Perianal Fistulas in Patients With Crohn's Disease, Part 1: Current Medical Management

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Abstract: Despite significant advances in the treatment of luminal inflammatory bowel disease, the treatment of perianal fistulas remains a clinical challenge. Perianal fistulas are traditionally described using the Parks classification based on their relationship to the external and internal anal sphincters. Traditional therapy for perianal fistulas focuses on antibiotics such as metronidazole or ciprofloxacin. However, medical management has expanded over the years to include immunomodulators and, most recently, biologic agents. Newer techniques such as intrafistulous biologic injections are also being explored as potentially effective treatments for patients with fistulizing disease. Here, in the first of a 2-part series on perianal fistulas in patients with Crohn's disease, we discuss the anatomy and classification of perianal fistulas as well as current medical therapies, including antibiotics, immunomodulators, biologic agents, and novel therapeutic agents. The second part of the series will focus on the surgical modalities that are available for patients with perianal fistulas in addition to novel endoscopic techniques and future therapies that are being investigated for the treatment of fistulizing Crohn's disease.

Crohn's disease (CD) is an immune-mediated, chronic inflammatory condition that affects the entire gastrointestinal tract and is often complicated by intestinal strictures and fistulas. Fistulas associated with CD can form between any segment of the intestine and either the skin or an adjacent organ, such as a contiguous loop of bowel, the bladder, or the vagina. Perianal fistulas affect roughly 5% to 40% of patients with CD, and the incidence increases with more distal disease (ie, colonic and rectal involvement) as well as with increased disease duration and severity.[1-4] In approximately 10% of patients with CD, perianal disease may predate other symptoms; however, approximately two-thirds of these patients will ultimately develop intestinal manifestations within 1 year.[1,2]

Symptoms of perianal fistulas include severe pain, purulent drainage, and fecal incontinence, leading to significant morbidity and a reduction in quality of life. Despite advancements in the medical

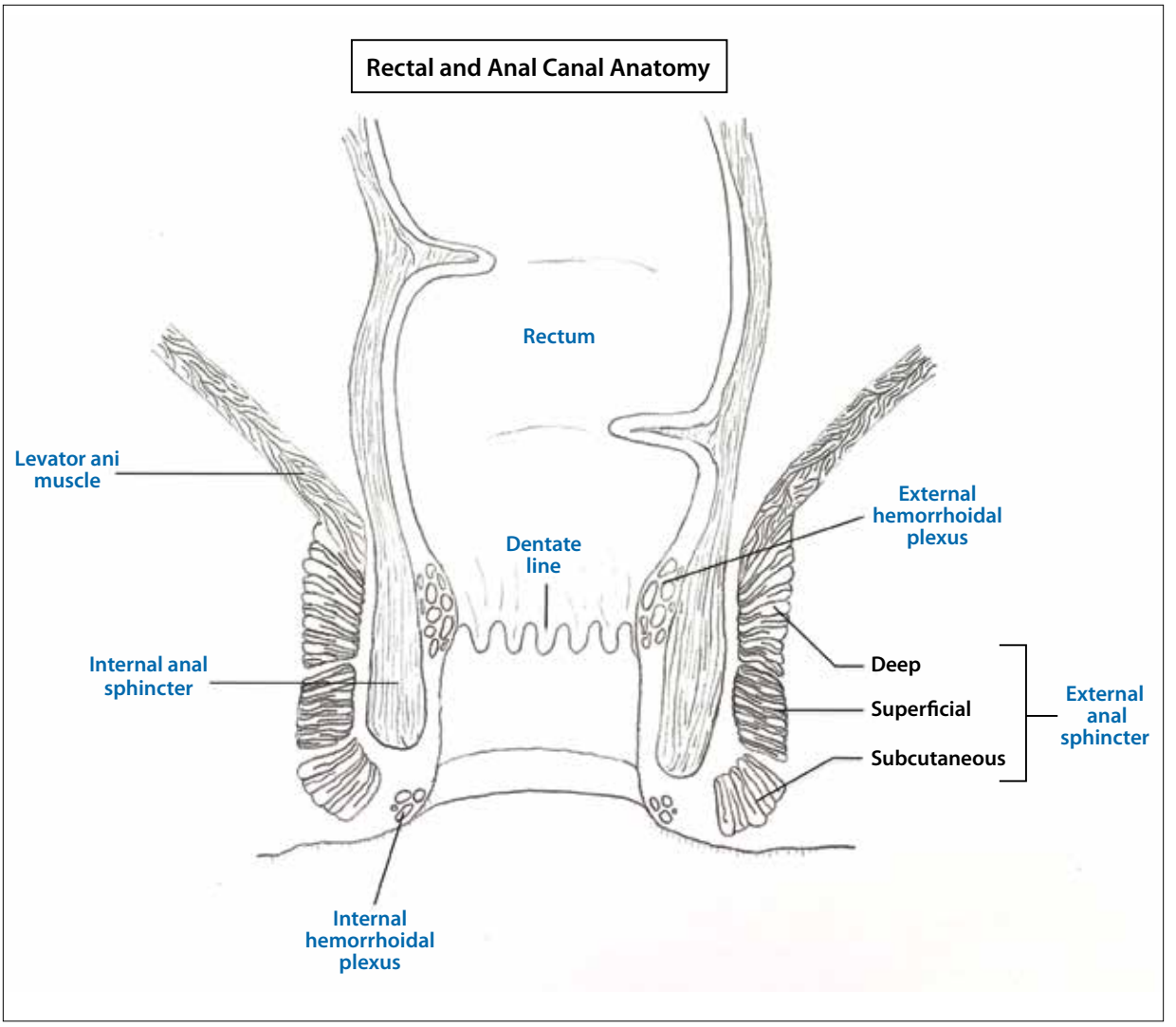

Figure 1. A diagram of the rectal and anal canal anatomy demonstrates the internal and external anal sphincters as well as the levator ani muscle.

