Long-term remission of ocular and extraocular manifestations in Behçet's disease using infliximab

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ABSTRACT

Objective. *To investigate the long-term effect of infliximab on ocular and extraocular manifestations in patients with Behçet's disease.*

Methods. *Seven patients with active Behçet's disease and treated with infliximab at Aichi Medical University Hospital for more than 18 months were included in the study. We evaluated visual acuity, the average number of uveitis attacks involving the posterior segment, and general disease activity every 2 months. The Behçet's Disease Current Activity Form (BDCAF) was used for an overall index of disease activity. Anti-infliximab antibody levels were examined in the patients' sera.*

Results. *The follow-up period after initial introduction of infliximab ranged from 19 to 40 months (mean ± SD, 32 ± 8.7 months). The number of infliximab infusions ranged from 12 to 24 (19 ± 4.4). By the 2-month follow-up, the frequency of uveitis attacks involving the posterior segment and the BDCAF scores were significantly improved compared to the 2 months before introducing infliximab. Anti-infliximab antibodies were detected in the sera of all examined patients.*

Conclusion. *Significant long-term improvement in both the frequency of uveitis attacks involving the posterior segment and overall disease activity was provided by the administration of infliximab to patients suffering from Behçet's disease, despite the presence of anti-infliximab antibodies.*

Introduction

Behçet's disease (BD) is a multisystem inflammatory disorder classified as systemic vasculitis with a chronic, relapsing course and involving multiple organs with four primary symptoms: recurrent aphthous ulcers of the oral mucosa; skin lesions, such as erythema nodosum and psedofolliculitis; uveitis; and genital ulcers. In the first description of the disease by Behçet, anterior uveitis with hypopyon was the typical ocular lesion (1), but a predominantly posterior or diffuse uveitis with retinal vasculitis was recently described as the main feature of this disease. Because these ocular lesions may threaten the patient's sight, the development of efficient treatments is desired.

Tumour necrosis factor alpha (TNF-α) is a pro-inflammatory cytokine, and recent reports have indicated that anti-TNF-α therapy is beneficial for the management of ocular lesions in BD patients. Sfikakis *et al*. were the first to show the effect of infliximab, a humanised mouse monoclonal antibody against human TNF-α, on sight-threatening episodes of uveitis in patients with BD (2), with a number of similar reports to follow (3-7). The mechanisms of uveitis induction by TNF-α in BD and the recovery induced by infliximab are still unclear. Recently, we showed that the presence of TNF-α alters the expression of matrix metalloproteinases and tissue inhibitor of metalloproteinases in cells comprising the blood–retinal barrier, and that infliximab counteracts this alteration (8), which may partially illustrate the pathological mechanisms of BD uveitis and infliximab therapy.

In addition to uveitis, extraocular manifestations of BD are controlled by infliximab (9). The efficacy of infliximab for neuro-BD was shown by magnetic resonance imaging (10-14). The beneficial effect of infliximab treatment on progressive neuro-BD is mediated by a reduction of IL-6 levels in the cerebrospinal fluid (12, 15). Sufficient evidence has also been provided for the efficacy of infliximab therapy in refractory entero-BD (16-20). Severe genital ulcers in patients with BD have also been successfully treated with infliximab (21, 22). Furthermore, complete remission was achieved for oral ulcers resistant

to topical and systemic treatment (23). Infliximab has been shown to have long-term efficacy for treating posterior uveitis in BD (24-29). Similarly, a long-term effect of infliximab has been reported in entero-BD (16). However, long-term efficacy in correlation with ocular and extraocular manifestations of BD has not yet been elucidated. In the present study, we examined visual acuity, the event frequency of posterior uveitis attacks, and general disease activity in BD patients scored using the Behçet's Disease Current Activity Form (BDCAF, 30) before and after treatment with infliximab for more than 18 months. We also evaluated the favourable effects and adverse events of infliximab in conjunction with the formation of anti-infliximab antibodies.

