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ROLE OF ANTI-VASCULAR ENDOTHELIAL GROWTH FACTORS IN THE TREATMENT OF CHRONIC AND RECURRENT CENTRAL SEROUS CHORIORETINOPATHY

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ABSTRACT

The study evaluate the role of anti-vascular endothelial growth factors (Anti-Vegf) in the treatment of chronic central serous chorioretinopathy (CSCR). It was a hospital base prospective interventional non randomized study. Patients with history of chronic CSCR lasting for more than 3 months were treated with intravitreal Bevacizumab 1.25mg or Ranibizumab 0.5mg after measurement of best corrected visual acuity (BCVA), intraocular pressure (IOP), dilated fundus examination and central macular thickness using OCT. Patient shows complete resolution of subretinal fluid and restoration of visual acuity to normal after 3months. In conclusion, intravitreal injection of anti-vegf results in restoration of normal vision in patient with CSCR.

Key words- Chronic central serous chorioretinopathy, neurosensory retinal detachment, Subretinal fluid, Anti-vascular endothelial growth factor, Optical Coherence Tomography.

INTRODUCTION

Central serous chorioretinopathy (CSCR) is a well-characterized disorder leading to serous neurosensory elevation of the central macula. The acute form of the disease is associated with focal leakage at the level of the retinal pigment epithelium (RPE) demonstrated with fluorescein angiography (FA) (Mitzy *et al.*, 2004). Fortunately, the disorder is self-limited in the majority of patients, who also regain excellent vision. Occasionally, the neurosensory detachment persists and leads to pigment epithelial and photoreceptor damage with visual impairment (Mitzy *et al.*, 2004).

The disease was first described by Von Graefe who coined the term ‘central recurrent retinitis in 1866 for recurrent serous macular detachment (Sudipta and Debmalya, 2017). In 1967, Gass explained the pathogenesis and clinical features and named it central serous choroidopathy (CSC) (Sudipta and Debmalya, 2017).

The disease is characterized by localized neurosensory retinal detachment (NSD) with or without focal pigment epithelial

detachments (PEDs) and altered retinal pigment epithelium (RPE) (Weenink, 2001). Two forms of the disease has been described, which can either be acute or chronic. The acute form usually resolves within 4 months, leaving mostly color discrimination defects in few patients. The chronic form is characterized by widespread tracks of RPE atrophy, showing reduced fundus autofluorescence (FAF) (Mitzy *et al.* 2004). Chronic form of the disease can also have irregular RPE detachments and long-standing intraretinal cystoid cavities (Lida, 2003).

Since the condition is self-limited in the majority of patients, who usually retain excellent vision, most clinicians prefer to observe these patients for three months before considering any treatment options for spontaneous resolution. Infrequently, neurosensory retinal detachment persists and leads to RPE and photoreceptor damage leading to chronic form of the disease (Nasar et al. 2017).

The exact pathogenesis of the disease is not fully understood, but abnormalities in the inner choroidal layers, such as venous congestion, ischemia and/or inflammation, lead to choroidal hyper permeability, secondary RPE damage, and serous detachment of the neural retina. (Liegl and Ulbig, 2014 and Nicholson et al., 2013).

Despite the extensive advances that have been made in the treatment of various macular disorders, there is still no FDA-approved treatment for central serous chorioretinopathy (CSC) (Howard and Michael, 2014).

Multiple treatment strategies have been explored, examples are focal argon laser photocoagulation, photodynamic therapy with half dose verteporpin (PDT), micropulse diode laser, *H. pylori* eradication with anti-bacterial therapy, intravitreal anti-VEGF, antioxidants, and systemic pharmacologics (corticosteroids antagonists, Aspirin and acetazolamide), but no documented prepared practice pattern regarding systematic treatment approach for this condition (Howard and Michael, 2014).

The purpose of this study is to evaluate the efficacy of Anti-vegf in the treatment of chronic CSCR at a tertiary eye hospital.

Materials and method

The study adhered to the tenant of Helsinki declaration. It was a prospective interventional non randomized study, involving 12 eyes of 12 patients that presented with chronic CSCR. Patients were recruited into the study after informed consent and explanation of the procedure as they presents to vitreoretinal department between January to December 2018 at Tertiary Eye Institute and Hospital, Bangladesh.

