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Targeting anti-fibrotic pathways in Crohn's disease – The final frontier?

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ABSTRACT

Intestinal fibrosis with stricture formation affects up to half of patients with Crohn's disease (CD), resulting in impaired quality of life, increased risk of surgical intervention, and associated patient morbidity. The underlying pathophysiologic mechansisms responsible for initiating and perpetuating intestinal fibrosis are complex, dynamic, and implicate both inflammation-dependent and independent pathways. Previously thought to be an irreversible complication of long-standing inflammation unresponsive to medical therapy, fibrostenotic CD has been traditionally managed with endoscopic or surgical approaches. However, recent advances in our understanding of the humoral, cellular, and environmental pathways driving intestinal fibrosis has the potential to fundamentally change these management paradigms for CD-related strictures. Furthermore, the promise of fibrosis treatments in other organ systems has encouraged hope that anti-fibrotic treatment approaches for CD may be within reach. Here, we summarize the key breakthroughs in our molecular understanding of intestinal fibrosis, review current medical, endoscopic, and surgical treatment approaches to CD-related strictures, propose future directions for anti-fibrotic therapy in CD, and identify crucial research questions in this field that require additional investigation.

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Abbreviations

ASCA	Anti-*Saccharomyces cerevisiae* antibody
ATG16L1	Autophagy-related-16L1
bFGF	basic fibroblast growth factor
CD	Crohn's disease
CEUS	contrast enhanced ultrasound
CT	computed tomography
CTGF	connective tissue growth factor
DAMP	damage-associated molecular pattern
DCE	dynamic contrast enhancement
EBD	endoscopic balloon dilation
ECM	extracellular matrix
EGF	epidermal growth factor
EMT	epithelial to mesenchymal transition
EndoMT	endothelial to mesenchymal transition
IBD	inflammatory bowel disease
IL	interleukin
IGF	insulin-like growth factor
IPF	idiopathic pulmonary fibrosis
LPS	lipopolysacchardie
MC	mesenchymal cell
MAMP	microbe-associated molecular pattern
MMP	matrix metalloproteinase
MR	magnetic resonance
MT-MR	magnetisation transfer MR
NOD	nucleotide-binding oligomerization domain-containing protein
OmpC	outer membrane protein C
PDGF	platelet derived growth factor
PRR	pattern recognition receptors
RCT	randomised controlled trial
ROC	receiver operator curve
ROCK	rho-associated protein kinase
SICUS	small intestinal contrast enhanced ultrasound
TIMP	tissue inhibitor of metalloproteinase
TGF	transforming growth factor
TLR	toll like receptor
TNF	tumour necrosis factor
TTS	through the scope
US	ultrasound

Introduction

Crohn's disease (CD) is a chronic, progressive and disabling inflammatory disorder of the gastrointestinal tract that culminates in structural bowel damage [1]. The development of fibrostenotic strictures are a feared complication in CD: up to 10% of patients have symptomatic strictures at diagnosis and approximately half will manifest a stricturing phenotype in long-term follow-up [2,3]. Furthermore, fibrosis progression reduces patient quality of life and may predispose to other disease-related complications including internal penetrating fistulae. Historically, it was postulated that intestinal fibrosis reflected the consequence of longstanding transmural inflammation and the end result of this process was the development of a fibrotic, irreversible stricture, unresponsive to medical anti-inflammatory therapy. These strictures would inevitably present with bowel obstruction requiring surgical resection [4].

However, advances in clinical and basic science research evaluating the dynamic nature of fibrosis pathogenesis has caused this paradigm to be revisited [5]. The delineation of critical molecular regulators of fibrosis has fuelled interest in identifying anti-fibrotic specific treatment targets and the development of anti-fibrotic therapies in other organ systems [6,7] has inspired hope that these approaches may also be successful in patients with inflammatory bowel disease (IBD). In this review, we summarize our current understanding of the pathogenesis of CD-related fibrosis, review the use of diagnostic tools for assessing intestinal strictures, provide an approach to medical, endoscopic, and surgical management of CD patients with stricturing disease, and forecast potential fibrosis-specific therapies in IBD. We also highlight gaps in our current knowledge that require additional investigation to bring anti-fibrotic treatments from the bench to the bedside.

