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Efficacy and Safety of Anti-Tumor Necrosis Factor-Alpha Agents for Patients with Intestinal Behcet's Disease: A Systematic Review and Meta-Analysis

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Purpose: Intestinal Behcet's disease (BD) is a systemic autoimmune disease for which treatment options are limited. As a prospective therapeutic strategy for intestinal BD, anti-tumor necrosis factor-alpha (anti-TNF-α) agents have received increasing attention. In this study, we conducted a systematic review and meta-analysis to evaluate the efficacy and safety of anti-TNF-α agents for patients with intestinal BD.

Materials and Methods: We searched PubMed, Embase, and Cochrane Library databases up to July 1, 2021 and articles that met the eligibility criteria were further assessed. Pooled rates were synthesized by a randomized effects model using Stata software.

Results: Eleven clinical trials covering 671 patients with intestinal BD were included. According to compositive data, the pooled rate for remission was 39% [95% confidence interval (CI) 26–52] in patients receiving anti-TNF-α agents. Intestinal symptoms were cured in 70% (95% CI 53–84) of the patients, and the rate for endoscopic healing was 65% (95% CI 52–78). Corticosteroid discontinuation was achieved in 43% (95% CI 28–58) of the patients, and the dose reduction of corticosteroid was 20.43 mg (95% CI 13.4–27.46). There were 239 adverse events and 80 serious adverse events during follow-up.

Conclusion: Our study indicated that anti-TNF-α agents may serve as an effective treatment with acceptable safety for patients with intestinal BD. However, more robust evidence from randomized controlled trials is urgently needed to assess the long-term efficacy and safety of anti-TNF-α agents for those patients.

Key Words: Anti-tumor necrosis factor-alpha, intestinal Behcet's disease, efficacy, safety, meta-analysis

INTRODUCTION

Behcet's disease (BD) is a chronic, multisystemic, and recurring disease characterized by relapsing oral and genital ulcers, ocular involvement, arthritis, skin lesions, and vascular, neurological, and intestinal disorders.[1] BD is more prevalent in the regions along the ancient Silk Road, which extends from the Mediterranean Region to eastern Asia. The estimated preva-

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lence of BD varies from 13.5 to 20 cases per 100000 in Japan, Korea, China, and Middle East, compared to low prevalence in the United States (from 0.12 to 0.33 cases per 100000)[2] and European countries.[3]

Intestinal BD refers to colonic ulcerative lesions documented by objective measures in patients with BD.[4] In previous reports, the incidence of intestinal involvement in BD patients has ranged from 3% to 26%,[5] being most frequent in eastern Asia but relatively rare in the Mediterranean area.[6,7] Abdominal pain is the most common symptom of intestinal BD,[8] which varies from mild abdominal discomfort to grievous abdominal pain. Intestinal lesions associated with BD might lead to severe complications of massive gastrointestinal bleeding or perforation,[9] which occur in 30% of intestinal BD patients and contribute mainly to the morbidity and mortality of BD.[10,11] It is critical to find effective measures to control inflammation and promote healing of these lesions.

The conventional use of treatments with 5-aminosalicylic acids, corticosteroid and immunomodulators continues to elicit a considerable number of refractory patients unable to achieve effective relief in clinical practice.[12] Surgery for these patients is usually required, although it is associated with high rates of postoperative recurrence,[13] with 5-year recurrence rates as high as 75%.[14] Additionally, systemic and local adverse effects of corticosteroids occur after long-time systemic administration, and intestinal BD patients with previous use of corticosteroids are prone to develop gastrointestinal rebleeding.[15] Hence, the discovery of new effective therapeutics is urgently needed.

The use of anti-tumor necrosis factor-alpha (anti-TNF-α) agents as treatment options for intestinal BD patients has been encouraged with accumulating evidence. Three monoclonal antibodies (infliximab, adalimumab, and golimumab), one soluble receptor (etanercept), and one antigen-binding fragment (certolizumab pegol) have been employed. Case reports or systematic reviews on the therapeutic effect of anti-TNF-α agents for patients with intestinal BD have been widely reported. Even more, anti-TNF-α agents have been regarded as the standard therapy for moderate-to-severe intestinal BD patients in Japan.[16] In this meta-analysis, published data on the efficacy and safety of anti-TNF-α agents in the management of intestinal BD patients were evaluated.

MATERIALS AND METHODS

The meta-analysis was carried out following the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P)[17] (Supplementary Table 1, only online).

Inclusion and exclusion criteria

We selected publications meeting the following conditions: 1) clinical studies regarded to intestinal BD patients; 2) anti-TNF-α agents used in treatment of patients; 3) included patients were adults; and 4) follow-up time of at least 24 weeks. The exclusion criteria included 1) demographic and baseline clinical information on patients or the outcomes were not described clearly; 2) data on anti-TNF-α for intestinal BD patients could not be extracted; and 3) publication was a conference abstract, case report, or a letter to editor and reviews.

Outcome measures

The efficacy of the anti-TNF-α agents was evaluated as the rate of patients achieving remission, cured intestinal symptoms, endoscopic healing, or cured non-intestinal BD symptoms and as the effect of corticosteroid sparing. The safety of the agents was assessed by the summative description of the number and severity of adverse events (AEs).

Search strategies

We searched the PubMed, Embase, and Cochrane Library databases from the inception dates to July 1, 2021. To ensure inclusion of all relevant studies, we applied medical subject headings (MeSH) and free words related to BD and anti-TNF-α agents. Also, the words "intestinal" or "bowel" or "intestine" or "entero" were crossed with to find related studies. The search was limited in Titles/Abstracts to filter out unrelated studies (Supplementary Table 2, only online).

Study selection and data extraction

Two investigators independently browsed the titles and abstracts of all searched items and retrieved the full text of all potentially relevant articles for further evaluation using the inclusion and exclusion criteria. The other two investigators independently extracted data from the included studies using collection forms. Disagreements between two investigators were resolved through discussion and, if necessary, through consultation with a third reviewer. We extracted data on the following: 1) demographic and baseline clinical information of the patients, 2) study design, 3) study location, 4) kind of anti-TNF-α agents, 5) number of patients achieving remission, 6) number of patients with intestinal symptom cure, 7) number of patients showing endoscopic healing, 8) patients acquiring corticosteroid free or reduction, 9) number of patients obtaining non-intestinal BD symptoms cure, and 10) AEs.