Patients with history of chronic CSCR lasting for more than 3 months or recurrent attacks of 2 or more episodes and were not using any medical treatment or have failed to response to laser treatment during the last 3 months, OCT evidence of SRF or PED involving the fovea, and persistant focal leakage in FFA despite laser treatment were included in the study.

Diagnosis of chronic or recurrent CSCR was made based on history of decrease vision for more than 3 months or recurrent attacks of

visual loss supported by focal leakage on FFA, and neurosensory serous retinal detachment in fovea on OCT.

All patients underwent best corrected visual acuity (BCVA) measurement using the snellen visual acuity chart, dilated fundus examination with 90D volk lens using slit lamp (model- Carl Zeiss Meditec AG, Goeschwitzer Strasse 51-52, 07745 jena, Germany, SN 1185469), Intraocular pressure (Goldmann applanation tonometer),OCT (Model- Spec-TR-03536, Heidelberg Engineering, Germany, SN 58001819TW), and FFA (Topcorn Retinal Camera 75-1, Hasunuma-cho, Itabashi-ku, Tokyo, Japan, SN-948695) at baseline.

Ethical approval was obtained from ethical committee of the institution. After informed consent and explanation of the procedure, patients were treated with intravitreal injection of either Bevacizumab 1.25mg in 0.05ml (Avastin, made in Switzerland by F. Hoffmann-La Roche Ltd, DRA NO. 214-4255-2008) or Ranibizumab 0.5mg in 0.05ml, (Lucentis by Novartis pharma, Singapore Reg No; SIN 13411P). Injection was administered 4mm posterior to the limbus in the superior temporal quadrant under aseptic measures, eyes was padded for two hours and patients were discharge on maxifloxacin 0.5% eye drop, 6 hourly for 7 days.

More than one dose of injection was given to eyes that failed to have significant resolution one month after first injection.

Patients were followed up at 1 week, one month and three months after injection. At each follow up visit, BCVA, Intraocular pressure and dilated funduscopy were recorded while OCT was performed, pre- and 3 months post injections to determine the central macular thickness (CMT).

Data obtained was entered into Microsoft excel and analysed using the SPSS software version 20.0. One sample t test was used to compare pre and post injection variables while independent t test was used to compare outcomes between Avastin and Lucentis injection. P value of < 0.05 was considered significant using the 95% confidence interval.

Experimental design

The study included 12 eyes of 12 patients who had chronic CSCR and were treated with anti-VEGF. The age at time of treatment ranged between 28 to 55years (mean 39.7$\pm$ 7.93). Eleven patients (91.7%) were male and1 patient (8.3%) was female. Twenty five percent (25%) of CSCR was in right (3 eyes) while 75% (9 eyes) was in left. Both of them had history of visual loss ranging from 3 to 6 months duration. Three patients (25%) had history of smoking ranging for 2- 20 years. All patients had visual reduction for at least 3 months prior to treatment with one or more focal RPE leaks and PED on FFA. FFA leakage was observed in 8 eyes (66.7%) and PED in 4 eyes (33.3%). Ten eyes (83.3%) had intravitreal Avastin while 2 eyes (16.7%) had Lucentis injection. Ten eyes (83.3%) had single dose of injection while the remaining two eyes had 2 doses and 3 doses of injection respectively (1 eye (8.3%) 2 doses, 1 eye (8.3%) 3 doses).

Pretreatment mean VA was 6/18, (ranged 1/60 to 6/24), p= 0.339, CI= 0.205-0.473. Following treatment mean VA improved to 6/12 at one week, (range 6/60 to 6/6), p= 0.516, CI=0.363-0.669, to 6/24 at 0ne month, (ranged 6/24 to 6/12), p=0.635, CI= 0.473-0.798, to 6/12 at three months (ranged 6/60 to 6/6), p= 0.635, CI=0.438-0.832 with BCVA of 6/7.5 (range 6/12 to 6/5), this difference was statistically significant, p value < 0.005, t= 0.658, CI 0.4388-0.8329.

The pre- treatment means central macular thickness (CMT) was 407µm $\pm$ 130, (ranged from 268-675µm). Significant reduction in CMT was observed at three months following injection to 205 $\pm$ 63µm (ranged 96-301µm), this difference was also statistically significant, p < 0.005. There was no statistical significant changes in the mean pre and post treatment IOP (pre- IOP was 11.75mmHg, range 7.00- 17.00mmHg, p=0.397, while post treatment was 12.33mmHg, range 10.00 – 17.00mmHg, p=0.138).

