

# Multicenter Study of Infliximab for Refractory Uveoretinitis in Behçet Disease

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**Objective:** To describe the effects of infliximab on refractory uveoretinitis in patients with Behçet disease during the first year of treatment.

**Methods:** Data were collected prospectively at 8 tertiary uveitis centers. Safety was analyzed in 63 patients. Efficacy was analyzed in 50 patients, after exclusion of those who had received infliximab for various reasons before the study.

**Results:** Eighty-nine percent (56 of 63) of the patients were male, with 70% (44 of 63) of the patients aged 25 to 44 years. The safety analysis demonstrated that 34 episodes of adverse effects occurred in 46% (29 of 63) of patients during 1 year, including 3 episodes of infusion reactions. No adverse effects were deemed serious. The efficacy analysis at 1 year showed that uveoretinitis had improved in 69% (33 of 48), had improved somewhat in 23% (11 of 48), was unchanged in 8% (4 of 48), and had worsened in no patients. The mean num-

ber of ocular attacks per 6-month period decreased from 2.66 at baseline to 0.44 during months 1 through 6 of infliximab therapy and to 0.79 during months 7 through 12. Forty-four percent (21 of 48) of patients had no ocular attacks during the 1-year period. Efficacy was best for patients with uveoretinitis duration of less than 5 years. The mean best-corrected visual acuity improved logarithm of the minimum angle of resolution from 0.736 at the first infliximab infusion to 0.616 at the end of 1 year ( $P=.01$ ).

**Conclusions:** Infliximab treatment for Behçet disease uveoretinitis was well tolerated, with nonserious adverse effects occurring in about half of the patients. At the end of 1 year, uveoretinitis had improved or improved somewhat in 92% (44 of 48) of patients, accompanied by improvement in the mean visual acuity.

*Arch Ophthalmol.* 2012;130(5):592-598

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**I**N 2008, BEHÇET DISEASE AFFECTED more than 17 000 individuals in Japan<sup>1</sup> and in 2002 represented 6.2% of new uveitis referrals to specialty clinics in Japan.<sup>2</sup> The 4 major manifestations of Behçet syndrome are oral aphthous ulcers, genital ulcers, skin lesions, and recurrent bouts of anterior or posterior uveitis.<sup>3</sup> In many patients, uveitis can be reduced using standard immunosuppressive drugs.<sup>4</sup> However, recurrent bouts of uveitis, particularly if the macula or optic disc is involved, lead to a visual acuity of 0.1 or less within 10 years of ocular symptom onset in 38.7% of eyes, despite immunosuppressive therapy.<sup>5</sup> Therefore, recurrent uveoretinitis must be regarded as vision-threatening ocular inflammation and warrants an aggressive approach.

Biologic agents have increasingly been used in patients with refractory ocular inflammation due to various origins, including sarcoidosis, birdshot chorioretinopa-

thy, and Behçet disease.<sup>6-8</sup> However, the application of these biologic agents has represented off-label use in most cases. Infliximab is a chimeric monoclonal antibody against tumor necrosis factor, a cytokine whose production from peripheral blood monocytes was increased in patients having Behçet disease with active

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uveitis vs those without active uveitis or control subjects.<sup>9</sup> An open-label trial of infliximab for refractory uveoretinitis in patients with Behçet disease showed a significant decrease in the mean number of ocular attacks compared with conventional therapy.<sup>10</sup> Based on this trial and an extension clinical trial, infliximab was approved by the Japanese Ministry of Health, Labour, and Welfare (MHLW) in January 2007 for the treatment of refractory

uveoretinitis associated with Behçet disease.<sup>11</sup> As a condition of approval, the MHLW mandated the collection of data on all patients with Behçet disease who were prescribed infliximab. The present study pools these data for the first year of treatment from 8 tertiary centers in Japan that specialize in this disease. The study objective was to describe the effects of infliximab on refractory uveoretinitis in patients with Behçet disease during the first year of treatment.

## METHODS

### PARTICIPANTS

Data were collected prospectively using prepared data forms among patients receiving their first infliximab infusion between January 26, 2007, and August 23, 2008, for the indication of refractory uveoretinitis associated with Behçet disease. During this period, 97 patients with Behçet disease were consecutively registered as having started infliximab treatment at 8 participating centers. Data forms for the first year of treatment were returned on 63 patients. The diagnosis of Behçet disease was made based on established criteria by the Behçet's Disease Research Committee of Japan.<sup>3</sup> Participating centers and physicians involved are listed at the end of this article. Data on various aspects of some patients included in the present study have been reported previously by individual centers.<sup>12-17</sup> Standard informed consent was obtained from patients by the treating physicians.

