VIEWPOINT

How early to take arms against a sea of troubles? The case for aggressive early therapy in Crohn's disease to prevent fibrotic intestinal strictures

Shail M. Govani, Ryan W. Stidham, Peter D.R. Higgins*

Division of Gastroenterology, University of Michigan, Ann Arbor, MI 48109, United States

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Abstract

While potent anti-inflammatory medications have reduced the symptoms of Crohn's disease, more than 60% of patients eventually require surgery due to the development of fibrosis. Even after the introduction of biologic drugs, the population-based rate of surgery for Crohn's disease has not decreased. We suspect this is due to late initiation of these therapies, after the fibrosis cascade is unstoppable. We review the evidence that suggests early aggressive therapy is beneficial, especially in patients diagnosed before age 40, and with ileal or perianal disease. Patients with symptomatic strictures may benefit from early surgery (before penetrating complications) followed by initiation of biologics. With increased early use of biologics and better control of inflammation, we hope to see a global reduction in intestinal fibrosis and related complications of Crohn's disease.

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Modern medical therapies in Crohn's disease (CD), including immunomodulators and biologic agents, have revolutionized disease treatment. However, a significant number of individuals will not respond to medications, most often due to intractable intestinal fibrosis. Despite the availability of anti-TNF therapy, 64% of patients with Crohn's disease still require surgical management within 30 years of diagnosis.

Pronounced intestinal stricturing frequently drives CD symptoms, even when existing intestinal inflammation is well controlled. Our understanding of fibrostenotic CD, from both animal models and human data, has advanced over the last decade and impacted our perspective on “top down” vs. “step up” therapy, as well as medical vs. surgical decision making. Improved appreciation of the biology and clinical implications of intestinal fibrosis should play a significant role in the management of Crohn's disease.

Stricturing CD behavior was defined by the World Congress of Gastroenterology in Vienna as "constant luminal narrowing" found by imaging or direct examination with...
obstructive signs and symptoms but without penetrating features. Data from international cohorts found 21.7% of CD had stricturing behavior, while 25.9% have penetrating features and 52.4% exhibited uncomplicated disease. While these classifications are helpful, CD behavior is a moving target over time. A review of one center’s longitudinal experience showed that while only 10% of the population displayed fibrostenotic behavior at diagnosis, by 10 years, 30% of the population will fit this behavioral pattern. Patients’ disease phenotype changes over the course of disease, with 27.1% of the uncomplicated patients (Vienna B1 classification) later being reclassified as having fibrostenotic disease (B2).

The development of intestinal fibrosis is believed to be caused by repeated episodes of inflammation followed by wound healing, leading to stricture formation, subsequent obstruction, and eventual penetrating complications. One might expect that the advent of more potent immunosuppressive therapies would reduce the incidence of stricturing disease, but there is little evidence demonstrating that we are actually modifying the natural history of Crohn’s disease. A retrospective review performed by Cosnes, et al. revealed no overall reduction in the need for surgery despite increasing use of thiopurine immunosuppression. Splitting 24 years of patient data into 5 cohorts based on the year of diagnosis, they found that the cumulative probability of stricture requiring surgery did not decrease significantly from 1978 to 2002. However, there are important caveats to consider in this data, including: (1) a low incidence of early and extended exposure to immunosuppression (only 9% had more than 3 months of medication), (2) unclear data on immunomodulator dose optimization, and only (3) a very brief time overlap with the biologic era. The question of whether immunosuppression prevents or halts the development of intestinal fibrosis, and how early in the disease course we need to intervene to change the natural history, remain unclear.

Anti-TNF therapy, especially in combination with immunomodulators, has improved rates of remission of inflammatory elements of Crohn’s disease activity, but does not treat pre-existing intestinal strictures. In fact, early data after the introduction of infliximab suggested that increased stricturing may occur following exposure to infliximab, presumably due to alteration or acceleration of wound healing. Using multivariable modeling of subgroup data from the TREAT registry, the authors demonstrated that after controlling for severity of disease, steroid use, duration of disease, and age, there was not a significant association between infliximab use and the development of stenosis (6). Using this multivariate model, they did identify that ileal disease, disease duration, and new use of steroids were associated with the development of strictures. While there was no significant association between infliximab and stricturing complications after controlling for other factors, the direction of the trend favors stenosis during use of infliximab, and the p value for infliximab, 0.22, is closer to 0.05 than one would expect for a medication that one would expect should reduce stenosis. A population-based study attempted to answer whether anti-TNF therapies reduced the need for Crohn’s disease surgeries. That study showed that the annual rate of small bowel and right colon resections in Crohn’s disease in the US remained stable from 1993 to 2004, while fistula surgeries increased during that time period. Since this study was done at the population level without direct information about infliximab use, it is difficult to draw conclusions about the use of biologics in individual cases, but there certainly was not a population-based effect of anti-TNF use on surgery rates in Crohn’s disease during that period. Perhaps there were no benefits of anti-TNF use on surgical rates due to the patterns of use in the early 2000s, which initially favored more intermittent use. Once fibrotic strictures have formed, anti-TNF therapy has not been shown to lead to resolution of these strictures. So it would not be terribly surprising that there was no anti-TNF benefit on the population level if the drug was being administered to those who already had fibrosis.