and surgical treatment of CD over the past decade, perianal fistulas still present a significant challenge to physicians. Successful therapeutic management of perianal fistulas would ideally include complete fistula closure. However, given the complexity of these lesions, many physicians have shifted their therapeutic goal from complete closure to reductions in pain and purulent drainage and an improvement in quality of life.[5] Although various medications and endoscopic and surgical techniques exist, there is no gold-standard treatment strategy for patients with perianal fistulas. However, it is clear that successful management requires a multidisciplinary approach with a gastroenterologist and a colorectal surgeon. Here, in the first of a 2-part series on perianal fistulas in patients with CD, we discuss the anatomy and classification of perianal fistulas as well as current medical therapies, including antibiotics, immunomodulators, biologic agents, and novel therapeutic agents. The second part of the series will focus on surgical interventions as well as novel endoscopic techniques and future therapies that are currently under investigation for the treatment of perianal fistulas in patients with CD.

Anatomy and Classification

Several perianal fistula classification systems have been described in the literature, the most common of which is the Parks classification. The Parks classification categorizes perianal fistulas based on their relationship to the external and internal anal sphincters (Figures 1 and 2).[6]

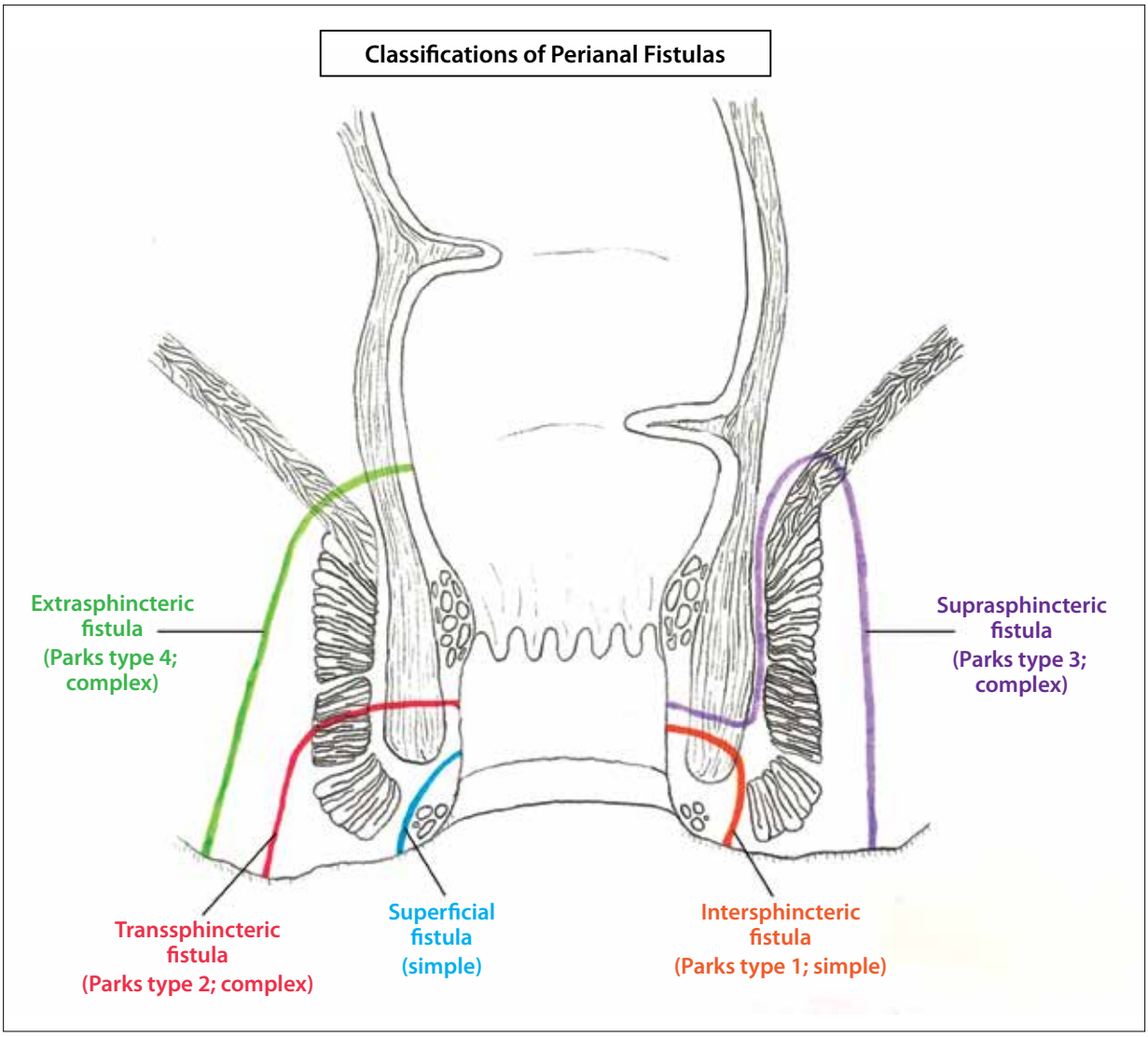

Figure 2. The Parks classification of perianal fistulas illustrates a superficial fistula, intersphincteric fistula (type 1), transsphincteric fistula (type 2), suprasphincteric fistula (type 3), and extrasphincteric fistula (type 4) in relation to the internal and external anal sphincter muscles. A revised classification from the American Gastroenterological Association Technical Review Panel defines perianal fistulas as simple or complex.