No criteria were given by the MHLW at the time of infliximab approval and data collection to define refractoriness in patients. In general, the uveitis specialists involved in this study interpreted refractory uveoretinitis to imply that a patient continued to have ocular attacks, despite the use of systemic immunosuppression, or was intolerant of such treatment.

### PRETREATMENT EVALUATION

Before initiating infliximab treatment, all patients underwent complete ophthalmological and internal medicine examinations, including tuberculin skin testing and a chest radiograph. Blood tests included baseline complete blood cell count, chemistries, liver function enzymes, and hepatitis B virus serologic testing. The administration of tuberculosis prophylaxis was left to the discretion of the treating physicians.

### INFLIXIMAB DOSING AND INFUSION REACTIONS

As per the MHLW treatment protocol, patients received intravenous infusions of infliximab (5 mg/kg) at weeks 0, 2, and 6 and every 8 weeks thereafter. Infusion reactions were defined as any adverse reaction developing during the infliximab infusion or after completion of the infusion for up to 2 hours.

### DATA COLLECTION AND STATISTICAL ANALYSIS

Forms were filled out by treating physicians at each participating center and were sent to a central data collection office for collation and analysis. As per the standardized MHLW criteria, adverse effects were severe if they resulted in death, were life threatening, required hospitalization or prolongation of hospitalization for treatment, or caused irreversible disability or dysfunction, congenital abnormalities or defects, or other severe medical conditions. Physicians were asked to report adverse effects in

**Table 1. Baseline Characteristics and Pertinent Medical Histories Among 63 Patients**

Characteristic	Value
Sex, No. (%)	
Male	56 (89)
Female	7 (11)
Age, y	
No. (%)	
<15	1 (2)
15 to <25	6 (10)
25 to <35	22 (35)
35 to <45	22 (35)
45 to <55	4 (6)
55 to <65	7 (11)
≥65	1 (2)
Mean (SD)	37.4 (11.6)
Medical history, No. (%) <sup>a</sup>	
Tuberculosis	6 (10)
Hepatitis B infection	1 (2)
Other disease <sup>b</sup>	38 (60)
Known drug allergies	9 (14)

<sup>a</sup>Some patients had more than 1 medical condition.

<sup>b</sup>Includes ocular and nonocular disease.

an open-ended question, as opposed to choosing from a list of potential adverse events known to be associated with infliximab.

Categorization of patients' uveoretinitis severity and treatment efficacy was left to the discretion of the treating physicians; no severity or efficacy terminology was specified. The consensus among the uveitis specialists participating in this study was that uveoretinitis was mild if it involved only the anterior segment without hypopyon, was moderate if it involved the anterior segment with hypopyon or involved the retina but not the macula or optic disc, and was severe if it involved the macula or optic disc. Similarly, the consensus on efficacy after initiation of infliximab therapy was that uveoretinitis had improved if no ocular attacks were observed, had improved somewhat if attacks were of decreased frequency and involved only the anterior segment, was unchanged if ocular attacks occurred at the same frequency or severity, and had worsened if ocular attacks occurred at a higher frequency or severity. Acute ocular attacks were managed at the discretion of the treating physicians, and this information was not collected.

Best-corrected visual acuity was assessed using Landolt ring charts. Decimal best-corrected visual acuity was converted to logarithm of the minimum angle of resolution before statistical analysis. Statistical comparisons were made using the Wilcoxon signed rank test.

## RESULTS

### BASELINE CHARACTERISTICS

As summarized in **Table 1**, 89% (56 of 63) of the patients were male, and 70% (44 of 63) of the patients were aged 25 to 44 years. Ten percent (6 of 63) of patients had a known history of tuberculosis, while 14% (9 of 63) of patients had known drug allergies. As summarized in **Table 2**, most patients had Behçet disease duration of less than 10 years, with a similar uveoretinitis duration. Uveoretinitis was severe in 83% (52 of 63) of patients. At least 3 ocular attacks in the 6-month period before starting infliximab had been documented in 33% (21 of 63)

