Development and Treatment of Fibrosis in Crohn’s Disease

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Intestinal fibrosis is a common complication of Crohn’s disease resulting in significant morbidity in 30% of patients. Several factors are associated with higher rates of progression to intestinal fibrosis in Crohn’s disease patients. These factors include genetics, location (ileal, jejunal or perianal disease), early age at diagnosis, the presence of more severe disease, smoking and the number of serologic markers present. Distinguishing intestinal fibrosis from inflammation is important because it affects treatment decisions. Of the available imaging studies, MRE is the most sensitive and specific. Once fibrosis is diagnosed, treatment options include endoscopic dilation, which is appropriate for shorter and less complicated strictures, or surgery, including resection or stricturoplasty. Following surgery, smoking cessation, 5-aminosalicylates, azathioprine/6-MP, antibiotics (metronidazole/ornidazole) and anti-TNF agents can all reduce the risk of disease recurrence, albeit modestly. However, no therapy has been identified that specifically targets the development of fibrosis in the susceptible patient.

INTRODUCTION

Crohn’s disease is a focal, asymmetric, transmural and occasionally granulomatous inflammation primarily affecting the gastrointestinal tract.1 In North America, the incidence of Crohn’s disease ranges between 3.1 to 14.6 cases per 100,000 person-years, and prevalence ranges between 26 to 199 cases per 100,000 persons.2 Disease location and behavior tend to vary not only between different patients but also in the same patient at different times. In one retrospective cohort of 297 patients with Crohn’s disease, while only 10.8% of patients had intestinal strictures (Vienna class B2) at the time of diagnosis, this percentage increased in the subsequent years to 32.2 and 31.3 in 10 and 25 years respectively.3

Classification of Crohn’s disease has evolved over time. In 1998 the World Congress of Gastroenterology Working Party suggested a classification system based on age at diagnosis (A1<40 or A2>=40), location (L1: Ileal, L2: Colonic, L3: Ileo-colonic, L4: Upper gastrointestinal) and behavior (B1: Non-stricturing, non-penetrating, B2: Stricturing, B3: Penetrating). This was referred to as the Vienna classification.4 Based on this classification, any Crohn’s disease patient can be assigned to one out of 24 categories. A Montreal modification was suggested in 2005, preserving the main structure while adding another age category for
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below 16 and changing perianal disease into a modifier that can be added to other classes. It also made it possible to combine L4 to L1-3 as a modifier. The main challenge with these classification systems is that while the location for Crohn’s disease is relatively stable, the disease commonly changes behavior with time, with the majority of patients progressing from non-stricturing, non-penetrating (B1) to stricturing (B2) or penetrating (B3) disease in subsequent years.

Stricturing and penetrating phenotypes are associated with a more complicated disease course, resulting in higher morbidity and surgery rates. Several factors have been linked to the development of stricturing disease in Crohn’s patients. Knowing these factors will help in predicting the disease course early on and maybe affecting the approach to management, thus patient outcomes.

The body responds to tissue injury by a series of tightly regulated events triggered by secretion of various mediators inducing cell proliferation, migration, and extracellular matrix (ECM) production. The normal wound healing process concludes with the resolution of inflammation and tissue remodeling. Stricturesing Crohn’s disease occurs when the process of wound healing becomes dysregulated. Mesenchymal cells (MSC) in the intestine including smooth muscle cells, myofibroblasts and fibroblasts, are key players in dysregulated wound healing and stricture formation. They undergo excess proliferation and hypertrophy and produce excess ECM proteins, particularly collagen I, that lead to obliteration of the submucosa and expansion of the muscularis propria leading to focal stricture formation. What is unique about Crohn’s disease is the focal nature of fibrosis with adjacent normal intestine, in contrast to other organs that undergo fibrosis, like the skin in systemic sclerosis, the liver in cirrhosis and the lungs in pulmonary fibrosis.

This review will discuss what is known about the predictors of fibrostenotic disease in a susceptible patient, the diagnosis of stenosis in symptomatic patients and the management of intestinal fibrosis and highlight the gaps in our knowledge regarding effective non-surgical treatments.

