Clinical Trial/Experimental Study

Medicine®

OPEN

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

Toshifumi Hibi (MD, PhD)[a,*], Shunsei Hirohata (MD, PhD)[b], Hirotoshi Kikuchi (MD, PhD)[c], Ukihide Tateishi (MD, PhD)[d], Noriko Sato (BSc)[e], Kunihiko Ozaki (MSc)[e], Kazuoki Kondo (MD, PhD)[e], Yoshiaki Ishigatsubo (MD, PhD)[f]

Abstract

Behçet disease (BD) is a multisystem disease associated with a poor prognosis in cases of gastrointestinal, neurological, or vascular involvement. We conducted a multicenter, prospective, open-label, single-arm phase 3 study to determine the efficacy, safety, and pharmacokinetics of infliximab (IFX) in BD patients with these serious complications who had displayed poor response or intolerance to conventional therapy.

IFX at 5 mg/kg was administered to 18 patients (11 intestinal BD, 3 neurological BD [NBD], and 4 vascular BD [VBD]) at weeks 0, 2, and 6 and every 8 weeks thereafter until week 46. In patients who showed inadequate responses to IFX after week 30, the dose was increased to 10 mg/kg. We then calculated the percentage of complete responders according to the predefined criteria depending on the symptoms and results of examinations (ileocolonoscopy, brain magnetic resonance imaging, computed tomography angiography, positron emission tomography, cerebrospinal fluid, or serum inflammatory markers), exploring the percentage of complete responders at week 30 (primary endpoint).

The percentage of complete responders was 61% (11/18) at both weeks 14 and 30 and remained the same until week 54. Intestinal BD patients showed improvement in clinical symptoms along with decrease in C-reactive protein (CRP) levels after week 2. Consistently, scarring or healing of the principal ulcers was found in more than 80% of these patients after week 14. NBD patients showed improvement in clinical symptoms, imaging findings, and cerebrospinal fluid examinations. VBD patients showed improvement in clinical symptoms after week 2 with reductions in CRP levels and erythrocyte sedimentation rate. Imaging findings showed reversal of inflammatory changes in 3 of the 4 VBD patients. Irrespective of the type of BD, all patients achieved improvement in quality of life, leading to the dose reduction or withdrawal of steroids. IFX dose was increased to 10 mg/kg in 3 intestinal BD patients, resulting in the improvement of clinical symptoms, CRP levels, and visual analogue scale score. Safety and pharmacokinetics profiles were comparable to those in patients with rheumatoid arthritis or Crohn disease. These findings support IFX as a new therapeutic option for patients with intestinal BD, NBD, or VBD.

Abbreviations: ANB = acute neurological Behçet disease, BD = Behçet disease, CD = Crohn disease, CPNB = chronic progressive neurological Behçet disease, CRP = C-reactive protein, CSF = cerebrospinal fluid, CT = computed tomography, ESR = erythrocyte sedimentation rate, IFX = infliximab, IL-6 = interleukin-6, MRI = magnetic resonance imaging, NBD = neurological Behçet disease, PET = positron emission tomography, QOL = quality of life, RA = rheumatoid arthritis, SF-36 = Short Form-36, TNF-α = tumor necrosis factor-α, VAS = visual analogue scale, VBD = vascular Behçet disease.

Keywords: infliximab, intestinal Behçet disease, neurological Behçet disease, vascular Behçet disease

Editor: Ken Rosenthal.

Funding: This study was funded by Mitsubishi Tanabe Pharma Corporation.

Toshifumi Hibi, Hirotoshi Kikuchi, and Yoshiaki Ishigatsubo have received consultant and lecture fees from Mitsubishi Tanabe Pharma. Shunsei Hirohata has received research support as well as consultant and lecture fees from Mitsubishi Tanabe Pharma. Ukihide Tateishi has received consultant fees from Mitsubishi Tanabe Pharma. Noriko Sato, Kunihiko Ozaki, and Kazuoki Kondo are employees of Mitsubishi Tanabe Pharma.

[a] Center for Advanced IBD Research and Treatment, Kitasato University Kitasato Institute Hospital, Tokyo, [b] Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Sagamihara, [c] Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, [d] Department of Diagnostic Radiology and Nuclear Medicine, Tokyo Medical and Dental University Graduate School of Medicine, Tokyo, [e] Mitsubishi Tanabe Pharma Corporation, Osaka, [f] Yokohama City University, Yokohama, Japan.

[*] Correspondence: Toshifumi Hibi, Center for Advanced IBD Research and Treatment, Kitasato University Kitasato Institute Hospital, 5-9-1 Shirokane, Minato-ku, Tokyo, Japan (e-mail: thibi@insti.kitasato-u.ac.jp).

Medicine (2016) 95:24(e3863)

Received: 1 March 2016 / Received in final form: 27 April 2016 / Accepted: 2 May 2016

Published online 1 May 2016

http://dx.doi.org/10.1097/MD.0000000000003863

1. Introduction

Behçet disease (BD) is a multisystem disease characterized by 4 major symptoms (recurrent oral aphthous ulcers, skin lesions, eye lesions, and genital ulcers) and 5 minor symptoms (arthritis without deformity or ankylosis, epididymitis, gastrointestinal lesions represented by ileocecal ulceration, moderate or severe central nervous system lesions, and vascular lesions).[1] Involvement of the intestinal tract (intestinal BD), the nervous system (neurological BD [NBD]), and the vascular system (vascular BD [VBD]) is rare, although such cases tend to have a poor prognosis.[2,3]

Intestinal BD, NBD, and VBD are generally treated using strong immunosuppressive agents such as steroids and immunomodulators. However, these medications are ineffective in some BD patients, who experience repeated relapses, sequelae, and eventually death.[1,4] Further, steroid treatment also poses problems of steroid dependency and adverse drug reactions associated with long-term use. The development of new therapeutic strategies for BD is therefore imperative.

Tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) are major inflammatory cytokines involved in the pathogenesis of BD.[5] TNF-α production is elevated in the intestinal tissues of intestinal BD patients[6] and in peripheral blood cells of VBD patients,[7] while IL-6 concentrations are elevated in the cerebrospinal fluid (CSF) of NBD patients.[8]

In 2007, infliximab (IFX), an anti-TNF-α monoclonal antibody, was approved in Japan for the treatment of BD-associated refractory retinitis/uveitis, on the basis of the results of a clinical study.[9] Available data on the efficacy of IFX in intestinal BD, NBD, and VBD have been obtained mainly from case studies and retrospective cohort clinical studies,[10–17] and only rarely from prospective clinical studies. Here, therefore, we conducted a multicenter, prospective, open-label, single-arm phase 3 study to evaluate the efficacy, safety, and pharmacokinetics of IFX in BD patients with the serious complications mentioned above. To our knowledge, this is the first prospective multicenter clinical trial of this agent in BD patients with serious complications.

2. Methods

This phase 3 clinical study (ClinicalTrials.gov, NCT01532570) was conducted under a prospective, open-label, single-arm clinical design at 21 medical institutions in Japan between January 2012 and May 2014.[18] The protocol was approved by the institutional review board at each medical institution. All patients gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. Mitsubishi Tanabe Pharma Corporation sponsored this clinical trial and was responsible for the collection of data.

2.1. Patients

The study subjects were patients who had been diagnosed as complete or incomplete type of BD with intestinal BD, NBD, or VBD as per the criteria defined by the Ministry of Health, Labour and Welfare (partially revised in 2010) for Japan, and who had insufficient response or intolerance to conventional therapy. Patients were restricted to those aged 16 to 75 years. With regard to type-specific eligibility criteria, intestinal BD patients had to have intestinal BD-associated symptoms (abdominal pain, diarrhea, melena, etc.) and endoscopic evidence of active ulcers in the intestine. NBD was classified as either acute NBD (ANB) or chronic progressive NBD (CPNB) in accordance with the diagnostic criteria for NBD. ANB patients had to have acute or subacute headache, pyrexia, or focal neurological symptoms and a cell count of $\geq$6.2 cells/mm^3 in the CSF or had to have developed acute or subacute symptoms at least twice during the year preceding enrollment, with a cell count of $\geq$6.2 cells/mm^3 in the CSF at the onset of symptoms. CPNB patients had to have neuropsychiatric symptoms (dementia-like symptoms, psychiatric symptoms, truncal ataxia, dysarthria, etc.) and a CSF IL-6 concentration of $\geq$17.0 pg/mL at enrollment and at the most recent measurement within the year preceding enrollment, or a CSF IL-6 concentration of $\geq$17.0 pg/mL at enrollment and evidence of brainstem atrophy on brain magnetic resonance imaging (MRI). VBD patients had to have active vasculitis lesions (deep vein thrombosis, aortic lesions, etc.) and abnormalities in inflammatory markers such as serum C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR) at enrollment.