Quality evaluation

The quality of each study was evaluated using the Joanna Briggs Institute's critical appraisal tools for case series (Supplementary Table 3, only online). Ten questions in the Joanna Briggs Institute's checklist were answered with yes, no, unclear, or not applicable to assess the quality of these studies. Discrepancies were solved by further evaluations and discussions or consultation with professionals.

Data analysis

Dichotomous variables, including remission, intestinal symp-

tom cure, endoscopic healing, corticosteroid free, and non-intestinal BD symptoms cure, were reported as rates. Considering some high rates reported in the included studies, arcsine transformation was used to calculate pooled rates.[18] The pooled estimates of response rates and their binomial 95% confidence intervals (CI) were calculated using a random-effect model.[19] We also employed I^2 statistics to quantify heterogeneity between studies. Once significant heterogeneity was detected (I^2>50% or p<0.05), subgroup analyses were conducted to seek the sources of heterogeneity, divided on the base of different anti-TNF-α agents, final evaluation point, and study design. Sensitivity analysis was utilized to assess the impact of a single study on the pooled results and the stability of meta-analysis results by omitting each study in sequence. Continuous variables including corticosteroid reduction were assessed by pooled analysis with mean differences, which were also estimated by random-effect model. Due to the limited number of available studies, publication bias was assessed using the Egger test, and p≤0.05 indicated significant publication bias.[20] All statistical analyses were conducted using the STATA 16.0 software (StataCorp, College Station, TX, USA).

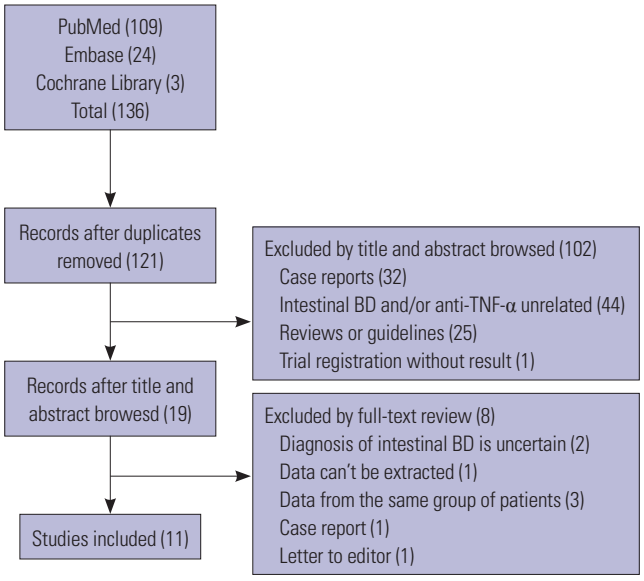

Fig. 1. Flow diagram for the selection process of included studies. BD, Behcet's disease; anti-TNF-α, anti-tumor necrosis factor-alpha.

RESULTS

Study selection

A total of 136 records was retrieved from the database search (PubMed: 109, Embase: 24, Cochrane Library: 3). Fig. 1 depicts the process of study selection. After duplicate removal, the titles and abstracts of 121 articles were browsed, and only 19 articles were eligible to be assessed by full text-review. Finally, 11 were included for analysis, and reasons for exclusion are shown in the diagram in Fig. 1.[6,12,21-29]

Characteristics and quality evaluation

Table 1 summarizes the characteristics and quality evaluation results of the included studies [quality evaluation details are shown in Supplementary Table 4 (only online)]. In total, 11 studies involving 671 patients were selected for analysis, and all studies were from eastern Asia. Six studies employed a prospective design, and the other five were retrospective. All included patients were definitely diagnosed with intestinal BD with endoscopic evidence of ulcers in the intestine.

Meta-analysis and publication bias

Remission

Clinical remission after anti-TNF-α therapy was achieved in 35 patients from six studies involving 89 patients in the last eval-

Table 1. Characteristics and Quality Evaluation of the Included Studies

Study	Location	Study type	Anti- TNF-α agents	Sample size	Male/ female	Age‡	Follow-up (week)	Multicenter	Quality evaluation*
Ma, et al.[26]	China	Retrospective	ETN	19	13/6	37±8.72	>104	N	7Y2U1N
Kinoshita, et al.[27]	Japan	Retrospective	IFX	15	7/8	45±16	104	N	10Y
Miyagawa, et al.[12]	Japan	Prospective	ADA/IFX/ETN/GLM†	49	12/37	41.3±14.1	52	N	8Y2U
Lee, et al.[6]	Korea	Retrospective	IFX	28	15/13	35 (9–62)	54	Y	8Y2U
Zou, et al.[21]	China	Prospective	IFX	27	12/15	37.52±12.8	104	N	10Y
Sugimura, et al.[25]	Japan	Retrospective	ADA/IFX	22	17/5	43 (15–72)	52	Y	9Y1U
Tanida, et al.[23]	Japan	Prospective	ADA	20	10/10	42.4±13.3	52	Y	10Y
Tanida, et al.[22]	Japan	Retrospective	ADA	8	4/4	46.6±18.7	52	N	8Y1U1N
Iwata, et al.[28]	Japan	Prospective	IFX	10	3/7	37.7±11.0	104	N	8Y2U
Hibi, et al.[29]	Japan	Prospective	IFX	11	5/6	35.0±13.4	54	Y	10Y
Suzuki, et al.[24]	Japan	Prospective	ADA	462	237/225	46.3±17.2	52–156	Y	9Y1N

anti-TNF-α, anti-tumor necrosis factor-alpha; ETN, etanercept; IFX, infliximab; ADA, adalimumab; GLM, golimumab; Y, yes; N, no; U, unclear.
*Study quality was evaluated by the Joanna Briggs Institute's critical appraisal tools for case series, †ADA=10, IFX=32, ETN=5, GLM=2, ‡Data are presented as mean±SD or median (range).