### Predictors of Fibrostenotic Disease

#### Genetic Predisposition

Over 160 genes identified by linkage analysis and genome wide association scan (GWAS) have been associated with IBD. These can be susceptibility genes predisposing the patient to developing the disease or disease modifying genes affecting the disease behavior. Several genetic variants that may relate to a predisposition or the development of fibrosis include NOD2, ATG16L, TNFSF15, STAT3 and Smad3. The most studied gene is NOD2, which has been linked to fibrostenotic Crohn’s disease; however, this association was not universal in all studies. A recent meta-analysis suggested that the presence of two NOD2 mutations is highly predictive of complicated disease course while the predictive power of a single mutation is weak. Genetic variants of several metalloproteinases and their inhibitors have also shown some association with a fibrostenotic course of Crohn’s disease.

#### Disease Location

Isolated ileal disease has been linked to the development of stricturing disease, in part explained by the small diameter of the small intestine which would lead to higher incidence of clinical signs and symptoms requiring intervention when a stricture forms. The presence of perianal disease at diagnosis is associated with progression to more severe disease forms, including fibrostenotic disease. A recent study reported that

### Table 1. Predictors of Fibrostenotic Crohn’s Disease

| Genetic: NOD2 mutation, metalloproteinases |
| Early age at diagnosis |
| Long duration of disease |
| Isolated ileal disease |
| Jejunal disease |
| Perianal disease at diagnosis |
| Serologic Markers: ASCA, anti-12, OmpC, ACCA, AMCA |
| Smoking |
| Frequency of relapses |
| Steroid use |
| Prior appendectomy |

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Disease Severity

Frequency of relapses and steroid use have been associated with changing behavior of Crohn’s disease from inflammatory to fistulizing or stricturing disease. Severity of the disease and long duration of disease are associated with the development of strictures or obstruction in Crohn’s disease patients.

Serologic Markers

The presence of multiple serologic markers (antibodies against microbial peptides) is associated with fibrostenotic Crohn’s disease and higher need for surgery. These include anti-Saccharomyces cerevisiae antibodies (ASCA), anti-Pseudomonas-associated sequence I2 antibodies (anti-I2), anti-outer membrane porin C (OmpC) of Escherichia coli antibodies, anti-chitobioside carbohydrate antibodies (ACCA), antilaminarin antibody (Anti-L) and anti-mannobioside carbohydrate antibodies (AMCA).

Patient Related Factors

Early age at diagnosis is linked to progression to stricturing disease. Conversely, patients diagnosed at older ages are more likely to have strictures at the time of diagnosis. Prior appendectomy is also linked to the development of a stricturing disease.

Crohn’s disease patients that smoke are at higher risk of progressing into a more severe disease behavior, including fibrostenotic disease, and tend to have higher risk of needing surgery for Crohn’s when compared to non-smokers.

Diagnosis of Fibrostenotic Disease

Small intestinal strictures are a major cause of intestinal obstruction and surgery in Crohn’s disease patients. The main challenge when a Crohn’s disease patient presents with intestinal obstruction is determining whether the stricture is predominantly inflammatory, which makes it amenable to medical treatment, or predominantly fibrotic, which would likely need invasive intervention. Clinical signs and symptoms of active disease, inflammatory markers, specifically CRP, and stool studies, including presence of blood and leukocytes, can help differentiate between the two. However, these markers are not phenotype specific, and given the multifocal nature of the disease, determining

Table 2. Imaging Studies to Distinguish Between Inflammatory and Fibrotic Strictures

<table>
<thead>
<tr>
<th>Imaging Study</th>
<th>Correct Distinction Rate When Compared to Histology</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound</td>
<td>40%</td>
<td>Radiation free</td>
<td>Operator dependent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Widely available</td>
<td></td>
</tr>
<tr>
<td>CTE</td>
<td>Limited data*</td>
<td>Fast</td>
<td>Less sensitive than MRE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Widely available</td>
<td>Radiation exposure</td>
</tr>
<tr>
<td>MRE</td>
<td>57-65%</td>
<td>More sensitive</td>
<td>Expensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radiation free</td>
<td>Less available</td>
</tr>
<tr>
<td>18F-FDG PET</td>
<td>53%</td>
<td>Limited data**</td>
<td>Expensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radiation exposure</td>
<td></td>
</tr>
</tbody>
</table>

* Data available show that CTE findings do not correlate well with tissue fibrosis when compared to histology. No studies have reported actual numbers.
** More studies are needed before FDG-PET is recommended for Crohn's disease.
whether the positive markers are reflective of a different inflamed area of the gut is not always possible. Imaging studies can be helpful in distinguishing between these two entities, thus guiding the management.

