CASE REPORT

Effect of Adalimumab on an Enterocutaneous Fistula in Patients with Crohn’s Disease: A Case Series

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Abstract

Crohn’s disease (CD) is characterized by transmural inflammation of the gastrointestinal tract, which predisposes patients to the formation of a fistula. The efficacy of adalimumab (ADA) for an enterocutaneous fistula remains unclear. In this report, we present a case series of 3 patients with enterocutaneous fistulizing CD treated with ADA. ADA treatment achieved sustained complete fistula closure in one patient. The other two cases, which failed to achieve fistula closure, had intestinal stenosis and were not receiving concomitant azathioprine. Combination therapy with ADA and azathioprine may be a useful option and an alternative to surgery for enterocutaneous fistulizing CD.

Key words: Crohn’s disease, enterocutaneous fistula, anti-TNF-α, adalimumab, azathioprine

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Introduction

Tumor necrosis factor-alpha (TNF-α) is a proinflammatory cytokine implicated in the pathogenesis of inflammatory bowel disease (IBD), in particular Crohn’s disease (CD) (1). Thus far, a variety of therapeutic approaches has been used to inhibit TNF-α in patients with CD, including the administration of infliximab (IFX) and adalimumab (ADA), which are the biologic agents currently approved for the treatment of IBD in Japan (2). IFX and ADA are immunoglobulin G1 (IgG1) monoclonal antibodies directed against TNF-α. They bind to both the soluble and transmembrane forms of TNF-α and are effective as both induction and maintenance therapy in patients with CD (3).

CD is characterized by transmural inflammation of the gastrointestinal tract, which predisposes patients to the formation of a fistula (4). Fistulas are classified into two different types, internal and external, according to their location and connection with contiguous organs. External fistulas connect the intestine with the perianal (perianal fistula) or abdominal skin (enterocutaneous fistula) (5, 6). Generally, more than 80% of patients with CD require some kind of surgery during their life, and the risk of reoperation is as high as 70% depending on the time after the first surgery (7). Before the advent of anti-TNF-α agents, most patients with CD with a fistula also required surgical treatment. However, since IFX is reported to produce rapid fistula (perianal fistula) closure in approximately two-thirds of patients, IFX is currently considered to be a possible alternative to surgery for patients with perianal disease (8). However, with regard to enterocutaneous fistulas very few reports thus far have described the efficacy of anti-TNF-α agents (9). In particular, studies focusing on the efficacy of ADA for patients with CD with enterocutaneous fistulas are very rare (10).

In this case series, we describe our experience with ADA in the treatment of three patients with CD with enterocutaneous fistulas.
Case Reports

Case 1

A 31-year-old man who underwent ileocolic colectomy for appendicitis and intra-abdominal abscess 2 years previously was referred to our hospital with a suspected enterocutaneous fistula in 2012. On admission, an abdominal computed tomography (CT) scan revealed wall thickness in the ileum and the ascending colon, and a fistulizing duct developed from the ascending colon to the abdominal wall (Fig. 1A-C). The initial laboratory studies showed an elevated C-reactive protein (CRP) level of 2.24 mg/dL and a decreased serum albumin level of 3.1 g/dL. Since enteroclysis revealed longitudinal ulcers in the ileum, and non-caseating granulomas existed in the surgically resected specimen, the patient was diagnosed with fistulizing CD. Despite receiving initial treatment with intravenous hyperalimentation (IVH), mesalazine (3.0 g/day), and ciprofloxacin (600 mg/day), the fistulas were active, with draining of muco-purulent discharge. Therefore, treatment with subcutaneous injections of ADA (160 mg at week zero, 80 mg at week two, and 40 mg every other week) was initiated, and 6-mercaptopurine (30 mg/day) was added instead of azathioprine due to azathioprine hepatotoxicity. After the initiation of ADA and 6-mercaptopurine, the amount of discharge decreased. Therefore, we gradually initiated an elemental diet, however, the fistula did not remain completely closed (Fig. 1D). We modified the patient’s treatment from ADA to IFX (5 mg/kg of body weight intravenously administered on weeks 0, 2, and 6, and every 8 weeks thereafter). However, a complete fistula closure was not achieved and the CT scan suggested a small abdominal abscess around the fistula (Fig. 1E). Therefore, the patient underwent right hemicolectomy. After surgical resection, the fistula was completely healed, and clinical remission was maintained with IFX.