Pathogenesis of intestinal fibrosis

Physiologic repair processes are programmed to restore tissue integrity after injury. In CD, chronic intestinal inflammation results in mucosal damage that triggers mesenchymal cells (MC) to produce extracellular matrix (ECM) and restore tissue integrity [8]. Conversely, the development of intestinal fibrostenosis represents an exaggerated tissue repair response, with pathologic collagen-rich ECM deposition and mesenchymal fibroblasts, myofibroblasts, and smooth muscle cell expansion [9]. During the normal tissue repair response, inflammation initiates a cascade of events that include the activation of immune cells and MCs, triggering the secretion of cytokines, proteases, chemokines, and growth factors [10]. This response is tightly controlled, limiting MC proliferation, migration, and ECM production, and is followed by resolution of inflammation and fibrotic signaling. However, in the setting of pathogenic tissue remodelling, the mechanisms that control the expression and degradation of ECM are not operative at the appropriate levels, and fibrogenic MSCs are not only maintained, but are expanded in number [11]. In CD patients, myofibroblasts are thought to be the major sites of increased type I collagen mRNA expression and collagen deposition in the muscularis [8]. However, intestinal smooth muscle cells isolated from CD also produce large amounts of ECM [12,13]. Histologically, this results in transmural thickening of the entire intestinal wall from mucsoa to muscularis propria, with dense deposits of collagen III and V bands [14], increased fibronectin and tenascin C [15], fibromuscular submucosal obliteration [16] and muscularis propria hyperplasia [17]. The mechanisms that trigger this fibrotic response are regulated by humoral, cellular, and environmental factors [18].

It is well-established that chronic inflammation is a critical mediator of fibrosis in CD. Major changes in DNA methylation and gene expression that promote fibrogenesis occur in the context of intestinal inflammation [19]. Transforming growth factor (TGF)-β is the key humoral factor implicated in CD-related fibrosis. TGF-β potently activates MCs towards a pro-fibrotic response [20] and signaling is regulated by the Smad pathway with activation of TGF-β1 receptor I kinase initiating downstream cellular activation of profibrotic genes [21,22]. Overexpression of TGF-β predisposes animal models to intestinal fibrosis and CD-related strictures demonstrate significantly elevated TGF-β production [23]. While developing therapeutics to block TGF-β signaling might appear attractive for treating fibrosis, modulating the activity of TGF-β within the context of CD should be approached with caution. On the one hand, reducing TGF-β-induced MC activation and fibrogenic activity could limit the remodelling process; however, reducing TGF-β′s immunoregulatory functions on regulatory T

lymphocytes may result in exacerbation of inflammation, a perspective supported by the fact that TGFβ1 knock-out animal models exhibit a systemic autoimmune syndrome [24]. Thus, strategies to selectively modulate TGF-β1 signaling, through enhancing endogenous regulatory pathways, or damping the activity of the other pro-fibrotic mediators, which feed into the TGF-β1/Smad pathway, may provide alternative approaches to treat fibrosis.

While the mechanisms that contribute to the loss of control in this system are not known, some have postulated that adaptive immune responses and the induction of chronic tissue inflammation may be responsible for aberrant MSC activation, proliferation and survival. To this end, a simplified view would suggest that Th2- and Th17-type immune responses contribute to pathogenic tissue remodelling in CD [10,25], however this has yet to be completely defined. Interleukin (IL)-13 is another cytokine that has been identified both *in vivo* and *in vitro* to regulate fibrosis. IL-13 enhances secretion of TGF-β1, induces smooth muscle contractility in CD, and downregulates fibroblast production of matrix metalloproteinases (MMP) that cull fibrotic collagen deposits [26]. Blocking IL-13-α2 receptors in mouse models of colitis attenuates inflammation-associated fibrosis [27]. IL-17A expression is also upregulated in CD-related strictures [28–30], with consequent downstream effects on collagen and myofibroblast tissue inhibitor of metalloproteinase (TIMP) 1 [31]. Finally, the overexpression of other growth factors, including epidermal growth factor (EGF), insulin-like growth factor (IGF-1&2), connective tissue growth factor (CTGF), platelet-derived growth factor (PDGF), and basic fibroblast growth factor (bFGF), appears to be important for fibrosis development and may be future targets for anti-fibrotic therapy [32].

