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Review Article

Management of Anal Fistula with Crohn's Disease

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Abstract

Crohn's disease (CD) causes gastrointestinal symptoms (i.e., diarrhea and abdominal pain), systemic symptoms (i.e., fatigue, anemia, weight loss, and fever), and perianal fistulas that produce anal pain. Because of the frequent occurrence of diarrhea and ulcers in the rectum, CD is often exacerbated by perianal abscesses and/or fistulas. Perianal fistulizing CD (PFCD) has an unknown etiology and recurring symptoms such as pain and discharge, which seriously affects the patient's quality of life (QOL). In the past, radical surgery was performed for PFCD, but due to the risk of anal sphincter impairment, conservative therapy using antibiotics and immunosuppressive medications is currently the first treatment option. PFCD management has greatly improved with the use of biologics such as the antitumor necrosis factor alpha (TNF-α) antibodies infliximab and adalimumab. In this review, the results of the administration of anti-TNF-α (certolizumab pegol), anti-interleukin-12/23 (ustekinumab), and anti-$\alpha_4\beta_7$ integrin antibodies (vedolizumab) were evaluated. Our investigation showed that these medications may be effective for maintenance therapy to prevent the recurrence of anal fistulas. In addition to biologics, molecular target drugs and even regenerative medicine using mesenchymal stem cells have been introduced to further expand the treatment options for consideration by medical personnel. We herein discuss the management of PFCD by focusing on studies conducted in the United States and Europe where researchers used recommended guidelines and consensus statements to evaluate the efficacy of each medication and published their findings in peer-reviewed journals.

Keywords

Crohn's disease, perianal fistula

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Introduction

The management of perianal fistulizing Crohn's disease (PFCD) is an extremely challenging and disabling task. In many cases, it is initially difficult to differentiate and diagnose Crohn's disease (CD) from complex perianal fistula in young patients. It needs to be determined whether the lesion is luminal or perianal. Patients with PFCD have a higher risk for hospitalization and surgery than those without[1,2]. In addition to causing pain, perianal disfigurement, and sometimes fecal incontinence, PFCD can negatively affect the patient's quality of life (QOL).

In the past, curative surgery was performed for PFCD. However, due to poor surgical results (i.e., fecal incontinence and recurrence), conservative therapy has been considered as the first treatment option for PFCD. In a dedicated randomized controlled trial (RCT), infliximab was the only biologic treatment that proved to be effective in PFCD treatment. Recently, a large number of biologics and molecular-targeted drugs have emerged. It seems that the treatment options have increased and the QOL of patients with PFCD has improved. Furthermore, regenerative medi-

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cine has emerged, and the treatment outcome for perianal fistula is improving.

The guidelines and consensus statements published by the American College of Gastroenterology (ACG) and the European Crohn's and Colitis Organization (ECCO), together with the European Society of Coloproctology, guides PFCD treatment[3,4].

Etiology and Pathogenesis

The incidence of perianal lesions in patients with CD has been reported to range from 20% to 40% worldwide, with Asian countries having the highest incidence of 30.3%-58.8%[5-8].

Perianal fistula affects approximately 25% of patients with CD[3,5,9,10].

Yamamoto et al. reported on the interim analysis of a nationwide Inception Cohort Registry Study of Patients with CD in Japan. Perianal lesions were present in 324 (48.2%) of 672 patients who were newly diagnosed with CD. The prevalence of perianal lesions was higher in patients aged <40 years than in those aged ≥40 years, and it decreased with age. Perianal fistulas (59.9%) and abscesses (30.6%) were the most common perianal lesions[11].

To date, the etiology of PFCD remains unclear. The pathogenesis of CD is currently thought to be due to intestinal barrier disruption, genetic factors, and changes in the intestinal microbiota, which lead to the activation of the body's innate immune system. There are two major pathologies that cause perianal abscesses or fistulas in patients with CD. One is a deep-penetrating anorectal ulcer, and the other is the cryptoglandular infection theory. PFCD arises from granulomatous anorectal inflammation, and it is unique in that the primary orifice can sometimes be within an ulceration rather than a cryptoglandular infection[12]. One theory for PFCD is that it may result from a deep-penetrating ulcer of the rectum or anus. Another is that PFCD may originate from an anal gland abscess. CD-associated fistulas appear as fissures that penetrate the intestinal wall and are surrounded by granulation tissue with acute (neutrophilic) and chronic (lymphocytic) inflammation. A fistula may exhibit a certain degree of epithelial lining and consist of a flattened intestinal epithelium without goblet cells or a squamous epithelium. However, a nonepithelialized fistula is usually covered with a thin layer of myofibroblasts, which locally form a new basement membrane[13]. Fistulas originate from epithelial defects caused by inflammation, and healing is inhibited in CD due to the reduced migration capacity of colonic lamina propria fibroblasts[14].

