Efficacy, Safety, and Pharmacokinetics of Multiple Administration of Infliximab in Behçet's Disease with Refractory Uveoretinitis

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ABSTRACT. ***Objective.*** Behçet's disease (BD) with uveoretinitis is a chronic refractory disease accompanied by ocular attacks. As the decrease in visual acuity due to ocular attack is seriously life-threatening, development of a new drug is anticipated.

Since tumor necrosis factor-α (TNF-α) is involved in the symptoms of BD, particularly the activity of ocular symptoms, suppression of TNF-α might be effective in treating BD with uveoretinitis. We conducted a clinical trial of infliximab, an anti-TNF-α chimeric monoclonal antibody, in patients with BD.

Methods. In this open label trial, the efficacy, safety, and pharmacokinetics of repeated administration of infliximab were evaluated in 13 patients with BD accompanied by refractory uveoretinitis. Infliximab was administered 4 times at Weeks 0, 2, 6, and 10 at doses of either 5 or 10 mg/kg by intravenous drip infusion. Frequency of ocular attacks was used as the primary index for evaluation of efficacy, with visual acuity and extraocular symptoms as secondary indices.

Results. The mean numbers of ocular attacks, converted to frequency per 14 weeks, were 3.96 times for the 5 mg/kg group and 3.79 times for the 10 mg/kg group during the observation period. Following treatment with infliximab, they decreased to 0.98 times and 0.16 times, respectively. A serious adverse event, tuberculosis, was observed in one case in the 10 mg/kg group. Serum infliximab concentration increased with dosage.

Conclusion. Administration of infliximab in patients with BD with refractory uveoretinitis suppressed the frequency of ocular attacks, and multiple administration was well tolerated, suggesting that infliximab is effective for this condition. (J Rheumatol 2004;31:1362–8)

Key Indexing Terms:
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Behçet's disease (BD) is a chronic, relapsing inflammatory disease that involves multiple organs with 4 primary symptoms: recurrent aphthous ulcers of oral mucosa, skin lesions such as erythema nodosum and pseudofolliculitis, uveitis, and genital ulcers. Uveoretinitis is particularly common and serious enough to often cause marked visual impairment that can lead to blindness.

Cyclosporine is a commonly used and powerful drug that is frequently adequate for suppression of ocular attacks that accompany BD[1]. However, some patients cannot receive adequate treatment with cyclosporine, which requires careful control due to adverse events such as kidney disorder. Moreover, there are patients whose ocular lesion activity may not be controlled even with cyclosporine[2].

Tumor necrosis factor-α (TNF-α) functions as a proinflammatory cytokine that aggravates uveitis in animal models of experimental autoimmune uveoretinitis (EAU)[3]. Moreover, anti-TNF-α antibody suppresses the onset of EAU[4]. In humans, production of TNF-α in intraocular T cell clones and peripheral monocytes was more active in patients with BD accompanied by uveoretinitis than in healthy controls[5], and TNF-α production in peripheral monocytes is

particularly higher the more active the ocular symptoms[6]. These findings suggest that TNF-α is deeply involved in the aggravation of BD and particularly the activity of ocular symptoms, and that inhibition of TNF-α might be effective in treating BD with uveoretinitis.

Infliximab is an anti-TNF-α chimeric monoclonal antibody, composed of an antigen-binding variable region from mice with high affinity to human TNF-α and a constant region of human IgG_1 (L chain: κ, H chain: γ1). Since clinical findings indicate infliximab has improved symptoms in rheumatoid arthritis (RA) and Crohn's disease[7,8], where TNF-α concentrations are abnormal, it is used as a therapeutic option for these diseases. The possibility of applying infliximab to other intractable inflammatory diseases is suggested, and use of infliximab has been reported to treat patients with BD[9-11].

We carried out an open label clinical trial to evaluate the efficacy, safety, and pharmacokinetics of infliximab administered 4 times at Weeks 0, 2, 6, and 10 at a dose of 5 mg/kg or 10 mg/kg in patients with BD complicated with uveoretinitis.

