The Efficacy of Medium- to Long-term Anti-TNF-α Antibody-based Maintenance Therapy in Behçet’s Disease Patients with Intestinal Lesions

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Abstract:
Objective Anti-tumor necrosis factor (TNF)-α antibody-based regimens are effective in Behçet’s disease (BD) with intestinal lesions. We therefore evaluated the efficacy of medium- to long-term anti-TNF-α antibody-based maintenance therapy of BD intestinal and non-intestinal lesions.

Methods In this retrospective study, the response to the treatment was assessed endoscopically and clinically. Treatment responders were transferred to maintenance therapy. We evaluated the sustain rate of maintenance therapy, reductions in the dose of prednisolone (PSL), and the presence of non-intestinal BD involvement before and after the start of anti-TNF-α antibody-based the maintenance therapy.

Patients We assessed 20 BD patients with intestinal lesions who underwent anti-TNF-α antibody-based therapy.

Results Treatment was discontinued in 3 patients (18%). Loss of response was noted in 1 (5.9%) patient. Maintenance therapy was continued in 13 (76%) patients. The cumulative sustain rates to maintenance therapy after 2, 4, and 6 years were 94%, 87%, and 72%, respectively. In the 13 patients with remission of intestinal lesions, the mean PSL dose decreased from 13.4±2.16 mg/day before treatment to 0.92±0.47 after treatment (p<0.0001). PSL was discontinued in 9 (69%) patients. Five of the 13 (38%) patients developed clinical features of non-intestinal BD during the remission-maintenance treatment.

Conclusion Our results demonstrated the efficacy of medium- to long-term anti-TNF-α antibody-based maintenance treatment against BD intestinal lesions. Nevertheless, some cases with well-controlled intestinal lesions developed active non-intestinal BD symptoms. The results highlight the importance of a carefully planned treatment strategy for BD patients with intestinal involvement.

Key words: Behçet’s disease, intestinal Behçet’s disease, steroids, anti-TNF-α antibody-based therapy, medium- to long-term maintenance therapy

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scribed, including punched-out esophageal ulcers, multiple erosions, and lesions resembling those of ulcerative colitis (8). Treatment of BD intestinal lesions includes 5-aminosalicylic acid (5-ASA) formulations, prednisolone (PSL), colchicine, and various other immunosuppressive agents, including azathioprine (9). However, the clinical outcome is sometimes poor, especially in severe cases, leading to serious hemorrhaging or intestinal perforation that requires surgery in some cases (10).

In 2001, Travis et al. (11) reported the efficacy of anti-TNF-α antibody-based therapy in the treatment of BD intestinal lesions. While the efficacy of infliximab (IFX) and adalimumab (ADA) in BD intestinal lesions has been demonstrated in Japan (12, 13), there are only a few reports on the long-term efficacy of anti-TNF-α antibody-based therapy in BD intestinal lesions (9).

The aim of the present study was to determine the response to medium- to long-term anti-TNF-α antibody-based maintenance therapy in BD patients with intestinal and non-intestinal lesions.

### Materials and Methods

The subjects of this retrospective study were 20 BD patients who had been treated at Tokyo Women’s Medical University Hospital’s Institute of Gastroenterology between January 2003 and June 2018. The intestinal lesions were treated in each patient using biologics-based remission-inducing therapy, followed by transferring to remission-maintenance therapy. We evaluated the rate of adherence to maintenance therapy with anti-TNF-α antibody-based regimens. In addition, the PSL dose time-course and the presence of non-intestinal BD symptoms were evaluated in patients for whom anti-TNF-α antibody-based maintenance therapy for intestinal lesions had been continued.

### The diagnosis of BD

The BD diagnostic criteria of the Japanese Ministry of Health, Labor and Welfare (MHLW) were used for making a BD diagnosis (Fig. 1). In Japan, BD is classified into complete, incomplete or suspected, based on four major clinical features; recurrent aphthous ulceration of the oral mucosa, evident dermal and ophthalmic clinical symptoms and signs, and vulvar ulceration, as well as the following minor features: joint symptoms, epididymitis, neural lesions, vascular lesions, and intestinal lesions.

