INTRAVITREAL INFLIXIMAB IN REFRACTORY UVEITIS IN BEHCET'S DISEASE

A Safety and Efficacy Clinical Study

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Purpose: To assess the safety and efficacy of intravitreal infliximab (1 mg/0.05 mL) in patients with refractory posterior uveitis in Behcet's disease.

Methods: Twenty patients were included in this study. Best corrected visual acuity (BCVA), vitreous haze (graded 0–4), vasculitis, retinitis, and papillopathy (presence or absence) were assessed at baseline, Day 1 and Week 2, 4, 6, 8, 12, and 18. Optical coherence tomography (OCT) central foveal thickness, fluorescein angiography, and flash electroretinogram were done at baseline and 4, 12, and 18 weeks.

Results: Mean baseline logMAR BCVA was 0.94 (20/160), had improved significantly by Week 2 to 0.6 (20/80) ($P < 0.0001$), and reached 0.36 (20/40) by Weeks 18 with three injections ($P < 0.0001$). Mean central foveal thickness OCT decreased significantly from baseline 361 μm to 180 μm at the end of follow-up ($P < 0.0001$). Profound decrease in mean vitreous haze gradings from two to 0.2 by the end follow-up ($P < 0.05$). There was a significant reduction in the number of patients with vasculitis (15 at baseline to 1 weeks at 18 weeks), retinitis (nine at baseline to none at 4 weeks), and papillitis (two at baseline to none at 4 weeks) ($P < 0.05$). No significant electrophysiological changes or ocular adverse inflammatory reactions were observed during the study period.

Conclusion: Intravitreal infliximab appeared to be safe and effective in treating uveitis in Behcet's disease and should be considered as an alternative to systemic therapies.

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Intravitreal injection of up to 2 mg of infliximab has proved to be safe in animal models (rabbits and primates).[1–6] These studies have shown no evidence of intraocular inflammation or toxicity by clinical, electrophysiological, and histopathological examination for up to 90 days even with three repeated monthly injections. However, the study conducted by Rassi et al[5] was the only one to report the development of severe intraocular inflammation in one eye out of 12 rabbit eyes at 90 days following three intravitreal injections (2 mg monthly). In addition, the half-life of intravitreal infliximab was found to be 6.5 days to 8.5 days,[1,7] and it is also capable of penetrating all retinal layers.[6] These animal study results should have set the stage for a relatively safe use of intravitreal infliximab in human eyes. Unfortunately, clinical studies conducted on patients so far have raised serious concerns about its safety and adverse effects.

These clinical studies have shown various and inconsistent results in terms of the safety and efficacy of intravitreal infliximab.[8–19] These studies were conducted on patients with refractory as well as naive cases of age-related macular degeneration choroidal neovascularization,[8–10,16–18] diabetic macular edema,[11,12] central retinal vein occlusion,[17] angiomatous malformations,[17] pseudophakic macular edema,[13] and uveitis.[11,14,15] The doses used ranged from 0.5 mg to 2 mg. Two studies have monitored injected eyes with flash electroretinogram

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(ERG) with mild reversible changes at 3 months in one study[9] (2 age-related macular degeneration eyes and two diabetic macular edema eyes using 0.5 mg), whereas with no changes in the other study (six age-related macular degeneration eyes using 2 mg) at 6 months.[18]

The initial study by Theodossiadis et al[8] in 2009 did not report any intraocular inflammation in three patients receiving two intravitreal injections of 1 mg and 2 mg for refractory age-related macular degeneration choroidal neovascularization with 7 months follow-up period. Later several clinical studies have reported severe intraocular inflammation following intravitreal injections of infliximab in nonuveitic patients.[9,10,12,13,16–18] This occurred with doses as low as 0.5 mg, in 15% to 100% of patients, and usually starts several weeks[3,4] after the intravitreal injections. These collected data have initiated a call for cautious use of intravitreal infliximab.[19,20]

On the other hand, studies investigating intravitreal infliximab in uveitis patients have shown improvement in vision, reduction in central foveal thickness (CFT) on optical coherence tomography (OCT), and reduction in inflammation with no reported adverse effects.[11,14,15] In our study, we have investigated the safety and efficacy of three consecutive intravitreal infliximab injections (1 mg/0.05 mL, 6 weeks apart) in carefully selected group of patients with refractory uveitis in Behcet's disease.

Patients and Methods

Approval of the study was obtained from the hospital's ethical committee. The study design and methodology followed the tenets of the Declaration of Helsinki. All patients were provided with written informed consent and received a thorough explanation of the study design, aims, and the off-label use of infliximab, its potential risks, and benefits. This is a prospective noncomparative interventional clinical study. The study was conducted on 20 eyes of 20 patients with refractory posterior uveitis in Behcet's disease who received three consecutive intravitreal injections of infliximab (1 mg/0.05 mL) 6 weeks apart.

