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Efficacy of Photodynamic Therapy Versus Intravitreal Bevacizumab Injection for Chronic Central Serous Chorioretinopathy

Kronik Santral Seröz Koryoretinopatide Fotodinamik Tedavinin ve İntravitreal Bevacizumab Enjeksiyonunun Etkinliği

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Özet

Amaç: Kronik santral seröz koryoretinopati (SSR) tedavisinde fotodinamik tedavi (PDT) ile intravitreal bevacizumab'ın (IVB) etkinliğini karşılaştırmak.

Yöntem: Semptomatik kronik SSR nedeniyle PDT (n=9) veya IVB (n=6) uygulanmış 15 hastanın 16 gözüne ait dosyalar retrospektif olarak incelendi. İki grup, en iyi düzeltilmiş görme keskinliği (EDGK), santral makülar kalınlık (SMK) ve subretinal sıvı (SRS) volümü açısından tedavi sonrası 1., 3. ve 6. aylarda karşılaştırıldı.

Bulgular: Tüm zaman dilimlerinde, ortanca EDGK açısından her iki grup benzerdi (p>0.05). SMK azalması açısından 1. ve 3. aylarda iki grup arasında anlamlı fark izlenirken (p<0.05), 6. ayda bu fark anlamlı değildi (p>0.05). SRS rezorpsiyonu 1. ve 3. aylarda PDT grubunda anlamlı olarak daha iyi iken 6. ayda bu fark anlamlı değildi (p>0.05).

Sonuç: Hem PDT hem de IVB enjeksiyonu kronik CSC'de görsel ve anatomik düzelme sağlamaktadır. Ancak PDT, tedavi sonrası üç aylık dönemde SMK'de ve SRS'de düzelme açısından IVB'den üstün görünmekterdir.

Anahtar Kelimeler: Kronik santral seröz koryoretinopati, fotodinamik tedavi, intravitreal bevacizumab.

Abstract

Objective: To compare the efficacy of photodynamic therapy (PDT) versus intravitreal bevacizumab (IVB) injection for the treatment of chronic central serous chorioretinopathy (CSC).

Method: The medical records of 16 eyes of 15 patients who received PDT (n=9) or IVB (n=6) for symptomatic chronic central serous chorioretinopathy (CSC) were retrospectively reviewed. Best-corrected visual acuity (BCVA), central macular thickness (CMT), and subretinal fluid (SRF) volume were compared between the two patient groups at baseline and at 1,3 and 6 months after treatment.

Results: Median BCVA was similar in both groups at all time points (p>0.05). The reduction of CMT was significant at the 1st and 3rd month (p<0.05), however, it was non-significant at the 6th month among two groups (p>0.05). SRF resorption was significantly better in the PDT group when compared to IVB group at the 1st and 3rd month (p<0.05), while it was non-significant at the 6th month (p>0.05).

Conclusion: Both PDT and IVB injection provided visual and anatomical recovery for chronic CSC. However, PDT appeared superior to IVB in terms of improving CMT and SRF throughout three months after treatment.

Keywords: Chronic central serous chorioretinopathy, photodynamic therapy, intravitreal bevacizumab.

Introduction

Central serous chorioretinopathy (CSC) is a sporadic disease occurring in young and middle-aged adults and is characterized with neurosensory and retinal pigment epithelial detachment (PED). Although CSC has been described as a benign and self-limiting disease, approximately 5% of patients develop chronic disease which often presents bilaterally as a multifocal and recurrent disorder, and may lead to permanent visual loss (1). The pathophysiology of CSC still remains unresolved. However, an increasing number of studies indicate that the two major mechanisms leading to neurosensory detachment are focal choroidal ischemia and leakage (2,3).

No treatment for chronic CSC has been well-established yet. Various medical treatments and focal laser photocoagulation (LP) have been attempted, but have resulted in poor outcomes (4,5).

