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Original research

Intravitreal bevacizumab administration for the treatment of chronic central serous chorioretinopathy

Aliagha Alishiri [a], Khosrow Jadidi [b,c], Seyed Aliasghar Mosavi [c], Hamidreza Torabi [b,*]

[a] Department of Ophthalmology, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
[b] Health Management Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
[c] Vision Health Research Center, Semnan University of Medical Sciences, Semnan, Iran

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Abstract

Purpose: To evaluate the effects of intravitreal bevacizumab (IVB) injection on chronic central serous chorioretinopathy (CSC).
Methods: In this prospective interventional case series, a total of 22 eyes of 22 patients, diagnosed with unresolved CSC for three months or longer, received 1.25 mg IVB injection. Also, in case of failure to achieve success parameters, double dose IVB injections continued in order to reach the complete subretinal fluid (SRF) absorption. A complete ophthalmic assessment was carried out one day, one week, and one-month post-injection, and then a monthly visit was performed, and re-injection was done if needed. Visual acuity, subretinal space volume (SSV), central macular thickness (CMT), and contrast sensitivity were measured and compared among baseline values and final post-treatment values.
Results: The mean best corrected visual acuity increased significantly from 0.70 ± 0.22 to 0.17 ± 0.15 logMAR (P <0.001), and the CMT showed a significant reduction from 557.36 ± 129.12 to 259.50 ± 116.73 μm (P <0.001). In addition, SSV decreased significantly from 10.53 ± 2.03 to 6.63 ± 1.80 (P = 0.001), and contrast sensitivity improved significantly from 13.8182 ± 2.64820 dB to 17.6818 ± 1.80967 dB (P <0.001).
Conclusion: In this series, SRF absorption occurred and visual acuity improved after IVB injections, however, further comparative studies are needed to show the effect of IVB in chronic CSC.

Keywords: Intravitreal bevacizumab; IVB; Chronic central serous chorioretinopathy; Treatment

Introduction

Central serous chorioretinopathy (CSC) is described as a chorioretinal disease, associated with the serous detachment of the neurosensory retina and/or retinal pigment epithelium (RPE). The major symptoms of CSC include blurred vision, associated with micropsia and metamorphopsia. This disease is most commonly reported in middle-aged men and can be intensified by psychosocial stress. In most cases, normal vision spontaneously recurs in a few months.[1]

In 80−90% of patients with acute CSC, detachment is spontaneously resolved in three months. Observation is generally the first therapeutic option in the acute stage of the disease. However, laser photocoagulation is also applied on RPE leakage sites in the event of persistent or recurrent detachment. This method can accelerate the resolution of detachment and reduce disease duration in patients. However, this modality is not risk-free and may lead to permanent scotoma, which can expand over time due to RPE scar and choroidal neovascularization (CNV) development.[2,3]

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* Corresponding author. Baqiyatallah University of Medical Sciences, Mollasadra Street, Vanak square, Tehran, Iran.
E-mail address: Dr_Hamidrezatorabi@yahoo.com (H. Torabi).
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Some reports have confirmed the positive effects of photodynamic treatment in chronic CSC, although this method is costly and there is a possibility of CNV development post-treatment.[4–6] Anti-vascular endothelial growth factors (anti-VEGFs) can be an alternative option in chronic CSC treatment due to their anti-permeability properties, besides leakage reduction as its general mechanism of action.[7]

Few studies with a limited sample size have been performed on the effectiveness of intravitreal bevacizumab (IVB) injection in chronic CSC.[7–9] Nonetheless, there is inadequate data in this field. Therefore, we aimed to evaluate the efficacy of IVB injection in chronic CSC treatment.

Methods

The review board and Ethics Committee of the Baqiyatallah Hospital approved this prospective case series, which was performed according to the Declaration of Helsinki. In addition, informed consent was obtained from the participants.