Inclusion Criteria

Refractory posterior uveitis in a systemically controlled Behcet's disease.

Behcet's disease. Behcet's disease was diagnosed based on the criteria of the International Study Group.[21] Disease classification was recorded in accordance with the Standardization of Uveitis Nomenclature Working Group criteria.[22]

Posterior uveitis. Posterior uveitis is defined as inflammation that predominantly affects the retina and/or choroid with any of the following: focal, multifocal, or diffuse chorioditis; retinitis; chorioretinitis; retinochorioditis; vasculitis; or neuroretinitis (papillitis).[22] In Behcet's disease, it is mainly retinitis, vasculitis, and papillitis.[21]

Refractory cases. Refractory cases in this study are those with ocular inflammations not responding to "systemic" therapies. Patients with Behcet's disease who have received one or two conventional systemic treatment modalities with adequate control of disease systemically and no adequate ocular response in the previous 3 months were included.

Conventional treatments. Conventional treatments are systemic immunosuppressive drugs other than infliximab and other tumor necrosis factor alpha (TNFα) inhibitors.

Exclusion Criteria

1. Patients receiving or who had received systemic infliximab or other TNFα inhibitors,
2. Patients with uncontrolled systemic Behcet's disease,
3. Patients who received previous intravitreal steroids (<6 months),
4. Patients with severe media opacity,
5. Patients with previous history of ocular surgery other than cataract surgery, and
6. Cataract surgery within the previous 6 months.

Patients' Examination

A) Patients were subjected to the following initial examinations:

1. Best corrected visual acuity (BCVA) measurements on Snellen Charts to be converted to logMARs.
2. Slit-lamp examination of anterior segment inflammation (iritis) and complications.
3. Measuring intraocular pressure (IOP) by Goldman applanation tonometry.
4. Dilated fundus examination by indirect ophthalmoscope using +20 diopter lens for grading of vitreous haze as follows: Grade 0: good view of nerve fiber layer, Grade +1: clear optic nerve and vessels but hazy nerve fiber layer, Grade +2: optic nerve and vessels are hazy, Grade +3: view of optic nerve only, and Grade +4: no optic nerve view.[23]
5. Dilated slit-lamp biomicroscopy for the presence or absence of vasculitis, retinitis, and papillopathy. *Vasculitis* is diagnosed clinically by retinal blood

vessels gliotic sheathing or occlusive vasculopathy in the presence of inflammation, and with fluorescein angiography (FA) by vascular staining, leakage, or occlusion.[22]
6. Patients also had the following at baseline: FA, flash ERG, and CFT OCT (Stratus III OCT; Carl Zeiss, Dublin, CA).

B) Follow-up clinical examinations were at Day 1, and Weeks 2, 4, 6, 8, 12 and 18. Each follow-up visit included: BCVA, slit-lamp examination, IOP, dilated fundus examination with grading of vitreous haze, and the presence or absence of vasculitis, retinitis, or papillopathy. CFT OCT and flash ERG were done at 4, 12, and 18 weeks. FA was done at the discretion of the examiner and not at every postinjection evaluation.

Drug Preparation

A vial containing 100 mg of commercially available infliximab powder (Remicade; Janssen Pharmaceutica, Buckinghamshire, United Kingdom) was reconstituted with 5 mL of sterile water, and 0.05 mL of this solution (1 mg of infliximab) was used for each patient and placed in a tuberculin syringe using aseptic techniques. The remaining syringes are kept in a sterile package at 2°C to 8°C for 6 weeks.[24] The intravitreal dose of infliximab used in this study is 1 mg/0.05 mL. Animal studies have shown intravitreal infliximab in doses up to 2 mg is safe[1–6] even with 3 monthly injections.[5] Since clinical trial in nonuveitic eyes showed severe intraocular inflammation with even a single low dose of 0.5 mg[9] and the 1 mg dose was shown to be effective in controlling uveitis in one study,[15] we decided to use this dose 1 mg and avoid the 1.5 mg and 2 mg doses that were reported for to effective as well in uveitic eyes.[11,14]

Injection Technique and Criteria for Reinjections

The eye was prepared in a standard fashion using 5% povidone-iodine, an eyelids speculum to stabilize the eyelids, and the injection of 1 mg (0.05 mL) was performed 3.5 mm to 4 mm posterior to the limbus, through the inferotemporal pars plana with a 30-gauge needle under topical anesthesia. After the injection, retinal artery perfusion was checked, and patients were instructed to administer topical antibiotics for 3 days. All patients were given detailed postinjection instructions and asked to call promptly if any pain or significant changes in vision occurred. Patients were seen on follow-ups, and repeated injections were given at 6-week intervals if reinjection criteria were met: 1) no evidence of significant flash ERG changes, 2) no evidence of adverse effects to the drug, and 3) signs of anatomical and/or functional improvement during the first 6 weeks.