Patients and methods

We retrospectively analysed the medical files of seven BD patients with uveitis who were treated with infliximab at Aichi Medical University Hospital for more than 18 months. Criteria for diagnosis were those defined by BD Research Committee of Japan (31). All of the patients showed an increase in the number of uveitis attacks involving the posterior segment for the 6 months prior to infliximab administration. Patients were given an initial intravenous infliximab infusion of 5 mg/kg, and then subsequent infusions 2 weeks, 6 weeks, and then every 8 weeks after the initial infusion. The study was approved by the medical ethics committee of Aichi Medical University Hospital. Peripheral blood samples were taken at the endpoint of the study, December 2010, from the patients who approved the measurement of antibodies against infliximab.

A complete ophthalmologic examination was performed at each visit, including best corrected visual acuity (BCVA), slit-lamp biomicroscopy, tonometry, and indirect ophthalmoscopy. Visual acuity was assessed using a Snellen chart with a scale of 0.1–1.5 and converted to the logarithmic minimum angle of resolution (logMAR) scale. Uveitis attacks involving the posterior segment were defined as an increased development of vitreous haze, the emergence of inflammatory sheathing of the retinal vessels, vascular occlusion, retinal hemorrhages, retinal infiltrate, macular oedema, or papillitis. The mean frequency of uveitis attacks and visual acuity recorded between month -2 and 0 were compared to the values recorded between month 0 and month 40. The month of first infliximab administration is defined as month 0.

Ocular and extraocular manifestations were recorded using the BDCAF score, which includes points about the number of times the patient experienced headache, oral aphthous ulcers, genital ulcers, erythema nodosum, papulopustular skin lesions, or other BD manifestations. We excluded "eye involvement" for BDCAF scores not taking into account ocular evaluation. Each episode of a manifestation declared by patients was rigorously judged by an ophthalmologist, physician, and dermatologist. Each manifestation was assigned a score every 2 months. The mean scores recorded between month -2 and 0 were used as a control for each patient.

A 5-mL peripheral blood sample was taken from each patient before their last infliximab infusion in December 2010. Venous blood samples were collected and centrifuged at 3,000 *g* for 10 minutes, aspirated, and stored at -80°C until analysis. Specific IgM and IgG isotype antibodies to infliximab (ATI) were measured using modified ELISA methods. In this assay, sera were considered positive when exceeding the cut off value, which was set at twice the optical density (OD 450 nm) of the negative control (sera from five healthy human participants) (32).

Infliximab (10 μg/mL in bicarbonate buffer, pH 9.6) was added to a 96-well microtiter plate and incubated overnight at 4°C. Step-diluted serum was added to each well and incubated for 1 hour at room temperature. After washing with PBS-Tween, biotinylated anti-human IgM (3 μg/mL; Rockland, Gilbertsville, PA, USA) was added for 30 minutes at room temperature. After washing, a 1/1,000 dilution of avidine peroxidase (GE Healthcare, Bio-Sciences Corp., Piscataway, NJ, USA) was added to each well. After 30 minutes, the plate was washed with PBS-Tween and subsequently developed with the substrate solution (TMB) (Roche Diagnostics K.K., Tokyo, Japan) for 30 minutes. The reaction was stopped with 0.4 M sulfuric acid.

The IgG fraction in the serum (300 μL) was purified by Protein A HP SpinTrap (GE Healthcare). The protein contents of the purified fraction were measured using a Micro BCA Protein Assay Reagent Kit (Pierce, Rockford, IL, USA). Infliximab was biotinylated

Table I. Patient characteristics.

Patient	Gender/age	Type (years)	Duration of treatment with IFX (months)	Treatment before IFX	Concomitant therapy with IFX	Total IFX	Total no. of uveitis attacks with IFX	HLA-B51	Adverse events
1	M/33	Complete	41	PSL/AZA	PSL/AZA	23	0	+	
2	M/23	Complete	35	PSL	AZA	20	0	–	
3	F/32	Complete	40	PSL/CyA	PSL/AZA	23	5	NA	Genital infection
4	M/26	Complete	19	–	AZA	14	2	NA	
5	F/32	Incomplete	30	PSL	AZA	18	0	+	Infusion reaction
6	M/25	Complete	41	CyA	AZA	24	2	NA	
7	M/42	Incomplete	21	–	AZA	12	2	+	Nausea

Type: Type of criteria for diagnosis of BD (31); IFX: infliximab; PSL: prednisolone; CyA: cyclosporine A; AZA: azathiorpine; NA: not available.

using the One-step Antibody Biotinylation Kit (Miltenyi Biotec Inc., Auburn, CA, USA). The biotinylated infliximab (0.2 μg/mL) was incubated for 1 hour at room temperature in 96-well microtiter plates pre-coated with 2 μg of the purified IgG fraction in 100 μL bicarbonate buffer (pH 9.6). After washing, a 1/1,000 dilution of avidine peroxidase (GE Healthcare) was added and incubated for 30 minutes at room temperature. After incubation, the plate was washed with PBS-Tween and developed with TMB.