Mechanical treatment with balloon dilation of strictures is another option for treatment of intestinal fibrosis. There are a number of case series that examine the success rate of dilation for palliative purposes. In properly selected patients with short segment strictures, obstructive symptom relief following a single dilation is near 70–80% at 1 year. Over a 5 year follow-up period after dilations, 40% of patients of those undergoing a single dilation and 60% with serial dilations experience sustained relief from obstructive symptoms without surgical resection.

If we are unable to medically treat established intestinal strictures with existing therapies, can we prevent fibrostenotic disease from developing? Further, if medical therapy could prevent fibrosis development, how early would we need to intervene to prevent significant stricture formation? In the Salmonella typhimurium mouse model of colitis, histologic inflammation was seen within 2 days of induction, with molecular markers of fibrosis present within 5 days. To determine how early inflammation needed to be controlled to prevent intestinal fibrosis, Salmonella-treated mice underwent levofloxacin rescue at day 2, 4, or 8 of the experiment and all mice were sacrificed at day 21. All 3 groups had a reduced inflammation score on histology at day 21 compared to untreated groups, but only very early treatment (by day 4) led to lower levels of profibrotic cytokines and prevention of fibrosis. This suggests that there was a “point of no return”, somewhere between days 4 and 8, after which the development of fibrosis in mice could not be halted with anti-inflammatory treatment. In a further experiment, Salmonella-infected mice were treated with levofloxacin on day 3, mimicking early aggressive treatment of inflammation in Crohn’s disease, and were sacrificed on day 4, 12 or 21. Early intervention led to reduced inflammation scores at all time points and evidence of reduced fibrosis later in the experiment. This suggests that very early intervention to reduce intestinal inflammation is critical in preventing fibrosis development.

Optimal timing of a sufficiently potent anti-inflammatory maintenance therapy is not a new theme in IBD research. Subgroup analysis of data from PRECISE 2 indicated that longer duration of Crohn’s disease was associated with lower efficacy of certolizumab. For patients with disease duration of less than a year, a response (drop in CDAI of >100) rate of 89% was found. This compared to a response rate of 57% among patients with disease duration of at least 5 years. Similar results have been noted with the use of adalimumab in early Crohn’s. Treatment with anti-TNF therapy early in the course of Crohn’s disease is significantly more efficacious. This may be due to a change in the pathology of the affected intestine from largely inflammatory to largely fibrotic, leading to decreased efficacy of anti-inflammatory therapies, despite their potency (Fig. 1).
The data directly comparing aggressive early therapy to a deliberate, step-up strategy is incomplete. D’Haens et al. demonstrated improved objective and clinical outcomes when using dual immunosuppression compared to conventional therapy. The patients assigned to conventional therapy were given IV steroids followed by a taper and later escalated to azathioprine and infliximab if necessary. The “top-down” group was given infliximab induction with azathioprine. If their disease flared later, they were given additional doses of infliximab and then steroids. While the “top-down” group had better outcomes at 26 and 52 weeks, at time points beyond 52 weeks there were no significant differences in outcomes between the 2 groups. However, this early study did not use maintenance infliximab as the standard of care, which might have significantly improved the outcomes in the top-down arm.

A better example of a comparison between an aggressive and moderate approach is the SONIC trial which studied patients early in their disease course with moderate to severe CD and no past history of immunomodulator or biologic use. Of those exposed to the combination therapy, 46% were in steroid free remission at week 50 compared to 24% among those who were on azathioprine alone. Further evidence that early and aggressive therapy is superior was found in a recent study of claims data. The patients who were started on a biologic early did better with fewer surgeries and less steroid use. This provides partial evidence favoring early aggressive therapy for improving outcomes, yet it raises additional issues of risk stratification, and who should receive dual immunosuppression.