Given the complexity of this classification, the American Gastroenterological Association (AGA) Technical Review Panel proposed a revised classification that defines perianal fistulas as either simple or complex (Figure 2). In this version, a simple fistula is one that is confined to the anal canal (either superficial, low transsphincteric, or low intersphincteric), has a single opening in the skin, and does not have an associated abscess.[1,7] In contrast, a complex perianal fistula passes through or above a significant amount of muscle (either high intersphincteric, high transsphincteric, extrasphincteric, or suprasphincteric) and is associated with multiple openings in the skin, a perianal abscess, or an anorectal stricture. Additionally, if the fistula connects with adjacent organs, such as the bowel, bladder, or vagina, it is considered complex.[1,7] In comparison to the traditional Parks classification system, the AGA's breakdown of fistulas into either simple or complex has proven to be much easier and more meaningful in the clinical setting, as a simple fistula is significantly easier to manage and poses little threat to continence.[5,7]

Medical Management

Antibiotics

Traditionally, antibiotics such as metronidazole and ciprofloxacin have been used as first-line therapy for patients

Table 1. Studies on Antibiotic Therapies for Perianal Fistula Closure

Study	Drug(s)	Study Type	Number of Patients	Findings
Bernstein et al[9]	Metronidazole	Open-label	21	Clinical response in 100% (21/21) of patients, and complete healing in 56% (10/18) of patients
Brandt et al[10]	Metronidazole	Follow-up	26	Successful discontinuation of antibiotic therapy in 28% of patients; 25% (4/16) had complete healing of the fistula
Thia et al[12]	Metronidazole and ciprofloxacin	RCT	25	At 10 weeks, 30% (3/10) of patients taking ciprofloxacin (NNT, 5.7)[a] and 0% (0/7) of patients taking metronidazole had complete fistula closure, compared with 12.5% (1/8) of patients taking placebo.
Jakobovits and Schuster[64]	Metronidazole	Prospective	8	100% (8/8) of patients had resolution of symptoms, there was a 20-fold reduction in the number of draining fistulas, and 100% (8/8) of patients reported side effects from antibiotic use (numbness, metallic taste).
Turunen et al[65]	Ciprofloxacin	Prospective	10	70% (7/10) of patients had clinical response, 20% (2/10) of patients had complete healing after 2 years, and 50% (5/10) of patients had relapse after stopping ciprofloxacin.
Solomon et al[66]	Metronidazole and ciprofloxacin	Case series	14	86% (12/14) of patients had clinical improvement, 36% (5/14) were able to stop therapy, and 64% (9/14) relapsed and required repeat therapy.
Wolf [67]	Ciprofloxacin	Case series	5	Resolution of perianal pain in 80% (4/5) of patients
Schneider et al[68]	Metronidazole	Case series	18	40% of patients experienced closure of active fistulas, and 20% experienced a reduction in drainage.
Maeda et al[13]	Metronidazole (ointment)	RCT	74	Reduction in PDCAI score in 32% (10/33) of patients taking metronidazole compared with 12% (5/41) of patients taking placebo at 4 weeks (NNT, 5.5[a]; *P*=.081)
Dejaco et al[14]	Metronidazole and/or ciprofloxacin + azathioprine	Prospective, open-label	52	Patients treated with azathioprine + metronidazole and/or ciprofloxacin had a significantly better response rate (48%) compared with patients taking only metronidazole and/or ciprofloxacin (15%; *P*=.03).
West et al[15]	Ciprofloxacin + infliximab	RCT	24	Clinical response in 73% (8/11) of patients in the infliximab + ciprofloxacin group compared with 38% (5/13) of patients in the infliximab + placebo group (NNT, 2.9[a]; odds ratio, 2.37; *P*=.07)
Dewint et al[16]	Ciprofloxacin + adalimumab	RCT	76	Clinical response in 71% (24/34) of patients in the adalimumab + ciprofloxacin group compared with 47% (17/36) of patients in the adalimumab + placebo group (NNT, 4.2)[a]

NNT, number needed to treat; PDCAI, Pediatric Crohn's Disease Activity Index; RCT, randomized, controlled trial.