**Table 2. Behçet Syndrome Characteristics Among 63 Patients**

Characteristic	Value
Behçet syndrome duration, y	
No. (%)	
<5	23 (37)
5 to <10	23 (37)
10 to <15	10 (16)
≥15	4 (6)
Unknown	3 (5)
Mean (SD)	6.6 (4.6)
Uveoretinitis duration, y	
No. (%)	
<5	26 (41)
5 to <10	23 (37)
10 to <15	11 (18)
≥15	3 (5)
Mean (SD)	6.9 (4.7)
Severity of uveoretinitis, No. (%)	
Mild	0
Moderate	11 (18)
Severe	52 (83)
No. of ocular attacks in the 6-mo period before starting infliximab, No. (%)	
0	12 (19)
1	10 (16)
2	13 (21)
≥3	21 (33)
Unknown	7 (11)
Cyclosporine use before starting infliximab, No. (%)	
Yes	31 (49)
No	18 (29)
Unknown	14 (22)

of patients. Almost half of the patients were using cyclosporine. Of those, many immediately discontinued their cyclosporine at the initiation of infliximab therapy, while others tapered to a lower maintenance dose.

#### INFLIXIMAB INFUSION AND TUBERCULOSIS PROPHYLAXIS

Infliximab infusions were administered initially in the outpatient clinic in 35 of 63 patients (56%) and in an inpatient setting in 28 of 63 patients (44%). Of those who received infusions as inpatients, 24 patients were subsequently given their infusions in the outpatient clinic. Seventeen of 63 patients (27%) received pharmacological tuberculosis prophylaxis.

#### SAFETY

As summarized in **Table 3**, 34 episodes of adverse effects were documented, occurring in 29 of 63 patients (46%) during 1 year. The most common events were dermatological, such as urticaria and rash. Infusion reactions were reported in 2 of 63 patients (3%) and consisted of 1 episode of transient dyspnea in one patient and 2 episodes of decreased blood pressure in the other patient. No adverse effects were judged to be serious by the MHLW criteria.

During the 1-year study period, infliximab therapy was discontinued in 3 patients (the last infusions were ad-

**Table 3. Adverse Effects of Infliximab Therapy Among 63 Patients**

Adverse Effect	No. of Episodes	No. of Patients <sup>a</sup>
General systemic		
Headache	1	1
Fever	1	1
Sweats	1	1
Chills	1	1
Nausea	1	1
Blood pressure elevation	2	1
Bradycardia	1	1
Decreased white blood cell count	1	1
Respiratory		
Coughing	1	1
Difficulty breathing	1	1
Upper airway inflammation	3	3
Dermatological		
Flushing	2	2
Urticaria	6	3
Rash, unspecified	4	4
Purigo	1	1
Pruritus	1	1
Infectious		
Tonsillitis	1	1
Infectious colitis	1	1
Infusion related		
Paresthesia at infusion site	1	1
Infusion reaction	3	2
<b>Total</b>	<b>34</b>	<b>29</b>

<sup>a</sup>Some patients experienced more than 1 adverse effect or more than 1 episode of the same adverse effect.

ministered at 154, 170, and 358 days, respectively, after the initial infusions). The reasons given for stopping infliximab were adverse effects in 2 patients and adverse effects and inadequate efficacy in 1 patient.

#### OVERALL CLINICAL EFFICACY

To assess efficacy only in patients who were infliximab naive, the efficacy analysis was performed after the exclusion of 11 patients who had previously received infliximab as part of the phase 2 clinical trial for Behçet disease<sup>10</sup> or who had received infliximab for other clinical indications. An additional 2 patients at 6 months and 4 patients at 12 months were excluded because of incomplete data.

At 6 months of infliximab therapy (n=50), uveoretinitis had improved in 33 patients (66%), had improved somewhat in 10 patients (20%), was unchanged in 6 patients (12%), and had worsened in 1 patient (2%). For the most part, these percentages remained stable at the 12-month evaluation (n=48), when uveoretinitis had improved in 33 patients (69%), had improved somewhat in 11 patients (23%), was unchanged in 4 patients (8%), and had worsened in no patients.

