

Anti-Tumor Necrosis Factor Therapy in Intestinal Behçet's Disease

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Intestinal Behçet's disease is a rare, immune-mediated chronic intestinal inflammatory disease; therefore, clinical trials to optimize the management and treatment of patients are scarce. Moreover, intestinal Behçet's disease is difficult to treat and often requires surgery because of the failure of conventional medical treatment. Administration of anti-tumor necrosis factor- α , a potential therapeutic strategy, is currently under active clinical investigation, and evidence of its effectiveness for both intestinal Behçet's disease and inflammatory bowel diseases has been accumulating. Here, we review updated data on current experiences and outcomes after the administration of anti-tumor necrosis factor- α for the treatment of intestinal Behçet's disease. In addition to infliximab and adalimumab, which are the most commonly used agents, we describe agents such as golimumab, etanercept, and certolizumab pegol, which have recently been shown to be effective in refractory intestinal Behçet's disease. This review also discusses safety issues associated with anti-tumor necrosis factor- α , including vulnerability to infections and malignancy. (**Gut Liver 2018;12:623-632**)

Key Words: Behcet syndrome; Intestinal Behcet's disease; Anti-tumor necrosis factor alpha; Infliximab; Adalimumab

INTRODUCTION

Behçet's disease (BD) is a chronic recurring multisystemic vasculitic disorder involving recurrent oral ulcers; genital ulcers; ocular lesions; skin manifestations; arthritis; and vascular, neurologic, and intestinal involvement.^{1,2} Intestinal BD is diagnosed when a patient with BD has both dominant gastrointestinal symptoms and typical intestinal ulcerative lesions on objective examinations.³ The intestinal involvement of BD is rare, ranging 5% to 20%, and it is more prevalent in East Asian countries, including Korea and Japan.⁴ Typical intestinal ulceration of intes-

tinal BD is oval in shape and deep with discrete border located in the ileocecal area.⁵ It can cause diarrhea, abdominal pain, gastrointestinal bleeding, or bowel perforation.^{6,7}

Intestinal BD has a heterogeneous range of clinical courses and symptoms, and a gold standard therapy remains elusive. Research on intestinal BD is relatively scarce because of the rarity of this disease.⁸ Moreover, intestinal BD is often refractory to conventional treatment such as corticosteroids and immunomodulators; therefore, alternative therapies are needed.⁹ Currently, anti-tumor necrosis factor- α (anti-TNF- α), a potential therapeutic strategy, is being evaluated, and evidence for its effectiveness has been accumulating. In Japan, anti-TNF- α has received approval to be used for the treatment of intestinal BD in cases where existing treatments are inadequate.^{10,11} One TNF- α receptor fusion protein (etanercept), three anti-TNF- α monoclonal antibodies (infliximab, adalimumab, and golimumab), and one anti-TNF- α PEGylated antigen-binding fragment (certolizumab pegol) are currently approved as anti-TNF- α therapies for several immune-mediated disorders.¹² This article reviews the progress in the management of intestinal BD, focusing on current anti-TNF- α usage and possible future perspectives.

PATHOGENESIS

The pathogenesis of intestinal BD is still unclear; in addition to genetic factors, immune dysfunction and multiple cytokines are associated with the development and progression of disease.¹³ Several data suggest a role of TNF- α in the pathogenesis of intestinal BD. Inflammation in intestinal BD is thought to be mediated by cytokines derived from T helper type 1 (Th1) lymphocytes, including TNF- α .¹⁴ T cells at the intestinal mucosal level produce a large concentration of TNF- α , and T cells induce inflammation leading to mucosal damage through abnormal cytokine production, especially during the active phase of the disease.^{15,16} Recently, Emmi *et al.*¹⁷ reported that in the early