[a]The NNT is 1/absolute risk reduction.

with fistulizing CD, although data supporting their efficacy are limited to small studies.[2,8] In one of the initial studies evaluating metronidazole use, 56% of patients had fistula closure after 6 to 8 weeks of therapy.[9] Although this study suggested that metronidazole is effective at inducing fistula closure, recurrence rates with antibiotic therapy are high. Brandt and colleagues studied metronidazole use in patients with perianal fistulas and found that only 28% of patients who had fistula healing were able to successfully discontinue therapy without recurrence (Table 1).[10] However, long-term use of antibiotics is associated with significant morbidity, making continued therapy less feasible.[8,9] No clinical guidelines on antibiotic selection exist, but ciprofloxacin has been shown to have higher rates of clinical improvement and complete fistula closure when compared to metronidazole, although the difference did not reach significance.[11,12] In addition to systemic therapy, the use of topical antibiotic ointments or creams for patients with perianal CD has been investigated. A randomized trial assessing the use of metronidazole topical

ointment reported an improvement in pain and drainage from the fistula tract.[13]

Although the use of antibiotics as long-term monotherapy for perianal CD is not ideal, studies have evaluated the efficacy of metronidazole or ciprofloxacin as adjuvant therapy with immunomodulators or biologic agents. In a prospective, open-label study looking at fistula closure, combination therapy of metronidazole and/or ciprofloxacin with azathioprine (AZA) was significantly more effective at achieving a clinical response (48%) when compared to metronidazole and/or ciprofloxacin alone (15%).[8,14] Furthermore, a double-blind, placebo-controlled study demonstrated that patients treated with infliximab (Remicade, Janssen) and ciprofloxacin tended to have a better clinical response than patients treated with infliximab and a placebo (odds ratio [OR], 2.37; *P*=.07).[8,15] Similarly, Dewint and colleagues evaluated the use of ciprofloxacin in combination with adalimumab (Humira, AbbVie) for patients with CD and found a clinical response in 71% of patients treated with adalimumab and ciprofloxacin compared with 47% of patients treated with adalimumab and placebo (*P*=.047).[16] These studies suggest that although antibiotics are not useful for long-term monotherapy, they can be effective as a bridge or as adjuvant therapy when combined with immunomodulators or biologic agents.

Immunomodulators

Thiopurines AZA and 6-mercaptopurine (6-MP) are commonly used for the treatment of perianal fistulas in patients with CD.[17] In the only prospective, randomized trial evaluating the efficacy of thiopurines in patients with fistulizing CD, 6-MP was found to be effective at inducing complete fistula healing.[18] Forty-three percent (9/21) of patients treated with 6-MP had complete fistula closure compared to 6% (1/17) of patients receiving a placebo. A meta-analysis by Pearson and colleagues[19] found that 54% (22/41) of patients with perianal CD who were treated with 6-MP or AZA had clinical improvement compared with 21% (6/29) of patients who received a placebo, with a pooled OR of 4.44 favoring fistula healing. In addition, 2 smaller studies have evaluated fistula closure in patients treated with either AZA or 6-MP.[20,21] Korelitz and Present demonstrated that 38% (13/34) of patients treated with 6-MP had complete fistula closure after 6 months of therapy, and an additional 26% (9/34) of patients had clinical improvement.[20] In a pediatric study, Jeshion and colleagues concluded that 67% of patients treated with AZA or 6-MP had improvement in fistula drainage, 73% had improvement in perianal tenderness, and 40% had fistula closure (Table 2).[21]

Methotrexate Although methotrexate is commonly used in patients with CD, the data are limited regarding its effect on perianal disease. Mahadevan and colleagues published one of the only studies to date evaluating the efficacy of intramuscular methotrexate on fistula closure.[22] In this case series, 25% (4/16) of patients receiving methotrexate had fistula closure, and an additional 31% (5/16) of patients had fistula improvement.[22] Interestingly, when switching to oral methotrexate or lowering the dose of intramuscular methotrexate, the majority of patients had fistula recurrence.[22]

Tacrolimus Tacrolimus is commonly used in patients who have undergone solid organ transplantation; however, some studies have suggested that the drug can be beneficial in patients with CD. A randomized, controlled trial investigating the efficacy of oral tacrolimus in patients with fistulizing CD found that 43% of patients treated with tacrolimus had fistula improvement compared with 8% of patients in the placebo group.[23] González-Lama and colleagues[24] studied the use of tacrolimus in 10 patients with fistulizing CD, and documented complete closure in 40% of patients and a partial clinical response in 50% of patients treated for 6 to 24 months. Research on topical tacrolimus in patients with perianal disease suggests possible efficacy in improving symptoms but not in inducing complete closure.[25]

Cyclosporine A Although multiple randomized, placebo-controlled trials have evaluated the efficacy of cyclosporine A (CSA) in patients with CD, none have specifically focused on fistula closure.[17] In a case series of 16 patients treated with CSA, Present and Lichtiger[26] reported complete closure in 44% (7/16) of patients and moderate improvement in an additional 44% (7/16) of patients treated with intravenous CSA over an average of 7.4 days. Interestingly, of the 10 patients who had previously failed 6-MP and/or AZA in this study, 9 (90%) had improvement in the fistula when treated with CSA.[17,26] In another study evaluating fistula closure in patients treated with intravenous CSA, 78% of patients showed a partial clinical response; however, 71% of those patients who were ultimately converted to oral CSA from intravenous CSA had relapse of their disease.[27] Therefore, CSA is likely best used as an intravenous rescue bridge to a more long-term immunomodulator or biologic therapy.

Thalidomide In patients with severely refractory disease, the use of thalidomide has been proposed. To date, 2 small studies in patients with fistulizing CD treated with thalidomide are available. Plamondon and colleagues[28] evaluated the use of thalidomide for patients with refractory CD and included 4 patients with perianal fistulas, all of whom had documented complete closure.