#### FREQUENCY OF OCULAR ATTACKS

As summarized in **Table 4**, the mean number of ocular attacks per patient decreased significantly from 2.66 (median, 2; range, 0-10) during the 6 months before start-

**Table 4. Efficacy of Infliximab by Location and Severity of Ocular Inflammatory Attacks<sup>a</sup>**

Inflammatory Attacks	No. (%) of Attacks [Mean No. of Attacks per Patient]					
	6-Month Period Before Starting Infliximab (n = 50)	Months 1-6 After Starting Infliximab (n = 50)		Months 7-12 After Starting Infliximab (n = 48)		
		Value	P Value <sup>b</sup>	Value	P Value <sup>b</sup>	P Value <sup>c</sup>
<b>Total</b>	<b>133 [2.66]</b>	<b>22 [0.44]</b>	<b>&lt;.001</b>	<b>38 [0.79]</b>	<b>&lt;.001</b>	<b>.02</b>
Location						
Anterior uveitis	16 (12) [0.32]	2 (9) [0.04]	.008	10 (26) [0.21]	.32	.07
Posterior uveitis	50 (38) [1.00]	7 (32) [0.14]	<.001	14 (37) [0.29]	<.001	.05
Panuveitis	65 (49) [1.30]	12 (55) [0.24]	<.001	14 (37) [0.29]	<.001	.39
Unknown	2 (2) [0.04]	1 (5) [0.02]	...	0 [0.00]	...	...
Severity						
Mild	35 (26) [0.70]	15 (68) [0.30]	.04	24 (63) [0.50]	.49	.18
Moderate	56 (42) [1.12]	3 (14) [0.06]	<.001	5 (13) [0.10]	<.001	.22
Severe	40 (30) [0.80]	4 (18) [0.08]	<.001	9 (24) [0.19]	<.001	.07
Unknown	2 (2) [0.04]	0 [0.00]	...	0 [0.00]	...	...

<sup>a</sup>The Wilcoxon signed rank test was used for statistical comparisons.

<sup>b</sup>Compared with the 6-month period before starting infliximab.

<sup>c</sup>Compared with months 1 through 6 after starting infliximab.

ing infliximab (baseline) to 0.44 (median, 0; range, 0-4) during months 1 through 6 of infliximab therapy and to 0.79 (median, 0; range, 0-5) during months 7 through 12 ( $P < .001$  vs baseline for both). The difference in the mean number of ocular attacks per patient between months 1 through 6 vs months 7 through 12 was statistically significant ( $P < .02$ ).

Thirty-eight of 50 patients (76%) had no ocular attacks during months 1 through 6, and 28 of 48 patients (58%) had no ocular attacks during months 7 through 12. Among 48 patients with complete efficacy data at 12 months, 21 (44%) had no ocular attacks, and 27 (56%) had at least 1 ocular attack during the 1-year period. Among 27 patients with at least 1 ocular attack, uveoretinitis had improved or improved somewhat in most of them according to the treating physicians; at 12 months, uveoretinitis had improved in 18 patients (67%), had improved somewhat in 7 patients (26%), was unchanged in 2 patients (7%), and had worsened in no patients.

#### EFFICACY BASED ON UVEORETINITIS DURATION

As shown in the **Figure**, the efficacy of infliximab during 1 year was best for patients with uveoretinitis duration of less than 5 years. However, infliximab therapy was judged to have improved uveoretinitis in more than half of the patients with a uveoretinitis duration of 5 years to less than 10 years or 10 years to less than 15 years.

#### EFFICACY BASED ON LOCATION AND SEVERITY OF UVEORETINITIS

Table 4 gives the number of ocular attacks at baseline and during months 1 through 6 and months 7 through 12 of infliximab therapy based on the location and severity of inflammatory attacks. During months 1 through 6, the mean number of ocular attacks per patient decreased markedly in all categories examined. However, during

months 7 through 12, a slight increase for all locations was observed compared with baseline, although these differences were not statistically significant. A small increase in the proportion of severe ocular attacks among all ocular attacks from months 1 through 6 (18% [4 of 22 attacks]) to months 7 through 12 (24% [9 of 38 attacks]) was observed.

Examination of individual cases revealed that all 9 patients who had ocular attacks during months 1 through 6 had a reduction in severity relative to baseline. Of 19 patients who continued to have ocular attacks during months 7 through 12, a total of 14 had a reduction in severity relative to baseline, while 5 had no reduction (although 3 of these 5 patients had a decrease in the number of ocular attacks compared with baseline).