MATERIALS AND METHODS

All subjects had BD accompanied by uveoretinitis that was cyclosporine-resistant (ocular attacks uncontrollable with cyclosporine); all were between 18 and 65 years of age, and all gave informed consent. Ethical committee approval was obtained for this study. The investigator registered patients who had experienced at least one ocular attack each during the retrospective period (14 weeks before the observation period) and during the observation period (maximum of 14 weeks before administration of infliximab), with a total of ≥ 3 attacks over the entire length of time.

In this study, infliximab (manufactured by Centocor, Inc., Malvern, PA, USA, and supplied free of charge by Tanabe Seiyaku Co., Ltd., Osaka, Japan) was administered at a constant dose of either 5 mg/kg or 10 mg/kg at Weeks 0, 2, 6, and 10 for over 2 hours of intravenous drip infusion. The target total number of cases was set as 12. The lower dose of 5 mg/kg was to be administered to 6 cases followed by the higher dose of 10 mg/kg to 6 other cases. The initial administration was done in remission (i.e., when inflammation subsided and there was no onset of another attack) with lessening or disappearance of inflammation. The use of immunosuppressants such as cyclosporine, 6-mercaptopurine ribosides, tacrolimus, and methotrexate was prohibited during the efficacy evaluation period. Concomitant use of systemic or local (subconjunctival, sub-Tenon's, retrobulbar) corticosteroids was permitted provided that the medication was given as a temporary treatment following ocular attacks. Efficacy was evaluated until 14 weeks after administration, and safety and pharmacokinetics were evaluated until 26 weeks after initial administration.

Incidence of ocular attacks, the primary efficacy endpoint for the study, was analyzed as follows. Ocular attacks were defined as inflammation at the anterior ocular segment (flare and the number of cells), vitreous body clouding, or fundal inflammation (edema, exudative plaque, bleeding, and white vascular sheaths) confirmed by ophthalmologic examinations such as slit-lamp microscopy and funduscopy. For each dosage group, the number of ocular attacks during the observation period and the efficacy evaluation period was converted to frequency per 14 weeks, and their mean values and standard deviation (SD) were calculated. Mean values and SD were also calculated for changes in ocular attacks between the observation period and the efficacy evaluation period. The frequency of ocular attacks before and after treatment was compared within each dosage group by Wilcoxon's signed-rank test, and the changes were compared between the 2 dosage groups by Wilcoxon's rank-sum test. Patients who no longer experienced any ocular attack following treatment were also counted, and the ocular attack disappearance rate was calculated.

For each dosage group, the number of ocular attacks during the retrospective period, the observation period, and the efficacy evaluation period was converted to frequency per 14 weeks, and their mean values and SD were calculated.

Visual acuity and extraocular symptoms were tallied as the secondary efficacy endpoints. Visual acuity during remission with lessening or disappearance of inflammation was measured before and after administration using Landolt ring charts[12].

With regard to extraocular findings, the extent of oral aphthous ulcers, genital ulcers, and skin lesions such as erythema nodosum, pseudofolliculitis, and subcutaneous thrombophlebitis was classified into 4 ranks.

In the assessment of safety, adverse events and those whose relationship with infliximab could not be denied were calculated by each dose group. Adverse events manifested from the start of administration until 2 hours after the end of administration were tallied as an infusion reaction. For inflammatory variables, C-reactive protein (CRP) values were measured using a quantitative method (latex immunoagglutination assay)[13] at Weeks 0, 2, 6, 10, 14, and 26. Antinuclear antibody (ANA) was also measured.

With respect to pharmacokinetics, the serum concentration of infliximab was measured by ELISA[14] on Days 0 and 3, and in Weeks 1, 2, 6, 10, 12, 14, 22, and 26. In Weeks 0, 2, 6, and 10, when infliximab was administered, the concentration was measured before administration and 1 hour after the completion of administration. Serum concentration of infliximab was measured to calculate C_{max} and trough values. Neutralizing antibody titer against infliximab was measured by ELISA[14].

RESULTS

The target total number of cases was set at 12. However, infliximab was administered to 13 cases — 7 cases in the 5 mg/kg group and 6 cases in the 10 mg/kg group (Table 1).

