Approaches in the treatment of perianal fistula in Crohn disease

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Abstract

Perianal fistula is a common complication of Crohn disease, and it is a great burden on the life and psychology of patients, but its treatment is still a difficult problem to face. In recent years, progress in the treatment of Crohn disease has progressed rapidly due to the advent of biological agents, but there has been a lack of research on perianal fistula in Crohn disease, and the direction of research has been scattered; therefore, the author reviews the traditional treatment of perianal fistula in Crohn disease in the context of the available literature and discusses emerging and potential therapeutic approaches.

Keywords
- Crohn Disease
- Perianal Fistula
- Medical Treatment
- Surgical Treatment
- Stem Cells

Introduction

Perianal fistula is one of the most challenging complications of Crohn disease. A community-based study showed its prevalence is of 20% in adults, and it has a cumulative incidence of 21% after 10 years and 26% after 20 years.[1] Perianal fistula in Crohn disease (pfCD) could be able to cause uncomfortable symptoms such as pain, persistent drainage, and incontinence, which can negatively affect all aspects of the life of the patient, from the limitation of daily activities to the impact on social relationships, as well as the emotional and psychological impact, severely affecting the quality of life of the patient.[2]

Although there are many medicines available for the treatment of pfCD, the main treatment is antitumor necrosis factor. Infliximab is the only biological therapy that has been proven effective in randomized controlled trials,[3] while the effectiveness and safety of other drugs remains to be proven. In recent years, local injection of mesenchymal stem cells has made significant progress in the treatment of pfCD, bringing new hope to patients with pfCD.[4] In addition, many local injections of biologic agents have shown benefit in patients with pfCD,[5,6] but randomized controlled trials are lacking to demonstrate their effectiveness, which nonetheless points to a new path for the treatment of pfCD. It is worth mentioning that hyperbaric oxygen seems to facilitate the closure of pfCD and may be a new treatment modality for pfCD in combination with other treatment options.[7] Thus, the present paper integrates the existing and potential treatment modalities for pfCD and presents a clear structure for subsequent studies.

The present work was performed at the China-Japan Union Hospital of Jilin University, China.

Medical Treatment

Antibiotic

The Chinese guidelines for inflammatory bowel disease recommended that ciprofloxacin and/or metronidazole be the preferred antibiotics for symptomatic simple perianal fistula and complex perianal fistula,[8] but no randomized controlled trials have shown that antibiotics are effective for treating pfCD. Bernstein et al. conducted a study of 21

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individuals with pfCD who were given metronidazole, which led to the current therapeutic use of ciprofloxacin or metronidazole for the treatment of pfCD; drainage, erythema, and induration were all significantly reduced, and 10 of 18 (56%) treated patients healed completely. However, many patients developed a metallic taste in the mouth, darkened urine, mild gastrointestinal discomfort, and peripheral neuropathy.[9] In a follow-up study of 26 patients with pfCD, it was found that disease activity increased in all patients once the dose was reduced, but perianal manifestations improved rapidly once the original dose was restored.[10]

In a randomized controlled experiment, 25 patients with pfCD were given either ciprofloxacin, metronidazole, or placebo, and the results showed that inducing remission of pfCD with ciprofloxacin or metronidazole was no more efficacious than placebo, but the ciprofloxacin group had higher rates of remission and treatment response than the metronidazole and placebo groups.[11] However, the results were not statistically significant due to the small sample size of the study, so neither the ECCO nor AGA recommend the use of antibiotics alone to induce remission and healing of pfCD.[12,13] Studies have shown that antibiotics can improve the efficacy of biological agents with a good safety profile.[14,15]

However, the widespread use of broad-spectrum antibiotics (including ciprofloxacin) has led to a progressive increase in the incidence of *Clostridium difficile* colitis, especially with the appearance of highly virulent fluoroquinolone-resistant strains with high mortality rates also associated with this,[16] so it is necessary to design placebo-controlled trials to determine the effectiveness of antibiotics to prevent these potential risks.

Biological Agents

Infliximab

Infliximab, a chimeric antitumor necrosis factor TNF-α monoclonal antibody, has been shown to be an effective treatment for pfCD. In a placebo-controlled trial, 94 patients with fistula in Crohn disease (85 with perianal fistula) were randomized to receive infliximab 5 mg/kg, infliximab 10 mg/kg, or placebo treatment. The results indicated that participants receiving infliximab had significantly higher remission rates than the placebo group and a shorter time to respond to the drug than placebo. Furthermore, infliximab was generally beneficial with or without combination therapy (such as antibiotics, azathioprine, or cortisol), and the benefit appeared to be dose-independent.[3] However, in recent years, higher levels of infliximab have been proven to be linked to the healing of the perianal fistula.[17] Therefore, randomized controlled trials comparing the healing and closure of fistula induced by different levels of infliximab are necessary. One study demonstrated a higher response rate with ciprofloxacin plus infliximab (73 percent) than with infliximab alone (39 percent).[14]