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stages of intestinal BD, both Th1 and Th17 cells produce a large amount of TNF- α . In the colonic tissue of patients with BD, interferon- γ (IFN- γ), TNF- α , and interleukin-17A (IL-17A) appeared to be key cytokines, even in a treated patient.¹⁸ Misumi *et al.*¹⁹ reported that anti-TNF- α treatment induced a significant increase in the number of cells secreting IFN- γ and expressing IL-12R β 1. The increasing number of IFN- γ producing cells in BD patients treated with infliximab means that anti-TNF- α could modulate the functional activity of T cells. TNF- α is also produced by $\gamma\delta$ T cells, and infliximab is capable of interfering with V γ 9/V δ 2T cell function in BD.²⁰ The regulation of $\gamma\delta$ T cells by anti-TNF- α might play an important role in the treatment of intestinal BD. Sugita *et al.*^{21,22} demonstrated that anti-TNF- α treatment induced the development of regulator T cells in patients with uveitis and BD. Therefore, blocking TNF- α function with anti-TNF- α and subsequent suppression of $\gamma\delta$ T cell expansion and activation is currently a potential therapeutic strategy.

ANTI-TNF AGENTS IN INTESTINAL BEHÇET'S DISEASE: THE CURRENT EVIDENCE

1. Infliximab

Infliximab is a chimeric monoclonal antibody biologic drug that was first demonstrated in 2001 as an effective new therapy for patients with steroid-dependent intestinal BD.²³ Infliximab is currently one of the most frequently described biologic agents for patients with intestinal BD. Infliximab was infused at 0, 2, and 6 weeks and every 8 weeks thereafter at 3–5 mg/kg in most studies (Table 1).^{24–30} Hassard *et al.*²³ reported that a patient treated with four doses of infliximab over a period of 6 months had improvement in gastrointestinal symptoms and extraintestinal symptoms, a decreased Crohn's Disease Activity Index at week 2, and marked endoscopic and histological improvement at week 10. Travis *et al.*³¹ used infliximab to induce remission in two patients with refractory intestinal BD (dose reduced to 3 mg/kg because of recent sepsis in one patient, and 5 mg/kg in the other). The ulcers healed with resolution of hematochezia and extraintestinal symptoms within 10 days, and remission was initially sustained for 12 months. Kram *et al.*³² reported that a patient treated with two doses of 5 mg/kg infliximab revealed ulcer healing and normalized erythrocyte sedimentation rate and C-reactive protein (CRP) levels. Clinical remission of intestinal BD after infliximab has been described in several case reports.^{33–37}

Combination therapy of infliximab and methotrexate was administered to 10 Japanese patients with refractory intestinal BD who failed to respond to conventional therapy, and it provided short- and long-term efficacy and tolerability as assessed by abdominal computed tomography (CT) and colonoscopy.²⁴ Intestinal manifestations, including tenderness and bleeding, disappeared within 3 months, and improvement was confirmed at only 2 weeks after the initiation of infliximab infusions in

all seven patients assessed on abdominal CT. Ileocecal ulceration disappeared in five patients (50%) at 6 months and nine patients (90%) at 12 months, as confirmed by colonoscopy. In a multicenter retrospective study, the primary outcome was reported using the disease activity index of intestinal Behçet's disease (DAIBD) score with 28 Korean patients with moderate to severe intestinal BD.^{25,38} The clinical response rates, defined as a decrease in the DAIBD score of 20 points or more from the baseline value, were 75.0%, 64.3%, 50.0%, and 39.1% at 2, 4, 30, and 54 weeks, respectively. Old age at diagnosis (≥ 40 years), female sex, longer disease duration (≥ 5 years), concomitant immunomodulator use, and achievement of remission at week 4 were predictive factors for a sustained response to infliximab treatment. This study was meaningful in that it was the first paper to evaluate the efficacy of biologics in intestinal BD using the DAIBD score. Infliximab was administered to 15 Japanese patients with refractory intestinal BD at a single center.²⁶ Clinical response, defined as a significant improvement in intestinal symptoms or a reduced CRP level, was observed in 12 (80%), 11 (64%), and eight (50%) patients at 10 weeks, 12 months, and 24 months, respectively. Clinical remission, defined as a significant improvement in intestinal symptoms and a reduced CRP level, was observed in four (27%), four (36%), and three (38%) patients at 10 weeks, 12 months, and 24 months, respectively. Zou *et al.*³⁰ reported the first cohort study of Chinese patients with intestinal BD in clinical practice. Clinical remission rates, defined as a decrease in the DAIBD score of 20 points or more from the baseline value, at 14 weeks, 30 weeks, and 52 weeks were 69.2%, 40%, and 55%, respectively. Clinical response rates, defined as a DAIBD score lower than 20 points, at 14 weeks, 30 weeks, and 52 weeks were 84.6%, 70%, and 70%, respectively. Interestingly, 18 patients (72%) achieved early mucosal healing at week 14. Judging from the above results, infliximab is considered to be a rapidly acting drug.