Table 1. Patient demographics.

	Dosage Group	
	5 mg/kg n = 7	10 mg/kg n = 6
Sex, n %		
Male	6 (85.7)	5 (83.3)
Female	1 (14.3)	1 (16.7)
Age, yrs, range	18–61	24–46
Mean ± SD	38.4 ± 16.3	37.5 ± 9.8
Primary symptoms, n (%)		
Aphthous ulceration* + skin lesion + ocular lesion	5 (71.4)	3 (50.0)
Aphthous ulceration* + skin lesion + ocular lesion + genital ulcer	2 (28.6)	3 (50.0)
Secondary symptoms, n (%)		
Arthritis**	4 (57.1)	3 (50.0)
Arthritis*** + digestive lesion***	0 (0.0)	1 (16.7)
None	3 (42.9)	2 (33.3)
Period of illness, yrs, n (%)		
≤ 3 years	4 (57.1)	1 (16.7)
3–6	1 (14.3)	4 (66.7)
> 6	2 (28.6)	1 (16.7)

* Aphthous ulceration: recurrent aphthous ulceration of oral mucosa. ** Arthritis: Arthritis without deformity or rigor. *** Digestive lesion: lesion in the digestive organ represented by ileocecal ulcer.

No difference was observed in patient background characteristics (sex, age, etc.) between the 5 mg/kg group and the 10 mg/kg group.

According to the International Uveitis Study Group classification system[15], all patients were classed as the chronic panuveitis type and were corticosteroid-resistant. The patients selected were those with a chronic and active posterior uveoretinitis with retinal vasculitis. They had periodic severe uveoretinitis flares even with standard systemic therapies.

In all 13 cases, no immunosuppresant other than cyclosporine was administered, and cyclosporine at dosages from 2.36 mg/kg to 5.88 mg/kg per day was prescribed before administration of infliximab, but it was discontinued entirely while infliximab was given. In both the 5 mg/kg and 10 mg/kg groups, administration of colchicine was continued in 5 cases in which it had been used prior to administration of infliximab.

After the onset of ocular attacks, patients were treated uniformly with subconjunctival decadron injection or 20–40 mg of prednisolone administered orally for 1 to 4 weeks as a temporary treatment, depending on the severity of the inflammation during the observation and the treatment periods.

With respect to the primary efficacy endpoints, as shown in Table 2, during the efficacy evaluation period, ocular attacks disappeared in 5 out of 7 cases in the 5 mg/kg group (ocular attack disappearance rate 71.4%), and in 5 of 6 cases in the 10 mg/kg group (ocular attack disappearance rate 83.3%). In the observation period, the mean frequency of ocular attacks was 4.0 times in the 5 mg/kg group and 3.8 times in the 10 mg/kg group, and a statistically significant difference was not observed between the dosage groups. During the efficacy evaluation period, they decreased significantly to 1.0 time in the 5 mg/kg group ($p = 0.031$) and 0.2 time in the 10 mg/kg group ($p = 0.031$).

The median duration of the observation period was 51.5 days (range 28–106 days). The total number of ocular attacks during the entire pretreatment period (retrospective period and observation period) was also investigated in a similar manner. The mean frequency of attacks during the pretreatment period (retrospective period and observation period) per unit period (14 weeks) was 3.5 ± 1.1 and 3.8 ± 1.7 times in the 5 mg/kg group and the 10 mg/kg group, respectively, which were comparable to those observed when the observation period alone was included in the pretreatment period. Thus, the frequency of ocular attacks per unit period (14 weeks) decreased significantly after infliximab administration in both the 5 mg/kg group and the 10 mg/kg group ($p = 0.047$, $p = 0.031$). No significant difference was observed in changes in the frequency of attacks before and after treatment between the 2 dose groups ($p = 0.353$). The number of ocular attacks converted to the frequency per 14 weeks was similar when the observation period alone was counted as the pretreatment period and when both retrospective period and observation period were included in defining the pretreatment period.

This result suggested that infliximab is effective in suppressing the occurrence of ocular attacks in patients with BD accompanied by uveoretinitis. A statistically significant

Table 2. Comparison of number of ocular attacks before and after treatment.