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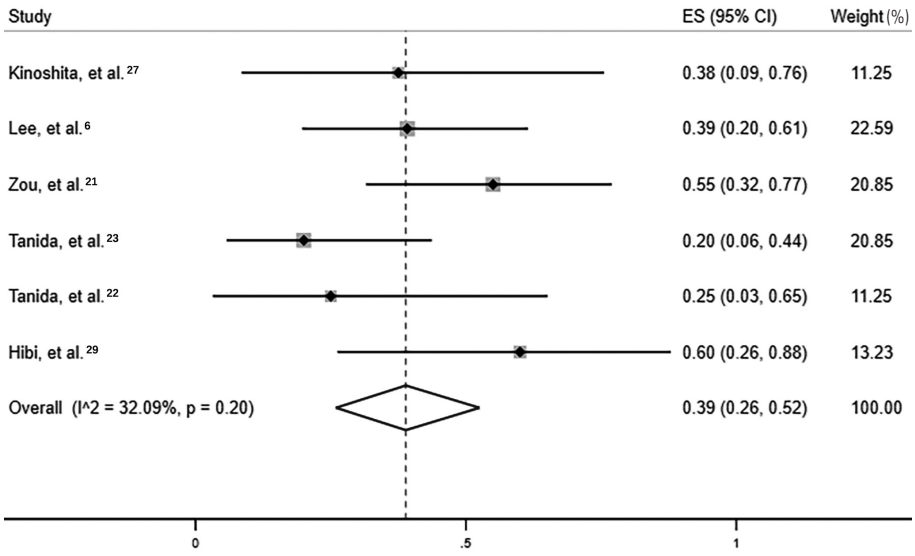

Fig. 2. Forest plot of the remission rate after anti-tumor necrosis factor-alpha treatment. ES, effect sizes; CI, confidence interval.

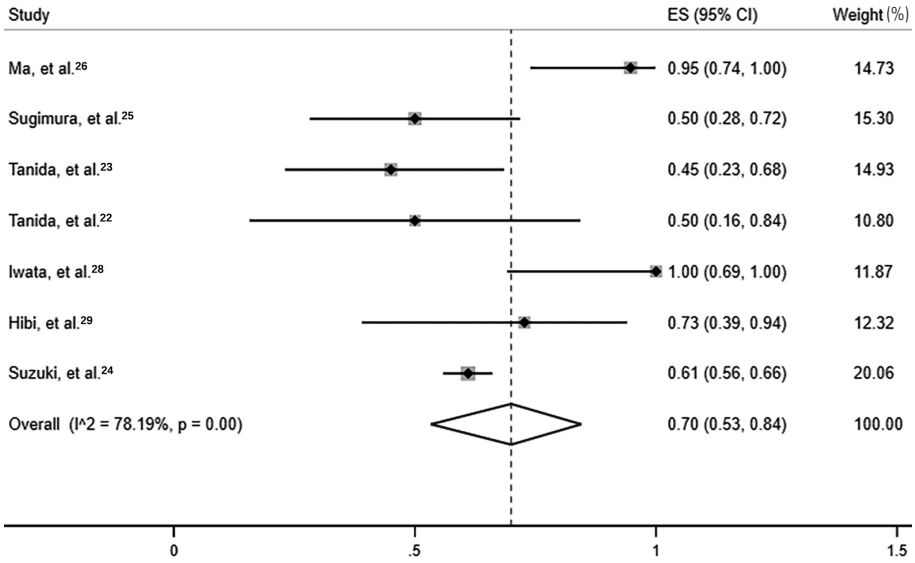

Fig. 3. Forest plot for the rate of intestinal symptom cure after anti-tumor necrosis factor-alpha treatment. ES, effect sizes; CI, confidence interval.

uation. As Fig. 2 showed, the pooled rate of remission was 39% (95% CI 26–52), and heterogeneity was recorded at 32.09% (p=0.20). There was no significant publication bias according to Egger test results (p=0.9636).

Intestinal symptom cure

Data on intestinal symptom cure (the complete disappearance of abdomen symptoms) were extracted from seven studies, including 457 patients, and 284 patients reached symptom remission. As indicated in Fig. 3, the pooled rate of intestinal symptom cure was 70% (95% CI 53–84), with heterogeneity at 78.19% (p<0.01). There was also no significant publication bias evidenced by the Egger test (p=0.5363).

Endoscopic healing

Nine studies involving 170 patients were evaluated for the complete healing of ulcers by endoscopy at the last follow-up evaluation. The number of patients acquiring endoscopic healing in each study was extracted. As Fig. 4 shows, the pooled proportion of endoscopic healing was 65% (95% CI 52–78). In this group of data, the statistical heterogeneity was 64.81% (p<0.01), suggesting moderate heterogeneity. There was no significant publication bias (p=0.5621).

Corticosteroid discontinuation and dose reduction

Five studies reported 84 of 223 patients achieving corticosteroid free status at the end of the follow-up period. The pooled

rate of corticosteroid discontinuation was 43% (95% CI 28–58) (Fig. 5A), and heterogeneity was at 41.62% (p=0.14), implying low heterogeneity. In addition, the reduction of corticosteroid was evaluated in three studies including 32 patients. A reduction in corticosteroid dose was detected by pooled analysis with a mean difference of 20.43 mg (95% CI 13.4–27.46), a significant difference (Fig. 5B). Statistical heterogeneity in the study results was insignificant with an I^2 of 0.00% (p=0.15).