When all four major clinical features were present, the patient was diagnosed as complete BD. Incomplete BD was diagnosed when one of the following three criteria were met: (i) presence of three of the four major features, (ii) presence of two of the major and two of the minor features, or (iii) presence of ophthalmic clinical signs or symptoms, together with one major feature and/or two of the minor features. Patients were suspected of BD when the major or minor features were reported repeatedly with the absence of a diagnosis of incomplete BD (14). In addition, both complete and incomplete BD with neural, vascular, and/or intestinal complications were classified as special-type BD.

Intestinal BD is defined as a condition that meets the criteria of complete or incomplete BD and typically presents with ulcerative lesions in the ileocecal region. Intestinal BD is known sometimes to involve atypical intestinal inflammatory lesions and punched-out esophageal ulcers (8). In the present study, intestinal BD included both punched-out esophageal ulcers and atypical intestinal inflammatory lesions. We also included BD-suspected patients with typical intestinal lesions, as intestinal BD afflicts only a small number of patients. Upon the diagnosis of BD intestinal lesions, patients were excluded if the lesions were thought to have been induced by drugs, such as nonsteroidal anti-inflammatory drugs and aspirin. Patients who were strongly suspected of having infectious diseases, simple ulcer,
Crohn’s disease, and/or ulcerative colitis were also excluded.

Route of administration of biological agents

IFX was used for induction therapy at 5 mg/kg body weight and administered by drip infusion during weeks 0, 2, and 6, followed by maintenance therapy, which was 5 mg/kg drip infusion at 8-week intervals. ADA was used for induction and administered subcutaneously at 160, 80, and 40 mg during weeks 0, 2, and 4, respectively, followed by maintenance therapy with subcutaneous administration of 40 mg at 2-week intervals.

The evaluation of the therapeutic efficacy against intestinal lesions

The efficacy was evaluated based on a combination of endoscopic findings and clinical symptoms (15). Clinical symptoms were categorized as follows in accordance with the Global Gastrointestinal Score (G-GIS): 0 for patients who were asymptomatic upon hospital admittance or at the time of the latest outpatient clinic visit; 1 for patients with symptoms that had no effect on their daily life; 2 for patients with symptoms that had some effect on their daily life; 3 for patients with symptoms that had a marked effect on their daily life; and 4 for patients with symptoms that had a severe effect on their daily life.

The endoscopic findings were categorized as follows based on the findings from endoscopy performed closest to the analysis: 0, no lesions; 1, lesions <25% the size and/or range of the initial lesions; 2, lesions 25% to 50% the size and/or range of the initial lesions; and 3, lesions ≥50% the size and/or range of initial lesions.

Regarding the induction of remission, patients with G-GIS 3 or 4 and endoscopic findings 3 were defined as primary non-responders. Those with G-GIS 0-2 and/or endoscopic findings of 0-2 were switched to remission-maintenance therapy. Clinical and endoscopic evaluations were made during treatment and after completion.

As the efficacy was evaluated not only for typical lesions but also atypical lesions and esophageal lesions, we added the lesion range to the endoscopic findings in accordance with the diagnostic criteria defined by Tanida et al. (13). In the present study, the disease activity was not evaluated directly by the C-reactive protein (CRP) level. However, during maintenance therapy, the disease activity was evaluated by endoscopy when the CRP level was elevated in combination with abdominal symptoms.

Judging from the combination of the clinical and endoscopic findings (Table 1), those who had withdrawn to loss of response (LOR) beyond the 12-week point, and those who required an increase in the dose or reduction of the administration duration of the anti-TNF-α antibody formula were defined as LOR. Responders who were able to continue remission-maintenance therapy were defined as remission cases. Those who discontinued treatment or switched to other therapeutic drugs past the 12-week point despite being responders were defined as discontinued cases. In the present study, when evaluating the anti-TNF-α-drug therapy continuation rate, we defined discontinued cases and LOR as the drop-out group.

In addition, changes in PSL dose were evaluated in patients who were still on remission-maintenance therapy at the time of the completion of the study.

The evaluation of the efficacy against non-intestinal symptoms

Patients who continued to receive maintenance therapy for remission of gastrointestinal symptoms were investigated for the presence of non-intestinal BD symptoms at the start and during treatment with anti-TNF-α antibody formula.