The results are presented as the mean ± standard deviation (SD). Statistical analysis was performed using the Mann-Whitney U-test. A p-value <0.05 was considered significant.

Results

The characteristics of the seven BD patients treated with infliximab are presented in Table I. Five of the patients were men and two were women, ranging in age from 23 to 42 years (mean age 30.0 years). The table includes the concomitant treatment with infliximab. Five of the seven patients allowed a measurement of antibodies against infliximab in their sera.

The BCVA values before and after beginning infliximab are shown in Figure 1A. Compared to control, BCVA values improvement during all periods examined after initiating infliximab treatment. In addition, infliximab significantly reduced the number of uveitis attacks involving the posterior segment in almost all time periods studied (p<0.05, Fig. 1B). In addition, the BDCAF scores after infliximab administration were significantly lower than the scores before treatment (p<0.05, Fig. 1C). BDCAF scores not taking into account ocular manifestation were also significantly lower after infliximab treatment compared to controls (p<0.05, Fig. 1D).

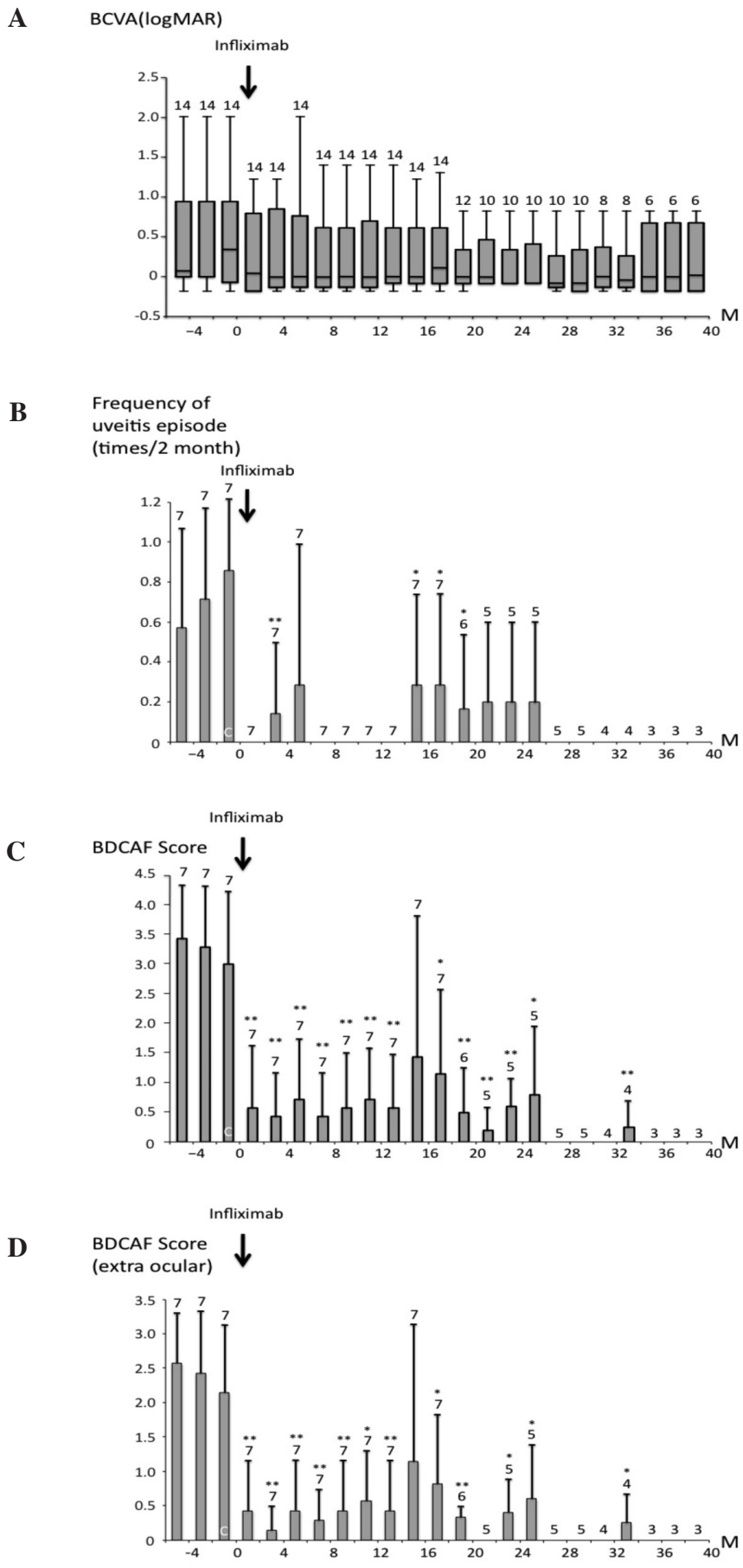

Fig. 1. (**A**) Best corrected visual acuity (BCVA) values represented by the logMAR scale, (**B**) frequency of uveitis involving the posterior segment, (**C**) overall indexes scored by Behçet's Disease Current Activity Form (BDCAF), and (**D**) indexes scored by BDCAF not taking into consideration ocular evaluations before and after the initiation of infliximab. Data are mean ± SD calculated every 2 months. *p<0.05, **p<0.01.

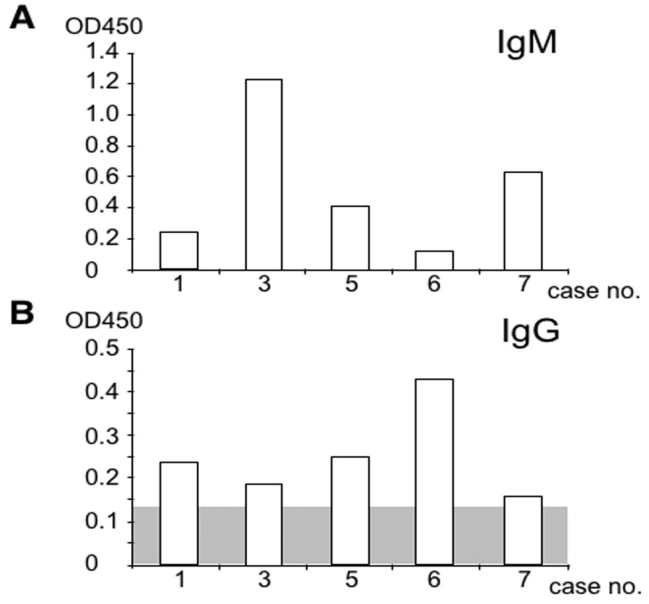