Case 2

A 59-year-old man who suffered from a fever, frequent episodes of diarrhea, left lower abdominal pain, and left inguinal swelling was admitted to another hospital for detailed examinations. A CT scan revealed an intra-abdominal abscess close to the sigmoid colon. Therefore, surgical drainage of the abscess was performed. However, an extensive skin ulcer appeared and expanded aggressively around the drainage catheter. Since the CT scan showed wall thickness of the sigmoid colon, sigmoidoscopy was performed, which suggested Crohn’s colitis. The patient was subsequently referred to our hospital.

On this admission, the patient complained of a painful skin ulcer and watery diarrhea occurring 4 times per day. A massive skin ulcer was located on the left lower abdominal wall, which was seeping pus and intestinal fluid. The laboratory data showed a remarkably decreased serum albumin

Figure 1. An enterocutaneous fistula in a 31-year-old man (Case 1). A: A water-soluble radiocontrast enema examination revealed an enterocutaneous fistula (arrow). B, C: A CT scan before ADA treatment showing a fistula (arrow). D: A CT scan before switching from ADA to IFX showing the wall thickness of the ileum and adhesion to the abdominal wall, which suggests that the enterocutaneous fistula was not closed. E: A CT scan after IFX treatment revealed abdominal abscesses around the fistula (arrow).
level to 1.1 g/dL and the CRP level was noticeably elevated to 3.83 mg/dL. A gastrografin enema showed an enterocutaneous fistula and a cobblestone appearance of the colon. Sigmoidoscopy also showed cobblestoning and a longitudinal ulcer, suggesting fistulizing Crohn’s colitis. We initiated therapy with ADA (160 mg at week zero, 80 mg at week two, and 40 mg every other week) and IVH without concomitant azathioprine due to hepatotoxicity. One month after the initiation of the treatment, the enterocutaneous fistula was temporally closed, and the hypoalbuminemia improved gradually. However, 3 weeks after starting an elemental diet, the enterocutaneous fistula suddenly opened again. The CT scan suggested that an intra-abdominal abscess had developed close to the enterocutaneous fistula. Therefore, ileostomy was performed. The patient is currently receiving IFX (5 mg/kg of body weight administered intravenously) every 8 weeks, however, the fistulas have not yet completely closed.

Case 3

A 43-year-old man with ileitis and local peritonitis underwent partial resection of the ileum. Because the surgically resected specimen revealed longitudinal ulcers and non-caseating granulomas in the ileum, he was diagnosed with CD. After surgical treatment, an enterocutaneous fistula developed from the ileum and he was referred to our hospital. Upon this examination, the laboratory results revealed a slightly elevated CRP level (1.11 mg/dL). Because the initial treatment with mesalazine (3 g/day) was not effective and an enterocutaneous fistula developing from the ileum to the abdominal wall was revealed by a gastrografin enema and CT scan (Fig. 2A, B), treatment with ADA (160 mg at week zero, 80 mg at week two, and 40 mg every other week) and oral azathioprine (50 mg/body/day) was initiated and the enterocutaneous fistula gradually closed even after starting an elemental diet (Fig. 2C). The patient has experienced complete fistula closure for the last 16 months with ADA and azathioprine therapy (Fig. 2D).

Discussion

Few reports have described the effect of ADA on patients with CD with enterocutaneous fistulas. In this case series, we described three cases with CD with enterocutaneous fistulas that were treated with ADA. We successfully achieved complete fistula closure in one case for more than 16
months. In two of the three cases, we could not achieve fistula closure, even though we switched the treatment from ADA to IFX.