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**Table 1. The Evaluation of BD Intestinal Lesions Based on the Combination of Endoscopic Findings and the G-GIS.**

| G-GIS     | 0: No lesions | 1: Lesions ≤25% the size and/or range of the initial lesions | 2: Lesions 25% to 50% the size and/or range of the initial lesions | 3: Lesions ≥50% the size and/or range of the initial lesions |
|-----------|---------------|-------------------------------------------------------------|---------------------------------------------------------------|-------------------------------------------------------------|
| 0         | Responder     | Responder                                                  | Responder                                                    | Loss of response                                            |
| 1         | Responder     | Responder                                                  | Responder                                                    | Loss of response                                            |
| 2         | Responder     | Responder                                                  | Responder                                                    | Loss of response                                            |
| 3         | Responder     | Loss of response                                           | Loss of response                                             | Loss of response                                            |
| 4         | Responder     | Loss of response                                           | Loss of response                                             | Loss of response                                            |

Prepared and cited from reference 13. BD: Behçet’s disease; G-GIS: Global Gastrointestinal Score
Ethical considerations

The criteria set for treatment with anti-TNF-α antibody were met by all patients. The need to use IFX or ADA, their risks, and countermeasures against potential complications were explained to each patient, and written informed consent was obtained.

The study protocol was reviewed and approved by the Human Ethics Review Committee of Tokyo Women’s Medical University. This study was registered at the Clinical Trials Registry.

Statistical analyses

Differences in the dose of PSL used before and after the administration of anti-TNF-α antibody were compared using Wilcoxon’s test. The survival curve for the adherence rate to anti-TNF-α antibody-based maintenance therapy was examined by the Kaplan-Meier method. Point estimates and interval estimates for all descriptive data are presented as the mean values or proportions plus the standard deviation or 95% confidence interval (CI). P values <0.05 were considered significant. All data were expressed as the mean±standard deviation. The JMP statistical analysis software program (version 11; SAS, Cary, USA) was used for all analyses.

Results

Subjects and treatments

Twenty BD patients underwent treatment with anti-TNF-α antibody-based regimens; one died of unrelated cause (Budd-Chiari syndrome) shortly after the initiation of the treatment and was therefore excluded from evaluation. Two other patients were excluded due to primary inefficacy based on clinical features at 12 weeks after the initiation of treatment. The remaining 17 patients were switched to anti-TNF-α antibody-based remission-maintenance therapy. Endoscopy was carried out within 12 weeks in 11 of the 17 patients (64.7%), and improvement of the lesions relative to the initial findings was identified in all patients.

The study subjects were 12 men and 5 women. At the initiation of the treatment; the mean body weight was 54.5±9.4 kg, and the mean CRP level was 1.09±2.13 mg/dL. The disease type was classified as complete BD (n=5), incomplete BD (n=10), and suspected BD (n=2). The mean age at the BD onset and at the detection of intestinal lesions was 23.4±11.8 and 28.6±10.1 years old, respectively. The anti-TNF-α antibody-based regimens were IFX and ADA in 7 and 10 patients, respectively, and the mean age at the initiation of administration was 38.6±12.4 years old. The purpose of using anti-TNF-α antibody-based regimens was to improve the activity of the disease in 12 cases and to reduce the PSL dose in 5 cases. In all patients, PSL was administered concomitantly at the initiation of anti-TNF-α antibody-based therapy, and the mean PSL dose was 17.9±15.1 mg/day. Furthermore, six patients were also treated with azathioprine at the initiation of anti-TNF-α antibody-based therapy. The G-GIS was 1, 2, 3, and 4 in 4, 3, 5 and 5 patients, respectively. Endoscopy showed typical punched-out ulcers in the ileocecal region in 10 patients, and intestinal lesions other than typical punched-out ileocecal lesions, such as ulcerative-colitis-like findings, were noted in 6 patients, while punched-out esophageal ulcers only were found in 1 patient. The mean duration of anti-TNF-α antibody-based therapy was 257.2±132.1 weeks (Table 2).