Unlike previous studies, only two out of six Japanese patients with refractory intestinal BD showed a good response, defined as improvement of endoscopic findings and successful tapering of corticosteroids.²⁷ One of them achieved clinical remission of gastrointestinal involvement. Another two patients achieved a partial response, and the remaining two patients had progression of or unchanged gastrointestinal lesions.

Hibi *et al.*²⁹ conducted the first prospective, open-label, single-arm, phase 3, multicenter clinical trial of infliximab in Japanese patients with BD. Of 18 patients with BD, 11 patients with intestinal BD were administered infliximab at a dose of 5 mg/kg at weeks 0, 2, and 6, and every 8 weeks thereafter until week 46. Complete response rates, defined as disappearance of clinical symptoms and healed or scarred ulcers, were 55%, 55%, and 60% at 14, 30, and 54 weeks, respectively. Dose reduction and withdrawal of steroids were achieved in 37.5%, 75.0%, and 100.0% of patients at 14, 30, and 54 weeks, respectively. Three patients with intestinal BD were administered an increased dose

Table 1. Infliximab Use in Patients with Intestinal Behçet's Disease

Author (year)	Country	Method	Participants	Intervention	Outcomes
Iwata <i>et al.</i> (2011) ²⁴	Japan	Retrospective, 1 center	10 Patients with intestinal BD refractory to conventional therapy	IFX 3–5 mg/kg (wk 0, 2, 6) with methotrexate	Primary outcome · Rate of disappearance of ileocecal ulceration at 6 and 24 mo: 50% and 90% Secondary outcome · Dose of steroid tapered at 24 mo: 22.0–1.8 mg/day
Lee <i>et al.</i> (2013) ²⁵	Korea	Retrospective, 8 centers	28 Patients with moderate to severe activity of intestinal BD (DAIBD \geq 40)	IFX 5 mg/kg (wk 0, 2, 6)	Primary outcome · Clinical remission at 2, 4, 30, and 54 wk (DAIBD <20): 32.1%, 28.6%, 46.2%, and 39.1% Secondary outcome
Kinoshita <i>et al.</i> (2013) ²⁶	Japan	Retrospective, 1 center	15 Patients with refractory intestinal BD to conventional therapy	IFX 5 mg/kg (wk 0, 2, 6) (n=10) IFX 5 mg/kg (wk 0, 2, 6) with azathioprine (n=5)	Primary outcome · Clinical remission at 10 wk, 12 mo, and 24 mo (improved symptom and normal CRP): 53%, 27%, and 38% Secondary outcome · Clinical response at 10 wk, 12 mo, and 24 mo (improved symptom or lower CRP): 27%, 36%, and 38%
Ideguchi <i>et al.</i> (2014) ²⁷	Japan	Retrospective, 1 center	43 (6 Treated with infliximab for intestinal BD) patients with intestinal BD to conventional therapy	-	Good response in 2 patients, partial response in 2, and unchanged GI lesions in 2 patients
Vallet <i>et al.</i> (2015) ²⁸	France	Retrospective, 12 centers	124 (9 Treated with infliximab for intestinal BD)	-	Primary outcome · Complete response: 5/9 (55.6%) Secondary outcome · Improvement of clinical manifestations in BD patients treated by infliximab: 7/9 (77.8%)
Hibi <i>et al.</i> (2016) ²⁹	Japan	Prospective, open-label, single-arm phase 3 study, 21 centers	18 (11 With intestinal BD) patients with refractory intestinal BD to conventional therapy	IFX 5 mg/kg (wk 0, 2, 6)	Primary outcome · Complete responder at 14, 30, and 54 wk (disappeared clinical symptom and healed or scarred ulcer): 55%, 55%, and 60% Secondary outcome · Dose reduction and withdrawal of steroids at 14, 30, 54 wk: 37.5%, 75.0%, and 100.0%
Zou <i>et al.</i> (2017) ³⁰	China	Retrospective, 1 center	27 Patients with moderate to severe activity of intestinal BD (DAIBD \geq 40)	-	Primary outcome · Clinical remission at 14, 30, and 52 wk (DAIBD <20): 69.2%, 40%, and 55% Secondary outcome · Clinical response at 14, 30, and 52 wk (Δ DAIBD \geq 20): 84.6%, 70%, and 70% · Mucosal healing at 14 wk: 72%

