

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

Managing Intestinal Fibrosis in Patients With Inflammatory Bowel Disease



Florian Rieder, MD
Associate Staff, Department of Gastroenterology, Hepatology and Nutrition
Digestive Diseases and Surgery Institute
Investigator, Department of Pathobiology
Lerner Research Institute
Cleveland Clinic
Cleveland, Ohio

G&H How often do patients with Crohn's disease and patients with ulcerative colitis develop intestinal fibrosis?

FR First of all, it is important to distinguish clinically apparent fibrosis (ie, stenosis, stricture, and intestinal obstruction) from the mere presence of fibrosis because fibrosis can be subclinical for a long period of time. More than 50% of Crohn's disease patients have clinically apparent intestinal obstruction due to fibrostenosis over their lifetime. As for ulcerative colitis patients, reports of stenosis in the colon vary between approximately 1% and 11%, depending upon their definition. In terms of fibrosis globally (ie, any type of fibrotic change or abnormal tissue repair), it has been hypothesized that some degree of fibrosis is present in 100% of patients with inflammatory bowel disease, although this fibrosis may remain subclinical and intestinal obstruction may not occur.

G&H What are the risk factors for the development of intestinal fibrosis?

FR The major risk factor appears to be chronic inflammation because there has been no report in the literature of intestinal fibrosis of the gut occurring in inflammatory bowel disease patients outside areas affected by inflammation. Hence, anything that drives chronic inflammation appears to be a risk factor for intestinal fibrosis, such as smoking in patients with Crohn's disease.

There are no specific biomarkers available that can predict fibrosis or fibrostenosis, although there are a variety of markers that can predict complicated Crohn's disease. Serologic markers that have been described include antimicrobial antibodies in the circulation of patients with inflammatory bowel disease, certain genes that have been linked to more complicated disease courses, and certain clinical factors, such as extensive small bowel disease, perianal disease location, early age at diagnosis, and early need for corticosteroid therapy. However, it is important to emphasize that these risk factors are not specific for fibrostenosis; they are only predictive of a more complicated disease phenotype.

In addition, RISK (the Pediatric RISK Stratification Study), which was sponsored by the Crohn's and Colitis Foundation, examined microbial and extracellular markers in the mucosa of pediatric patients and noted that certain bacteria and extracellular matrix molecules of pediatric patients with Crohn's disease may be predictive of fibrostenosis. However, in general the accuracy of these markers does not allow them to be used in routine clinical practice.

G&H What is the role of the gut microbiome in intestinal fibrosis?

FR Findings from RISK suggest that certain microbial patterns may be predictive of fibrostenosis. The microbiome activates immune and nonimmune cells to produce

profibrotic factors, and the microbiota can directly activate intestinal fibroblasts toward the profibrogenic phenotype, which my colleagues and I are currently studying. The idea that the microbiome plays an important role in fibrostenosis is supported by preclinical cell culture experiments, animal models, evidence from humans in the biomarker field, and the antimicrobial response of an individual, which can be measured by antimicrobial antibodies in the circulation. An increased concentration of antimicrobial antibodies in the circulation has been found in patients with inflammatory bowel disease who have fibrostenosis.

G&H How can intestinal fibrosis be detected?

FR One of the most significant challenges in this field is that the current techniques to detect fibrostenosis are insufficient, as they are not validated or not accurate enough to be reliably used in clinical practice. The most advanced techniques presently available in this area are delayed enhancement magnetic resonance (MR) imaging and magnetization transfer MR imaging, but these techniques are not validated. Currently under exploration are ultrasound-based techniques such as ultrasound elastography. Other attempts have been undertaken to diagnose fibrosis, or the fibrotic component of a stricture, using endoscopy, biopsies, or biomarkers, but none of these techniques are accurate enough to be used. Diagnosis of a fibrotic component of a stricture is difficult in Crohn's disease patients because there is almost a complete overlap between inflammation and fibrosis; separating these 2 processes is one of the biggest obstacles for developing future antifibrotic therapy.

G&H What is the typical treatment course for intestinal fibrosis?