MCs are crucial effector cells in fibrosis pathogenesis. MC activation occurs in response to a host of different autocrine and paracrine signals, microbe-associated (MAMP) and damage-associated (DAMP) molecular patterns, growth factors, pro-inflammatory cytokines, lipid mediators, and pattern recognition receptors (PRRs) [32]. Disease-activated MCs in CD present as fibroblasts and myofibroblasts that are phenotypically characterized by increased migration and proliferation, promoting ECM deposition [33]. In contrast, ECM turnover is primarily regulated by MMPs. Synthesized by macrophages, MMPs degrade ECM components [34], remove apoptotic cells that promote fibrosis [35], and produce IL-10 that inhibits fibroblast TGF-β-dependent collagen production [36]. Interestingly, fibrosis reversal observed after strictureplasty has been hypothesized to be secondary to changes in macrophage polarization after surgery [18]. Stricture development in CD reflects an imbalance in ECM turnover, caused by either reduced MMP-driven degradation or increased MC-ECM production.

Given the central role of cellular mechanisms in fibrosis pathogenesis, attenuating the accumulation of MCs has been proposed as a treatment approach in stricturing CD. The increase in MC numbers is thought to be driven primarily from enhanced proliferation and aberrant survival cues/responses, however other origins have been suggested. Inflammation-dependent epithelial-to-mesenchymal transition (EMT) or endothelial-to-mesenchymal transition (EndoMT) describe the process by which fully mature epithelial and endothelial cells can transform back into MCs and subsequently re-enter the pool of fibroblasts producing collagen [37,38]. However, this process has been shown to be reversible *in vivo* in renal, pulmonary, and cardiac models of fibrosis [39–41]. Potentially, transitioning MCs back to fibroblasts may alleviate strictures and is an avenue of investigation in CD.

Pro-fibrotic factors are equally important in sustaining stricture progression, even in the absence of inflammation [42]. Recently, it has been shown that local ECM composition and stiffness may actively contribute to fibrosis development. In response to IL-6, CD fibroblasts synthesize increased levels of KIAA1199 hyaluronan-degrading enzyme that generate DAMP hyaluronan fragments. These fragments further stimulate local fibrosis and inflammation [43]. Additionally, mechanical stiffness of the ECM, determined by both ECM collagen composition and mesenchymal and smooth muscle contraction within stricutres, has been shown to independently stimulate MCs without other pro-inflammatory activating factors [44,45]. Therapeutic intervention by a locally acting rho-associated protein kinase (ROCK) inhibitor, blocking MC to sense their stiffened ECM, led to prevention and reversal of experimental fibrosis [46].

Finally, environmental factors, particularly components of the intestinal microbiome, are required for fibrosis development. In CD, impaired mucosal barrier function from chronic inflammation results in increased bacterial translocation into the mucosa, facilitating host-microbiome interactions mediated by intestinal cell sensing of MAMPs through PRRs. This results in fibroblast activation towards a pro-fibrogenic phenotype [47]. In hepatic models, exposure to lipopolysaccharide (LPS) in the portal vein promotes liver fibrosis and in intestinal fibroblasts, flagellin induces pro-inflammatory and pro-fibrotic expression [48,49]. Gene variants affecting bacterial sensing, recognition, or processing, such as mutations in nucleotide-binding oligomerization domain-containing protein (NOD2), are associated with fibrostenotic CD [50] and animal models devoid of fecal microbiota are protected against stricture development [51]. Thus, modifying microflora-derived signals by changing the intestinal microbiome may be an another treatment approach for patients with stricturing CD.

Assessing the patient with fibrostenosing CD

The clinical presentation and natural history of CD patients with stricturing disease is heterogeneous. Although patients may have incidentally discovered asymptomatic strictures that progress for years without clinical manifestations, at least 20–30% of CD patients in both population-based studies and tertiary care referral centers develop symptomatic fibrostenosis over long-term follow-up [52,53]. Typical symptoms include abdominal distension and bloating, cramping, abdominal pain (especially post-prandially), dietary restriction, nausea, and vomiting [54]. In addition to obstructive symptoms, there is also a significant overlap with penetrating disease complications as it is posited that internal fistulae develop in high pressure regions generated upstream from a stricture [55]. Patients undergoing resection for intestinal obstruction frequently have entero-enteric fistulae and the positive predictive value of fistulae for predicting stricutres may be as high as 85% [56]. Most strictures develop at sites of inflammation or anastomosis, particularly in the ileum or ileocolic region where the luminal diameter is narrower compared to the colon, although upper gastrointestinal and colorectal strictures have also been described [4].

