

Efficacy of Infliximab in Patients with Refractory Uveitis Associated with Behçet Disease

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Abstract

Background: Ocular involvement in Behçet disease is responsible for severe morbidity by causing nongranulomatous panuveitis and retinal vasculitis. In some cases, recurrent attacks cannot be controlled by conventional immunosuppressives and corticosteroid or interferon. The aim of this study is to investigate the efficacy of infliximab treatment in patients with refractory uveitis associated with Behçet disease.

Methods: Nine patients with Behçet disease related uveitis were included in the study. Uveitis had been refractory to treatment with either a combination of cyclosporine-A, azathioprine, and corticosteroid or interferon α -2a monotherapy in all patients. Patients received infliximab infusions (5 mg/kg) at weeks 0, 2, 6, and every 8 weeks thereafter. In patients receiving interferon α -2a at the time of initiation of infliximab therapy, interferon was ceased before starting infliximab. We evaluated visual acuity, ocular inflammatory attacks, and adverse effects.

Results: The Patients consist of seven men and two women; their ages ranging from 28 to 49 years. The mean follow-up after initiating infliximab therapy was 14.4 months. Four of the patients had no ocular inflammatory attacks during follow-up. Two of the remaining five patients developed a mild anterior uveitis only once after the start of infliximab infusions. Three of the patients had a mild panuveitis attack 2-4 months after the initiation of infliximab therapy. Best corrected visual acuity (BCVA) improved at least 2 lines in 6 (33.3%) eyes, from no light perception to hand motion in one eye, and from light perception to hand motion in another eye. BCVA remained stable in 9 (50%) eyes. In one patient, infliximab treatment was terminated owing to HPV+genital warts at 8th month of therapy. No other adverse effects were noticed apart from temporary infusion reaction and urticaria-like rash.

Conclusions: With a follow-up period ranging from seven to thirty three (7-33) months, infliximab was effective and well tolerated in refractory Behçet uveitis.

Keywords: Behçet disease; Infliximab; Uveitis; Retinal vasculitis

Introduction

Behçet disease (BD) is a relapsing-remitting systemic inflammatory disorder with unknown etiology and characteristic geographical distribution along the ancient Silk Road. Behçet disease mostly affects young adults. It affects both male and female equally with the male gender having a risk factor for more severe involvement. The major manifestations of BD are recurrent oral and genital ulcers, typical skin lesions and ocular involvement [1]. Ocular involvement is responsible for most frequent morbidity of BD by causing nongranulomatous panuveitis and retinal vasculitis. It also affects both arterial and venous structures [2]. Relapsing course of ocular inflammation leads to permanent damage of intraocular structures such as maculopathy, retinal vessel occlusions, and optic atrophy. It also leads to sight threatening disease [3].

In some cases, recurrent attacks and damages caused by the disease can not be controlled by the combination of conventional immunosuppressive therapy including azathioprine, cyclosporine and corticosteroid. Therefore, biologic agent use in BD management has been increasing in patients with refractory uveitis [4].

Although the pathogenesis of BD is poorly understood, inflammation in Behçet disease is thought to be associated with T helper type 1 lymphocytes and their derivatives; foremost among them, TNF α [5,6].

Infliximab is a chimeric monoclonal antibody against TNF α and it neutralizes both soluble and membrane bound forms [7]. Infliximab has Food and Drug Administration (FDA) approval for severely active Crohn's disease. Also, it was approved for refractory uveoretinitis

related to BD by Japanese Ministry of Health, Labour, and Welfare in January 2007.

The aim of this study is to investigate the efficacy and safety of infliximab (IFX) treatment in patients with refractory uveitis associated with Behçet disease.

Patients and Methods

A retrospective chart review was performed on nine Behçet patients who received intravenous infliximab therapy (Remicade® Schering-Plough Co., Ireland) for refractory uveitis associated with Behçet disease from April 2009 to April 2013. All these patients met the international diagnostic criteria of the International Study Group for BD [1]. Medical records were reviewed for gender, age, duration of BD, previous immunosuppressive and/or corticosteroid use, duration of the infliximab therapy, ocular inflammatory attacks, and adverse effects.