FR Patients with Crohn's disease who have intestinal obstruction due to fibrostenosis are typically hospitalized and designated nil per os. A nasogastric tube may be placed to decompress the intestinal tract, and most patients receive intravenous corticosteroids to reduce intestinal swelling and open up the obstruction. In these patients, intravenous corticosteroids work very well in the acute setting, although there has only been 1 small observational study in this area. Other possible treatment options are to use immunosuppressive therapies such as anti-tumor necrosis factor (TNF) antibodies and to perform endoscopic therapies such as balloon dilation or surgical therapies such as resection or strictureplasty. Anti-TNF therapy in patients with Crohn's disease-associated obstruction has a surgery-free rate of approximately 60% after 2 years.

Overall, treatment algorithms recommend trying the best medical therapy first to avoid endoscopic or surgical intervention. However, in reality, most patients who present with intestinal obstruction due to fibrostenosis and have Crohn's disease will end up having at least 1 surgery during their lifetime. Disease invariably recurs in the setting of Crohn's disease, so many of these patients have restricting disease several years after the first resection and will need to go through the same cycle again.

In ulcerative colitis patients, strictures occur in the colon, and, thus, there is a risk of malignancy. Doctors should be very thorough in ruling out malignancy by using extensive biopsies or brushing of the stricture. If there is a late-onset stricture that is rapidly progressing even when biopsies or brushings are negative, the risk of malignancy is significant, which often then warrants a surgical resection.

G&H Are there any antifibrotic therapies available?

FR There is no specific antifibrotic therapy available. There has been an emergence of more and more improved therapies in biologic inflammatory bowel disease treatment, which has resulted in better control of inflammation. However, this has not appeared to significantly reduce the incidence of stricture formation in patients with inflammatory bowel disease. Current medical anti-inflammatory therapies temper the situation but do not appear to cure or treat the fibrotic component. Thus, additional mechanisms, other than chronic inflammation, are likely important in the development of stricturing disease.

G&H When, more specifically, should endoscopy and surgery be used to treat intestinal fibrosis, and which of the various techniques are most common?

FR Endoscopy is an option for treating strictures if they are in reach of endoscopy—which most are because stricture location follows the location of the inflammation, and the most common location of inflammation in Crohn's disease is the terminal ileum, which is accessible by endoscopy. Endoscopic therapy can only be used if there are no contraindicating concomitant features, such as internal penetrating disease, dysplasia, or malignancy, and only if the stricture is not too long (the cutoff is 5 cm).

Endoscopic therapy is performed by placing the endoscope proximal to the stricture and then deploying a balloon, withdrawing the endoscope with the deployed balloon into the stricture, and stretching it open (retrograde technique). If the stricture cannot be passed with the endoscope, but the proximal end can be visualized,

the endoscope can be placed distally to the stricture and the balloon then deployed into the stricture (antegrade technique). However, before endoscopic therapy is performed, cross-sectional imaging must be used to make sure that the aforementioned contraindicating features are not present.

Surgical techniques depend upon the location and length of the stricture. There are several options for strictureplasty, or bowel-preserving surgery, but this type of intervention is contraindicated when there are concomitant features such as an abscess, fistula, dysplasia, or malignancy. The various techniques include Heineke–Mikulicz strictureplasty, Finney strictureplasty, and Michelassi strictureplasty.

Surgical resection is another option and can be used whenever endoscopy or strictureplasty cannot be performed. Surgical resection essentially consists of taking out the affected bowel and reconnecting the rest of the bowel afterward.

G&H What side effects are possible with these treatments?

FR The drive to develop an antifibrotic therapy is led by the complication and side-effect profiles of the alternate treatment options. For example, the complications associated with endoscopic therapy are hospitalization, perforation, and bleeding in approximately 3% of patients. For surgical resection and strictureplasty, there is a significant amount of morbidity and hospitalizations. Thus, the ultimate goal is to prevent the need for endoscopic or surgical interventions through the development of an antifibrotic therapy.

G&H Can intestinal fibrosis be completely reversed?

