Prognostic factor for the response to intravitreal bevacizumab treatment in central serous chorioretinopathy patients.

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Abstract

Objective To evaluate prognostic factors associated with good response to intravitreal bevacizumab (IVB) treatment in central serous chorioretinopathy (CSC) patients.

Methods We retrospectively reviewed ninety-four eyes of 94 CSC patients who received intravitreal bevacizumab injection (IVB) (0.05 ml, 1.25 mg) as a first line treatment. Patients were divided into two groups as good responders and poor responders based on optical coherence tomography (OCT) findings 1 month after the first injection of intravitreal bevacizumab. Good responders were defined as complete resolution of subretinal fluid (SRF) on OCT 1 month after IVB. We compared baseline visual acuity, duration of symptoms, angiographic findings on fluorescein angiography, central retinal thickness (CRT), macular volume (MV), subfoveal choroidal thickness (SFCT) between two groups.

Results 42 eyes were included as good responder and 52 eyes as poor responders. Mean age was 47.8 ± 7.4 year old in good responders and 50.6 ± 7.8 year old in poor responders. Baseline visual acuity (logMAR) was better in good responders than poor responders, 0.19 ± 0.19 and 0.29 ± 0.19 respectively ($p=0.015$). SFCT was significantly thicker in good responders than poor responders $419.7 \pm 103.2 \mu\text{m}$ and $376.0 \pm 99.0 \mu\text{m}$ respectively ($p=0.040$). Prevalence of chronic cases was higher in poor responders (33/52) than good responders (15/42), ($p=0.012$). There was no statistical significance in age, sex, CRT, MV between two groups. **Conclusion** Intravitreal injection of bevacizumab can be potential option for the treatment of CSC patients, especially in case of recent onset, better baseline visual acuity with thicker choroid on OCT.

Background

Central serous chorioretinopathy (CSC) is characterized by localized serous sensory detachment of neurosensory retina.¹ In the majority of patients, serous retinal detachment resolves spontaneously; however, some patients with CSC develop progressive visual loss from persistent serous retinal detachment, cystoid macular degeneration or retinal pigment epithelium (RPE) decompensation.² The pathogenesis remains unclear, but is associated with hyperpermeability of choroid and retinal pigment epithelial dysfunction.^{3,4} There are no gold standard treatment for CSC, focal laser photocoagulation, photodynamic therapy (PDT), intravitreal injections of anti-vascular endothelial growth factor (VEGF), corticosteroid antagonists, and acetazolamide have been used to promote the resorption of subretinal fluid in CCS patients.⁵⁻⁹ Intravitreal bevacizumab (IVB), a recombinant humanized monoclonal anti-VEGF antibody, has been reported to be effective and safe for the treatment of CSC patients.^{10,11} In previous study, Jung et al. suggest that IP-10 and VEGF may contribute to the pathogenesis of CSC. And intravitreal bevacizumab was helpful in some of the patients with CSC, who showed higher levels of VEGF in the aqueous humor.¹² There were recent studies regarding clinical characteristics of CSC patients who had better response to intravitreal injection of bevacizumab.^{13,14} But it is not clearly known which factors would predict favorable or unfavorable response to intravitreal bevacizumab treatment in CSC patients.

Herein, we investigated the prognostic clinical factors associated with initial response to intravitreal injection of bevacizumab in treatment naïve CSC patients.

Methods

Study design and participants

We retrospectively reviewed the medical record was of CSC patients who were treated with intravitreal injection of bevacizumab under diagnosis of CSC at GangneungAsan Hospital, Gangneung, Korea, from July, 2013 to April 2018.

The study was approved by the Institutional Review Board of GangneungAsan Hospital and this study followed the tenets of the Declaration of Helsinki.

We included treatment naïve CSC patients who showed leakage on fluorescein angiography (FA) and serous sensory retinal detachment on OCT. Exclusion criteria were as follows: (1) patients who received any previous treatment for CSC such as focal laser photocoagulation, PDT, systemic carbonic anhydrase inhibitors, (2) steroid induced CSC patients, (3) patients who had co-existing macular pathologies such as diabetic retinopathy, severe epiretinal membrane or age related macular degeneration, (4) patients with spherical equivalence $>+3.00$ or <-6.00 Diopter.

Ophthalmic examinations

The patients underwent comprehensive ophthalmic examinations, including best corrected visual acuity (BCVA), dilated fundus examination, FA and spectral domain optical coherence tomography (SD-OCT) with enhanced depth imaging technique (EDI-OCT).