Photodynamic therapy (PDT) with verteporfin has been used for the treatment of chronic CSC in recent years, and seems to have a beneficial effect. PDT has shown better anatomical and functional outcomes compared to photocoagulation in chronic CSC (6-8). Although PDT seems to be a safer method when compared to LP, it also may cause ocular

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side effects including retinal pigment epithelium (RPE) atrophy, secondary choroidal neovascularization and aggravation of choriocapillaris ischemia (9).

Any therapy that decreases the excessive choroidal permeability may be potentially helpful in CSC. Bevacizumab (Avastin, Genentech), an antibody to vascular endothelial growth factor (VEGF), is known to have antipermeability effects and therefore it may target the pathophysiology of CSC theoretically. Both anatomical and functional improvements following intravitreal bevacizumab (IVB) injection in patients with chronic CSC have been reported in case series (10-13).

In this study, we aimed to compare the anatomical and functional outcomes of PDT versus IVB injection in the treatment of chronic CSC.

Material and Method

We retrospectively evaluated 16 eyes of 15 patients with symptomatic CSC lasting longer more than 6 months. All patients had ophthalmoscopic signs corresponding to chronic CSC; subretinal fluid (SRF) and/or serous PED involving the fovea in optical coherent tomography (OCT), and active focal leaks with diffuse RPE decompensation in fluorescein angiography (FA). Exclusion criteria included evidence of any macular or chorioretinal disorder unrelated to CSC, previous treatment with LP, PDT or intravitreal injection, any systemic contraindication for PDT or FA, and patients who were unable/reluctant to give informed consent.

PDT was performed according to the age-related macular degeneration protocol as previously reported (14). In standard PDT, total light energy of 50 J/cm2, a light dose rate of 600 mW/cm2, and a duration of photosensitization of 83 seconds were performed with the guidance of FA.

All intravitreal bevacizumab injections were performed by the same physician (HAT) with a uniform protocol. The ocular surface was irrigated with 5% betadine solution 2 minutes prior to the injection. A lid speculum was then placed and a 2.5 mg/0.1 ml bevacizumab injection was performed 3.5 mm posterior to the limbus.

Retreatment with the same protocol was performed if a decrease in BCVA of at least one line in Snellen chart and/or an elevation in CMT and SRF on two repeated exam was observed.

Each patient underwent best corrected visual acuity (BCVA) measurement with Snellen charts, ophthalmic examination with dilated retinal fundoscopy, OCT (Spectral OCT/SLO™ system, OTI Ophthalmic Technologies, Inc., Canada) and FA at baseline. Patients were evaluated at the 1st, 3rd and 6th month. SRF measurement was performed using the "caliper" option of the OCT and central macular thickness (CMT, mean thickness in the central 1000-µm diameter area) was determined automatically and was analyzed by OCT software. Main outcome measures were the changes in mean BCVA, CMT and SRF.

Statistical analysis was performed with the SPSS software. A p value of 0.05 was considered statistically significant. Wilcoxon rank test was used to compare the initial and subsequent value of each variable in the same group. Mann Whitney U test was used to compare the values of each variable between the two groups. The study was performed with informed patient consent and conducted under a protocol approved by the local ethics committee and in accordance with the ethical standards stated in the 1964 Declaration of Helsinki.

Results

16 eyes of 15 patients with chronic CSC (14 male and one female) were evaluated. All cases in this study exhibited features of chronic CSC, with serous macular detachment, diffuse RPE atrophy and/or RPE detachment in fundoscopy and FA. Ten eyes of 9 patients were treated with PDT, and 6 eyes of 6 patients were treated with IVB. The median age was 47 years (min 40, max 65 years) in the PDT group and 48 years (min 46, max 61 years) in the IVB group ($p>0.05$). The median duration of visual symptoms at presentation was 12 months (min 8- max 84 months) in the PDT group and 24 months (min 12- max 84 months) in the IVB group ($p>0.05$). Baseline BCVA, CMT and SRF were also comparable between two groups

(p>0.05). Patients' baseline data are summarized at Table 1.