BD, Behçet's disease; IFX, infliximab; DAIBD, disease activity score for intestinal BD; CRP, C-reactive protein; GI, gastrointestinal.

of 10 mg/kg, and the disease was not controlled and worsened in one patient.

Currently, a prospective, open-label, single-arm, phase 3, multicenter clinical trial of infliximab in Korean patients with refractory intestinal BD is recruiting participants (ClinicalTrials.gov, NCT02505568). Participants will receive infliximab 5 mg/kg infusion at weeks 0, 2, and 6 for the induction phase and after that every 8 weeks until week 32 in the maintenance phase. The mean decrease in DAIBD scores of 20 or more will be evaluated primarily, and adverse events will be monitored throughout the study.

2. Adalimumab

Adalimumab is a completely humanized IgG1 monoclonal anti-TNF- α antibody which could bind to TNF- α and prevent it from binding to its receptors. It was the third TNF- α inhibitor approved by the U.S. Food and Drug Administration (FDA), after infliximab and etanercept. Adalimumab has been approved for indications including juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease (CD), ulcerative colitis (UC), hidradenitis suppurativa, psoriasis, and panuveitis.³⁹ It was recently approved and recommended as a standard therapy for intestinal BD in Japan, Taiwan, and South Korea.^{11,40}

There are few available reports regarding adalimumab efficacy for intestinal BD (Table 2).⁴¹⁻⁴⁴ In 2007, van Laar *et al.*⁴⁵ reported the first case series presenting patients with BD with systemic disease treated with adalimumab. One patient was diagnosed with intestinal BD and was treated with infliximab and other immunosuppressive agents for nearly 3 years. A high dose of adalimumab, 40 mg/week, was administered subcutaneously for refractory and life-threatening intestinal BD, and the patient achieved complete response and remained stable for nearly 2 years. In 2011, De Cassan *et al.*⁴⁶ presented the first case of adalimumab administered as the first anti-TNF- α in a patient with intestinal BD. Two siblings with mucocutaneous ulcerations and ileocolitis received adalimumab at an induction dose of 80 mg subcutaneously, followed by 40 mg 2 weeks later and a maintenance schedule of 40 mg every other week. Both clinical response and complete remission were achieved stable after induction therapy, allowing corticosteroid-free remission for nearly 1 year.

There was a case report about the efficacy of adalimumab with combined hematologic disorders. Generally, patients with intestinal BD with myelodysplastic syndrome (MDS) involving trisomy 8 are refractory to conventional medical therapies and infliximab.⁴⁷ Kimura *et al.*⁴⁸ demonstrated a favorable effect of adalimumab in patients with refractory intestinal BD and in those with MDS involving trisomy 8.

The relationship between adalimumab and pathologic finding has also been studied. Mizoshita *et al.*⁴⁹ reported that loss of ectopic mucin 5AC glycoprotein expression may be important for the improvement of ileocecal ulcer lesions in patients with

adalimumab-treated intestinal BD.

Tanida *et al.*⁴¹ conducted the first prospective, open-label, single-arm, phase 3, multicenter clinical trial of adalimumab in 20 Japanese patients with intestinal BD. All patients received induction treatment with 160 mg adalimumab at week 0 and 80 mg at week 2 and maintenance therapy with 40 mg every other week from weeks 4 to 50. Complete remission rate, defined as marked improvement of global symptoms and endoscopic assessment score, was 20% at both weeks 24 and 52. Complete response rate, defined as marked improvement of global symptoms or endoscopic assessment score, was 45% and 60% at weeks 24 and 52, respectively. Inoue *et al.*⁴³ followed up these patients and evaluated the long-term safety profile and effectiveness of adalimumab through 100 weeks in patients rolled over from a 52 week-clinical trial. At weeks 52 and 100, 60% and 40% of patients showed clinical response, and 20% and 15% of patients showed complete remission, respectively. The overall incidence of adverse events during the study was comparable to that in other studies investigating patients with inflammatory bowel diseases.