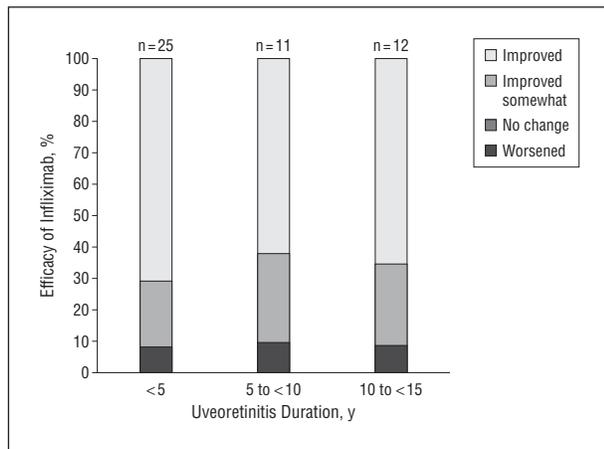
#### VISUAL ACUITY

The mean best-corrected visual acuity (logarithm of the minimum angle of resolution) for 50 patients (90 eyes) included in the efficacy analysis improved from 0.736 at the first infliximab infusion to 0.616 at the end of 1 year. This difference was significant ( $P = .01$ ) using the last observation carried forward method.

#### COMMENT

Several case series have shown the efficacy of infliximab for treating uveitis associated with Behçet disease.<sup>6,7,10,12-27</sup> To our knowledge, the present study is the first to examine infliximab use for this disease in a prospective multicenter study among many patients.

As expected, most patients were male and were aged 25 to 44 years. What was somewhat surprising was that 10% (6 of 63) of the patients had a known history of tuberculosis; 27% (17 of 63) received pharmacological tuberculosis prophylaxis. In Japan, tuberculosis remains at moderately high incidence and prevalence levels<sup>28</sup>; there-



**Figure.** Efficacy in 48 patients who completed 1 year of infliximab therapy by duration of uveoretinitis associated with Behçet syndrome. The number of patients who improved, improved somewhat, or did not change was 18, 5, and 2 for duration of less than 5 years; 7, 3, and 1 for a duration of 5 to less than 10 years; and 8, 3, and 1 for a duration of 10 to less than 15 years, respectively. No patients experienced worsening of their uveoretinitis.

fore, reactivation or new infection is of concern. Of note, in the phase 2 trial of infliximab for Behçet disease uveoretinitis in Japan, 1 of 13 patients was reported to have activation of latent tuberculosis.<sup>10</sup> The present analysis of 63 patients during 1 year revealed no cases of active tuberculosis or other severe infections. Severe pulmonary infections involving *Pneumocystis jiroveci* and *Histoplasma capsulatum* can occur during infliximab therapy, with numerous cases of the former reported in Japan.<sup>29-31</sup> However, these infections occurred in patients with diseases such as rheumatoid arthritis, most of whom were older; therefore, age-related comorbidities may have had a role. The mean age of our patients with Behçet disease was 37.4 years, with 81% (51 of 63) of patients younger than 45 years. Because Behçet disease uveoretinitis is a chronic disease, further observation of this cohort is needed to better evaluate the risk of opportunistic infection. Other possible severe adverse effects, such as thromboembolic events, have been reported in patients with uveitis<sup>6</sup> but were not observed in our study.

This study confirmed previous infliximab efficacy results among patients with Behçet disease uveoretinitis. The number of ocular inflammatory attacks was significantly reduced during months 1 through 6 and months 7 through 12 of infliximab treatment compared with baseline. Twenty-one of 48 patients (44%) had no ocular attacks during the entire 12-month period. Among patients in whom ocular attacks continued, uveoretinitis in most of them improved or improved somewhat. Furthermore, although efficacy was best for patients with uveoretinitis duration of less than 5 years, infliximab was effective in those who had had the disease for longer periods.

Although the overall frequency of ocular attacks declined compared with baseline, a statistically significant increase in the mean number of ocular attacks per patient was observed during months 7 through 12 (0.79 attacks) compared with months 1 through 6 (0.44 attacks). There was also a trend toward an increased proportion of severe attacks among all ocular attacks and a higher mean number of severe attacks per patient. Hu-

man antichimera antibodies (HACAs) have been implicated in the observed decline in therapeutic response to infliximab among patients with inflammatory bowel disease.<sup>32,33</sup> Although HACA titers were not measured in the present study, it is possible that the development of HACAs may have led to a gradual rise in frequency or severity of ocular attacks over time during the 1-year period. The development of HACAs may also be related to the occurrence of ocular attacks observed close to the next planned infliximab infusion in patients with Behçet disease,<sup>12,15-17</sup> a time when serum levels of infliximab are low.<sup>16</sup> Moreover, some patients in our study continued using cyclosporine, while others did not, and this may have influenced drug responses and the development of HACAs. Further analysis of our data relative to concomitant cyclosporine use is ongoing and will be the subject of a future publication.

