ENHANCED DEPTH IMAGING OPTICAL COHERENCE TOMOGRAPHY OF THE CHOROID IN VOGT–KOYANAGI–HARADA DISEASE

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Purpose: Optical coherence tomography (OCT) using enhanced depth imaging (EDI) allows evaluation of choroidal thickness. Our objective was to analyze subfoveal choroidal thickness by EDI-OCT before and after the initiation of high-dose corticosteroid treatment in 8 patients (16 eyes) with new-onset acute Vogt–Koyanagi–Harada (VKH) disease.

Methods: Retrospective review of clinical records.

Results: The outer border of the choroid was not evident by EDI-OCT in any patients at presentation. Subfoveal choroidal thickness was measurable by 1 week after the initiation of treatment (mean, 578 μm) and decreased thereafter (mean at 1 month, 397 μm; 3 months, 392 μm; 6 months, 384 μm; 12 months, 332 μm). Rebound of choroidal thickening was observed in three patients (five eyes) during corticosteroid tapering in the absence of other evidence of increased inflammation. Peripapillary atrophy was present at 12 months in 6 of 6 eyes that had a choroidal thickness >550 μm at 1 week after initiating treatment, in contrast to none of the 8 eyes with a choroidal thickness ≤550 μm ($P = 0.0003$).

Conclusion: Enhanced depth imaging–optical coherence tomography revealed decreasing choroidal thickness with high-dose corticosteroid treatment in our patients. Choroidal thickness as measured by EDI-OCT may serve as a marker for degree of choroidal inflammation in acute VKH disease.

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Vogt–Koyanagi–Harada (VKH) disease is a bilateral, diffuse granulomatous panuveitis associated with central nervous system and/or auditory signs in the early stage and integumentary depigmentation in the late stage.[1] VKH disease is believed to be caused by an autoimmune response directed against melanocytes in the choroid and elsewhere in the body.[2] The pathologic process involves a diffuse choroiditis in the acute phase, and thus, choroidal thickening is one of the criteria required by the Revised Diagnostic Criteria for VKH disease.[3] B-scan ultrasonography has been used to measure choroidal thickness and to monitor the response to corticosteroid treatment in VKH disease.[1,4] However, ultrasonography is somewhat cumbersome to perform, its results are examiner-dependent, and it produces only poor quality images that are inadequate for quantitative analysis. Indocyanine green angiography (IA) has also been used to assess choroidal inflammation in VKH disease; however, this test is invasive, involves systemic administration of dye, and produces images that are also difficult to assess in a quantitative fashion.[5,6]

Optical coherence tomography (OCT) using spectral domain (SD) technology has revealed many features of the serous retinal detachment (SRD) observed in acute VKH disease[7]; however, standard SD-OCT cannot adequately image the choroid. Recently, a new method of SD-OCT termed enhanced depth imaging (EDI) has been shown to be capable of visualizing the full thickness of choroid.[8,9] The advantages of EDI-OCT include that it is noninvasive, does not involve systemic administration of dye, is relatively examiner-independent, and produces images of choroidal thickness that are easily quantifiable. Furthermore, the data obtained

may be stored digitally for direct analysis of sequential follow-up tests. Enhanced depth imaging–optical coherence tomography has been used to measure choroidal thickness in normal eyes and highly myopic eyes.[9,10] In this report, we describe EDI-OCT findings in 8 patients with new-onset acute VKH disease, before and during the course of corticosteroid treatment over 12 months of follow-up.

Materials and Methods

We reviewed the clinical records of 8 consecutive patients (6 men and 2 women) who presented to the Ocular Inflammation Service of the Kyorin Eye Center, Kyorin University Hospital, between December 2009 and July 2011, and who were diagnosed with new-onset acute VKH disease using the Revised Diagnostic Criteria.[3] Other uveitic conditions were excluded by medical history and/or ancillary testing. None of the patients had a history of penetrating ocular trauma or intraocular surgery.

Fluorescein angiography was performed at the initial visit before treatment (baseline), then as judged clinically necessary during the subsequent follow-up. Both standard OCT and EDI-OCT were performed using the Heidelberg Spectralis instrument (Heidelberg Engineering, Heidelberg, Germany), with retinal scans performed along horizontal and vertical planes through the center of the fovea. Enhanced depth imaging–optical coherence tomography was performed by positioning the instrument close to the eye to obtain an inverted image, with use of the image averaging (100 images) and eye tracking features of the instrument as has been detailed elsewhere.[8,9] Resulting vertical and horizontal images were viewed using the Heidelberg Eye Explorer software (version 1.6.2.0; Heidelberg Engineering). Choroidal thickness was determined by measuring the distance, under the center of the fovea, between the outer border of the hyperreflective line corresponding to the retinal pigment epithelium and the outer border of the choroid. Enhanced depth imaging–optical coherence tomographic images were assessed by three independent masked observers. The three readings obtained were averaged separately for vertical and horizontal images. The average of the vertical and horizontal thicknesses was then taken and used as the choroidal thickness for each time point for each eye. Rebound of choroidal thickening was defined as increased thickness of the choroid >100 μm over the previous lowest measurement obtained during corticosteroid tapering. This definition was based on the fact that the standard deviation for mean choroidal thickness was 52.8 μm at 1 month, a time at which SRD had resolved in all eyes;

100 μm would be approximately twice this standard deviation and therefore imply a value outside 95% of values assuming a normal distribution.

All patients were treated initially with pulse intravenous methylprednisolone (a single pulse consisting of 1000 mg/d for 3 consecutive days) followed by oral prednisolone at a dose of approximately 1.0 mg/kg/d to be tapered over 9 months to 12 months. Some patients received >1 pulse of intravenous methylprednisolone based on the degree of remaining subretinal fluid by funduscopy and OCT and on the results of fluorescein angiography performed at 5 days to 7 days after the last day of intravenous therapy. Standard OCT and EDI-OCT were performed before initiation of treatment (baseline), every 2 days to 3 days over the first 2 weeks, and then about monthly thereafter. Optic disk photographs taken at baseline, 6 months, and 12 months were used to determine the development of peripapillary atrophy (PPA). The length of atrophy along the disk margin was measured, and development of PPA was defined as the presence of new atrophy, with a ratio of length of atrophy-to-disk circumference of 1:3 or greater.

This study was approved by the Kyorin University Hospital Research Ethics Committee and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from each patient. The Wilcoxon signed rank test was used to compare choroidal thickness at different visits. Nominal data were analyzed with the Fisher exact probability test. $P < 0.05$ was considered to be statistically significant.

Results

Sixteen eyes of eight patients with new-onset acute VKH disease were examined. The mean age at presentation was 44.7 years (range, 30–75 years). All patients were categorized as having the incomplete type of VKH disease by the Revised Diagnostic Criteria[3] because no patients were observed to develop integumentary depigmentation during the mean follow-up period of 15.0 months (range, 9–20 months). Based on clinical response to the initial treatment, three patients received one pulse, four patients received two pulses, and one patient received three pulses of intravenous methylprednisolone. Two or more pulses were administered in patients for incomplete resolution of subretinal fluid and/or incomplete resolution of optic disk inflammation based on leakage observed by fluorescein angiography at 5 days to 7 days after the last day of intravenous administration. Table 1 shows the course of SRD and best-corrected visual acuity for all eyes over 12 months. All 16 eyes had SRD involving the fovea at baseline, with complete disappearance

Table 1. Patient Characteristics, Presence or Absence of Serous Retinal Detachment, and Best-corrected Visual Acuity Before and During Corticosteroid Treatment

Patient	Gender	Age (Years)	Eye	Number of Methyl prednisolone IV Pulse Given	Follow-Up (Months)	SRD Present or Absent*/BCVA						
						Before	1W	2W	1M	3M	6M	12M
1	Female	41	OD	2	16	+0.6	+ 0.5	-0.8	-1.2	-1.2	-1.2	-1.2
			OS			+0.7	+0.5	-0.4	-1.2	-1.2	-1.2	-1.2
2	Male	49	OD	3	16	+0.4	+0.4	+0.4	-0.8	-1	-1.2	-1.2
			OS			+0.5	+0.4	+0.6	-1	-1.2	-1.2	-1.2
3	Male	44	OD	1	16	+0.6	+0.7	-0.6	-0.8	-1.2	-1.2	-1.2
			OS			+0.3	+0.5	-0.5	-0.9	-1.2	-1.2	-1.2
4	Male	30	OD	2	9	+0.2	+0.5	+0.9	-1.2	-1.2	-1.2	not done
			OS			+0.5	+0.5	-0.7	-1.2	-1.2	-1.2	not done
5	Male	49	OD	1	19	+0.5	+0.7	-1.2	-1.2	-1.2	-1.2	-1.2
			OS			+0.6	+0.7	-1	-1.2	-1.2	-1.2	-1.2
6	Female	33	OD	1	20	+0.1	+0.8	+1.2	-1.2	-1.2	-1.2	-1.2
			OS			+0.1	+0.8	+1	-1.2	-1.2	-1.2	-1.2
7	Male	37	OD	2	12	+0.4	+0.5	+0.7	-1.2	-1.2	-1.2	-1.2
			OS			+0.6	+0.4	+0.7	-1.2	-1.2	-1.2	-1.2
8	Male	75	OD	2	12	+0.5	+0.4	+0.5	-0.8	-0.9	-1.2	-1.2
			OS			+0.4	+0.3	-0.6	-0.9	-1.0	-1.2	-1.2

Abbreviations used: IV, intravenous; SRD, serous retinal detachment; BCVA, best-corrected visual acuity; W, week(s); M, month(s); OD, right eye; OS, left eye.
*"+"indicates that SDR was present,"-"indicates that SRD was absent.

of the SRD in 8 eyes by 2 weeks and in all eyes by 1 month. At baseline, the best-corrected visual acuity ranged from 0.1 to 0.7, and all eyes achieved a best-corrected visual acuity of 1.2 during the follow-up period, although there appeared to be a delay between complete disappearance of SRD by OCT and full recovery of vision. By 6 months, patients had been tapered down to an oral prednisolone dose of 10 mg/d to 25 mg/d, and at 12 months, 4 patients had been tapered completely off the oral prednisolone while 3 patients were still on a dose of 5 mg/d to 10 mg/d.

Figure 1 shows the course of mean choroidal thickness for all 16 eyes over the 12 months of follow-up. Before treatment, the outer border of the choroid was not clearly visible by EDI-OCT. At 1 week after initiating treatment, the outer border of the choroid could be delineated in all eyes, and the mean choroidal thickness was determined to be 578.9 ± 187.9 μm (range, 364–1050 μm). At 1 month, the choroidal thickness was observed to be reduced in all eyes compared with those eyes at 1 week ($P = 0.0012$), with a mean choroidal thickness of 397.8 ± 52.8 μm (range, 336–515 μm). Thereafter, the mean choroidal thickness remained roughly stable at 392.2 ± 120.8 μm (range, 248–696 μm) at 3 months ($P = 0.0006$), 384.7 ± 90.9 μm (range, 205–506 μm) at 6 months ($P = 0.0019$), 411.0 ± 190.9 μm (range, 242–893 μm) at 9 months ($P = 0.0045$), and 332.1 ± 64.1 μm (range, 255–424 μm) at 12 months ($P = 0.0012$). In 4 patients treated with multiple pulses of intravenous corticosteroids (Patients 2, 4, 7,

and 8), choroidal thickness after the second or third pulse was found to have decreased >50 μm in all eyes compared with those after the first pulse treatment. In the remaining patient (Patient 1), choroidal thickness after the first pulse (411 μm in right eye, 442 μm in left eye) decreased only slightly after a second pulse (402 μm in right eye, 430 μm in left eye).

