Effectiveness of Biological Agents in the Treatment of Pediatric Patients with Crohn's Disease and Anal Fistulae

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Keywords

Crohn's disease · Anal fistula · Biological agents · Quality of life

Abstract

Introduction: Anal fistulae have a significant impact on the quality of life of patients with Crohn's disease (CD). In this cross-sectional study, we aimed to determine whether biological agents were effective in treating anal fistulae in patients with CD. **Methods:** Fifty-three patients diagnosed with CD were retrospectively enrolled. Their data regarding symptoms, treatments, and disease progression from January 2007 to December 2016 were reviewed from the medical records. Fifteen (28%) patients with CD were complicated by anal fistulae. **Results:** The male-to-female ratio was 13:2, and the mean age at onset was 11 years and 6 months. Among the 15 patients, 14 (93%) had anal fistulae as an initial symptom. Almost all patients were treated by providing elemental diet, 5-aminosalicylic acid, and steroids as induction therapy. Biological agents were used in 8 patients (53.3%), and fistula closure was confirmed in all of them. Among the 7 patients not treated with biological agents, 1 (14.3%) had a recurrent anal fistula, while another had incomplete fistula closure. Regarding surgical management, 2 patients were treated using the

seton method, and no patients required a colostomy. **Conclusion:** Treatment with biological agents is highly effective concerning the closure of anal fistulae in patients with CD, and reducing pain may improve their quality of life.

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Introduction

An anal fistula greatly impacts a patient's quality of life due to behavioral restrictions, as a result of pain and secretions following a diagnosis of Crohn's disease (CD). The mortality rate of patients with CD lesions in the anal region was reported to be 15–50% overseas [1]. According to the report by the Japan Child Inflammatory Bowel Disease Registry Research [2], anal fistula complications are relatively common, occurring at a rate of 33.3% and often preceding other symptoms. There are several reports stating that biological agents are effective for induction or maintenance therapy in pediatric patients with active perianal fistula lesions and in those who had undergone surgical interventions [3]. In this study, we aimed to examine the effectiveness of biological agents for anal fistulae associated with CD.

Materials and Methods

Patients

We conducted a retrospective study on pediatric patients with CD with anal fistulae observed in our department. Among 53 patients diagnosed with CD in our department between January 2007 and December 2016, the medical records of 15 patients (28%) who had concurrent anal fistulae were reviewed. Adult cases of CD were excluded. Our study protocol complied with the ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Juntendo University Hospital (approval number: 19-208). We disclosed the contents of this study and provided the opportunity to our participants to refuse or discontinue participation. The variables of interest were the following: time of initial symptoms; blood test results; endoscopic findings, such as lesion site; presence of a growth disorder; treatments used, such as 5-aminosalicylic acid (5-ASA), steroids, biological agents, and nutritional therapy; and details on the clinical course including anal fistula closure. We also summarized the following characteristics for each patient: background, reason for induction, timing of induction, and effectiveness of treatment. Overall, 8 out of 15 patients who had used biological agents were also retrospectively studied. In this study, growth disorder was defined as height <-1.5 SD.

Diagnosis

The diagnosis of CD was based on the following criteria [4]:

- Longitudinal ulceration. Mucosal cobblestoning. Noncaseating epithelioid cell granuloma.
- Irregular to widespread gastrointestinal tract round or aphthoid ulcer. Characteristic anal lesion. Characteristic gastroduodenal lesion. Definitive diagnosis: Presence of major criterion A or B. Presence of major criterion C and minor criterion a or b. Presence of all minor criteria.

Statistical Analysis

For the descriptive statistical analysis, average values and standard deviations were calculated using Microsoft® Excel 2010 (Microsoft Corp., Redmond, WA, USA).

Results

In total, the data of 53 patients with CD diagnosed at our department (male, 37; female, 16; age at onset, 10.5 ± 4.1 years [range, 0–20 years]) were assessed.