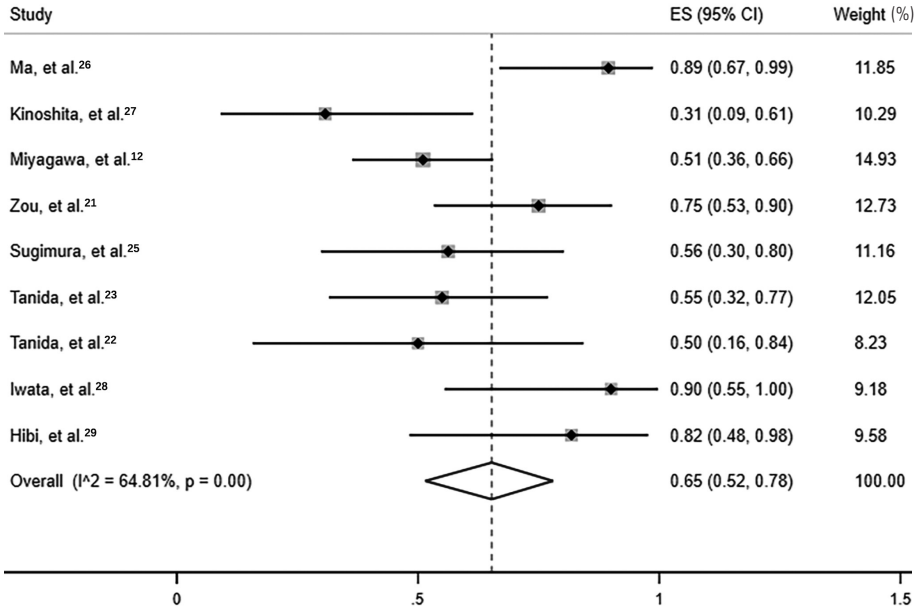

Fig. 4. Forest plot of the endoscopic healing rate after anti-tumor necrosis factor-alpha treatment. ES, effect sizes; CI, confidence interval.

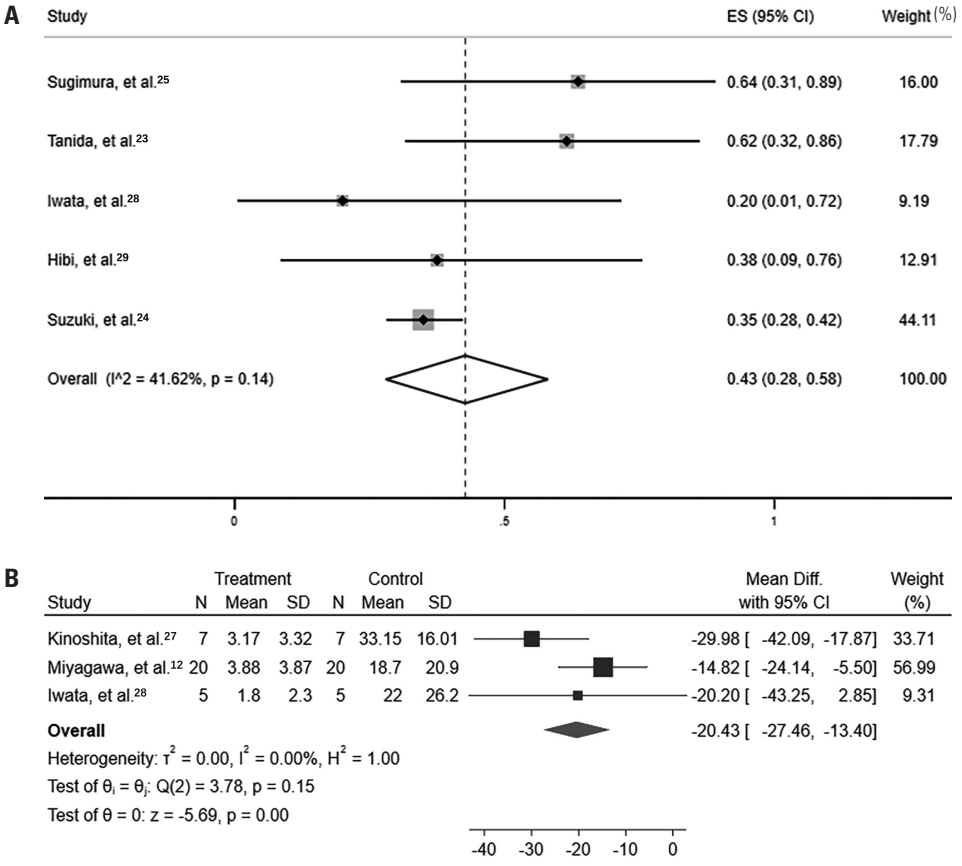

Fig. 5. Forest plot of corticosteroid-sparing effects. (A) Forest plot of the corticosteroid discontinuation rate after anti-TNF-α treatment. (B) Forest plot of the corticosteroid dose reduction after anti-TNF-α treatment. anti-TNF-α, anti-tumor necrosis factor-alpha treatment. ES, effect sizes; CI, confidence interval.

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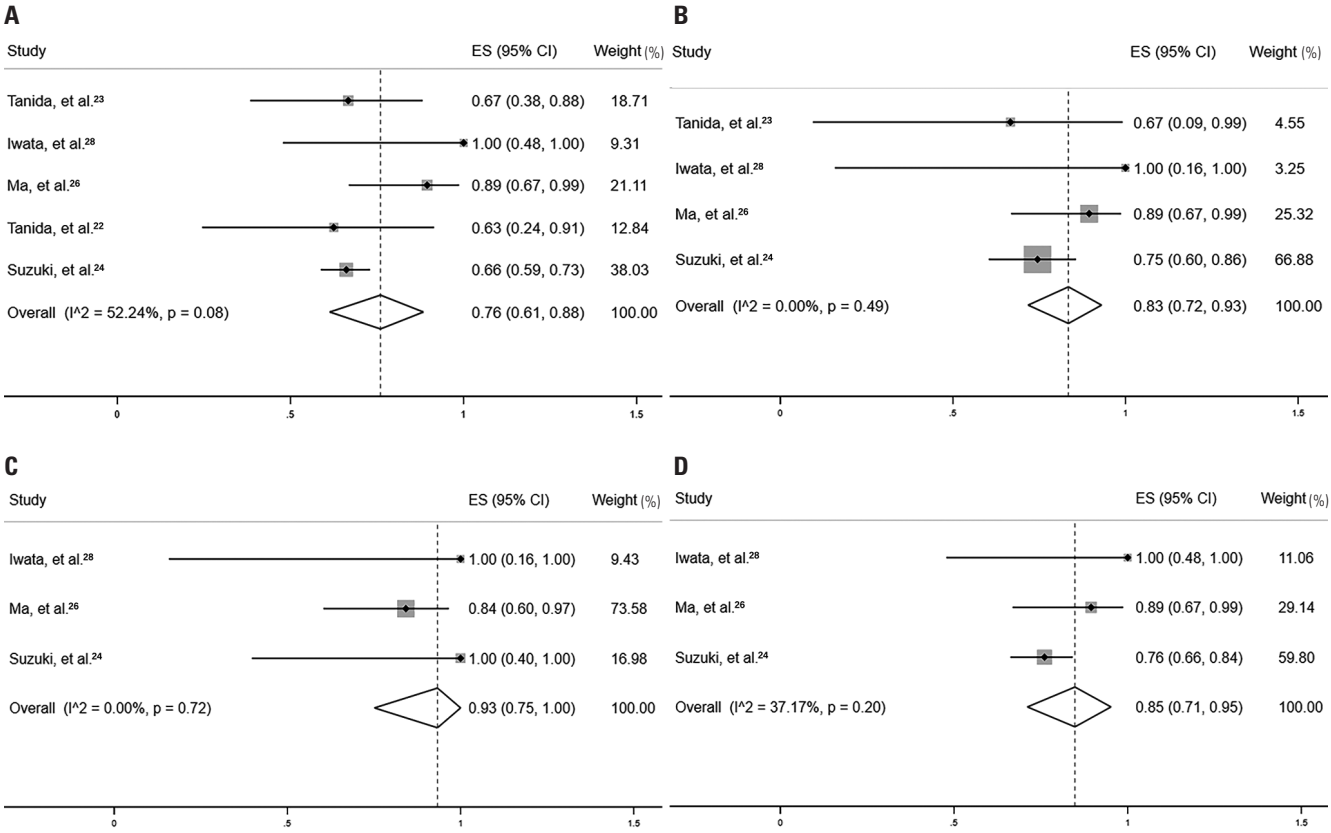

