Original Article

Intravitreal Bevacizumab for Treatment of Central Serous Chorioretinopathy

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Abstract

Purpose: To compare the outcomes of treatment with intravitreal bevacizumab (IVB) versus observation in central serous chorioretinopathy (CSCR).

Methods: In a retrospective comparative study, records of 45 patients with CSCR were reviewed. Twenty-two patients received IVB (1.25 mg/0.05 ml) while 23 subjects were observed. All subjects underwent measurement of best corrected visual acuity (BCVA) and intraocular pressure (IOP), dilated fundus examination and optical coherence tomography (OCT) imaging at baseline and follow up visits. Outcome measures included central macular thickness (CMT) and BCVA in logarithm of minimum angle of resolution (logMAR) notations.

Results: Mean age was 44.1 ± 9.3 (range: 24 to 64) years and mean follow-up period was 10.4 ± 11.2 (range: 3 to 43; median: 6) months. All patients demonstrated resolution of neurosensory detachment and improvement in visual acuity. At final visit, there was no significant difference in mean CMT between the IVB and observation groups (275 vs 284 μm, $P > 0.05$). Mean baseline logMAR visual acuity was 0.38 ± 0.24 in the IVB group which improved to 0.24 ± 0.31 at final follow-up ($P = 0.011$); mean baseline logMAR visual acuity was 0.42 ± 0.28 in the observation group and improved to 0.12 ± 0.18 ($P = 0.001$). Visual improvement was more marked in the observation group (0.30 vs 0.14 logMAR, $P < 0.05$) and mean final visual acuity was also significantly better ($P = 0.05$).

Conclusion: There was no significant difference between IVB injection and observation in terms of anatomical outcomes of treatment for CSCR. In terms of visual outcomes, observation was superior to IVB injection.

Keywords: Intravitreal Bevacizumab (Avastin); Central Serous Chorioretinopathy; Macular Thickness; Observation

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INTRODUCTION

Central serous chorioretinopathy (CSCR) is an idiopathic condition characterized by serous neurosensory retinal detachment at the posterior pole, often in association with serous retinal pigment epithelial (RPE) detachment.[1] CSCR patients usually have good visual prognosis. In the majority of patients, CSCR is self-limited and patients usually regain a final visual acuity (VA) which is equal to VA prior to the disease. However, a number of patients may develop visual impairment due to persistent RPE and photoreceptor damage.[2,3]

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The underlying pathologic mechanism in CSCR is not completely understood. Abnormalities of choroidal circulation including venous congestion, lobular ischemia and multiple areas of hyperpermeability have been seen in indocyanine green angiography (ICGA) of patients with CSCR.[4-6] Gass postulated that an increase in the permeability of choriocapillaries results in RPE detachment and exudation of fluid into the subretinal space.[1] Recent studies using enhanced depth imaging optical coherence tomography (EDI-OCT) also showed that the choroid is very thick in patients with CSCR which might indicate increased hydrostatic pressure in the choroid.[7,8]

Clinicians usually prefer to observe patients with acute CSCR for 3-4 months because most cases recover spontaneously. Conventional treatments such as laser photocoagulation or photodynamic therapy (PDT) have been used in some cases with acute or chronic CSCR.[9,10] However, these modalities may entail complications including RPE changes, excessive choriocapillaris hypoperfusion and secondary choroidal neovascularization, or may not be sufficiently effective.[11-14]

Vascular endothelial growth factor (VEGF) is produced by retinal and choroidal cells in response to ischemia and has been implicated as the major mediator of vascular hyperpermeability.[15] VEGF results in increased vascular permeability and edema by uncoupling endothelial cell-to-cell junctions.[16] Antibodies to VEGF may reduce choroidal hyperpermeability. Bevacizumab (Avastin; Genentch Inc., San Francisco, CA, USA), a humanized monoclanal antibody to VEGF, has been shown to entail anti-permeability properties. Recently, a number of reports have demonstrated favorable outcomes after intravitreal bevacizumab (IVB) injection without serious adverse effects in patients with CSCR.[17-20] In this study, we aimed to compare the anatomic and functional outcomes of IVB injection in patients with CSCR and compare it to that in patients who did not receive any intervention and were simply observed.