Table 1 shows the background characteristics of the 15 patients with anal fistulae (sex ratio [male:female participants], 13:2; age at onset, 11.6 ± 3.0 years [range, 2–15 years]; age at diagnosis, 12.7 ± 3.0 years [range, 4–16 years]). Among the 15 patients, 14 (93.3%) had anal fistulae as the initial symptom. Surgical management using the seton method was performed in 2 patients. Initial induction therapy of 5-ASA was administered to all 15 patients (100%); 13 (86.7%) and 10 (66.7%) patients underwent elemental diet and steroid therapies, respectively. The sites of lesions by the Paris classification [5] and the

Table 1. Clinical background of 15 patients with CD who had an anal fistula

Characteristic	N = 15
Sex	13 male, 2 female
Age at onset, years	11.6 ± 3.0
Range, years	2–15
Age at diagnosis, years	12.7 ± 3.0
Range, years	4–16
An anal fistula is the first symptom	14 (93.3%)
Surgical treatment (seton method)	2 (13.3%)
Induction therapy	
ED	13 (86.7%)
5-ASA	15 (100%)
PSL	10 (66.7%)

Data are presented as means $\pm$ standard deviation or as numbers and percentages. CD, Crohn's disease; ED, elemental diet; 5-ASA, 5-aminosalicylic acid; PSL, prednisolone.

Table 2. Background characteristics of 8 patients treated with biological agents

Characteristic	N = 8
Sex	
Male	6
Female	2
Age at diagnosis, years	12.1 ± 4.0
Range, years	2–15
Duration from diagnosis to introduction, months	47 ± 50.3
Range, months	3–162
Formulation used	
IFX	7
ADA	1
Used PSL at the time of introduction	4 (50%)
PCDAI at the time of introduction (score)	16.6 ± 6.6
Range (score)	10–27.5
Surgical treatment (seton method)	1 (12.5%)

Data are presented as means $\pm$ standard deviations or as numbers and percentages. PSL, prednisolone; IFX, infliximab; ADA, adalimumab; PCDAI, Pediatric Crohn's Disease Activity Index.

presence of a growth disorder in the 15 patients are presented in Figure 1. Four (26.6%) and 6 (40%) patients had lesions in L2 and L3, respectively. Colonic lesions were observed in all patients, and a growth disorder was found in 7 patients (46.6%).

Table 2 shows the background characteristics of the 8 patients treated with biological agents. An indication for

Fig. 1. Area of the lesion by the Paris classification [4] and the presence or absence of a growth disorder in 15 pediatric patients with CD and anal fistula. The sites of the lesion were L2 and L3 in 4 (26.6%) and 6 patients (40%), respectively. Growth disorder was observed in 7 patients (46.6%). CD, Crohn's disease.

Fig. 2. Lesion sites in patients using biological agents and the presence or absence of a growth disorder. L2 and L3 were the most frequent sites, occurring in 3 patients each (37.5%). A total of 6 patients (75%) with growth disorders were admitted.

the introduction of biological agents was relapsed or worsening symptoms in steroid-dependent patients, owing to the gradual reduction or abrupt discontinuation of steroids. In 7 of these patients, although their abdominal symptoms improved, the symptoms of the anal fistula remained unchanged and even worsened in some cases, which was attributed to the use of biological agents by these patients. The ratio of male-to-female participants treated with biological agents was 6:2, and the average age at diagnosis was 12.1 ± 4.0 years (range, 2–15 years). The average time period from diagnosis to the introduction of biological agents was 47 ± 50.3 months (range, 3–162 months). A total of 7 patients received infliximab (IFX), while only 1 patient received adalimumab (ADA). In this study, there were 1 and 7 patients with simple and complex fistulas, respectively. Four patients (50%) were receiving steroids at the time of biological agent introduction, and surgery using the seton method was performed in 1 patient. The Pediatric CD Activity Index (PCDAI) score was 16.6 ± 6.6 (range, 10–27.5) at the time of biological agent introduction, which corresponds to a mild

severity in all patients. The site of the lesions in patients using biological agents and those with a growth disorder is shown in Figure 2. L2 and L3 were the most frequent lesion sites, and lesions at these sites occurred in 3 patients (37.5%). Six patients (75%) had a growth disorder.

Among the 7 patients who were not receiving biological agents, 1 patient (14.3%) had an anal fistula that failed to close, while 6 patients (85.7%) had confirmed closure of their fistulae. However, 1 patient had a recurrence of the fistula. Although the severity of the anal fistulae was not high in the 8 patients who had received biological agents, it was difficult to discontinue steroid administration in those whose fistulae did not improve and who had impaired quality of life as a result. However, all patients on biological agents eventually had their fistulae closed, and there was no recurrence thereafter. Particularly, at 8 weeks after the induction of IFX, 7 out of 8 (87.5%) patients had their fistulae closed. Furthermore, all 4 patients who received steroids had their steroids discontinued, and all 6 patients with growth disorders had improved symptoms.