Combination therapy of adalimumab with disease-modifying antirheumatic drugs does not appear to be significantly superior to adalimumab monotherapy.⁴⁴ There were no differences between monotherapy and combination therapy in terms of efficacy, time to response, relapses, and adalimumab discontinuation in 100 consecutive patients with BD over a period of 24 months. Moreover, the frequency and time to response for adalimumab were not associated with a previous loss of response of other anti-TNF- α agents. Conversely, the relapse frequency and adalimumab discontinuation at the 2-month follow-up evaluation were significantly higher among patients that had previously experienced failure of an anti-TNF- α agent.

A prospective, multicenter clinical study on adalimumab lasting up to 50 weeks in Japanese patients with BD (NCT01243671) has been completed but has not yet been published. A prospective, open-label, single-arm, phase 3, multicenter clinical trial of adalimumab in Korean patients with intestinal BD is recruiting participants (ClinicalTrials.gov, NCT 02687828). Once these two studies are completed, further evidence for adalimumab in intestinal BD will be established.

3. Etanercept

Etanercept is a dimeric humanized anti-TNF- α antibody, manufactured by recombinant DNA techniques, has a greater binding affinity by the combination of two naturally occurring soluble human TNF receptors linked to the Fc portion of an IgG1.⁵⁰ Etanercept has been approved for indications including rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis but not for inflammatory bowel diseases. Etanercept has proved to be effective in controlling intestinal BD with a good safety profile (Table 3).⁵¹⁻⁵³ Watanabe *et al.*⁵⁴ reported the case of one

Table 2. Adalimumab Use in Patients with Intestinal Behçet's Disease

Author (year)	Country	Method	Participants	Intervention	Outcomes
Tamida <i>et al.</i> (2015) ⁴¹	Japan	Prospective, open-label, uncontrolled, phase 3 study, 12 centers	20 Patients with refractory intestinal BD to conventional therapy	ADA, 160 mg (wk 0), 80 mg (wk 2), 40 mg (wk 4)	Primary outcome · Complete remission at 24 and 52 wk (marked improvement of global symptom and endoscopic assessment score): 20% and 20% Secondary outcome · Clinical response at 24 and 52 wk (marked improvement of global symptom or endoscopic assessment score): 45% and 60%
Tamida <i>et al.</i> (2016) ⁴²	Japan	Retrospective, 1 center	8 Patients with refractory intestinal BD to conventional therapy	ADA, 160 mg (wk 0), 80 mg (wk 2), 40 mg (wk 4)	Primary outcome · Complete remission at 24 and 52 wk (marked improvement of global symptoms and endoscopic assessment score): 25% and 25% Secondary outcome · Clinical response at 24 and 52 wk (marked improvement of global symptom or endoscopic assessment score): 62.5% and 75%
Inoue <i>et al.</i> (2017) ⁴³	Japan	Prospective, open-label, uncontrolled, phase 3 study, 12 centers	20 Patients with refractory intestinal BD to conventional therapy	ADA, 160 mg (wk 0), 80 mg (wk 2), 40 mg (wk 4)	Primary outcome · Complete remission at 52 and 100 wk (marked improvement of global symptom and endoscopic assessment score): 20% and 15% Secondary outcome · Clinical response at 52 and 100 wk (marked improvement of global symptom or endoscopic assessment score): 60% and 40%
Vitale <i>et al.</i> (2017) ⁴⁴	Italy	Retrospective, multicenter	100 (13 With intestinal BD) patients with refractory intestinal BD to conventional therapy or previous anti-TNF α therapy	-	Primary outcome · Complete disappearance of BD-related clinical signs within the 12 wk from the start of adalimumab therapy: 81/100 patients Secondary outcome · Number of patients remaining on adalimumab therapy at the 24-mo follow-up visit: 67/100 patients

BD, Behçet's disease; ADA, adalimumab; TNF, tumor necrosis factor.