Another explanation for fistula formations is the extracellular matrix remodeling mechanism triggered by increasing the activation of some of the matrix metalloproteinases (MMPs), such as MMP-3 and MMP-9. Bacteria also plays a role in the occurrence and persistence of both idiopathic (cryptoglandular) and CD perianal fistulas[15].

Classification

The Parks Classification has been used mainly for perianal anal fistulas and CD. However, AGA proposed an easier classification that is currently being used in clinical practice for CD perianal fistulas[16]. A clear distinction is made between simple and complex fistulas. Intersphincteric, intrasphincteric, and transsphincteric fistulas below the dentate line with a single external opening are classified as simple fistulas, whereas high intersphincteric, high transsphincteric, suprasphincteric, and extrasphincteric fistulas with multiple external openings are classified as complex fistulas.

The Perianal Disease Activity Index was developed to evaluate the activity of perianal disease in CD.

Diagnosis

If anal symptoms appear in patients who have already been diagnosed with CD, endoanal ultrasonography and magnetic resonance imaging (MRI) should be adopted to observe the position and running of the fistula as well as the degree of pus accumulation. Perianal CD fistulas characteristically have a hypoechogenic fistula tract surrounded by a well-defined hyperechogenic area with a thin hypoechogenic edge, known as "Crohn's Ultrasound Fistula Sign"[17].

In Japan, examination under anesthesia (EUA) is not a standard practice. However, in the USA and Europe, it is considered to be the standard practice for examining and diagnosing fistulas. EUA should be performed by a licensed colorectal surgeon under general or lumbar anesthesia. The surgeon performing EUA can obtain tissue samples for pathological diagnosis and place the drainage seton at the same time. It has been found that it is better to place the seton when the antitumor necrosis factor alpha (TNF-α) is given for perianal fistula with CD[18].

Medical Treatment

Guidelines such as those issued by the ACG and ECCO can help direct PFCD treatment[3,19].

When medical treatment is performed, it is desirable to start treatment after performing seton drainage. A top-down approach is preferable over a bottom-up approach as evidence suggests that the former is associated with an increased number of PFCD patients not requiring surgery[20].

A retrospective study investigated the efficacy of steroid-sparing therapy (immunomodulators and/or anti-TNF-α medications) in reducing the risk of perianal fistulizing complications in patients newly diagnosed with CD. In this study, newly diagnosed CD patients without perianal disease

received steroid-sparing therapy for at least 90 days and exhibited a 59% reduced risk of developing perianal fistulizing complications 2 years after treatment as opposed to those who did not receive the therapy[21].

Contrary to these findings, a retrospective study compared the recurrence rate of fistula in 76 patients with perianal CD in the early (<30 days, median: 12 days) and late (>30 days, median: 250 days) infliximab induction groups. Furthermore, the patients in both groups had a loose seton inserted for perianal CD. The results indicated that the recurrence rates of fistula were low in both groups (6 patients overall, 8%), there was no difference in the timing of infliximab initiation, and there were no occurrences of abscesses or perianal sepsis in either group[22].

1. Conservative therapy

Antibiotics

Antibiotics should be included in the treatment to prevent local sepsis and maintain clinical response. Ciprofloxacin and metronidazole are commonly used for perianal CD. The ECCO guidelines do not recommend the use of antibiotics alone for fistula closure for patients with CD and complex perianal fistula[19].

Combination treatment with antibiotics and azathioprine was significantly superior to antibiotic therapy alone in achieving week-20 clinical response in a prospective open-label study (48% vs. 15%, $P = 0.03$)[23].