All patients had sight threatening eye disease and had been

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treated with either combination of cyclosporine, azathioprine and corticosteroid or interferon monotherapy. Criteria for initiation of infliximab therapy were either persistent inflammation or recurrent attacks under conventional immunosuppressives or interferon, or occurrence of side effects causing discontinuation of these agents.

Patients received infliximab infusions at a dose of 5 mg/kg at 0, 2, 6 and every 8 weeks thereafter. In patients receiving interferon at the time of initiating infliximab therapy, the interferon was ceased before starting infliximab therapy. Corticosteroids were tapered, with the goal of eventual discontinuation. Azathioprine was maintained to inhibit the development of antichimeric antibodies.

Before the initiation of infliximab therapy, all patients were evaluated by internal medicine specialist. A complete laboratory work-up was done including complete blood count, erythrocyte sedimentation rate, chest x-ray, purified protein derivative (PPD), urinalysis, kidney and liver function, and C-reactive protein. Patients who were PPD positive received 300 mg/day isoniazid prophylaxis for 9 months.

After the first application of the IFX therapy, patients were seen at the second week and then at every fourth week until the end of the infliximab infusions. All patients underwent complete ophthalmic examination including Snellen visual acuity, intraocular pressure (IOP) measurement, slit lamp biomicroscopy, and dilated fundus examination. Also fundus fluorescein angiography (FF 450 IR, Carl Zeiss, Dublin, CA, USA) and spectral optical coherence tomography (SD-OCT) (Cirrus high-definition OCT; Carl Zeiss, Dublin, CA, USA) was performed when necessary.

Main outcome measures were change in visual acuity, frequency of ocular inflammatory attacks and adverse effects.

Institutional review board's approval was obtained, and the study was conducted in compliance with the Declaration of Helsinki. All patients signed an informed consent before proceeding with intravenous infliximab therapy.

All analyses were conducted with the SPSS 15.0 software package (SPSS Inc., Chicago, ILL., USA). The p value less than 0.05 was considered to be statistically significant.

Results

Nine patients (7 male and 2 female) were included in this study. The mean age of the patients at the onset of BD and at the time of initiation of IFX therapy was 26.4 (range: 21-34) years and 35.8 (range: 28-49) years respectively. The mean duration of Behçet disease was 9.4 (range: 1-28) years. All patients had bilateral ocular involvement. Demographic and ocular characteristics of patients with Behçet disease and clinical course of the uveitis under infliximab therapy are summarized in Table 1. Purified protein derivative test was positive (≥ 10 mm) in four of the patients (44.4%) and these patients used 400 mg/ day isoniazid prophylaxis for 9 months.

Prior to IFX therapy, 6 patients (66.6%) received corticosteroid, azathioprine, and cyclosporine; 1 patient (11.1%) received cyclosporine and then IFN α -2a; 1 patient (11.1%) received cyclosporine, azathioprine and then IFN α -2a; and 1 patient (11.1%) was treated with only IFN α -2a.

Infliximab therapy was started on two patients because of side effects related to conventional immunosuppressive agents. Patient 6 started receiving IFX therapy due to bone marrow suppression while Patient 7 started receiving it due to highly increased liver and kidney function tests under conventional immunosuppressives. Also, infliximab

therapy started been administered on Patient 3 due to cystoid macular edema which is resistant to retrobulbar corticosteroid injections in his right eye under conventional immunosuppressives. Except for these three patients, the others started receiving IFX therapy due to persistent and/or recurrent ocular inflammatory attacks.

Four (44.4%) of the patients remained attack-free throughout the infliximab infusions. Two (22.2%) of the patients (Patient 4 and 7) developed only mild anterior uveitis in the 5th and 8th months of the therapy, respectively. Topical corticosteroids were prescribed and quickly tapered in all patients. Three (33.3%) of the patients (Patient 1, 2, and 5) developed posterior uveitis. In Patient 1, posterior uveitis occurred in the second month of the therapy and 2 mg/kg azathioprine and 3 mg/kg cyclosporine-A were added to treatment. Also, the interval between infliximab infusions was shortened to 6 weeks. In Patient 2, posterior uveitis developed in the 3rd month and 2.5 mg/kg azathioprine was added to her treatment regimen. During follow-up, mild anterior uveitis developed in the 6th month which was resolved with topical corticosteroid quickly. The decrease in peripheral retinal vasculitis of patient 2 under IFX was shown in Figure 1. In Patient 5, posterior uveitis attack occurred in the 4th month, and 0.5 mg/kg prednisone was prescribed and tapered to 5 mg/day in the following 5 months. Thereafter, 5 mg/day prednisone was continued. No more ocular inflammatory attack was seen throughout infusions.