Outcome Measures

Comparing the following baseline parameters to each study visit:

1. Changes in mean BCVA in logMAR.
2. Changes in mean CFT by OCT.
3. Changes in the inflammatory parameters:
   - Mean vitreous haze grading.
   - Number of patients with retinitis, vasculitis, and papillitis. Patients were either diagnosed with or without retinitis; vasculitis or papillitis, any feature of it is considered as posterior uveitis.
4. Changes in mean flash ERG a- and b-wave amplitudes and implicit times.

Systemic Therapy

The Department of Internal Medicine (Cairo University) systemic therapy protocol for patients with Behcet's disease and posterior uveitis (vasculitis, retinitis, and papillitis) is a regimen adapted and modified from the EULAR recommendations for the management of Behcet's disease.[25] We start with 0.5 g to 1 g methylprednisolone as daily pulse therapy (intravenous line) for three consecutive days, followed by oral prednisolone 0.75 mg/kg to 1 mg/kg body weight for 4 weeks to be tapered gradually later on. Cyclophosphamide (in intravenous line, 500 mg/m^2 body surface area) starts on Day 4 after the three consecutive daily doses of methylprednisolone, to be repeated every month or 6 months. After the initial 6 months, azathioprine 2 mg·kg·$^{-1}$ day^{-1} to 2.5 mg·kg·$^{-1}$ day^{-1} or cyclosporine 2 mg·kg·$^{-1}$ day^{-1} to 5 mg·kg·$^{-1}$ day^{-1} replaces cyclophosphamide. In aggressive and severe cases or when an eye is still involved, infliximab infusion is considered; however, in our study, those cases were offered intravitreal infliximab.

Statistical Analysis

Data were statistically described in terms of mean ± standard deviation, median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Freidman's test with Conover test for paired (matched) samples as post hoc multiple two-group comparisons. For comparing categorical data, Chi square (±2) and McNemar's tests were performed. Agreement was tested using kappa statistic. Correlation between various variables was done using

Spearman rank correlation equation. P values <0.05 was considered statistically significant. All statistical calculations were done using the computer program SPSS (Statistical Package for the Social Science; SPSS Inc, Chicago, IL) version 15 for Microsoft Windows and Stats Direct statistical software version 2.7.2 for Microsoft Windows (StatsDirect Ltd, Cheshire, United Kingdom).

Results

In this study, 20 eyes of 20 patients with refractory posterior uveitis in Behcet's disease were included. Patients with ocular activities despite a systemically controlled disease were referred to us from the Department of Internal Medicine where those with posterior uveitis were included in this study for intravitreal injections. The patients included had their initial eye examinations recorded following referral, with no record of prior BCVA. Patients were then given three consecutive intravitreal injections of infliximab (1 mg/0.05 mL) 6 weeks apart, for 18 weeks in the 20 study eyes.

Baseline demographics, ocular clinical finding, and therapies are shown in Table 1. The patients' mean age was 31.40 ± 3.45 years (range: 26 years–38 years), with 19 male patients (95%). Eighteen patients had history of previous ocular activities and two patients had their first attacks of uveitis. All 20 patients had bilateral involvement, of which 19 patients had unilateral inflammation with no activities in the other eyes. Only one patient had a bilateral inflammation, and

Table 1. Baseline Patients' Demographics; Ocular Clinical Findings (Both Eyes); and Topical and Systemic Treatments

Patient	Age, Years	Sex	BCVA in logMAR (Snellen)	Ocular Findings in Injected Eyes		Topical Treatment	Systemic Treatment	Ocular Findings in Noninjected Eyes
				Anterior Segment	Posterior Segment			
1	28	M	1 (20/200)	PS, No activity	VH, VS, PP	Timolol	Prednisolone, Azathioprine, Cyclophosphamide	PS
2	26	M	1.77 (20/1,000)	No activity	VH, VS, R	—	Cyclophosphamide	No activity
3	32	M	0.77 (20/100)	No activity	VH, VS	—	Cyclophosphamide	No activity
4	31	M	1 (20/200)	C&F	VH, R	Timolol, Pred	Cyclophosphamide	C&F, VH
5	29	M	0.77 (20/100)	No activity	VH, VS	—	Azathioprine, Cyclophosphamide	No activity
6	34	M	1.77 (20/1,000)	No activity	VH, VS, R	Timolol	Prednisolone, Cyclophosphamide	No activity
7	34	M	0.77 (20/100)	C&F	VH, R	Timolol, Pred	Cyclophosphamide	No activity
8	34	M	1 (20/200)	No activity	VH, VS	—	Cyclophosphamide	No activity
9	38	M	0.60 (20/80)	No activity	VH, VS	—	Prednisolone, Azathioprine	No activity
10	32	M	1 (20/200)	No activity	VH, VS, R, PP	—	Cyclophosphamide	No activity
11	28	M	0.77 (20/100)	No activity	VH, VS	—	Prednisolone, Azathioprine	No activity
12	32	M	0.60 (20/80)	C&F	VH, R	Pred	Cyclophosphamide	No activity
13	28	M	0.60 (20/80)	No activity	VH, VS	—	Cyclophosphamide	No activity
14	28	M	0.77 (20/100)	No activity	VH, VS	—	Prednisolone	PS, cataract
15	37	M	0.77 (20/100)	C&F	VH, VS	Timolol, Pred	Prednisolone, Azathioprine	No activity
16	35	M	1.079 (20/250)	No activity	VH, R	—	Cyclophosphamide	No activity
17	26	M	1 (20/200)	No activity	VH, VS, R	—	Prednisolone, Azathioprine	No activity
18	33	F	1 (20/200)	No activity	VH, VS	—	Cyclophosphamide	No activity
19	30	M	0.77 (20/100)	C&F	VH, R	Pred	Prednisolone, Azathioprine	No activity
20	33	M	1 (20/200)	No activity	VH, VS	—	Prednisolone, Cyclophosphamide	No activity