Fig. 2. Anti-infliximab antibody (ATI) levels from the five examined patients. Values are reported as the optical density (OD 450 nm). (**A**) Anti-infliximab-specific IgM. OD 450 of the serum at a dilution of 1:540. Negative control was set to zero. (**B**) Anti-infliximab-specific IgG. OD 450 of the serum at a dilution of 1:1,000. Twice the optical density (OD) of the negative control from five normal human sera was defined as ATI-negative and is indicated as the grey area.

Interestingly, uveitis attacks increased 14-26 months after the administration of infliximab, BDCAF scores not taking into account ocular manifestation tended to increase together.

The ATI level of each patient is shown in Figure 2. The OD 450 values of serum at a dilution of 1:540 and 1:1,000 are shown for IgM-type ATI and IgG-type ATI, respectively. ATI-negative IgG type is indicated by a grey area. Variations in the levels of IgM and IgG types were found among the patients, but all of the ATI levels in the patients were positive compared to controls. No severe adverse event was experienced in any of the patients, but genital infection, infusion reaction, and nausea were confirmed in patients 3, 5, and 7, respectively (Table I). Each event was appropriately settled without any prolonged after-effects.

Ocular and extraocular manifestations recognised in patients during treatment are summarised in Figure 3. The number of both ocular and extraocular manifestations, particularly mouth ulceration, erythema, and eye involvement, drastically decreased with infliximab administration.

Discussion

The present study demonstrated that infliximab has long-term efficacy as an anticipated therapy for both the ocular and extraocular manifestations of BD despite the formation of ATI.

