

# ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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## Perianal Fistulas in Patients With Crohn's Disease



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### G&H What is the prevalence of perianal fistulas in patients who have Crohn's disease?

**DS** Several studies throughout the world, including one that my colleagues and I did more than 20 years ago in Olmsted County, have estimated that approximately 20% to 25% of patients with Crohn's disease will develop at least 1 perianal fistula. Recently, researchers have looked back at the patient population in Olmsted County, focusing on patients who were diagnosed with Crohn's disease after the introduction of anti-tumor necrosis factor (TNF) agents. There is a suggestion that starting anti-TNF therapies earlier in patients with Crohn's disease may be somewhat protective. Some of the more recent cohorts have lower rates of fistula formation, giving hope that it might be possible to avoid the development of fistulas.

### G&H What are the main risk factors for the development of Crohn's disease perianal fistulas?

**DS** The biggest risk factor is having inflammation in the rectum. It is thought that one of the main causes of fistulas is ulcerations in the rectum that extend over time to develop into fistulas. Having an inflammatory component in the rectum, particularly the distal rectum, puts a patient at risk of developing a fistula. In fact, research has shown that patients with rectal inflammation have as high as a 90% risk of developing a fistula.

### G&H What are the main symptoms of the different types of Crohn's disease perianal fistulas?

**DS** Many different symptoms can occur depending on where the fistula is located and whether it is associated with an abscess. However, most patients present with purulent drainage and pain. They also have a higher rate of incontinence. If a fistula involves other organs such as the vagina, which is not uncommon, the patient may

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have recurrent urinary tract infections or pass air or stool through the vagina. For all of these reasons, Crohn's disease perianal fistulas can have a very negative impact on a patient's quality of life and are one of the more debilitating manifestations of Crohn's disease. Crohn's disease patients who have perianal fistulas have a much higher rate of depression and anxiety.

### G&H Does a patient with Crohn's disease who has perianal fistulas require different treatment than a patient who has Crohn's disease without perianal fistulas?

**DS** Most of the medical treatments are the same. For some of the advanced therapies, higher doses may be needed or higher drug levels may need to be achieved because of the greater degree of inflammation associated with the development of fistulas. Higher drug levels may be needed to obtain an optimal response because perianal fistulas are in an important area, the anal sphincter, which is vital in maintaining continence. It is very important to control fistula healing to avoid problems with the anal sphincter. Thus, gastroenterologists need to work very closely with colorectal surgeons and radiologists to optimize outcomes and prevent complications of perianal Crohn's disease such as fecal incontinence and pain.

**G&H** How effective is anti-TNF therapy in this setting in the short and long term?

**DS** The introduction of anti-TNF therapy in the late 1990s dramatically improved treatment of Crohn's disease perianal fistulas, with approximately two-thirds of patients responding to induction dosing. Unfortunately, throughout the course of a year, most patients develop recurrent disease even when continuing anti-TNF therapy. Only approximately 30% to 40% of patients are able to maintain fistula closure. Thus, although anti-TNF therapy is the best medical treatment currently available, the majority of patients develop recurrent fistulizing disease.

**G&H** Has research been conducted on the use of newer medical therapies for inducing and/or maintaining healing of Crohn's disease perianal fistulas?

**DS** Both vedolizumab (Entyvio, Takeda) as well as ustekinumab (Stelara, Janssen) have been looked at in secondary analyses of their pivotal trials for the treatment of patients who had a draining fistula at the time of enrollment. Both of these agents showed some benefit in patients who had fistulizing disease. My colleagues and I conducted a separate trial focused on the use of vedolizumab in Crohn's disease patients with perianal fistulas and found a significant fistula closure rate. Either of those agents are options for patients who do not respond to anti-TNF therapy.

The Janus kinase inhibitor upadacitinib (Rinvoq, AbbVie) has also been looked at in a secondary analysis of its pivotal trial and showed a fairly significant benefit for patients with fistulizing Crohn's disease. Currently, that is the agent I use if a patient with Crohn's disease perianal fistulas does not respond to anti-TNF therapy.

**G&H** Is there a role for using stem cell therapy in this setting?

**DS** This is somewhat of a controversial topic. The ADMIRE 2 trial, which looked at using adipose-derived stem cells to treat Crohn's disease refractory perianal fistulas, has been completed. Although all of the data have not been released yet, Takeda recently announced the top-line results. Even though it appeared as if the stem cells were effective, there was not a significant difference between the placebo and treatment arms because the placebo arm had such a high fistula closure rate. As such, it is not clear whether this product will become available for Crohn's disease patients with perianal fistulas in the United States. On the other hand, in Europe, the ADMIRE 1 trial was conducted with a very similar design and did show a significant benefit for patients who were randomized to stem cell therapy. Therefore, this treatment option is available for Crohn's disease patients with perianal fistulas in Europe and Japan.