In a double-blind, placebo-controlled trial of 24 patients with perianal CD who received ciprofloxacin or a placebo in addition to infliximab, the response rates at week 18 were 73% and 39% in the ciprofloxacin and placebo groups, respectively ($P = 0.12$)[24].

A multicenter, double-blind, placebo-controlled study of 76 patients with perianal CD evaluated the efficacy of adalimumab in combination with ciprofloxacin and found that the clinical responses at week 12 were 71% and 47% in the adalimumab plus ciprofloxacin and adalimumab plus placebo groups ($P = 0.047$). Moreover, the remission rate at week 12 was significantly higher in the combination than in the placebo group (65% vs. 33%, $P = 0.009$)[25].

Immunosuppressors

The ECCO guidelines do not recommend the use of thiopurine monotherapy (azathioprine, mercaptopurine) for fistula closure in patients with CD and complex perianal fistula[19].

There are only a few prospective randomized studies that investigated the azathioprine, 6-mercaptoprine, or methotrexate immunosuppressor in the treatment of anoperineal CD. A secondary analysis of two randomized, placebo-controlled trials comparing infliximab with placebo for perianal CD and anti-TNF therapy plus immunomodulator therapy with anti-TNF alone in perianal CD found no difference in fistula outcomes between induction and maintenance therapy[26,27].

Azathioprine and 6-mercaptopurine (6-MP)

A meta-analysis of three RCTs using azathioprine and 6-MP revealed that there was no significant effect on fistula improvement or closure compared with the placebo group[28]. However, the Cochrane analysis was limited by the small sample size of 18 patients and the low overall quality of the patient inclusion data.

Pearson et al. conducted a meta-analysis on 70 patients with CD and fistula who received either azathioprine or 6-mercaptopurine and found that healing was complete in 54% of the treated patients versus 21% of the controls[29].

A subgroup analysis of a 1980 trial designed to evaluate the efficacy of 6-MP in the treatment of CD revealed that patients treated with 6-MP had a higher likelihood of fistula healing than those who received placebo. In this study, Present et al. analyzed data from 83 patients and conducted a subgroup analysis on 36 patients who developed a fistula. Most fistulas occurred in the perianal region, with 31% of the patients in the 6-MP group showing fistula closure compared with only 6% of the patients in the placebo group[30].

Some of the findings suggest that combination therapy using thiopurine with anti-TNF is effective in the treatment of fistulas. Colombel et al. found that the inclusion of azathioprine in anti-TNF therapy exerted a complementary effect, thereby increasing its likelihood to achieve steroid-free clinical remission in the general study population[31].

Cyclosporine

Present et al. used intravenous cyclosporine in the treatment of 16 patients who did not respond to conventional medical therapy and found that 88% experienced improvement and 44% experienced closure[32].

Tacrolimus

Tacrolimus for PFCD is included in the ACG recommendations, but it is only recommended to be used as short-term therapy owing to its potential toxicity[3].

Sandborn et al. conducted a multicenter, double-blind, placebo-controlled trial in which 46 patients (43 with PFCD) were randomly assigned to receive tacrolimus or a placebo. Only 27 patients completed this 10-week study. The intent-to-treat analysis revealed greater fistula improvement in the tacrolimus group (43% vs. 8% on placebo, $P = 0.01$), but there was no effect on fistula closure. Furthermore, as the deleterious side effects were more common in the tacrolimus group, the authors recommended a dose reduction when using tacrolimus in PFCD treatment[33].

Methotrexate

Methotrexate can be used as a second-line treatment after azathioprine or 6-MP when the latter fails or gives rise to intolerance. Methotrexate acts more quickly than azathioprine; also, fistula closure was observed in 25% of the patients[12].

Biological drugs (see Table 1)

Table 1. Biological Drugs for Fistulizing Crohn's Disease.