Table 2. Studies on Immunomodulator Therapies for Perianal Fistula Closure

Study	Drug(s)	Study Type	Number of Patients	Findings
Present et al[18]	6-MP	RCT	36	6-MP closed fistulas in 43% (9/21) of patients; placebo closed fistulas in 6% (1/17) of patients (NNT, 4).[a]
Pearson et al[19]	AZA and 6-MP	Meta-analysis	41	54% (22/41) of patients in 5 studies had a clinical response on AZA or 6-MP compared with 21% (6/29) of patients in the placebo group (pooled odds ratio, 4.44; 95% CI, 1.50-13.20)
Korelitz and Present[20]	6-MP	Case series	34	38% (13/34) of patients had fistula closure with 6-MP; an additional 26% (9/34) had clinical improvement.
Jeshion et al[21]	AZA and 6-MP	Case series	20 (pediatric)	67% (10/15) of patients had improvement in fistula drainage, 73% (11/15) had improvement in tenderness, and 40% (6/15) had fistula closure.
Rhodes et al[69]	AZA	RCT	6	50% (3/6) of patients receiving AZA had fistula improvement, and 16% (1/6) had worsening drainage.
O'Brien et al[70]	AZA or 6-MP	Case series	26	31% (8/26) of patients had fistula closure; 54% (14/26) had partial healing of the fistula.
Mahadevan et al[22]	Methotrexate	Case series	33	25% (4/16) of patients had fistula closure, and 31% (5/16) had fistula improvement. Fistula recurrence occurred when switching from intramuscular to oral methotrexate or decreasing the dose of methotrexate.
Sandborn et al[23]	Tacrolimus	RCT	48	43% (21/48) of patients treated with tacrolimus had fistula improvement compared with 8% (4/48) of patients in the placebo group (NNT, 2.9).[a]
González-Lama et al[24]	Tacrolimus	Pilot study	10	40% (4/10) of patients had complete clinical response, and 50% (5/10) had partial clinical response (decrease in fistula size, drainage, or pain).
Hanauer and Smith[71]	Cyclosporine A	Case series	5	Resolution of drainage in 83% (10/12) of fistulas at a mean of 7.9 days; relapse in 66% (2/3) of fistulas
Lichtiger[72]	Cyclosporine A	Case series	10	Initial response in 60% (6/10) of patients; none had sustained response
Present and Lichtiger[26]	Cyclosporine A	Case series	16	Fistula closure occurred in 44% (7/16) of patients; 36% (5/14) of patients relapsed when switched to oral cyclosporine A
Egan et al[27]	Cyclosporine A	Case series	18	78% (7/9) of patients had partial clinical response; 71% (5/7) had relapse after stopping intravenous therapy
Plamondon et al[28]	Thalidomide	Case series	25	82% (9/11) of patients had fistula closure; 50% (12/25) of patients had significant side effects requiring termination of drug.
Ehrenpreis et al[29]	Thalidomide	Open-label, non-RCT	22	46% (6/13) of patients had remission of the fistula.
Fickert et al[30]	Mycophenolate mofetil	Case series	4	75% (3/4) of patients had complete fistula closure.
Wenzl et al[73]	Mycophenolate mofetil	Non-RCT	8	88% (7/8) of patients had fistula closure; 13% (1/8) had recurrence of the fistula.

6-MP, 6-mercaptopurine; AZA, azathioprine; NNT, number needed to treat; RCT, randomized, controlled trial.

[a]The NNT is 1/absolute risk reduction.

However, nearly half of the entire cohort terminated the use of thalidomide due to severe side effects, including neuropathy and leukopenia.[28] In addition, Ehrenpreis and colleagues performed an open-label trial looking at the use of thalidomide in patients with refractory CD. In this study, 46% (6/13) of patients with a perianal fistula

had clinical improvement in the fistula after 12 weeks of therapy.[29] Lenalidomide, an analogue of thalidomide, has the potential to be effective with significantly less toxicity, although its use in CD has not been studied.[5]

Mycophenolate Mofetil Mycophenolate mofetil, an immunomodulator less commonly used to treat patients with CD, has been shown to be effective in patients with fistulizing disease. In a study evaluating 4 patients with treatment-refractory perianal disease, 75% (3/4) had complete fistula closure for the first time in their clinical course.[30]

All of these immunomodulators have shown promise in treating patients with perianal fistulas, but the majority of the studies to date are smaller case series, and large randomized trials are needed.

Biologic Agents

Infliximab Infliximab, a monoclonal antibody against tumor necrosis factor (TNF) α and the first biologic agent approved to treat inflammatory bowel disease, is often considered the gold-standard therapy for patients with perianal fistulas. In 1999, Present and colleagues published the first randomized, placebo-controlled trial evaluating the efficacy of infliximab in 94 patients with fistulizing CD (Table 3).[31] Overall, 68% of patients receiving infliximab had a 50% or more reduction in fistula drainage compared with 26% of patients receiving placebo (P=.002).[2,31] For a secondary endpoint, the study also looked at complete fistula healing, which was seen in 55% of patients receiving infliximab compared with 13% of patients receiving placebo (P=.001).[31] A secondary analysis with data from the ACCENT II (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen in Patients With Fistulizing Crohn's Disease) trial showed significantly higher rates of fistula closure with maintenance infliximab (36%) compared to placebo (19%) after 54 weeks of treatment (P=.009).[32,33]