6-year-old Japanese girl with refractory intestinal BD who was successfully treated with etanercept. Although infliximab was administered first in this patient, it was switched to etanercept because an infusion reaction to the drug prevented its further use. In terms of oral ulcers, skin lesions, and uveitis, it has been demonstrated that the remission rate of lesions was significantly higher in the etanercept-treated group than in the conventional therapy group.⁵⁵⁻⁵⁷ Ma *et al.*⁵¹ conducted a retrospective study to compare etanercept administration with conventional therapy (corticosteroids 1 mg/kg/day or methotrexate 15 mg orally once per week) in terms of the outcomes of patients with intestinal BD treated with. Etanercept was administered subcutaneously at a dose of 25 mg twice a week. After administering the drugs for 3 months, all the patients underwent double-balloon enteroscopy to confirm the healing rate of intestinal ulcers. There was an 89.47% healing rate of intestinal ulcers in the etanercept-treated group and a 51.42% healing rate in the conventional-treated group. Etanercept therapy was associated with a higher healing rate of intestinal ulcers than conventional therapy ($p < 0.05$). However, etanercept is the only anti-TNF- α agent that has not shown any efficacy in inflammatory bowel disease (IBD). Etanercept has also been implicated in the emergence of paradoxical IBD, meaning it can produce symptoms similar to those it is used to treat.⁵⁸ Dallochio *et al.*⁵⁹ reported eight cases of IBD following etanercept therapy for idiopathic juvenile arthritis. Braun *et al.*⁶⁰ analyzed the data from nine trials including seven

placebo-controlled trials and two open studies and found that 14 IBD cases (2.2 per 100 patient-years) occurred in patients with ankylosing spondylitis AS treated with etanercept, which was significantly different from infliximab therapy ($p = 0.01$). There is still no large prospective randomized clinical trial of etanercept use in patients with intestinal BD. It is still questionable whether etanercept is truly effective in patients with intestinal BD because intestinal BD has a similar clinical appearance to that of IBD.

4. Golimumab

Golimumab is created with genetically engineered mice immunized with human TNF, resulting in the expression of fully humanized antibodies.⁶¹ Golimumab is approved for the treatment of UC by the U.S. FDA in 2013. Only a few data are available on golimumab in patients with intestinal BD (Table 3). Vitale *et al.*⁵² retrospectively assessed the long-term efficacy and safety of golimumab in patients with intestinal BD. The BD Current Activity Form (BDCAF) was used to evaluate disease activity in this study. Of 17 patients, six patients were administered golimumab for gastrointestinal involvement. All patients in the study underwent golimumab therapy for poorly controlled disease despite previously undergoing conventional treatment and after the failure of at least one or more biologic agents. BD manifestations disappeared after a mean of 5 weeks, and 12 patients still continued the treatment after a mean of 18 months.

Table 3. Etanercept, Golimumab, and Certolizumab Pegol Uses in Patients with Intestinal Behçet's Disease

Author (year)	Country	Method	Participants	Intervention	Outcomes
Ma <i>et al.</i> (2014) ⁵¹	China	Retrospective, 1 center	19 Patients treated with etanercept 19 Patients treated with conventional therapy (corticosteroid or methotrexate)	Etanercept 25 mg twice a wk with prednisolone 1 mg/kg/day and methotrexate 15 mg/wk	Primary outcome · Complete disappearance of BD-related clinical signs within 12 wk from the start of adalimumab therapy: 81/100 patients Secondary outcome · Number of patients remaining on adalimumab therapy at 24-mo follow-up visit: 67/100 patients · Sustained clinical benefit at the time of data enrollment: 12/17 (70.6%) · BD-related manifestation at 3 mo: 16/17 (94.1%)
Vitale <i>et al.</i> (2017) ⁵²	Italy	Retrospective, 3 centers	17 (6 Patients; GI tract involvement) patients treated with conventional therapy and at least another biological agent	Golimumab 50 mg every 30 day	BD Current Activity Form score: decreased significantly ($p = 0.002$)
Lopalco <i>et al.</i> (2017) ⁵³	Italy	Retrospective, 1 center	13 (5 Patients; GI tract involvement) patients treated with conventional therapy and at least another biological agent	Certolizumab 400 mg (0, 2, and 4 wk), 200 mg every 2 wk	Improvement of clinical manifestations: 53.84%

BD, Behçet's disease; GI, gastrointestinal.