Infliximab has been used as an important tool for induction and maintenance therapy in patients with pfCD, but the side effects of long-term use of infliximab, the optimal timing of its administration, and the optimal interval between doses for maintenance therapy still needs to be extensively investigated.[5] A recent study has shown that local injection of infliximab along the perianal fistula seems to be a safe and effective method that deserves our continued exploration. In addition, the combination therapy of infliximab-based regimens to induce fistula closure also needs to be further developed.

Adalimumab

Adalimumab, a recombinant fully human immunoglobulin G1 monoclonal antibody administered subcutaneously, binds human TNF with high specificity and modulates biological responses induced or modulated by TNF, and is effective in inducing healing of pfCD. In a study, 117 patients with fistula in Crohn disease (97% with perianal fistula) were randomly assigned to 3 treatment groups: adalimumab 40 mg every other week, adalimumab 40 mg weekly, or placebo, and fistula remission was observed at 56 weeks, showing a gradual increase in fistula closure rate over time in the adalimumab-treated group. At 16 weeks, a statistically significant difference in fistula closure rates was found between the placebo and adalimumab groups. Patients treated with adalimumab had a markedly lower mean number of fistulae drained each day than those treated with placebo (1.34 in the placebo group; 0.88 in the adalimumab group, $p = 0.002$). Approximately 60% of adalimumab-treated fistula healed after 2 years of treatment, and adalimumab was well tolerated.[18]

One study showed that adalimumab combined with ciprofloxacin was more effective than adalimumab monotherapy in treating patients with pfCD, but the beneficial effects of the initial combination were not maintained after discontinuation of the antibiotic.[15] It is worth noting that adalimumab can be used not only as a first-line treatment for patients with pfCD, but also for patients who are refractory or intolerant to infliximab.[19] Some studies have shown that local high-concentration injection of adalimumab may be beneficial to the rapid healing of pfCD.[6] However, due to the tiny sample size and lack of controlled trials, a large number of trials are needed to demonstrate and assess the advantages and disadvantages of adalimumab in the treatment of pfCD.

Certolizumab

Certolizumab is a polyethylene humanized Fab' fragment that binds to tumor necrosis factor α. Schreiber et al. conducted a study of certolizumab on treating fistula in Crohn disease in which 58 patients (55 of 58 patients with perianal fistula) who responded to induction therapy with certolizumab in the PRECISE 2 study were randomized into 2 groups: placebo group, certolizumab 400 mg every 4 weeks, and observed for fistula closure rate at week 26. At week 26, 73% of the patients in the certolizumab group had a fistula closure of at least 50%, and 67% had a fistula closure of 100%, 39% of the patients in the placebo group had a fistula closure of at least 50%, and 31% had a fistula closure of 100%.[20] Although there was no statistical difference in outcomes at

week 26, more patients in the certolizumab group achieved fistula closure and patients tolerated certolizumab well compared with the placebo group, and only one patient in the certolizumab group developed a perineal abscess. These data suggest that certolizumab maintenance therapy may provide benefit to patients with pfCD. There are few clinical trials related to certolizumab for the treatment of pfCD to definitively assess its effectiveness in patients with pfCD, so further studies are warranted.

Vedolizumab

Vedolizumab is an intestine-selective α4β7 integral protein antagonist. Feagan et al. conducted an exploratory study of 45 patients with pfCD in the GEMINI 2 trial and found that the vedolizumab group had higher fistula closure rates at weeks 14 and 52 compared with the placebo group.[21] Despite the lack of statistical significance, the findings imply that vedolizumab may be helpful in patients with pfCD and should be investigated further in prospective clinical trials.

Ustekinumab

Ustekinumab, a monoclonal antibody against the p40 subunit of interleukin 12 and interleukin 23, has been shown to have a significantly higher response rate than placebo in patients with moderate-to-severe Crohn disease, but little research is known about ustekinumab in patients with pfCD. A meta-analysis demonstrated the potential effectiveness of ustekinumab, with 41 and 17% of patients experiencing response and remission of fistulae after 1 year of treatment with ustekinumab alone, respectively.[22] However, because there are few randomized controlled trials, its efficacy and safety in patients with pfCD needs to be further investigated.