The risk of treating all patients with Crohn’s aggressively at the time of diagnosis includes an increased risk of infection and malignancy and the increased costs associated with biologic therapy. Several studies have explored the risk of infection associated with anti-TNF therapy. While increased infections were found, no infectious mortality difference was found between those treated with infliximab compared to those who were not in these large studies. There was also no difference in the number of malignancies or infections between the 2 groups at week 54. They did note that the risk for infection among those treated with infliximab appeared to be highest during concomitant use of steroids.

The data on the costs associated with anti-TNF therapy in Crohn’s disease is limited and would be highly dependent on the local health care system and the duration of a cost study. While the initial costs of biologic medications are higher than thiopurines, there may be fewer hospitalizations and surgeries in patients with stricturing disease (as there are for fistulizing CD) which could save costs in the long run. A cost-effectiveness analysis using UK costs did suggest that a net reduction in costs could occur with more potent early therapy.

These data suggest that the benefits of biologics in early high-risk Crohn’s disease can outweigh the risks. We also suspect that very early aggressive therapy may be required to prevent fibrostenotic complications in high risk patients. However, the clinical evidence to support this position is limited. One would expect that if this was true, we would see a protective effect of infliximab use against fibrostenotic complications in the TREAT registry, and that the number of surgeries would be decreasing since the advent of infliximab. Based on our findings in the mouse model of intestinal fibrosis, we could be missing the potential protective benefits of infliximab because it is rarely used as first line therapy, in part because it can be difficult to identify which patients are at high risk for complications at the time of diagnosis.

A number of studies have identified risk factors that portend a disabling course. A retrospective review at one tertiary center found that 85% of their patients suffered a “disabling course” within 5 years (defined as >2 courses of steroids or steroid dependence, persistent disabling symptoms, surgery for fistulizing disease, use of immunosuppressants). They found that age at diagnosis <40, the presence of perianal disease, and initial need for steroid use independently predicted disabling disease. Another study found that 60% of patients eventually suffered a penetrating or stricturing complication over the course of 20 years. Again, age and disease location (Je)unal or ileal) appeared to be the strongest predictors of stricturing complications. Based on this data, we would recommend that patients who have ileal disease, perianal involvement, and diagnosis before age 40 be strongly considered for early biologic therapy at the time of diagnosis.
An alternative approach to risk stratification is the use of serologic and genetic markers. These have been demonstrated in several studies to identify patients at high risk for future surgery. Of the serological markers, antibodies directed against *Pseudomonas fluorescens* (I2) in particular predict fibrostenotic complications and small bowel surgery. In addition to serological makers, Abreu et al. identified variants in the NOD2 gene that are associated with fibrostenotic disease. While these appear promising, they are costly and have not been compared head to head with the free clinical predictors listed above. It remains to be seen what the best approach to identifying high-risk patients will be.

However, even if high-risk patients are reliably identified, the finding of the rapid irreversibility of fibrogenesis in the mouse model is daunting. Some patients will present rapidly after the onset of symptoms, will clearly have markers of high risk disease behavior, and be willing to start on a very early biologic in the course of disease. However, for many patients with Crohn’s disease, a delay in diagnosis of several years is not uncommon. This makes the first surgery more difficult to avoid, even with aggressive biologic therapy at the time of diagnosis. This may explain part of why decreases in surgical rates in Crohn’s disease have not yet occurred. For these patients, a timely surgery (including early strictureplasty if appropriate) followed by early aggressive therapy to prevent recurrence may be a better long-term option, rather than waiting for obstruction or perforating complications to occur before more difficult surgeries are needed. Limited evidence suggests that timely surgery followed by aggressive medical therapy may produce excellent outcomes, as the efficacy of biologic therapy after surgical resection appears to be remarkably good. The ongoing PREVENT trial is designed to add to the evidence base on post-operative prevention of recurrence. The potential benefits of potent biologics in changing the natural history of Crohn’s disease on a population level. This may be simply because of the timing of the use of these anti-inflammatory therapies, or it may indicate a fundamental problem with the biology of fibrosis. If intestinal fibrogenesis becomes independent of inflammation within days of onset, the path to changing the natural history of Crohn’s disease may require specific anti-fibrotic therapies.

Conflicts of interest
The authors have no conflict of interest to disclose.

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Statement of authorship:
SMG was involved in the initial draft and review of the manuscript.
RWS provided critical review of the manuscript.
PDRH provided critical review and was involved in the project conception.
All authors read and approved the final manuscript.

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**Figure 2** Algorithm for initiation of biologics in patients with a new diagnosis of Crohn’s disease. In this flow diagram, the clinical indicators of a future disabling course are identified as prompts to use early combination therapy. We also specifically suggest that those with symptomatic stenosis should undergo surgery and early initiation of combination therapy.
References