In the PDT group, median BCVA was 0.2 (min 0.05-max 0.7) at baseline, and improved to 0.63 (min 0.12 - max 1.0) at 6 months (p=0.012). In the IVB group, median BCVA was 0.7 (min 0.3- max 0.9) at baseline and remained stable at all time points (p>0.05). Median CMT decreased significantly at all time points (p<0.05) in the PDT group from 290 µm (min 215-max 473) to 130 µm (min 90-max 238) at 6 months (p=0.012) while the reduction in the IVB group was insignificant at all time points, a decrement from 270 µm (min 135-max 320) to 180 µm (min 110-max 250) (p>0.05) at 6 months. Median SRF decreased significantly at all time points (p<0.05) in the PDT group, from 182 µm (min120-max 274) to 0 µm (min 0-max 124) at 6 months (p=0.018). However, it remained stable at all time points in the IVB group and decreased from 130 µm (min 60-max 160) to 70 µm (min 0- max 200) (p>0.05). Table 2 shows median values of BCVA, CMT and SRF for all time points.

Compared with baseline, an improvement in BCVA was seen in both groups and the difference was insignificant among the groups at all time points. Considering the CMT reduction, PDT provided better results than IVB at the 1st and 3rd month (p=0.012 and 0.039, respectively). When compared to IVB, better results were seen in PDT group considering the SRF reduction, however these results were only significant at the 1st and 3rd month with a p value was 0.004 and 0.016, respectively.

None of patients needed a second PDT treatment in the PDT group, while two of six patients needed bevacizumab reinjection at the third month visit in IVB group.

During the follow-up period, systemic or ocular complications associated with PDT or IVB injection were not observed, including adverse events associated with verteporfin infusion or CNV in the low-fluence PDT group. No clinical evidence of uveitis, inflammation, or endophthalmitis was observed in the ranibizumab group.

Discussion

CSC is an idiopathic disorder characterized by accumulation of subretinal fluid under macula and the chronic form may associated with severe visual loss (1). The pathogenesis of the disorder is not precisely known, thus it is hard to put forward a standard treatment for chronic CSC.

In this retrospective clinical trial, we compared the efficacy of standard-fluence PDT and IVB injection in the treatment of chronic CSC. An improvement in BCVA and resolution of subretinal fluid was observed in PDT group, while both of them remained stable in IVB group.

Different therapies have been applied which target choroidal perfusion and permeability problems have been attempted in the treatment of CSC including acetazolamide, beta-blockers, vitamins, non-steroidal anti-inflammatory medications, even finasteride. However, the results were not satisfying (15-17). Focal LP for the management of CSC remains a controversial issue. LP has been reported to accelerate the resolution of detachment; however it does not improve final vision and recurrence rates. Furthermore, LP may lead a new leakage point or choroidal neovascularization (5).

PDT with verteporfin has been used to treat chronic CSC in recent years. Although the exact mechanism of PDT in CSC is not well-established, it has been suggested that PDT may induce short-term choriocapillaris hypoperfusion and long-term choroidal vascular remodeling thus decreasing choroidal hyperpermeability. The first case of chronic CSC treated by PDT to achieve a significant increase in VA and improvement of serous macular detachment was reported by Piccolino et al. (18). Since then, several different studies have reported good results with PDT with standard doses of verteporfin to treat chronic CSC (7,8). The largest study was performed by Ruiz-Moreno et al. (19), including 82 eyes of 72 patients. They reported complete anatomical improvement in all patients and BCVA gain in 60% of the cases following PDT with standard dosage. However, PDT has not become the standard therapy for chronic CSC as it might lead to secondary RPE changes, choriocapillaris hypoperfusion, and CNV development as a result of choriocapillaris occlusion. To improve PDT safety in chronic CSC, PDT parameters have been modified in recent studies. Several

small studies have reported favorable results with half-dose verteporfin, a faster infusion and a shorter drug–light interval (20,21).

In the current study, standard PDT protocol was performed as previously reported (14). In our PDT group, BCVA improved in 8 of 10 eyes and remained stable in 2 eyes at the end of the follow-up (p=0.012). The reduction in CMT was also significant, falling from 290 µm to 130 µm at the end of the follow-up. Complete resolution of SRF was observed in 8 of 10 eyes at the first month and 9 of 10 eyes at the 3rd and 6th months which was statistically significant for all time points. These results are correlated with previous studies and confirm the anatomical and functional success of PDT in these patients (7,8,19).