Exclusion criteria were as follows: intestinal manifestations that were not differentiated from acute appendicitis, infectious enteritis, Crohn disease (CD), intestinal tuberculosis, or drug-induced enterocolitis; history of resection of intestinal lesions; neurological manifestations that were not differentiated from infection/allergic meningitis/encephalitis/myelitis, systemic lupus erythematosus, brain/spinal cord tumor, vascular disorders, syphilis, multiple sclerosis, psychiatric disease, or sarcoidosis; vascular manifestations that were not differentiated from Takayasu arteritis, Buerger disease, or arteriosclerotic aneurysm; history of treatment with IFX or other biological drugs for intestinal BD, NBD, or VBD; history of treatment with IFX within 1 year before enrollment for diseases other than intestinal BD, NBD, or VBD or discontinuation of previous IFX treatment due to adverse events; history of a surgical procedure within 4 weeks before enrollment; history or complications of a serious infection requiring hospitalization, opportunistic infection, or tuberculosis within 6 months before enrollment; active hepatitis B or C, or hepatitis B virus carrier status; history of human immunodeficiency virus infection; and a history of congestive heart failure, demyelinating diseases or lymphoproliferative disease, or malignant tumor within 5 years before enrollment.

2.2. Study design

IFX at a dose of 5 mg/kg was intravenously infused to patients at weeks 0, 2, and 6, and every 8 weeks thereafter until week 46. If a patient showed a response to IFX by week 30 but thereafter lost the response and the physician deemed that dose escalation was necessary, a dose of 10 mg/kg was administered every 8 weeks until week 46.

Concomitant use of biological drugs, except for IFX, cyclosporin, tacrolimus, and alkylating agents, was prohibited from enrollment to week 54. Changes to the dose of other anti-BD drugs, including azathioprine, 6-mercaptopurine, methotrexate, and aminosalicylic acid, and starting new treatment with or adding these drugs to the regimen, were prohibited from enrollment to evaluation at week 30. However, withdrawal or dose reduction of oral steroids was permitted in line with improvements in symptoms after week 0.

2.3. Assessments

Assessments were made in consideration of the specific characteristics of intestinal BD, NBD, and VBD. We assessed clinical symptoms, findings in ileocolonoscopic, brain MRI, computed tomography (CT) angiography, positron emission tomography (PET) studies, CSF (cell count and IL-6 concentration) analysis

results, and inflammatory marker (CRP or ESR) levels. We also calculated the percentage of complete responders, defined as those who met the BD type-specific criteria described in Table 1. The primary endpoint was the percentage of complete responders at week 30. Secondary endpoints were the percentages of complete responders at weeks 14 and 54, patient visual analogue scale (VAS) score, Short Form-36 (SF-36) score with regard to physical health, and oral steroid dosage. In addition, we evaluated the major and the other symptoms of BD and assessed the pharmacokinetics and safety of IFX.

For intestinal BD patients, the clinical symptoms were scored at weeks 0, 2, and 6, and every 4 weeks thereafter. Ileocolonoscopy was performed at weeks 0, 14, 30, and 54, and scores were determined in terms of changes in the length of the major axis of the principal intestinal ulcer from that at week 0. Additionally, serum CRP levels were measured at weeks 0, 2, and 6, and every 4 weeks thereafter. For NBD patients, the severity of clinical symptoms was scored at weeks 2 and 6 and every 4 weeks thereafter in terms of changes from the data recorded at week 0. Brain MRI was performed at weeks 0, 14, 30, and 54, and the high-intensity areas in ANB patients and the brainstem area in CPNB patients were scored by comparison to the area measurements made at week 0. Cell count (ANB only) and IL-6 concentrations in the CSF were measured at weeks 0, 14, 30, and 54. Further, for ANB patients, the incidence of acute or subacute attacks occurring between weeks 0 and 30 and between weeks 30 and 54 was determined. For VBD patients, we scored the changes in the degree of swelling, pain, or other VBD-associated clinical symptoms at weeks 2 and 6 and every 4 weeks thereafter in terms of the status at week 0. Changes in CT or PET/CT findings were scored at weeks 14, 30, and 54 by comparison with those at week 0. In addition, the levels of serum CRP and ESR were measured at weeks 0, 2, and 6, and every 4 weeks thereafter, and the incidence of venous thrombosis between weeks 0 and 30 and between weeks 30 and 54 was calculated. Details of the scores are provided in Table 1.

Images obtained from NBD and VBD patients were centrally assessed by 2 BD specialists from the image assessment committee who were blinded to patient symptoms and time of imaging. IFX concentration was measured using an enzyme-linked immunosorbent assay[19] (Mitsubishi Tanabe Pharma Corporation, Osaka, Japan).

2.4. Statistical analyses

The full analysis set was used for efficacy analysis. Patient characteristics and efficacy at each time point and at the final point of treatment at 5 mg/kg were assessed in terms of the percentage, frequency, or descriptive statistics. Missing data in the primary endpoint were compensated for using the last observation carried forward method. Safety was assessed on an intention-to-treat basis, and the incidence and percentages of adverse events and adverse drug reactions were calculated.

3. Results

3.1. Patient disposition

After enrollment, IFX at 5 mg/kg was administered to 18 BD patients (11 intestinal BD, 3 NBD [2 ANB and 1 CPNB], and 4 VBD) (Fig. 1). Before week 30, 1 ANB patient withdrew consent and discontinued treatment with IFX. Subsequently, 14 BD patients (8 intestinal BD, 2 NBD, and 4 VBD) received a dose of 5 mg/kg IFX until week 54. The dose was increased to 10 mg/kg after week 30 in 3 intestinal BD patients, 1 of whom then discontinued treatment due to exacerbation of symptoms.

Patient characteristics are shown in Table 2. Skin lesions were the most common major symptom (15/18 [83%]). Among the 11 intestinal BD patients, the ileum (9 patients; 82%) was the most common lesion site, followed by the cecum and ascending colon (3 patients each; 27%), transverse colon and descending colon (1 patient each; 9%), and others (2 patients; 18%). No patients had lesions in the rectum. Of the 4 VBD patients, 3 (75%) had venous lesions (deep vein thrombosis of the lower extremity, 1; others, 2), and 1 (25%) had arterial lesions (arterial occlusion).

3.2. Efficacy

Eleven (61%) of the 18 BD patients showed a complete response at an early stage (week 14). This ratio of complete responses was maintained at week 30, the primary endpoint (61%, 11/18) (Table 3), and then increased to 69% (11/16) at week 54 and 67% (12/18) at the final point of 5 mg/kg therapy. Efficacy of IFX was maintained for up to 1 year. By BD type, the percentage of complete responders at week 30 was 55% (6/11) among intestinal BD patients, 33% (1/3) among NBD patients, and 100% (4/4) among VBD patients.

3.3. Intestinal BD

Clinical symptoms at week 0 were very mild in 3 patients with intestinal BD, mild in 5, and moderately severe in 3. The percentage of patients showing an improvement in clinical symptoms compared to that at week 0 was 64% (7/11) at week 2 and gradually increased to 73% (8/11) at week 14 and 91% (10/11) at week 30 (Fig. 2A). In addition, the percentage of patients showing an improvement in clinical symptoms was 80% (8/10) at week 54 and 82% (9/11) at the final point of 5 mg/kg therapy. The percentage of patients with no clinical symptoms was 36% (4/11) at week 2, which gradually increased to 64% (7/11) at week 30 and 80% (8/10) at week 54. The percentage of intestinal BD patients with no clinical symptoms at the final point of 5 mg/kg therapy was 73% (8/11).

Healing or scarring of the principal intestinal ulcer was recorded at week 14 in 9 (82%) patients, and most patients showed no recurrence until week 54 (Fig. 2B). The percentage of patients with healing or scarring of the principal ulcer was 82% (9/11) at week 30, 89% (8/9) at week 54, and 82% (9/11) at the final point of 5 mg/kg therapy.

Median serum CRP level was 0.20 mg/dL (interquartile range: 0.00–1.00 mg/dL) at week 0. This then decreased or remained low from week 2 up to week 54 in most intestinal BD patients (Fig. 2C), as follows: 0.00 mg/dL (0.00–0.00 mg/dL) at week 2, 0.15 mg/dL (0.00–0.80 mg/dL) at week 14, 0.10 mg/dL (0.00–2.20 mg/dL) at week 30, 0.10 mg/dL (0.00–0.20 mg/dL) at week 54, and 0.10 mg/dL (0.00–0.20 mg/dL) at the final point of 5 mg/kg therapy.