BCVA results were converted to the logarithm of the minimum angle of resolution (logMAR) scale for the comparison. FA (Topcon TRC-50IX, Tokyo, Japan) was performed, we categorized the patients into focal leakage type and diffuse leakage type based on FA findings (Figure 1). Heidelberg Spectralis (Heidelberg Engineering) was used to obtain SD-OCT images of the macula using a custom $25^\circ \times 25^\circ$ volume acquisition protocol to obtain a set of high-speed scans from each eye. Using the protocol, 25 cross-sectional B-scan images were obtained, each of which was composed of 512 A-scans. Choroidal images were obtained using the EDI technique. Subfoveal choroidal thickness (SFCT) was vertically measured from the outer border of the RPE to the inner border of the sclera by two retina specialists (Joe and Yang) using calipers and Heidelberg Eye Explorer software (Figure 2). The mean data of two different measurements were used for comparison in this study. Central retinal thickness (CRT) and macular volume (MV) was obtained automatically and manually adjusted when the reference line was deviated.

Six weeks after intravitreal injection of bevacizumab, we performed BCVA, fundus examination and OCT. We compared ophthalmic findings and variables before IVB and 1 month after IVB to investigate the parameters which were associated with initial response. We divided the patients into two groups based on the status of subretinal fluid on OCT 1 month after IVB. Good responders were defined who showed

complete resorption of subretinal fluid on OCT, whereas poor responders showed incomplete resorption of SRF on OCT 1 month after initial IVB(Figure 3).

We compared BCVA, duration of symptoms, SFCT, CRT, MV and fluorescein leakage type on FA.

Statistics

The independent t-test was used to compare BCVA, SFCT, CRT and MV between bevacizumab good responders and poor responders. The Fisher's exact test was used to analyze the relationship between each group (responsive or nonresponsive) and sex, acute or chronic status, FA findings (focal leakage or diffuse leakage). Clinical characteristics were compared between the bevacizumab good responders and poor responders with independent t-test IBM SPSS ver. 21.0 (IBM Corp., Armonk, NY, USA) was used to perform all analyses, and $p < 0.05$ was considered statistically significant.

Results

Ninety four eyes of 94 patients were included in this study. Forty two patients were included in good responders and 52 were in poor responders. Table 1 shows demographic characteristics and ophthalmic variables of the population in this study. Mean age of good responders was 47.8 ± 7.4 year-old and that of poor responders was 50.6 ± 7.8 , good responders were younger but there was no statistical significance. Baseline BCVA was significantly better in good responders than poor responders, 0.20 ± 0.20 (logMAR) and 0.30 ± 0.20 (logMAR). Good responders showed thicker SFCT ($419.7 \pm 103.2 \mu\text{m}$) than poor responders ($376.0 \pm 99.0 \mu\text{m}$) (Table 1). There was no statistical significance in CFT and MV between good responders and poor responders ($p = 0.998$ and $p = 0.498$, respectively) at initial presentation. We defined acute CSC when the symptom duration was less than three months and chronic when the symptom duration was longer than 3 months. We investigated the prevalence of acute and chronic cases in both groups and compared. Prevalence of acute cases were more in good responders than poor responders (24 out of 42 and 19 out of 52, $p = 0.029$). There were no significant differences in FA leakage type and sex ratio between both groups ($p = 0.198$ and $p = 0.776$, respectively, Table 1).

1 month after IVB, CRT was thinner and MV was less in good responders than poor responders, those results were statistically significant ($p = 0.000$ vs $p = 0.001$ respectively). Post-IVB BCVA was significantly better in good responders, also ($p = 0.000$).

We investigated the correlation between BCVA and CRT, or MV. There was no significant correlation between BCVA and CRT, or MV ($p = 0.918$ and 0.490 respectively, Table 1) at initial presentation. Two studies commonly showed thicker choroid responded better to IVB in CSC patients.