Best corrected visual acuity (BCVA) of patients treated with infliximab infusions were also analyzed in the 18 eyes of the 9 patients. Best corrected visual acuity improved at least 2 lines in 6 (33.3%) eyes. It improved from no light perception to hand motion in one eye (Patient 5, OD), and from light perception to hand motion in another eye (Patient 9, OD). Best corrected visual acuity remained stable in 9 (50%) eyes. Within the stable group, two eyes had 20/20 visual acuity. Visual acuity did not improve in patients who already had concomitant ophthalmologic pathologies. Patient 3 had epiretinal membrane formation in his left eye. Patient 4 had optic atrophy and macular scar in both eyes. Patient 5 had optic atrophy in his right eye. Patient 7 had foveal atrophy in both eyes on OCT scans with a central macular thickness of 74 μ m and 81 μ m respectively (Figure 2). Patient 8 had complicated cataract, occlusio pupillae, and optic atrophy in his right eye. Patient 9 had optic atrophy in his right eye and posterior subcapsular cataract in his left eye. BCVA reduced in only one eye (patient 6, OD) due to posterior subcapsular cataract progression. Initial and final visual acuities of each patient were summarized in Table 1.

Five (55.5%) of the patients received concomitant

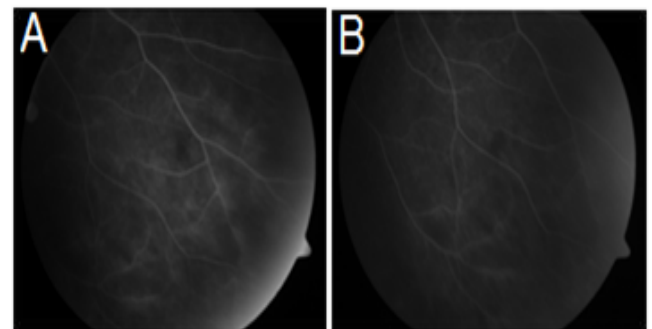


Figure 1: (A) Peripheral vasculitis in fluorescein angiograms of Patient 2 before initiation of IFX, (B) decrease of peripheral vasculitis at 6th month of IFX therapy.

immunosuppressives throughout injections. Patient 1 was prescribed 2 mg/kg azathioprine and 3 mg/kg cyclosporine-A in the 2nd month. Patient 2 was prescribed 2.5 mg/kg azathioprine in the 3rd month because of posterior uveitis attack. Patient 5 was started at 0.5 mg/kg prednisolon in the 4th month due to posterior uveitis attack. This Patient was using 5 mg/kg cyclosporine-A due to gastrointestinal manifestations of BD. Patient 3 and 9 continued with 2 mg/kg azathioprine throughout IFX infusions to inhibit the development of antichimeric antibodies. The remaining four patients received only intravenous IFX infusions.

The mean duration of infliximab therapy was 14.4 months (range: 7-33 months). Three patients (33.3%) were still on infliximab treatment when data was collected. Three patients (33.3%) were discontinued IFX due to disappearance of attacks under treatment. One patient (Patient 4) was lost to follow-up 7 months after the initiation of IFX. In Patient 1, during the 9th month of the IFX therapy, mild anterior uveitis attack occurred and 1+ anterior chamber cells persisted for the following

six months. With the thought that anti-infliximab antibodies might decrease response to treatment, IFX was replaced with adalimumab. The patient was placed on subcutaneous adalimumab therapy with 40 mg dosage every two weeks. In patient 2, infliximab therapy was terminated because of HPV (+) genital warts at 8 months after initiation of therapy.

