Effects of the Concomitant Use of Low-dose Clarithromycin with an Anti-TNFα Antibody in a Patient with Intestinal Bechet Disease

Junichi Iwamoto, Masashi Murakami, Naoki Konishi, Tadakuni Monma, Hajime Ueda, Shoichiro Yara, Takeshi Hirayama, Tadashi Ikegami, Akira Honda and Yasushi Matsuzaki

Abstract:
A 66-year-old Japanese male with a history of Bechet disease exhibited oral and genital ulcers, and a round deep ileocecal ulcer. He was treated with a combination of mesalazine and 20 mg/day of prednisolone (PSL), but was only partially responsive to PSL and we were not able to reduce the steroid dosage. Adalimumab was also administered. However, the ulcer was not completely responsive, and weaning the patient off PSL remained impossible. In contrast, additional treatment with clarithromycin completely healed the refractory active ulcer and left only a scar. Furthermore, the ulcer has since maintained the scar stage despite successfully weaning the patient from PSL.

Key words: intestinal Bechet disease, anti-TNFα antibody, clarithromycin

Introduction
Bechet disease (BD) is a chronic relapsing disease characterized by recurrent oral and genital ulcers, eye lesions, skin lesions, arthritis, central nervous system lesions, vascular lesions and gastrointestinal lesions (1). The prevalence of BD is high in the countries along the Silk Road, which extends from eastern Asia to the Mediterranean basin (2).

Gastrointestinal involvement is one of the clinical manifestations of BD (3). Gastrointestinal involvement often presents with symptoms, such as abdominal pain and diarrhea and it is sometimes complicated by intestinal perforation (3). Ileocecal ulcer is the most common lesion in the gastrointestinal tract, but lesions in the ascending colon, transverse colon and esophagus are also sometimes involved in this disease (3).

Various therapeutic medications including 5-aminosalicylic acid (5-ASA) (4), corticosteroid (5, 6) and colchicine (7) have been used as conventional treatments for intestinal BD. Although surgery is a treatment option for refractory intestinal BD cases, the postoperative recurrence rate remains high (8).

Several studies have shown that Infliximab, a TNFα inhibitor, is effective in the treatment of intestinal BD that is refractory to conventional medication (9, 10). Furthermore, the efficacy of Adalimumab, a fully human anti-TNFα monoclonal antibody, has also been reported in the treatment of intestinal BD (11). However, the withdrawal of corticosteroids remains difficult in a considerable number of cases that are successfully controlled with anti-TNFα therapy.

Recently, the effectiveness of clarithromycin in a patient with refractory intestinal BD has been reported (12). Clarithromycin is a well-known antibiotic, but it also exhibits pharmacological effects on the immune system by suppressing the cytokine production such as TNFα, IL-1α, IL-1β, IL-6 and by increasing the synthesis of IL-10 in macrophages (13, 14). We herein report another case of intestinal BD that was successfully treated with the concomitant use of low-dose clarithromycin and an anti-TNFα antibody. Clarithromycin was effective, not only for healing the ileocecal ulcerative lesion, but also for allowing the patient to be weaned from corticosteroids.
Case Report

A 66-year-old Japanese male with a 12-year history of BD was referred to our hospital in April 2011 for detailed examination and further treatment. He was first diagnosed as having intestinal BD at a previous hospital in 2000.

He had some occasional pain in the right lower quadrant of the abdomen at the first visit to our hospital. His body temperature was 36.6°C and his pulse rate was 70 beats/min. He exhibited both oral and genital ulcers. Laboratory studies showed that his hemoglobin concentration was 13.6 g/dl, erythrocyte sedimentation rate was 13 mm/h and C-reactive protein was 1.09 mg/dl. A stool examination for conventional enteric pathogens was negative, and the cytomegalovirus antigenemia test was also negative. Colonoscopy showed a round deep ileocecal ulcer (FigureA). Upper gastrointestinal endoscopy showed no remarkable findings re-
lated to intestinal BD. Video capsule endoscopy showed no ulcer in the small intestine except for the ileocecal region. A histological examination of the colonic biopsy specimens from the round deep ileocecal ulcer showed no formation of epithelioid cell granuloma.