To further analyze these data based on the degree of inflammation, choroidal thickness for each eye was graphed separately for the 3 patients who received only 1 pulse of intravenous methylprednisolone (Figure 2A) and for the 5 patients who required 2 or 3 pulses based
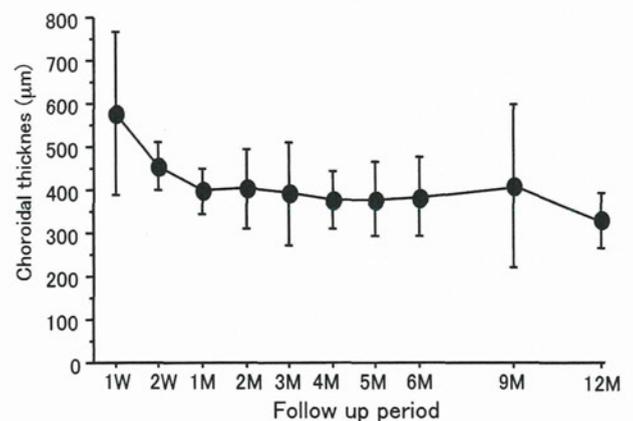

Fig. 1. Mean choroidal thickness as measured by EDI-OCT in 16 eyes (8 patients) with acute VKH disease after initiating high-dose corticosteroid treatment. Bars indicate standard deviations. Statistical significance was calculated in comparison to the value at 1 week by Wilcoxon signed rank test. W, week(s); M, month(s).
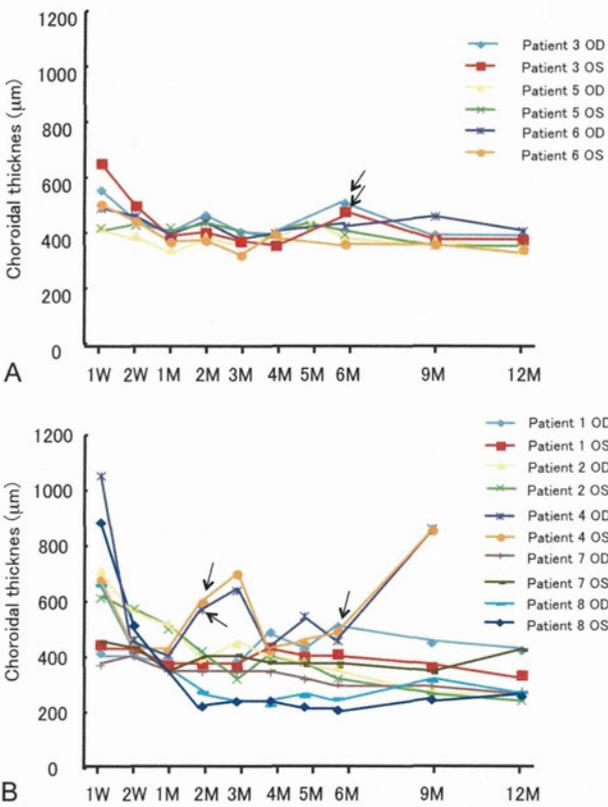
Fig. 2. Choroidal thickness as measured by EDI-OCT in each eye of (**A**) 3 patients who received 1 pulse of intravenous methylprednisolone and (**B**) 5 patients who received 2 pulses (Patients 1, 4, 7, and 8) or 3 pulses (Patient 2) of intravenous methylprednisolone. All patients continued with oral corticosteroid treatment thereafter, tapered slowly over the follow-up period. At 6 months, patients were still receiving oral prednisolone at a dose of 10 mg/d to 25 mg/d. At 12 months, 4 patients had been tapered completely off the oral prednisolone while 3 patients were still on a dose of 5 mg/d to 10 mg/d. Arrows indicate points in time at which rebound of choroidal thickening was noted. Rebound of choroidal thickening was defined as increased thickness of the choroid (>100 μm) over the previous lowest measurement obtained during corticosteroid tapering. W, week(s); M, month(s).

on the initial clinical response (Figure 2B). Rebound of choroidal thickening (defined in the Materials and Methods section) during corticosteroid tapering was observed in both eyes of Patient 3 at 6 months in the group receiving only 1 pulse. In contrast, in the group requiring more than one pulse of intravenous methylprednisolone initially, rebound of choroidal thickness was observed in the right eye of Patient 1 at 6 months and in both eyes of Patient 4 at 2 months and 9 months. Interestingly, no eyes had evidence of recurrent inflammation by slit-lamp biomicroscopy and funduscopy during the follow-up period, including the five eyes with rebound of choroidal thickness. In Patient 1, choroidal thickness in the right eye remained somewhat thickened out to 12 months with continued tapering of treatment but there was no clinical evidence of

Table 2. Relationship Between Rebound of Choroidal Thickening During Steroid Tapering and Presence of Peripapillary Atrophy at 6 Months*

	Peripapillary Atrophy Present†	Peripapillary Atrophy Absent
Rebound (5 eyes)	3	2
No rebound (11 eyes)	2	9
Total (16 eyes)	5	11

*P = 0.222 by Fisher exact probability test.
†Presence of PPA was defined as a ratio of atrophy-to-disk circumference of 1:3 or greater.

recurrent inflammation. In Patient 3, the choroidal thickness in both eyes reverted to previous baseline values within 3 months also despite continued tapering of treatment. Patient 4 did not return for further follow-up after 9 months, and thus, the outcome in this patient is unclear.

As shown in Tables 2 and 3, 5 eyes with rebound in choroidal thickness developed PPA by 6 months, while the same was true for only 2 of the 11 eyes without rebound, although this difference was not statistically significant (P = 0.2445). Development of PPA was also examined based on early choroidal thickness. Because the mean choroidal thickness was 578.9 μm at 1 week after initiating treatment, we used 550 μm as an arbitrary cutoff. As shown in Table 3, 5 of 8 eyes with a choroidal thickness >550 μm at 1 week developed PPA by 6 months compared with the same being true for none of the 8 eyes with choroidal thickness ≤550 μm at 1 week (P = 0.0256). Similarly, Table 4 shows that for eyes followed out to 12 months, 6 of 6 eyes with a choroidal thickness >550 μm at 1 week developed PPA by 12 months compared with the same being true for none of the 8 eyes with a choroidal thickness ≤550 μm at 1 week (P = 0.0003). Color fundus photographs, fluorescein angiographic images, and EDI-OCT images of 2 representative cases are shown in Figures 3–6.

Table 3. Relationship Between Choroidal Thickness >550 μm at 1 Week and Presence of Peripapillary Atrophy at 6 Months*

	Peripapillary Atrophy Present	Peripapillary Atrophy Absent
Choroidal thickness >550 μm (8 eyes)	5	3
Choroidal thickness ≤550 μm (8 eyes)	0	8

*P = 0.0256 by Fisher exact probability test.

Table 4. Relationship Between Choroidal Thickness >550 μm at 1 Week and Presence of Peripapillary Atrophy at 12 Months*

	Peripapillary Atrophy Present	Peripapillary Atrophy Absent
Choroidal thickness >550 μm (6 eyes)	6	0
Choroidal thickness ≤550 μm (8 eyes)	0	8

*P = 0.0003 by Fisher exact probability test.

Discussion

Enhanced depth imaging–optical coherence tomographic images clearly showed bilateral, diffusely thickened choroid in all patients with acute VKH disease at 1 week after starting systemic high-dose corticosteroid treatment. Furthermore, this choroidal thickening was observed to decline over the first 1 month of therapy. These observations are consistent with the histopathologic appearance of acute VKH disease with thickened choroid due to diffuse infiltration of lymphocytes, macrophages, and epithelioid cells.[11] In addition, IA of eyes with acute VKH disease has shown leakage from choroidal vessels and diffuse choroidal hyperfluorescence, indicating that hyperpermeability of choroidal vessels may also be contributing to the choroidal thickening [12,13] The present study also demonstrated that decreased choroidal thickness correlated with improvement in the SRD and visual recovery during the course of treatment. This is similar to what was reported by other Japanese investigators who followed up patients with acute VKH disease using EDI-OCT over the first 14 days of treatment.[14]
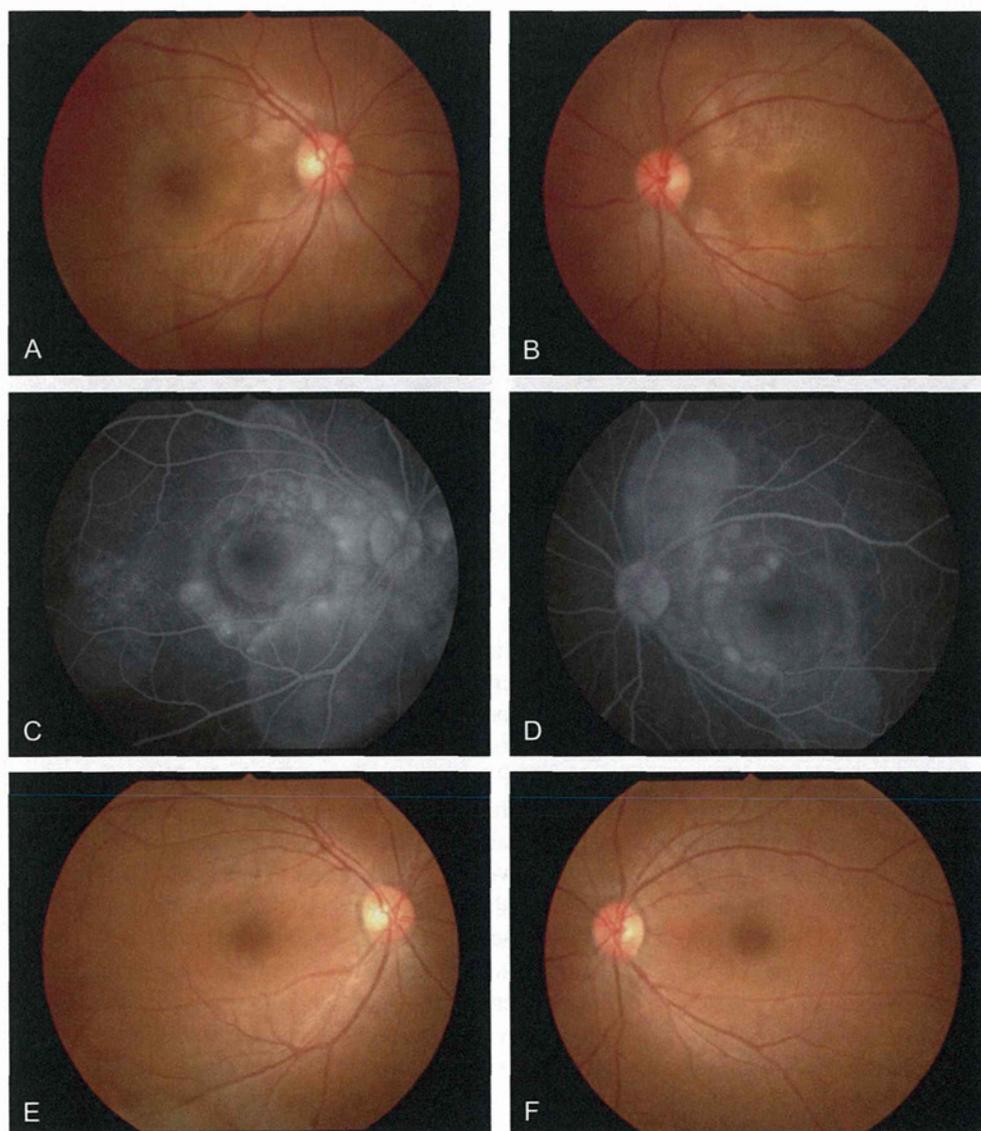