M, Male; F, Female; BCVA, Best Corrected Visual Acuity; C&F, Cells&Flare; PS, posterior synechae; VH, vitreous haze; VS, vasculitis; PP, papillitis; R, Retinitis; Timolol, timolol maleate eye drops; Pred, Prednisone Acetate eye drops.

intravitreal injection was given to the eye with the worst vision and more severe posterior inflammation. The other eye, of this bilateral case, had mainly anterior involvement and was treated with topical steroids with no intravitreal injections or change in systemic therapies. All patients had FA done at baseline, and all but three patients had FA done during the study visits. Those three patients had mild systemic reaction with the dye on the first injections.

Topical therapies

Five study eyes and one contralateral eye had mild anterior iritis and were treated with topical prednisone acetate eye drops. Five study eyes received topical timolol maleate eye drops to control a slightly elevated intraocular pressure (Table 1). These topical eye drops were initiated with the initial examinations and were not changed during the study period. The mean IOP remained stable with no statistically significant difference in IOP before and after repeated injections throughout the study period (Table 2).

Changes in mean BCVA and CFT OCT in the study eyes. Baseline BCVA (mean logMAR 0.94 ± 0.32 [20/160]) improved significantly by Week 2 (mean logMAR 0.60 ± 0.18 [20/80], $P < 0.0001$) and continued to improve by Week 4 (mean logMAR 0.41 ± 0.18 [20/50], $P < 0.0001$). There were no statistically significant difference in BCVA between Weeks 4, 6, and 8. BCVA worsened by Week 12 (mean logMAR 0.51 ± 0.23 [20/63], $P = 0.0001$) then reimproved again by Week 18 (mean logMAR 0.36 ± 0.19 [20/40], $P < 0.0001$) (Table 2, Figure 1). The mean baseline CFT OCT (361 μm) improved significantly by Week 4 to 239 μm ($P < 0.0001$) and continued to improve by Week 12 to 210 μm ($P < 0.0001$) and Week 18 to 180 μm ($P < 0.0001$) (Table 2, Figure 1).

Changes in mean vitreous haze grading in the study eyes. There was a statistically significant improvement in vitreous haze throughout the study, mean vitreous haze grading decreased from two at baseline to 0.2 at the end of follow-up ($P < 0.0001$). Baseline mean vitreous haze grading was two, improved significantly by Week 2 to 0.45, and continued to improve by Week 4 to 0.2. The vitreous haze worsened at Weeks 6 and 12 to a mean grade of 0.35 and 0.4, respectively. It then reimproved by Week 8 and 12 to a mean of 0.1 and 0.2, respectively, following reinjections (Table 2, Figure 2).

Changes in rate of vasculitis, retinitis, and papillopathy in the study eyes. There was a statistically significant reduction in the number of patients with active vasculitis from 15 patients before injection to only 1 patient at the end of follow-up ($P < 0.001$). Before injections, there were 15 patients with active vasculitis, which continued to be reduced throughout the study period to 11 patients at Week 2, and dramatic reduction to two patients at Week 4; then only one patient had vasculitis at Week 12 till the end of the study (Table 2, Figure 3). Preinjections, there were nine patients with active retinitis that was significantly ($P < 0.001$) reduced to three patients at Week 2, then none at Week 4 and for the rest the study period (Table 1, Figure 3). Preinjection, there were two patients with papillopathy, 1 patient at Week 2, and none at Week 4 ($P < 0.001$) till the end of follow-up (Table 2, Figure 3).

