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Alimentary Tract

Real-world efficacy of adalimumab and infliximab for refractory intestinal Behçet's disease

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ABSTRACT

Background: Anti-tumor necrosis factor-α agents are important for managing refractory intestinal Behçet's disease. Few studies have reported the efficacy of anti-tumor necrosis factor-α monoclonal antibodies for intestinal Behçet's disease due to its rarity.
Aims: The aim was to examine the efficacy of anti-tumor necrosis factor-α antibodies for intestinal Behçet's disease in real-world practice.
Methods: This was a retrospective review of medical records at 4 hospitals in Japan. Global gastrointestinal symptom and endoscopic assessment scores were analyzed in intestinal Behçet's disease patients given anti-tumor necrosis factor-α agents at 3 and 12 months after the start of therapy.
Results: Of 53 intestinal Behçet's disease patients, 22 received anti-tumor necrosis factor-α monoclonal antibody treatment. At the first line, 14 were given adalimumab, and 8 were given infliximab. After 3 and 12 months of treatment, 7 and 11 patients showed complete response of gastrointestinal symptom scores, respectively, and 5 and 9 showed complete remission of the endoscopic assessment score, respectively. Three patients switched anti-tumor necrosis factor-α agents.
Conclusion: Anti-tumor necrosis factor-α monoclonal antibodies are effective for refractory intestinal Behçet's disease in real-world situations. Switching anti-tumor necrosis factor-α agents may be useful for failure of first-line anti-tumor necrosis factor-α therapy in some refractory cases.

1. Introduction

Behçet's disease (BD) is a multisystem, immune-mediated, inflammatory disorder characterized by recurrent oral aphthous ulcers, uveitis, skin lesions, and genital ulcers [1]. Approximately 15–20% of patients with BD have intestinal ulcers that are associated with symptoms [2]. Gastrointestinal tract involvement in BD is followed by severe complications, including massive bleeding, bowel perforation, and fistulas, which can lead to significant morbidity and mortality [3]. BD is treated conventionally with corticosteroids, immunomodulators such as azathioprine and 6-mercaptopurine (6-MP), and anti-tumor necrosis factor-α (TNF-α) agents [4]. However, the management of intestinal BD has not yet been properly established. Recently, there has been evidence suggesting that biologics such as infliximab (IFX) and adalimumab (ADA) are effective in the treatment of intestinal BD. Marked improvement and complete remission were confirmed in 60% and 20% of intestinal BD patients given ADA at week 52, evaluated by global gastrointestinal (GI) symptom and endoscopic assessment scores, respectively [2]. The improvement in clinical symptoms and healing or scarring of the principal intestinal ulcer by IFX injection were confirmed in about 80% of intestinal BD patients [5]. However, there is little evidence for anti-TNF-α therapy in intestinal BD in real-world practice.

Thus, the efficacy of anti-TNF-α monoclonal antibodies for intestinal BD, using the global GI symptom and endoscopic assessment scores at 3 and 12 months after the start of anti-TNF-α therapy, is reported.

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2. Patients and methods

2.1. Patients and treatment

Twenty-two consecutive active intestinal BD patients were administered anti-TNF-α agents at Nagoya City University Hospital, Aichi Medical University Hospital, Japan Community Health Care Organization Chukyo Hospital, and Toyokawa City Hospital. This study was approved by the Institutional Review Board at each hospital and was conducted in accordance with the guidelines of the International Conference on Harmonization and ethical principles originating in the Declaration of Helsinki. All participating patients were recruited after informed consent was obtained. Before the start of anti-TNF-α therapy, bacterial infectious enteritis was ruled out by stool cultures. *Clostridium difficile* infection was ruled out by *Clostridium difficile* toxin testing and stool cultures, and cytomegalovirus infection was ruled out by pathological analysis of lesions [6,7].

The Japanese criteria for the diagnosis of intestinal BD, which are widely used, were applied, as below [1,8].