Fig. 3. Color fundus and fluorescein angiographic images of a representative case (Patient 6). The patient was a 33-year-old woman who complained of 1 week of bilateral reduced vision accompanied by headaches. On initial examination, lobular SRDs in the posterior pole with mild disk hyperemia were observed in both eyes (A, B). The best-corrected visual acuity was 0.1 in right eye and 0.1 in left eye. Fluorescein angiography (late phase shown) revealed pooling of dye in the subretinal space and disk staining (C, D). Systemic treatment with high-dose corticosteroids (involving 1 pulse of intravenous methylprednisolone) was initiated, and both eyes recovered to a best-corrected visual acuity of 1.2 and a normal-appearing fundus without PPA at 6 months (E, F). No late manifestations of skin or hair depigmentation developed in this patient.
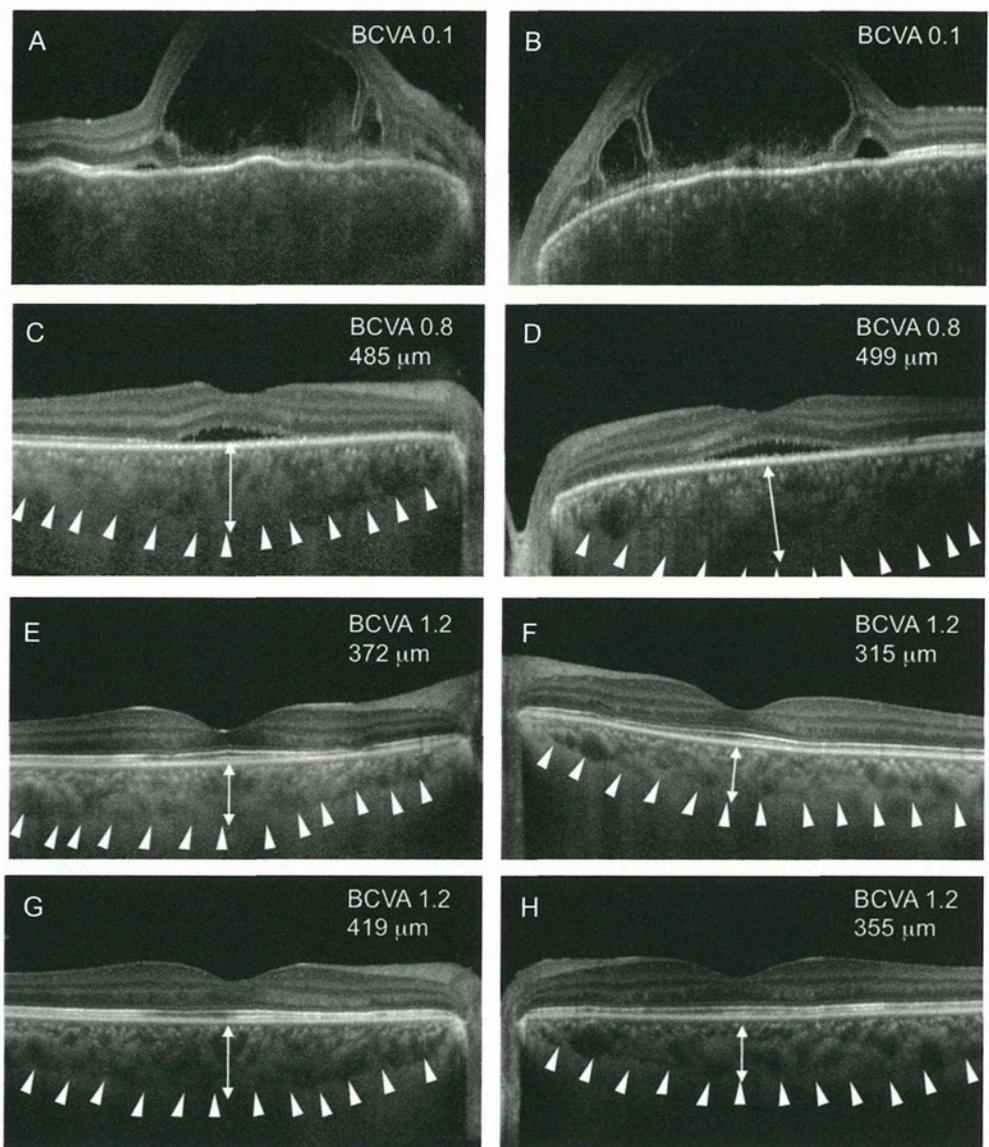
Fig. 4. Enhanced depth imaging–optical coherence tomography horizontal images of the right eye (left column) and the left eye (right column) of Patient 6 described in Figure 3. Choroidal thickness was not measurable in either eye before treatment (**A**, **B**). Thereafter, the outer border of the choroid could be delineated (white arrowheads), and the subfoveal choroidal thickness in the right and left eyes was, respectively, 485 μm and 499 μm at 1 week (**C**, **D**), 372 μm and 315 μm at 3 months (**E**, **F**), and 419 μm and 355 μm at 6 months (**G**, **H**). BCVA, best-corrected visual acuity.

Rebound of choroidal thickening was observed in five eyes of three patients during corticosteroid tapering in the absence of any other sign of recurrent inflammation. This occurred in both patients who had received 1 pulse, or who had received 2 or 3 pulses. An IA study suggested that recurrent subclinical choroidal inflammation occurs in a high proportion of patients with VKH disease during corticosteroid tapering.[13] However, the significance of such "setbacks," whether by findings on IA or EDI-OCT, on rates of clinically observable recurrences or visual outcomes remains to be shown. In our study, doses of corticosteroids were tapered in a standard fashion depending on fundus appearance and fluorescein angiographic findings and not based on the EDI-OCT data. Thus, despite rebound choroidal thickness observed on

EDI-OCT in some eyes, standard tapering did not lead to an observable recurrence of inflammation over the study period. Furthermore, rebound choroidal thickening was not found to be associated with the development of PPA in our patients (Table 2). Taken together, it is clear that the choroid is massively thickened during the acute stage of VKH disease and reduces with treatment. However, it is unclear whether or not treatment decisions should be based on choroidal thickness alone at this time. There was no other clinical evidence of recurrent inflammation over the follow-up period in the three patients, in whom rebound choroidal thickening was observed. Therefore, the more invasive testing of patients using IA was not performed. It would be important to attempt to correlate EDI-OCT findings with IA findings, particularly because this has been
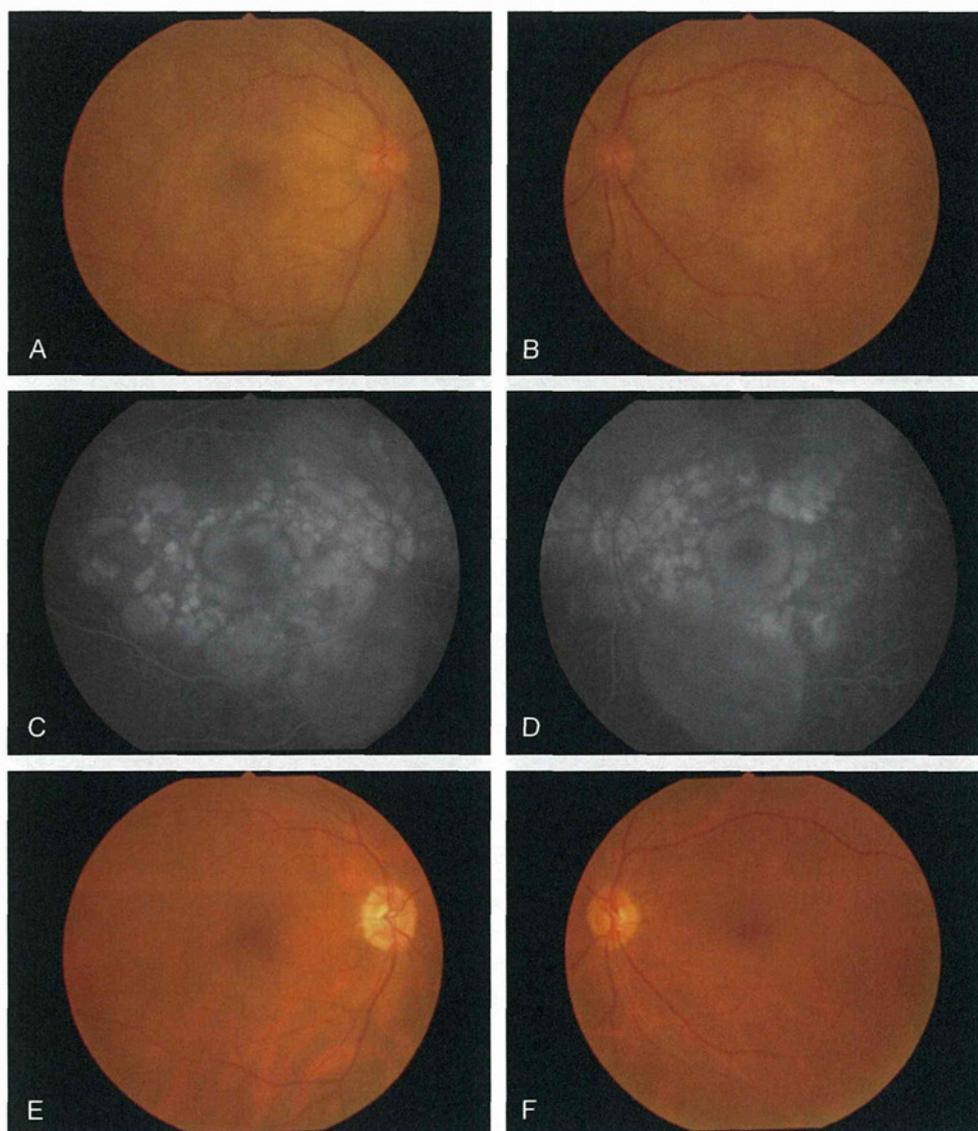
Fig. 5. Color fundus and fluorescein angiographic images of a representative case (Patient 8). The patient was a 75-year-old man who complained of 1 week of bilateral reduced vision accompanied by headache. On initial examination, SRDs in the posterior pole with mild disk hyperemia were observed in both eyes (**A, B**). The best-corrected visual acuity was 0.5 in right eye and 0.4 in left eye. Fluorescein angiography (late phase shown) revealed pooling of dye in the subretinal space (**C, D**). Systemic treatment with high-dose corticosteroids was initiated (involved 2 pulses of intravenous methylprednisolone), and both eyes recovered to a best-corrected visual acuity of 1.2. Sunset glow fundus changes and PPA developed by 12 months (**E, F**). No late manifestations of skin or hair depigmentation developed in this patient.

the dominant mode of evaluating the choroid in the recent literature. Furthermore, in the current study, the mean choroidal thickness of the 14 eyes followed out to 12 months was 332 μm (Figure 1). However, one study reported that the mean subfoveal choroidal thickness in 12 normal Japanese patients was 283 μm.[15] Therefore, it remains possible that our VKH disease patients had residual choroidal inflammation even at 12 months after initiating treatment, and we hope to analyze this with longer follow-up using EDI-OCT.

Perhaps the most useful finding from this study was that marked choroidal thickening of >550 μm at 1 week after initiating treatment (a time when the thickness first became measureable in all eyes by EDI-OCT) was statistically correlated with the development of PPA. Furthermore, the association between choroidal thickness at 1 week and the development