Monitoring infliximab drug levels is common, as higher infliximab serum levels (trough levels >3 μg/mL) are associated with an improved generalized clinical response. However, the effect of drug levels specifically on fistula improvement remains unclear.[2] A recent case series studied the relationship between serum infliximab levels and perianal fistula closure, and concluded that patients who had a clinical response had higher median serum levels of infliximab compared with patients who did not have improvement.[34] Using a multivariate regression, this same study suggested that infliximab levels of 9.25 μg/mL at week 2 and 7.25 μg/mL at week 6 are highly predictive of fistula closure.[34] In a subsequent, larger study, patients with complete fistula healing who were treated with infliximab had higher serum infliximab levels compared with patients who did not have healing. This study concluded that serum infliximab levels of 10 μg/mL or higher are required to treat patients with active perianal disease.[35]

Although combination therapy with infliximab and a thiopurine has proved to be superior to monotherapy in patients with luminal CD, there are no studies evaluating the efficacy of dual therapy in patients with perianal fistulas.[36] Given that fistulizing disease is often thought to represent a more severe form of luminal CD, it is plausible that combination therapy would also improve fistula closure rates. Further studies are needed to better determine the best combination of therapies and the ideal serum infliximab target levels for fistula closure.

Adalimumab Although infliximab is often thought to be the gold standard in the treatment of patients with perianal fistulizing CD, adalimumab is increasingly being recognized as an alternative therapy. In the CLASSIC I (Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn's Disease) trial—one of the initial trials with adalimumab—32 patients with active perianal fistulas were studied, with fistula closure documented in 75% of patients on adalimumab (40 mg for the loading dose followed by 20 mg every 2 weeks) compared with 17% of patients who received placebo.[37] Interestingly, the number of patients who had clinical improvement or complete fistula closure did not increase with higher dosing of adalimumab.[37] In a subsequent study, Sandborn and colleagues evaluated the use of adalimumab in patients with active perianal disease associated with CD.[38] The authors found no significant difference in fistula improvement or closure in patients who received adalimumab compared with patients who received placebo after 4 weeks of induction therapy.[38] Although this study did not show a significant improvement with adalimumab therapy, it is possible that the follow-up period was insufficient. Looking at longer follow-up periods, the CHARM (The Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance) trial reported fistula closure in 33% of patients treated with adalimumab (80 mg for the loading dose followed by 40 mg every 2 weeks) compared with 13% of patients treated with placebo after 56 weeks of therapy.[39] Further analysis of this data set showed that of the patients with healed fistulas at week 52, 90% (28/31) had continued remission after 2 years of treatment.[40] Although combination therapy with adalimumab and a thiopurine has not been studied specifically, the use of adalimumab and ciprofloxacin together was found to be significantly more effective

Table 3. Studies on Biologic Therapies for Perianal Fistula Closure

Study	Drug	Study Type	Number of Patients	Findings
Present et al[31]	Infliximab	RCT	94	68% (43/63) of patients on infliximab had ≥50% reduction in fistula drainage compared with 26% (7/31) on placebo; fistula healing occurred in 55% (35/63) of patients on infliximab compared with 13% (4/31) treated with placebo (NNT, 2.4).[a]
Sands et al[33]	Infliximab	RCT	304	At week 54, complete healing was seen in 36% (33/91) of patients in the infliximab group compared with 19% (19/98) of patients in the placebo group (NNT, 5.9).[a]
Davidov et al[34]	Infliximab	Case series	36	The average infliximab level in patients with a clinical response was 4.1 μg/mL compared with 0.14 μg/mL in patients without a clinical response.
Yarur et al[35]	Infliximab	Case series	117	Patients with fistula healing had higher serum infliximab levels than patients without healing (15.8 vs 4.4 μg/mL).
Strik et al[74]	Infliximab + adalimumab	Case series	66	Patients with fistula closure had higher serum infliximab and adalimumab levels.
Hanauer et al[37]	Adalimumab	RCT	299	Fistula improvement in 75% (24/32) of patients treated with adalimumab; complete closure in 75% (24/32) of patients treated with adalimumab
Sandborn et al[38]	Adalimumab	RCT	325	Fistula improvement was seen in 15% (3/20) of patients treated with adalimumab and in 20% (5/25) of patients treated with placebo at 4 weeks.
Colombel et al[39]	Adalimumab	RCT	117	Complete closure in 33% (23/70) of patients treated with adalimumab vs 13% (6/47) of patients treated with placebo after 56 weeks (NNT, 5)[a]
Colombel et al[40]	Adalimumab	Follow-up	117	Sustained remission in 90% (28/31) of patients at 2 years
Castaño-Milla et al[75]	Adalimumab	Case series	46	Absence of drainage in 41% (19/46) of people treated with adalimumab at 6 months and 29% of people on adalimumab at 12 months
Sandborn et al[41]	Certolizumab pegol	RCT	662	30% (14/46) of patients treated with certolizumab pegol had fistula closure compared with 31% (19/61) of patients in the placebo group.
Schreiber et al[42]	Certolizumab pegol	RCT	428	54% (15/28) of patients on certolizumab pegol had closure compared with 43% (13/30) of patients on placebo after 26 weeks (NNT, 9.1).[a]
Schoepfer et al[44]	Certolizumab pegol	Survey study	50	73% (8/11) of patients had a >50% reduction in fistula drainage.
Schreiber et al[43]	Certolizumab pegol	RCT	58	36% (10/28) of patients on certolizumab pegol had fistula closure compared with 17% (5/30) of patients in the placebo group (NNT, 5.3).[a]
Sandborn et al[49]	Vedolizumab	RCT	368	Patients receiving vedolizumab every 8 weeks had higher rates of fistula closure compared to patients receiving placebo.
Tadbiri et al[50]	Vedolizumab	Case series	35	43% (15/35) of patients had complete remission, and 6% (2/35) had partial remission at 14 weeks of therapy.
Sandborn et al[45]	Ustekinumab	RCT	526	Fistula improvement was seen in 47% of patients treated with ustekinumab compared with 30% in the placebo group.
Feagan et al[46]	Ustekinumab	RCT	397	Fistula response was seen in 80% of patients receiving ustekinumab compared to 46% of patients receiving placebo after 44 weeks of therapy (NNT, 2.9).[a]
Battat et al[47]	Ustekinumab	Case series	62	66% (41/62) of patients had fistula improvement, and 33% (20/62) had fistula closure after 6 months of therapy.
Wils et al[76]	Ustekinumab	Case series	12	Fistula improvement in 67% (8/12) of patients on ustekinumab