**G&H** When is surgical treatment indicated?

**DS** My bias, and much of my research and other studies have borne this out, is that gastroenterologists need to work very closely with surgeons in order to optimize outcomes as well as the benefits of medical therapy. When I have a patient who has been diagnosed with a perianal fistula, for the most part I almost always involve a surgeon immediately to help clean up any purulence and place

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setons to help control fistula healing. The body's natural tendency is to try to close off the internal and external openings of the fistula tract very quickly because the openings are not normal. A long tract with inflammatory material can lead to a recurrent abscess. Controlling the infection right away and then starting advanced therapy is the way to obtain the best outcomes, at least currently, for patients with perianal disease.

It is particularly important to use both medical and surgical therapy to obtain the best outcomes in patients who have complex fistulizing disease. Surgical treatment is about as effective as medical therapy alone. In

combination, there is a much higher rate of fistula improvement, both in the short and long term.

### **G&H** How can setons be best placed and removed?

**DS** Setons are always placed by the surgeon at the time of an examination under anesthesia and are very helpful for controlling fistula healing. What is evolving currently is when they should be removed. The common practice now is to remove a seton when the drainage stops or slows down, which is generally around week 6 to 12 with advanced therapies. However, imaging studies have shown that the inflammatory component of the fistula tract lasts quite a bit longer than that. Early removal might be associated with a higher rate of fistula recurrence. I have long been an advocate of leaving setons in and using imaging to decide when they can be removed so the fistula can close. My colleagues and I have shown in several small studies that this approach has improved fistula healing rates fairly dramatically.

However, the ADMIRE 2 trial calls this into question because it appears as if closure of the internal opening of a fistula tract has a significant role in promoting fistula healing. Going forward, I think surgeons will place setons in patients at initial diagnosis, and the timing of seton removal will be determined by imaging. Once significant improvement in the inflammatory component is seen on imaging, closure of the internal opening of the fistula tract can be performed to get the fistula to close completely.

Seton removal is often performed by the surgeon. However, at some institutions such as my own, seton removal is done by the gastroenterologist after reviewing the imaging and seeing significant fistula improvement; this way, the patient does not have to be sent back to the colorectal surgeon.

### **G&H** Are there any ways to reduce the risk of fistula recurrence?

**DS** As mentioned, approximately two-thirds of patients will develop a recurrent perianal fistula over the course of a year. Several factors may increase this risk, including having an anal stricture, multiple fistulas, or multiple tracts. One of the ways to help improve fistula healing is to use imaging to monitor healing of the fistula. Several trials have shown that using imaging to guide medical and surgical decisions, such as when to remove the seton and when to intensify medical therapy, can dramatically reduce the rate of fistula recurrence.

### **G&H** Which imaging modalities are most effective?

**DS** Most institutions use pelvic magnetic resonance imaging (MRI) because that is where most of their expertise lies. There are some institutions, including mine, where endoscopic ultrasound is used to monitor fistula healing. If that tool is available, it is quite useful. For instance, when using endoscopic ultrasound at the time of colonoscopy, a decision can be made immediately as to whether a seton can be removed if it looks like the inflammatory component of the fistula has improved.

I would like to emphasize that endoscopic ultrasound, transperineal ultrasound, and pelvic MRI are all extremely accurate at defining fistula anatomy. I encourage providers to leverage these technologies to monitor fistula healing and use them to help inform treatment decisions to improve outcomes. I like to say that reimaging fistula tracts to make sure inflammation has improved is analogous to repeating a colonoscopy when starting advanced therapy for luminal disease. The absence of the inflammatory component on imaging should be considered the equivalent of mucosal healing when doing colonoscopy for luminal disease, and should be used to decide the course of treatment, including when to increase medical therapy, when to remove setons, and potentially when to close the internal opening of the fistula tract to optimize outcomes. If providers do not use imaging to help monitor outcomes and just go by physical examination for patients with complex fistulizing disease, it may be difficult to achieve the best outcomes for patients.

### **G&H** Are there any other treatment considerations that should be taken into account in this patient population?

**DS** Because this manifestation of Crohn's disease has such a negative impact on a patient's quality of life and because it can affect the whole person, it is very important to treat patients using a multidisciplinary team approach. A consensus document advocating for such an approach will be coming out soon. Certainly, a mental health provider is key, given the higher rates of anxiety and depression associated with Crohn's disease perianal fistulas. A dietitian is very helpful as well because many of these patients avoid eating or restrict certain foods in order to reduce symptoms, which can have a detrimental effect on their overall health. Having a team approach of a dietitian, mental health provider, colorectal surgeon, radiologist, and gastroenterologist is key to treating the whole patient and optimizing outcomes.

### **G&H** What are the next steps in research regarding Crohn's disease perianal fistulas?

**DS** A number of companies are looking at different ways of delivering stem cells for fistulizing disease. I think stem cell therapy has a great deal of promise and am looking forward to seeing study results. In my opinion, the most significant immediate need is to determine how important it is and when to close the internal opening of a fistula tract to improve outcomes. That has not been routinely done, but recent studies suggest that it may have a significant role for improving fistula healing outcomes. I would be interested in guidance on this issue.

### Disclosures

*Dr Schwartz has served as a consultant for AbbVie, Janssen, Takeda, Gilead, BMS, and Avbios and as a Data and Safety Monitoring Board member for Tract.*

### Suggested Reading

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