Dosage Group	Case	Pretreatment						Posttreatment		
		Registration Period + Observation Period*			Observation Period*			Efficacy Evaluation Period**		
		Measured Number	Period, days	Calculated Frequency†	Measured Number	Period, days	Calculated Frequency†	Measured Number	Period, days	Calculated Frequency†
5 mg/kg	1	4	148	2.6	1	50	2	0	99	0
	2	4	161	2.4	1	63	1.6	0	100	0
	3	7	189	3.6	3	91	3.2	0	99	0
	4	6	135	4.4	3	37	7.9	0	98	0
	5	3	131	2.2	1	33	3	1	101	1
	6	7	134	5.1	2	36	5.4	0	77	0
	7	8	183	4.3	4	85	4.6	6	100	5.9
	Mean††		3.5			4.0			1.0	
10 mg/kg	8	9	132	6.7	1	34	2.9	1	100	1
	9	6	144	4.1	3	46	6.4	0	100	0
	10	6	155	3.8	2	57	3.4	0	98	0
	11	4	126	3.1	1	28	3.5	0	94	0
	12	3	198	1.5	1	100	1	0	101	0
	13	8	204	3.8	6	106	5.5	0	56	0
	Mean††		3.8			3.8			0.2	

* Observation period: a maximum of 14 weeks from the beginning of observation until initial administration (ophthalmologic examination was conducted every 2 weeks). ** Posttreatment efficacy evaluation period: 14 weeks following administration (ophthalmologhic examination was conducted every 2 weeks). † Number of attacks × period (14 weeks). †† Mean value of the number of ocular attacks converted to frequency per 14 weeks.

difference was not observed between the dosage groups in the levels of changes in the frequency of ocular attacks before and after treatment (p = 0.617).

Visual acuity, one of the secondary efficacy endpoints, is given in Table 3. Administration of infliximab improved the visual acuity of either or both eyes in 5 out of 7 cases in the 5 mg/kg group and in 4 of 6 cases in the 10 mg/kg group. Visual acuity was improved in most of the subjects whose ocular attacks had disappeared. After administration, no ocular attack has been observed in any of these cases.

Oral aphthous ulceration, one of the extraocular findings, was observed in 2 cases in the 5 mg/kg group and 3 cases in the 10 mg/kg group (Table 3), erythema nodosum in one case in the 5 mg/kg group, and folliculitis in 4 cases in the 5 mg/kg group and 3 in the 10 mg/kg group, before the treatment. No subject showed symptoms of genital ulcers and subcutaneous thrombophlebitis. After administration of infliximab, oral aphthous ulceration disappeared in both cases in the 5 mg/kg group and 2 out of 3 cases in the 10 mg/kg group, erythema nodosum disappeared, and folliculitis, acne-like lesions, disappeared in 2 of 4 cases in the 5 mg/kg group, and one of 3 cases in the 10 mg/kg group. Adverse events were observed in all subjects in both groups.

Table 4. Main adverse events (AE) classified by relationship. Data are incidence per total number of patients (%).

	5 mg/kg Group, n = 7	10 mg/kg Group n = 6
Patients with AE	7 (100.0)	6 (100.0)
AE, n	43	30
Diarrhea	4 (57.1)	1 (16.7)
Common cold	4 (57.1)	
Malaise	3 (42.9)	1 (16.7)
Nausea	3 (42.9)	1 (16.7)
Pyrexia	2 (28.6)	2 (33.3)
Headache	1 (14.3)	2 (33.3)
Increased systolic BP	1 (14.3)	2 (33.3)
Epigastric distress	2 (28.6)	
Vomiting	2 (28.6)	
Decreased diastolic BP	2 (28.6)	
Arthralgia		2 (33.3)
Constipation		2 (33.3)

Data are incidence per total number of patients (%).

Table 4 shows adverse events that were observed in 2 or more subjects. Major adverse events include diarrhea, common cold, malaise, nausea, and pyrexia.

Adverse events classified as infectious diseases were noted in 5 subjects in the 5 mg/kg group and 2 subjects in

Table 3. Visual acuity and extraocular findings.