Electroretinogram in the study eyes. There was no statistically significant difference in flash ERG (scotopic and photopic b-wave amplitude and implicit time) between baseline and 4, 12, or 18 weeks (Table 3, Figure 4).Figure 5 shows a patient's FA and OCT revealing clinical improvement inflammatory activity during the study period which was observed in most patients.

Table 2. Mean BCVA in logMAR (Snellen), CFT OCT, IOP, Vitreous Haze Grading, and Number of Patients With Retinitis, Vasculitis, and Papillitis at Baseline and Each Study Visit

	Mean Changes of the Different Parameters Through the Study Period						
	BCVA in logMAR (Snellen)	CFT OCT (μm)	IOP (mmHg)	Vitreous Haze Grading	No. Patients		
					Vasculitis	Retinitis	Papillitis
Baseline	0.94 (20/160)	361	14.30	2	15	9	2
Day 1	0.94 (20/160)	350	14.70	2	15	9	2
Week 2	0.60 (20/80)	290	15.20	0.45	11	3	1
Week 4	0.41 (20/50)	239	14.70	0.2	2	0	0
Week 6	0.44 (20/50)	220	14.10	0.35	2	0	0
Week 8	0.38 (20/50)	200	14.25	0.1	2	0	0
Week 12	0.51 (20/63)	210	13.80	0.4	1	0	0
Week 18	0.36 (20/40)	180	14.30	0.2	1	0	0

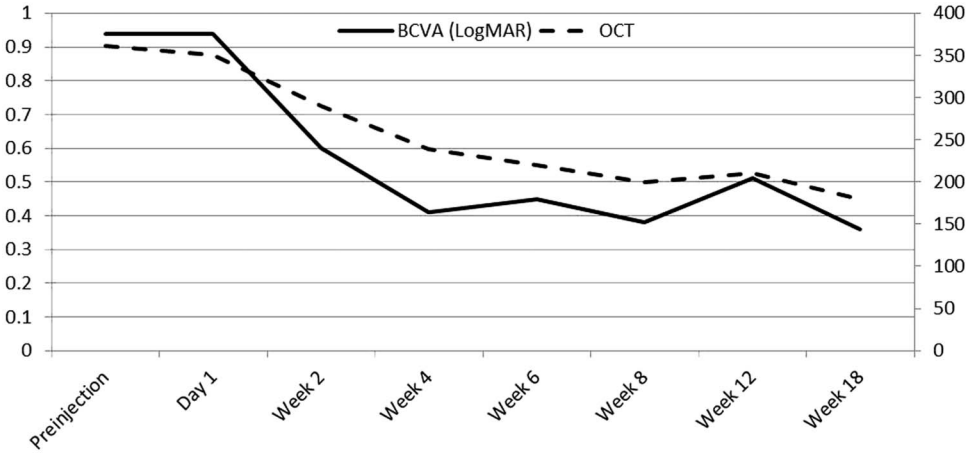

Fig. 1. Shows changes in the mean BCVA in logMARs and mean CFT OCT in microns throughout the study. Mean BCVA in logMARs at baseline = 0.94 ± 0.32 (20/160), Week 2 = 0.60 ± 0.18 (20/80), Week 4 = 0.41 ± 0.18 (20/50), Week 6 = 0.44 ± 0.17 (20/50), Week 8 = 0.38 (20/50), Week 12 = 0.51 ± 0.23 (20/63), and Week 18 = 0.36 ± 0.19 (20/40).

Subconjunctival hemorrhage was observed in four patients after injection. No other complications were detected (no endophthalmitis, retinal detachment, or significant increase in IOP). There were no ocular or extraocular side effects detected, and the used dose was tolerated by all patients. There were no observed immunological reactions detected after the injections in any of the injected eyes. None of the patients required any surgical interventions during the 18 weeks.

Discussion

Behcet's disease is a multisystem inflammatory disorder characterized by recurrent orogenital ulcers and recurrent ocular inflammation. It frequently involves the joints, skin, central nervous system, and gastrointestinal tract. It is classified as a systemic vasculitis that can involve both the arteries and veins of almost any body organ.[26,27] The etiology remains unknown. Ocular involvement in Behcet's disease is common and ranges from 30% to 70%. Ocular Behcet's disease usually presents with chronic relapsing panuveitis, retinitis, and retinal vascultis and has devastating effects on vision.[26,28] Behcet's disease is characteristically a bilateral inflammation in about 80% of cases and unilateral in 20%.[29–32] However in our study, all our patients had bilateral involvement, but 19 patients had "activity" (inflammation) in one eye only and only one patient had bilateral activity. The other eye for that patient with bilateral activity had a milder inflammation with mainly anterior segment involvement and was treated with topical steroids with no intravitreal injections or change in systemic therapies.