Type	Mechanism	Drug	ECCO [a] Guidelines	ACG [b] Clinical Guideline	Study
Anti-TNFα [c]	Suppresses the action of TNF-α (one of the cytokines), which causes inflammation	Infliximab	Recommend for the induction and maintenance of remission in complex perianal fistulae in CD	Strong recommendation Moderate level of evidence	ACCENT II
		Adalimumab	Suggest use for induction and maintenance of remission in complex perianal fistulae in CD	Strong recommendation Low level of evidence	CLASSIC I GAIN CHARM ADHERE CHOICE ADAFI
		Certolizumab pegol	Insufficient evidence to recommend as a treatment for complex perianal fistulae in CD	Strong recommendation Low level of evidence	PRECISE 1 PRECISE 2
Anti-IL12/23 [d]	Suppresses the action of IL-12 and IL-23, which causes inflammation in the gastrointestinal tract by activating the inflammatory cells	Ustekinumab	Insufficient evidence to recommend as a treatment for complex perianal fistulae in CD	-	UNITI-1 UNITI-2 CERTIFI GETAID
Anti-IL23 [d]	Suppresses the action of IL-23 by binding to the p19 subunit of the human IL-23 cytokine	Risankizumab	A lack of evidence to recommend as a treatment for complex perianal fistulae in CD	-	-
Anti-$\alpha_4\beta_7$ Integrin	Suppresses the function of integrin, which is involved in the prevention of inflammation caused by excessive lymphocyte invasion into the intestinal mucosa	Vedolizumab	Insufficient evidence to recommend as a treatment for complex perianal fistulae in CD	-	GEMINI 2 The ENTERPRISE GETAID
JAK [e] inhibitor	Inhibits the activity of one or more of the JAK enzymes and tyrosine kinase	Upadacitinib	Insufficient evidence to recommend as a treatment for complex perianal fistulae in CD	-	-

[a] ECCO: The European Crohn's and Colitis Organisation
[b] ACG: The American College of Gastroenterology
[c] TNF: Necrosis Factor Alpha
[d] IL: Interleukin
[e] JAK: Janus kinase

Anti-TNF-α

TNF-α is an inflammatory cytokine produced in excess in the mucosa and lamina propria of the CD-affected intestine. Infliximab, adalimumab, and certolizumab pegol are monoclonal antibodies that target TNF-α. The introduction of anti-TNF-α agents has greatly improved the management of PFCD.

(1) Infliximab and related clinical study

Infliximab was the first CD drug approved by the US Food and Drug Administration in 1998. In an RCT, infliximab was found to help promote the closure of perianal fistulas and sustain this response for more than 1 year. Complete response (defined as no draining fistula at two consecutive visits at least 4 weeks apart) was observed in 4 of 31 patients (12.9%) in the placebo group and 29 of 63 patients (46%) in the infliximab group (relative risk (RR): 3.57; 95% confidence interval (CI): 1.38-9.25)[26].

ACCENT II

ACCENT II was a multicenter, randomized, double-blind, placebo-controlled study that evaluated the efficacy of infliximab maintenance therapy. The initial response rate to induction therapy was observed in 195 of 282 patients (67%). The time to loss of response was significantly longer for patients who received infliximab maintenance therapy than for those who received placebo maintenance (more than 40 weeks vs. 14 weeks, $P < 0.001$). At week 54, no draining fistulas were observed in 19% of the patients in the placebo maintenance group compared with 36% of the patients in the infliximab maintenance group ($P = 0.009$)[27]. The ECCO guidelines recommend infliximab for the induction and maintenance of remission in complex perianal fistulas in CD[19].

In complex fistulas, once local sepsis has been controlled by surgical drainage and/or antibiotics, anti-TNF drugs (infliximab, adalimumab) are the first-line treatments with or without associated immunomodulators. Furthermore, the

combination of surgery and anti-TNF therapy has additional benefits for healing[34].

(2) Adalimumab and related clinical studies

The ECCO guidelines suggest that adalimumab may be used for the induction and maintenance of remission in complex perianal fistulas in CD[19].

CLASSIC I

In 2006, Hanauer et al. conducted an RCT to examine the dose-response relationship of adalimumab in 299 patients who had never undergone anti-TNF therapy. The patients were randomly assigned to receive either a placebo or adalimumab. Only 11% of the randomized patients (32/299) experienced draining enterocutaneous or perianal fistulas at screening and at baseline and were unevenly distributed across the treatment groups. The rates of fistula improvement and remission for the adalimumab-treated patients and those receiving placebo were not significantly different[35].