It is difficult to compare our treatment outcomes with those of previous studies. However, a 1978 study<sup>34</sup> revealed that Japanese patients with Behçet disease had a mean of 1.61 ocular attacks per year when taking cyclophosphamide (50-100 mg/d) vs 3.94 ocular attacks per year when not receiving immunosuppression. A 1999 study<sup>35</sup> from Japan reported that patients with Behçet disease had a mean of 0.21 ocular attacks per 4-week period when using cyclosporine (5 mg/kg/d) compared with 0.60 ocular attacks per 4-week period when receiving no immunosuppression. The baseline patient characteristics and the reporting methods differed in these studies compared with our study; nonetheless, our infliximab results seem to compare favorably. It is known that the frequency of ocular attacks in Behçet disease decreases over time after onset of the disease. A Japanese study<sup>5</sup> examining this issue in patients receiving standard immunosuppression demonstrated that the mean frequency was 4.1 ocular attacks during the first year and 3.2 ocular attacks during the second year, with a subsequent decrease to 1.4 ocular attacks during the 10th year after onset of Behçet disease. Nevertheless, the decreased frequency of ocular attacks after 1 year of infliximab therapy in the present study greatly surpasses these reported rates of decline among patients receiving standard immunosuppression alone. Finally, perhaps the best support for the use of infliximab comes from the fact that the case series reporting efficacy involved patients having Behçet disease with refractory disease, who had recurrences despite standard immunosuppressive regimens.<sup>6,7,10,18-27</sup>

Strengths of our study include the collection of data among a large sample of patients in a prospective manner and the involvement of multiple centers, representing a wide spectrum of disease and treatment patterns. Furthermore, a single definition for diagnosing Behçet disease was used based on established criteria. Weaknesses of our study include the open-label design without a sham group for comparison, the absence of criteria for efficacy and severity ratings, and the short infliximab therapy follow-up period (1 year) given that this ocular disease usually continues with inflammatory recurrences for several years, if not decades. Furthermore, only acute inflammation that was clinically observable by the physicians at the time of clinic visits, whether scheduled or unscheduled, was considered an ocular attack. Therefore, the number or severity of ocular

attacks may have been underestimated, although we assume that severe ocular attacks would have brought patients to the ophthalmologist for an unscheduled visit because of reduced vision. In addition, only 63 of 97 eligible patients from 8 centers were included in any analysis, and only 48 were included in the 1-year efficacy analysis. It is possible that patients not included in the present analysis had more adverse effects or worse efficacy. The influence of concomitant therapy also requires close examination, as already stated. Finally, the infliximab dose (5 mg/kg every 8 weeks during maintenance therapy) available for use in this study was limited by the MHLW guidelines. Patients with continued recurrence of ocular attacks, particularly those with severe attacks, may require more frequent or greater doses of infliximab, as has been reported for the treatment of various types of uveitis.<sup>7,10,36</sup>

New methods of assessing ocular inflammation would be useful to judge the severity of disease and the response to infliximab treatment. Fluorescein angiography has been used as a surrogate marker for the overall level of ocular inflammation by scoring retinal vascular and optic disc fluorescein leakage at times of clinical quiescence.<sup>17</sup> Other methods that may prove useful involve assessing the activation of various cytokines and other inflammation-related molecules by examining gene expression. Such analysis has been performed in autoimmune noninfectious uveitis,<sup>37</sup> in Behçet disease with uveitis,<sup>38</sup> and in rheumatoid arthritis and inflammatory bowel disease before and after the initiation of infliximab therapy.<sup>39,40</sup>

In summary, the present study among 63 patients having Behçet disease with refractory uveoretinitis demonstrated that infliximab was well tolerated, with nonserious adverse effects occurring in about half of the patients. At the end of 1 year, uveoretinitis had improved or improved somewhat in 92% (44 of 48) of patients, accompanied by improvement in the mean visual acuity. Forty-four percent (21 of 48) of patients had no ocular attacks during the 1-year period, while the remainder experienced a marked overall reduction in the frequency and severity of attacks compared with baseline.

**Submitted for Publication:** July 1, 2011; final revision received November 27, 2011; accepted December 1, 2011.

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**Financial Disclosure:** Drs Okada and Ohno report receiving lecture fees and grant support from Mitsubishi Tanabe Pharma, the distributor of infliximab in Japan.

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**Additional Contributions:** The Ocular Behçet's Disease Research Group of Japan acknowledges the administrative assistance of Mitsubishi Tanabe Pharma, the distributor of infliximab in Japan.

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