Notably, combination therapy of golimumab with DMARDs resulted in better outcomes as compared to golimumab monotherapy. Golimumab could be an effective therapy agent for patients with intestinal BD. However, further studies on wider populations need to be conducted to draw a conclusion about the effectiveness of golimumab for intestinal involvement of BD.

5. Certolizumab pegol

Certolizumab pegol is the only PEGylated anti-TNF- α biologic approved for the treatment of rheumatoid arthritis and CD. It is a humanized antigen-binding fragment of a monoclonal antibody which is conjugated to polyethylene glycol. Data about therapy with certolizumab pegol for BD are scarce (Table 3). Lopez et al.⁵³ reported treatment with certolizumab pegol for 13 patients with BD who were refractory to standardized therapies and previous biologic agents. The 13 patients had involvement of different organs, and five patients started certolizumab for intestinal involvement of BD. Certolizumab was treated at an induction dose of 400 mg at 0, 2, and 4 weeks, followed by 200 mg every 2 weeks. Of the 13 patients, seven patients (53.84%) experienced a satisfactory response at the last follow-up visit (mean, 9.28 months). The mean BDCAF score was decreased, but this did not reach statistical significance ($p=0.51$). Further studies enrolling a larger number of patients are needed to validate the effectiveness of certolizumab pegol for patients with intestinal BD.

ANTI-TNF AGENTS IN INTESTINAL BEHÇET'S DISEASE: SAFETY ISSUES

Current knowledge about the complications of anti-TNF- α agents is mostly based on controlled clinical trials in treating IBD or rheumatoid diseases. Data derived from studies of their use for intestinal BD are scarce. Table 4 shows the complications associated with anti-TNF- α agents in recent studies including more than 10 patients with intestinal BD. There were no malignancies in these studies. There were some serious infections and infusion reactions, and tuberculosis was observed in one Japanese patient.⁴¹ Lee et al.²⁵ reported one gastrointestinal sepsis requiring surgical resection after 16 weeks of infliximab therapy. Zou et al.³⁰ reported one case of severe pneumonia requiring hospitalization in a patient treated with infliximab. Inoue et al.⁴³ reported three serious infections, including intestinal abscess, appendicitis, and perforated appendicitis in patients treated with adalimumab. Theoretically, inhibiting TNF could reduce the immunity of host system to increase a proper defense against infectious organisms. Although the benefits of TNF inhibitor therapy are amendable, concerns have been raised about the risk of infectious and malignant complications.⁶²

Although the risk of lymphoma is an important concern associated with therapy for IBD, there are limited data on the risk of non-Hodgkin's lymphoma (NHL) among anti-TNF- α agent users in IBD.⁶³ The standardized incidence ratio (SIR) of NHL was 3.23 (95% confidence interval [CI], 1.5 to 6.9) in a previous meta-analysis that involved a majority of patients using

Table 4. Adverse Events of Biologics in Patients with Intestinal Behçet's Disease

Author (year)	Country	Method	Intervention	Patients with malignancies	Patients with severe infection	Patients with infusion reaction	Adverse event of interest
Iwata et al. (2011) ²⁴	Japan	Retrospective, 1 center	Infliximab	0/10	0/10	0/15	-
Lee et al. (2013) ²⁵	Korea	Retrospective, 8 centers	Infliximab	0/28	1/28	6/28	-
Kinoshita et al. (2013) ²⁶	Japan	Retrospective, 1 center	Infliximab	0/15	0/15	1/15	-
Hibi et al. (2016) ²⁹	Japan	Prospective, open-label, single-arm phase 3 study, 21 centers	Infliximab	0/11	0/11	1/11	-
Zou et al. (2017) ³⁰	China	Retrospective, 1 center	Infliximab	0/27	1/27	0/27	-
Tanida et al. (2015) ⁴¹	Japan	Prospective, open-label, uncontrolled, phase 3 study, 12 centers	Adalimumab	0/20	1/20	2/20	1 Tuberculosis
Inoue et al. (2017) ⁴³	Japan	Prospective, open-label, uncontrolled, phase 3 study, 12 centers	Adalimumab	0/20	3/20	3/20	-
Vitale et al. (2017) ⁴⁴	Italy	Retrospective, multicenter	Adalimumab	0/13	0/13	1/13	-
Ma et al. (2014) ⁵¹	China	Retrospective, 1 center	Golimumab	0/19	0/19	0/19	-