IFX dose was increased to 10 mg/kg after week 30 in 3 patients with intestinal BD due to loss of response. Among these, the dose was increased in 1 patient at week 46 due to recurrence of abdominal pain, which caused some difficulties in daily activities. After dose escalation, the clinical symptoms and VAS score of the patient improved. In the 2nd patient, IFX dose was increased at week 38 due to abdominal pain, fever, diarrhea, and melena with high serum CRP level. However, although serum CRP levels, VAS score, and clinical symptoms improved after dose escalation, the disease could not be controlled and worsened at week 54. In the 3rd patient, IFX dose was increased at week 30 due to recurrence of

Table 1

Definition of complete responders and assessment criteria.

Intestinal BD	Definition of complete responders	• Clinical symptoms associated with intestinal BD have disappeared.		
		• Ileocolonoscopic examination shows that ulcers at the lesion site are healed or scarred compared to baseline. In addition, the patient shows no new active lesions.		
	Assessment criteria	Score	Clinical symptoms	The length of the major axis of the principal intestinal ulcer compared to size at week 0
		0	No symptoms	Healed or scarred
		1	Very mild	Reduced to $\leq$25%
		2	Mild	Reduced to $>$25% to $\leq$50%
		3	Moderate	Reduced to $>$50%, no change, or increased
		4	Severe	–
ANB	Definition of complete responders	(a) Patients with acute or subacute headache, pyrexia, or localized neurological symptoms at enrollment.		
		• Acute or subacute headache, pyrexia, or localized neurological symptoms that had been observed before administration have disappeared and have not reappeared up to the time of the evaluation.		
		• High-intensity areas on brain MRI have disappeared, and no new areas have appeared up to the time of evaluation.		
		• Both cell count and IL-6 concentrations in the CSF decreased compared to baseline and remained low up to the time of evaluation.		
		(b) Patients with acute or subacute headache, pyrexia, or localized neurological symptoms twice or more within one year before enrollment.		
		• Acute or subacute headache, pyrexia, or localized neurological symptoms are continuously absent up to the time of evaluation.		
		• Brain MRI images demonstrate continuous absence of new high-intensity areas up to the time of evaluation.		
		• Abnormal cell count and IL-6 concentrations (above the upper limit of the standard level) before administration improved since administration and have remained low up to the time of evaluation. Normal cell count and IL-6 concentrations (within the reference ranges) before administration have not been elevated up to the time of evaluation.		
	Assessment criteria	Score	Clinical symptoms compared to those at week 0	The size of high-intensity areas compared to week 0
		0	No symptoms	No high-intensity areas
		1	Improved	Reduction
		2	Unchanged	No change or increase
		3	Worsened	–
CPNB	Definition of complete responders	• Exacerbation of clinical symptoms associated with CPNB has been continuously absent compared to baseline at any time up to the time of the evaluation.		
		• Progression of atrophy of the brainstem on brain MRI has been continuously absent compared to baseline at any time up to the time of the evaluation.		
		• IL-6 concentration in the CSF has decreased compared to baseline and has remained low.		
	Assessment criteria	Score	Clinical symptoms compared to those at week 0	Brainstem area compared to week 0
		0	No symptoms	Unchanged
		1	Improved	Reduced
		2	Unchanged	–
		3	Worsened	–
VBD	Definition of complete responders	• Exacerbation of clinical symptoms associated with VBD compared to baseline has been continuously absent up to the time of evaluation.		
		• Exacerbation of imaging findings compared to baseline has been continuously absent up to the time of evaluation.		
		• Inflammatory markers (CRP or ESR) levels have been decreased compared to baseline and remain low up to the time of the evaluation.		
	Assessment criteria	Score	Clinical symptoms compared to those at week 0	CT or PET/CT findings compared to those at week 0
		0	No symptoms	Improved
		1	Improved	Unchanged
		2	Unchanged	Worsened
		3	Worsened	–

ANB = acute neurological Behcet disease, BD = Behçet disease, CPNB = chronic progressive neurological Behcet disease, CRP = C-reactive protein, CT = computed tomography, ESR = erythrocyte sedimentation rate, IL-6 = interleukin-6, MRI = magnetic resonance imaging, NBD = neurological Behçet disease, PET = positron emission tomography, VBD = vascular Behçet disease.

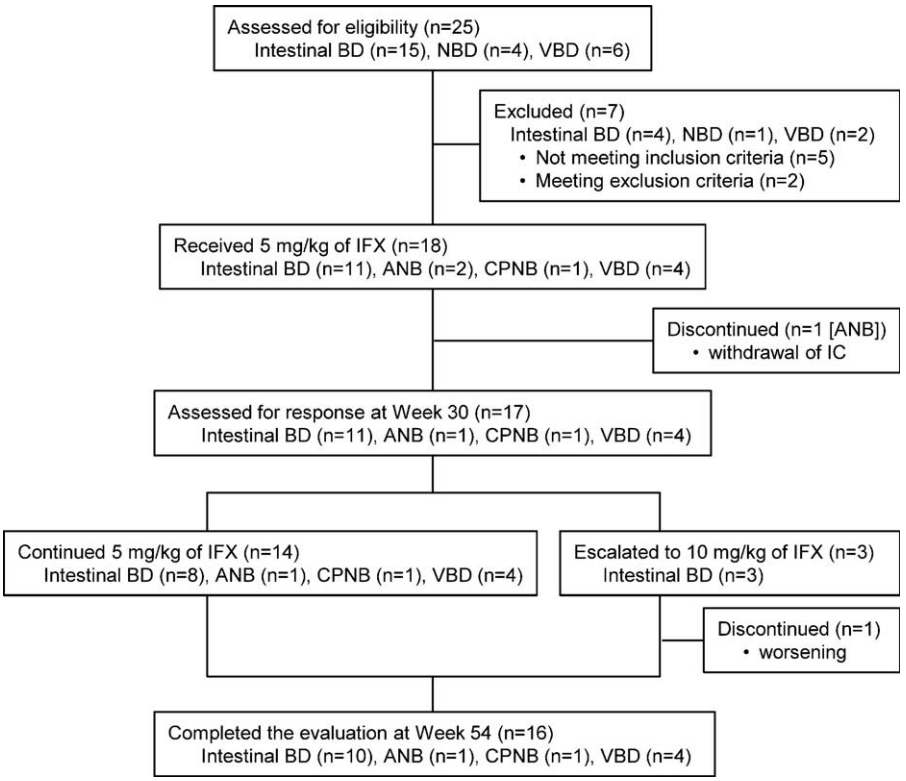

Figure 1. Patient disposition and flow chart of the study. ANB = acute neurological Behçet disease, BD = Behçet disease, CPNB = chronic progressive neurological Behçet disease, IC = informed consent, IFX = infliximab, NBD = neurological Behçet disease, VBD = vascular Behçet disease.

Table 2

Baseline characteristics of patients.

Characteristic	All 3 types n = 18	Intestinal BD n = 11	NBD			VBD n = 4
			All NBD, n = 3	ANB, n = 2	CPNB, n = 1	
Male sex, n (%)	10 (56)	5 (45)	2 (67)	1 (50)	1 (100)	3 (75)
Age (years)	37.6 ± 11.4	35.0 ± 13.4	38.3 ± 8.5	30, 38	47	44.0 ± 2.9
Weight (kg)	67.8 ± 17.9	63.0 ± 16.9	64.3 ± 11.0	58, 58	77	83.8 ± 18.5
Time since diagnosis of BD (months)	91.3 ± 80.7	76.1 ± 78.0	64.0 ± 61.9	52, 131	9	153.5 ± 85.5
Time since diagnosis of intestinal BD, NBD, or VBD (months)	51.5 ± 74.0	62.5 ± 82.3	9.7 ± 7.0	3, 17	9	52.5 ± 79.0
Complete type*, n (%)	1 (6)	1 (9)	0 (0)	0 (0)	0 (0)	0 (0)
Symptoms, n (%)						
Recurrent aphthous ulcers on oral mucosa	9 (50)	5 (45)	1 (33)	1 (50)	0 (0)	3 (75)
Skin lesions	15 (83)	8 (73)	3 (100)	2 (100)	1 (100)	4 (100)
Ocular lesions	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	1 (25)
Genital ulcers	5 (28)	4 (36)	0 (0)	0 (0)	0 (0)	1 (25)
Arthritis without deformity or sclerosis	4 (22)	3 (27)	0 (0)	0 (0)	0 (0)	1 (25)
Epididymitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal lesion represented by ileocecal ulceration	11 (61)	11 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Vascular lesions	4 (22)	0 (0)	0 (0)	0 (0)	0 (0)	4 (100)
Central nervous system lesions, moderate or severe	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Concomitant medication, n (%)						
Corticosteroids	14 (78)	8 (73)	3 (100)	2 (100)	1 (100)	3 (75)
Immunomodulators	1 (6)	1 (9)	0 (0)	0 (0)	0 (0)	0 (0)
Aminosalicylates	8 (44)	8 (73)	0 (0)	0 (0)	0 (0)	0 (0)
Prostaglandin analogs	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	1 (25)
Anticoagulants	2 (11)	0 (0)	0 (0)	0 (0)	0 (0)	2 (50)
Antiplatelet agents	3 (17)	0 (0)	0 (0)	0 (0)	0 (0)	3 (75)
NSAIDs	5 (28)	4 (36)	0 (0)	0 (0)	0 (0)	1 (25)
Colchicine	6 (33)	4 (36)	0 (0)	0 (0)	0 (0)	2 (50)

Data are shown as the mean ± standard deviation, except where indicated otherwise. ANB = acute neurological Behcet disease, BD = Behçet disease, CPNB = chronic progressive neurological Behcet disease, NBD = neurological Behçet disease, NSAIDs = nonsteroidal anti-inflammatory agents, VBD = vascular Behçet disease.