Dosage Group	Case	Visual Acuity		Oral Aphthous Ulceration		Erythema Nodosum		Folliculitis	
		Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment
5 mg/kg	1	R —	—	0	0	1	0	3	3
		L 0.1	0.2						
	2	R 0.1	0.1	1	0	0	0	0	0
		L —	—						
	3	R 0.08	0.2	0	0	0	0	1	1
		L HM	0.01						
	4	R HM	0.02	0	0	0	0	0	0
		L 0.05	0.05						
	5	R 0.03	0.04	0	0	0	0	0	0
		L —	—						
	6**	R 0.07	0.07	1	0	0	0	3	3
		L HM	0.01						
	7**	R 0.08	0.07	0	0	0	0	1	0
		L 1.2	1.2						
10 mg/kg	8	R 0.02	0.01	1	0	0	0	1	1
		L 0.07	0.04						
	9	R 0.2	0.3	0	0	0	0	0	0
		L 0.03	0.08						
	10	R 0.2	0.15	1	0	0	0	3	0
		L —	—						
	11	R 0.15	0.1	0	0	0	0	0	0
		L 0.03	0.1						
	12	R —	—	3	3	0	0	3	3
		L 0.03	0.07						
	13**	R 0.06	0.1	0	0	0	0	0	0
		L HM	HM						

3: Symptoms were present at all times and never disappeared. 2: Symptoms were present in more than half the days in a 4-week period. 1: Symptoms were present in fewer than half the days in a 4-week period. 0: No symptoms. Final evaluation point was used for post treatment. * Blind eye or no ocular attack. ** Treatment discontinued. HM: hand motion.

the 10 mg/kg group, with the common cold and pyrexia as the major events.

Adverse events classified as infusion reaction were noted in 5 subjects in each group, with malaise, pyrexia, decreased diastolic blood pressure, and increased systolic blood pressure as the major events. The number of subjects experiencing infusion reactions specific to each time of administration was 7 after the first administration, 4 after the second, 2 after the third, and one after the fourth. Among the 7 subjects experiencing infusion reactions after the first administration, one had another reaction after the second administration. Among the 4 subjects showing infusion reactions after the second administration, one had another reaction after the third administration. Wheal appeared in one subject during the third and fourth administrations, and the trial treatment was discontinued for that subject without completing the fourth administration.

Serious adverse events, classified as infectious diseases such as miliary tuberculosis, tuberculous meningitis, and upper respiratory infection, were observed in one subject in the 10 mg/kg group. This patient was found to have latent tuberculosis. Treatment of the patient with infliximab was terminated after the second administration because of persistent fever. Subsequent tests on gastric juice culture and spinal fluid sample were both polymerase chain reaction-positive for tubercle bacilli.

Abnormal changes in clinical laboratory data, defined in principle as changes of 25% or more in blood test values and worsening by one degree or more in urinalysis results, were classified by causal relationship with infliximab. Major abnormal changes in the data with an undeniable causal relationship included abnormal urinalysis in the 5 mg/kg group, and increased ALP, increased LDH, increased eosinophil count, increased monocyte count, increased GOT, increased GPT, and hematuria positive in the 10 mg/kg group.

Baseline CRP concentration was relatively low because the initial administration was given while ocular attacks were in remission, and the level decreased further in most of the patients after infliximab administration (Figure 1). Subject 7 in the 5 mg/kg group showed a common cold during CRP measurement at Weeks 2, 6, and 14; Subject 13 in the 10 mg/kg group showed upper respiratory tract infection, pyrexia, and peritonsillar abscess during CRP measurement at Weeks 2 and 6; and Subject 10 showed sinusitis during CRP measurement at Week 6.

Although ANA was also observed following treatment in 2 cases in the 10 mg/kg group, lupus-like syndrome was not observed.

Since the measurement using ELISA of neutralizing antibody is obstructed by the presence of infliximab in serum, the cases with infliximab were excluded. Neutralizing antibody could be evaluated in 4 cases in the 5 mg/kg group and 3 cases in the 10 mg/kg group, among which the antibody was detected in one case in the 5 mg/kg group.