The patients included in this study were generally young. We introduced infliximab before the establishment of irreversible visual disturbances due to severe Behçet's uveitis. The BCVAs of all patients appeared favorable throughout the study. Our previous *in vitro* study suggested that infliximab is more effective if administered before TNF-α increases around the ocular cells (8), which may suggest that maintaining an appropriate concentration of infliximab around ocular cells is beneficial for preventing a uveitis attack in active BD. Anti-TNF-α treatment is considered by some as a first-line therapy for patients with Behçet's uveitis (33), and our present study may support this approach.

Serum infliximab levels and the formation of ATI may be important for evaluating the clinical response in chronic inflammatory diseases. We detected both IgM and IgG-type ATIs in all patients, though not in the same proportion in each patient. For example, case 3 expressed mostly IgM, whereas case 6 expressed mostly IgG. This finding may suggest a switch from IgM-type to IgG-type ATI progressing in each patient. Low trough levels of infliximab are associated with the presence of ATI in patients with rheumatoid arthritis (5) or ankylosing spondylitis (34). The formation of ATI correlates with functional infliximab levels and clinical responses in rheumatoid arthritis (35, 36) and ankylosing spondylitis (34). On the other hand, no clear evidence shows that ATIs have an impact on efficacy in clinical practice for Crohn's disease (37). The presence of ATI has been demonstrated in patients with BD (38, 39), but our present data indicated favorable long-term clinical responses to infliximab in BD patients despite the presence of ATI. The relevance of ATI to the clinical response is unclear, but infliximab appears to be sufficiently effective despite the presence of ATI in the present study.

Our modified ELISA methods are not expected to be affected by infliximab in the serum and are capable of measuring specific IgM and IgG isotype ATI. However, the presence of infliximab in the serum is still a confounding factor for the measurement of ATI by ELISA. Sugita *et al*. measured serum infliximab levels in patients and showed that levels 8 weeks after infusion decreased to less than one-tenth the levels 1 hour after infusion in 84% of cases examined (39). Thus, we collected a peripheral blood sample from each patient before their last infliximab infusion, the time assumed for the lowest infliximab levels in the serum.

Baert *et al*. reported that the concentration of ATI in patients taking immunosuppressive agents, such as azathioprine (AZA), methotrexate (MTX), or 6-mercaptopurine (6-MP), is significantly lower than the concentration in those not taking these agents, and that the development of ATI is associated with an increased risk of infusion reactions (40). Vermeire *et al*. demonstrated that concomitant immunosuppressive therapy using MTX or AZA reduces ATI formation associated with infliximab treatment, improves the pharmacokinetics of infliximab, and that there is no difference between MTX and AZA in reducing these risks (41). Hanauer *et al*. showed that the incidence of ATI and infusion reactions in the absence of concomitant immunomodulators, such as 6-MP, AZA, and MTX, is significantly higher than the incidence in the presence of these chemicals (42). These three reports studied Crohn's disease. Here, we used AZA with infliximab for all patients, and three showed