During follow-up period, no patient reported serious or life-threatening adverse effect. Patient 2 developed temporary infusion reaction while Patient 7 developed urticaria-like rash at first infliximab infusion which did not recur again during rest of the injections. Except for these two patients, no other adverse effects were noted.

Discussion

Ocular manifestations of BD could result in severe vision loss and sight threatening conditions [8,9]. The goal of management should be rapid and sustainable suppression of ocular inflammation to prevent permanent damage in retina and optic disc. Conventional immunosuppressive agents such as azathioprine, cyclosporine-A, and corticosteroid as well as second-line agents such as interferon α-2a have proven to be effective in BD management. However, these agents could be inadequate for controlling inflammation in severe cases or side effects could limit their use [10]. An open label study reported that IFX is superior to conventional therapy for reducing inflammatory attacks in patients with refractory uveitis [11]. The present study reported data in nine BD patients with posterior uveitis resistant to conventional immunosuppressives and/or interferon. The mean follow-up period of these patients was about 14 months. This study confirmed previous studies regarding infliximab efficacy and safety of long-term infliximab treatment in refractory uveitis associated with BD [12-14]. Another important finding of the present study is that IFX has now been shown to be effective also in interferon resistant cases.

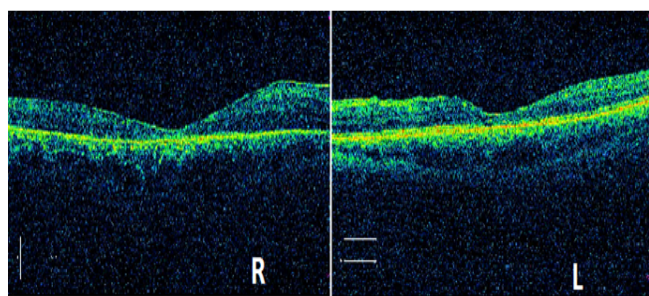


Figure 2: Decreased central macular thickness and epiretinal membrane formation in both eyes of Patient 7. R: Right Eye; L: Left Eye; MAU: Mild Anterior Uveitis; PU: Posterior Uveitis.

Patient no	Sex	Age (years)	Duration of disease (years)	Treatment prior to infliximab	VA at the initiation of infliximab* RE-LE	VA at last visit on infliximab* RE-LE	Concomitant immunosuppressive	Ocular inflammatory attacks	relapse time (months)	INAH prophylaxis	Duration of infliximab therapy (months)	Last follow up status
1	F	28	3	Cyc-A*** IFN α-2a	20/40 20/20	20/32 20/20	AZA, Cyc-A Started at 2 nd month	MAU** PU	9 2	—	15	Switched to adalimumab
2	F	31	1	CS, AZA*** IFN α-2a	20/40 20/25	20/40 20/20	AZA Started at 3 rd month	PU MAU	3 6	—	8	Discontinued due to (HPV+genital warts)
3	M	38	8	CS, AZA, Cyc-A	20/200 20/32	20/50 20/32	AZA	None	—	—	8	Discontinued
4	M	38	10	IFN α-2a	20/640 20/640	20/800 20/500	—	MAU	5	+	7	Out of follow-up
5	M	30	8	CS, AZA, Cyc-A	NLP 20/200	HM 20/200	CS, Cyc-A CS started at 4 th month	PU	4	+	33	Continues infliximab
6	M	32	11	CS, AZA, Cyc-A	20/400 20/63	20/640 20/32	—	None	—	—	23	Discontinued
7	M	41	7	CS, AZA, Cyc-A	20/1250 20/100	20/200 20/100	—	MAU	8	+	11	Discontinued
8	M	49	28	CS, AZA, Cyc-A	NLP 20/25	NLP 20/25	—	None	—	+	18	Continues infliximab
9	M	36	9	CS, AZA, Cyc-A	LP HM	HM 20/200	AZA	None	—	—	7	Continues infliximab

*VA: Visual Acuity; RE: Right Eye; LE: Left eye.