of PPA was stronger at 12 months ($P = 0.0003$) compared with that at 6 months ($P = 0.0256$). Although it remains unclear exactly why VKH patients with more severely thickened choroid develop PPA, the present data suggest that greater severity of initial choroidal inflammation creates greater tissue destruction in the active phase and consequently greater tissue atrophy (including PPA) in the convalescent phase. Retinal dysfunction as assessed by multifocal electroretinography has been documented to be more pronounced in VKH eyes with PPA when compared with eyes with no PPA.[16] It has also been reported that implicit times are significantly delayed in eyes with some PPA compared with those without PPA, indicating that development of PPA may be a marker for retinal dysfunction in VKH disease.[16] Finally, it has also been shown that the development of PPA is associated with
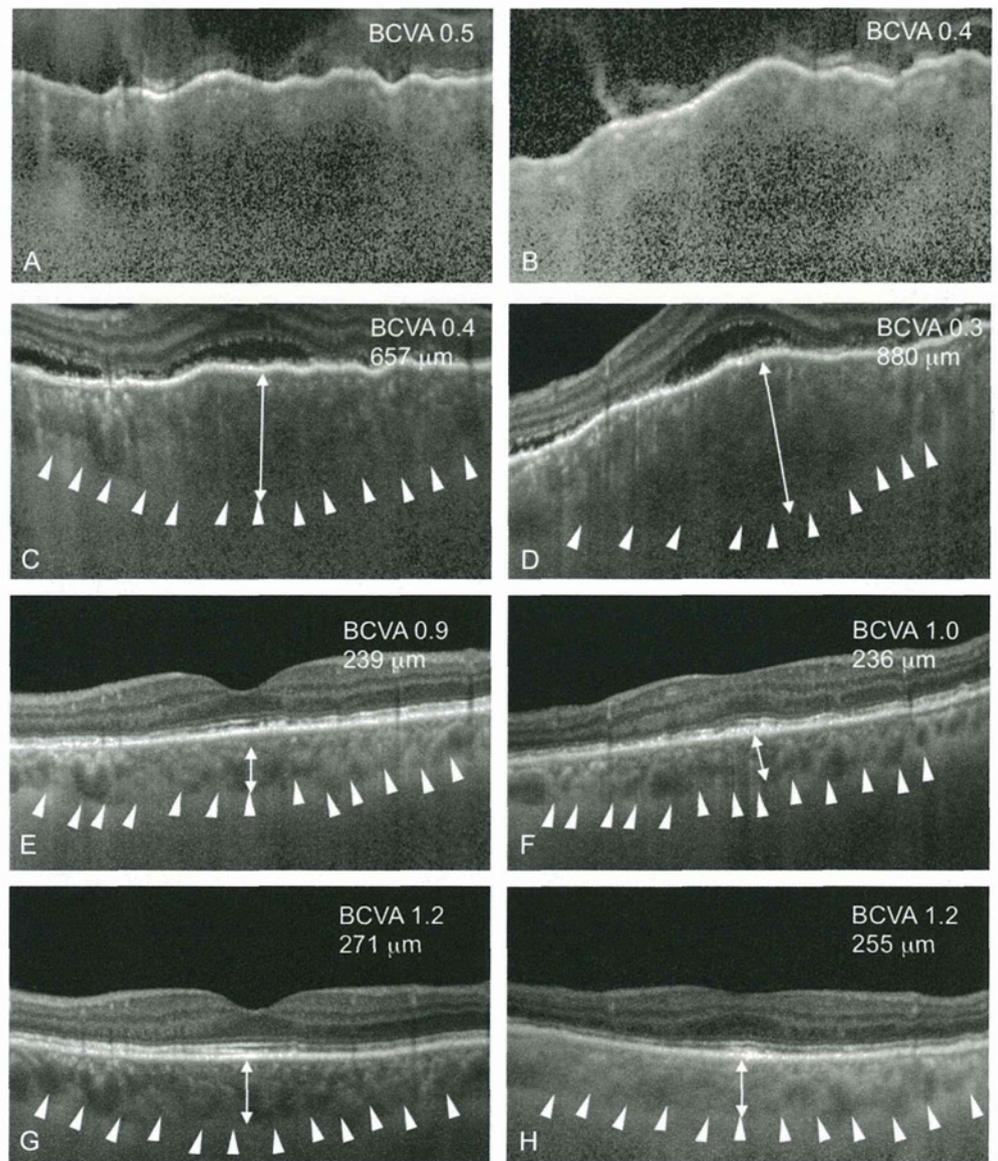
Fig. 6. Enhanced depth imaging–optical coherence tomography horizontal images of the right eye (left column) and the left eye (right column) of Patient 8 described in Figure 5. Choroidal thickness was not measurable in either eye before treatment (**A, B**). Thereafter, the outer border of the choroid could be delineated (white arrowheads), and the subfoveal choroidal thickness in the right and left eyes was, respectively, 657 μm and 880 μm at 1 week (**C, D**), 239 μm and 236 μm at 3 months (**E, F**), and 271 μm and 255 μm at 12 months (**G, H**). BCVA, best-corrected visual acuity.

delayed or inadequate immunosuppressive therapy.[17] Taken together, we speculate that choroidal thickness as measured by EDI-OCT in the early stage of acute VKH disease may aid in predicting visual outcome.

Using the EDI-OCT method, the outer border of the choroid was not discernable in any eyes at presentation; choroidal thickness was first measureable at approximately 1 week of treatment. One possible explanation for this is that the choroidal layer at presentation was thicker than the depth range of the Spectralis OCT (approximately 1000 μm) as has been suggested by Maruko et al[14] in their study of acute VKH disease over the first 14 days of treatment. A second possibility is that the severely inflamed choroid before treatment renders its border with the sclera indistinguishable by OCT.

The limitations of this study include that the follow-up period of 12 months may be inadequate because some patients were still on systemic corticosteroids albeit at low doses. Furthermore, it is well known that VKH disease patients may develop clinical recurrences even years after the onset of initial disease. In addition, our study examined a relatively small sample size of eight patients and did not include any patients with clinical recurrences. Furthermore, as stated above, our EDI-OCT findings were not compared with IA findings. However, we are continuing to use EDI-OCT in these and other patients, and our future goal is to evaluate the utility of this method in patients with VKH disease who do experience clinically evident recurrent inflammation and to compare EDI-OCT findings with IA findings.

In conclusion, EDI-OCT demonstrated marked thickening of the choroid in eyes with acute VKH disease in a noninvasive and easily quantifiable fashion. Choroidal thickening declined during the course of high-dose corticosteroid treatment in all eyes, and all eyes recovered to a best-corrected visual acuity of 1.2 with disappearance of SRD. Rebound choroidal thickening was observed in five eyes of three patients during the course of standard corticosteroid tapering, although these eyes did not have funduscopic findings of recurrent inflammation. Furthermore, rebound choroidal thickening was not associated with the development of PPA. However, choroidal thickness >550 μm at 1 week after initiating corticosteroid therapy was associated with the development of PPA at 6 months and 12 months and therefore may serve as a predictor of treatment outcomes. Overall, we believe that EDI-OCT measurements of choroidal thickness aid greatly in our assessment of choroidal inflammation in acute VKH disease.

Key words: Vogt–Koyanagi–Harada disease, optical coherence tomography, choroiditis, choroidal thickness, uveitis.

Acknowledgment

References

1. Moorthy RS, Inomata H, Rao NA. Vogt-Koyanagi-Harada syndrome. Surv Ophthalmol 1995;39:265–292.
2. Sugita S, Takase H, Taguchi C, et al. Ocular infiltrating CD4+ T cells from patients with Vogt-Koyanagi-Harada disease recognize human melanocyte antigens. Invest Ophthalmol Vis Sci 2006;47:2547–2554.
3. Read RW, Holland GN, Rao NA, et al. Revised diagnostic criteria for Vogt-Koyanagi-Harada disease: report of an international committee on nomenclature. Am J Ophthalmol 2001; 131:647–652.
4. Forster DJ, Cano MR, Green RL, Rao NA. Echographic features of the Vogt-Koyanagi-Harada syndrome. Arch Ophthalmol 1990;108:1421–1426.
5. Okada AA, Mizusawa T, Sakai J, Usui M. Videofunduscopy and videoangiography using the scanning laser ophthalmoscope in Vogt-Koyanagi-Harada syndrome. Br J Ophthalmol 1998;82:1175–1181.
6. Bouchenaki N, Herbort CP. The contribution of indocyanine green angiography to the appraisal and management of Vogt-Koyanagi-Harada disease. Ophthalmology 2001;108:54–64.
7. Ishihara K, Hangai M, Kita M, Yoshimura N. Acute Vogt-Koyanagi-Harada disease in enhanced spectral-domain optical coherence tomography. Ophthalmology 2009;116:1799–1807.
8. Spaide RF, Koizumi H, Pozonni MC. Enhanced depth imaging spectral-domain optical coherence tomography. Am J Ophthalmol 2008;146:496–500.
9. Margolis R, Spaide RF. A pilot study of enhanced depth imaging optical coherence tomography of the choroid in normal eyes. Am J Ophthalmol 2009;147:811–815.
10. Fujiwara T, Imamura Y, Margolis R, et al. Enhanced depth imaging optical coherence tomography of the choroid in highly myopic eyes. Am J Ophthalmol 2009;148:445–450.
11. Inomata H, Kato M. Vogt-Koyanagi-Harada disease. In: Vinken PJ, Bruyn GW, Klawans HL, McKendall RR, eds. Handbook of Clinical Neurology, Viral Disease. Vol 12. Amsterdam, The Netherlands: Elsevier Science Publishers; 1989:611–626.
12. Iida T, Hagimura N, Otani T, et al. Choroidal vascular lesions in serous retinal detachment viewed with indocyanine green angiography [in Japanese]. Nippon Ganka Gakkai Zasshi 1996;100:817–824.
13. Herbort PC, Mantovani A, Bouchenaki N. Indocyanine green angiography in Vogt-Koyanagi-Harada disease: angiographic signs and utility in patient follow-up. Int Ophthalmol 2007;27: 173–182.
14. Maruko I, Iida T, Sugano Y, et al. Subfoveal choroidal thickness after treatment of Vogt-Koyanagi-Harada disease. Retina 2011;31:510–517.
15. Ikuno Y, Maruko I, Yasuno Y, et al. Reproducibility of retinal and choroidal thickness measurements in enhanced depth imaging and high-penetration optical coherence tomography. Invest Ophthalmol Vis Sci 2011;52:5536–5540.
16. Chee SP, Luu CD, Cheng CL, et al. Visual function in Vogt-Koyanagi-Harada patients. Graefes Arch Clin Exp Ophthalmol 2005;243:785–790.
17. Jap A, Luu CD, Yeo I, Chee SP. Correlation between peripapillary atrophy and corticosteroid therapy in patients with Vogt-Koyanagi-Harada disease. Eye (Lond) 2008;22:240–245.

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ORIGINAL ARTICLE

Infliximab Monotherapy Versus Infliximab and Colchicine Combination Therapy in Patients with Behçet's Disease

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ABSTRACT

Purpose: To compare infliximab monotherapy with infliximab and colchicine combination therapy in Behçet's disease.

Methods: Clinical records of 14 Behçet's disease patients who were administered infliximab with or without colchicine were retrospectively reviewed. Patients who were given other immunosuppresants after initiation of infliximab therapy were excluded. The frequency of ocular attacks and best-corrected visual acuity were investigated.

Results: Seven patients received monotherapy and 7 received combination therapy. The mean frequency of ocular attacks significantly decreased from 2.14 to 0.22 per 6 months in monotherapy group and from 2.57 to 0.18 per 6 months in combination therapy group. No significant difference was observed between both groups in the frequency of ocular attacks and in changes in best-corrected visual acuity during 0 to 24 months.

Conclusions: Infliximab is as efficacious as infliximab and colchicines together in Behçet's disease treatment. This study suggests that colchicine administration is not necessary in Behçet's disease patients receiving infliximab.

Keywords: Behçet's disease, colchicine, combination therapy, infliximab, monotherapy

Behçet's disease is a chronic systemic inflammatory disease clinically manifesting as uveitis, recurrent oral aphthous ulcers, genital ulcers, and skin lesions. Uveitis is characterized by acute episodes of anterior uveitis, often with hypopyon, posterior uveitis, or panuveitis. Ocular attacks severely damage the optic nerve and retina, often leading to blindness. It is important for visual prognosis to decrease ocular attacks and control ocular inflammation.

Colchicine and immunosuppressive agents, such as cyclosporine, methotrexate, azathioprine, and corticosteroid, have been used for Behçet's disease treatment. Colchicine modulates chemokine and prostanoid production, inhibits neutrophil and endothelial cell adhesion molecules, and eventually decreases neutrophil degranulation, chemotaxis, and phagocytosis, thus reducing the initiation and amplification of inflammation. Although these drugs are frequently adequate for suppression of ocular attacks, in some patients uveitis is uncontrollable even with these drugs.[1]

Tumor necrosis factor (TNF)-α plays a key role in immune responses and inflammation and is highly secreted in the peripheral blood in the active phase in Behçet's disease patients.[2] Infliximab, a monoclonal antibody against TNF-α, is able to suppress inflammation by neutralizing the biological activity of TNF-α. Infliximab has been used to treat psoriasis, Crohn disease, ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis, and ulcerative colitis.[3,4] In Japan infliximab was approved for refractory retinochoroiditis therapy in Behçet's disease in January 2007.

Although many studies have reported the efficacy of infliximab, a consensus on combination therapy of infliximab and other anti-inflammatory agents has not yet been reached. To date, no study has compared infliximab monotherapy and infliximab and colchicine combination therapy in Behçet's disease patients. The aim of this study was to evaluate the efficacy of colchicine therapy in Behçet's disease patients receiving infliximab therapy.

MATERIALS AND METHODS

Clinical records of consecutive patients with Behçet's disease who were given infliximab with or without colchicine at the Yokohama City University Hospital between January 2007 and February 2010 were retrospectively reviewed. All cases were diagnosed according to standard criteria proposed by the Japan Behçet's Disease Research Committee.[5] Patients who could be followed for ≥ 6 months before and after infliximab therapy were included. Patients who were given immunosuppressive agents such as azathioprine, cyclosporine, and corticosteroid other than colchicine after initiation of infliximab therapy were excluded from the study. Infliximab (5 mg/kg body weight) was administered at 0, 2, and 6 weeks and every 8 weeks thereafter. In case of diminished efficacy of infliximab, the administration interval was shortened from 8 to 6 weeks. Colchicine was administered orally at 0.5–1.5 mg per day.