Discussion

In our study, 14 patients (93.3%) among the 15 diagnosed with CD complicated by an anal fistula in our department achieved fistula closure. Biological agents were introduced in 8 patients (53.3%); all of them were able to withdraw from steroids. They all achieved fistula closure without any recurrence. Patients with CD complicated by anal fistula may have an early improvement of their anal fistula after biological agent introduction at an early stage, which shows a potential for a rapid quality of life advancement.

CD pathogenesis is associated with inflammatory cytokines, such as tumor necrosis factor- α (TNF- α). TNF- α accumulates in the lamina propria of the inflamed mucosa in patients with CD [6]. Furthermore, the fecal levels of TNF- α increased in pediatric patients with CD [7]. TNF- α induces the expression of inflammatory chemokines and adhesion factors, which are involved in leukocyte migration to the sites of inflammation, leukocyte activation, and acute-phase protein production. Anti-TNF- α monoclonal antibody, one of the biological agents used in cases of CD, has the following functions: (1) binding and neutralizing soluble TNF- α produced by activated macrophages, (2) a dissociating effect on TNF- α bound to the TNF- α receptor, and (3) an anti-inflammatory action due to the cytotoxic action on TNF- α -producing cells [8].

Currently, anti-TNF- α monoclonal antibodies include IFX and ADA. They act as homologous biological agents and IFX is the most widely used. There are no studies comparing whether IFX or ADA should be used as induction therapy in biologically naïve patients with CD. According to the European Crohn's and Colitis Organization (ECCO) guidelines, biological agents are selected without definite criteria [9].

IFX is a chimeric anti-TNF- α monoclonal antibody, of which 75% is human derived and 25% mouse derived. In 1993, Derkx et al. were the first to report that IFX had a dramatic therapeutic effect in severe CD, which did not improve with steroid or immunomodulatory therapy [10]. Recently, induction and maintenance of remission was found to dramatically increase in adult patients with CD on IFX therapy [11]. In a study on patients with CD with an anal fistula, those in the IFX group (55%) had a higher rate of fistula closure than those in the placebo group (13%) [12].

In pediatric patients, there was a report [13] examining the efficacy of anti-TNF- α antibody preparations for those with CD with anal fistula. Especially, 60, 40, and 50% of patients with CD complicated with anal fistula were in remission, were keeping remission for 12 months

and maintained remission afterward, and showed closure of the anal fistula, respectively. In our study, the anal fistula was closed in all cases using the anti-TNF- α antibody preparation, which was a better result than the corresponding in previous reports. Further, in 2007, Hyams et al. [14] reported the results of the REACH trial, evaluating the efficacy and safety of IFX in moderate-to-severe pediatric patients with CD, confirming that IFX therapy was effective. Teitelbaum et al. [15] and Afzal et al. [16] reported that IFX was effective in the treatment of anal fistulae in 6 out of 8 patients (75%). In addition, early introduction of IFX was effective for maintenance of long-term remission in 14 out of 15 patients [17]. A retrospective observational study at another institution [18] that examined the efficacy of IFX for patients with CD with anal fistula stated that the anal fistula was closed in 70% of patients and highlighted the efficacy of IFX in such patients. Similarly, in our study, closure of the anal fistula was confirmed in all 7 patients using IFX, and there was no recurrence. Therefore, IFX is considered to be effective for patients with CD with anal fistula without local infection. In particular, there have been many reports [15, 16, 19] stating that IFX is effective in patients with anal fistulae, resulting in an improvement in their quality of life. Conversely, after making a thorough search, it was determined that the effectiveness of biological agents other than IFX for the treatment of anal fistulae remains unknown. A report by Ruemmele et al. [20] reported that 44.4% of patients with CD with anal fistula had their anal fistulae closed by 12 weeks after starting ADA, but the effects of using biologics other than IFX for anal fistula remain unknown. In our study, only 1 case used ADA, but closure was confirmed at 8 weeks after induction.