1. A diagnosis of intestinal BD can be made if:
   - A There is a typical oval-shaped large ulcer in the terminal ileum, OR
   - B There are ulcerations or inflammation in the small or large intestine, and clinical findings meet the diagnostic criteria of BD ([8,9]).
2. Acute appendicitis, infectious enteritis, tuberculosis, Crohn's disease, nonspecific colitis, drug-associated colitis and other diseases that mimic intestinal BD should be excluded by clinical findings, radiology, and endoscopy before a diagnosis of intestinal BD is made.

According to the Japanese protocol, the patients received 160 mg of ADA by subcutaneous administration at week 0 and 80 mg at week 2, and subsequent subcutaneous doses of 40 mg were given as a maintenance dose every other week thereafter [2]. Intravenous IFX injections of 5 mg/kg were given as maintenance therapy every 8 weeks, in accordance with the Japanese protocol [5]. If the intestinal BD patients showed loss of response to 5 mg/kg of IFX, the dose was escalated to 10 mg/kg, which was approved in Japan.

2.2. Global GI symptom scores

The global GI symptom scores were assessed before and 3 and 12 months after the start of anti-TNF-α therapy. At each study visit, patients assessed the degree that 3 individual GI symptoms (diarrhea, pain, and abdominal discomfort/bloating) affected daily life using the same 4-point scale [2,5]. Complete response is defined as a posttreatment score of 0. A marked improvement response is defined as a decrease of 3 points compared to the pretreatment score. An improvement response is defined as a decrease of 2 points compared to the pretreatment score. No change or aggravated is defined as a decrease of 1 point or a constant or increased score compared to the pretreatment score.

2.3. Endoscopic assessment

The endoscopic efficacy evaluations were classified as complete remission (CR), marked improvement, improvement, and no change (or aggravated) at 3 and 12 months after the start of anti-TNF-α therapy [2,5]. CR was defined as complete ulcer healing. A marked improvement (MI) was defined as present when the largest ulcer was ≤1/4 original size. An improvement was defined as present when the largest ulcer was between 1/2 and 1/4 original size. No change or aggravated was defined as present when the largest ulcer was still ≥1/2 original size or had expanded. Ulcer size was evaluated via photography by comparing it with an object of known size (e.g., biopsy forceps or endoscopic measuring) [2].

Table 1
The baseline characteristics of intestinal Behçet's disease patients with and without anti-tumor necrosis factor-α treatment (n = 53).

Characteristics	Anti-TNF-α treatment (+)	Anti-TNF-α treatment (−)
Number of patients	22 (41.5%)	31 (58.5%)
Sex (female/male)	5/17	13/18
Non-GI BD symptoms		
Oral aphthous ulcer	16	26
Skin lesion	10	15
Eye inflammation	3	5
Genital ulcer	8	8
Global GI symptom scores		
0	0	26
1	1	5
2	5	0
3	7	0
4	9	0
Previous operation	2	9
1st line anti-TNF-a antibody		
Adalimumab	14	–
Infliximab	8	–
Concomitant medication		
Systemic corticosteroids	11	11
5-Aminosalicylates	11	17
Immunosuppresants (AZA or 6-MP)	5	8
Ciclosporin	1	0
Tacrolimus	0	0
Colchicine	3	14
GMA	0	0
Previous biologics	0	0

BD, Behçet's disease; TNF, tumor necrosis factor; GI, gastrointestinal; AZA, Azathioprine; 6-MP, 6-mercaptopurine; GMA, granulocyte and monocyte adsorptive apheresis.