* Patients having all 4 primary symptoms.

Table 3

Proportion of complete responders.

	Complete responders (%)					
			NBD			
	All 3 types	Intestinal BD	All NBD	ANB	CPNB	VBD
Week 14	61 (11/18)	55 (6/11)	33 (1/3)	0 (0/2)	100 (1/1)	100 (4/4)
Week 30 (primary endpoint)	61 (11/18)	55 (6/11)	33 (1/3)	0 (0/2)	100 (1/1)	100 (4/4)
Week 54	69 (11/16)	60 (6/10)	50 (1/2)	0 (0/1)	100 (1/1)	100 (4/4)
Final point of 5 mg/kg therapy	67 (12/18)	64 (7/11)	33 (1/3)	0 (0/2)	100 (1/1)	100 (4/4)

ANB = acute neurological Behcet disease, BD = Behcet disease, CPNB = chronic progressive neurological Behcet disease, NBD = neurological Behçet disease, VBD = vascular Behçet disease.

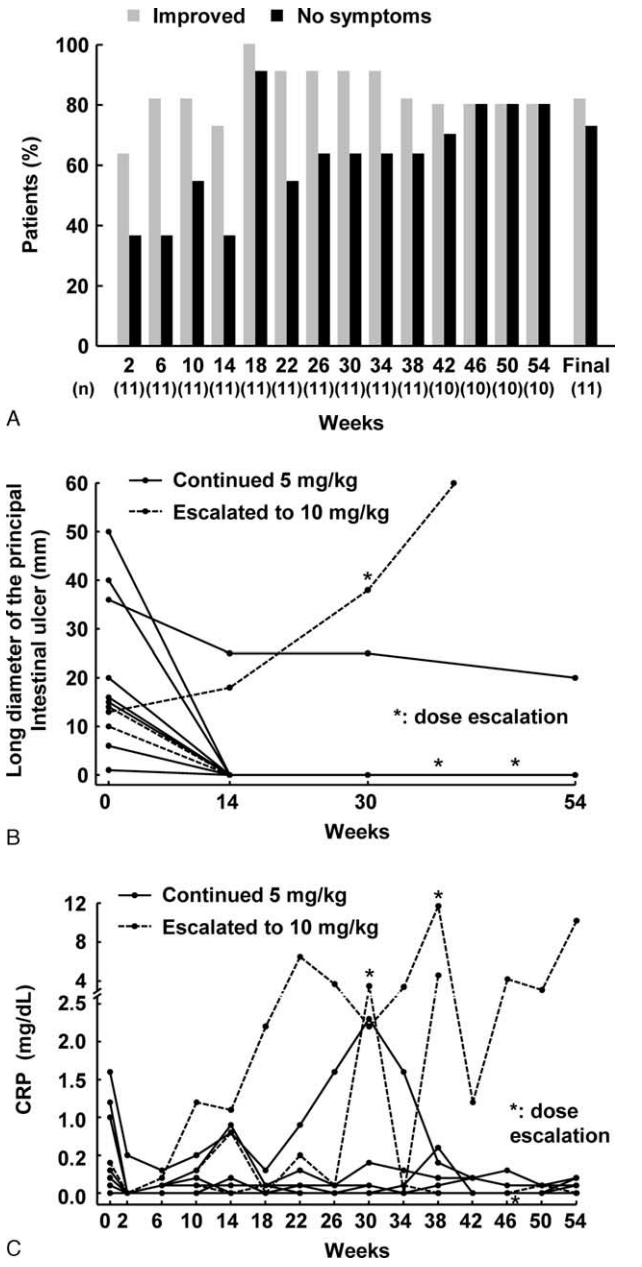

Figure 2. Efficacy of infliximab on intestinal Behçet disease. (A) Percentage with improved or cured clinical symptoms, (B) changes in size of major ulcers for each patient, and (C) changes in serum C-reactive protein (CRP) levels for each patient.

abdominal pain and an increase in the size of the principal ulcer. Although the stomach pain, serum CRP level, and VAS score improved after dose escalation, the disease worsened after 2 doses of 10 mg/kg, and the patient was withdrawn from the study.

3.4. NBD

One ANB patient (patient 1) had acute symptoms (fever and headache) and elevated cell count and IL-6 concentration in the CSF at week 0 (37 cells/μL and 145 pg/mL, respectively) (Fig. 3A). At week 2, the acute symptoms disappeared, and the cell count and IL-6 concentration decreased to 7 cells/μL and 1.8 pg/mL, respectively. Aside from a mild headache at week 22, no acute symptoms occurred at other measurement time points, and CSF analysis did not show any evidence of inflammation until week 54 (at week 54: cell count, ≤1 cell/μL; IL-6 concentration, 1.5 pg/mL). FLAIR MRI at week 0 showed high signal intensity in the posterior part of the right lenticular nucleus to the posterior limb of the internal capsule, while FLAIR MRI images showed a small area of high-intensity in the genu of the right internal capsule to the globus pallidus; however, these areas shrank in size by weeks 2, 14, and 30, and the high-intensity area in the right internal capsule was further reduced at week 54. Although 2 episodes of attack (acute symptoms) were reported during the 12 months before the start of administration (1st episode: diplopia and aphagia; 2nd episode: vertigo, nausea, fever, headache, and diplopia), only a single mild attack (mild headache) occurred after the start of IFX treatment. MRI did not depict any new areas of high signal intensity during the study period.

The other ANB patient (patient 2) reported headache as a chronic symptom but did not have any acute symptoms or abnormalities on CSF analysis (cell count 3 cells/μL and IL-6 concentration of 2.5 pg/mL) at week 0 (Fig. 3B). Although the patient experienced headache and dull headache as chronic symptoms until week 22, no acute symptoms occurred after the start of IFX treatment. However, this patient withdrew consent and discontinued the study at week 22. CSF cell count was 2 cells/μL both at week 14 and withdrawal. CSF IL-6 concentration was 23.0 pg/mL at week 14 and 6.5 pg/mL at withdrawal. The high-intensity areas in the right forehead and parietal lobe seen on FLAIR MRI of the head at week 0 were reduced at both week 14 and at withdrawal. Although this patient experienced 2 episodes of attack (acute symptoms) in the year preceding the start of IFX treatment (1st episode: headache; 2nd episode: headache and malaise), the attacks did not occur after the start of treatment, although the evaluation period was relatively short.

One CPNB patient (patient 3) showed slightly slow reactions with a relatively high CSF IL-6 concentration of 64.5 pg/mL at week 0 (Fig. 3C). Despite an increase to 430.0 pg/mL at week 2, no changes in clinical symptoms compared to week 0 were noted. At week 6, all clinical symptoms had resolved, and no symptoms