The frequency of ocular attacks before and after infliximab therapy and best-corrected visual acuity (BCVA) at 0 and 24 months were evaluated. Ocular attacks were defined as acute episodes of retinal vasculitis with hemorrhage or exudate, an increase in the opacity of the vitreous body, and iridocyclitis with hypopyon or anterior chamber cells (≥ 3+), confirmed by ophthalmologic examinations such as slit-lamp microscopy and fundoscopy. For each group, the number of ocular attacks after infliximab therapy was converted to frequency per 6 months. BCVA was measured using Landolt ring charts and decimal visual acuity. Cases in which cataract surgery was performed to improve visual acuity during the observation period were excluded.

This study was approved by the Yokohama City University Ethics Committee. Informed consent was obtained for all patients. This was conducted in accordance with Declaration of Helsinki.

Statistical Analysis

The frequency of ocular attacks before and after infliximab therapy was compared within each group by the Wilcoxon's signed-rank test. The frequency of ocular attacks and changes in BCVA of both groups were compared by the Mann-Whitney U test. $p < .05$ was considered significantly different. All results were expressed as means ± SD.

RESULTS

Fourteen patients were included, 7 each in the monotherapy and combination therapy groups. No difference was observed in patient background characteristics between both groups (Table 1). Twelve patients had ocular attacks as panuveitis, and 2 in the monotherapy group had attacks of anterior uveitis alone without hypopyon during observation period. However, both of them had panuveitis attacks as well as other patients during disease duration. Due to the ineffectiveness of previous treatment with various immunosuppressive agents, all patients were converted to infliximab.

The median duration of the observation period was 25.0 ± 12.3 months in the monotherapy group and 33.2 ± 18.6 months in the combination therapy group. The mean infusion interval was 7.29 ± 0.95 weeks in monotherapy group and 7.43 ± 0.98 weeks in the combination therapy group. The mean frequency of ocular attacks decreased from 2.14 ± 0.38 to 0.22 ± 0.28 in the monotherapy group and from 2.57 ± 0.79 to 0.18 ± 0.19 in the combination therapy group. In both groups, the frequency of ocular attacks significantly decreased ($p < .05$). No significant difference was observed between both groups in the frequency of ocular attacks before or after infliximab therapy (Figure 1).

BCVA of 7 eyes of 4 cases in monotherapy group and 6 eyes of 3 cases in combination therapy group that could be followed for 24 months were evaluated (Table 3, Figure 2). The right eye of case 3 and both eyes of cases 8 and 11 were excluded because they had undergone cataract surgery during infliximab therapy. Changes in BCVA were evaluated after classifying the patients as follows: an increase of ≥2 lines, a decrease of ≥2 lines, and no change. At 24 months, all eyes in the monotherapy group and 83.3% of eyes in the combination therapy group maintained or increased ≥2 lines in BCVA examination. The right eye of case 12 was the only eye with a decrease of ≥2 lines in the examination. No significant difference was observed between both groups in changes in BCVA.

TABLE 1 Demographic characteristics of patients

Treatment	IFX, n (%)	IFX + col, n (%)
Sex		
Male	6 (85.7)	7(100)
Female	1 (14.3)	0 (0.0)
Onset age (mean ± SD)	28.3 ± 9.7	34.6+ 10.9
Period of illness (mean ± SD)	5.9 ± 4.4	9.6 ± 6.8
Duration of IFX therapy		
>45 months	0 (0.0)	3 (42.9)
30–45	4 (57.1)	1 (14.3)
15–30	0 (0.0)	1 (14.3)
6–15	3 (42.9)	2 (28.6)
Mean ± SD	25.0 ± 12.3	33.2 ± 18.6
Infusion interval	7.29 ± 0.95	7.43 ± 0.98
Major symptoms		
Ocular lesion	7 (100)	7 (100)
Oral aphthous ulceration	7 (100)	7 (100)
Skin lesion	4 (57.1)	4 (57.1)
Genital ulcer	2 (28.6)	1 (14.3)
Minor symptoms		
Arthritis	2 (28.6)	2 (28.6)
Gastrointestinal lesion	0 (0.0)	0 (0.0)
Vascular lesion	0 (0.0)	1 (14.3)
Central nervous system lesion	0 (0.0)	1 (14.3)

Note. IFX, infliximab; col, colchicine.

Regarding adverse effects, cytomegalovirus infection was observed in 1 patient (case 8 in Table 2) receiving combination therapy and cured through valganciclovir administration. In this patient, an infusion reaction was observed. Infliximab therapy was continued at a lower infusion speed and pretreatment with oral anti-allergic agents and corticosteroid. No serious adverse effects were observed in other patients.

DISCUSSION

The frequency of ocular attacks after infliximab initiation significantly decreased in both groups. There were no ocular attacks in 4 patients in the monotherapy group and 3 in the combination therapy group. In 3 patients, the observation period after infliximab therapy with no ocular attacks was >30 weeks (32–49). Infliximab therapy is effective in Behçet's disease,[6–9] and findings from this study support this. No significant difference
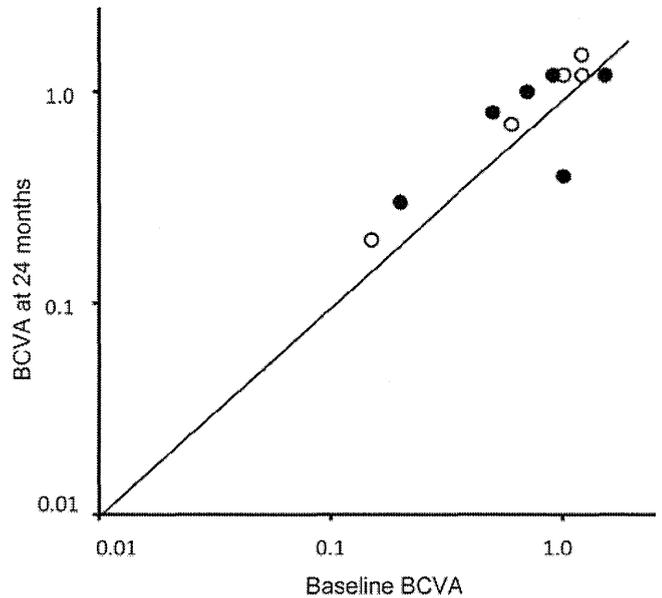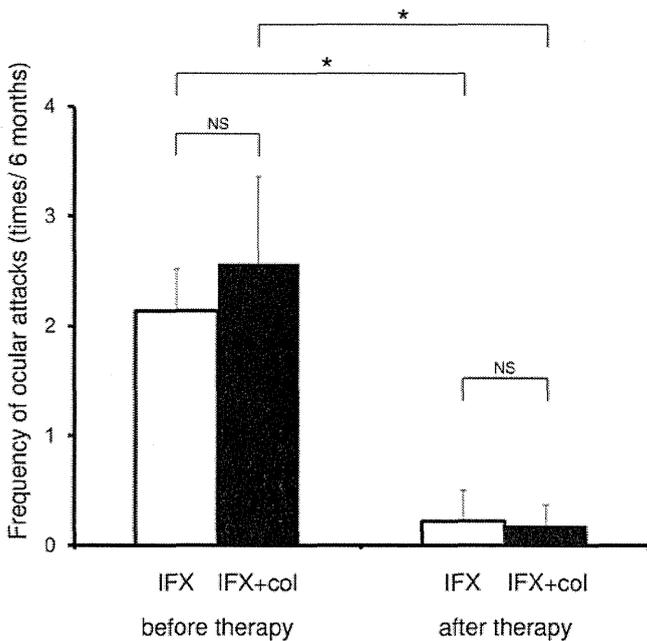

FIGURE 1 Frequency of ocular attacks (times/6 months) at 6 months before and after infliximab initiation. Statistical analysis was performed using the Mann-Whitney U test or Wilcoxon's signed-ranks test. *$p < .05$; NS, no significance.

FIGURE 2 Best-corrected visual acuities at the initiation point and 24 months after infliximab therapy. Open square, infliximab monotherapy; black square, combination therapy; BCVA, best-corrected visual acuity.

TABLE 2 Frequency of ocular attacks before and after IFX therapy

		6 months before IFX therapy		After IFX therapy			
	Case	Treatment	Number of ocular attacks	Duration of IFX therapy (months)	Infusion interval (weeks)	Number of ocular attacks	Frequency of recurrence (per 6 months)
IFX monotherapy	1	Col	2	37	6	3	0.49
	2	col	2	36	8	0	0
	3	CsA	2	34	6	3	0.53
	4	Col	2	32	8	0	0
	5	col	2	11	7	1	0.54
	6	col	2	11	8	0	0
	7	col, PSL	3	14	8	0	0
Mean ± SD			2.14 ± 0.38	25.0 ± 12.3	7.29 ± 0.95		0.22 ± 0.28
IFX + col	8	col, PSL	2	54	8	1	0.11
	9	col	2	49	8	0	0
	10	col	2	48	8	2	0.25
	11	col	3	36	6	3	0.5
	12	col, CsA	4	27	8	1	0.22
	13	col, PSL	3	10	8	0	0
	14	col	2	9	6	0	0
Mean ± SD			2.57 ± 0.79	33.2 ± 18.6	7.43 ± 0.98		0.18 ± 0.19

IFX, infliximab; col, colchicine; CsA, cyclosporine A; PSL, prednisolone.

TABLE 3 Changes in visual acuities

Best-corrected visual acuity	Before IFX therapy		After IFX therapy	
	IFX monotherapy (%)	IFX + col (%)	IFX monotherapy (%)	IFX + col (%)
a				
≥1.0	3 (42.9)	2 (33.3)	4 (57.2)	2 (33.3)
0.5–0.9	3 (42.9)	3 (50.0)	2 (28.6)	2 (33.3)
0.2–0.4	0 (0.0)	1 (16.7)	1 (14.3)	2 (33.3)
≤0.1	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)
b				
Visual acuity change	IFX monotherapy (%)	IFX+col (%)		
Increase of >2 lines	3 (42.9)	3 (50.0)		
No change	4 (57.2)	2 (33.3)		
Decrease of >2 lines	0 (0.0)	1 (16.6)		

[a]Best-corrected visual acuity in IFX monotherapy and combination therapy of IFX and col.
[b]Visual acuity changes in IFX monotherapy and combination therapy of IFX and col.
IFX, infliximab; col, colchicine.

was observed in the frequency of ocular attacks between both groups, which suggests that both therapies equally suppress ocular inflammation.

The right eye of case 12 was the only eye with a decrease of >2 lines in BCVA examination at 24 months. Although 1 ocular attack occurred at 24 months after infliximab initiation, gradual progression of posterior subcapsular cataracts seemed to be the general result in terms of decreased visual acuity. All other eyes maintained or showed an increase of >2 lines at 24 months. It was considered that decrease of ocular attacks and control of inflammation result in good visual prognosis.

Colchicine is generally used for mucocutaneous and joint manifestations.[10] In this study, 8 patients had skin lesions and 4 had arthritis. All of them showed a trend toward improvement in these manifestations after infliximab therapy, and there was no difference between infliximab monotherapy and combination of colchicine. According to eye involvement, colchicine may be used in anterior uveitis, and there is no positive finding by randomized trial showing the efficacy of colchicine for posterior uveitis or retinal vasuculitis.[10] The European League Against Rheumatism recommends a treatment regime that includes azathioprine and systemic corticosteroids for ocular involvement of Behçet's disease.[11] In Japan colchicine remains first choice for prevention of ocular attack with chorioretinitis in patients with Behçet's disease, and cyclosporine or infliximab are administered in resistant cases.

Because of developments in immunopharmacological studies, many drugs have become available for inflammatory disease treatment. Among them, infliximab has shown great efficacy against diseases such as Behçet's disease, rheumatoid arthritis, Crohn disease, and ankylosing spondylitis. Numerous studies have reported that combination therapy led to equal or superior treatment results in Crohn disease,[12–14] rheumatoid arthritis,[15] and ankylosing spondylitis.[16] Perez-Guijo et al. reported a greater reduction in Bath Ankylosing Spondylitis Disease Activity Index scores with infliximab and methotrexate

combination therapy than with infliximab alone.[16] Lichtenstein et al. reported that concomitant immunomodulators did not improve either efficacy or pharmacokinetics in inflammatory bowel disease patients who received maintenance infliximab.[13] Combination of infliximab with other immunosuppressive agents in Behçet's disease treatment has also been reported.[17–19] For the treatment of refractory posterior uveitis in Behçet's disease patients, combination therapy of infliximab and azathioprine and/or cyclosporine is recommended.[18] Combination of infliximab with azathioprine and/or cyclosporine and/or methotrexate might be superior to monotherapy for sustained ocular remission in prospective studies.[19] However, significant difference over infliximab monotherapy was observed only for the combination with cyclosporine. Moreover, no previous study has compared monotherapy with infliximab and colchicine combination therapy for Behçet's disease.