GAIN

In 2007, Sandborn et al. reported on the results of a randomized, double-blind, placebo-controlled trial designed to determine whether patients with no tolerance or a lost response to infliximab would benefit from adalimumab. Of the 325 patients, 45 (14%) had either an enterocutaneous or a perianal fistula. The induction of remission at week 4 did not differ between the groups[36].

CHARM

Colombel et al. conducted a multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy of adalimumab and its ability to maintain remission. In this study, the patients were randomly assigned to either receive a placebo, adalimumab every 2 weeks, or adalimumab once a week. Of the 778 patients, 130 (15.2%) were found to have a draining enterocutaneous or perianal fistula. The fistula closure rates were higher in the adalimumab than in the placebo group at 26 weeks (30% vs. 13%, $P = 0.043$) and at 56 weeks (33% vs. 13%, $P = 0.016$). In addition, during the open-label extension period of the trial, 90% of the patients experienced fistula healing at week 56, and it was reported that these patients still experienced fistula healing 1 year later[37,38].

ADHERE

The results of a study that combined CHARM and ADHERE indicated that there was no significant increase in the risk of serious AEs in patients treated with adalimumab (RR: 1.21; 95% CI: 0.43-3.38)[19]. Maintenance of fistula healing, perianal sepsis cure, stoma-free survival, and QOL after 56 weeks were also analyzed, but the results were inconclusive due to the varying durations of the follow-up periods[39].

CHOICE

In an open-label single-arm multicenter Phase IIIb trial evaluating the efficacy of adalimumab in patients with moderate to severe CD who had failed or were no longer responding to infliximab, received adalimumab induction and maintenance therapy. Of the 673 patients, 88 (13%) had enteric or perianal fistulas, of whom 34 (40%) had completely healed fistulas[40].

ADAFI

A multicenter, randomized, double-blind, placebo-controlled trial conducted by Dewint et al. found that the combination of adalimumab and ciprofloxacin had better clinical efficacy and achieved higher remission rates than adalimumab monotherapy for PFCD. CD patients with an active perianal fistula were randomized to receive either adalimumab for 2 weeks followed by ciprofloxacin or a placebo for 12 weeks. Subsequently, the patients were continued on adalimumab alone and reevaluated at week 24. A 50% reduction in fistulas from allocation to week 12 (71% vs. 47%, $P = 0.047$) was observed in the ciprofloxacin and placebo groups, but at week 24, there was no significant difference in clinical response between the two treatment groups ($P = 0.22$). The remission rates were 65% and 33% in the ciprofloxacin and placebo groups ($P = 0.009$), respectively[25].

Duration of anti-TNF therapy

The results of some studies have indicated that more than half of the patients relapse after the discontinuation of anti-TNF therapy. Patients who discontinue therapy due to clinical remission are less likely to relapse than those who discontinue therapy without remission[27,41-43]. Therefore, the continued use of anti-TNF therapy is recommended even for patients who achieve clinical remission of a perianal fistula.

(3) Certolizumab pegol and related clinical studies

Certolizumab pegol is a pegylated human Fab fragment that binds to TNF-α.

It is marginally effective in the treatment of PFCD, but there is no significant difference in remission rates. The ACG strongly recommends using it despite the low evidence for its efficacy[3]. However, the ECCO guidelines do not recommend the use of certolizumab pegol due to insufficient evidence[19].

There is insufficient evidence to recommend use of certolizumab pegol as a treatment for complex perianal fistulae in patients with CD.

PRECISE 1

In a multicenter, randomized, double-blind, placebo-controlled trial, patients with moderate to severe CD were randomized to receive either certolizumab pegol or a placebo. At baseline, 107 (16%) of the 662 patients had a fistula, and there was no difference in fistula closure at 26 weeks after allocation. However, statistical analysis revealed that the evidence for the use of this agent was low due to the limited number of patients with fistulas in this study[44].

PRECISE 2

In another trial, 428 patients who responded to certolizumab pegol remission induction therapy at 6 weeks were ran-

domized to receive either certolizumab pegol or a placebo. A total of 58 patients (14%) developed fistulas, and 15 (54%) of the 28 patients in the certolizumab pegol group and 13 (43%) of the 30 patients in the placebo group experienced remission at 26 weeks[45].