Identifying CD patients at high risk for eventual fibrostenosis is challenging [57]. Clinical features associated with aggressive disease include diagnosis at <40 years, perianal fistulae, early need for corticosteroid or biologic therapy, smoking, and deep ulcerations on endoscopy; however, these features do not predict fibrostenosis specifically [58]. Similarly, serologic markers may also identify patients at-risk patients but not specifically stricturing disease. CD patients with antibodies towards anti-*Saccharomyces cerevisiae* (ASCA), anti-bacterial flagellin CBir1 (anti-CBir1), anti-Pseudomonas-associated sequence I2 (anti-I2), or anti-*Escherichia coli* outer membrane protein C (anti-OmpC) are more likely to develop disease-related complications [59]. Potential candidate biomarkers with higher specificity for fibrostenosis include anti-

glycan antibodies [60] and serum human chitinase 3-like 1 (YKL-40) growth factor, which stimulates myofibroblast collagen production [61]. However, prospective longitudinal studies are needed to determine if these serologic markers can be used to predict long-term stricture-related outcomes.

In contrast to clinical and serologic markers, genetic variants encoding immunoregulatory proteins, inflammatory cytokines, and fibrogenic factors may serve as a more specific marker for fibrostenotic CD. Most notably, mutations in NOD2 and autophagy-related-16L1 (ATG16L1) have been shown to correlate with small bowel obstruction [62,63]. A single NOD2/CARD15 variant increases the risk of stricturing CD by two-fold [62]. Several other genetic mutations have also been associated with fibrostenotic CD, including mutations in toll-like receptor (TLR)-4, chemokine fractalkine receptor CX3CR1, IL23 receptor, IL12B, and MMP3 [57]. Although the use of genetic or epigenetic biomarkers is promising, their current clinical application is limited due to low carriage frequency and incomplete phenotypic penetrance. Recently, high quality information was dervied from the pediatric RISK inception cohort. 913 patients were analysed for genotype, serology, clinical factors and ileal gene expression signatures. 9% developed complications during follow up. A validated risk model was able to predict complicated CD at diagnosis with an area under the receiver operator curve (ROC) of 0.72 [64]. Interestingly, certain bacterial strains at diagnosis were linked to the later development of fibrostenosis.

The diagnosis of a fibrotic stricture in CD is primarily made on the basis of cross-sectional imaging, which is highly sensitive and specific for identifying both small intestinal and colonic stenoses [65]. Conversely, although the presence of luminal narrowing can be appreciated endoscopically, this is a suboptimal technique for stricture assessment. First, fibrostenosis is a transmural process and endoscopy only permits evaluation of the mucosal surface. Second, although endoscopy allows for assessment of mucosal inflammation and tissue sampling, biopsies reflect the processes occurring in superficial tissues and no validated histopathological scoring system for fibrosis currently exists. Third, not all strictures are endoscopically accessible, particularly if there are multiple strictures, a distal impassable narrowing, or in the context of an acute obstruction and there is interobserver variability in stricture detection, particularly if the stricture is non-occlusive.

For these reasons, cross-sectional imaging has become the mainstay of stricture assessment, either by ultrasound (US, including small intestinal contrast enhanced ultrasonography SICUS or CEUS), or computed tomography (CT) or magnetic resonance (MR) enterography or enteroclysis. Radiographic definitions of a stricture are heterogeneous in the literature depending on the cohort and modality, although it is generally agreed that the radiographic appearance should include localised luminal narrowing (luminal diameter reduced by $\geq$ 50% relative to normal adjacent bowel loops), bowel wall thickening (increase in wall thickness of $\geq$ 25% in the maximally thickened area), and pre-stricture dilation (small bowel diameter >3 cm) [54]. All three of these modalities have comparable accuracy (US sensitivity 79% specificity 92%, CT sensitivity 89% specificity 99%, MR sensitivity 89% specificity 94%) [65] and the clinical decision for choosing which modality to use is dependent on patient-, disease-, and resource-related factors.