The TNFα belongs to a group of proinflammatory cytokines produced by macrophages and T cells and plays a key role in inflammation and apoptosis.[33] In

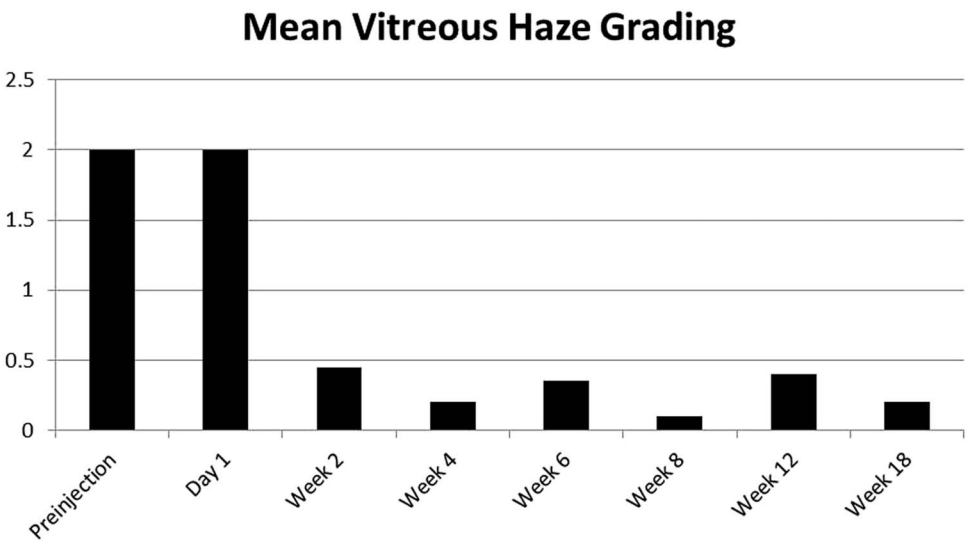

Fig. 2. Changes in the mean grades in vitreous haze throughout the study.

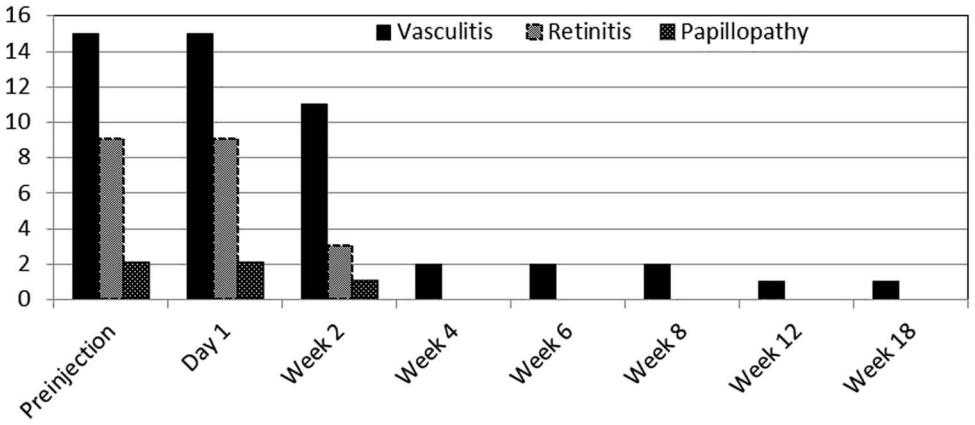

Fig. 3. Changes in the number of patients with vasculitis, retinitis, and papillitis throughout the study period.

the eye, TNFα appears to participate in the pathogenesis of various inflammatory disorders. Increased levels of this cytokine have been found in the serum of patients with active uveitis. TNFα has also been detected in increased levels in eyes with a variety of inflammatory conditions.[34] Infliximab is a chimeric human immunoglobulin G1 (IG1) with a mouse variable fragment having TNFα affinity and neutralizing capacity. The potent anti-inflammatory effects of infliximab make them a valid alternative for the control of noninfectious ocular inflammation, particularly when standardized treatment protocols involving steroids and antimetabolites have failed.[35–39]

Farvardin et al[11] in 2010 used 1.5 mg intravitreal infliximab in 10 eyes with noninfectious uveitis that failed to respond to systemic treatment. They reported significant visual improvement and significant reduction of CFT by OCT at 1 month. Later, Markomichelakis et al[15] in 2012 used 1 mg of intravitreal infliximab for refractory uveitis in Behcet's disease with significant improvement in vision, reduction in CFT by OCT, and reduction in inflammation at 1 month. In their second study, Farvardin et al[14] in 2012 have reported the use of 1.5 mg intravitreal infliximab in noninfectious uveitis with a 6-month follow-up that showed recurrence after initial improvement. None of these three studies have used repeated injections and none used flash ERG to monitor retinal toxicity of the intravitreal injection. On the other hand, in nonuveitic eyes, two studies have used flash ERG to monitor retinal toxicity following a single intravitreal injection of infliximab.[9,18] To the best of our knowledge, this is the first study to assess safety using flash ERG and the efficacy of three consecutive intravitreal injections (6 weeks apart) of infliximab for refractory posterior uveitis in Behcet's disease.