Immunosuppression

Mercaptopurine

Azathioprine or 6-MP is often used as a maintenance treatment option for patients with pfCD in China.[8] A meta-analysis showed that azathioprine and 6-MP were better than the placebo group in inducing remission of pfCD, but the quality of the evidence was low because of sparse data.[23] When azathioprine or 6-MP is combined with infliximab in patients with pfCD, it can prolong the effect of initial infliximab treatment on the closure of perianal fistula in Crohn patients;[24] therefore, the ECCO does not recommend the use of mercaptopurine as monotherapy in patients with pfCD,[12] but there is a lack of valid evidence as to whether biologic agents should be combined with immunosuppressive agents in patients with pfCD.

Tacrolimus

Tacrolimus is a calcineurin inhibitor, and a randomized controlled experiment found that 0.2 mg/kg/day of oral tacrolimus improved fistula drainage but did not relieve fistulae in Crohn patients.[25] However, due to the high nephrotoxicity of tacrolimus, this may limit the use of high-dose tacrolimus to only when other treatments are ineffective. In addition, topical tacrolimus may be safe and effective for patients with pfCD.[26] However, a huge number of studies are required to prove this.

Surgical Treatment

Seton Drainage

Long-term seton drainage is a simple and effective treatment for pfCD, with a total success rate of 87.5% in a study showing its efficacy in treating perianal abscesses in patients with Crohn fistula while preserving the function of the anal sphincter.[27] Thornton et al. also showed that long-term line drainage relieved the symptoms of patients with complex pfCD and reduced the thickness of the anal wall.[28]

Fistulotomy

In Crohn patients with low-level simple anal fistula, anal fistulotomy is the most common treatment method.[29] However, the long-term recurrence rate is high, with 7, 16, 26, and 39% of patients recurring at 12, 24, 48, and 72 months after surgery, respectively, and most recurrences occurring at another site.[30]

Advancement Flaps

A meta-analysis reported data on 135 patients with pfCD using this procedure, with a clinical healing rate of 66% and a recurrence rate of 30%, suggesting that this treatment is a proper choice for patients with pfCD.[31] A retrospective study by Stellingwerf et al. showed that 12 of 20 patients (60%) with pfCD treated with this procedure achieved clinical healing, similar to the results of the above meta-analysis, and had higher healing rates when combined with antitumor necrosis factor or immunosuppressive agents.[32]

Ligation of the Intersphincteric Fistula Tract

Ligation of the intersphincteric fistula tract (LIFT) is a procedure similar to advancement flaps that preserves the function of the anal sphincter in the treatment of complex pfCD and has received increasing attention in recent years. Fifteen patients with pfCD were treated with LIFT in a prospective study, with healing rates of 60 and 33% at 2 and 12 months, respectively, suggesting that this procedure may be an option for the treatment of pfCD.[33]

Fibrin Glue

Fibrin glue activates thrombin to form a fibrin clot, which mechanically closes the perianal fistula and permanently eliminates the fistula as the fibrin clot dissolves while promoting the tissue healing process. A total of 71 patients with pfCD were randomly assigned to a fibrin glue injection group or an observation group in an experiment. The clinical remission rate after 8 weeks was 38% in the fibrin glue injection group compared with 16% in the observation group, and the efficacy in the simple fistula group was much higher than that of the complex fistula group. In addition, the majority of patients who achieved clinical remission at week 8 maintained it to week 16. It is worth noting that fibrin glue injections have few adverse effects and anal incontinence, and therefore may be tried in Crohn disease

patients with complex perianal fistula before more invasive surgery.[34] The use of fibrin glue before more invasive surgery can be tried in patients with complex fistula.

Anal Fistula Plug

The anal fistula plug (AFP) is a natural, resorbable, xenobiotic material derived from the submucosa of the porcine small intestine, which provides structural support, provides sites for cell attachment, and promotes tissue healing after injury.[35] In a randomized controlled trial, 106 patients with pfCD were randomly divided into an AFP group and a control group (seton drainage alone). The AFP group had a fistula closure rate of 31.5% after 12 weeks, while the control group had a rate of 23.1%.[36] Therefore, the ECCO does not recommend the use of AFP as a routine treatment because its efficacy is similar to that of seton drainage alone treatment.[37]

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) have received much attention in recent years for their ability to regulate inflammatory processes, and, recently, adipose-derived MSCs have made significant advances in the treatment of patients with pfCD. In a randomized double-blind controlled trial, 212 patients with pfCD were randomly divided into an allogeneic adipose-derived MSC group (107 patients) and a placebo group (105 patients) and evaluated for fistula remission at 24 weeks. The results showed that the comprehensive remission rates of anal fistula in the allogeneic adipose-derived mesenchymal stem cell group and the placebo group were 50% and 34%, respectively. The most common adverse effects were rectal pain, anal abscess and nasopharyngitis, and 17% of patients in the allogeneic adipose-derived MSC group had treatment-related adverse effects compared with 29% in the placebo group, thus indicating that MSCs were well tolerated.[4] The 131 patients in this study completed 52 weeks of follow-up, and at 52 weeks, a significantly higher percentage of patients in the allogeneic adipose-derived MSC group (56.3%) achieved a combined remission when compared with the control group (38.6%), and the patients tolerated well the treatment throughout the 52 weeks.