US avoids ionizing radiation and permits real-time assessment of dynamic bowel peristalsis. However, this technique is operator-dependent, and visualization, particularly of the more proximal small bowel, may be challenging in patients with obese body habitus. CT is widely available, rapid, allows assessment of extra-intestinal disease manifestations, and is the modality of choice in emergent settings such as an acute obstruction. However, CT exposes the patient to ionizing radiation and in young patients who will require repeated examinations, may not be ideal for elective investigation. MR permits superior soft-tissue characterization and has high spatial resolution, although requires administration of luminal contrast to distend the small bowel, is more expensive, requires specialized radiology expertise, and availability may be limited in some jurisdictions.

Evaluating the degree of inflammatory versus fibrotic stricturing carries important treatment implications for whether patients are likely to respond to anti-inflammatory therapies such as corticosteroids or biologics. However, this dichotomy is largely artificial as in clinical practice, most strictures contain a mix of inflammatory and fibrotic components [66]. Conventional imaging is unable to measure the relative degree of intestinal fibrosis and the absence of radiographic inflammation alone does not accurately predict presence of fibrotic changes [67]. Alternative imaging techniques have been developed to improve fibrosis differentiation. MR enterography with delayed gadolinium enhancement quantified by the percentage gain between 70 s and 7 min has been shown to distinguish severe from mild-to-moderate fibrosis [68]. Other techniques under investigation include MR with dynamic contrast enhancement (DCE) [69], magnetisation transfer MR (MT-MR) [70], positron emission tomography (PET)-MR [71], and shear wave velocity on US elastography [72]. These protocols are not routinely available in all centers and they yet have to be externally validated.

Managing patients with intestinal fibrosis

General principles

Managing CD patients with intestinal fibrosis is complex and treatment decisions should be informed by a multidisciplinary team of gastroenterologists, radiologists, and colorectal surgeons [57]. The appropriate therapeutic approach varies based on the acuity of presentation and stricture characteristics, including length, location, angulation, complexity, and associated features such as luminal inflammation, fistula, abscess/phlegmon, or cancer. Patients with acute bowel obstruction represent a medical emergency. They should be hospitalized, receive intravenous fluid resuscitation and electrolyte correction, undergo urgent cross-sectional imaging, be considered for nasogastric decompression, and have early surgical consultation. On the other hand, patients with intermittent symptoms can be considered for elective outpatient medical, endoscopic, or surgical treatment strategies, and asymptomatic patients may not require immediate intervention.

Although most strictures in CD are the consequence of the inflammatory and fibrostenotic cascade described previously, clinicians should be cognizant that they can also rarely develop secondary to malignancy and there should be a low threshold for obtaining endoscopic biopsies to exclude dysplasia. Small intestinal adenocarcinomas remain rare in CD, but the risk of malignancy is substantially elevated in patients with colonic strictures [73]. Up to 3.5% of CD patients with a colonic stricture undergoing surgical resection have evidence of dysplasia or malignancy, even after negative preoperative endoscopic brushings or biopsy [74]. At 10 years after stricture diagnosis, colorectal cancer developed in 4.9% of CD patients [73]. Thus, patients with rapidly progressive disease or constitutional symptoms should be evaluated for malignancy.

Medical management

Currently available medical therapies for CD are not effective for inducing or sustaining regression of established fibrosis. Rather, medical management should focus on limiting the inflammatory

components of CD-related strictures, with the aim of reducing bowel wall edema and thickness and increasing the luminal diameter to relieve obstructive symptoms [75]. Patients presenting with acute bowel obstructions are often trialed with a course of intravenous corticosteroids (e.g. methylprednisolone 40–60 mg daily). There are potential advantages and pitfalls to this approach. Many patients will experience symptomatic obstruction relief with a combined approach of nasogastric decompression, bowel rest, and corticosteroids within 72 h [76]. However, over half of patients will develop a recurrence and eventually require surgical intervention, especially if the symptom-free interval is short (<8 months). A pitfall to using rescue corticosteroids is that for patients with predominantly fibrotic strictures who will invariably require surgery, exposure to high-dose preoperative corticosteroids may increase the risk of postoperative complications [77]. Therefore, the decision to treat patients presenting with an acute obstruction with corticosteroids should ideally be made in conjunction with a colorectal surgeon.