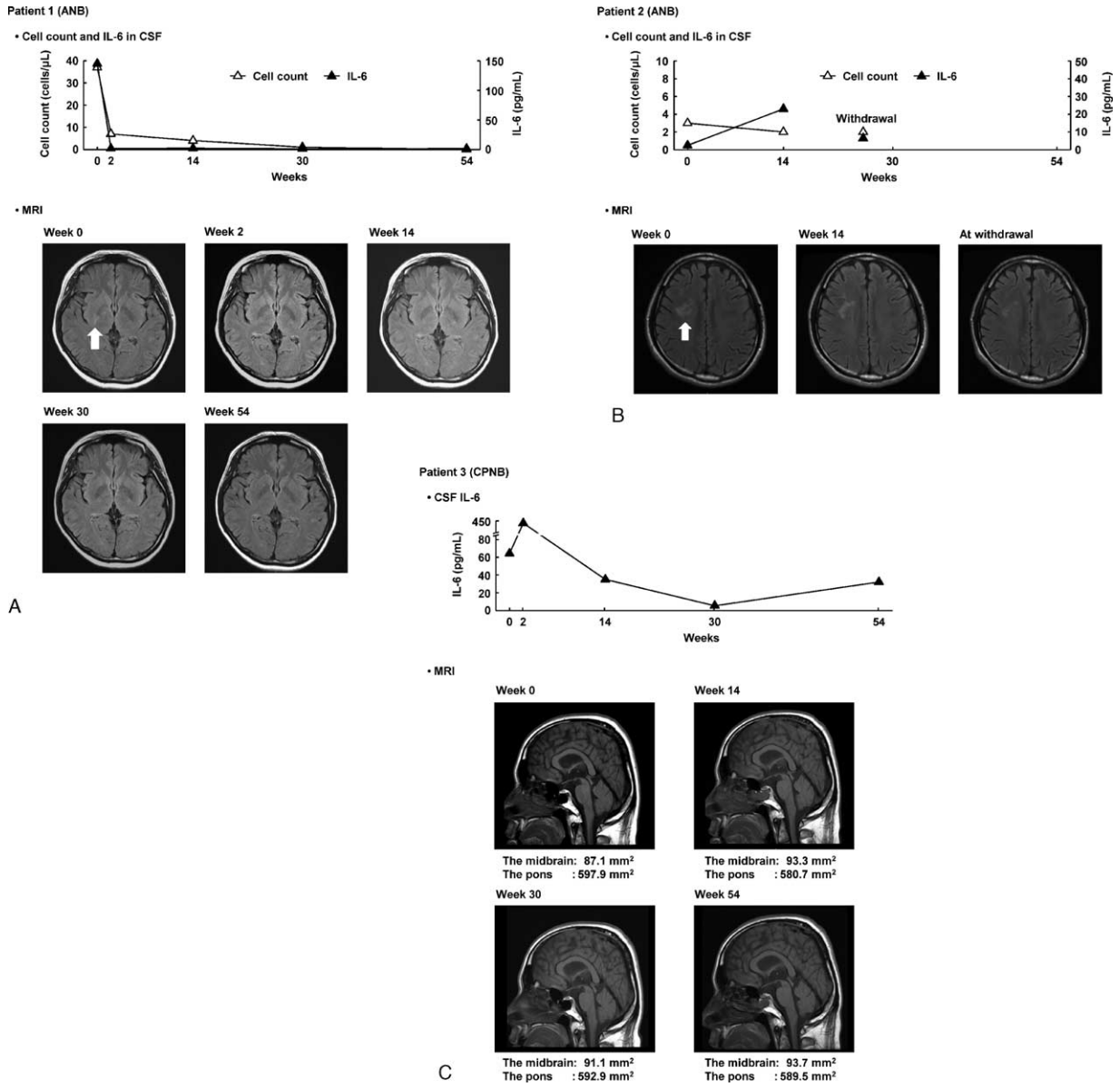

Figure 3. Efficacy of infliximab on neurological Behçet disease. (A) CSF cell count, CSF IL-6 concentration, and FLAIR MRI images in patient 1 (ANB); (B) CSF cell count, CSF IL-6 concentration, and FLAIR MRI images in patient 2 (ANB); and (C) CSF IL-6 concentration and T1-weighted MRI images in patient 3 (CPNB). ANB = acute neurological Behçet disease, CPNB = chronic progressive neurological Behçet disease, CSF = cerebrospinal fluid, IL-6 = interleukin-6, MRI = magnetic resonance imaging.

(0 points) appeared until week 54. CSF IL-6 concentration declined to 35.1 pg/mL at week 14 and further decreased to 5.4 pg/mL at week 30, but slightly increased at week 54 (32.1 pg/mL). At week 0, T1-weighted MRI of the head did not reveal any abnormalities. The areas of the midbrain and pons were 87.1 and 597.9 mm^2, respectively, at week 0 and remained nearly unchanged until week 54 (93.7 and 589.5 mm^2, respectively).

3.5. VBD

At week 2, clinical symptoms were improved (1 point) or absent (0 points) in 3 of the 4 VBD patients (Fig. 4A). Aggravation of clinical symptoms did not occur in any of the VBD patients, and improvement was maintained between weeks 38 and 54. Imaging findings at week 14 showed improvement in inflammation (0 points) in 3 of the 4 patients, which continued until week 54. In the remaining VBD patient, imaging findings depicted no aggravation until week 54. PET/CT images of the patient with thrombophlebitis of the lower legs who showed improvement are shown in Fig. 4B. At week 0, inflammation was observed around the veins of the lower legs (slightly more severe in the right lower leg). These inflammatory changes ameliorated at week 14 and showed further improvement at weeks 30 and 54. At this last evaluation, both lower limbs showed no marked difference in severity. With respect to the patient with arterial occlusion in the right armpit, the right radial artery was not palpable and the right extremity was numb at week 0. The arterial occlusion slightly improved at week 14 and further improved at weeks 30 and 54.

Changes in the serum CRP level and ESR in VBD patients are shown in Fig. 4C and D. The median serum CRP level was 0.90 mg/dL at week 0, which decreased to 0.25 mg/dL at week 2. Levels stayed low at weeks 14, 30, and 54, with median values of

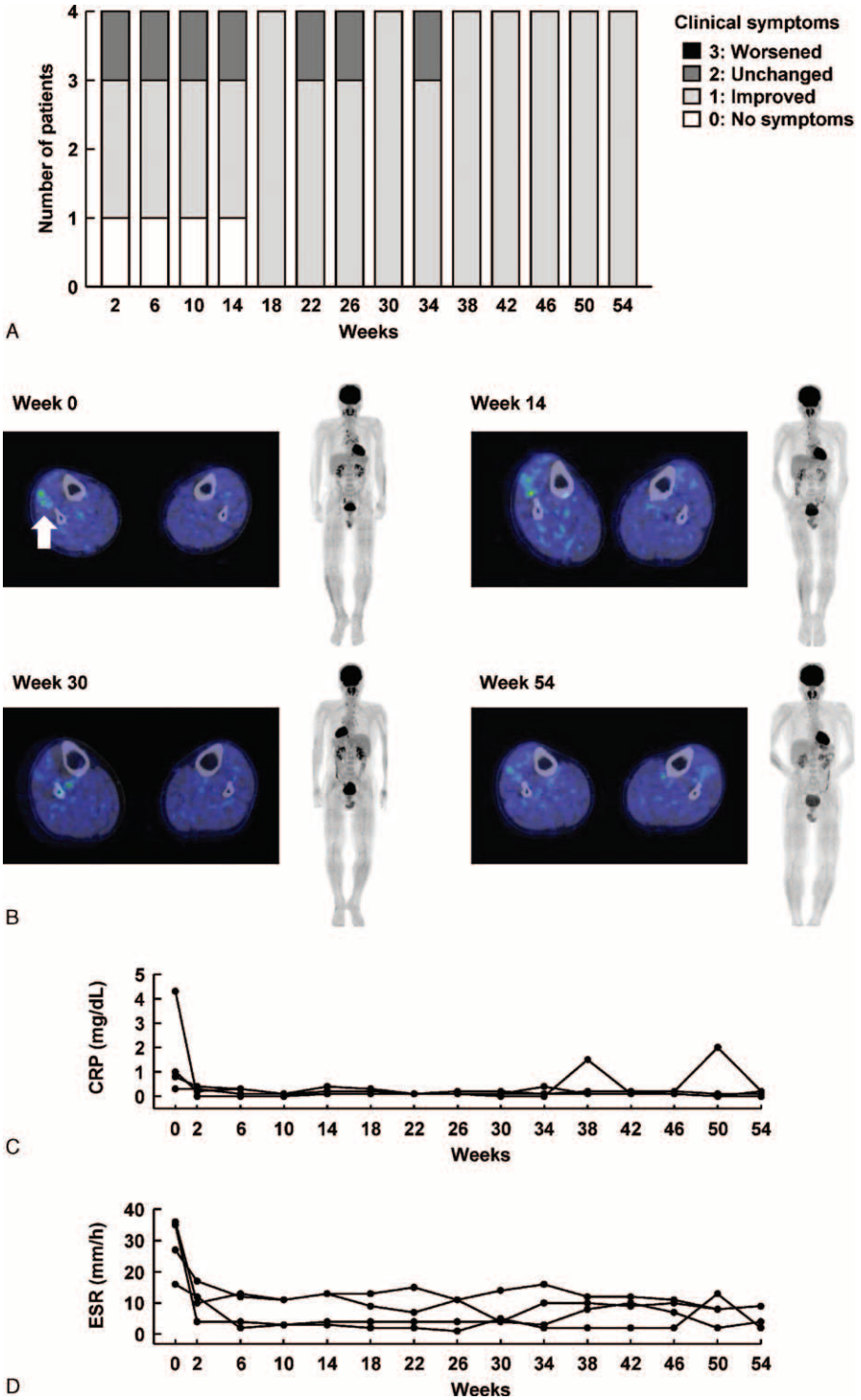

Figure 4. Efficacy of infliximab on vascular Behçet disease. (A) Change in clinical symptoms, (B) PET/CT images of thrombophlebitis of the lower legs in a representative patient, (C) changes in serum CRP level for each patient, and (D) changes in serum ESR for each patient. CRP = C-reactive protein, CT = computed tomography, ESR = erythrocyte sedimentation rate, PET = positron emission tomography.