Sustain rate to anti-TNF-α antibody-based maintenance therapy

Maintenance therapy instituted after remission was discontinued by 3 (18%) patients who had been treated with IFX. One developed thyroid cancer, one had an infusion reaction (IR), and one was switched to a different agent upon the patient’s request. The efficacy of treatment based on the endoscopic and clinical findings was categorized as responder in 13 (76%) and LOR in 1 (5.9%). Of the 13 responders, 11 were endoscopically determined to be showing mucosal healing, and 2 were remarkably improved (Fig. 2). The CRP level of the responders remained almost negative (<0.33 mg/dL for the duration of the maintenance treatment. After the initiation of anti-TNF-α antibody-based therapy, azathioprine was administered to one patient and was discontinued in two patients due to side effects. Furthermore, of the 5 (ADA 3/IFX 2) patients treated with azathioprine, 1 patient with IFX discontinued treatment due to LOR. The CRP level in 1 patient was persistently positive (0.7-1.75 mg/dL) before it was categorized as LOR by endoscopy. The sustain rate to the maintenance therapy in the 17 patients was 94%, 87%, and 72% after 2, 4, and 6 years, respectively (Fig. 3).

Reductions in the PSL dose

The serial changes in the PSL dose were evaluated in the 13 patients categorized as responders. Mid-process completion of PSL was achieved by 9 patients (69%), and dose reduction was achieved in 4 patients (31%). The mean PSL dose before the initiation of anti-TNF-α antibody-based therapy was 13.4±2.16 mg/day and was reduced to 0.92±0.47 mg/day at the completion of observation (p<0.0001; Fig. 4).

Non-intestinal BD symptoms

Of the 13 patients categorized as responders, a clinical examination at baseline identified non-intestinal clinical features in six patients, including oral aphthus ulcerations in five, ophthalmic manifestations in one, dermal features in one, vulvar ulcers in one, and joint symptoms in two. Of these six patients, four had non-intestinal symptoms during the observation period despite well-controlled intestinal lesions. In addition, although no symptoms were encountered before initiation in one subject, dermal symptoms eventually developed during the observation period. Non-intestinal

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symptoms ultimately appeared in five patients during the observation period despite well-controlled intestinal lesions. Of these patients, five had oral aphthous ulcer formation, one developed dermal manifestations, one vulvar ulceration, and one showed joint symptoms (Fig. 5).

**Discussion**

We evaluated in the present study the efficacy of medium- to long-term anti-TNF-α antibody-based treatment in BD patients with intestinal lesions who had received remission-induction treatment. Remission, defined clinically, was successfully induced in 17 (89%) patients, by week 12. Our findings are similar to those reported by Kinoshita et al. (16) who noted an 80% rate of remission induction at week 10, defined based on abdominal symptoms and CRP levels. The reason for the high remission rate in our study is probably mainly related to the evaluation being limited to clinical symptoms.

With regard to intestinal BD, the reported efficacy of medium- to long-term treatment with anti-TNF-α antibody ranges from 39% to 67% at 12-24 weeks and 55% at 100 weeks (13, 15-19). In the present study, the mean observation period was 257.2 weeks (minimum: 70.6 weeks; maxim-
mum: 527.4 weeks). During this period, 1 subject (5.9%) was categorized as LOR, 3 patients (18%) withdrew from the study, and maintenance therapy was continued in 13 patients (76%). Considering LOR and withdrawal as dropping out, the sustenance rates of maintenance therapy after 2 and 4 years were 94% and 87%, respectively, which were higher than previously reported (13, 15-19).

Regarding the factors that influence the response to such therapy and induction of remission, Kinoshita et al. (16) identified melena, a fever, and disease severity as underlying causes of a poor response. The present and previous studies may differ in the severity of the condition of the target patients and the use of PSL. Tanida et al. (13) reported a remission induction rate after 8-12 weeks of 55% in patients with a G-GIS of 3 or 4. In the present study, the number of patients with mild BD (i.e., those with a G-GIS of 1 or 2), was 7 (38.9%). In contrast, the reported combination rate of PSL therapy at the time of induction of remission ranged from 47% to 65% in the study of Tanida et al. (13, 16), while in the present study, the combination rate was 100%; however, the PSL dose was lower than that reported by Kinoshita et al. (16) at the initiation of anti-TNF-α antibody-based therapy.