Biologic therapies, namely with tumour necrosis factor (TNF)-α antagonists, have been used in patients with stricturing CD. Initial concerns that treatment with TNF antagonists would accelerate stricture formation as a consequence of rapid ulcer healing [78] have not been substantiated in randomised controlled trials (RCTs) or large treatment registries [79,80]. A recent large multicentre observational cohort study (CREOLE) conducted by GETAID evaluated the efficacy of adalimumab in patients with symptomatic small bowel strictures [81]. At week 24, 61% of patients reached the primary endpoint of avoiding corticosteroids, endoscopic dilation, surgery, adverse events, or switching to an alternative TNF antagonist. Approximately 50% of these patients fulfilled these criteria at two years of follow-up. However, it should be cautioned that approximately half of patients in this cohort still ultimately required surgery. Patients were more likely to achieve the primary endpoint in this study if they were concurrently using immunosuppressants, had a short duration of obstructive symptoms but high degree of symptom severity, manifested severe delayed T1 enhancement on MRE, did not have fistulizing disease, or did have pre-stenotic dilation $\geq$ 30 mm [81]. Currently, data for vedolizumab and ustekinumab for the treatment of stricturing CD is not available.

Endoscopic management

Endoscopic treatment of fibrostenotic CD-related strictures includes endoscopic balloon dilation (EBD), intralesional corticosteroid or TNF antagonist injection, and placement of biodegradable or removable stents. EBD has been the most commonly applied endoscopic treatment modality, and requires strictures to be within reach of either upper endoscopy, colonoscopy, or balloon-assisted enteroscopy. Overall, technical success rates are high. Bettenworth et al. evaluated outcomes in 1463 CD patients treated by EBD and identified that 80.3% of patients achieved short-term symptomatic relief [82]. Major complications such as bleeding, perforation, or hospitalization after EBD are uncommon (2.7%). The most predictive factor of technical success with EBD in multivariable analysis was short stricture length (<=5 cm) whereas the presence of inflammation, naïve vs. anastomic stricture, and technical features did not affect either success or complication rates [82]. Most clinicians use through-the-scope (TTS) pneumatic balloons for dilation, and there is substantial heterogeneity in the technical approach. We advocate using a conservative, graded method with respect to choosing the balloon size to minimize the risk of overdilation and perforation, dilation times of 45–60 s per balloon, and repeat endoscopic assessment at 6–12 months post-procedure with consideration for repeated dilation if symptoms recur or luminal diameter is restricted preventing passage of the colonoscope or endoscope.

Whilst technical success rates with EBD are high, EBD may only be a temporizing measure with respect to preventing surgery. In a retrospective study of 258 patients with stricturing ileocolonic CD, Lan et al. demonstrated that patients treated with initial ileocoloic resection had a reduced need for second surgery and longer surgery-free survival (11.1 vs. 5.4 years, $p < 0.001$) compared to patients managed initially by EBD [83]. In observational studies, approximately 30–50% of patients will require multiple dilations or undergo eventual surgical resection [84–86]. However, EBD may still be a valuable therapeutic adjunct as a bridge to surgery to allow time to improve the patient's nutritional status and optimize their medical management. Particularly after EBD of strictures with active mucosal inflammation, the clinician should consider escalating medical anti-inflammatory therapy. In a retrospective cohort study of 54 CD patients undergoing EBD for ileocolonic anastomotic strictures, patients receiving combination TNF antagonist and immunomodulator after EBD had a lower risk of needing repeated dilations (HR 0.23), with severe inflammation (defined by Rutgeerts i4) at the anastomosis being predictive of the need for surgical resection (HR 4.33) [87].