NNT, number needed to treat; RCT, randomized, controlled trial.

[a]The NNT is 1/absolute risk reduction.

than adalimumab alone (65% vs 33%; *P*=.009).[16] This difference was significant at week 12 of therapy, but it was not maintained at week 24, suggesting that combination therapy with antibiotics is perhaps more useful for induction than for maintenance.[2,16]

Certolizumab Pegol Certolizumab pegol (CZP; Cimzia, UCB) is a humanized monoclonal antibody against TNF-α with a pegylated Fab fragment. CZP is commonly used to treat moderate to severe CD; however, data are limited on its efficacy for perianal fistulizing disease. In the PRECISE (Pegylated Antibody Fragment Evaluation in Crohn's Disease: Safety and Efficacy) 1 and 2 trials, which included a small number of patients with perianal fistulas, CZP use was not associated with significantly higher fistula closure rates.[41] More specifically, in the first trial, 30% (14/46) of patients treated with CZP had fistula closure as compared with 31% (19/61) of patients in the placebo group after 26 weeks of treatment.[41] In the second trial, which only included patients who had a response to induction therapy, 54% (15/28) of patients in the treatment group had fistula closure compared with 43% (13/30) of patients in the placebo group, confirming the findings of the first study that fistula closure was not significantly better with CZP treatment.[42] In contrast, more promising results were published from a subsequent study that focused on the use of CZP in fistulizing CD, with complete closure seen in 36% of patients on CZP compared with 17% of patients on placebo (*P*=.038).[43] Similarly, in a survey study, 73% of patients treated with CZP had a reduction of more than 50% in fistula drainage after 6 weeks of therapy.[44] Given the variability in the results from the limited studies currently available, larger studies are needed to properly evaluate the efficacy of CZP in fistulizing CD.

Other Biologic Agents To date, there are no dedicated trials evaluating the efficacy of newer biologic agents, such as vedolizumab (Entyvio, Takeda) or ustekinumab (Stelara, Janssen) in treating perianal fistulizing CD. However, subgroup analyses on initial trials and smaller case series have been published with promising results. In a subgroup analysis of the CERTIFI (Crohn's Evaluation of Response to Ustekinumab Anti–Interleukin-12/23 for Induction) trial on ustekinumab, fistula healing rates were significantly higher in the treatment group (47%) compared with the placebo group (30%) after 22 weeks of treatment.[2,45] Similarly, in the IM-UNITI (A Study to Evaluate the Safety and Efficacy of Ustekinumab Maintenance Therapy in Patients With Moderately to Severely Active Crohn's Disease) trial, fistula response was seen in 80% of patients receiving ustekinumab compared with 46% of patients receiving placebo after 44 weeks of treatment.[2,46] In a poster presentation, Battat and colleagues[47] reported fistula improvement in 66% of patients and fistula closure in 33% of patients treated with ustekinumab after 6 months of therapy. Supporting these findings, a multicenter, open-label study from 2016 showed fistula improvement in 61% (11/18) of patients treated with subcutaneous ustekinumab.[48]

Vedolizumab, a monoclonal antibody against the α4β7 integrin, inhibits leukocyte trafficking to the small bowel and is the first gut-specific biologic agent approved for the treatment of moderate to severe CD. Given its relatively recent approval in 2014, there are limited data on its use in patients with perianal CD. A subgroup analysis from the initial vedolizumab trial in patients with CD (GEMINI II; Study of Vedolizumab in Patients With Moderate to Severe Crohn's Disease) concluded that patients who were treated with vedolizumab had higher rates of fistula closure compared to patients who received placebo.[49] In a post hoc analysis of a 1-year prospective, multicenter, cohort study, 35 patients with active perianal disease (30 patients with a perianal fistula and 5 patients with an anal fissure) were studied; complete remission was seen in 43% of patients treated with vedolizumab for 14 weeks.[50] After 1 year of therapy, 54.3% of the patients who had complete fistula closure maintained remission.[50]

Over time, more experience using these novel agents as well as larger prospective studies will help to clarify their efficacy in treating perianal fistulas and better define their role among other, more well-studied biologic agents.