The anti-permeability effect of anti-angiogenic agents such as bevacizumab, an antibody to vascular endothelial growth factor (VEGF), may provide beneficial effects at this point. The exact mechanism of IVB in chronic CSC is unknown but it is possible that bevacizumab ameliorates choroidal hyperpermeability which is caused by choroidal ischemia. As it is known, choroidal ischemia is one of the leading events in the pathogenesis of CSC and this may cause an increase in VEGF concentration. Intravitreal use of bevacizumab for chronic CSC was first reported by Niegel et al. (22). Since then, several studies have been reported and the results suggest that intravitreal use of bevacizumab is safe and effective for the treatment of chronic CSC (10-13). In the current study, BCVA improved in 4 of 6 cases at the end of follow-up, after IVB injection (p>0.05). A statistically non-significant reduction in CMT and SRF was also observed at all time points. All these results are also in correlation with the results of previous studies and confirm the anatomical and functional success of IVB injection.

To the best of our knowledge, there is only one report comparing PDT (with low-fluence) and IVB injection in patients with chronic CSC (23). They reported an improvement in visual acuity, a decrease in FA pooling and CMT in both group, however the difference between two groups was nonsignificant. In the present study, when compared with baseline, at all measurements, an improvement in BCVA and a reduction in CMT and SRF was observed in both groups, however the results were better in PDT group for the first three months.

The most important limitation of this study is being a non-randomized and retrospective study. Although our baseline characteristics were similar, baseline BCVA of each group doesn't seem to be same (0.2 vs 0.7, p=0.08). This may be problematic in a retrospective study with a small number of enrolled patients, thus we were unable to exclude the possibility of our findings being the result of chance alone. Another limitation is that, the 6-month follow-up period is relatively short considering the natural course of the disease.

In conclusion, our findings demonstrated that PDT was superior to IVB for controlling CMT and SRF for the first three months of chronic CSC treatment. Larger controlled studies with longer follow-up will be required to fully determine the efficacy and safety of these treatments in chronic CSC.

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Table 1. Patients' baseline characteristics and median values of BCVA, CMT and SRF

Data	Treatment		p value
	PDT	IVB	
Sex (n)			
Male	8	6	>0.05
Female	1	0	>0.05
Age (year)	47 (40-65)	48 (46-61)	>0.05
Disease duration (month)	12 (8-84)	24 (12- 84)	>0.05
BCVA	0.2 (0.05-0.7)	0.7 (0.3-0.9)	=0.08
CMT (µm)	290 (215-473)	270 (135-320)	>0.05
SRF (µm)	182 (120- 274)	130 (60-160)	>0.05

Table 2. Median values of BCVA, CMT and SRF for all time points

Data	Baseline	Month		
		1	3	6
PDT				
BCVA	0.2 (0.05-0.7)	0.4 (0.1-0.9) *p>0.05*	0.7 (0.1-1.0) *p>0.05*	0.63 (0.12-1.0) *p=0.012*
CMT (µm)	290 (215-473)	140 (82-208) *p<0.01*	150 (90-232) *p<0.01*	130 (90-238) *p=0.012*
SRF (µm)	182 (120- 274)	0 (0-90) *p<0.01*	0 (0-78) *p<0.01*	0 (0-124) *p=0.018*
IVB				
BCVA	0.7 (0.3-0.9)	0.7 (0.4-1.0) *p>0.05*	0.5 (0.3-1.0) *p>0.05*	0.8 (0.4-1.0) *p>0.05*
CMT (µm)	270 (135-320)	200 (170-330) *p>0.05*	190 (170-370) *p>0.05*	180 (110-250) *p>0.05*
SRF (µm)	130 (60-160)	105 (0-205) *p>0.05*	70 (0-200) *p>0.05*	105 (0-115) *p>0.05*