In 2011, Schreiber et al. conducted a post hoc analysis of PRECISE 2. Of the 58 PFCD patients who showed clinical response to induction therapy using certolizumab pegol at week 6, 55 (95%) of them had anal fistulas. Furthermore, complete fistula closure at 26 weeks was achieved by 36% and 17% of the patients in the certolizumab pegol and placebo groups, respectively (P = 0.038). However, no significant difference was observed between the two groups for more than 50% fistula closure at 26 weeks[46].

(4) Ustekinumab and related clinical studies

There is insufficient evidence to recommend the use of ustekinumab for the treatment of fistulas in patients with CD and complex perianal fistulas[19].

UNITI-1, UNITI-2, and CERTIFI

A post hoc analysis integrating the results on fistula healing from large placebo-controlled trials using ustekinumab for CD (CERTIFI, UNITI-1, and UNITI-2) revealed that there was a trend toward higher rates of fistula symptom resolution by week 8 using ustekinumab therapy compared with the placebo (25% vs. 14%), and these increased to 80% vs. 46% by week 44. However, only 10.8% to 15.5% of the patients had active PFCD[47]. Two studies reported on the maintenance of response. In the IM-UNITI and CERTIFI-M trials, 54% (21/39) of the patients assigned to active therapy maintained response compared with 27% (11/41) of the placebo patients (RR: 1.82; 95% CI: 1.04-3.17; P = 0.04), indicating a statistically significant difference in favor of ustekinumab[48].

GETAID

The GETAID BioLAP Study Group conducted a national multicenter retrospective cohort study of patients with either active or inactive PFCD and who received ustekinumab treatment. Success was achieved in 57 (38.5%) of the 148 patients with a 48-week median followup period[49].

Moreover, retrospective evaluations of the clinical efficacy of ustekinumab for perianal CD were associated with the aforementioned results in a meta-analysis, and the results indicated a 56% fistula response and 17% fistula remission after 52 weeks of treatment[50].

In 2016, Khorrami et al. retrospectively included ustekinumab in a multicenter, open-label study to explore the efficacy and safety of ustekinumab in patients with refractory CD. A total of 116 patients were enrolled in this study, and 11 (61%) of the 18 patients with active perianal fistula improved. However, two patients developed perianal disease while receiving ustekinumab[51].

Ma et al. evaluated the clinical, endoscopic, or radiographic response to ustekinumab and the remission outcomes for 167 patients with CD, and of the 45 CD patients who had anorectal disease at the time of introduction of ustekinumab, 14 (31.1%) were completely cured, as confirmed by a pelvic MRI and pelvic contrast-enhanced ultrasound[52].

Yao et al. evaluated the efficacy of UST in a real-world setting of PFCD patients. The fistula clinical remission rate and response rates were 40.7% and 63.0%, respectively, with a significant reduction in the perianal CD Activity Index value (5.0 [3.0, 8.0] vs. 7.5 [5.0, 10.0], $P < 0.001$) and Crohn's Anal Fistula Quality of Life value (23.5 [9.3, 38.8] vs. 49.0 [32.3, 60.0], $P < 0.001$). Radiological healing, partial response, no change, and deterioration were observed in 44.8%, 31.4%, 13.4%, and 10.4% of the patients, respectively[53].

(5) Risankizumab

Risankizumab is one of the interleukin 23 (IL-23) antagonists. Risankizumab selectively binds to the p19 subunit of the human IL-23 cytokine and inhibits its interaction with the IL-23 receptor. However, the ECCO guidelines state that there is a lack of evidence for the efficacy of risankizumab in the treatment of PFCD[19].

(6) Vedolizumab and related clinical studies

The use of vedolizumab in the treatment of fistulas has not yielded any significant beneficial evidence[19].

GEMINI 2

An exploratory analysis was conducted to evaluate the efficacy of vedolizumab in patients with fistulizing CD who participated in the GEMINI 2 trial. The analysis was aimed at evaluating placebo-controlled induction and maintenance therapy in patients with moderately to severely active CD. In patients with one or more fistulas, fistula closure was observed in 28% of the patients in the vedolizumab group versus 11% of the patients in the placebo group at 14 weeks after treatment and 31% of the patients in the vedolizumab group versus 11% of the patients in the placebo group at 52 weeks. In patients with perianal abscesses only, fistula closure was observed in 34% of the patients in the vedolizumab group versus 15% of the patients in the placebo group at 14 weeks[54].