3. Results

3.1. Patient characteristics

Of the 53 intestinal BD patients in the 4 hospitals, 22 (41.5%) received anti-TNF-α therapy. The baseline characteristics of intestinal BD patients treated with (n = 22) and without (n = 31) anti-TNF-α therapy are shown in Table 1. In the group with anti-TNF-α therapy, the female/male ratio was 5/17, and the median age at the start of anti-TNF-α therapy was 43.0 years (range 15–72 years). The median disease duration at the start of anti-TNF-α therapy was 5.7 years (range 0.1–18 years). Regarding non-GI BD symptoms, oral aphthous ulcers, skin lesions, eye inflammation, and genital ulcers were observed in 16, 10, 3, and 8 cases, respectively. Regarding global GI symptom scores before anti-TNF-α therapy, scores of 1, 2, 3, and 4 were found in 1, 5, 7, and 9 cases, respectively. With regard to the number of ulcers in the ileocecum or the oral side of an anastomosis, 9, 2, 3, and 7 intestinal BD patients had 1, 2, 3, and ≥4 lesions, respectively (one case had no data on the number of ulcers). For concomitant medication, 11 patients received prednisolone, 11 received 5-aminosalicylates, 5 received immunosuppressants (azathioprine, AZA; 6-mercaptopurine, 6-MP), 1 received cyclosporine, 3 received colchicine, and none had previously been given biologic therapy (Table 1). None of the patients had serious adverse events requiring termination of ADA or IFX therapy.

In the group without anti-TNF-α therapy, the female/male ratio was 13/18. Regarding non-GI BD symptoms, oral aphthous ulcers,

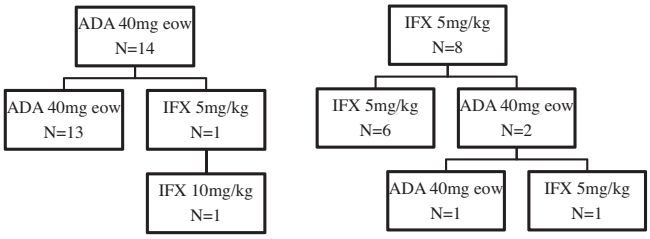

Fig. 1. Disposition and flow of the 22 patients who received anti-tumor necrosis factor-α. ADA, adalimumab; IFX, infliximab; eow, every other week.

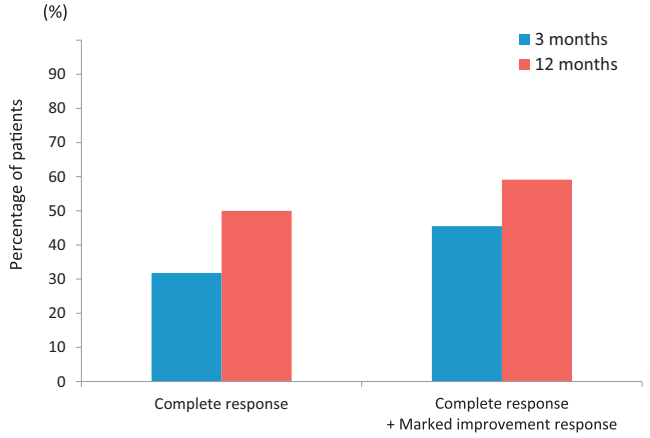

Fig. 2. Global gastrointestinal symptom assessment at 3 and 12 months after the start of first-line anti-tumor necrosis factor-α therapy.

skin lesions, eye inflammation, and genital ulcers were observed in 26, 15, 5, and 8 cases, respectively. Regarding global GI symptom scores, scores of 0 and 1 were found in 26 and 5 cases, respectively. For concomitant medication, 11 patients received prednisolone, 17 received 5-aminosalicylates, 8 received immunosuppressants, and 14 received colchicine, and none had previously been given biologic therapy (Table 1).

3.2. ADA and IFX therapy

Twenty-two cases received anti-TNF-α therapy (Fig. 1, Table 1), with 14 receiving ADA and 8 receiving IFX as the first-line anti-TNF-α. Of the 14 cases with first-line ADA administration, 1 had second-line IFX and third-line IFX dose escalation (10 mg/kg) after first-line ADA treatment (Case-ADA to IFX to IFX increased). Of the 8 cases with first-line IFX administration, 1 had second-line ADA after first-line IFX treatment (Case-IFX to ADA), and 1 had second-line ADA and third-line IFX at the standard dose (5 mg/kg) after first-line IFX treatment (Case-IFX to ADA to IFX).