This study examined 22 eyes of 22 patients with chronic CSC for three months (or longer) and best corrected visual acuity (BCVA) below 0.4. Diagnosis of chronic CSC was established based on the following findings: history of metamorphopsia and blurred vision for three months or longer; neurosensory detachment on optical coherence tomography (OCT) and ophthalmoscopy; and fluorescein angiography (FA) pattern. There is no consensus on the definition of chronic CSC; however, in many studies, CSC more than 3 months has been considered chronic CSC.[10–13]

On the other hand, the exclusion criteria were as follows: 1) concomitant macular diseases; 2) severe media haziness precluding OCT assessment; 3) history of hypertension, diabetes mellitus, rheumatic diseases, malignant diseases and chemotherapy treatment, thyroid diseases, cardiovascular diseases, smoking and endocrine disorders (Cushing disease); 4) treatment with systemic corticosteroids; 5) history of intraocular surgery or recent eye trauma; 7) use of psychotropic drugs, Eplerenone, Spironolactone and other anti-steroid drugs; and 8) non-compliance. A complete ophthalmic analysis was carried out for all patients.

First, 1.25 mg IVB (Avastin; Genentech, Inc., CA, USA for F. Haffmann-La Roche Ltd., Switzerland) was injected in all the eyes under sterile conditions using a 30-guage needle from the supratemporal quadrant 4 mm from the limbus. Then a complete ophthalmic assessment was carried out one day, one week, and one month following IVB injection, and then a monthly visit was done. In addition, a masked optometrist determined BCVA, which was converted to the logarithm of minimum angle of resolution (logMAR) and compared with the baseline after final visit.

Spectralis spectral-domain OCT (Heidelberg Engineering Inc., Heidelberg, Germany) was done every one month after IVB injection. An optician blinded to the study measured central macular thickness (CMT) in a circle (1 mm) centered at the fovea. Subretinal space volume (SSV) was evaluated using a built-in segmentation-modifying tool of spectral domain optical coherence tomography (SD-OCT) at the macular center. Contrast sensitivity test was also performed using the Metrovision MonPack 3 monitoring system. Moreover, fundus FA was done to observe different patterns of CSC.

The success of treatment was defined as absorption of subretinal fluid (SRF) in OCT. Moreover, in case of failure to achieve success after the first injection, IVB injections with a double dose (2.5 mg) continued in 4-week intervals to reach the final target. A double dose IVB injection has been used in some studies to treat ocular diseases and has led to different results.[14–16] For data analysis, paired *t*-test was applied at a significance level of 0.05.

Results

A total of 22 eyes from 22 patients were recruited to this prospective, consecutive, interventional study. The demographic data are summarized in Table 1.

The first injection was performed for all patients, and 16, 6, and 2 patients required the second, third, and fourth injections. All patients were followed for 4 months after first injection.

The SRF was absorbed in 6 eyes (27.3%) one month after first injection, in 10 additional eyes (45.5%) one month after second injection, in 4 eyes (18.2%) one month after third injection, and in 1 eye (4.5%) after forth injection. In 1 eye (4.5%), the SRF remained unresolved at final follow-up.

BCVA increased in all eyes during the follow-up period (Table 2). The mean BCVA was 0.70 ± 0.22 logMAR at baseline, which significantly improved to 0.17 ± 0.15 logMAR ($P < 0.001$) at the final visit. Also, CMT decreased from 557.36 ± 129.12 to 259.50 ± 116.73 μm ($P < 0.001$) (Table 3). SSV decreased significantly from 10.53 ± 2.03 to 6.63 ± 1.80 μm ($P = 0.001$). Moreover, contrast sensitivity improved significantly from 13.8182 ± 2.64820 dB to 17.6818 ± 1.80967 dB ($P < 0.001$) in the last follow-up. Finally, in 21 cases, anatomic and functional success were achieved. During the follow-up, no recurrence of attack occurred in the eyes. Also, no significant complications such as endophthalmitis or cataract formation were reported. During the follow-up, increased intraocular pressure (>21 mmHg) did not occur.

The most frequent angiographic pattern was expansile dot in 11 eyes, followed by smock stack pattern in 5 eyes, diffuse leakage in 5 eyes and no leakage in one eye. Final success did not happen in only one eye with no fluorescein leakage.

Discussion

Different drugs have been used for the treatment of CSC, including beta-blockers, acetazolamide, ketoconazole, non-

Table 1
Demographic data of patients.