Fig. 6. Forest plot for the rate of non-intestinal BD symptom cure after anti-tumor necrosis factor-alpha treatment. (A) Oral aphthous ulcers. (B) Genital ulcers. (C) Ocular involvement. (D) Skin lesions. BD, Behcet's disease; ES, effect sizes; CI, confidence interval.

Publication bias on corticosteroid discontinuation and dose reduction was both insignificant (p=0.5025; p=0.8847 respectively).

Non-intestinal BD symptoms

Information on common symptoms of BD, including oral aphthous ulcers, genital ulcers, ocular involvements, and skin lesions, were collected and analyzed.[2] In five studies, 158 of 230 patients with oral aphthous ulcers were cured after anti-TNF-α therapy, with a pooled rate of 76% (95% CI 61–88) (Fig. 6A). Four studies reported that 59 of 75 patients were cured of genital ulcers at a pooled rate of 83% (95% CI 72–93) (Fig. 6B). Twenty-two of 25 patients with ocular involvements achieved cure in three studies, and the pooled proportion was 93% (95% CI 75–100) (Fig. 6C). Skin lesions were cured in 95 of 120 patients as reported by three studies, and the pooled rate was 85% (95% CI 71–95) (Fig. 6D). The statistical heterogeneities of the four symptoms were not high with I^2 values of 52.24%, 0.00%, 0.00%, and 37.17%, respectively. There was no significant publication bias as evidenced by Egger test results (p=0.4513, 0.7886, 0.7312, and 0.4716, respectively).

Subgroup analysis

Results of subgroup analysis of intestinal symptom cure and endoscopic healing are shown in Table 2. Heterogeneity was high in the meta-analysis of intestinal symptom cure (I^2=78.19%, p<0.01). However, subgroup analysis, the adalimumab treatment group (I^2=13.29%, p=0.32), group with a final evaluation point less than 52 weeks (I^2=0.00%, p=0.95), and multicenter group (I^2=13.89%, p=0.32) heterogeneity was not found. Likewise, there was moderate heterogeneity when endoscopic healing was analyzed (I^2=64.81%, p<0.01). However, heterogeneity was not detected in further subgroup analysis in the adalimumab treatment group (I^2= 0.00%, p=0.81), final evaluation point less than 52 weeks group (I^2=41.79%, p=0.13), and multicenter group (I^2=16.21%, p=0.30). The subgroup analysis indicated that the kind of anti-TNF-α agent, final evaluation point, and study design may account for most of the heterogeneity.

Sensitivity analysis

Sensitivity analysis was performed for intestinal symptom cure and endoscopic healing. As shown in Table 3, meta-analysis of these two results were both robust. Notably, for intestinal symptom cure, when we omitted the data of Ma, et al.,[26] the results showed a fluctuation in pooled effect size (0.64) and heterogeneity (I^2=67.77%, p=0.01). Similarly, when we omitted the data of Iwata, et al.,[28] the results also displayed similar fluctuations. Accordingly, these two studies were regarded as outliers and to have likely contributed to the heterogeneity. Interestingly, after excluding these two studies, the heterogeneity was significantly decreased (I^2=0.00%, p=0.43), with a pooled effect

Table 2. Subgroup Analysis

	Number of studies	Pooled effect sizes	95% CI	Heterogeneity	
				I^2 (%)	*p* value
Intestinal symptom cure	7	0.70	0.53–0.84	78.19	<0.01
Anti-TNF-α agents					
IFX	2	0.87	0.51–1.00	74.90	0.05
ADA	3	0.59	0.50–0.67	13.29	0.32
Last evaluation time (weeks)					
≤52	3	0.48	0.34–0.62	0.00	0.95
>52	4	0.84	0.58–0.99	86.60	<0.01
Types of studies					
Retrospective	3	0.69	0.31–0.97	84.05	<0.01
Prospective	4	0.70	0.48–0.89	78.37	<0.01
Multicenter studies					
Y	4	0.59	0.52–0.67	13.89	0.32
N	3	0.88	0.56–1.00	76.54	0.01
Previously treatment					
Refractory to traditional therapy	5	0.77	0.49–0.97	80.88	<0.01
Endoscopic healing	9	0.65	0.52–0.78	64.81	<0.01
Anti-TNF-α agents					
IFX	4	0.70	0.45–0.91	71.82	0.01
ADA	2	0.53	0.36–0.71	0.00	0.81
Last evaluation time (weeks)					
≤52	6	0.62	0.50–0.74	41.79	0.13
>52	3	0.70	0.31–0.98	83.96	<0.01
Types of studies					
Retrospective	4	0.59	0.30–0.85	76.89	<0.01
Prospective	5	0.68	0.53–0.82	58.81	0.05
Multicenter studies					
Y	3	0.62	0.46–0.78	16.21	0.30
N	6	0.66	0.46–0.84	75.37	<0.01
Countries of studies conducted					
Japan	7	0.58	0.45–0.72	49.91	0.06
China	2	0.81	0.66–0.92	26.60	0.24
Previous treatment					
Refractory to traditional therapy	6	0.68	0.47–0.87	71.33	<0.01

CI, confidence interval; IFX, infliximab; ADA, adalimumab; Y, yes; N, no.

size of 0.60. In the analysis of endoscopic healing, heterogeneity decreased significantly (I^2=53.20%, p=0.04), with a pooled effect size of 0.61 when we omitted the data from Ma, et al.,[26] indicating this study might contribute to the heterogeneity in endoscopic healing results.

