ORIGINAL ARTICLE

Intravitreal Bevacizumab in Central Serous Chorioretinopathy

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ABSTRACT

Objective: To evaluate the effect of intravitreal bevacizumab injection in patients with central serous chorioretinopathy (CSCR).

Study Design: Quasi-experimental study.

Place and Duration of Study: Layton Rehmatullah Benevolent Trust Eye and Cancer Hospital, Lahore, from July 2010 to April 2011.

Methodology: There were 43 eyes of 32 adult patients with CSCR. Patients with choroidal neovascularization, prior treatment for CSCR, history of thromboembolism, intraocular pressure more than 21 mmHg, history of retinal detachment, intraocular inflammation, and allergy to fluorescence were excluded from study. All patients had intravitreal injection of off label bevacizumab. At baseline and follow-up visits, patients had best corrected visual acuity (BCVA) and central macular thickness (CMT) measurement with optical coherence tomography. They were followed-up for 6 months. Outcome measures included BCVA and CMT. Wilcoxon Signed Ranks test was used for evaluation of BCVA and CMT.

Results: There were 26 (81.3%) males and 6 (18.7%) females with 21 (65.5%) cases of unilateral and 11 (34.5%) cases of bilateral involvement. Mean age was 39.09 ± 8.49 years. Nineteen (59.4%) eyes showed less than 6 months involvement and 13 (40.6%) eyes showed more than 6 months involvement. Mean number of injections required was 2.37 ± 1.24 in acute cases and 3.05 ± 1.39 in chronic cases. Overall mean of required injections was 2.67 ± 1.34. Median visual acuity at baseline was 0.25 and at 6 months was 0.7 ($p < 0.001$). Median CMT at baseline was 557 μ and at 6 months was 286 μ ($p < 0.001$).

Conclusion: Intravitreal bevacizumab injection was associated with visual improvement and reduced neurosensory detachment.

Key words: *Central serous chorioretinopathy. Bevacizumab. Optical coherence tomography. Intravitreal injection.*

INTRODUCTION

Central serous chorioretinopathy (CSCR) is characterized by an idiopathic serous neurosensory detachment primarily affecting the macula.[1] CSCR is associated with retinal pigment epithelial (RPE) leakage and angiographic RPE and choroidal hyper-permeability.[2] CSCR is among the top ten most common diseases that affect the macula. CSCR is a common disorder in young and middle aged patients. In most cases, recovery of vision follows acute episodes. However, there can be permanent loss of vision with repeated episodes, persistent macular detachment or diffuse disease.[3] About 5% of patients experience severe permanent visual loss.[4] It frequently manifests symptomatically in one eye, while 18% of cases may be bilateral. Research indicates that the disease process in CSCR is more diffuse and shows bilateral retinochoroidal dysfunction, even when the disease is manifesting clinically only in one eye.[5]

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CSCR is commonly associated with type-A personalities, organ transplantation, systemic lupus erythematosus and Cushing disease.[6]

Patients with CSCR show impaired autonomic response with significantly decreased parasympathetic activity and significantly increased sympathetic activity.[6] Glucocorticoids and possibly adrenergic hormones play a role in the pathophysiology of CSCR and exert their effects on the retinal pigment epithelium, choroid or both.[8] CSCR has been associated with the abnormalities of choroidal circulation.[8,9] There is development of choroidal ischaemia that possibly leads to hyperpermeability of the choroidal vessels. Leakage in the choroid might affect the overlying retinal pigment epithelium and lead to serous RPE detachment and neurosensory detachments.[3]

Photodynamic therapy, laser photocoagulation and pharmacological agents (acetazolamide, propranolol, mifepristone and ketoconazole) have been used to treat CSCR. However, these treatment options serve only to shorten the duration of symptoms and have no effect on the recurrence rate and the final visual acuity.[10] In cases with chronic diffuse or persistent focal leakage, retinal pigment epithelium may decompensate leading to gradual visual loss with a less favourable visual prognosis.[11]

The pathophysiology of CSCR remains unclear.[1] Recent studies relying on indocyanine green angiography (ICG) have shown that the aetiology may begin with the changes in choroidal permeability.[12] It seems reasonable to target the choroidal vascular changes with new strategies to treat CSCR. Bevacizumab, being an antibody to vascular endothelial growth factor (VEGF), as well as having antipermeability properties, therefore, may theoretically reverse the changes seen in CSCR.

This study was performed to evaluate the efficacy of intravitreal bevacizumab for the treatment of neurosensory detachment in cases of CSCR.

METHODOLOGY

The study was conducted after the approval of research/ethical committee of the hospital. This prospective study included 43 eyes of 32 patients with CSCR. Both genders between 22 and 54 years were included. Patients having acute or chronic CSCR were studied. Acute CSCR was defined as resolution of disease before 6 months, while chronic CSCR persisted longer than 6 months. Inclusion criteria were subfoveal fluid documented by OCT and active leak documented by fundus fluorescein angiography. Exclusion criteria were choroidal neovascular membrane, prior treatment with laser photocoagulation, traspupillary thermotherapy or photodynamic therapy, history of thromboembolic events including stroke, transient ischaemic attacks and myocardial infarction, history of previous treatment with intravitreal anti-VEGF, intraocular pressure more than 21 mmHg, history of retinal detachment, intraocular inflammation, history of allergic reaction to fluorescence.