He had been treated with mesalazine (3,000 mg/day) and prednisolone (PSL; 5-20 mg/day) by the previous doctor. He continued the treatment with mesalazine and 20 mg/day PSL at our hospital. The deep ileocecal ulcer was partially responsive to PSL, but it was difficult to reduce the PSL dosage (FigureB). Azathioprine and colchicine were added, but they were ineffective. In January 2014, adalimumab, a fully human anti-TNFα monoclonal antibody was administered because of the steroid-dependency. Although a reduction in the size of the giant ileocecal ulcerative lesion was observed after the administration of adalimumab, the ulcer did not heal completely and withdrawal from PSL remained impossible (FigureC). In June 2015, after written informed consent was obtained from the patient, clarithromycin (200 mg/day) was added to the adalimumab and PSL treatment. After the additional treatment with clarithromycin, the refractory round deep ileocecal ulcer healed completely to a scar (FigureD). Despite the withdrawal from PSL, the ileocecal ulcer has maintained the scar stage by the concomitant use of low-dose clarithromycin with adalimumab (FigureE). The clinical course is shown in Figure 2.

Discussion

Cases of refractory intestinal Bechet disease are common in clinical practice. Some cases with refractory punched out lesions present with severe complications, such as intestinal perforation, that require surgical treatment (3). Intestinal BD cases are treated with 5-ASA, IM, corticosteroid and colchicine, as conventional therapies (4, 5, 6, 7). In particular, corticosteroids have been used in refractory cases and many cases cannot be weaned and become corticosteroid-dependent. Anti-TNFα antibody is effective for intestinal BD refractory to conventional treatment (9-11). A previous study on the effects of adalimumab on intestinal BD demonstrated the endoscopic improvement to be 55% at week 8-12 and 65% at week 52, while the improvement of GI symptoms was 75% at week 8-12 and 90% at week 52 (11).

However, if the anti-TNFα antibody treatment is not sufficiently effective, then a reduction in the corticosteroid dosage is difficult and it is not possible to withdraw the corticosteroids. While surgery is a treatment option for refractory intestinal BD, it has been reported that the postoperative recurrence rate remains high (8).

In our case, while the refractory punched out ulcerative lesion tended to improve with the corticosteroid treatment, the ulcer relapsed when the corticosteroid dose was reduced. Adalimumab, a fully human anti-TNFα monoclonal antibody, was administered because the patient was steroid-dependent. Although a reduction in the size of giant ileocecal ulcerative lesion was observed after the adalimumab administration, the ulcer did not heal completely and a reduction of steroids was thus impossible.

Clarithromycin has been used for the treatment of chronic respiratory diseases due to its immunomodification effects (15) as well as its antibiotic effects. A previous study demonstrated that clarithromycin treatment was effective for Crohn’s diseases (16). A recent report has indicated that low-dose clarithromycin treatment is effective against refractory intestinal BD (12). Hakozaki et al. reported that long-term treatment with low-dose clarithromycin, which was administered for recurrent pneumonia, was effective for intestinal BD that was refractory to conventional treatment, including glucocorticoid, colchicine and salazosulfapyridine (12). It was suggested that the efficacy of clarithromycin is re-
lated to its immune-modifying effects rather than any direct antibacterial effects (12, 15). Clarithromycin suppresses the cytokine production such as TNFα, IL-1α, IL-1β, while it increases the synthesis of IL-10 in macrophages (13, 14).

In the present case, the concomitant use of low-dose clarithromycin with anti-TNFα antibody was effective and the refractory punched out ileocecal ulcerative lesion has since remained in remission and the patient has been able to be weaned from corticosteroids. A previous study showed that the endoscopic appearance of ulcers improves rapidly with adalimumab treatment. However, no improvement was observed for more than 17 months of adalimumab treatment in this case. These results suggest that the concomitant use of low-dose clarithromycin and adalimumab was critically effective rather than the prolonged use of adalimumab alone. Similarly, we have to consider the effects of corticosteroids on the healing of ileocecal ulcers. However, the scarring of ileocecal ulcer was never observed using corticosteroids for more than 4 years until low-dose clarithromycin and adalimumab was added to the treatment regimen. Furthermore, we have been able to withdraw corticosteroid administration in this case for more than one year. Therefore, we concluded that the concomitant use of low-dose clarithromycin and adalimumab was effective, rather than the long-term use of corticosteroids.