Safety evaluation

The safety of anti-TNF-α agents was evaluated according to the number and severity of AEs reported in the included studies. We systematically reviewed 10 studies (AEs were not mentioned in the study of Sugimura, et al.[25]) consisting of 649 patients. There were 239 AEs in total; 80 were serious adverse events (SAEs). Forty eight patients dropped out of studies because of AEs. 201 AEs and 49 SAEs reported with the specific manifestations are shown in Table 4. Among them, infections were the most reported AEs (86/239) and SAEs (19/80). Three patients died during the follow-up period due to severe infection in 2 patients and malignancy in 1 patient. Among these, one death caused by severe infection was ruled out as the result of adalimumab treatment, and the causal relationship between adalimumab use and the other two deaths was indeterminable.

DISCUSSION

In this meta-analysis, we investigated the efficacy of anti-TNF-α agents for intestinal BD patients and summarized results on their safety. Overall, our review indicates that anti-TNF-α agents

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Table 3. Sensitivity Analysis

Study omitted	Pooled effect sizes	95% CI	Heterogeneity	
			I^2 (%)	*p* value
Intestinal symptom cure				
Ma, et al.[26]	0.64	0.48–0.78	67.77	0.01
Sugimura, et al.[25]	0.74	0.54–0.90	80.74	<0.01
Tanida, et al.[23]	0.74	0.56–0.90	79.89	<0.01
Tanida, et al.[22]	0.72	0.54–0.87	81.44	<0.01
Iwata, et al.[28]	0.64	0.49–0.78	69.84	0.01
Hibi, et al.[29]	0.70	0.51–0.86	81.58	<0.01
Suzuki, et al.[24]	0.72	0.48–0.92	80.33	<0.01
Combined	0.70	0.53–0.84	78.19	<0.01
Endoscopic healing				
Ma, et al.[26]	0.61	0.48–0.73	53.20	0.04
Kinoshita, et al.[27]	0.69	0.56–0.81	58.99	0.02
Miyagawa, et al.[12]	0.68	0.52–0.82	62.93	0.01
Zou, et al.[21]	0.64	0.48–0.78	66.71	<0.01
Sugimura, et al.[25]	0.66	0.51–0.80	68.74	<0.01
Tanida, et al.[23]	0.67	0.51–0.81	68.38	<0.01
Tanida, et al.[22]	0.67	0.52–0.80	68.40	<0.01
Iwata, et al.[28]	0.62	0.48–0.76	63.41	0.01
Hibi, et al.[29]	0.63	0.49–0.77	66.74	<0.01
Combined	0.65	0.52–0.78	64.81	<0.01

CI, confidence interval.

Table 4. Information on AEs Reported in the Included Studies

Reported adverse reaction	AEs	SAEs
Infections	86	19
Investigations	22	5
Gastrointestinal disorders	20	10
General disorders and administration site conditions	19	6
Infusion reaction	15	0
Tuberculosis	4	1
Light headaches	4	0
Hepatic relevant	4	0
Non-cutaneous vasculitis	3	0
Bronchitis	3	0
Interstitial pneumonia	2	1
Allergic reaction	2	0
Cystitis	2	0
Viral enteritis	2	0
Severe pneumonia	1	1
Intestinal stricture related	1	1
Malignancy	1	1
Autoimmune disease	1	1
Pancytopenia	1	1
Worsening of the underlying disease	1	1
Cataract	1	1
One case of AE: tonsillitis, sinusitis, paronychia, urticaria, abscess formation, herpes zoster		

AEs, adverse events; SAEs, serious adverse event.

have high efficacy for intestinal BD with acceptable safety.

However, it is worth noting that not all included studies used identical diagnostic criteria. In these studies, intestinal BD was diagnosed by widely accepted criteria, such as Japanese BD criteria, International Study Group, or Mason-Barnes criteria, etc. Comparing sensitivities and specificities from multiple diagnostic tests, one study showed that the International, Japanese, and Mason-Barnes criteria were the most accurate, compared with others.[30] It seems highly likely that different diagnostic criteria adopted may not be prone to produce significant bias.

In this study, we proposed that the pooled rate for remission of intestinal BD patients after anti-TNF-α therapy was 39%. It is noteworthy that definitions for intestinal BD remission were not unified in the selected studies. Two studies (Lee, et al.[6] and Zou, et al.[21]) defined remission as a disease activity index of intestinal BD (DAIBD) score of <20. Two studies from Tanida, et al.[22,23] defined remission as a global gastrointestinal symptom score and endoscopic score of 0. Kinoshita, et al.[27] defined remission as complete disappearance of gastrointestinal symptoms accompanied by normalized serum C-reactive protein. Hibi, et al.[29] defined complete responders as those whose clinical symptoms disappeared with healed ulcers. To sum up, these definitions all underscored the relief of systemic inflammation and overall remission. Therefore, our results on remission had low heterogeneity. Ozguler, et al.[31] proposed that 34/64 (54%) patients with gastrointestinal involvement achieved clinical remission after infliximab therapy by reviewing five studies. Among these, three studies were included in our analysis. Research from Naganuma, et al.[32] was excluded due to being a case report, and the study of Hatemi, et al.[33] was abandoned due to inability to extract data because of mixing the therapy with thalidomide.