In 5 cases with previous immunosuppressant treatment in the group with anti-TNF-α therapy, all patients had received oral AZA treatment followed by at least 6 months before the start of anti-TNF-α therapy.

3.3. Global GI symptom assessment

The global GI symptom assessments at 3 and 12 months after the start of first-line anti-TNF-α therapy are shown in Fig. 2. At 3 months, 31.8% (7/22) and 13.6% (3/22) of patients achieved complete response and marked improvement response, respectively. At 12 months, 50.0% (11/22) and 9.1% (2/22) of patients showed complete response and marked improvement response, respectively. At 3 and 12 months, 45.4% (10/22) and 59.1% (13/22) showed complete response and marked improvement response, respectively (Fig. 2).

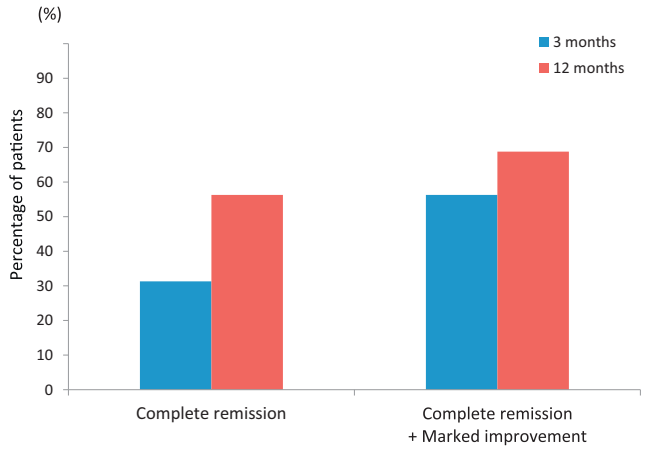

Fig. 3. Endoscopic assessment at 3 and 12 months after the start of first-line anti-tumor necrosis factor-α therapy.

Of 22 intestinal BD patients treated with first-line anti-TNF-α therapy, 19 received more than one year of anti-TNF-α therapy without another second-line biologic therapy. The remaining 3 cases received less than one year of anti-TNF-α therapy without another second-line biologic therapy. All 3 cases had surgical resection at less than one year of first-line anti-TNF-α therapy, since anti-TNF-α therapy was ineffective. All lesions surgically resected had giant oval-shaped deep punched-out ulcers, and no granulomas were detected histologically, effectively ruling out tuberculosis or Crohn's disease.

3.4. Endoscopic assessment

Of 22 intestinal BD patients treated with anti-TNF-α therapy, 16 could be evaluated endoscopically before and at 3 and 12 months after the start of first-line anti-TNF-α therapy. Their endoscopic assessments at 3 and 12 months after the start of first-line anti-TNF-α therapy are shown in Fig. 3. Three cases had endoscopic assessments before and at 3 months after the start of first-line anti-TNF-α therapy, but no endoscopic evaluation at 12 months was performed in these 3 cases, because they underwent surgical resection due to aggravation of the disease, despite first-line anti-TNF-α therapy. The remaining 3 cases were not evaluated endoscopically before the start of first-line anti-TNF-α therapy.

At 3 months, 31.3% (5/16) and 25.0% (4/16) of patients achieved CR and MI, respectively. At 12 months, 56.3% (9/16) and 12.5% (2/16) of patients showed CR and MI, respectively. At 3 and 12 months, 56.3% (9/16) and 68.8% (11/16) showed CR and MI, respectively (Fig. 3).

3.5. Steroid-free remission

Of 22 intestinal BD patients in the group with anti-TNF-α therapy, 11 (50.0%) had received prednisolone when anti-TNF-α treatment started. Of the 11 cases receiving prednisolone, 4 (36.4%) became steroid-free at 3 months after the start of first-line anti-TNF-α therapy. Of these 4 patients, 2 (18.2%) achieved complete response on the global GI symptom scores, and none achieved CR on endoscopic assessment. At 12 months after the start of first-line anti-TNF-α therapy, 7 patients (63.6%) became steroid-free. Of these 7 patients, 6 (54.5%) achieved complete response on the global GI symptom scores, and 5 (45.5%) achieved CR on endoscopic assessment.