**CT/CTE**

CT scan is widely used for the diagnosis of Crohn’s disease and its complications. CT enterography (CTE) is a modification of conventional CT that uses multidetector CT (MDCT) scanners for high spatial and temporal resolution imaging of the small bowel and multi-planar reconstruction following the ingestion of enteric contrast, typically PEG solution or ultra low dose barium with sorbitol. CTE has good sensitivity and specificity in detecting active Crohn’s disease, with sensitivity ranging between 60%-90% and specificity around 90%. However, small bowel stricture without CTE findings of inflammation does not correlate with tissue fibrosis.

**MRI/MRE**

Magnetic Resonance Imaging (MRI) has been utilized in the diagnosis of Crohn’s disease, with reported sensitivities and specificities ranging between 88-98 and 78-100% respectively for the detection of the disease. Addition of enteric contrast, Magnetic resonance enterogram (MRE) is useful for detecting intestinal and other intra-abdominal complications of Crohn’s disease. MRE has greater efficacy than CTE or MRI alone at distinguishing the relative proportion of inflammation and fibrosis in intestinal strictures. These findings correlate best with surgical histopathology.

**Transabdominal Ultrasound and Contrast-Enhanced Ultrasound**

Abdominal ultrasound can be used to diagnose Crohn’s disease, with sensitivity between 84-93% and specificity of 98% in some studies. Newer ultrasound modalities including doppler ultrasound, contrast enhanced ultrasound and ultrasound elasticity imaging have shown promising results in distinguishing between inflammatory and fibrotic strictures, therefore predicting patients that will require surgery.

**18F-FDG PET**

18F-FDG PET and PET/CT have been gaining increased interest lately with studies showing potential use in diagnosing Crohn’s disease and providing a noninvasive, quantitative measure of inflammation. By itself, PET scanning does not provide good measure of intestinal fibrosis.

**Capsule Endoscopy**

Although capsule endoscopy has good diagnostic yield in the detection of mucosal lesions of Crohn’s disease, the presence of strictures, either symptomatic or silent, puts the patient at risk for capsule retention. If necessary, a patency (dummy) capsule should be tried first to insure that no blockage is present.

**Which Imaging Study Should be Chosen?**

Ultrasound is a safe, widely available and radiation free test, but is operator dependent. The availability of newer US based modalities is limited which limits its use as a primary diagnostic tool in IBD.

MRE and CTE have comparable diagnostic yield in the detection of the extent of the disease and its complications, with MRE being slightly more sensitive. Current data suggest that MRE is superior to CTE in detecting strictures, with sensitivity and specificity of 92% and 90% respectively for MRE versus 85% and 100% respectively for CTE. They also can help guide operative approach. In terms of distinguishing between strictures caused by fibrosis and those caused by active inflammation, when compared to histology, detection rates were 57% for MRE, 53% for 18-FDG-PET/CT, and 40% for ultrasound. Notably the combination of FDG-PET/CT and US or MRE and US resulted in a100% detection rate and was better than either alone in the detection of strictures requiring surgery or endoscopic dilation. CTE findings of active inflammation in a stricture correlated well with histology; however, CTE findings of a stricture without inflammation did not predict the presence or absence of tissue fibrosis. In one study the accuracy of MRE for detecting mural fibrosis was 64.9%; this increased to 83.3% when inflammation was absent. Contrast enhanced US offers additional benefit in distinguishing inflammation from tissue fibrosis.

CT/CTE is widely available which makes it an appealing test for many clinicians; however, radiation exposure with repeated imaging, especially in the predominantly young-aged Crohn’s disease population, raises concerns for both patients and clinicians. MRI has no radiation exposure. The limitations against the widespread utilization of MRE are mainly the lack of standardized MRE protocols, high cost, lack of experienced MR radiologists and long scanning.
times. More data is needed, including efficacy and cost-effectiveness, before 18F-FDG PET and PET/CT can be recommended for Crohn’s disease.