Infliximab serum concentration (median) following the initial administration increased with dosage. The profile for multiple administrations was similar to that following the initial administration. Both C_{max} and trough values increased with dosage. Elimination half-life at the end-phase after the final administration showed no difference between the 2 groups ($p = 0.202$).

DISCUSSION

The number of patients in Japan with BD is estimated to be about 18,400[16], the greatest number within a single country in the world. Ocular lesions occur in about 70% of these patients with BD. It is believed that 10% of them cannot be controlled with the available therapies[17].

In this study, infliximab treatment was given to patients with active BD accompanied by uveoretinitis whose ocular attacks could not be controlled by standard therapy. Multiple administration of infliximab at a dosage of 5 mg/kg or 10 mg/kg resulted in disappearance or reduction of ocular attacks following treatment, suggesting that infliximab is effective for BD accompanied by uveoretinitis.

Regarding visual acuity during remission, many cases showed improvement. As visual acuity improved in most of the cases whose ocular attacks had disappeared, it was suggested that the reduced incidence of ocular attacks yielded by treatment with infliximab brought favorable results for the clinical course of visual acuity.

While efficacy of infliximab was very high whether administered at 5 mg/kg or 10 mg/kg, no significant difference was noted in changes in the incidence of ocular attacks between the 2 groups.

Sfikakis, *et al*[9] reported that when 5 patients with panuveitis in BD were treated with a single infusion of infliximab at 5 mg/kg, ocular inflammation was suppressed. Munoz-Fernandez, *et al*[10] reported that 3 administrations of infliximab at 5 mg/kg in one patient with panuveitis in BD led to a striking reduction of inflammatory cells. These reports support our results.

In this study we set up an observation period of a maximum of 14 weeks before beginning administration of infliximab, and compared the frequency of ocular attacks per unit period of 14 weeks between observation period and the efficacy evaluation period. It was considered that efficacy on suppression of ocular attacks could be objectively evaluated in this way.

With respect to extraocular findings, oral aphthous ulcers and skin lesions, such as erythema nodosum and pseudofolliculitis, were present before the administration of infliximab. Although there were few cases with these symptoms, infliximab caused them to disappear, suggesting that infliximab is effective for these extraocular symptoms in BD.