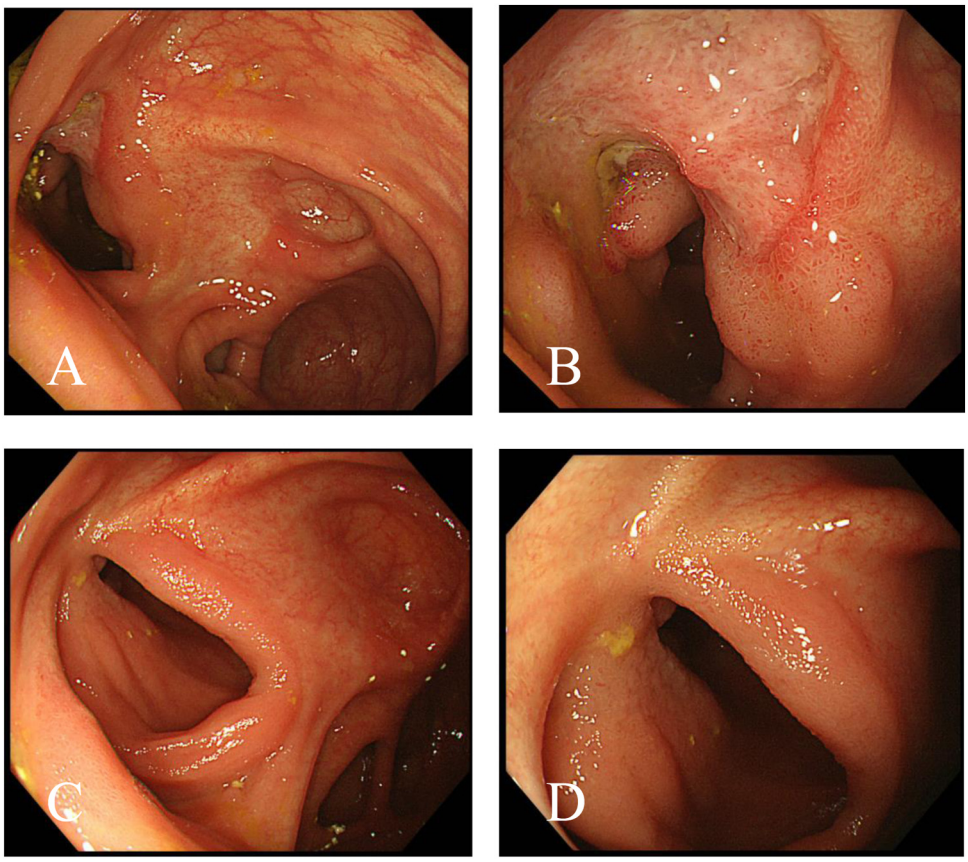

Fig. 4. A big punched-out-like ulcer is seen endoscopically in the ileocecal valve before the start of infliximab dose escalation therapy (A, B), and mucosal healing of the lesion is observed endoscopically at 12 months after the therapy (C, D).

3.6. Switching of anti-TNF-α agents

Of 22 intestinal BD patients treated with anti-TNF-α therapy, 3 (13.6%) switched anti-TNF-α agents because of the loss of response to first-line or second-line anti-TNF-α therapies with an increase of ≥1 point on the global GI symptom scores followed by at least 3 months. All 3 cases received more than one year of first-line anti-TNF-α therapy before the switch to second-line anti-TNF-α therapy. In the Case-ADA to IFX to IFX increased, endoscopic mucosal healing was confirmed at 12 months after the start of IFX dose escalation therapy (Fig. 4). In the Case-IFX to ADA to IFX, the anti-TNF-α therapy has been continued with improvement response of the global GI symptom assessment after the switch of anti-TNF-α agents. In the Case-IFX to ADA, the anti-TNF-α therapy was not sufficiently effective, despite the switch of anti-TNF-α agents. Consequently, several surgical resections were performed for this patient.