Discussion

Anti-VEGF intravitreal injection is one of major option for the treatment of CSC, and previously published articles were focused on chronic and recurrent cases. Most studies showed favorable outcomes, but not

all cases of chronic and recurrent CSC patients respond to IVB well.^{10, 11, 15}

The aim of this study was to investigate the prognostic factor for IVB in treatment-naïve CSC patients and there were few studies regarding this topic. Kim et al. published bevacizumab responders showed significantly thicker SFCH at baseline and great reduction in SFCT after intravitreal injection of bevacizumab.¹⁴ In this study, authors compared only choroid thickness variation between bevacizumab responders and poor responders with thirty eyes of 30 patients and the relationship between late indocyanine green angiography (ICGA) findings and the responsiveness to IVB. The other study showed CSC patients with thicker choroid and better initial visual acuity was correlated with better response to IVB treatment in 42 chronic recurrent CSC patients.¹³ The result of this study was similar with our result, but only included chronic CSC cases. Traditionally, abnormality of barrier function in RPE was considered as a primary cause in CSC patients. With advancement in imaging modalities such as ICGA, abnormal choroidal vasculature was considered as a main cause.^{16, 17} Jirarattanasopa et al. showed the association between choroidal thickness and choriovascular permeability on ICGA.¹⁸ This indirectly means that the role of anti-VEGF treatment in CSC patients would be better in thicker choroid which was more vascular permeable. Also those results strengthened the rationale for anti-VEGF treatment in CSC patients.

Our study has some limitation of retrospective design. Furthermore, we did not include an untreated control group of CSC eyes. It is possible that some good responder patients experienced spontaneous improvement or resolution. However, we minimized this possibility by excluding patients with symptom duration that was <3 months. Further studies should be prospectively designed and include an untreated control group.

The sample size was relatively larger than previous studies. We treated IVB injection in acute CSC patients who needed rapid visual recovery when they could not have focal laser treatment. This was the main difference from previous studies, which have been used IVB mostly in chronic or recurrent CSC cases.

Conclusions

CSC patients with relatively acute onset, thicker subfoveal choroid and better initial VA had shown better response to IVB in our study. Based on our results, IVB can be a primary treatment for CSC eyes with thicker subfoveal choroid and good VA even in acute phase.

List Of Abbreviations

IVB: Intravitreal bevacizumab

CSC: Central serous chorioretinopathy

PDT: Photodynamic therapy

logMAR: Logarithm of minimum angle of resolution

VEGF: Vascular endothelial growth factor

FA: Fluorescein angiography

SFCT: Subfoveal choroidal thickness

CRT: Central retinal thickness

MV: Macular volume

Declarations

-Ethics approval and consent to participate

The study was approved by the Institutional Review Board of GangneungAsan Hospital and this study followed the tenets of the Declaration of Helsinki.

-Availability of data and material

All the data supporting the conclusions of this article are included within the article and its figures.

- Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

- Competing interests

The author has no financial or conflicting interest.

- Funding

No funding was obtained for this study.

- Authors' contributions

Dr. Lee is the first author who wrote this article and 2nd and 3rd authors contributed to data analysis.

Corresponding author conducted to design this study.

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Tables

Table 1 Comparision of characteristics between good and poor responders.

	Good responders(n=42)	Poor responders(n=52)	P value
Age (year)	47.8±7.4	50.6±7.8	0.080*
Male : Female	36:6	39:13	0.302 [†]
Duration	24:18	18:34	0.029 [†]
Acute : Chronic			
FA leakage	19:23	22:30	0.776 [†]
Focal :Diffuse			
Baseline			
BCVA (logMAR)	0.20±0.20	0.30±0.20	0.015*
SFCT (μ)	419.7±103.2	376.0±99.0	0.040*
CRT (μ)	431.6±92.0	431.9±102.8	0.988*
MV (mm ³)	9.7±1.3	9.9±1.1	0.478*
Post IVB			
BCVA (logMAR)	0.11±0.14	0.24±0.20	0.000*
CRT (μ)	255.2±26.9	346.9±82.4	0.000*
MV (mm ³)	8.9±0.7	9.4±0.9	0.001*

BCVA=Best corrected visual acuity, SFCT=Subfovealchoroidal thickness

CRT=Central retinal thickness,MV=Macular volume, IVB=Intravitrealbevacizumab

*Student T test, [†]Chi-square test

Figures

Figure 1

Fluorescein angiography findings in central serous chorioretinopathy. (A) Focal leakage type was defined as the presence of well-defined homogeneous spots. (B) Diffuse leakage type was defined as the presence of an area with hyperfluorescence without focal well-defined spots

Figure 2

Measurement of SFCT on EDI-OCT image. SFCT was vertically measured from the outer border of the retinal pigment epithelium to the inner border of the sclera.

Figure 3

Response to initial IVB in central serous chorioretinopathy. (A) Good responder was defined as the complete resorption of SRF on OCT after 1 month IVB (B) Poor response was defined as the incomplete resorption of SRF on OCT after 1 month IVB