METHODS

In this retrospective comparative study, we reviewed the charts of patients who were diagnosed with CSCR between January 2008 and December 2012. The diagnosis of CSCR was established by the presence of serous macular detachment on dilated fundus examination, a typical fluorescein leakage pattern on fluorescein angiography (FA) and subretinal fluid accumulation evident on OCT. Each patient had underwent a comprehensive ocular examination including determination of best corrected visual acuity (BCVA) and intraocular pressure (IOP) measurement, biomicroscopic and dilated fundus examination, and central macular thickness (CMT) measurement on OCT (RTVue-100, Optovue Inc., Fremont, CA, USA). Patients were excluded if other conditions which could compromise visual acuity were present and if there was a history of photodynamic therapy or intravitreal injection of anti-VEGF medications. All subjects included in the study were followed for at least 3 months.

Patients who were treated with an intravitreal injection of 0.05 ml (1.25 mg) bevacizumab (Avastin, Roche, Basel, Switzerland) were considered as the IVB injection group and subjects who were only observed without any medication or intervention served as the control group. IVB injection was performed 3.5-4.0 mm from the limbus in the inferotemporal quadrant using a 30-gauge needle under strict aseptic conditions within two weeks of diagnosis. Written informed consent, explaining all potential risks and possible benefits of IVB injection and the off-label nature of this treatment was obtained from all patients in the IVB injection group. Treatment was performed according to ethical standards of the 1964 Declaration of Helsinki.

At follow-up visits, BCVA was determined using the Snellen chart and converted to logarithm of minimum angle of resolution (logMAR) notations for statistical analysis. Patients were examined at the slit lamp and underwent a dilated fundus examination. Macular OCT was performed at all follow-up intervals. FA was performed at the discretion of the physician. In the presence of subretinal fluid on OCT and persistent leakage on FA, additional IVB injection was performed in some patients at least two months following the primary injection.

Statistical analyses were performed using NCSS (Number Cruncher Statistical System) 2007 and PASS (Power Analysis and Sample Size) 2008 Statistical Software (Kaysville, Utah, USA). The data obtained were analyzed using frequency and descriptive statistics. The primary outcome measures were changes in BCVA and CMT. Normally distributed data were compared between the study groups using Student's *t*-test and Paired Samples *t*-test within each group. Abnormally distributed data were analysed using Mann-Whitney U test between the groups and Wilcoxon Signed Ranks test within each group. For all tests, *P*-values less than 0.05 were considered as statistically significant.

RESULTS

A total of 45 eyes of 45 patients were diagnosed with CSCR during the study period and followed at our clinics. Mean age of the patients was 44.1 ± 9.3 (range: 24 to 64) years and mean follow-up period was 10.4 ± 11.2 (range: 3 to 43; median: 6) months. The IVB and observation groups included 22 and 23 patients, respectively. In the IVB group, mean age was 46.1 ± 8.1 (range: 30 to 60) years and mean follow-up duration was 12.1 ± 12.8 (range: 3 to 43) months. In the observation group, mean age was

42.2 ± 10.1 (range: 24 to 64) years and mean follow-up was 8.8 ± 9.4 (range: 3 to 40) months. The study groups were comparable in terms of age and duration of follow-up ($P > 0.05$). Baseline logMAR visual acuity was 0.38 ± 0.24 in the IVB group and 0.42 ± 0.28 in the observation group. Baseline CMT was 410 ± 87 µm in the IVB group and 458 ± 128 µm in the observation group. Baseline logMAR visual acuity and CMT were comparable between the two groups ($P = 0.151$). Patients' demographics and baseline characteristics are summarized in Table 1.