**+1 anterior chamber reaction developed and persisted for following six months.

***Cyc-A and AZA were used before.

LP: Light Perception; NLP: No Light Perception; HM: Hand Motion; CS: Corticosteroids; Cyc-A: Cyclosporin-A; AZA: Azathioprine; IFN α-2a: Interferon-α-2a; MAU: Mild Anterior Uveitis; PU: Posterior Uveitis

Table 1: Demographic and ocular characteristics of patients with Behçet disease and clinical course of the uveitis under infliximab therapy.

Four (44.4%) of the patients remained attack-free throughout the infliximab infusions. Two (22.2%) of them developed mild anterior uveitis only once. Three (33.3%) of the patients developed posterior uveitis which was quickly resolved with the addition of low-dose conventional immunosuppressive agents. These results propose that IFX is a better choice of treatment to control resistant ocular inflammatory attacks than traditional treatment modalities. In accordance with present study, Benitez del Castillo et al. showed that infliximab is safer than conventional immunosuppressives for refractory uveitis especially in patients with predominant retinal vasculitis and vitritis, stabilizing the course of the illness and maintaining visual acuities [15]. Also, Keino et al. reviewed medical records of 14 patients with BD and showed that IFX was effective in reducing ocular inflammatory attacks, background retinal and disc vascular leakage [16].

Persistent ocular inflammatory attack occurred in only one patient in the 9th month of the therapy. Ito et al. reported three similar cases of acquired resistance to infliximab after 1 year of administration and suggested dosage increase or combination therapy to overcome resistance [17]. In the present study, persistent ocular inflammatory attack was thought to be associated with development of anti-infliximab antibodies and treatment was replaced with adalimumab injections.

Tognon et al. identified seven BD patients and showed that infliximab therapy considerably reduced the required daily dose of both corticosteroid and immunosuppressive drugs [13]. In another series of 12 patients, all patients were able to reduce their daily dose of steroids and the frequency of ocular relapses decreased [18]. In our study, five (55.5%) of the patients required low-dose concomitant immunosuppressive therapy throughout injections. In three patients, additional immunosuppressive therapy was started due to posterior uveitis while two patients continued with azathioprine throughout infliximab infusions to inhibit the development of antichimeric antibodies. Prednisone was stopped at the beginning of IFX infusions in all patients, but it was started again in only one patient in the 5th month of IFX therapy. This was due to panuveitis attack.

Cystoid macular edema is one of the challenging ocular manifestations of Behçet disease. In the present study, infliximab therapy was initiated on one of the patients due to cystoid macular edema which is resistant to retrobulbar corticosteroid injections combined with conventional immunosuppressive drugs. Macular edema resolved quickly under infliximab infusions. Markomichelakis et al. reported that infliximab was efficient to resolve chronic cystoid macular edema associated with uveitis [19].

Best corrected visual acuity improved at least 2 lines in 6 (33.3%) eyes. It improved from no light perception to hand motion in one eye and from light perception to hand motion in another eye. It remained stable in 9 (50%) eyes. Best corrected visual acuity reduced in only one eye due to posterior subcapsular cataract progression. These results confirm good control of ocular inflammation under IFX. Some of the patients already had severe structural damage and poor visual acuity at the time of their first admission to our clinic. Therefore, visual acuity of these patients did not change more than 2 lines. The present study indicates that if IFX treatment is started before permanent eye damage, vision would be protected and visual outcomes could be better.

Tuberculosis is one of the best described complications of IFX therapy [11,18]. In the present study, isoniazid prophylaxis was given to patients with positive PPD tests for 9 months. The common side effects of IFX reported in other studies included frequent respiratory and urinary infections, infusion reactions, headache, malaise, diarrhea

and dizziness [3,11,20]. During follow-up period, IFX infusions were well-tolerated and no patient reported serious or life-threatening adverse effects. Two patients developed temporary infusion reaction and urticaria-like rash at first infliximab infusion.

In conclusion, IFX treatment was found to be an effective and safe option for maintenance of clinical remission in refractory posterior uveitis associated with Behçet disease. The limitations of this study are its retrospective nature, small number of patients and lack of control group. Further prospective, randomized controlled studies in larger number of patients with longer follow-up periods are needed to clarify long term efficacy of IFX.

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