On the other hand, adverse events such as infectious

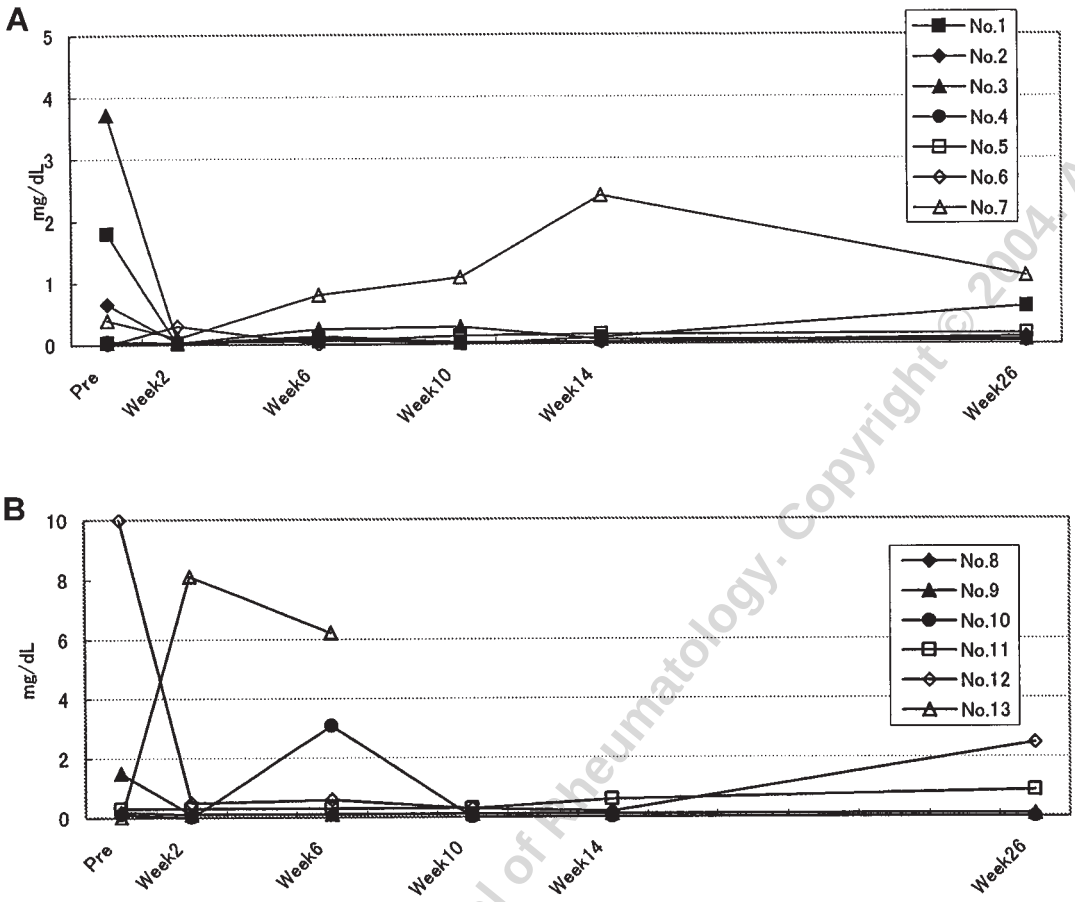

Figure 1. Changes in CRP values after infliximab administration. A. 5 mg/kg group; B. 10 mg/kg group.

disease, infusion reactions, and positive ANA were also observed, although, with the exception of one patient, they were not serious. Since a serious adverse event classified as infectious disease was observed in one subject in the 10 mg/kg group, it was estimated that all these adverse events were possibly related to the study drug, since infliximab could have affected the immune system and increased the patients' sensitivity to infections.

Infusion reactions were noted in 10 out of 13 patients. The high incidence of such reactions appears to have resulted from inclusion of all adverse events occurring from the start of each administration up to 2 hours post-dosing. All these adverse events were mild except one case of moderate pyrexia. Treatment was discontinued in one patient because of infusion reaction (wheal), which was also mild.

However, these adverse events were indicated in reports on the clinical trials and postmarketing surveillance for RA or Crohn's disease, and were not specific to BD.

Local or systemic overproduction of TNF-α has been thought to be a cause of inflammatory diseases. Infliximab has shown efficacy against inflammatory diseases by displaying antagonism against TNF-α, which is observed as suppression of ocular attacks in BD, reduction in the number of tender and swollen joints in patients with RA, and lowering of the Crohn's Disease Activity Index and improvement in endoscopic findings in patients with Crohn's disease, as reported. However, it is suggested that local production of a certain level of TNF-α may be involved in defending the host against infection, and serious infectious diseases have been reported during infliximab therapy[18]. Therefore, any signs of infection have to be closely observed when prescribing infliximab.

Our results indicate infliximab is useful for patients with BD who cannot be sufficiently treated with standard therapies. With the reservation that the risk versus benefit of infliximab treatment has to be taken into consideration, we think that patients with early ocular involvement would benefit more from this treatment.

Followup investigation after the final administration of infliximab revealed relapses of ocular attacks about 12 weeks after the final administration in the cases in which ocular attack had been suppressed. This finding suggests that the improved clinical symptoms as a result of infliximab reflect suppression of the seriousness of the condition. Because of the occurrence of ocular attacks while the inflix-

imab remained present in the blood 12 weeks after the final administration, we are now conducting a longterm administration study in which infliximab is given over the course of about a year at Weeks 0, 2, and 6, and then every 8 weeks for a total of 8 times, to achieve complete remission of ocular attacks that aggravate visual acuity.

In this study, both 5 mg/kg and 10 mg/kg doses were equally effective, suggesting that 5 mg/kg is more appropriate than the 10 mg/kg dose. In the ongoing longterm administration study, however, the same patients who participated in the present study are being treated with the same dosage of infliximab (either 5 or 10 mg/kg) that they received in this study.

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