Can We Change the Natural History of Fibrostenotic Crohn’s Disease?

Based on the available data, there is evidence to suggest that early intervention can affect the course of disease; however, more data is needed in order to understand how this affects the development of fibrostenotic disease. Early azathioprine (AZA) or AZA/biologic therapy decreases the probability of progression from inflammatory into a more complicated disease behavior, decreases the risk of surgery and prolongs time to first surgery. One study in the pediatric population showed that early use of AZA/6-MP was associated with fewer hospitalizations but did not affect the rates of surgery for these patients in the first two years after diagnosis; however, surgery is a rare event in the first two years of pediatric Crohn’s disease. Maintenance therapy with infliximab induced mucosal healing, with a trend toward lower rates of hospitalization that was not statistically significant. Early combined immunosuppression (infliximab and azathioprine) provided significantly better mucosal healing with a trend towards fewer intestinal resections compared to conventional therapy with corticosteroids followed by step up therapy if needed. Subset analysis of the CHARM study showed that Adalimumab therapy compared to placebo was associated with lower hospitalization and surgery rates in one year. It is clear that more studies are needed before it can be said that early intervention prevents fibrosis in Crohn’s disease patients.

Management of Intestinal Fibrosis

Once significant fibrosis is established in the intestine, medical therapy alone has little to offer. Although initial trials of infliximab were stopped due to concern that infliximab can induce stricture formation, subsequent data did not reproduce these findings. The effect of infliximab correlates well with the degree of inflammation in the stricture, with better response in strictures with higher inflammatory component, but there is no evidence that infliximab can induce stricture formation or worsen an existing stricture. In one small study, oral Tranilast (N-3’,4’ dimethoxycinnamoyl) showed positive results in prevention of stricture progression in patients with Crohn’s disease.

Endoscopy

Endoscopic dilatation is an appropriate option in Crohn’s disease strictures, especially strictures less than 4-7 cm in length. It is still not clear whether injection of steroids into the strictures after dilatation reduces the risk of recurrence or not. Intraloesional injection of infliximab was effective in relieving colonic stricture in one small series.

Surgery

Two surgical options are available: Stricturoplasty and resection. Stricturoplasty is usually preferred for short strictures and when trying to preserve the length of the small intestine, while resection is usually needed for long strictures and for cases complicated by abscess, peritonitis, infection or suspicion of cancer.

It is still not clear whether surgery is superior to endoscopic dilatation in management of strictures. A recent meta-analysis did not demonstrate superiority of one method over the other, primarily due to the limited availability of comparable data.

Disease Recurrence

After endoscopic dilatation, two meta-analyses have reported a surgery-free outcome rate of 79% and 58% of the patients in a median follow up of 21 and 33 months, respectively, outcomes were better in short strictures (less than 4-5 cm). Following surgery, recurrence rates steadily increase with time, reaching up to 50% in 20 years. Several studies have evaluated factors increasing the risk of clinical, endoscopic or surgical recurrence after initial surgery secondary to any cause (i.e. stricture, fistula, obstruction from active inflammation), but limited data specifically examined the actual incidence of tissue fibrosis before and after surgery. Several factors have been found to affect recurrence.

Smoking

Smokers with Crohn’s disease have a higher risk of disease recurrence after surgery. Meta-analysis showed that these patients have 2.5 fold increased risk of surgical recurrence and 2 fold increased risk of clinical recurrence compared to non-smokers. Ex-smokers have lower recurrence rates when compared to smokers, suggesting that smoking cessation can improve outcomes post-surgery.