Table 3. Mean Flash ERG b-Wave Implicit Time (milliseconds) and Amplitudes (Micrvolts) in Photopic and Scotopic Conditions at Baseline, 4, 12, and 18 Weeks

	Mean Photopic ERG		Mean Scotopic ERG	
b-Wave	Implicit Time	Amplitude	Implicit Time	Amplitude
Preinjection	36.20	18.34	37.90	26.93
Week 4	34.87	18.55	37.79	27.21
Week 12	36.49	17.92	38.01	26.98
Week 18	36.05	18.13	37.74	27.04

Safety of Intravitreal Infliximab

In our study, we found that intravitreal infliximab in the described dose and frequency (1 mg/0.05 mL, three injections/6 weeks) to be well tolerated by all patients clinically and by electrophysiological assessment. There were no statistically significant difference in flash ERGs (scotopic and photopic b-wave amplitude and implicit time) between baseline and the different study visits up to 18 weeks. The electrophysiological results in this study match previous clinical[9,18] and animal studies[1–6] for the same dose, which confirms that intravitreal injection of infliximab in 1 mg or 2 mg is not toxic to the intraocular tissue especially the retina.

However, the main concern with the intravitreal use of this drug remains to be the development of intraocular immunogenic reaction. Although this reaction is reported in a high percentage of eyes with nonuveitic diseases,[8–10,12,13,16–18] yet it was not reported by the three studies investigating intravitreal infliximab for uveitis.[11,14,15]

We did not observe clinically any increased intraocular inflammatory reactions in any of the injected eyes during all study visits. Although, it is difficult to assess an immunogenic reaction to the drug in already inflamed eyes, yet we did not even observe changes in the pattern of the inflammations in any of the study eyes during the study visits compared with preinjection status. None of our patients needed vitrectomy or

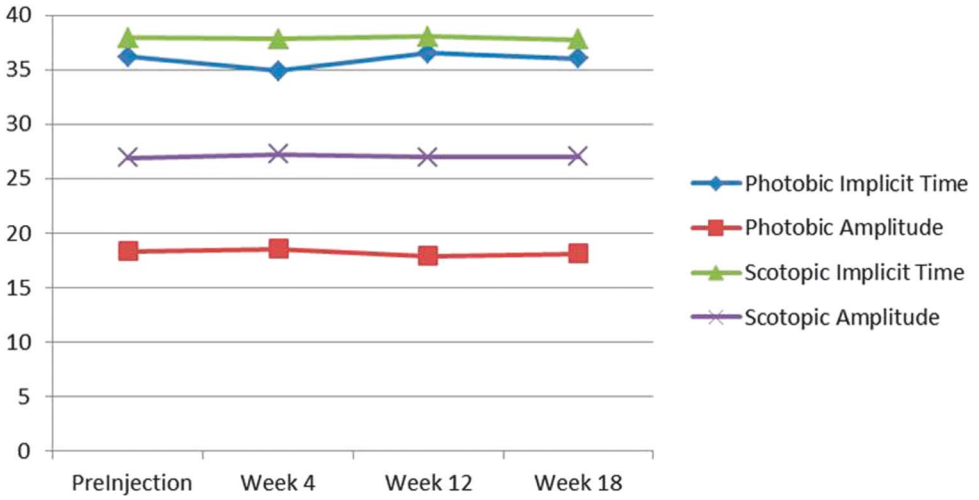

Fig. 4. Mean flash electroretinogram b-wave implicit time (milliseconds) and amplitudes (microvolts) in photopic and scotopic conditions throughout the study visits.

any surgical interventions in their eyes during the study period, as previously reported after intravitreal infliximab.[10,12,17] There were no other clinical ocular or systemic adverse effects reported during the study; however, we did not assess systemic human antichimeric antibodies.

Efficacy of Intravitreal Infliximab

In our study, the mean BCVA in logMAR (Snellen) has significantly improved from a baseline mean of 0.94 (20/160) to 0.6 (20/80), 0.41 (20/50), 0.51 (20/63), and 0.36 (20/40) at Weeks 2, 4, 12, and 18, respectively ($P < 0.0001$). There was no statistically significant difference in BCVA between Weeks 4, 6, and 8. However, BCVA worsened at Week 12 and was significantly worse than Week 8 ($P < 0.0001$) which coincided with an increased mean vitreous haze grading. BCVA also showed nonsignificant deterioration between Weeks 4 and 6, again coinciding with deteriorated vitreous haze grading. This may be explained by the waning effect of the intravitreal dose and is an indication for the need of shorter intervals between injections. The changes in BCVA corresponded to the changes in CFT by OCT. The mean baseline CFT (361 μm) improved significantly by Week 4 (239 μm, $P < 0.0001$) and continued to