In this review, we presented a pooled rate of intestinal symptom cure of 70% and that of endoscopic healing of 65%. Watanabe, et al.[34] reported that the rates for complete disappearance of abdomen symptoms and ulcers were 20.0%–54.5% (at 24–30 weeks) and 20.0%–60.0% (at 52 weeks), respectively. This discrepancy may be attributable to the fact that only two articles were referenced in their study, while more were included in ours. In our analysis, with the intervention of anti-TNF-α agents, the pooled proportion of intestinal BD patients achieving corticosteroid discontinuation was 43%, but in a review of systematic BD patients, 57% of patients acquired corticosteroids free status.[35] The pooled reduction in dose of corticosteroid was 20.43 mg after anti-TNF-α agent intervention in our study. Even if the results are encouraging, they merely reflect compositive data from limited studies, and more empirical evidence is needed to avoid selection bias.

Interestingly, 111 patients from seven studies were refractory to conventional therapies (corticosteroids and/or immunomodulators).[6,22,23,26-29] For these patients, a pooled analysis of remission rate with anti-TNF-α agents was conducted. Five studies

reported related information, and the pooled remission rate in patients refractory to conventional therapies was 34% (95% CI 22–48), with no significant heterogeneity detected (I^2=18.13%, p=0.30). Intestinal symptom cure and endoscopic healing were also investigated in subgroup analysis (Table 2), which suggested that anti-TNF-α agents are still effective for patients refractory to conventional therapies.

However, not all potential sources of heterogeneity can be traced sufficiently. Even though the studies from Lee, et al.[6] and Zou, et al.[21] included all patients with moderate-to-severe activity assessed by the DAIBD, we were unable to obtain a persuasive pooled effect size because their outcome measures were not identical. Furthermore, 25 patients with abdominal surgery history were reported in 5 studies.[6,12,21,25,27] Surgical operation may be associated with resistance to pharmacological therapies to some degree. However, extraction of the related data based on the current literatures was not feasible. Therefore, more high-quality studies are needed to evaluate the efficacy of anti-TNF-α agents for patients with different disease activity and to compare efficacy between patients with and without previous surgical history.

In view of the results of our sensitivity analysis, we deemed that the work from Ma, et al.[6] and/or Iwata, et al.[28] might have contributed to the heterogeneity in the results on intestinal symptom cure and endoscopic healing. Other than 5 of 49 patients using etanercept in the study of Miyagawa, et al.,[12] the work from Ma, et al.[26] was the only included study in which all patients were treated with etanercept monotherapy. Etanercept is a human TNF receptor p75 Fc fusion protein different from monoclonal antibodies used in other included studies, such as infliximab, adalimumab, and golimumab. Although a randomized controlled trial reported significant effectiveness for etanercept in systematic BD patients,[36] as the only ineffective anti-TNF-α agent ever tried for the treatment of inflammatory bowel disease, the efficacy of etanercept for intestinal BD patients is still questionable.[37] In our included studies, only Iwata, et al. reported a combination of infliximab and methotrexate with a small sample size of 10 patients. Therefore, this was likely a source of bias.

Particular attention should be paid to the safety of anti-TNF-α agents for intestinal BD patients. In this review, most AEs were mild to moderate, including infections, gastrointestinal disorders, administration site conditions, and infusion reactions. It is worth noting that 80 (12%) patients experienced severe AEs. In addition, 4 patients developed tuberculosis after anti-TNF-α treatment, two of whom had tested positive for tuberculosis at baseline screening. One patient who was treated for pre-existing chronic myelomonocytic leukemia experienced relapse thereof during the follow-up period.[24] Meanwhile, the safety of anti-TNF-α therapy in ulcerative colitis has been evaluated in 2088 patients, and a frequency of serious side effects of 16.9% was reported.[38] Despite a lower frequency of SAEs was indicated in our study, further research is needed to explore the feasibility of anti-TNF-α agents for treatment of intestinal BD.

There were several limitations of this study that should be mentioned. First, the sample size of the study was small. Second, the lack of placebo controls and RCTs should be noted, which may weaken the strength of the data. Additionally, although treatment history and concomitant therapeutic agents might influence the efficacy of anti-TNF-α agents, we could not adequately and easily track this information in the included articles. Finally, all 11 included studies were performed in eastern Asia, and thus, whether the conclusion of this analysis could be generalized to all regions of the world is uncertain.

In conclusion, our systematic review and meta-analysis of 11 studies suggested that anti-TNF-α agents offers satisfactory therapeutic efficacy for patients with intestinal BD. Effective measures should be taken to prevent or control common AEs, such as infections, gastrointestinal disorders and infusion reactions. High level evidence based on RCTs and clinical trials of larger sample size are required to further evaluate the efficacy and safety of anti-TNF-α agents for intestinal BD patients.

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AUTHOR CONTRIBUTIONS

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REFERENCES

1. Cheon JH, Kim WH. An update on the diagnosis, treatment, and prognosis of intestinal Behçet's disease. Curr Opin Rheumatol 2015;27:24-31.
2. Sakane T, Takeno M, Suzuki N, Inaba G. Behçet's disease. N Engl J Med 1999;341:1284-91.
3. Cho SB, Cho S, Bang D. New insights in the clinical understanding of Behçet's disease. Yonsei Med J 2012;53:35-42.
4. Lee HJ, Cheon JH. Optimal diagnosis and disease activity monitor-