0.15, 0.10, and 0.15 mg/dL, respectively. Median serum ESR was 31.0 mm/hour at week 0, declining to 11.0, 8.5, 4.5, and 6.5 mm/hour at weeks 2, 14, 30, and 54, respectively. Neither clinical symptoms nor imaging findings showed evidence of the development of new lesions throughout the investigational period. No newly occurring venous thrombosis was noted in any of the 4 VBD patients during the study period.

3.6. Improvement of quality of life (QOL) in patients with gastrointestinal lesions, central nervous system lesions, and vascular lesions

Among BD patients, VAS score (mean ± standard deviation) improved over time, from 49.8 ± 24.2 mm at week 0 to 34.2 ± 28.3 mm, 27.5 ± 22.9 mm, 24.6 ± 25.5 mm, and 17.0 ± 21.8 mm

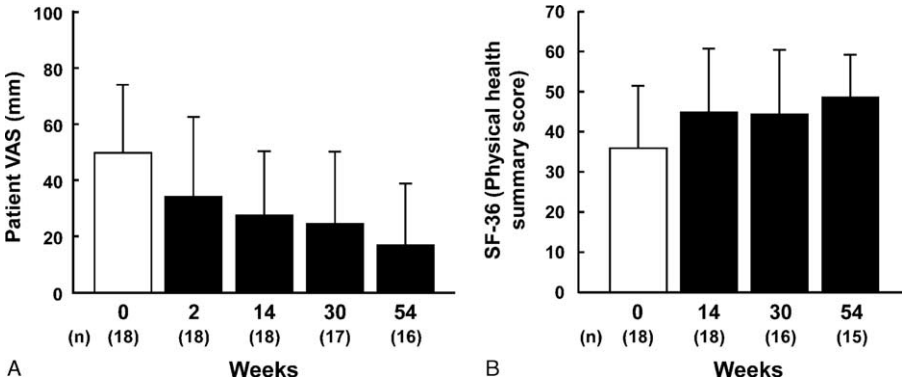

Figure 5. Effects of infliximab on quality of life in patients with intestinal, neurological, and vascular Behçet disease. (A) Patient VAS score, (B) SF-36 score (physical health summary score). Data are shown as the means ± standard deviation. SF-36 = Short Form-36, VAS = visual analogue scale.

at weeks 2, 14, 30, and 54, respectively (Fig. 5A). The SF-36 score (mean ± standard deviation) was 35.9 ± 15.6 at week 0, and then improved to 44.9 ± 15.9, 44.4 ± 16.0, and 48.6 ± 10.6 at weeks 14, 30, and 54, respectively (Fig. 5B). VAS and SF-36 scores improved across all types of BD.

3.7. Steroid dose reduction and withdrawal

Of the 14 BD patients treated with oral steroids at week 0, doses were reduced in 6 at week 14 and in these 6 as well as in an additional 1 at week 30 (n = 7 total; Table 4). Two of these 7 patients were eventually free from treatment with steroids, both with intestinal BD. These 7 BD patients remained on reduced steroid doses until week 54 or were free from steroid use by then. By week 54, steroid doses were reduced in another 2 patients, and one of these 2 patients eventually withdrew from steroid use. Steroid dose was reduced across all types of BD. Six of the 9 patients with reduced steroid doses showed complete responses, and 2 of these 6 were free from steroid treatment successfully. No patients required initiation of oral steroid treatment or an increase in dosage during the study period.

3.8. Effects on major symptoms of BD

More than 60% of BD patients who had oral aphtha (n = 18), skin symptoms (n = 18), or genital ulcers (n = 18) at week 0 had improved by week 2 (Fig. 6A). The percentage showing improvement after week 6 ranged from 73% to 91% for oral aphtha, 73% to 100% for skin symptoms, and 83% to 100% for genital ulcer and the percentage with no symptoms (0 points) increased after week 2, suggesting that the efficacy of IFX was maintained. One patient had eye symptoms at week 0 that resolved by week 2 and did not recur during the course of the study.

3.9. Effects on all symptoms of BD (assessed by physicians or patients)

At week 2, the percentages of patients showing slight improvement (1 point) or improvement (0 points) in all symptoms of BD as assessed by physicians and patients were 61% (11/18) and 61% (11/18), respectively (Fig. 6B). Percentages of patients showing slight improvement or improvement as assessed by the physicians and patients were 94% (17/18) and 83% (15/18) at week 14, 100% (17/17) and 76% (13/17) at week 30, and 94% (15/16) and 88% (14/16) at week 54, respectively. These percentages clearly remained high, irrespective of whether reporting was by physicians or patients. Percentages of patients showing improvement as assessed by physicians were 33% (6/18) at week 2, 61% (11/18) at week 14, 71% (12/17) at week 30, and 75% (12/16) at week 54; the corresponding percentages as assessed by patients were 17% (3/18), 50% (9/18), 47% (8/17), and 50% (8/16).

3.10. Pharmacokinetics

No marked differences in serum IFX concentration were noted by BD type among patients treated with a dose of 5 mg/kg. Trough serum IFX concentrations were stably maintained for each BD type after week 14 (Fig. 7). In the 3 intestinal BD patients whose doses were increased to 10 mg/kg after week 30 due to loss of response, trough serum IFX concentrations rose after the dose escalation (7.78–18.74, 0.96–6.01, and 4.39–9.77 μg/mL).

3.11. Safety

The incidence of adverse events across all patients was 94% (17/18), with the following type breakdown: 91% (10/11) in intestinal BD patients, 100% (3/3) in NBD patients, and

Table 4

Incidence of dose reduction and withdrawal of steroids.

	All 3 types (n = 18)	Intestinal BD (n = 11)	NBD (n = 3)	VBD (n = 4)
Patients using steroids at week 0, n	14	8	3	3
Patients with dose reduction (withdrawal), n				
Week 14	6 (0)	3 (0)	1 (0)	2 (0)
Week 30	7 (2)	4 (2)	1 (0)	2 (0)
Week 54	9 (3)	5 (3)	1 (0)	3 (0)
Final point of 5 mg/kg therapy	10 (3)	5 (3)	2 (0)	3 (0)

BD = Behçet disease, NBD = neurological Behçet disease, VBD = vascular Behçet disease.

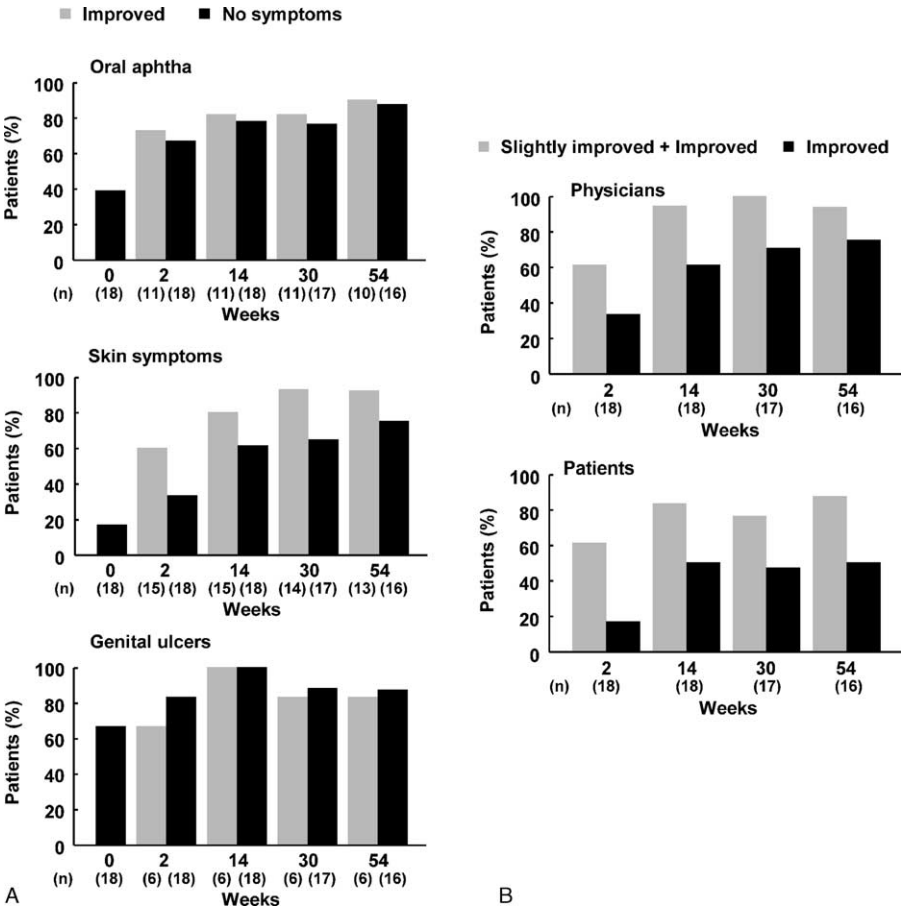

Figure 6. Efficacy of infliximab on major symptoms of Behçet disease (BD) and global assessment of overall disease activities by physicians and patients. (A) Major symptoms of BD (oral aphtha, skin symptoms, and pudendal ulcer), (B) assessment of overall disease activities of BD (assessed by physicians or patients).

