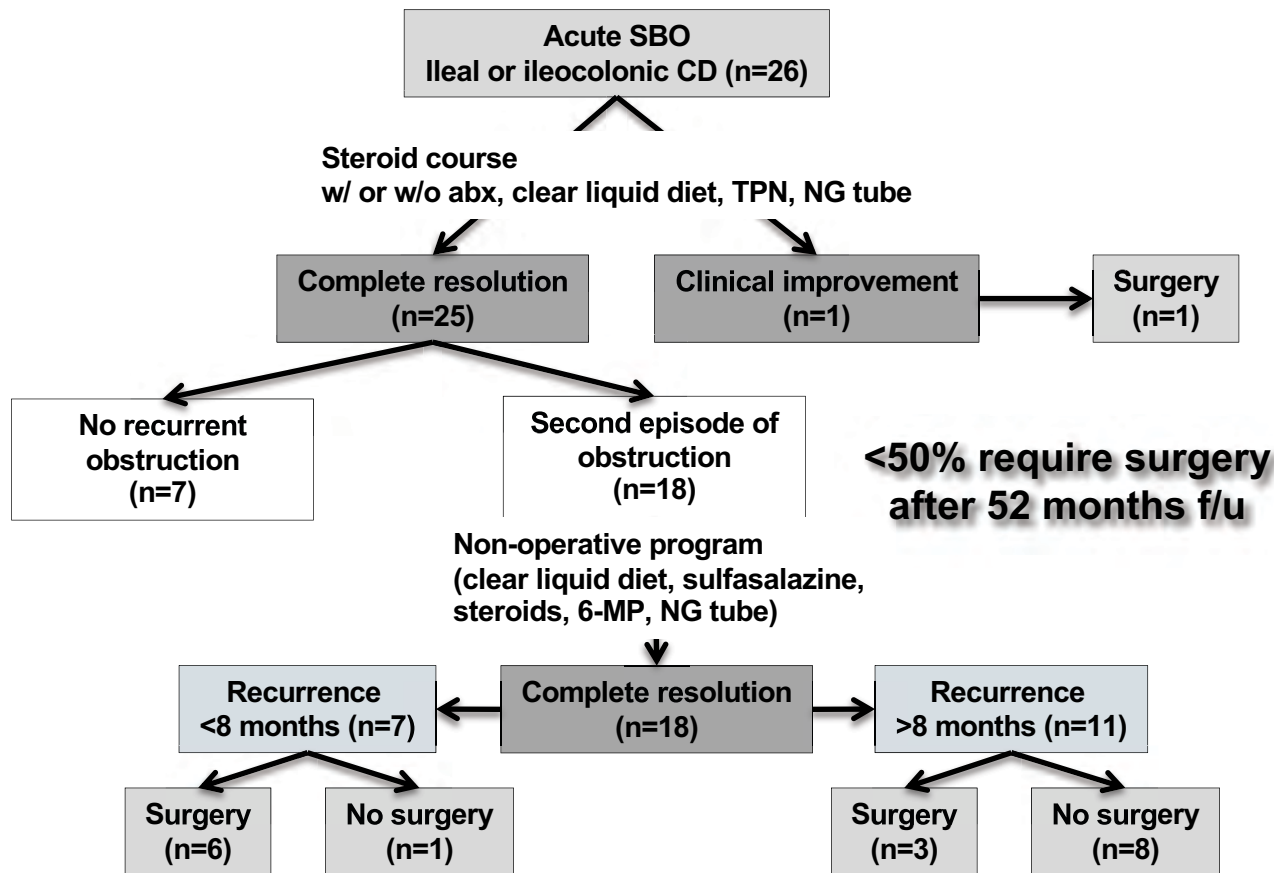


7. Ulcer with neural hyperplasia



6. Obliterative muscularization of the submucosa

Prognosis for Non-operative Management: Corticosteroids



Median f/u: 52 months.

SBO = small bowel obstruction; TPN = total parenteral nutrition; NG = nasogastric; MP = mercaptopurine.

Yaffe, et al. *J Clin Gastroenterol.* 1983.

Colonic Strictures – Proceed with Caution

- IBD-associated strictures
- No pre-operative evidence of dysplasia or cancer

	Low-grade dysplasia	High-grade dysplasia	Cancer
Crohn's disease	1%	0.4%	0.8%
Ulcerative colitis	2%	2%	5%

Detection of dysplasia or cancer in 3.5% of patients with inflammatory bowel disease and colonic strictures

Colonic Strictures – Proceed with Caution

- IBD-associated strictures
- No pre-operative evidence of dysplasia or cancer

Risk factors for malignancy

- Disease duration
- Location proximal to splenic flexure
- Symptomatic large bowel obstruction

Detection of dysplasia or cancer in 3.5% of patients with inflammatory bowel disease and colonic strictures