It has been considered that internal and external fistulas rarely heal spontaneously or as a result of drug treatment; therefore, they frequently require surgery (8). Although the use of immunomodulatory agents is associated with the improvement and closure of fistulas, no significant effect has yet been demonstrated (8, 11-13). However, since anti-TNF-α agents, such as IFX and ADA, have emerged as effective treatment options with many clinical benefits for patients with CD, it is anticipated that they may be alternatives to surgery for CD patients with fistulas. Recently, the ACCENT II trial (A Crohn’s Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen in Patients with Fistulizing Crohn’s Disease) evaluated the efficacy of repeated infusions of IFX for the closure of fistulas among patients who had a response to induction IFX therapy and reported that 36% of the patients had a complete absence of draining fistulas 54 weeks after the initiation of IFX treatment (14). In the CHARM trial (The Crohn’s Trial of the Fully Human Antibody Adalimumab for Remission Maintenance), ADA was reported to achieve complete fistula closure in 33% of the patients at week 56 (15). The ADHERE trial (Additional Long-Term Dosing with HUMIRA to Evaluate Sustained Remission and Efficacy in Crohn’s disease) evaluated maintenance therapy for fistula healing and demonstrated that the long-term healing of draining fistulas could be maintained for more than 2 years (16). However, thus far, the efficacy of anti-TNF-α agents for enterocutaneous fistulas remains unclear, because many cases in those trials were patients with perianal fistulizing CD. Recently, Amiot and colleagues retrospectively reviewed the outcome of patients with CD with enterocutaneous fistulas, excluding perianal fistulas, treated with anti-TNF-α agents (9). In that report, it was concluded that anti-TNF-α therapy may be effective in up to one-third (33%) of patients and the results strengthened the viewpoint that the concomitant use of steroids, an association with stenosis, and a fistula with multiple tracts are significant predictors of anti-TNF-α therapy failure (9). Although this case series included only three cases, we also demonstrated that one of three cases (33%) showed complete remission of the enterocutaneous fistula and maintained closure for more than 16 months with ADA and azathioprine therapy. In the other two cases that failed to achieve fistula closure, both showed intestinal stenosis, but not obstruction, in the ascending colon (Case 1) and in the sigmoid colon (Case 2). Unfortunately, both cases developed abdominal abscesses around the fistula. Therefore, we speculate that in patients with CD with enterocutaneous fistulas without intestinal stenosis and abdominal abscesses, ADA therapy may be an effective alternative to surgery.

Regarding the use of a concomitant agent, we previously evaluated the efficacy of ADA with concomitant azathioprine for the induction and maintenance of clinical remission in patients with CD and reported that scheduled ADA with concomitant azathioprine may be more effective for clinical remission achievement at 24 weeks (17). In a systematic review and meta-analysis, Kopylov and colleagues also concluded that combination therapy with ADA and an immunomodulator was mildly superior to ADA monotherapy for the induction of remission in CD (18). Regarding other concomitant agents, steroid use at enterocutaneous fistula onset has been reported to be a negative predictor of anti-TNF failure (9). Moreover, a higher level of CRP is reported to be a significant negative predictor in patients treated with biological agents, although these reports describe patients with rheumatoid arthritis and ankylosing spondylitis (19, 20). Interestingly, in this case series, the two cases that failed to achieve fistula closure did not receive azathioprine, and the case that showed sustained complete remission of the fistula received concomitant azathioprine; additionally, the initial CRP level of case 3 was the lowest among these three patients.

In conclusion, we reported the efficacy of ADA for the treatment of an enterocutaneous fistula in patients with CD. Combination therapy with ADA and azathioprine may be a useful treatment option and an alternative to surgery for the treatment of enterocutaneous fistulizing CD in the absence of intestinal stenosis and abdominal abscesses.

The authors state that they have no Conflict of Interest (COI).

References


