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Effect of Intravitreal Ranibizumab in CSCR with Ink Blot Type of Leakage and NSD More Than 3 Months Duration

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Abstract

Objective: To evaluate the effect of intravitreal Ranibizumab in CSCR with ink blot type of leakage and NSD> 3 months duration. *Study Design:* Prospective Study. *Place and Duration of Study:* Base Hospital Delhi Cantt, New Delhi 110010 and Army College of Medical Sciences. *Methodology:* 20 eyes of 20 adult patients with CSCR were included in the prospective study of duration 08 weeks (02 months). Patients with bilateral CSCR, smoke stack and diffuse leakage of dye on FFA, choroidal neovascularization, treated cases of CSCR, history of thromboembolism, and intraocular inflammation were excluded from the study. After informed consent, all patients were given intravitreal injection of Ranibizumab. Best corrected visual acuity (BCVA) and central macular thickness (CMT) measurement with OCT and pattern of leaks were recorded on FFA at baseline and follow up at 02 and 08 weeks. The outcome measures were mainly BCVA status, CMT on OCT and changes in pattern of leaks on FFA pre and post Anti VEGF. *Results:* There were 15 (75%) males and 5 (25%) females. All cases were unilateral. Mean age was 39.09 ± 8.49 years. 11 (55%) eyes showed between 3to6 months involvement and 9 (45%) eyes showed more than 6 months involvement. All the cases were treated with single intravitreal dose of 0.5 mg Ranibizumab. After 08 weeks followup, It was observed that the CSCR with ink blot pattern showed moderate visual gain as well as 66.6% decrease in leak intensity on FFA ($p < 0.001$). In addition, mean CMT on OCT showed 70% ($p < 0.001$) decrease at 02 months follow up period. *Conclusion:* Intravitreal Ranibizumab injection was associated with improvement in BCVA, decrease in intensity as well as delay in onset of ink blot pattern of leaks on FFA and improvement in mean CMT as well as decreased NSD height on OCT in patients of CSCR.

Keywords: Central Serous Chorioretinopathy; Injection Ranibizumab; Optical Coherence Tomography, Intravitreal Injection.

Introduction

Central Serous Chorioretinopathy (CSCR), a condition which is characterized by an idiopathic serous neuro sensory 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 affecting the macula and 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].

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CSCR 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].

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]. It is associated with 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.1Recent 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.

Laser photocoagulation is applied to the site of fluorescein leakage. Although this has been proved to reduce the duration of the serous detachment, it has no effect on the final visual prognosis.

More recently, photodynamic therapy has been reported to be a more effective treatment with a lower complication rate for patients with subfoveal or juxtafoveal leaks.

Ranibizumab, being an antibody to vascular endothelial growth factor A (VEGF-A), as well as having anti-permeability properties therefore, may theoretically reverse the changes seen in CSCR.

This study was performed to evaluate the effect of intravitreal Ranibizumab in CSCR with ink blot type of leakage and NSD in more than 3 months duration

Methodology

The study was conducted after the approval of research/ethical committee of the hospital. This prospective study included 20 eyes of 20 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 3 months, while chronic CSCR persisted longer than 3 months.

Inclusion criteria were subfoveal fluid documented by OCT and active leak ink blot type documented by fundus fluorescein angiography. Exclusion criteria were bilateral cases of CSCR, case with smoke stack and diffuse leaks on FFA, choroidal neovascular membrane, prior treatment with laser photocoagulation, transpupillary thermotherapy or photodynamic therapy, history of thromboembolic events including stroke, transient ischaemic attacks, intraocular inflammation and history of previous treatment with intra vitreal anti-VEGF.