infliximab with concomitant immunomodulators.⁶⁴ In addition to NHL, the persistent use of anti-TNF- α beyond 1 year was associated with an even greater risk of melanoma skin cancer among patients with CD (adjusted odds ratio [OR], 3.23; 95% CI, 1.28 to 3.33).⁶⁵ The greatest risk was evident in recent users of combined thiopurines and anti-TNF- α agents (adjusted OR, 5.85; 95% CI, 3.2 to 10.8). According to the European Crohn's and Colitis Organisation guidelines, prolonged combination therapy of thiopurines and anti-TNF- α beyond 2 years in young men should be avoided to limit the risk of hepatosplenic T cell lymphoma.⁶⁶ Intestinal BD is the most common along the ancient "Silk Road" route in the Far East and in the Mediterranean basin, and the prevalence of lymphoma and skin cancer is very low in this area.⁶⁷ Current guidelines for malignancy in Asian patients with IBD focus on the surveillance of colorectal cancer.⁴⁰ Patients with IBD are at increased risk for overall, intestinal, and hematological cancer.⁶⁸ Likewise, intestinal BD is frequently associated with bone marrow disorders such as MDS and aplastic anemia.⁶⁹ Therefore, close monitoring and identification of individual risk factors for malignancy is an important principle in biologic therapy for intestinal BD.

In terms of infection, analyses of infliximab safety data indicated no increase in infections during infliximab therapy in patients with CD or UC.⁷⁰ The proportion of patients who experienced a serious infection was similar between infliximab group and the placebo group in five pivotal phase 3 IBD trials (ACCENT I, ACCENT II, SONIC, ACT 1, and ACT 2). A larger proportion of patients with UC, not CD, treated with infliximab with immunomodulator had at least one infection compared to the no immunomodulator treatment group. Especially, tuberculosis and viral hepatitis are endemic in East Asian countries. In a multicenter, observational Korean study, the adjusted SIR of tuberculosis was 41.7 (95% CI, 25.3 to 58.0), compared with that of the matched general population.⁷¹ Present or past hepatitis B infection was found in 40.62% of patients with IBD and in 27.58% of the patients without IBD in a Chinese study ($p < 0.001$).⁷² Previous examination and vaccination before the use of anti-TNF- α and continuous evaluation for tuberculosis and hepatitis in patients with intestinal BD are mandatory.

SUMMARY AND FUTURE DIRECTION

Intestinal BD is a chronic, relapsing inflammatory disease that is associated with a severe disease course, such as perforation and bleeding. Many patients fail to respond to conventional treatments with corticosteroids and immunomodulatory agents, including thiopurines. Although the clinical remission rate at 1 month to corticosteroid therapy in intestinal BD was high, the response showed a decreasing at 1 year (46.3% vs 35.2%).¹⁰ Moreover, the cumulative relapse rates at 1, 2, 3, and 5 years were 5.8%, 28.7%, 43.7%, and 51.7% in patients with intestinal BD who received thiopurine therapy, respectively.⁷³

Currently, anti-TNF- α agent therapy has demonstrated significantly favorable outcomes in patients with intestinal BD who are refractory to or intolerant to conventional therapy. Therefore, anti-TNF use will be gaining more popularity in terms of intestinal BD management in the near future. Its indications will also be more broadened. However, additional studies of larger cohorts of patients are needed to clarify the rationale underlying the outcomes observed in each of the previous small studies. Additionally, possible complications including infection, vaccination, and malignancy surveillance should be considered during biologic therapy for intestinal BD. It has not yet been determined if vedolizumab, a novel anti-integrin therapy for the treatment of IBD, could be a promising alternative therapeutic option for patients with intractable intestinal BD.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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