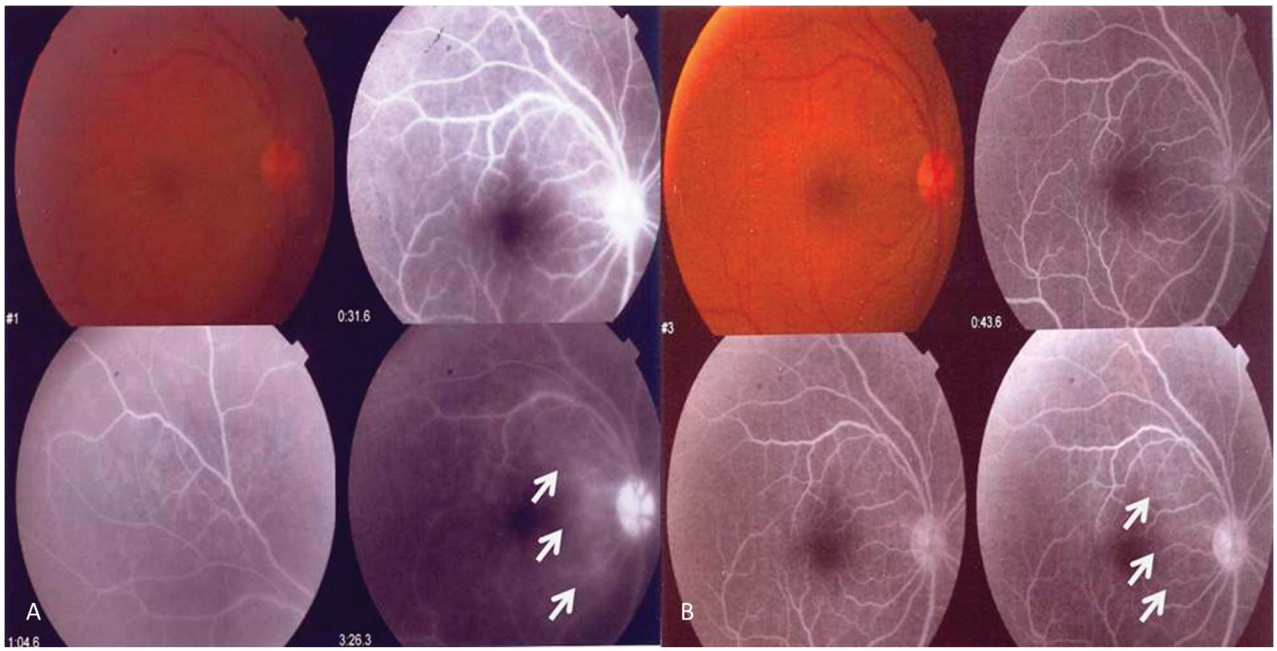

Fig. 5. Fluorescein angiogram for patient 9, preinjection (**A**) and 4 weeks after injection (**B**) showing reduced vasculitis and leakage (arrows) and papillitis.

improve by Week 12 (210 μm, $P < 0.0001$) and Week 18 (180 μm, $P < 0.0001$).

In this study, all parameters of intraocular inflammation showed dramatic improvement during the study period. We can see that the maximum drug effect was reached at 4 weeks. Vitreous haze reached its lowest rate at 4 weeks, and only two patients had vasculitis, and no patients had retinitis or papillitis at 4 weeks. There was mild increase of vitreous haze between 4 and 6 weeks, and between 8 and 12 weeks with rapid control of activity after reinjections of the second and third injections, respectively. The result of our study confirms the favorable visual and anatomical outcomes of intravitreal infliximab that were reported by Farvardin et al[11,14] and Markomichelakis et al[15] on eyes with uveitis. All previous three studies as well as ours have shown significant control of intraocular activities within weeks with significant improvement of BCVA and reduction of macular edema by OCT.

To the best of our knowledge, our study is the largest to date to be reported on the safety and efficacy of intravitreal injections of infliximab in patients with uveitis. We are also the first to use repeated intravitreal injections and monitor such uveitic eyes with flash ERG in addition to clinical examination. Based on the results of our study and previous clinical studies, intravitreal infliximab appeared to be very effective in cases of posterior noninfectious uveitis including Behcet's disease. The intravitreal infliximab dose of 1 mg was well tolerated with no observed adverse effects clinically and by flash ERG. However, these effects were temporary and reinjections were needed perhaps at intervals shorter than 6 weeks. We should, however, consider the limits of this study; small in size, nonrandomized, short duration, and an open label design. At this stage, we still believe in the cautious use of this drug, especially in nonuveitic eyes, until larger randomized clinical trials with longer durations establish a better understanding of the benefits versus the risks of using intravitreal infliximab.

Key words: intravitreal, infliximab, uveitis, Behcets disease.

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