While it is considered an advantage that concomitant administration of infliximab and immunosuppressive agents may increase the immunosuppressive efficacy,[15,16] prevent the development of neutralizing antibodies,[20,21] and reduce infusion reactions,[22] only 1 patient who had an infusion reaction in this study was in the combination therapy group. In contrast, it was reported that the combination of azatioprine and anti-TNF-α biologic agents increased the relative risk of serious and opportunistic infections.[23] While no one had an adverse event or infusion reaction in the monotherapy group, 1 patient in the combination therapy group was infected with cytomegalovirus. Therefore, suppression of the immune system by combination therapy may increase the risk of infection in patients and compromise patient condition compared to monotherapy.

In the event of diminished efficacy of infliximab in our study, we did not increase infliximab dose, but rather shortened the infusion interval. It is thought the trough serum infliximab level correlates with the magnitude of infliximab efficacy.[24] Furthermore, low circulating drug levels cause the development of anti-infliximab antibodies.[25] Kopylov et al. reported that in patients with Crohn

disease, who did not respond to the standard infliximab dose (5 mg/kg/8 weeks), shortening the dosing interval to 6 weeks appeared to be at least as effective as altering the dosage level to either 10 mg/kg/8 weeks or 5 mg/kg/4 weeks.[26] Ohno et al. reported that 5- and 10-mg/kg doses of infliximab were equally effective in Behçet's disease treatment.[27] In patients with unsatisfactorily controlled rheumatoid arthritis, infliximab is administered by increasing infliximab dosage and shortening the infusion interval.

Limitations of this study include the small number of cases as well as its design. To confirm the efficacy, the number of cases included in the study needs to be increased. Furthermore, because colchicine administration in this study was poorly controlled, the efficacy of colchicine was most likely inadequate. However, in Japan, infliximab has been approved for refractory retinochoroiditis therapy in Behçet's disease, and this study may provide an indication of the usefulness of discontinuation of colchicine as a conventional therapy at infliximab initiation. Although infliximab is generally recommended for posterior uveitis not anterior uveitis,[19] in this study, infliximab alone was effective for the suppression of anterior uveitis as well as posterior uveitis. Moreover, the results of our study indicate that the efficacy of infliximab monotherapy in Behçet's disease patients is equivalent to that of infliximab and colchicine combination therapy. This study suggests that colchicine administration is not necessary in Behçet's disease patients receiving infliximab therapy.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES

[1] Cocco G, Chu DC, Pandolfi S. Colchicine in clinical medicine: a guide for internists. *Eur J Intern Med*. 2010;21:503–508.
[2] Turan B, Gallati H, Erdi H, et al. Systemic levels of the T cell regulatory cytokines IL-10 and IL-12 in Bechçet's disease: soluble TNFR-75 as a biological marker of disease activity. *J Rheumatol*. 1997;24:128–132.
[3] Travassos WJ, Cheifetz AS. Infliximab: use in inflammatory bowel disease. *Curr Treat Options Gastroenterol*. 2005;8: 187–196.
[4] Smolen JS, Emery P. Infliximab: 12 years of experience. *Arthritis Res Ther*. 2011;25:13 (Suppl 1):S2 Review.
[5] Mizushima Y. Recent research into Bechçet's disease in Japan. *Int J Tissue React*. 1998;10:59–65.
[6] Tabbara KF, Al-Hemidan AI. Infliximab effects compared to conventional therapy in the management of retinal vasculitis in Behçet's disease. *Am J Ophthalmol*. 2008;146:845–50.e1.
[7] Al-Rayes H, Al-Swailem R, Al-Balawi M, et al. Safety and efficacy of infliximab therapy in active Behçet's uveitis: an open-label trial. *Rheumatol Int*. 2008;29:53–57.
[8] Accorinti M, Pirraglia MP, Paroli MP, et al. Infliximab treatment for ocular and extraocular manifestations of Behçet's disease. *Jpn J Ophthalmol*. 2007;51:191–196.
[9] Niccoli L, Nannini C, Benucci M, et al. Long-term efficacy of infliximab in refractory posterior uveitis of Behçet's

disease: a 24-month follow-up study. *Rheumatology (Oxford)*. 2007;46:1161–1164.
[10] Evereklioglu C. Current concepts in the etiology and treatment of Behçet's disease. *Surv Ophthalmol*. 2005;50:297–350.
[11] Hatemi G, Silman A, Bang D, et al. EULAR recommendations for the management of Behçet's disease. *Ann Rheum Dis*. 2008;67:1656–1662.
[12] Brian Feagan, John McDonald, Remo Panaccione, et al. A randomized trial of methotrexate in combination with infliximab for the treatment of Crohn's disease. *Gastroenterology*. 2008;135:294–295.
[13] Lichtenstein GR, Diamond RH, Wagner CL, et al. Clinical trial: benefits and risks of immunomodulators and maintenance infliximab for IBD-subgroup analyses across four randomized trials. *Aliment Pharmacol Ther*. 2009;30:210–226.
[14] Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med*. 2010;362:1383–1395.
[15] Lipsky PE, van der Heijde DM, St Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med*. 2000;343:1594–1602.
[16] Pérez-Guijo VC, Cravo AR, Castro Mdel C, et al. Increased efficacy of infliximab associated with methotrexate in ankylosing spondylitis. *Joint Bone Spine*. 2007;74:254–258.
[17] Iwata S, Saito K, Yamaoka K, et al. Efficacy of combination therapy of anti-TNF-α antibody infliximab and methotrexate in refractory entero-Behçet's disease. *Mod Rheumatol*. 2011;21:184–191.
[18] Sfikakis PP, Markomichelakis N, Alpsoy E, et al. Anti-TNF therapy in the management of Behcet's disease: review and basis for recommendations. *Rheumatology (Oxford)*. 2007;46:736–741.
[19] Arida A, Fragiadaki K, Giavri E, et al. Anti-TNF agents for Behçet's disease: analysis of published data on 369 patients. *Semin Arthritis Rheum*. 2011;41:61–70.
[20] Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med*. 2003;348:601–608.
[21] Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumor necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomized phase III trial. *Lancet*. 1999;354:1932–1939.
[22] Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum*. 1998;41:1552–1563.
[23] Marehbian J, Arrighi HM, Hass S, et al. Adverse events associated with common therapy regimens for moderate-to-severe Crohn's disease. *Am J Gastroenterol*. 2009;104:2524–2533.
[24] 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;19:478–487.
[25] Svenson M, Geborek P, Saxne T, et al. Monitoring patients treated with anti-TNF-alpha biopharmaceuticals: assessing serum infliximab and anti-infliximab antibodies. *Rheumatology (Oxford)*. 2007;46:1828–1834.
[26] Kopylov U, Mantzaris GJ, Katsanos KH, et al. The efficacy of shortening the dosing interval to once every six weeks in Crohn's patients losing response to maintenance dose of infliximab. *Aliment Pharmacol Ther*. 2011;33:349–357.
[27] 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;31:1362–1368.

INFLAMMATORY DISORDERS

Correlation between elevation of serum antinuclear antibody titer and decreased therapeutic efficacy in the treatment of Behçet's disease with infliximab

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Abstract

Background Infliximab, an anti-TNF-α monoclonal antibody, administered to Behçet's disease (BD) patients in Japan with refractory intraocular inflammation, has shown excellent clinical results. However, some patients demonstrate a decreased response to infliximab during the course of the treatment. In the present study, we investigated the correlation between this reduced therapeutic effect and elevation of the serum antinuclear antibody (ANA) titers in patients with BD who were undergoing infliximab therapy.

Methods Seventeen patients (14 males and three females) with uveitis in BD who were undergoing treatment with infliximab for 2 years or longer were enrolled. Their blood test results and clinical histories were obtained from medical records.

Results One patient (5.9%) was ANA-positive prior to the initiation of infliximab, and 11 patients (64.7%) developed positive ANA during the therapy. The appearance of ANA was observed 6 months after the initiation of the infliximab therapy, and its titers gradually increased. None of the patients showed lupus symptoms. Five patients (29.4%) have suffered from ocular inflammatory attacks since the sixth month from the initiation of infliximab treatment and all of them were ANA-positive. In contrast, four patients (23.5%) who were ANA-negative experienced no ocular attacks during the follow-up period.

Conclusions Here we report the positive conversion and subsequent elevation of serum ANA titers in some patients with BD after the initiation of infliximab therapy. Since all recurrences of uveitis were shown only in the ANA-positive patients, serum ANA titer may be a helpful biomarker for predicting the recurrence of ocular attacks in BD patients treated with anti-TNF-α antibody therapies.

Keywords Behçet's disease · Retinal vasculitis · Uveitis · Antinuclear antibody · Infliximab · Biomarker · Anti-TNF-α monoclonal antibody

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Introduction

Behçet's disease (BD) is a chronic systemic inflammatory disease characterized by recurrent oral aphthous ulcers, genital ulcers, skin lesions, gastrointestinal involvement, vasculitis, neurological manifestations, and intraocular inflammation. BD is one of the major etiologies of endogenous uveitis in Japan [1], however, its prevalence and clinical features vary among countries and ethnic groups [2, 3]. Recurrent episodes of inflammatory ocular attacks can cause severe visual loss. To prevent the relapse of intraocular inflammation, colchicine and various immunosuppressive

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agents are administered including cyclosporine A (CyA), which is a selective immunosuppressive agent of T-lymphocytes. However, some patients cannot use these drugs due to intolerable side-effects. Moreover, some patient's diseases are refractory to these agents and can progress to vision loss [4–6].

Infliximab (IFX) is a chimeric monoclonal antibody to TNF-α that can minimize the immunological response when used in humans [7]. It neutralizes both membrane-binding and soluble TNF-α, in addition to suppressing TNF-α production by macrophages. IFX is commonly administered to patients with rheumatoid arthritis [8, 9], Crohn's disease [10], psoriasis [11, 12], and in case of refractory uveitis with non-infectious etiologies including BD [13–20]. IFX is effective for preventing relapse of intraocular inflammations in BD and its efficacy has been well documented in previous studies [13–19]. In Japan, IFX was approved for use in BD patients with refractory uveoretinitis by the Ministry of Health, Labour and Welfare, Japan in January 2007 based on the excellent results from multicenter clinical trials [15, 21]. Though IFX is an excellent agent in the treatment of the BD with refractory uveoretinitis, it has been observed to have decreased efficacy in a subset of BD patients with uveoretinitis [19]. One report showed the development of autoantibodies including antinuclear antibody (ANA) during IFX treatment in BD [22], however, the mechanisms and the meanings of it remain unknown.

In the present study, we investigated ANA titers of the BD patients receiving IFX therapy and examined the correlation between the elevation of ANA and the therapeutic efficacy.

Materials and methods

BD patients with refractory uveoretinitis who had been administered IFX for 2 years or longer were enrolled at Hokkaido University Hospital. The results of their blood tests and clinical histories were obtained from medical records. BD was diagnosed based on the criteria set by the BD Research Committee of Japan, which is part of the Ministry of Health, Labour and Welfare, Japan [23]. The level of ocular inflammation was graded by means of the Standardization of Uveitis Nomenclature (SUN) grading criteria [24]. When a patient showed more than two steps of increase in level of inflammation or increase from grade 3+ to 4+, it was considered an inflammatory ocular attack. Ocular attacks of BD flare up repeatedly and usually disappear within a few weeks. Each ocular attack shows a varying degree of uveitis including only mild iridocyclitis or severe obstructive retinal vasculitis with retinal exudates. The number of ocular attacks was counted regardless of the severity and added both eyes.

Patients were administered 5 mg/kg of IFX intravenously at weeks 0, 2, and 6 as the initial series of infusions and thereafter every 8 weeks. Serum ANA and anti-double-stranded DNA (dsDNA) antibodies were examined prior to IFX infusion. ANA titers were quantified using an indirect immunofluorescence technique using human epithelial (Hep2) cells. Results were classified as positive (ANA≥80) or negative (ANA≤40) according to previous reports [25–31]. Anti-dsDNA antibodies were identified using enzyme-linked immunosorbent assay (ELISA).