Patients fulfilling the inclusion criteria were selected from Retina Clinic of LRBT. Patients were asked to sign the informed consent. Sociodemograhic profile like name, age, gender and history of current disease with respect to symptoms, severity and duration was taken. At baseline and follow-up visits, examination included detailed anterior segment examination with slit lamp, visual acuity with Snellen's chart (converted into decimal), intraocular pressure measurement with Goldman's applanation tonometer and dilated fundus examination. Fundus fluorescence angiography (FFA) to document leak was performed at baseline examination while optical coherence tomography (OCT) to document retinal thickness was done at baseline and at each follow-up visit 4 weeks apart. Outcome measures were resolution of neurosensory detachment and improvement of visual acuity.

In all patients, the intravitreal injection of off label bevacizumab was performed in a standard protocol in the operation theater under complete aseptic conditions. Proparacaine 0.5% topical eye drops were instilled followed by scrubbing of eyelids by 10% povidone-iodine and conjunctiva instilled with 5% povidone-iodine several minutes before the procedure. A sterile eyelid speculum was used to set apart the lids. Topical 2% lidocaine was instilled at the site of injection in the inferotemporal quadrant. Bevacizumab was injected through the pars plana 3.5 – 4.0 mm posterior to the surgical limbus using a 30-guage needle at a dose of 1.25 mg in 0.05 ml. Post-injection, a sterile cotton swab is placed at the site of injection to prevent reflux of vitreous or drug. Topical antibiotic drop was instilled. A sterile eye pad was placed that was removed after 2 hours. Patients were instructed to apply topical antibiotic drops 4 times a day for 5 days. Postinjection follow-up included repeated clinical examination. Patients were assessed for adverse events including elevated intraocular pressure, cataract progression, retinal detachment, post-injection inflammation and endophthalmitis. Follow-up visits were scheduled to next day, 1 week, then monthly till the end of follow-up. Repeated OCT was performed after every 4 weeks till the end of follow-up. A repeated injection of bevacizumab was performed after 4 weeks for persistent or recurrent CSCR documented by OCT imaging.

All this information was entered into Statistical Package for Social Sciences (SPSS) version 17 and analyzed accordingly. The variables analyzed were demographics (age, gender) and examination. The quantitative data (age) was presented with simple descriptive statistics like mean and standard deviation. Median was calculated for BCVA and CMT. The qualitative data (gender) presented as frequency and percentage. Wilcoxon Signed Ranks test was used for central macular thickness and BCVA. P-value equal to or less than 0.05 was considered statistically significant.

RESULTS

This study included 43 eyes of 32 patients with CSCR. There were 26 (81.3%) males and 6 (18.7%) females. Mean age was 39.09±8.49 years. There were 21 (65.5%) cases of unilateral involvement and 11 (34.5%) cases of bilateral involvement. Out of unilateral cases there were 10 (31.1%) right eyes and 11 (34.4%) left eyes. Nineteen (59.4%) eyes showed less than 6 months involvement and 13 (40.6%) eyes showed more than 6 months involvement. In 14 (43.8%) cases pigment epithelial detachment was present while 18 (56.2%) eyes showed no pigment epithelial detachment. Fifteen (46.9%) patients presented with complaint of decreased vision, 7 (21.9%) patients presented with positive scotoma, 1 (3.1%) patient presented with defect of color vision, 5 (15.6%) patients presented with metamorphopsia and 4 (12.5%) patients complained of micropsia as their main presenting complaint. Regarding systemic risk factor for the development of CSCR, we could identify 3 (9.4%) patients having tension, 1 (3.1%) with history of full arm burn, 1 (3.1%) with history of acid peptic disease, 1 (3.1%) with hepatitis C, 1 (3.1%) with

history of hypertension, 2 (6.3%) had history of infertility, 1 (3.1%) with menstrual irregularities, 3 (9.4%) were using *Naswar, Gutka* and cigarette, 1 (3.1%) patient was using oxymetazoline nasal spray, 1 (3.1%) patient was suffering from psychosis and she was on antipsychotic treatment, 3 (9.4%) patients were using sex arousal tablets, 2 (6.3%) patients were using steroids, 1 (3.1%) patient was doing dieting for weight reduction, while in 11 (34.4%) cases we could identify no systemic risk factor. Subretinal precipitates were present in 12 (37.5%) patients while 20 (62.5%) patients showed no such finding. On FFA there were 32 (74.4%) patients who showed ink blot pattern while 4 (9.3%) patients revealed smoke stack pattern and 7 (16.3%) patients showed diffuse leakage.

There was visual improvement in follow-up visits (Table I). Comparison of visual acuity was made between baseline and 6 months ($p < 0.001$). Median central macular thickness is shown in Table II. Difference between baseline and 6 month CMT was statistically significant ($p < 0.001$).