Intrafistulous Biologic Injections

Injecting a biologic agent into a fistula tract is a novel technique that is being investigated for the treatment of perianal fistulas.[2] The first case series to evaluate the use of intrafistulous injections of infliximab included 9 patients and documented a remission or partial response rate of 83%.[51] In a subsequent pilot study, 15 patients were treated with local injections of infliximab at the internal and external orifices of the perianal fistula; 67% of patients had complete closure of the fistula after 3 to 12 sessions.[52] Although these 2 initial studies had very encouraging results on the use of local biologic injections to improve symptoms, a study from Italy assessing intrafistulous infliximab injections documented fistula closure in only 36% of patients in the study.[53] Alessandroni and colleagues[54] documented fistula closure in 88% of patients who received local infliximab injections every 4 to 6 weeks. Intrafistulous injections are not limited to infliximab; to date, 3 studies have been published evaluating the efficacy of local adalimumab injections. Tonelli and colleagues[55] studied 12 patients who received intrafistulous adalimumab injections and

Table 4. Studies on Intrafistulous Biologic Injections for Perianal Fistulas

Study	Drug	Study Type	Number of Patients	Dose (mg)	Number of Treatments; Dosage Interval	Findings
Lichtiger[51]	Infliximab	Case series	9	20	3; 1-2 weeks	44% (4/9) of patients had complete fistula healing; 33% (3/9) of patients had a partial response at 4 weeks.
Poggioli et al[52]	Infliximab	Case series	15	15-21	3-12; 4 weeks	67% (10/15) of patients had fistula healing after up to 12 injections.
Alessandroni et al[54]	Infliximab	Open-label, non-RCT	12	20-25	≥2; 4-6 weeks	Persistent closure was seen in 88% (7/8) of patients 12 months after injection and concomitant fistulectomy.
Asteria et al[53]	Infliximab	Pilot study	11	20	1-4; 4 weeks	73% (8/11) of patients had a clinical response; 36% (4/11) had fistula closure.
Tonelli et al[55]	Adalimumab	Pilot study	12	20	4-16; 2 weeks	75% (9/12) of patients had complete cessation of drainage and significant improvement in disease activity score.
Laureti et al[56]	Adalimumab	Case series	33	40	≥2; 2 weeks	40% of patients had complete fistula closure after an average of 9 injections following surgery.
Poggioli et al[77]	Adalimumab	Case series	16	40	2 or 4; 2 weeks	13% (2/16) of patients had healing after 2 injections; 19% (3/16) had healing after 4 injections.

RCT, randomized, controlled trial.

documented the absence of drainage in 75% of patients. Furthermore, Laureti and colleagues[56] evaluated the use of local adalimumab injection after surgical treatment of complex perianal fistulas in patients with CD and reported complete fistula closure in 40% of patients after an average of 9 injections (Table 4). The findings of these studies are promising; however, there is a significant amount of variation in the protocols used, making it difficult to interpret and reproduce these results. More controlled studies are needed on TNF inhibitors and other biologic agents to assess their ability to induce fistula closure without the systemic side effects associated with more traditional infusions or injections.

Other Medical Therapies

Hyperbaric Oxygen Therapy Although the exact mechanism behind its efficacy remains unclear, hyperbaric oxygen therapy is thought to enhance the oxygen burst necessary for the phagocytic killing of anaerobic bacteria and to facilitate tissue repair.[57] The first study on the use of hyperbaric oxygen therapy for the treatment of fistulizing CD showed improvement in 1 patient with multiple complex, refractory perianal fistulas.[58] In a subsequent study, Colombel and colleagues[59] published a case series on hyperbaric oxygen therapy for CD that demonstrated that 37.5% of patients had partial fistula healing and 37.5% had complete fistula closure. All of the patients with complete closure had adjuvant perianal surgery, suggesting the use of hyperbaric oxygen as a complement to surgery.[59] Lavy and colleagues demonstrated complete fistula closure in 50% of patients who underwent 20 daily hyperbaric oxygen treatments.[60] None of the patients reported adverse events; however, tympanic membrane rupture and sinus damage have been reported.[61]

Adsorbent Carbon Spherical adsorbent carbon is an oral agent comprising porous carbon particles from 0.2 to 0.4 mm that binds to and removes toxic and inflammatory factors, including TNF-α.[62] In a randomized, double-blind, placebo-controlled trial evaluating adsorbent carbon in patients with CD, there was a statistically significant improvement in fistula closure with adsorbent carbon compared with placebo (30% vs 10%).[62] However, a large, multicenter, placebo-controlled trial was unable to replicate these results, reporting no significant difference in fistula healing when comparing carbon therapy with placebo after 4 and 8 weeks of treatment.[63] Therefore, the effectiveness of adsorbent carbon in patients with fistulizing CD remains unclear.

Summary

Despite significant advances in the treatment of luminal CD over the past decade, the management of perianal fistulizing disease remains a clinical challenge. Although traditional therapy for perianal disease includes antibiotics such as metronidazole or ciprofloxacin and immunomodulators, the introduction of biologic agents has changed the treatment algorithm. In spite of the numerous large randomized, controlled trials for CD therapies, research on the management of perianal fistulas is limited and is mostly made up of open-label cohorts, case series, and subgroup analyses of larger studies. There is no gold-standard therapy for patients with perianal disease; however, infliximab is often thought to be associated with the highest rates of fistula closure. The role for new biologic therapies with novel targets in the treatment of patients with perianal fistulas remains to be seen. Some of the more innovative techniques, such as intrafistulous biologic injections, may only be available at large, academic, tertiary care centers; however, the goal is for these therapies to become available to a broader community of patients through future research and education. Many of these new therapies offer great promise, but it is ultimately a multidisciplinary approach involving gastroenterologists and colorectal surgeons that will offer patients with perianal fistulizing CD the most promise in the future.

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