RESULTS

Table 1 shows the visual outcome following intravitreal injection of anti-vascular endothelial growth factors (avastin or lucentis). It was observed that at 3 months post injection 91.6% (11 eyes) achieved normal to near normal VA and 100% of the eyes achieving normal visual following best correction with spectacle.

Table 1: Pre and Post Treatment Visual Outcome

Mean VA Pre / % eye	Post VA 1WK	Post VA 1 Month	Post VA 3 Months	BCVA
1/60(8.3%)	6/38(8.3%)	6/18(25%)	6/38(8.3%)	6/12(8.3%)
6/60(8.3%)	6/24(8.3%)	6/12(16.7%)	6/18(25%)	6/9 (41.7%)
6/38(16.7%)	6/18(25%)	6/9(33.3%)	6/12(8.3%)	6/6 (25%)
6/18(33.3%)	6/12(8.3%)	6/6(25%)	6/9(25%)	6/5 (25%)
6/12(16.7%)	6/9(41.7%)	_	6/6(33.3%)	_
6/9(16.7%)	6/6(8.3%)	_	_	_
Total (100%)	12 eyes (100%)	12 eyes (100%)	12 eyes (100%)	12 eyes (100%)

The figures in Brackets denotes number of eyes in percentage.

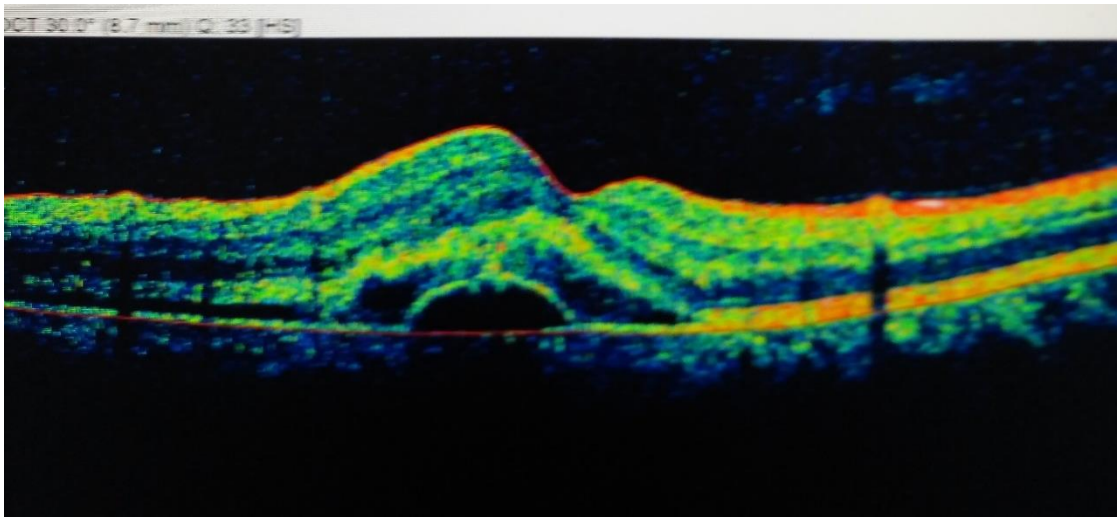
Table 2 compares visual outcome and central macular thickness between Avastin and Lucentis injection and it was observed that there was no statistically significance difference between the two drugs in relations to visual acuity improvement and reduction in central macular thickness, p value > 0.005.