Age (mean ± SD)	42.31 ± 6.63
Gender (male:female)	15:7
Eye (right:left)	10:12

SD: Standard deviation.

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Table 2
Best corrected visual acuity (BCVA) changes following intravitreal bevacizumab (IVB) injection.

	Number of included cases	Mean	Standard deviation	*P*-value (compared to before each injection)
Base line	22	0.709	0.222	
One month after first injection	22	0.293	0.184	<0.001
One month after 2nd injection	16	0.197	0.240	<0.001
One month after 3rd injection	6	0.182	0.145	0.001
One month after 4th injection	2	0.173	0.155	0.045

steroidal anti-inflammatory drugs, and vitamins, all without any proven benefits.[3,17] The literature suggests different applications of laser photocoagulation for CSC.[4] According to some studies, laser photocoagulation reduces the disease duration, while some researchers argue that this procedure does not improve the final vision, progression to the chronic stage or recurrence. In addition, constant scotoma may occur, which increases with the expansion of RPE scar over time and possibly leads to CNV development.[2,3] Photodynamic therapy (PDT) directed at RPE leaks might accelerate exudation resolution in CSC by decreasing the choroidal blood flow in these areas, which leads to leakage cessation.[18] Although there are no phase 3 randomized clinical trials, PDT is currently considered the treatment of choice for chronic CSC cases.[19] PDT is a relatively expensive method and also requires special equipment and high skills that may not be available everywhere. It may also lead to rare complications including choroidal ischemia, CNV, and RPE atrophy.[20–24] In this study, we assessed the efficacy of IVB injection for the treatment of chronic CSC. IVB injection is more available and requires less equipment and also less experience and skills.

Some recent case series have used indocyanine green-guided PDT for patients with chronic CSC.[25] Ober and colleagues applied PDT in a small-scale pilot study and reported the promising treatment of focal RPE leakage in CSC, resulting in visual improvement.[26] In addition, ICG-guided PDT was applied in a study by Piccolino et al.[6] on 16 eyes with chronic CSC. One month after the treatment, serous retinal detachment was completely resolved in 75% of eyes and 69% of eyes showed visual improvement (one or more lines) three months following PDT. Nevertheless, secondary RPE changes occurred in 31% of eyes at the PDT site, which was deemed to be associated with hypoxic damage due to choriocapillaris occlusion.

Table 3
Central macular thickness (CMT) changes following intravitreal bevacizumab (IVB) injection.

	Number of included cases	Mean	Standard deviation	*P*-value (compared to before each injection)
Base line	22	557.36	129.12	
One month after first injection	22	340.14	85.24	<0.001
One month after 2nd injection	16	277.75	78.20	<0.001
One month after 3rd injection	6	265.33	90.23	0.018
One month after 4th injection	2	259.5	116.73	0.041

There are controversies regarding the pathophysiology of CSC. RPE defect or dysfunction may be effective in the serous retinal detachment development in CSC.[18,27,28] Gass suggested that choroidal vascular hyper-permeability is the main cause of CSC development and later ICG-based studies supported this theory.[29–31] Hydrostatic pressure elevation in the choriocapillaris may lead to leakage and result in serous retinal detachment.[32] It is suggested that increased VEGF concentration secondary to choroidal ischemia may finally lead to choroidal hyper-permeability; therefore, anti-VEGF agents may be effective in the treatment of eyes with CSC[33,34]; however, to date, there is no document regarding VEGF elevation in the eyes with CSC.

Our study showed that BCVA increased from 0.70 ± 0.22 to 0.17 ± 0.15 logMAR, and CMT decreased from 557.36 ± 129.12 to 259.50 ± 116.73 μm. During the follow-up, recurrence did not take place. In a study by Entazari et al.,[35] the mean BCVA before treatment was 0.60 ± 0.25 logMAR, which changed to 0.50 ± 0.18 after two months and 0.29 ± 0.19 after six months. This finding is consistent with our study. Furthermore, the mean CMT was 370 ± 65 μm, which reduced to 208 ± 23 μm, in agreement with our study.