In a recent randomized controlled trial in China, 22 patients with pfCD were randomly divided into an autologous fat-derived MSC group and a control group, and their fistula closure was evaluated after 3, 6, and 12 months. After 3, 6, and 12 months, the fistula healing rates of the autologous adipose-derived mesenchymal stem cell group and the control group were 90.9 and 45.5%, 72.7 and 54.5%, and 63.6 and 54.5%, respectively. The postoperative quality of life and sphincter function were better than those of conventional surgery, and the safety data showed that they were well tolerated.[38] Therefore, autologous fat-derived stem cell injection is also a safe and effective treatment for pfCD.

Although the mechanism of action of adipose-derived MSCs is yet to be determined in human trials, clinical studies have found that expanded adipose-derived MSCs can exert immunomodulatory effects.[39] Overall, local injection of adipose-derived MSCs is a minimally invasive, safe, and effective treatment for Crohn fistula, but many issues remain to be addressed, including the ideal cell dose, injection frequency, and optimal cell delivery method, as well as a comparison of the efficacy of autologous and allogeneic adipose-derived MSCs.

Other Surgical Treatments

For complex pfCD, when treatment with medication and surgery is unsuccessful, a temporary fecal diversion is sometimes required for symptomatic relief, which has the advantage of being relatively less invasive surgically, promoting repair of the perianal fistula, and without the risk of fecal incontinence. In a study of 31 patients with perianal Crohn disease who got a temporary fecal diversion, 81% had early remission, 68% required a proctocolectomy, only 26% had complete remission, and only 10% regained bowel integrity.[40] These data suggest that a fecal diversion is only a temporary alternative procedure and that most patients will eventually require a proctocolectomy. For patients with severe and refractory pfCD, the rectum with permanent stoma is the last option. Rectal resection with the permanent stoma should be performed as soon as possible after the failure of medicine or local treatment for complex fistulas with serious lesions in the rectum, anal incontinence, and anal stenosis to relieve the symptoms of the patient.[41]

Hyperbaric Oxygen

Hyperbaric oxygen therapy is the breathing of 100% oxygen at higher than normal atmospheric pressure: typically 202-253 kPa (equivalent to 2.0-2.5 absolute atmospheres); hyperbaric oxygen therapy promotes wound healing by positively affecting various cells involved in wound healing through oxidative stress.[42] A study enrolled 20 patients with pfCD who received 100% oxygen at 243-253 kPa once daily on weekdays for 8 weeks and observed improvements in perianal disease activity index (PDAI) and magnetic resonance imaging (MRI) at 16 weeks, showing improvements in clinical, radiological, and biochemical parameters compared with controls.[7] After 1 year of follow-up, the clinical and radiological improvements in the 20 patients with pfCD were similar to those seen at 16 weeks.[43] This demonstrated the effectiveness of hyperbaric oxygen for long-term improvement of pfCD. The main adverse effect of hyperbaric oxygen was pneumatic injuries, but these were mostly resolved after treatment. Thus, the feasibility, efficacy, and safety of hyperbaric oxygen as a potential treatment modality for patients with pfCD are good, but due to the lack of randomized controlled trials, we still need a large number of studies to confirm its effectiveness and explore the best way to use it.

Conclusion

Perianal fistula remains one of the most difficult issues in the management of Crohn disease patients. Although many biological agents have begun to be used in the treatment of pfCD, their efficacy and safety have not been proven. Surgical treatment is still an essential component of the treatment for pfCD. But the disadvantages of surgical

treatment are obvious. It can relieve symptoms in the short term, but the long-term curative effect is not exact, and the recurrence rate of fistula is high, which causes a great burden on the economy and psychology of the patient. Intralesional injection of stem cells has brought new hope for the treatment of patients with pfCD, and future research should focus on mesenchymal stem cell therapy, including its mechanism of action, frequency of administration, cell dose, and combination therapy regimens. Hyperbaric oxygen therapy appears to be a potential adjunct to the treatment of pfCD, but its long-term effectiveness and safety remain to be demonstrated. In the future, we should explore more treatment options, multidisciplinary comprehensive treatment, improve the symptoms of patients, improve the quality of life of patients, and bring benefits to patients.

Conflict of Interests

The author has no conflict of interests to declare.

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