All patients in both study groups had complete or near complete resolution of subretinal fluid and demonstrated improvement in visual acuity during the follow-up period. At the final visit, mean CMT in the IVB and observation groups were 275 ± 79 µm and 284 ± 67 µm, respectively ($P = 0.670$). Mean decrease in CMT was 135 ± 73 µm in the IVB group and 173 ± 140 µm in the observation group ($P = 0.256$, Mann-Whitney U test). The decrease in CMT was significant in both study groups ($P = 0.001$ for both groups, paired samples *t*-test). Changes in CMT are shown in Table 2.

Sixteen out of 22 subjects in the IVB group received only one injection while the remaining 6 cases had more injections. Mean CMT was 315 ± 84 µm after the first IVB injection and the mean decrease in CMT was 95 ± 80 µm ($P = 0.001$). Subgroup analysis revealed that baseline and final CMT were similar in subjects with only one IVB injection versus those with more injections ($P > 0.05$, Mann-Whitney U test).

Mean baseline logMAR visual acuity was 0.38 ± 0.24 in the IVB group which improved to 0.24 ± 0.31 at final follow-up ($P = 0.011$); mean baseline logMAR visual acuity was 0.42 ± 0.28 in the observation group and improved to 0.12 ± 0.18 at final follow-up ($P = 0.001$). Improvement was more marked in the observation group as compared to the IVB group (0.30 vs 0.14 logMAR, $P < 0.05$). Mean final logMAR visual acuity of the observation group was also significantly better than that of the IVB group (0.12 vs 0.24, $P = 0.05$). Changes in logMAR BCVA are shown in Table 3. None of the patients in either group lost vision during follow-up.

No ocular or systemic complications related to IVB injection were detected during the follow-up period.

Table 1. Demographics and baseline characteristics of patients with central serous chorioretinopathy

Characteristics	IVB (*n*=22)	Observation (*n*=23)	*P*
Age (years)	46.1±8.1	42.2±10.1	0.175
Gender (male:female)	17:5	13:10	
Follow-up period (months)	12.1±12.8	8.8±9.4	0.327
Baseline visual acuity (logMAR)	0.38±0.24	0.42±0.28	0.739
Baseline CMT (µm)	410±87	458±128	0.151

IVB, intravitreal bevacizumab; logMAR, logarithm of the minimum angle of resolution; CMT, central macular thickness; *n*, numbers

Table 2. Mean baseline and final central macular thickness

CMT (µm)	Groups (mean±SD)		*P*
	IVB	Observation	
Baseline	410.0±87.14	457.87±127.69	0.151[a]
Final	275.0±79.06	284.35±66.92	0.670[a]
Final-baseline difference	135±72.6	173.52±140.08	0.256[b]
P	0.001[c]	0.001[c]	

[a]Student *t*-test; [b]Mann-Whitney U-test; [c]Paired samples *t*-test. CMT, central macular thickness; IVB, intravitreal bevacizumab; SD, standart deviation

Table 3. Mean logarithm of the minimum angle of resolution best corrected visual acuity at baseline and final visits

BCVA (LogMAR)	Groups, mean±SD (median)		*P*[a]
	IVB	Observation	
Baseline	0.38±0.24 (0.35)	0.42±0.28 (0.3)	0.739
Final	0.24±0.31 (0.15)	0.12±0.18 (0)	0.046*
Baseline-final difference	0.13±0.29 (0.11)	0.30±0.29 (0.30)	0.048*

logMAR, logarithm of the minimum angle of resolution; BCVA, best corrected visual acuity; IVB, intravitreal bevacizumab; SD, standart deviation; [a]Mann-Whitney U test