The ENTERPRISE

A randomized, double-blind trial comparing two intravenous vedolizumab regimens in patients with moderately to severely active CD with one to three active perianal fistulas who did not respond to anti-TNF therapy demonstrated that by week 30, 54% of the patients exhibited a 50% reduction in fistulas and 43% achieved 100% closure[55].

GETAID

In a large multicenter cohort study of patients with perianal CD (previously treated with at least one anti-TNF agent) treated with vedolizumab, 102 of the 151 eligible patients had active perianal lesions. Of the 102 patients, 23 (22.5%) was successfully treated with vedolizumab. Of the

49 patients with inactive perianal CD, 15 (30.6%) experienced recurrence of perianal disease and 11 (22.4%) required a dedicated treatment[56].

(7) Upadacitinib

The Janus Kinase (JAK) inhibitors are a group of medications that treat the various types of autoimmune diseases. These drugs inhibit the acti vity of one or more of the JAK enzymes and tyrosine kinase. Upadacitinib is now indicated for the treatment of Crohn's disease as one of the JAK inhibitors. However, the ECCO guidelines state that there is insufficient evidence for the efficacy of upadacitinib in the treatment of PFCD[19].

2. Surgical treatment

Advancement flaps

A comprehensive review of the literature revealed 11 studies that treated PFCD patients with advancement flaps. The findings based on the results of the followup of 135 patients indicated that 66% of the patients were cured of anal fistula[57].

Stellingwerf et al. conducted a meta-analysis and found no significant difference in the success rates between advancement flaps and ligation of the intersphincteric fistula tract (LIFT) for 64 patients with PFCD (61% vs. 53%). However, the incontinence rates were significantly higher after the flap surgery than LIFT (7.8% vs. 1.6%)[58].

In an RCT conducted in 2020, 126 patients with high perianal CD fistulas with a single internal opening were randomly assigned to the following groups: chronic seton drainage for 1 year, anti-TNF therapy for 1 year, and surgical closure after 2 months under a short-course anti-TNF. Surgical closure was an advancement flap and LIFT. Seton treatment was associated with a high reintervention rate (10/15 vs. 6/15 anti-TNF and 3/14 surgical closure patients, P = 0.02). No substantial differences in perianal disease activity and QOL between the three treatment groups were observed[59]. The ECCO guidelines suggest advancement flap as a treatment option for selected patients with CD and complex fistula in the absence of proctitis[19].

Fibrin glue

The use of fibrin glue for the treatment of PFCD was evaluated in an open-label RCT with 77 patients randomized for the instillation of fibrin glue into the fistula tract or no further treatment after the removal of the seton. The overall clinical remission rates at week 8 were 38% and 16% for fibrin glue and for the observation group, respectively (P = 0.04)[60]. The ECCO guidelines recommend against the use of fibrin glue in the treatment of patients with complex perianal CD fistula[19].

LIFT

Sirany et al. reviewed the literature and found 26 studies that performed LIFT (1 RCT and 25 cohort/case series). In these studies, the primary healing rates ranged from 47% to 95%[61].

In a prospective study conducted by Gingold et al. involving 15 CD patients with transsphincteric fistulas treated with LIFT, 67% of the patients achieved healing of the LIFT site at 12 months[62]. The ECCO guidelines recommend LIFT as a treatment option for selected patients with CD and complex perianal fistula[19].

3. Regenerative medication

Stem cells

In recent years, the local injection of mesenchymal stem cells (MSCs) has shown promising results in the treatment of PFCD.

MSCs are a heterogeneous subset of stromal stem cells. They are characterized by a multilinear differentiation as well as a powerful immunomodulatory effect and are able to mitigate inflammation.

Qiu et al. systematically evaluated the efficacy and safety of stem cell therapy (SCT) for patients diagnosed with CD through a comprehensive review and meta-analysis. They found that SCTs are an effective and safe treatment for patients with medically refractory CD or CD-related fistulas[63].

(1) Allogeneic adipose-derived SCT

There are conflicting data on allogeneic adipose-derived SCT for the induction and maintenance of remission in complex perianal fistulas in CD.