Out of 43 eyes, 11 resolved with one injection, 9 resolved with 2 injections, 11 resolved with 3 injections, 7 resolved with 4 injections and 5 resolved with 5 injections. Mean number of injections required was 2.37±1.24 in acute cases and 3.05 ± 1.39 in chronic cases. Overall mean of required injections was 2.67 ± 1.34.

Table I: BCVA at baseline and follow-up visits.

Timing	BCVA (decimal) Median
Baseline	0.25
1 month	0.50
3 months	0.60
6 months	0.70

Key: BCVA= best corrected visual acuity

Table II: Median CMT.

Timing	CMT µ Median
Baseline	557
1 month	378
3 months	334
6 months	286

CMT= central macular thickness; µ = micron

DISCUSSION

In this prospective study, the effect of intravitreal injection of bevacizumab to resolve neurosensory detachment in cases of CSCR was studied. There was reduction in CMT at all follow-up visits and there was improvement in BCVA noted at all follow-up visits.

The precise pathophysiology of CSCR remains unclear. There is no standard treatment for it. Various medical treatments have been attempted for it, including acetazolamide, beta-blockers, vitamins and non-steroidal anti-inflammatory medicines, all without clear benefit.[13,14] Laser photocoagulation may accelerate the resolution but it can result in permanent scotoma, which may enlarge with time, and laser can induce choroidal neovascularization (CNV).[15] Indocyanine green (ICG)-guided photodynamic therapy (PDT) has been used for the treatment of CSCR.[16] But PDT is expensive and cases of CNV and severe choroidal ischaemia have been reported with use of PDT.[17,18]

Bevacizumab is a recombinant humanized full-length monoclonal antibody that binds all isoforms of VEGF. The bevacizumab molecule can penetrate the retina and is transported into the RPE, the choroid and photoreceptors outer segments after intravitreal injection.[19] Intravitreal bevacizumab has been utilized to treat ocular disorders, which are associated with neovascularization or vascular leakage as a result of an underlying disease.[20] Niegel first reported the use of intravitreal bevacizumab for the treatment of CSCR.[21] The results suggested that intravitreal use of bevacizumab was safe and effective for the treatment of CSCR. In this study, it was demonstrated that intravitreal bevacizumab injection in patients with CSCR could bring resolution of subretinal fluid, which was accompanied by improvement of visual acuity. The mechanism by which the intravitreal bevacizumab therapy brings relief is unknown but it may be related to its ability to affect vascular permeability.[1] Recent studies relaying on ICG have shown that the aetiology of CSCR rests on choriocapillaris, in which a focal increase in the permeability of the choriocapillaris overwhelms the RPE and causes leakage of fluid into the subretinal space and subsequent RPE detachment. The hyperpermeability of choriocapillaris may be caused by capillary and venous congestion, possibly because of choroidal ischemia. Localized choroidal ischaemia has been observed in normal fellow eyes of some patients of CSCR.[12] Choroidal ischemia in CSCR may induce an increase in the concentration of VEGF, which has profound effects on vascular permeability.[1,22] Theoretically reduce level of VEGF may improve choroidal ischaemia.

In this study intravitreal bevacizumab was used to treat CSCR. Visual acuity improved from baseline 0.25 to 0.70 at final follow-up visit that was statistically significant. Median CMT at baseline was 557 µ and at 6 month was 286 µ. Difference between baseline and 6 month CMT was statistically significant, $p < 0.001$.

These results are in agreement with the outcome of the study of Mehany and coauthors.[5] Their results showed that intravitreal bevacizumab injection was associated with visual improvement and reduced neurosensory detachment. In their study mean number of injections used were 2. These results are also in agreement with the results of Torres-Soriano and coauthors who reported in a study of 6 eyes that visual acuity improved in all cases by 1 month after treatment (intravitreal bevacizumab injection) and remained stable until the

examination at the third month.[24] However, they used higher concentration dose of bevacizumab (2.5 mg). These results are in agreement with the work of Schaal and coauthors.[10] They studied 12 eyes with chronic CSCR in which patients received 2 ± 1 intravitreal injections of bevacizumab during a follow-up of 24 ± 14 weeks. The change in BCVA was significant. Central retinal thickness decreased significantly over follow-up.

These results conclude anatomic and functional improvement following intravitreal bevacizumab injections, which suggest that VEGF may be involved in fluid leakage in patients with CSCR. The results suggest a possible role for anti-VEGF agents in the treatment of CSCR. However, limitations of this study include a short follow-up and small number of patients. Further evaluation of intravitreal bevacizumab for CSCR patients in controlled randomized large number of patients with longer follow-up period are necessary to confirm the efficacy and safety of bevacizumab and to determine the ideal protocol for this new promising treatment.

CONCLUSION

Intravitreal bevacizumab injection was associated with visual improvement and reduced neurosensory detachment. These short-term results suggest that intravitreal bevacizumab injection may constitute a promising therapeutic option in central serous chorioretinopathy.

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