4. Discussion

The results of the present study provide evidence that anti-TNF-α monoclonal antibody therapy is effective for the improvement of global GI symptoms in real-world practice. At 3 and 12 months, 45.4% (10/22) and 59.1% (13/22) of patients showed complete response and marked improvement response, respectively, suggesting improvement of their quality of life (Fig. 2). In addition, it was shown that anti-TNF-α monoclonal antibodies improved the mucosal inflammation endoscopically at the induction and maintenance stages. At 3 and 12 months, 56.3% (9/16) and 68.8% (11/16) showed endoscopic CR and MI, respectively (Fig. 3). In 20 intestinal BD patients treated with ADA therapy, 45% had GI symptom and endoscopic assessment scores of 1 or lower at week 24 of treatment, and 60% had such scores by week 52 [2]. CR was achieved in 20% of intestinal BD patients with ADA administration at weeks 24 and 52 [2]. The percentage of intestinal BD patients showing an improvement in clinical symptoms was 64%, 73%, 91%, and 80% at weeks 2, 14, 30, and 54, respectively, in 11 intestinal BD patients treated with IFX [3]. The percentage of intestinal BD patients with no clinical symptoms was 36%, 64%, and 80% at weeks 2, 30, and 54, respectively, in intestinal BD patients treated with IFX [3]. Healing or scarring of the principal intestinal ulcer was recorded at week 14 in 82% of patients, and the percentage of patients with healing or scarring of the principal intestinal ulcer was 82% and 89% at weeks 30 and 54, respectively, in intestinal BD cases treated with IFX [3]. In the Korean multicenter retrospective study, the clinical response rates at 2, 4, 30, and 54 weeks were 75%, 64.3%, 50%, and 39.1%, respectively, with clinical remission rates of 32.1%, 28.6%, 46.2%, and 39.1%, respectively [10]. We consider that anti-TNF-α monoclonal antibody therapy is very useful for the improvement of clinical symptoms and the mucosal inflammation of lesions detected endoscopically in intestinal BD patients in real-world practice.

In the present study of 53 intestinal BD patients, 22 (41.5%) received anti-TNF-α therapy. In Japan, 50.0% of Crohn's disease patients had biologic therapies (IFX or ADA), while 10.8% of ulcerative colitis patients had biologic therapies (IFX or ADA) [11]. The rate of biologic medication use in intestinal BD patients is similar to that in Crohn's disease cases in Japan. Regarding switching anti-TNF-α agents, to the best of our knowledge, there has been only one report of switching anti-TNF-α monoclonal antibodies in intestinal BD cases [12]. In the present study, 3 (13.6%) of 22 intestinal BD patients treated with anti-TNF-α therapy switched

anti-TNF-α agents, and the switch was very useful for secondary failure of first-line anti-TNF-α therapy in one case with IFX dose escalation (Case-ADA to IFX to IFX increased). However, further studies in a large population should be performed to clarify the usefulness of switching anti-TNF-α agents in intestinal BD patients, since the present study involved only a small population. With regard to the long-term efficacy and safety of anti-TNF-α therapy, at weeks 52 and 100, 60.0% and 40.0% of patients treated with ADA showed marked improvement, respectively, and 20.0% and 15.0% of patients showed complete remission of 15 intestinal patients treated with ADA, respectively [13]. The incidence of adverse events through week 100 was 544.4 events/100 person-years, which was comparable to the incidence through week 52 (560.4 events/100 person-years) [13]. In the present study, none of the patients had serious adverse events requiring termination of ADA or IFX therapy. Further studies should be performed to clarify the long-term efficacy and safety of anti-TNF-α therapy in intestinal BD patients.