Other endoscopic techniques that have been proposed include triamcinolone corticosteroid injection into CD-related strictures. Although this approach has been successful in reflux-related esophageal strictures, one prospective study in pediatric CD demonstrated benefit, but one study in adult CD was prematurely terminated due to worse outcome in patients with corticosteroid injection in CD-strictures [88,89]. Case reports of injecting TNF antagonists into CD-associated strictures have been reported as successful [90,91] although this approach has not been widely accepted, particularly in light of cost considerations and findings from the CREOLE study suggesting possible benefit to systemic TNF antagonist administration. Endoscopic stenting is a mainstay of managing malignancy-associated strictures; however, this approach has been met with hesitation in CD primarily due to procedure-related adverse events. Over 60% of patients undergoing metal stenting for CD experience major complications including stent migration and fistula formation leading to perforation [92]. Reports of using removable metal stents or biodegradable stents that maintain radial force for 6–8 weeks have been published [93,94]. While the short-term success rates are high, long-term data are required. Finally, use of sphincterotome or needle knife endoscopic stricturotomy should still be considered experimental and require further evaluation [95].

Surgical management

There are multiple indications for surgery in patients with stricturing CD. Patients with long (>5 cm), complex (tightly angulated), endoscopically inaccessible or technically infeasible strictures for EBD, associated features such as abscess, fistula, or dysplasia/malignancy, and patients with acute bowel obstruction with or without peritonitis should be considered for surgical intervention. In fact, early surgery may prolong clinical remission and reduce re-operation risk when compared to medical or endoscopic treatment in these settings [83,96,97].

While short fibrotic strictures are well-suited for resection, clinicians will inevitably face the challenge presented by patients with multifocal, extensive, or recurrent strictures. Repeated surgical resections increase the risk of short bowel syndrome [98]. Bowel preserving strictureplasty can be considered in patients with jejunoileal strictures without accompanying complications, and reduces the risk of postoperative anastomotic leak [5]. Several different strictureplasty techniques have been described and are

classified as either "conventional" (Heineke-Mikulicz and Finney techniques) or "non-conventional" (Michelassi technique) strictureplasties [99]. The Heineke-Mikulicz procedure is best suited for short strictures <10 cm, the Finney-like procedure for strictures between 10 and 25 cm, and the isoperistaltic Michelassi technique for multiple, close strictures or patients at high risk for SBS [99]. All of these techniques have similar rates of recurrence: approximately 35% of patients have disease recurrence after strictureplasty after 4–8 years of follow-up [100].

All patients should have their surgical risk optimized preoperatively. This includes improving nutritional status before surgery and minimizing corticosteroid exposure. Laparoscopic approaches should be considered if feasible [101]. Postoperatively, the risk of disease recurrence should be discussed [102]. Importantly, patients with CD who continue to smoke after surgery have nearly universal rates of disease recurrence and aggressive strategies to promote smoking cessation should be pursued [103].

Novel treatment approaches and future outlook

The paradigm of CD-related inflammation leading to irreversible fibrostenotic stricture formation, obstruction, and surgery is being revisited. Fibrosis reversibility has been observed in other organ systems including the skin, liver, and kidney [104–106] and improved understandings of the mechanisms driving fibrosis has allowed the development of an expanding pipeline of specific anti-fibrotic drugs targeting molecular pathways implicated in fibrogenesis [107,108]. Although specific agents have yet to enter clinical trials in CD, early successes in other organs have shown promise.

Pirfenidone and nintedanib have been recently approved for the treatment of idiopathic pulmonary fibrosis (IPF). Pirfenidone is an orally delivered pyridine derivative that inhibits TGF-β and TNFα, although the precise mechnaisms in IPF have not been completely established [109]. In phase 3 placebo-controlled RCTs, treatment with pirfenidone was associated with reduced declines in vital capacity [6,110,111]. In the ASCENT trial, 555 IPF patients were randomised to pirfenidone or placebo: after 52 weeks of treatment, there was a 47.9% relative reduction in the proportion of patients experiencing $\geq$ 10% decline in predicted forced vital capacity (FVC) and a significant increase in progression-free survival ($p < 0.001$) [110]. Nintedanib is a small molecule oral inhibitor of tyrosine kinase PDGF, FGF, and VEGF receptors. Similarly, treatment with nintedanib reduced the rate of vital capacity decline and disease progression compared to placebo [7]. Both therapies are potential future options in fibrostenotic CD.