In Europe and the United States, the ECCO/ESPGHAN guidelines for children with CD were revised in 2014, and early administration of IFX had been recommended in adult and pediatric patients, in which resistance to treatment was expected [21]. In Japan, the guidelines for the treatment of pediatric CD [22] were revised in 2019. In principle, it was considered the use of biological agents when the performed treatment with nutritional therapy, 5-ASA preparations, steroids, and immunomodulators do not provide significant improvement. Among them, considering the use of biological agents for early introduction in patients with extensive small bowel lesions, steroid-resistant or dependent cases, and severe anal lesions is essential. However, consultation with a pediatric gastroenterologist is recommended before using biological agents.

Antibiotics may be useful for anal fistulae; however, no evidence has been provided regarding their use in pediat-

ric patients. Treatment guidelines for pediatric CD with anal fistulae of mild severity, not affecting daily life, include incision, drainage, and antibiotic and surgical management using the seton method in moderate cases with persistent pain. In severe cases, not amenable to any of the various treatments, colectomy may be required.

In addition, a report by Forsdick et al. [23] showed a closure of anal fistula in 70% of patients with CD with anal fistula using IFX but recurrence in 1/4 of those patients, which indicated the need for surgical treatment. Therefore, the treatment of CD with anal fistula required a combination of medical and surgical treatments. Our department has a policy of implementing the seton method in the case of refractory or recurrent anal fistula. However, we did not perform the seton procedure if the fistula improved after the induction of biological agents before the seton procedure.

In addition, it is recommended that immunosuppressive therapy with an immunomodulator or biological agent should be introduced after controlling local infections [4, 22]. However, the timing and severity of symptoms at the introduction of immunosuppressive therapy have not been established.

Even in this study, IFX was used in 7 patients and was effective in all cases. Regarding the timing of IFX induction, it was reported that top-down therapy, which introduces IFX at an early stage of diagnosis, has a higher remission and mucosal clearance rate than step-up therapy, which introduces IFX after disease activity has increased and after starting steroids or immunomodulators [24].

However, IFX is a chimeric antibody containing 25% amino acid sequences derived from mice, as aforementioned. Attention must be paid to allergic and delayed hypersensitivity reactions during its administration. In contrast, as ADA is a fully human antibody, serious reactions rarely occur [8].

In addition, there have been several reports stating that hepatosplenic T-cell lymphoma developed following combination treatment with anti-TNF- α antibody and immunomodulators [25, 26]. Interestingly, combination therapy with immunomodulators could increase the risk of lymphoproliferative disorders compared to single-agent therapy with an anti-TNF- α antibody alone [27].

Based on these findings, careful examination of intractable cases is essential despite the effectiveness of biological agents in improving symptoms and achieving anal fistula closure. Therefore, it is important to screen patients for infectious diseases, such as viral hepatitis and tuberculosis, and include these conditions while obtaining informed consent.

The study had some limitations. As the targeted number of patients was small and the study was conducted at a single institution, regional characteristics and patient histories may have affected the results. In addition, the effectiveness of biological agents in anal fistulae has not been scientifically proven. In the future, it is necessary to validate these results by including a larger number of patients at multiple facilities beyond this region.

To conclude, after conducting a retrospective review of the data of 15 patients with CD complicated by anal fistulae in our department, we found that regardless of the severity of symptoms in patients, their quality of life could be rapidly improved by introducing biological agents at the early stages of CD. Based on the obtained results, we have changed our policy to introduce aggressive anti-TNF- α agents in anal fistulas with improved perianal infection. Only a few pediatric patients with CD received biological agents in this study. However, the optimal timing for the introduction of these agents remains unclear. This concept is an important issue and should be explored in future studies.

Statement of Ethics

This study protocol complied with the ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Juntendo University Hospital (approval number: 19-208).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Nobuyasu Arai, Takahiro Kudo, Kazuhide Tokita, Reiko Kyo-do, Masamichi Sato, Eri Miyata, Kenji Hosoi, Tamaki Ikuse, and Keisuke Jimbo: substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work. Takahiro Kudo, Keisuke Jimbo, Yoshikazu Oh-tsuka, and Toshiaki Shimizu: drafting the work or revising it critically for important intellectual content. All authors: final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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