In terms of patients’ background factors, the high proportion of patients with mild BD and the high rate of use of PSL at remission probably contributed to the remission rate and influenced the long-term maintenance. With respect to the PSL, 9 of the 13 (69%) patients discontinued this treatment. Furthermore, four of these patients started the anti-TNF-α antibody-based regimen to reduce the PSL dose, with discontinuation proving successful in two of the four. In some patients, PSL dose reduction was difficult, especially those with non-intestinal BD involvement.

Among the non-intestinal BD features, ophthalmic, neural, and vascular pathologies have negative effects on the long-term prognosis and quality of life. For this reason, various anti-TNF-α antibody-based regimens have been used, and some have been reported to successfully induce maintenance. In addition, anti-TNF-α antibody-based treatment is thought to (18, 20, 21) be effective against recurrent aphthous ulceration, vulvar ulceration, and joint symptoms (22-24). Tanida et al. (13) showed that the administration of ADA to 15 patients with intestinal BD (all 15 had oral aphthous ulcers, and 3 had vulvar ulcers at baseline) resulted in the complete clearance of these ulcers after 52 weeks’ treatment with ADA in 67% of the patients. Compared with the present study, during the induction of remission of intestinal lesions by anti-TNF-α antibody-based
maintenance therapy, sufficient control of non-gastrointestinal symptoms could not be achieved in 5 of the 13 (38.5%) patients. The large number of patients with non-gastrointestinal symptoms even after the initiation of anti-TNF-α antibody-based therapy may have been due to the long observation period. Furthermore, symptoms were analyzed on an all-or-none basis, so patients who showed the alleviation of symptoms after treatment were categorized as non-responders.

BD is associated with various inflammatory cells and cytokines (6). For example, IL-23 is an essential factor required for increasing the population of pathogenic CD4+ T cells, which is characterized by the production of IL-17, IL-6, and TNF-α (6). For intestinal and non-intestinal lesions of BD, in which anti-TNF-α antibody-based therapy is ineffective, other treatments may be effective. Vitale et al. reported that IL-1 inhibitors, tocilizumab, rituximab, alemtuzumab, ustekinumab, interferon-α-2a, and apremilast, may be potential agents for the future management of BD (25).

One subject withdrew from the present study after being diagnosed with thyroid cancer. The potential involvement of anti-TNF-α antibody-based therapy in the pathogenesis of cancer needs to be considered. However, a review of the literature showed no increase in the incidence of lymphoma or cancer in patients treated with anti-TNF-α antibody (26, 27). In addition, there are no reports showing a clear correlation between BD and cancer. Nevertheless, further studies are needed to determine the true carcinogenicity of long-term anti-TNF-α antibody-based regimens.

Previous studies described patients who did not develop recurrence despite a lack of treatment of BD for an extended time (28). It is possible that our study included patients in

Figure 5. Non-intestinal BD symptoms in the 13 patients categorized as responders.
whom anti-TNF-α antibody-based therapy could have been discontinued. Other studies, however, have described a weak response rate and development of IR in patients in whom anti-TNF-α antibody-based treatment for rheumatoid arthritis and inflammatory bowel disease was discontinued and then re-initiated (29-31). Therefore, it is currently difficult to consider discontinuation of anti-TNF-α antibody therapy in patients who show persistent remission. Further research is needed to elucidate the BD pathology and the mechanism underlying inflammation, to predict the patients who will benefit most from anti-TNF-α antibody-based therapy or other immunomodulators, and to assess whether or not such treatments should be continued after prolonged remission.

Several limitations associated with the present study warrant mention. The study design was retrospective in nature and carried out at a single institution with a small number of patients. The study did not include control patients who had been treated with placebo or other drugs. Furthermore, approximately 50% of the patients were treated concomitantly with azathioprine or other immunomodulators, such as those used for treatment of non-intestinal symptoms and intestinal lesions. It is possible that these medications directly or indirectly influenced the therapeutic outcome.

**Conclusion**

We demonstrated in the present study the potential beneficial effects of medium- to long-term anti-TNF-α antibody-based maintenance treatment of BD intestinal lesions. However, non-intestinal symptoms appeared even in those patients who showed satisfactory control of intestinal lesions.

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

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