100% (4/4) in VBD patients, showing no marked difference among BD types (Table 5). Infections occurred in 11 patients. Regarding the infections reported in more than 10% of patients, we observed upper respiratory tract infection (5/18), nasopharyngitis (4/18), gastroenteritis (2/18), and infectious enteritis (2/18). With regard to serious adverse events, worsening of the underlying disease and cataracts were observed in 1 intestinal BD patient. A causal relationship between these serious adverse events and IFX was ruled out because the 1st patient had similar worsening of the underlying disease with small bowel perforation even before enrollment, and the cataract in the 2nd patient was considered to be a result from a long-term use of oral steroids. In the 3 intestinal BD patients who were administered an increased dose of 10 mg/kg, the only adverse event that occurred after the dose escalation was the worsening of the underlying disease, as mentioned above.

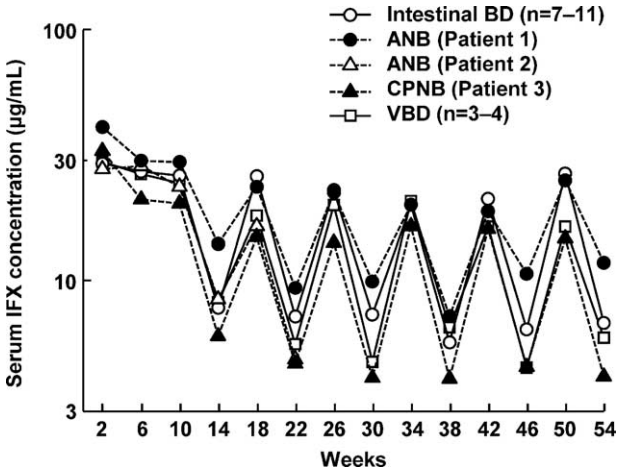

Figure 7. Changes in serum infliximab concentration. Data of patients with intestinal and vascular BD are shown as the median. ANB = acute neurological Behçet disease, BD = Behcet disease, CPNB = chronic progressive neurological Behçet disease, IFX = infliximab, VBD = vascular BD.

4. Discussion

In those patients with intestinal BD, NBD, and VBD who had displayed a poor response or intolerance to conventional therapy, efficacy of IFX was observed soon after starting treatment and was maintained until week 54 of treatment. No major differences in the safety or pharmacokinetics of IFX were noted between our study population versus patients receiving treatment with IFX in rheumatoid arthritis (RA) or CD.

IFX has been reported to exert its effects in BD via a number of mechanisms, including neutralization of TNF-α and subsequent suppression of γδT cell expansion, activation, and cytotoxic activity[20] and a decrease in the levels of CSF IL-6 through cytotoxic effects on monocytes/macrophages.[15] Further, IFX has been found to be effective in treating intestinal BD,[10–12,17] NBD,[13–15,17] and VBD.[16,17] However, most of these reports

Table 5

Safety profile.

	All 3 types (n = 18)	Intestinal BD (n = 11)	NBD (n = 3)	VBD (n = 4)
Days of follow-up, mean (range)	366.9 (210–386)	375.2 (323–386)	322.7 (210–380)	377.3 (374–380)
10 mg/kg	89.7 (50–114)[a]	89.7 (50–114)[a]	–	–
Mean dose, n	7.8	7.9	7.0	8.0
10 mg/kg	1.7[*]	1.7[a]	–	–
Any adverse events	17 (94)	10 (91)	3 (100)	4 (100)
Infections	11 (61)	7 (64)	1 (33)	3 (75)
Infusion reactions	1 (6)	1 (9)	0 (0)	0 (0)
Adverse events leading to discontinuation of study drug	0 (0)	0 (0)	0 (0)	0 (0)
Any adverse drug reactions	12 (67)	8 (73)	1 (33)	3 (75)
Any serious adverse events	2 (11)	2 (18)	0 (0)	0 (0)
Worsening	1 (6)	1 (9)	0 (0)	0 (0)
Cataract	1 (6)	1 (9)	0 (0)	0 (0)
Serious infections	0 (0)	0 (0)	0 (0)	0 (0)
Serious infusion reactions	0 (0)	0 (0)	0 (0)	0 (0)

Data are shown as the number of patients (%) except where indicated otherwise. BD = Behçet disease, NBD = neurological Behçet disease, VBD = vascular Behçet disease.
[*] n = 3.

were case studies and retrospective cohort clinical studies, and little data are available from prospective clinical studies.

We obtained novel data on IFX through comprehensive assessment of clinical symptoms, morphological characteristics, and levels of inflammatory markers in intestinal BD, NBD, and VBD patients. Approximately 60% of our population treated with IFX showed a complete response at week 14, and efficacy was maintained until the end of the study at week 54. The percentage of complete responders at week 30 (primary endpoint) was 61%. Similar to the French retrospective study,[17] the findings from our prospective study suggest that IFX is indeed effective for BD patients with these serious complications.

In intestinal BD patients, the clinical symptoms and endoscopic findings improved soon after starting treatment, as evidenced by reductions in serum CRP levels, and this efficacy was maintained until week 54. Our present findings for IFX were comparable to previous findings from studies using other TNF inhibitors, such as adalimumab[21] or etanercept,[22] in terms of efficacy against intestinal BD. Healing or scarring of the principal ulcer was achieved in more than 80% of such patients in the present study, suggesting that IFX has potent mucosal healing effects. Mucosal healing in intestinal BD patients has been reported to predict the long-term prognosis, in terms of the risk of clinical relapse and surgery.[23] Therefore, IFX is expected to maintain low disease activity in the long term, which subsequently may reduce the need for surgery.

In CPNB patients, IFX has been reported to reduce CSF IL-6 concentrations and thereby inhibit the progression of CPNB.[15] In the present study as well, IFX lowered CSF IL-6 concentrations and resolved clinical symptoms in a CPNB patient without the occurrence of brainstem atrophy. In ANB patients, IFX lowered the cell count and IL-6 concentrations in the CSF and inhibited the onset of attacks. Onset of attacks in NBD patients may lead to the onset or progression of cerebellar disorder-associated gait disorders, dysarthria, and dysuria and then to cognitive impairment, neurological disorders, and personality changes.[24] Although our study involved a relatively small number of NBD patients, our findings suggest that IFX inhibits the onset of attacks and improves or inhibits NBD-associated progressive pathological conditions. Therefore, IFX may improve the overall prognosis in NBD patients.

In VBD patients, analysis of clinical symptoms, imaging findings, and inflammatory markers demonstrated the efficacy of IFX soon after starting treatment, with effectiveness maintained until week 54. PET/CT findings showed that IFX administration improved thrombophlebitis and arterial occlusion by decreasing the severity of inflammation. Neither the aggravation of VBD nor inflammation was newly seen in any patient receiving IFX treatment during the present study, suggesting that the antiinflammatory effects of IFX inhibit the progression of VBD.

QOL is relatively poor among BD patients.[25] However, in the present study, IFX improved the VAS and SF-36 scores, irrespective of the type of BD. This effect suggests that, by resolving BD symptoms, IFX improves the QOL of BD patients. In the present study, IFX treatment also allowed a reduction in dose or withdrawal of steroid treatment in all BD types, while also improving BD-associated symptoms. IFX improved not only the major symptoms, including recurrent oral aphthous ulcers, skin lesions, eye lesions, and genital ulcers, but also all the other symptoms of BD, from treatment initiation up to week 54. One patient with eye symptoms at baseline did not develop any eye symptoms or ocular attacks throughout the course of the study. In addition, IFX has been reported to suppress the frequency of ocular attacks in patients with BD with refractory uveoretinis.[9] We therefore believe that IFX treatment is effective against all symptoms of BD.

The efficacy of IFX in treating RA and CD has been reported to depend on its serum concentration, and dose escalation up to 10 mg/kg is possible.[26–31] In the present study, 3 intestinal BD patients who met the dose escalation criteria were administered IFX at 10 mg/kg. After dose escalation, clinical symptoms, serum CRP level, and VAS score continuously or temporarily improved, accompanied by an increase in serum IFX concentration. In spite of the paucity of a number of BD patients, our observations suggest that a dose of 10 mg/kg is useful in those who lose response at 5 mg/kg, as is the case with RA and CD.