Table 2: Comparison of Visual outcome between Avastin and Lucentis Injection

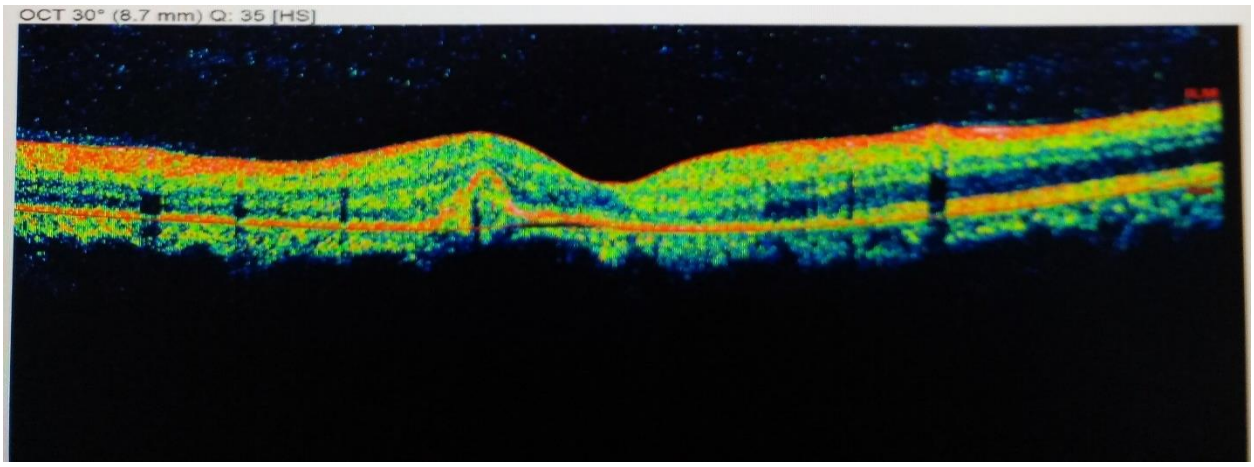
Type of antivegf	Pre VA	VA 1 WK	VA 1 Month	VA 3 Months	Pre CMT	Post CMT	Total (eyes)
Avastin	6/18	6/12	6/9.5	6/9.5	435.0	204.2	10(83.3%)
Lucentis	6/15	6/18	6/9	6/9	471.0	206.5	2(16.7%)
P- Value	0.280	0.086	0.163	0.460	0.028	0.998	12(100%)

All values are in mean

Photograph 1, depicts the pre-treatment OCT changes with significant increase in central macula thickness.



Photograph 1; Pre- treatment OCT



Photograph 2; Post- treatment OCT

Photograph 2: shows significant reduction in central macular thickness and resolution of subretinal fluid with subsequent re-attachment of neurosensory retina following treatment with intravitreal anti-vascular endothelial growth factor.

DISCUSSION

Central serous choreoretinopathy is characterized by neurosensory retinal detachment overlying areas of RPE atrophy and pigment mottling (Amr, 2015).
Various options of medical treatments have been attempted for this disorder but yet no single approved FDA treatment.

This study includes 12 eyes with chronic or recurrent CSCR, majority 91.7% of them were male and 8.3% female, similar findings was reported in two studies (Howard and Michael 2014 and Hanumunthadu 2018) that prevalence of Central serous chorioretinopathy (CSC) is higher in male than female (affects roughly 10 men and two women per 100,000 people), and they are often younger and middle aged working individuals with high visual demands as it was also observed in this study. All eyes were treated with intravitreal Avastin or lucentis and it was observed that 91.6% achieved normal to near normal vision 3 months after injection which increase to 100% following correction with spectacle.
Similar study by Mitzy *et al.* (2004) reported recovery or preservation of visual acuity, present in all 8 patients that were treated with intravitreal bevacizumab, as well as resolution or diminished of subretinal fluid by OCT and improved fluorescein leakage and choroidal hyperpermeability. They concluded that the mechanism by which intravitreal bevacizumab works in CSC is not known; however, it may be related to its ability to affect vascular permeability (Mitzy *et al.* 2004).

The pathophysiology is also poorly understood, but the advent of indocyanine green angiography presented evidence of choroidal involvement in the disease (Mitzy *et al.* 2004).

Schaal *et al.* (2009) findings observed to be lower than the findings in the in this study, is possible that some of the patients he treated have already developed complications prior to institution of treatment which made the percentage of visual improvement and reduction in CRT to be lower compared to 100% improvement that was observed in this study.
The percentage increase in vision is much higher in this study than in the previous study (Amr 2015), and this may be attributed to smaller sample size.

Also study by Kim and Lee (2013) reported significant increase in BCVA, decrease central macular thickness and resolution of neurosensory detachment in patients following intravitreal injection of ranibuzumab for treatment of acute CSCR.

CONCLUSION

Intravitreal injection of anti-vascular endothelial growth factors have been proved to be effective and may be considered as the goal standard method for treatment of recurrent and chronic central serous chorioretinopathy leading to complete resolution of SRF and recovery of normal vision.

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