DISCUSSION

CSCR is a benign self-limited condition characterised by idiopathic serous detachment of the neurosensory retina. A number of hypotheses have been proposed regarding the pathophysiology of CSCR. Dysfunction of the RPE with reversal of liquid transport may play a role in the development of serous retinal detachment.[21,22] Studies based on ICGA findings in patients with CSCR have demonstrated evidence of choroidal lobular ischemia, choroidal venous congestion and multiple areas of vascular hyperpermeability.[4,5] Choroidal hyperpermeability may cause RPE decompensation and damage with subsequent leakage of fluid into the subretinal space.[23] RPE damage may also occur by shedding of outer photoreceptor segments with a primarily intact blood-retinal barrier and result in accumulation of fluid in the subretinal space.[24-26]

There is no established treatment for CSCR. The high spontaneous remission rate favors conservative management and lifestyle counselling as the first-line of therapy. Spontaneous resolution of detachment without any intervention is expected in approximately 90% of cases. If the detachment persists for more than six months, intervention may be considered. In some cases, earlier intervention may be necessary due to high

occupational demands for binocular vision. Although there is no strong evidence for early treatment of CSCR, many retina specialists suggest that acetazolamide, laser photocoagulation, PDT or intravitreal anti-VEGF injections be used.[9-20,27-29] There are some studies in the literature supporting the benefit of early treatment of CSCR. These studies propose that the potential advantage of early resolution may be mediated by a lower rate of RPE degeneration in treated eyes.[27,28] However, there are complications associated with focal thermal laser photocoagulation and PDT. These include scotoma formation, loss of contrast sensitivity, foveal damage, RPE damage, choroidal ischemia and choroidal neovascularisation. Therefore, these modalities should be used with caution in such eyes with a high potential for spontaneous recovery.[30-34]

The vascular endothelial growth factor (VEGF) is a well known and potent inducer of vascular permeability. Bevacizumab is a full-length antibody that binds all isoforms of VEGF. There are many reports on the efficacy and safety of intravitreal bevacizumab in retinal disorders.[35-37] Nevertheless, the role of anti-VEGF agents for treatment of CSCR is not well-known. In some studies, the possible benefits of an anti-VEGF agent in CSCR were proposed on the basis of choroidal ischemia and hyperpermeability as pathogenethic mechanisms of CSCR.[18-20] Choroidal ischemia may cause an increase in the concentration of VEGF, and anti-VEGF agents may reduce choroidal hyperpermeability by blocking VEGF activity. Although several reports have supported the efficacy of IVB injection in CSCR, there are no studies demonstrating increased levels of VEGF in CSCR.[17-20] Even in a study on VEGF levels in the aqueous humor, the difference between the concentration of VEGF in the aqueous humor of CSCR versus controls was not significant.[22]

In the current study, our results demostrated that IVB injection in CSCR was not superior to observation considering the anatomical and functional results. Although not statistically significant, reduction of foveal thickness was even greater in the observation group (173 μm vs 135 μm). In line with our study, Lim et al showed that IVB injection led to no positive or negative effects in terms of earlier remission, or better functional or anatomical results in patients with acute CSCR.[38] Interestingly, regarding functional results, we observed that improvement of visual acuity was more marked in the observation group. The safety profile of IVB appears favorable due to a low rate of ocular and systemic adverse events; however, it is not a procedure with zero risks and serious complications such as cataracts, retinal breaks, endopthalmitis and even death due to thromboembolic events may occur.[37,39] Patients with CSCR are relatively young and have a high life expectancy. The possibility of adverse events with IVB injection should be considered seriously in these patients. None of the patients in the present study experienced a significant adverse event associated with IVB injection.

There are several limitations to this study including the small number of patients and the retrospective nature of the study. Further prospective randomized controlled studies are necessary to determine the efficacy of anti-VEGF treatment in CSCR.

In summary, we found no significant differences between IVB injection and observation regarding anatomical outcomes of treatment in CSCR. In terms of functional outcomes, observation was even superior to IVB injection.

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Conflicts of Interest

There are no conflicts of interest.

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