The efficacy of MSCs in treating perianal fistula in CD is due to their anti-inflammatory effects and ability to engraft and differentiate into healthy tissue. Allogeneic MSCs from adipose tissue (Cx601-darvadstrocel) were evaluated in a phase 3 RCT with 212 patients. At week 52, a higher percentage of patients treated with darvadstrocel achieved composite remission compared to the control group (56.3% vs. 38.6%; P = 0.010). Composite remission was defined as the closure of all treated external orifices and absence of accumulation >2 cm on an MRI scan. At week 104, 14 of the 25 (56%) patients in the darvadstrocel group and 6 of the 15 (40%) patients in the control group reported clinical remission. No serious AEs were reported at week104.

A 2018 meta-analysis compared MSCs of differing origins to the control group at 6-24 weeks (OR= 3.06 [95% CI: 1.05-8.90]; P = 0.04) and at 24-52 weeks (OR= 2.37 [95% CI: 0.90-6.25]; P = 0.08), and found that there was improved perianal fistula healing without a significant increase in AEs. Results from the phase III ADMIRE-CD II trial, presented in February 2024, showed that the primary endpoint of composite remission at 24 weeks was not met[19].

(2) Autologous adipose-derived stem cells

Autologous adipose-derived stem cells (ASCs) are taken from the patient undergoing treatment and is not a donor-based therapy. Treatment involving ASCs may be effective

for CD patients with complex perianal fistula owing to its good tolerability and safety[19].

Lee et al. filled the fistula tract with a mixture of ASCs and fibrin glue, and patients who did not have complete closure of the fistula at 8 weeks were given a second injection. After 12 months, 88.5% of the patients had maintained complete closure of fistula[64].

A different trial conducted at six different institutions included 24 patients at the 6-month followup point, of whom 56.3% achieved complete clinical response, which was confirmed by MRI[65].

A prospective study evaluated the efficacy of a technique in which freshly harvested autologous fatty tissue was injected into a perianal CD fistula. A total of 21 patients received ASCs, with additional injections given to those whose fistulas had not healed after 6 weeks and those who experienced recurrence. A total of 12 patients (57%) had completely healed fistulas 6 months after the last ASC injection[66].

(3) Bone marrow-derived MSCs (bmMSCs)

A total of 21 patients with refractory PFCD were randomly divided into groups and given MSC injections of 1×10^7 (n = 5, group 1), 3×10^7 (n = 5, group 2), 9×10^7 (n = 5, group 3), or a placebo (solution with no cells, n = 6). At week 12, completely healed fistulas were observed in 3 (33.3%) of the nine patients in group 1, 6 (85.7%) of the seven patients in group 2, 2 (28.6%) of the seven patients in group 3, and 3 (33.3%) of the nine patients in the placebo group. These effects were stable through to week 24 and were even increased to six of the nine (66.7%) patients in group 1 (P = 0.06 group 2 vs. placebo, weeks 12 and 24)[67].

Furthermore, the long-term outcome from the same data of the previous double-blind dose-finding study for the local bmMSC therapy was identified in 21 patients with refractory PFCD. Of the 15 patients, 13 (87%) treated with bmMSCs were available for long-term followup. Four patients in cohort 2 experienced a closure of their fistula 4 years after bmMSC therapy. Four (63%) and five (43%) patients in cohort 1 and experienced closure of their fistula. The bmMSCs have also shown to be effective in these therapies (1×10^7 group 1, 3×10^7 group 2, 9×10^7 group 3)[68].

Conclusion

CD is an intractable disease with an unclear etiology. It is often accompanied by perianal fistulas. However, the new treatment methods and therapeutic agents alone or in combination with others are making significant progress. PFCD is a chronic disease requiring long-term treatment and followup. Therefore, it is important to receive optimal treatment at the appropriate time.

Conflicts of Interest

There are no conflicts of interest.

Author Contributions

Shota Takano: concept; drafting of the text, and table; responsible for the overall content. Yasushi Nakamura, Kohei Tamaoka, Takafumi Yoshimoto, Yasue Irei and Yoriyuki Tsuji: involved in the drafting of the article. All authors reviewed and approved the final document for publication.

Disclaimer

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