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5-aminosalicylates
Evidence suggests that mesalamine has a minimal effect in reducing the clinical but not endoscopic recurrence post-surgery in Crohn’s disease.56, 62, 63, 64

Antibiotics
Use of metronidazole or ornidazole after surgery is superior to placebo in preventing both clinical and endoscopic recurrence; however, this effect did not persist beyond the first year after surgery.60, 63, 64

Azathioprine/6-MP
Use of AZA/6-MP may have modest effect in preventing post-operative recurrence; however, positive results have not been seen in all studies.60, 62, 63, 64, 65

Anti-TNF Therapy
The available data show that infliximab is effective in preventing post-operative clinical and endoscopic recurrence.60, 62, 63 Adalimumab too can prevent endoscopic recurrence up to one year post-surgery.63, 66 These studies have not specifically examined patients resected for fibrotic strictures, however.

Probiotics, corticosteroids including budesonide have not been shown to have a significant effect on postoperative recurrence, and in the case of corticosteroids, have the potential disadvantage of increasing collagen production.60, 62, 63, 64

Future Directions
It is increasingly clear that once initiated, fibrosis and stricture formation can progress in the absence of active inflammation. A number of experimental therapies directed more specifically at stricture formation have been the subject of recent investigations. These include such agents as angiotensin-converting enzyme (ACE) inhibitors, HMG-CoA-reductase inhibitors, resveratrol, anti-integrin directed therapy, and IGF-I antagonists.67, 68

Macrophages exhibit different functional phenotypes during the phases of wound healing. Thus, they have been a point of interest for therapeutic target in reducing fibrosis and improving chronic wound healing.69 The supplementation of exogenous macrophages has been shown by Dannon and colleagues to accelerate wound healing.70 Therefore, altering a macrophage’s phenotype, ex vivo, could drive it towards a reparative phenotype promoting tissue regeneration once re-introduced.

TGF-β is a key mediator of both the intestine’s immune response and disordered wound healing and fibrosis that follows inflammation. TGF-β or its Smad signaling intermediates could be considered as therapeutic targets to inhibit or prevent fibrosis. The lessons learned from transgenic animals, however, have shown us that absence of TGF-β or TGF-β signaling, with the exception of Smad3, is associated with significant perinatal mortality. This occurs as a result of a loss of a potent immune regulator and thus, multifocal inflammation and massive infiltration of inflammatory cells into major organs. Other potential targets could be matrix metalloproteinases (MMP), proteinases that regulate dissolution of extracellular matrix (ECM), or tissue inhibitors of metalloproteinases (TIMP). Since the effects of increased MMP expression, e.g. collagenases, could decrease net ECM levels, it would be expected, however, to increase mucosal ulcerations and worsen the inflammatory complications of Crohn’s disease.

Altering the gut microbiota can affect the expression of profibrotic genes. Several ongoing lines of investigation will inform us on how to therapeutically intervene in patients with specific phenotypes.

1. Studies to analyze the diversity, composition, and structure of the intestinal microbiome.

2. Studies to define the metabolic environment (metabolom) at the mucosal interface between intestinal microbiota and the host (patient) susceptible to CD.

The ultimate goal is to elucidate the mechanisms by which genetic variants in a patient susceptible to CD lead to the development of clinical CD and its specific phenotypes, such as fibrostenosis; thereby, in addition to identifying potential therapeutic targets, providing the ability to predict its development and likely disease course.

SUMMARY
About one third to one half of patients with Crohn’s disease experience strictures at some point in their lives. Both genetic and environmental factors play a role in the development of fibrosis. While early medical therapy can potentially prevent stricture formation, more studies are needed to better define those patients that will likely benefit from aggressive medical therapy early (continued on page 40)
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in the disease course. Key to effective management is distinguishing between inflammatory and fibrosis as their management is different. Clinical signs and symptoms, laboratory values and imaging studies such as CTE and MRE can be helpful in distinguishing between the two. CTE is more widely available while MRE is more sensitive and avoids exposure to ionizing radiation. Accurate pre-operative evaluation of the stricture guides therapy, endoscopic dilatation is an effective strategy for short (less than 4-7 cm) strictures, while surgery is needed for longer and more complicated strictures. After surgery, smoking cessation, metronidazole, ornidazole, azathioprine, 6-MP and anti-TNF agents offer some help in preventing post-operative recurrence; however, no medical therapy specifically targets the development of intestinal fibrosis. Whether future strategies will be effective in identifying the susceptible patient and whether fibrosis can be prevented is unknown.

References