The observation that strictureplasty surgery can lead to regression of fibrosis fuels the hope to successfully treat fibrostenosis [112]. Given that strictureplasties are mainly performed in the mid small bowel outside of reach of conventional endoscopy makes the investigation of this model challenging. The development of the technique of strictureplasties over the ileocecal valve [112], a system in which regression of stenosis has been observed, now allows serial endoscopies and sampling, which may drive discovery of anti-fibrotic pathways.

Finally, the largest hurdle to testing anti-fibrotics is the lack of accepted clinical trial endpoints for fibrostenosis. To overcome this challenge, a seminal international study group has convened to provide a framework for trial design and endpoints to assist investigators and regulators in the development of new drugs. This includes patient reported outcome tools and radiology indices, which will form the basis of future clinical trials [54].

Summary

The development of fibrostenotic strictures in CD is a dynamic process, mediated by both inflammatory and fibrogenic mechanisms. Control of inflammation alone may not halt disease progression although our improved understanding of fibrosis pathophysiology has facilitated the identification of fibrosis-specific targets that may result in reversal of established strictures. The evaluation of CD-related strictures relies on accurate transmural disease assessment, primarily through cross-sectional imaging by US, CTE, or MRE. However, the differentiation between fibrotic and inflammatory stricture components by conventional imaging remains an unmet challenge. The management of fibrostenotic CD should be decided in conjunction with a multidisciplinary team. Control of luminal inflammation with anti-inflammatory therapies, including biologic agents, is critical for reducing pro-inflammatory mediators of fibrosis. Endoscopic and surgical interventions may be required in patients who are not responsive to medical therapy alone or present with disease complications such as acute obstruction or penetrating disease. The pipeline for antifibrotic-specific therapies is promising, and novel treatments that target fibrosis-specific molecular pathways are in reach but will require formal testing in CD clinical trials.

Practice points

- Fibrostenosis is a common complication in patients with CD and often presents in conjunction with penetrating fistulae
- Patients with fibrostenotic CD should be managed by a multidisciplinary team of gastroenterologists, radiologists, and colorectal surgeons
- Stricture characterization is essential: US, CTE, and MRE are all accurate modalities for evaluating strictures and choice of imaging should be tailored to the clinical setting, resource availability, and patient- and stricture-related factors
- Endoscopic balloon dilation is safe and effective – it should be considered for patients with short-segment (<=5 cm), non-angulated, anastomotic or naïve strictures. Other endoscopic techniques are experimental and require further investigation
- Surgical management is the mainstay for patients with strictures unresponsive to medical or endoscopic treatment, or for those with associated complications such as abscess, fistula, or malignancy

Research agenda

- Standardized characterization of strictures on cross-sectional imaging is needed: this requires the development of valid, reliable, reproducible, and responsive stricture-specific indices for US, CTE, and MRE
- The traditional paradigm that fibrostenosis is irreversible is being revisited. Novel therapies targeting different molecular components of the inflammatory and fibrotic pathways driving stricture formation require testing in dedicated trials enrolling patients with CD
- Approval of novel therapies for fibrostenotic CD will require demonstration that valid endpoints are achievable with treatment. Candidate outcomes include radiographic, patient-reported, or biomarker targets, but these require further evaluation

Conflicts of interest

C.M., B.C. S.A.H, and C.E.P. have no conflicts of interest to declare.

V.J. has received has received consulting fees from AbbVie, Eli Lilly, GlaxoSmithKline, Arena pharmaceuticals, Genetech,

Pendopharm, Sandoz, Merck, Takeda, Janssen, Robarts Clinical Trials, Topivert, Celltrion; speaker's fees from Takeda, Janssen, Shire, Ferring, Abbvie, Pfizer.

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F.R. is consultant to Allergan, AbbVie, Boehringer-Ingelheim, Celgene, Cowen, Gilead, Gossamer, Helmsley, Jannsen, Koutif, Metacrine, Pliant, Pfizer, Receptos, RedX, Roche, Samsung, Takeda, Thetis, UCB.

Author contributions

Study concept and design: C.M., F.R; drafting of the manuscript: C.M., F.R; critical revision of the manuscript for important intellectual content: all authors; obtained funding: N/A; study supervision: C.M., F.R.

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