https://doi.org/10.3349/ymj.2022.63.2.148

ing of intestinal Behçet's disease. Intest Res 2017;15:311-7.
5. Hassard PV, Binder SW, Nelson V, Vasiliauskas EA. Anti-tumor necrosis factor monoclonal antibody therapy for gastrointestinal Behçet's disease: a case report. Gastroenterology 2001;120:995-9.
6. Lee JH, Cheon JH, Jeon SW, Ye BD, Yang SK, Kim YH, et al. Efficacy of infliximab in intestinal Behçet's disease: a Korean multicenter retrospective study. Inflamm Bowel Dis 2013;19:1833-8.
7. Yazici Y, Yurdakul S, Yazici H. Behçet's syndrome. Curr Rheumatol Rep 2010;12:429-35.
8. Lee CR, Kim WH, Cho YS, Kim MH, Kim JH, Park IS, et al. Colonoscopic findings in intestinal Behçet's disease. Inflamm Bowel Dis 2001;7:243-9.
9. Hisamatsu T, Naganuma M, Matsuoka K, Kanai T. Diagnosis and management of intestinal Behçet's disease. Clin J Gastroenterol 2014;7:205-12.
10. Hatemi I, Esatoglu SN, Hatemi G, Erzin Y, Yazici H, Celik AF. Characteristics, treatment, and long-term outcome of gastrointestinal involvement in Behcet's syndrome: a strobe-compliant observational study from a dedicated multidisciplinary center. Medicine (Baltimore) 2016;95:e3348.
11. Park YE, Cheon JH. Updated treatment strategies for intestinal Behçet's disease. Korean J Intern Med 2018;33:1-19.
12. Miyagawa I, Nakano K, Iwata S, Nakayamada S, Saito K, Hanami K, et al. Comparative study of corticosteroid monotherapy, and TNF inhibitors with or without corticosteroid in patients with refractory entero-Behcet's disease. Arthritis Res Ther 2019;21:151.
13. Jung YS, Yoon JY, Lee JH, Jeon SM, Hong SP, Kim TI, et al. Prognostic factors and long-term clinical outcomes for surgical patients with intestinal Behcet's disease. Inflamm Bowel Dis 2011;17:1594-602.
14. Park JJ, Kim WH, Cheon JH. Outcome predictors for intestinal Behçet's disease. Yonsei Med J 2013;54:1084-90.
15. Park J, Cheon JH, Park YE, Lee YJ, Lee HJ, Park SJ, et al. Risk factors and outcomes of acute lower gastrointestinal bleeding in intestinal Behçet's disease. Int J Colorectal Dis 2017;32:745-51.
16. 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 Behçet's disease: indication of anti-TNFα monoclonal antibodies. J Gastroenterol 2014;49:156-62.
17. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;350:g7647.
18. Freeman MF, Tukey JW. Transformations related to the angular and the square root. Ann Math Stat 1950;21:607-11.
19. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.
20. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.
21. Zou J, Ji DN, Cai JF, Guan JL, Bao ZJ. Long-term outcomes and predictors of sustained response in patients with intestinal Behcet's disease treated with infliximab. Dig Dis Sci 2017;62:441-7.
22. Tanida S, Mizoshita T, Nishie H, Ozeki K, Katano T, Shimura T, et al. Long-term efficacy of adalimumab in patients with intestinal Behcet's disease: eight consecutive cases. J Clin Med Res 2016;8:334-7.
23. Tanida S, Inoue N, Kobayashi K, Naganuma M, Hirai F, Iizuka B, et al. Adalimumab for the treatment of Japanese patients with intestinal Behçet's disease. Clin Gastroenterol Hepatol 2015;13:940-8.e3.
24. Suzuki Y, Hagiwara T, Kobayashi M, Morita K, Shimamoto T, Hibi T. Long-term safety and effectiveness of adalimumab in 462 patients with intestinal Behçet's disease: results from a large real-world observational study. Intest Res 2021;19:301-12.
25. Sugimura N, Mizoshita T, Sugiyama T, Togawa S, Miyaki T, Suzuki T, et al. Real-world efficacy of adalimumab and infliximab for refractory intestinal Behçet's disease. Dig Liver Dis 2019;51:967-71.
26. Ma D, Zhang CJ, Wang RP, Wang L, Yang H. Etanercept in the treatment of intestinal Behcet's disease. Cell Biochem Biophys 2014;69:735-9.
27. Kinoshita H, Kunisaki R, Yamamoto H, Matsuda R, Sasaki T, Kimura H, et al. Efficacy of infliximab in patients with intestinal Behçet's disease refractory to conventional medication. Intern Med 2013;52:1855-62.
28. Iwata S, Saito K, Yamaoka K, Tsujimura S, Nawata M, Hanami K, et al. Efficacy of combination therapy of anti-TNF-α antibody infliximab and methotrexate in refractory entero-Behçet's disease. Mod Rheumatol 2011;21:184-91.
29. 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 (Baltimore) 2016;95:e3863.
30. Ferraz MB, Walter SD, Heymann R, Atra E. Sensitivity and specificity of different diagnostic criteria for Behçet's disease according to the latent class approach. Br J Rheumatol 1995;34:932-5.
31. Ozguler Y, Leccese P, Christensen R, Esatoglu SN, Bang D, Bodaghi B, et al. Management of major organ involvement of Behçet's syndrome: a systematic review for update of the EULAR recommendations. Rheumatology (Oxford) 2018;57:2200-12.
32. 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 Behçet's disease. Inflamm Bowel Dis 2008;14:1259-64.
33. Hatemi I, Hatemi G, Pamuk ON, Erzin Y, Celik AF. TNF-alpha antagonists and thalidomide for the management of gastrointestinal Behçet's syndrome refractory to the conventional treatment modalities: a case series and review of the literature. Clin Exp Rheumatol 2015;33:S129-37.
34. Watanabe K, Tanida S, Inoue N, Kunisaki R, Kobayashi K, Nagahori M, et al. Evidence-based diagnosis and clinical practice guidelines for intestinal Behçet's disease 2020 edited by Intractable Diseases, the Health and Labour Sciences Research Grants. J Gastroenterol 2020;55:679-700.
35. Arida A, Fragiadaki K, Giavri E, Sfikakis PP. Anti-TNF agents for Behçet's disease: analysis of published data on 369 patients. Semin Arthritis Rheum 2011;41:61-70.
36. Melikoglu M, Fresko I, Mat C, Ozyazgan Y, Gogus F, Yurdakul S, et al. Short-term trial of etanercept in Behçet's disease: a double blind, placebo controlled study. J Rheumatol 2005;32:98-105.
37. Park Y, Cheon JH. Update on the treatment of Behcet's disease of the small bowel with biologic agents. Curr Gastroenterol Rep 2020;22:24.
38. Lv R, Qiao W, Wu Z, Wang Y, Dai S, Liu Q, et al. Tumor necrosis factor alpha blocking agents as treatment for ulcerative colitis intolerant or refractory to conventional medical therapy: a meta-analysis. PLoS One 2014;9:e86692.