It is important to note that refractory cases with active inflammation in the intestinal mucosa still remain, despite anti-TNF-α monoclonal antibody therapy. In the present study, 3 (13.6%) patients received less than one year of anti-TNF-α therapy without second-line other biologic therapy, and all 3 cases underwent surgical resection at less than one year of first-line anti-TNF-α therapy, since anti-TNF-α therapy was ineffective. The surgical intervention rate remains high, at 31% to 46% 10 years after diagnosis, so to prevent surgery and reduce relapses, sustained remission should be the goal of medical therapy for intestinal BD [13]. The development of biologic therapies other than anti-TNF-α therapy is needed for refractory intestinal BD, although several studies on the effects of various biologics, such as etanercept, anakinra, canakinumab, and tocilizumab, have been conducted [3].

In conclusion, anti-TNF-α monoclonal antibodies are effective as induction and maintenance therapies in refractory intestinal BD patients, being considered a standard therapy for this disease in real-world practice. Switching anti-TNF-α agents may be useful for secondary failure of first-line anti-TNF-α therapy in some refractory cases.

Conflict of interest

None declared.

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References

[1] Hisamatsu T, Ueno F, Matsumoto T, Kobayashi K, Koganei K, Kunisaki R, et al. The 2nd edition of consensus statements for the diagnosis and management of intestinal Behcet's disease: indication of anti-TNFalpha monoclonal antibodies. J Gastroenterol 2014;49:156–62.
[2] Tanida S, Inoue N, Kobayashi K, Naganuma M, Hirai F, Iizuka B, et al. Adalimumab for the treatment of Japanese patients with intestinal Behcet's disease. Clin Gastroenterol Hepatol 2015;13, 940–8.e3.
[3] Park YE, Cheon JH. Updated treatment strategies for intestinal Behcet's disease. Korean J Intern Med 2018;33:1–19.
[4] Naganuma M, Sakuraba A, Hisamatsu T, Ochiai H, Hasegawa H, Ogata H, et al. Efficacy of infliximab for induction and maintenance of remission in intestinal Behcet's disease. Inflamm Bowel Dis 2008;14:1259–64.
[5] Hibi T, Hirohata S, Kikuchi H, Tateishi U, Sato N, Ozaki K, et al. 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 2016;95:e3863.
[6] Mizoshita T, Tanida S, Tsukamoto H, Ozeki K, Katano T, Nishiwaki H, et al. Adalimumab treatment in biologically naive Crohn's disease: relationship with ectopic MUC5AC expression and endoscopic improvement. Gastroenterol Res Pract 2014;2014:687257.
[7] Mizoshita T, Katano T, Tanida S, Hirano A, Miyaki T, Ozeki K, et al. Prospective comparison of preference and efficacy of adalimumab and infliximab for treating ulcerative colitis naive to antitumor necrosis factor therapy. Medicine 2017;96:e7800.
[8] Suzuki Kurokawa M, Suzuki N. Behcet's disease. Clin Exp Med 2004;4:10–20.
[9] Criteria for diagnosis of Behcet's disease. International Study Group for Behcet's Disease. Lancet 1990;335:1078–80.
[10] Lee JH, Cheon JH, Jeon SW, Ye BD, Yang SK, Kim YH, et al. Efficacy of infliximab in intestinal Behcet's disease: a Korean multicenter retrospective study. Inflamm Bowel Dis 2013;19:1833–8.
[11] Matsumoto T, Yanai S, Toya Y, Ueno M, Nakamura S. Internet-orientated assessment of QOL and actual treatment status in Japanese patients with inflammatory bowel disease: the 3I survey. J Crohns Colitis 2015;9:477–82.
[12] Karube H, Kamoi K, Ohno-Matsui K. Anti-TNF therapy in the management of ocular attacks in an elderly patient with long-standing Behcet's disease. Int Med Case Rep J 2016;9:301–4.
[13] Inoue N, Kobayashi K, Naganuma M, Hirai F, Ozawa M, Arikan D, et al. Long-term safety and efficacy of adalimumab for intestinal Behcet's disease in the open label study following a phase 3 clinical trial. Intest Res 2017;15:395–401.