No marked differences in safety were noted among patients by BD type. The safety of IFX administration in the present study was comparable to that determined previously in studies with other diseases, including RA,[26,27] CD,[28–31] and BD with refractory uveoretinitis.[9]

Interpretation of our study is limited by the small population and a lack of any controls. BD is a rare disease in Japan, particularly intestinal BD, NBD, and VBD. After consulting with the Pharmaceuticals and Medical Devices Agency of Japan, the sample size was set to be at least 3 patients per disease type, with a total of 15 patients, in consideration of the number of these

patients available and the registration criteria for this study. Our study population was therefore quite small. In addition, we were unable to include a control group for ethical reasons as well as a lack of appropriate control agents and the small number of subjects. We therefore consider it necessary to collect additional data using other methods, such as postmarketing surveillance.

In conclusion, IFX is effective and well tolerated in the treatment of intestinal BD, NBD, and VBD patients with poor response or intolerance to conventional therapy. We believe that the antiinflammatory effect of IFX at the sites of intestinal, neurological, and vascular lesions may help improve morphological changes (ileocecal ulcerations, high-intensity lesions on brain, brainstem atrophy, thrombophlebitis, etc.), clinical symptoms, and QOL and also help reduce steroid dose. IFX may therefore represent a promising new therapeutic option for use in BD patients with these serious conditions.

Acknowledgements

The authors thank the patients, study personnel, and the following investigators who took part in this study: Tatsuya Atsumi, Hokkaido University Graduate School of Medicine; Toshifumi Ashida and Atsuo Maemoto, Sapporo Higashi Tokushukai Hospital; Tomonori Ishii, Tohoku University School of Medicine; Yasuo Suzuki, Department of Internal Medicine, Toho University Sakura Medical Center; Hajime Kono, Teikyo University School of Medicine; Nagamu Inoue, Keio University School of Medicine; Tetsuji Sawada, Tokyo Medical University; Mitsumasa Kishimoto, St. Luke's International Hospital; Keishi Fujio, Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo; Hideo Yoshida, Anjo Kosei Hospital; Kenji Watanabe and Hirokazu Yamagami, Osaka City University Graduate School of Medicine; Shiro Nakamura, Department of IBD, Hyogo College of Medicine; Hiroaki Dobashi, Department of Internal Medicine, Faculty of Medicine, Kagawa University; Toshiyuki Matsui, Fukuoka University Chikushi Hospital.

References

[1] Saadoun D, Wechsler B. Behçet's disease. Orphanet J Rare Dis 2012;7:20.
[2] Suzuki Kurokawa M, Suzuki N. Behcet's disease. Clin Exp Med 2004;3:10–20.
[3] Ideguchi H, Suda A, Takeno M, et al. Behçet disease: evolution of clinical manifestations. Medicine 2011;90:125–32.
[4] Hisamatsu T, Naganuma M, Matsuoka K, et al. Diagnosis and management of intestinal Behçet's disease. Clin J Gastroenterol 2014;7:205–12.
[5] Pineton de Chambrun M, Wechsler B, Geri G, et al. New insights into the pathogenesis of Behçet's disease. Autoimmun Rev 2012;11:687–98.
[6] Imamura Y, Kurokawa MS, Yoshikawa H, et al. Involvement of Th1 cells and heat shock protein 60 in the pathogenesis of intestinal Behçet's disease. Clin Exp Immunol 2005;139:371–8.
[7] Yüksel S, Eren E, Hatemi G, et al. Novel NLRP3/cryopyrin mutations and pro-inflammatory cytokine profiles in Behçet's syndrome patients. Int Immunol 2014;26:71–81.
[8] Hirohata S, Kikuchi H. Changes in biomarkers focused on differences in disease course or treatment in patients with neuro-Behçet's disease. Intern Med 2012;51:3359–65.
[9] Ohno S, Nakamura S, Hori S, et al. Efficacy, safety, and pharmacokinetics of multiple administration of infliximab in Behçet's disease with refractory uveoretinitis. J Rheumatol 2004;31:1362–8.
[10] Travis SP, Czajkowski M, McGovern DP, et al. Treatment of intestinal Behçet's syndrome with chimeric tumour necrosis factor alpha antibody. Gut 2001;49:725–8.
[11] Naganuma M, Sakuraba A, Hisamatsu T, et al. Efficacy of infliximab for induction and maintenance of remission in intestinal Behçet's disease. Inflamm Bowel Dis 2008;14:1259–64.
[12] Kinoshita H, Kunisaki R, Yamamoto H, et al. Efficacy of infliximab in patients with intestinal Behçet's disease refractory to conventional medication. Intern Med 2013;52:1855–62.
[13] Ribi C, Sztajzel R, Delavelle J, et al. Efficacy of TNF α blockade in cyclophosphamide resistant neuro-Behçet disease. J Neurol Neurosurg Psychiatry 2005;76:1733–5.
[14] Fujikawa K, Aratake K, Kawakami A, et al. Successful treatment of refractory neuro- Behçet disease with infliximab: a case report to show its efficacy by magnetic resonance imaging, transcranial magnetic stimulation and cytokine profile. Ann Rheum Dis 2007;66:136–7.
[15] Kikuchi H, Aramaki K, Hirohata S. Effect of infliximab in progressive neuro-Behçet's syndrome. J Neurol Sci 2008;272:99–105.
[16] Adler S, Baumgartner I, Villiger PM. Behçet's disease: successful treatment with infliximab in 7 patients with severe vascular manifestations. A retrospective analysis. Arthritis Care Res 2012;64:607–11.
[17] Vallet H, Riviere S, Sanna A, et al. Efficacy of anti-TNF alpha in severe and/or refractory Behçet's disease: multicenter study of 124 patients. J Autoimmun 2015;62:67–74.
[18] Investigator's brochure: infliximab; 2015. Available at: http://www.pmda.go.jp/drugs/2015/P20150824001/index.html. (in Japanese). [Accessed February 15, 2016].
[19] Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor α monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998;41:1552–63.
[20] Accardo-Palumbo A, Giardina AR, Ciccia F, et al. Phenotype and functional changes of Vγ9/Vδ2 T lymphocytes in Behçet's disease and the effect of infliximab on Vgamma9/Vdelta2 T cell expansion, activation and cytotoxicity. Arthritis Res Ther 2010;12:R109.
[21] Tanida S, Inoue N, Kobayashi K, et al. Adalimumab for the treatment of Japanese patients with intestinal Behçet's disease. Clin Gastroenterol Hepatol 2015;13:940–8.
[22] Ma D, Zhang CJ, Wang RP, et al. Etanercept in the treatment of intestinal Behcet's disease. Cell Biochem Biophys 2014;69:735–9.
[23] Yim SM, Kim DH, Lee HJ, et al. Mucosal healing predicts the long-term prognosis of intestinal Behçet's disease. Dig Dis Sci 2014;59:2529–35.
[24] Hirohata S, Kikuchi H, Sawada T, et al. Clinical characteristics of neuro-Behcet's disease in Japan: a multicenter retrospective analysis. Mod Rheumatol 2012;22:405–13.
[25] Bodur H, Borman P, Ozdemir Y, et al. Quality of life and life satisfaction in patients with Behçet's disease: relationship with disease activity. Clin Rheumatol 2006;25:329.
[26] Rahman MU, Strusberg I, Geusens P, et al. Double-blinded infliximab dose escalation in patients with rheumatoid arthritis. Ann Rheum Dis 2007;66:1233–8.
[27] Takeuchi T, Miyasaka N, Inoue K, et al. Impact of trough serum level on radiographic and clinical response to infliximab plus methotrexate in patients with rheumatoid arthritis: results from the RISING study. Mod Rheumatol 2009;19:478–87.
[28] Suzuki Y, Matsui T, Ito H, et al. Circulating interleukin 6 and albumin, and infliximab levels are good predictors of recovering efficacy after dose escalation infliximab therapy in patients with loss of response to treatment for Crohn's disease: a prospective clinical trial. Inflamm Bowel Dis 2015;21:2114–22.
[29] St Clair EW, Wagner CL, Fasanmade AA, et al. The relationship of serum infliximab concentrations to clinical improvement in rheumatoid arthritis: results from ATTRACT, a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2002;46:1451–9.
[30] Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002;359:1541–9.
[31] Hibi T, Sakuraba A, Watanabe M, et al. Retrieval of serum infliximab level by shortening the maintenance infusion interval is correlated with clinical efficacy in Crohn's disease. Inflamm Bowel Dis 2012;18:1480–7.