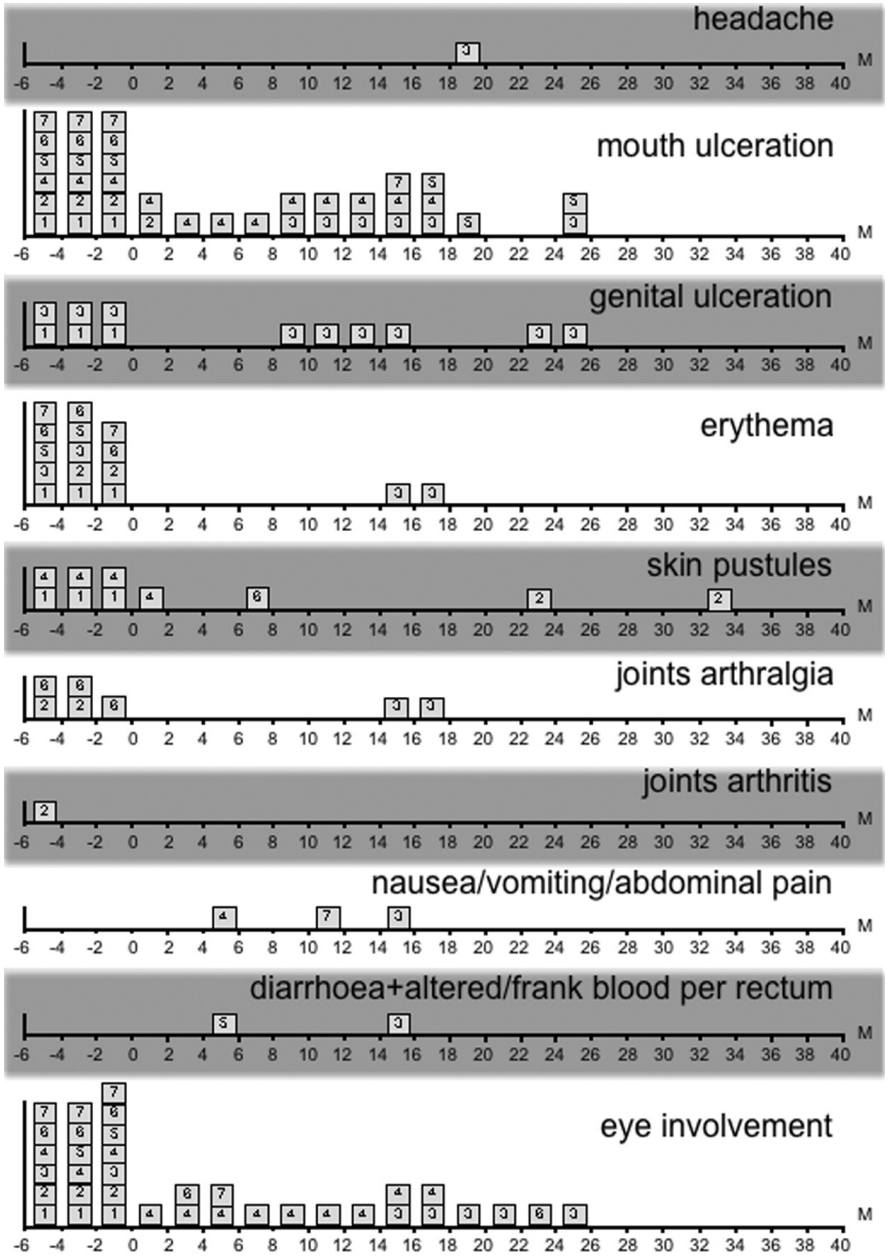

Fig. 3. Ocular and extraocular manifestations in patients before and after infliximab administration. Numbers in the boxes indicate the cases exhibiting each manifestation during each time period. The "eye involvement" BDCAF score included anterior, intermediate, and posterior uveitis. Indexes for nervous system involvement and major vessel involvement are not shown here because no patients presented with these manifestations in the study.

mild adverse effects but did not need to terminate infliximab treatment. The occurrence of severe adverse effects may have been suppressed by using AZA, but further clinical investigations are necessary to clear it.

In the present study, the number of uveitis attacks increased at 14-26 months (Fig. 1). Interestingly, as shown in Fig. 1 and 3, extraocular manifestations also increased during the same period, which may indicate sympathised improvements in ocular and extraocular manifestations with the use of infliximab. Increased TNF-α or a degraded protective system against TNF-α in each tissue may have induced these manifestations. The formation of ATI in serum might be involved in transient deteriorations. However, the precise mechanism of the transient deterioration in manifestations is unclear.

Patient 3 showed genital infection after infliximab administration. We do not regard this infection as an adverse event caused by infliximab. We previously reported the improvement of recurrent genital ulcers and severe genital infections using infliximab (21). The genital findings were not completely avoiding with infliximab use, but the event frequency was significantly decreased. Patient 3 also showed recurrent uveitis attacks after infliximab administration. We appropriately used prednisolone (2.5-30 mg/day orally) as a concomitant therapy with IFX (Table I). Fortunately, we managed to control the uveitis attacks using the standard infusion intervals. Thus, we concluded that all seven patients in this study showed a good response to infliximab and that no relapse occurred during treatment. However, this case series was small, and these results cannot be generalised to all patients with Behçet's disease. A large case series study is necessary for more detailed understanding.

Our small case series showed the long-term effect of infliximab on ocular and extraocular manifestations in patients with Behçet's disease, despite the presence of anti-infliximab antibodies.

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