FR Intestinal fibrosis is not a one-way street from inflammation to fibrosis and then to stricture formation, intestinal obstruction, and surgery, as commonly thought. Observational data have shown that patients undergoing strictureplasty experience regression of strictures over time. Thirty percent of patients who undergo this procedure have to undergo repeat surgery after 5 years, but only 3% of patients need it because of problems at the site of the prior strictureplasty. In other words, the indication for surgery rests elsewhere. During the second surgery, doctors have assessed the site of the strictureplasty and have observed that fibrosis regresses. This has also been found in serial ultrasound studies of strictureplasties over time. Researchers from the University of Leuven performed strictureplasty over the ileocecal valve and were able to follow the regression of fibrosis with endoscopy. Thus,

there have been observations that fibrosis is reversible, but doctors have not been successful in reversing fibrosis with medical therapy.

G&H What recent developments or advances have there been in this area?

FR This is one of the fastest-moving fields within inflammatory bowel disease. Recent advances have been made in the area of novel mechanisms of disease. Of particular interest are the phenomenon of fibrosis progressing independently of inflammation, and environmental factors such as the microbiome influencing fibrosis. Novel animal models have been developed, and there is a good deal of work being done in the area of biomarkers to predict or detect intestinal fibrosis. This includes imaging such as novel ultrasound or MR techniques. Parallel to this, researchers are embarking on developing and validating clinical trial endpoints and protocols to test novel anti-fibrotic agents.

Dr Rieder has done consulting for UCB, Celgene, Samsung, Roche, Pliant, Thetis, Boehringer Ingelheim, Helmsley, and RedX; has served on advisory boards for AbbVie, UCB, Receptos, Celgene, and Thetis; and has served on the speakers bureau for AbbVie.

Suggested Reading

- Bettenworth D, Gustavsson A, Atreja A, et al. A pooled analysis of efficacy, safety, and long-term outcome of endoscopic balloon dilation therapy for patients with stricturing Crohn's disease. *Inflamm Bowel Dis*. 2017;23(1):133-142.
- Bouhnik Y, Carbonnel F, Laharie D, et al; GETAID CREOLE Study Group. Efficacy of adalimumab in patients with Crohn's disease and symptomatic small bowel stricture: a multicentre, prospective, observational cohort (CREOLE) study. *Gut*. 2018;67(1):53-60.
- Gordon IO, Agrawal N, Goldblum JR, Fiocchi C, Rieder F. Fibrosis in ulcerative colitis: mechanisms, features, and consequences of a neglected problem. *Inflamm Bowel Dis*. 2014;20(11):2198-2206.
- Kugathasan S, Denson LA, Walters TD, et al. Prediction of complicated disease course for children newly diagnosed with Crohn's disease: a multicentre inception cohort study. *Lancet*. 2017;389(10080):1710-1718.
- Latella G, Rieder F. Intestinal fibrosis: ready to be reversed. *Curr Opin Gastroenterol*. 2017;33(4):239-245.
- Rieder F. The gut microbiome in intestinal fibrosis: environmental protector or provocateur? *Sci Transl Med*. 2013;5(190):190ps10.
- Rieder F, Fiocchi C, Rogler G. Mechanisms, management, and treatment of fibrosis in patients with inflammatory bowel diseases. *Gastroenterology*. 2017;152(2):340-350.e6.
- Rieder F, Kessler S, Sans M, Fiocchi C. Animal models of intestinal fibrosis: new tools for the understanding of pathogenesis and therapy of human disease. *Am J Physiol Gastrointest Liver Physiol*. 2012;303(7):G786-G801.
- Rieder F, Latella G, Magro F, et al. European Crohn's and Colitis Organisation topical review on prediction, diagnosis and management of fibrostenosing Crohn's disease. *J Crohns Colitis*. 2016;10(8):873-885.
- Specia S, Rousseaux C, Dubuquoy C, et al. Novel PPAR γ modulator GED-0507-34 Levo ameliorates inflammation-driven intestinal fibrosis. *Inflamm Bowel Dis*. 2016;22(2):279-292.