In another study conducted by Torres Soriano et al., all five cases received IVB (2.5 mg/0.1 cc), indicating improvement in visual acuity, fluorescein angiographic leakage, as well as reduced neurosensory detachment after treatment.[7] Their study included patients with recurrent CSC episodes, CSC patients with a history of reduced visual acuity for more than three months, and patients with acute CSC and major discomfort in visual acuity.

In a study on 12 eyes from chronic CSC patients, Schaal et al. revealed that IVB injection improved BCVA, as well as CMT.[9] This finding is comparable to our study, although they used multiple injections of bevacizumab (2.5 mg) in six-to eight-week intervals. In our study, the mean volume of SRF before treatment was 10.5327 ± 2.038 μL, which changed to 8.4291 ± 1.539 μL after the first injection. In the same way, in the study by Schaal and colleagues, complete absorption of SRF was demonstrated in 50% of the patients.

In the retrospective study, Chung et al. evaluated the efficacy of IVB injection in the treatment of 77 eyes from 71 patients with chronic, atypical, or recurrent CSC.[36] They injected IVB in 6-week intervals until SRF absorption and then based on an as-needed protocol according to OCT findings. At month 3 post-treatment, the mean BCVA and CMT improved significantly and was maintained during the one-year follow-up time. They found that improvement in BCVA was significant in eyes with chronic or recurrent CSC but was not statistically significant in eyes with atypical CSC. In

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another retrospective study, Unlu and co-workers assessed the subfoveal choroidal thickness (SFCT) changes following IVB injection in eyes with CSC.[37] They treated 21 eyes with 1.25 mg IVB injection (IVB group) compared with 16 eyes in the control group. At month 3, improvement of visual acuity, SRF absorption, and SFCT reduction happened in all cases in both study groups; however, reduction of SFCT was significantly greater in the control group. The authors concluded that IVB injection is not superior to observation in the management of CSC. Unlike our study, Unlu et al. included patients with acute CSC.

In a prospective study, patients with chronic CSC who were treated with 1.25 mg IVB injection (12 eyes) were compared with low-fluence PDT (10 eyes).[38] At 9-month follow-up time, visual acuity improvement was better in the IVB injection group; however, the difference was not significant. The mean IVB injection was 3.0 ± 1, and the mean PDT re-treatment was 1.6 ± 0.6 during the follow-up period (9 months). The author concluded that IVB injection can be a treatment modality for chronic CSC, which was compatible to our study results. Also, a combination of PDT with IVB injection may be effective in the management of chronic CSC.[39–41] Naseripour et al. evaluated the efficacy of half-dose verteporfin PDT in the treatment of chronic CSC.[42] They reported that SRF was resolved in 96.2% of eyes after 12-month follow-up. In our study, complete resolution of SRF happened in 95.5% of eyes at the final follow-up visit; however, 3-month response of half-dose PDT was higher in Naseripour et al.'s study compared to our study. PDT is currently the treatment of choice for chronic CSC, and IVB may serve as an alternative option.

Additionally, the mean contrast sensitivity in our patients was 13.8182 ± 2.64820 dB before treatment, which significantly changed to 17.6818 ± 1.80967 dB after the treatment ($P = 0.000$). Contrast sensitivity in these patients suggests a relative improvement; therefore, despite a near-complete recovery of vision, the contrast sensitivity level may not be normal.

The most frequent FA pattern in our patients before the onset of treatment was expansile dot and smoke stack patterns, respectively, while the lowest pattern was the diffuse pattern. One of the patients had no leakage on FA, and complete improvement did not happen in this case after treatment. Consequently, FA pattern in patients with chronic CSC seems to be effective in responding to IVB injection. According to a study by Torres Soriano et al., leakage reduction using FA was shown in five patients with the expansile dot pattern.[7] Similarly, in our study, 11 out of 22 patients showed this pattern, which decreased leakage.

Our study was only conducted in a single hospital and did not have a control group which are limitations. The small sample size and non-comparative design do not allow a clear conclusion.

In conclusion, our study demonstrated that IVB injection may lead to absorption of exudative retinal detachment and result in visual function improvement in chronic CSC. However, further randomized clinical trials with a control group and a larger sample size are necessary to evaluate the treatment of CSC using anti-VEGF agents.

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