In conclusion, this refractory ileocecal ulcerative lesion in BD improved after treatment with the concomitant use of low-dose clarithromycin with an anti-TNFα antibody. Our case indicates the possibility that the concomitant use of low-dose clarithromycin with an anti-TNFα antibody could be one of the treatment options for steroid withdrawal in patients with intestinal BD. The further accumulation of such cases is needed, because the number of reported cases of intestinal BD treated with low-dose clarithromycin remains limited.

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

References

1. Krause I, Weinberger A. Behcet’s disease. Curr Opin Rheumatol 20: 82-87, 2008.
2. Saadoun D, Wechsler B. Behcet’s disease. Orphanet J Rare Dis 7: 20, 2012.
3. Sakane T, Takeno M, Suzuki N, Inaba G. Behcet’s disease. N Engl J Med 341: 1284-1291, 1999.
4. Jung YS, Hong SP, Kim TJ, Kim WH, Cheon JH. Long-term clinical outcomes and factors predictive of relapse after 5-aminosalicylate or sulfasalazine therapy in patients with intestinal Behcet disease. J Clin Gastroenterol 46: e38-e45, 2012.
5. Toda K, Shiratori Y, Yasuda M, Enya M, Uematsu T, Shimazaki M, Fukutomi Y, Kato T, Moriwaki H. Therapeutic effect of intra-articular prednisolone injection in severe intestinal Behcet’s disease. J Gastroenterol 37: 844-848, 2002.
6. Hisamatsu T, Naganuma M, Matsuoka K, Kanai T. Diagnosis and management of intestinal Behcet’s disease. Clinical journal of gastroenterology 7: 205-212, 2014.
7. Mochizuki M. Immunotherapy for Behcet’s disease. Int Rev Immunol 14: 49-66, 1997.
8. Iida M, Kobayashi H, Matsumoto T, Okada M, Fuchigami T, Yao T, Fujishima M. Postoperative recurrence in patients with intestinal Behcet’s disease. Dis Colon Rectum 37: 16-21, 1994.
9. Kinoshita H, Kunisaki R, Yamamoto H, Matsuura R, Sasaki T, Kimura H, Tanaka K, Naganuma M, Maeda S. Efficacy of infliximab in patients with intestinal Behcet’s disease refractory to conventional medication. Intern Med 52: 1855-1862, 2013.
10. Hibi T, Hirohata S, Kikuchi H, Tateishi U, Sato N, Ozaki K, Kondo K, Ishigatsubo Y. Infliximab therapy for intestinal, neurological, and vascular involvement in Behcet disease: Efficacy, safety, and pharmacokinetics in a multicenter, prospective, open-label, single-arm phase 3 study. Medicine 95: e3863, 2016.
11. Tanida S, Inoue N, Kobayashi K, Naganuma M, Hirai F, Iizuka B, Watanabe K, Mitsuymasa K, Inoue T, Ishigatsubo Y, et al. Adalimumab for the treatment of Japanese patients with intestinal Behcet’s disease. Clin Gastroenterol Hepatol 13: 940-948 e943, 2015.
12. Hakozaki Y, Mitani K, Okada C, Terada H, Kobari S. Effective Treatment of Intestinal Behcet’s Disease with Long-Term, Low-Dose Clarithromycin. Case Rep Gastroenterol 7: 122-126, 2013.
13. Takeshita K, Yamagishi I, Harada M, Otomo S, Nakagawa T, Mizushima Y. Immunological and anti-inflammatory effects of clarithromycin: inhibition of interleukin 1 production of murine peritoneal macrophages. Drugs under experimental and clinical research 15 (11-12): 527-533, 1989.
14. Morikawa K, Watabe H, Arakawa M, Morikawa S. Modulatory effect of antibiotics on cytokine production by human monocytes in vitro. Antimicrobial agents and chemotherapy 40: 1366-1370, 1996.
15. Shinkai M, Henke MO, Rubin BK. Macrolide antibiotics as immunomodulatory medications: proposed mechanisms of action. Pharmacology & therapeutics 117: 393-405, 2008.
16. Inoue S, Nakase H, Matsuura M, Ueno S, Uza N, Kitamura H, Mikami S, Tamaki H, Kasahara K, Chiba T. Open label trial of clarithromycin therapy in Japanese patients with Crohn’s disease. Journal of gastroenterology and hepatology 22: 984-988, 2007.