Statistical analyses were performed using the Mann–Whitney U test; p values <0.05 were considered to be statistically significant. This study followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Hokkaido University Hospital.

Results

The demographics and clinical characteristics of the 17 Japanese patients, i.e., 14 (82.4%) males and three (17.6%) females ranging in age from 15 to 58 (mean age: 36.9) years, enrolled in the study are listed in Table 1. The rate of ocular inflammatory attacks during 6 months prior to the initiation of IFX was 3.8±2.1 (mean±SD). IFX therapy significantly reduced the rate of ocular attacks to 0.7±1.1 during the first 6 months after the initiation of IFX (p<0.01).

Table 1 Characteristics of Behçet's disease patients treated with IFX

Case	Age (years)	Sex	Treatment before IFX initiation	Concomitant treatment with IFX
1	39	M	CyA, Col, PSL	–
2	33	M	Col, PSL	PSL
3	58	M	Col	–
4	42	M	Col	–
5	40	F	PSL	PSL
6	31	M	Col	–
7	44	M	PSL	PSL
8	54	M	CyA, PSL	PSL
9	17	M	CyA, Col	–
10	52	M	Col	–
11	10	M	–	–
12	49	M	CyA	–
13	40	M	CyA	–
14	40	F	CyA	–
15	36	F	PSL	PSL
16	15	M	PSL	–
17	28	M	–	–

IFX – infliximab, CyA – cyclosporine A, Col – colchicine, PSL – prednisolone

Eight patients (47.1%) achieved no relapse of ocular inflammatory attacks between the first infusion and the 24-month visit. Five patients (29.4%) experienced only one ocular inflammatory attack and four patients (23.5%) experienced several ocular attacks during the follow-up period. It was not necessary to administer concomitant drugs with IFX for 12 patients. Three of five patients who were previously administered oral prednisolone (PSL) could decrease and gradually stop their therapy after IFX initiation. Two of these patients required continued PSL administration to control neurological symptoms.

Best-corrected visual acuities (BCVA) were reported 1 year after the initiation of IFX; IFX therapy had successfully maintained their vision acuity (Fig. 1).

ANA profiles and the frequency of ocular attacks in BD patients treated with IFX are shown in Table 2. One patient (5.9%) was ANA-positive prior to the initiation of IFX. Anti-dsDNA antibodies were never detected prior to IFX induction. The change in ANA-positive rates is shown in Fig. 2. The positive conversion of ANA became common 6 months after the initiation of IFX, and the positive titers continued to increase. At the end of the follow-up period, 13 patients (76.4%) were identified positive for ANA (Fig. 2). One patient (5.9%) developed anti-dsDNA antibodies (case #14). However, none of the patients showed lupus symptoms.

The correlation of ocular attacks with elevation of ANA titer is shown in Fig. 3. At the 6th month after the IFX induction, five patients (29.4%) were ANA-positive and 12

(70.6%) were negative. In the ANA-positive group, three patients (60%) had ocular inflammatory attacks during the first 6 months after IFX administrations, whereas in the ANA-negative group, four (33.3%) patients had these attacks. Ocular attacks were much milder than those before IFX therapy both in the ANA-negative group and ANA-positive group.

However, since the 6th month of IFX therapy, all of five patients (29.4%) suffering from a relapse of ocular inflammatory attacks were ANA-positive, and three of five patients had multiple ocular attacks. In two of these three patients, the administration interval was shortened from 8 to 7 weeks, and this successfully led to a lower rate of the ocular attacks. On the other hand, all of four patients (23.5%) with negative ANA had no ocular attacks.

Discussion

ANA appeared in the sera of BD patients 6 months after IFX induction, and its titer gradually increased. It was reported that the development of ANA and anti-dsDNA antibodies is seen during the course of anti-TNF-α therapy in patients with some autoimmune diseases such as rheumatoid arthritis [32–34], psoriasis [35], Crohn's disease [36], and BD [22]. In the present study, 75.0% of the patients converted to ANA-positive during the course of IFX therapy and positive ANA titers (1:80) had been detected in one patient on study enrolment. This patient experienced a twofold increase in

Fig. 1 Visual acuity before and after initiation of IFX. Best-corrected visual acuities (BCVA) 1 year after the initiation of IFX. IFX therapy successfully maintained the visual acuity in these patients
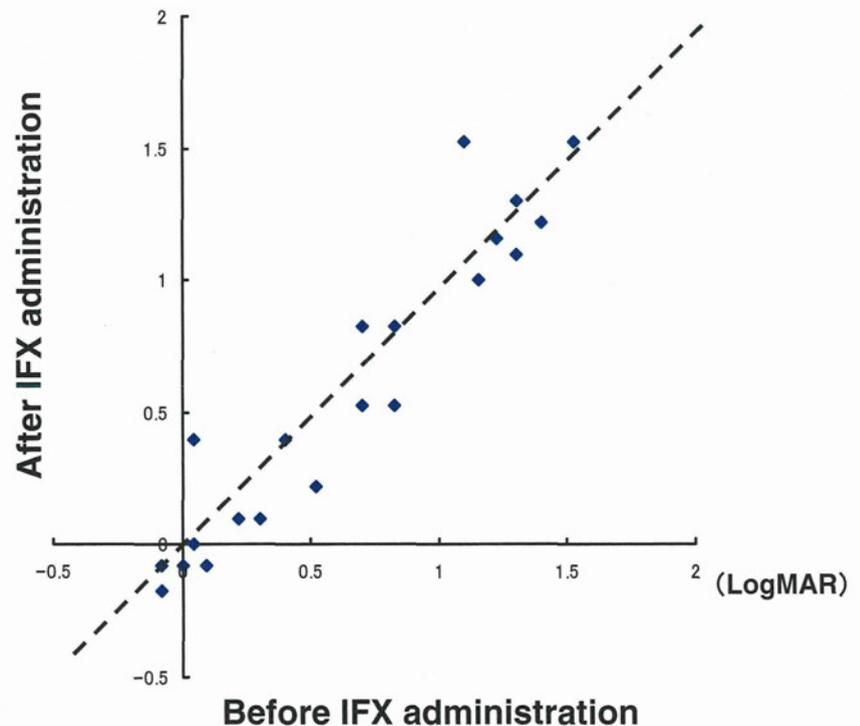
Table 2 ANA profile and the rate of ocular attacks of Behçet's disease patients treated with IFX

Case	Frequency of ocular attacks -6~0 month	ANA (titer) 0 month	Frequency of ocular attacks 0~6 month	ANA (titer) 6 month	Frequency of ocular attacks 6~12 month	ANA (titer) 12 month	Frequency of ocular attacks 12~18 month	ANA (titer) 18 month	Frequency of ocular attacks 18~24 month	ANA (titer) 24 month
1	0	0	0	80	0	40	0	80	0	80
2	2	0	0	0	0	0	0	0	0	40
3	8	0	0	0	0	0	0	0	0	40
4	4	0	0	40	0	80	0	80	0	160
5	4	0	0	40	0	80	0	80	0	160
6	5	0	0	40	0	160	0	320	0	640
7	3	0	0	40	0	80	0	160	0	640
8	1	0	0	40	0	40	0	40	0	40
9	4	0	1	0	0	40	0	40	0	80
10	2	0	1	0	0	80	0	80	0	80
11	4	0	1	0	0	0	0	0	0	0
12	4	40	1	80	0	80	0	80	0	80
13	4	0	0	160	1	80	0	160	0	80
14	7	0	1	160	5	160	4	320	3	640
15	2	0	0	40	1	80	1	80	0	40
16	6	80	2	160	1	160	1	160	0	160
17	4	0	4	40	1	80	0	40	0	40

ANA positive: ANA titer≥80, ANA – anti nuclear antibody

the titer (1:160). Only one patient (5.9%) converted to anti-dsDNA antibody-positive during the follow-up period. These findings are consistent with previous studies of other autoimmune rheumatoid diseases, which reported that 25–71% and 4–46% patients became positive for ANA and anti-dsDNA antibodies after IFX initiation in case of psoriasis and rheumatoid arthritis [32, 37, 38]. In these previous studies, a small number of patients had lupus-like symptoms [39–41]. Suhler EB et al. also reported the results of a prospective study in which 23 patients with non-infectious uveoretinitis including four

of BD patients were enrolled [42]. In the report, ANA titers developed in 15 (75.0%) of the 20 patients and two patients with very high titer showed arthritis. Although none of the patients in our study have shown lupus symptoms, we have to observe the patients very carefully.

It is still unknown how ANA and anti-dsDNA antibodies develop during IFX therapy. One possible explanation is that TNF-α may up-regulate cellular expression of the adhesion molecule CD44, which plays a role in the
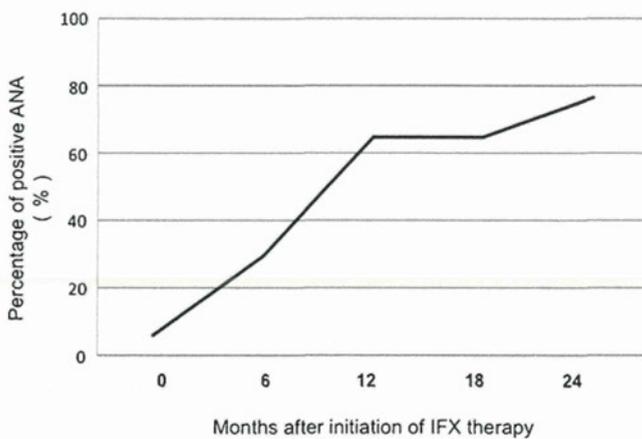

Fig. 2 Frequencies of ANA positivity in BD patients undergoing IFX therapy. The positive conversion of ANA became frequent 6 months after the initiation of IFX, and its positivity rate gradually increased
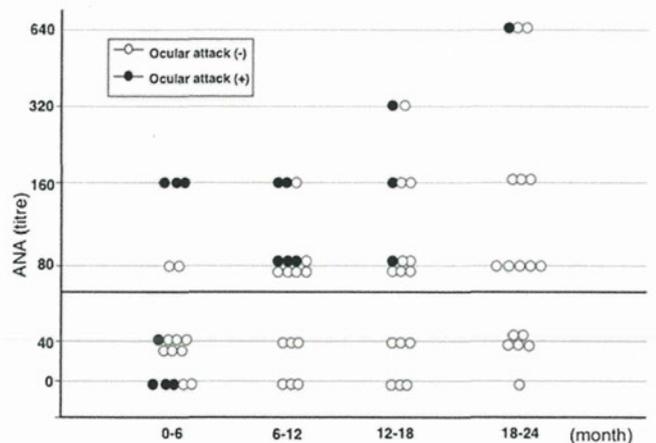

Fig. 3 Correlation of ocular attacks with elevation of ANA titer. Since the 6th month of IFX therapy, all five patients (23.5%) suffering from a relapse of ocular inflammatory attack were ANA-positive, and three of five patients had ocular attacks more than once throughout the observation period

clearance of apoptotic neutrophils by phagocytes [43, 44]. Impaired clearance of apoptotic cells and reduced CD44 expression on leukocytes has been reported in systemic lupus erythematosus (SLE) [45, 46]. IFX may down-regulate CD44 expression and induce an immune reaction toward their own nuclei by impairment of the clearance of apoptotic cells.

In the present study, we also demonstrated the association between the development of ANA and reduced effects of IFX therapy in BD patients. Only a few studies have reported the association of serum ANA development with the effects of IFX [35, 42]. Pink et al. reported that ANA titer was associated with the loss of response to anti-TNF-α therapy in psoriasis. In our study, during 6 months after the initiation of IFX therapy, several patients experienced mild ocular inflammatory attacks, both in the ANA-positive and ANA-negative groups. Presumably, it takes some time for IFX to exert an inhibitory effect on severe ocular inflammation in BD patients. However, after the 6th month IFX therapy, the cases suffering from the relapse of ocular inflammatory attacks were limited to ANA-positive patients. Similar to the study in psoriasis [35], these results suggest that the development of elevated levels of serum ANA may be associated with the reduction of IFX efficacy for BD patients. Suhler EB et al. mentioned no clear relation between the development of ANAs and ocular therapeutic response [42]. The subjects in the report included a variety of uveitis cases, in contrast to our study, which targeted only BD. The tight disease enrollment may be the reason why we could show the relation between recurrences of uveitis and high titer of ANA.

The exact association between ANA and IFX also remains unknown. It has also been found that repeated infusion of IFX leads to induction of antibodies to IFX (ATI) that reduce the efficacy of IFX. This phenomenon has been a serious issue in rheumatoid arthritis [47], Crohn's disease [48], psoriasis [49, 50] and BD [51] therapy. ANA and ATI, both of which appear during the course of IFX treatment, are likely to be involved in the reduced efficacy of IFX; however, the correlation between the two antibodies remains to be elucidated. We speculate that repeated administration of protein agents such as IFX may activate a systemic immune response, leading to the production of various autoantibodies including ANA and ATI. Therefore, detection of high titer of ANA indicates the development of ATI in the patients. According to this theory, the patients, such as cases #6 and #7, with high ANA titer (640×) may have already had ATI. These patients should be monitored closely for further symptoms. If the theory is confirmed that ATI is strongly correlated with the decreased therapeutic efficacy of IFX, we need to consider concomitant use of immune modulatory medicine in BD.

IFX has provided a new way to maintain good vision for a long time in many BD patients with severe uveitis. However, in certain cases IFX becomes less effective while long-term use of IFX. Serum ANA titers may be one of the helpful biomarker to predict IFX ineffectiveness.

References

1. Kitamei H, Kitaichi N, Namba K, Kotake S, Goda C, Kitamura M, Miyazaki A, Ohno S (2009) Clinical features of intraocular inflammation in Hokkaido, Japan. Acta Ophthalmol 87:424–428
2. Kitaichi N, Miyazaki A, Iwata D, Ohno S, Stanford MR, Chams H (2007) Ocular features of Behçet's disease: an international collaborative study. Br J Ophthalmol 91:1579–1582
3. Kitaichi N, Miyazaki A, Stanford MR, Iwata D, Chams H, Ohno S (2009) Low prevalence of juvenile-onset Behçet's disease with uveitis in East/South Asian people. Br J Ophthalmol 93:1428–1430
4. Kaklamani V, Vaiopoulos G, Kaklamanis P (1998) Behçet's disease. Semin Arthritis Rheum 27:197–217
5. Sakane T, Takeno M, Suzuki N, Inaba G (1999) Behçet's disease. N Engl J Med 341:1284–1291
6. Zouboulis C (1999) Epidemiology of Adamantiades-Behçet's disease. Ann Med Interne (Paris) 150:488–498
7. Knight D, Trinh H, Le J, Siegel S, Shealy D, McDonough M, Scallon B, Moore M, Vilcek J, Daddona P (1993) Construction and initial characterization of a mouse-human chimeric anti-TNF antibody. Mol Immunol 30:1443–1453
8. Elliott M, Maini R, Feldmann M, Long-Fox A, Charles P, Bijl H, Woody J (1994) Repeated therapy with monoclonal antibody to tumour necrosis factor alpha (cA2) in patients with rheumatoid arthritis. Lancet 344:1125–1127
9. Maini R, St Clair E, Breedveld F, Furst D, Kalden J, Weisman M, Smolen J, Emery P, Harriman G, Feldmann M, Lipsky P (1999) Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 354:1932–1939
10. Hanauer S, Feagan B, Lichtenstein G, Mayer L, Schreiber S, Colombel J, Rachmilewitz D, Wolf D, Olson A, Bao W, Rutgeerts P, Group AIS (2002) Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 359:1541–1549
11. Zhang Z, Schmitt J, Wozel G, Kirch W (2009) Treatment of plaque psoriasis with biologics. A meta-analysis of randomized controlled trials. Med Klin (Munich) 104:125–136
12. Nestle F, Kaplan D, Barker J (2009) Psoriasis. N Engl J Med 361:496–509
13. Sfikakis P, Theodossiadis P, Katsiari C, Kaklamanis P, Markomichelakis N (2001) Effect of infliximab on sight-threatening panuveitis in Behçet's disease. Lancet 358:295–296

14. Muñoz-Fernández S, Hidalgo V, Fernández-Melón J, Schlincker A, Martín-Mola E (2001) Effect of infliximab on threatening panuveitis in Behçet's disease. Lancet 358:1644

15. Ohno S, Nakamura S, Hori S, Shimakawa M, Kawashima H, Mochizuki M, Sugita S, Ueno S, Yoshizaki K, Inaba G (2004) Efficacy, safety, and pharmacokinetics of multiple administration of infliximab in Behçet's disease with refractory uveoretinitis. J Rheumatol 31:1362–1368

16. Sfikakis P, Kaklamanis P, Elezoglou A, Katsilambros N, Theodossiadis P, Papaefthimiou S, Markomichelakis N (2004) Infliximab for recurrent, sight-threatening ocular inflammation in Adamantiades-Behçet disease. Ann Intern Med 140:404–406

17. Tugal-Tutkun I, Mudun A, Urgancioglu M, Kamali S, Kasapoglu E, Inanc M, Gül A (2005) Efficacy of infliximab in the treatment of uveitis that is resistant to treatment with the combination of azathioprine, cyclosporine, and corticosteroids in Behçet's disease: an open-label trial. Arthritis Rheum 52:2478–2484

18. Accorinti M, Pirraglia M, Paroli M, Priori R, Conti F, Pivetti-Pezzi P (2007) Infliximab treatment for ocular and extraocular manifestations of Behçet's disease. Jpn J Ophthalmol 51:191–196

19. Niccoli L, Nannini C, Benucci M, Chindamo D, Cassarà E, Salvarani C, Cimino L, Gini G, Lenzetti I, Cantini F (2007) Long-term efficacy of infliximab in refractory posterior uveitis of Behçet's disease: a 24-month follow-up study. Rheumatology (Oxford) 46:1161–1164

20. Al-Rayes H, Al-Swailem R, Al-Balawi M, Al-Dohayan N, Al-Zaidi S, Tariq M (2008) Safety and efficacy of infliximab therapy in active Behçet's uveitis: an open-label trial. Rheumatol Int 29:53–57

21. Yamada Y, Sugita S, Tanaka H, Kamoi K, Kawaguchi T, Mochizuki M (2010) Comparison of infliximab versus ciclosporin during the initial 6-month treatment period in Behçet disease. Br J Ophthalmol 94:284–288

22. Elezoglou A, Kafasi N, Kaklamanis PH, Theodossiadis PG, Kapsimali V, Choremi E, Vaiopoulos G, Sfikakis PP (2007) Infliximab treatment-induced formation of autoantibodies is common in Behçet's disease. Clin Exp Rheumatol 25:S65–S69

23. Mizushima Y (1988) Recent research into Behçet's disease in Japan. Int J Tissue React 10:59–65

24. Jabs DA, Nussenblatt RB, Rosenbaum JT, Group SoUNSW (2005) Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol 140:509–516

25. Fritzler MJ, Pauls JD, Kinsella TD, Bowen TJ (1985) Antinuclear, anticytoplasmic, and anti-Sjögren's syndrome antigen A (SS-A/Ro) antibodies in female blood donors. Clin Immunol Immunopathol 36:120–128

26. de Vlam K, De Keyser F, Verbruggen G, Vandenbossche M, Vanneuville B, D'Haese D, Veys EM (1993) Detection and identification of antinuclear autoantibodies in the serum of normal blood donors. Clin Exp Rheumatol 11:393–397

27. Forslid J, Heigl Z, Jonsson J, Scheynius A (1994) The prevalence of antinuclear antibodies in healthy young persons and adults, comparing rat liver tissue sections with HEp-2 cells as antigen substrate. Clin Exp Rheumatol 12:137–141

28. Tan EM, Feltkamp TE, Smolen JS, Butcher B, Dawkins R, Fritzler MJ, Gordon T, Hardin JA, Kalden JR, Lahita RG, Maini RN, McDougal JS, Rothfield NF, Smeenk RJ, Takasaki Y, Wiik A, Wilson MR, Koziol JA (1997) Range of antinuclear antibodies in "healthy" individuals. Arthritis Rheum 40:1601–1611

29. Fernandez SA, Lobo AZ, Oliveira ZN, Fukumori LM, AM Prigo, Rivitti EA (2003) Prevalence of antinuclear autoantibodies in the serum of normal blood donors. Rev Hosp Clin Fac Med Sao Paulo 58:315–319

30. Watanabe A, Kodera M, Sugiura K, Usuda T, Tan EM, Takasaki Y, Tomita Y, Muro Y (2004) Anti-DFS70 antibodies in 597 healthy hospital workers. Arthritis Rheum 50:892–900

31. Al Jabri AA, Al Buloshi MS (2004) Anticardiolipin and antinuclear antibodies in the adult healthy Omani individuals. Saudi Med J 25:313–317

32. De Rycke L, Kruithof E, Van Damme N, Hoffman IE, Van den Bossche N, Van den Bosch F, Veys EM, De Keyser F (2003) Antinuclear antibodies following infliximab treatment in patients with rheumatoid arthritis or spondylarthropathy. Arthritis Rheum 48:1015–1023

33. Elkayam O, Burke M, Vardinon N, Zakut V, Yitzhak RB, Paran D, Levartovsky D, Litinsky I, Caspi D (2005) Autoantibodies profile of rheumatoid arthritis patients during treatment with infliximab. Autoimmunity 38:155–160

34. Eriksson C, Engstrand S, Sundqvist KG, Rantapää-Dahlqvist S (2005) Autoantibody formation in patients with rheumatoid arthritis treated with anti-TNF alpha. Ann Rheum Dis 64:403–407

35. Pink AE, Fonia A, Allen MH, Smith CH, Barker JN (2010) Antinuclear antibodies associate with loss of response to antitumour necrosis factor-alpha therapy in psoriasis: a retrospective, observational study. Br J Dermatol 162:780–785

36. Nancey S, Blanvillain E, Parmentier B, Flourié B, Bayet C, Bienvenu J, Fabien N (2005) Infliximab treatment does not induce organ-specific or nonorgan-specific autoantibodies other than antinuclear and anti-double-stranded DNA autoantibodies in Crohn's disease. Inflamm Bowel Dis 11:986–991

37. Smith CH, Jackson K, Bashir SJ, Perez A, Chew AL, Powell AM, Wain M, Barker JN (2006) Infliximab for severe, treatment-resistant psoriasis: a prospective, open-label study. Br J Dermatol 155:160–169

38. Charles PJ, Smeenk RJ, De Jong J, Feldmann M, Maini RN (2000) Assessment of antibodies to double-stranded DNA induced in rheumatoid arthritis patients following treatment with infliximab, a monoclonal antibody to tumor necrosis factor alpha: findings in open-label and randomized placebo-controlled trials. Arthritis Rheum 43:2383–2390

39. Cairns AP, Duncan MK, Hinder AE, Taggart AJ (2002) New onset systemic lupus erythematosus in a patient receiving etanercept for rheumatoid arthritis. Ann Rheum Dis 61:1031–1032

40. Debandt M, Vittecoq O, Descamps V, Le Loët X, Meyer O (2003) Anti-TNF-alpha-induced systemic lupus syndrome. Clin Rheumatol 22:56–61

41. Favalli EG, Sinigaglia L, Varenna M, Arnoldi C (2002) Drug-induced lupus following treatment with infliximab in rheumatoid arthritis. Lupus 11:753–755

42. Suhler EB, Smith JR, Wertheim MS, Lauer AK, Kurz DE, Pickard TD, Rosenbaum JT (2005) A prospective trial of infliximab therapy for refractory uveitis: preliminary safety and efficacy outcomes. Arch Ophthalmol 123:903–912

43. Osada A, Nakashima H, Furue M, Tamaki K (1995) Up-regulation of CD44 expression by tumor necrosis factor-alpha is neutralized by interleukin-10 in Langerhans cells. J Invest Dermatol 105:124–127

44. Hart SP, Dougherty GJ, Haslett C, Dransfield I (1997) CD44 regulates phagocytosis of apoptotic neutrophil granulocytes, but not apoptotic lymphocytes, by human macrophages. J Immunol 159:919–925

45. Herrmann M, Voll RE, Zoller OM, Hagenhofer M, Ponner BB, Kalden JR (1998) Impaired phagocytosis of apoptotic cell material by monocyte-derived macrophages from patients with systemic lupus erythematosus. Arthritis Rheum 41:1241–1250

46. Cairns AP, Crockard AD, McConnell JR, Courtney PA, Bell AL (2001) Reduced expression of CD44 on monocytes and neutrophils in systemic lupus erythematosus: relations with apoptotic neutrophils and disease activity. Ann Rheum Dis 60:950–955