Patients fulfilling the inclusion criteria were selected from Retina Clinic of Base Hospital Delhi cantt. Informed consent was taken from all patients. Socio demographic 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) and optical coherence tomography (OCT) to document leak and retinal thickness respectively was performed at baseline examination and at each follow-up visit which was 4 weeks apart after intervention with Anti VEGF agent. Outcome measures were changes in pattern of leaks of ink blot variety on FFA and resolution of neurosensory detachment measured as CMT on OCT

All patients were instructed to instill E/D moxifloxacin 6 times one day prior to the intervention. In all patients, the intravitreal injection of Ranibizumab was given 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 inserted. Topical proparacaine was instilled and the preferred site of injection was the supero-nasal quadrant. Inj Ranibizumab 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 0.5 mg in 0.05 ml. Post-injection, a sterile cotton swab is placed at the site of injection to prevent reflux of vitreous or the drug. Topical antibiotic drop was instilled and a sterile pad placed few hours. Patients were instructed to apply topical antibiotic drops 4 times a day for 5 days. Post injection 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, at appx 1 week, at 04 weeks and at 08 weeks. Repeated OCT was performed after every 4 weeks. The FFA was repeated at 08 weeks duration to observe the changes in pattern of leaks and at times at 04 weeks too.

The data 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. Mean was calculated for BCVA and CMT. The qualitative data (gender) presented as frequency and percentage. P-value equal to or less than 0.05 was considered statistically significant.

Results

This study included 20 eyes of 20 patients with CSCR. There were 15 (75%) males and 5 (25%) females. Mean age was 39.09 ± 8.49 years. 11(55%) eyes showed less than 6 months involvement and 9(45%) eyes showed more than 6 months involvement however all were over 03 months duration. All patients presented with complaint of decreased vision. 7(23.3%) patients presented with positive scotoma and 8(26.7%) patients presented with metamorphopsia as their main presenting complaint.

On FFA, only patients with ink blot pattern leaks on FFA were included in study. Total number of Ink Blot leaks were 20. 9(45%) patients showed ink blot leaks on FFA in supero-nasal quadrant of posterior pole, 6(30%) in infero-nasal quadrant of posterior pole, 3(15%) in supero-temporal quadrant of posterior pole and 2(10%) in infero-temporal quadrant of posterior pole. 8 (40%) patients had one leak and 12(60%) had two or more than two leaks.

Mean CMT (central macular thickness) on OCT was 375 μm with a sub foveal neuro-sensory detachment.CMT decreased in 16 patients while in 04 it increased or remained the same. As far as BCVA is concerned it improved by 2 lines or more in 13 patients and in the remaining the either there was deterioration or the vision remained static. FFA picture of Ink Blot leaks showed significant decrease in intensity as well as size in 13 patients out of 20.

A gain of two lines was considered significant. Table 3 shows the various parameters of BCVA (snellen's converted to decimal), NSD on OCT and FFA picture base line and post inj Ranibizumab. Figure 4 shows the baseline as well as post inj Ranibizumab BCVA . Mean CMT on OCT was 375

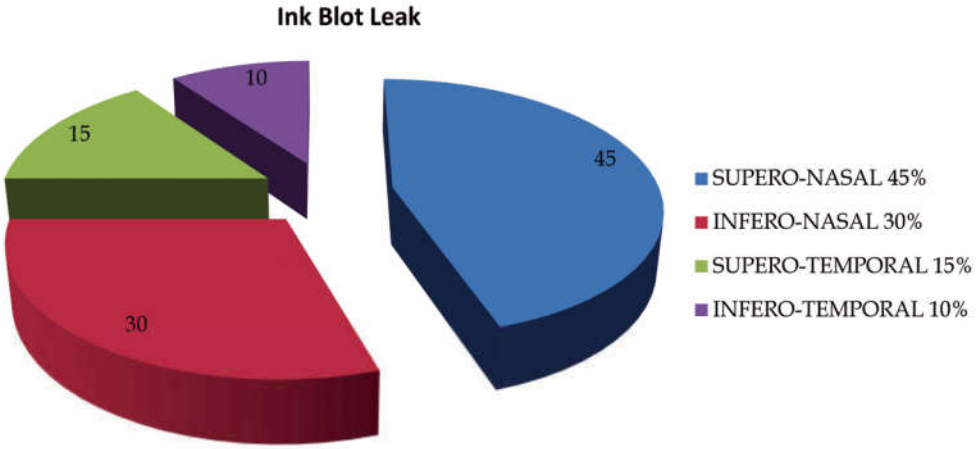

Fig. 1: Showing pattern of leak of ink blot type on Fluorescein Angiography (FA) in 20 eyes

Fig. 1: above shows different patterns of leaks of ink blot type encountered during FFA at time of presentation. Figure 2 shows the the typical FFA pattern while Figure 3 shows the resolution of NSD on OCT.

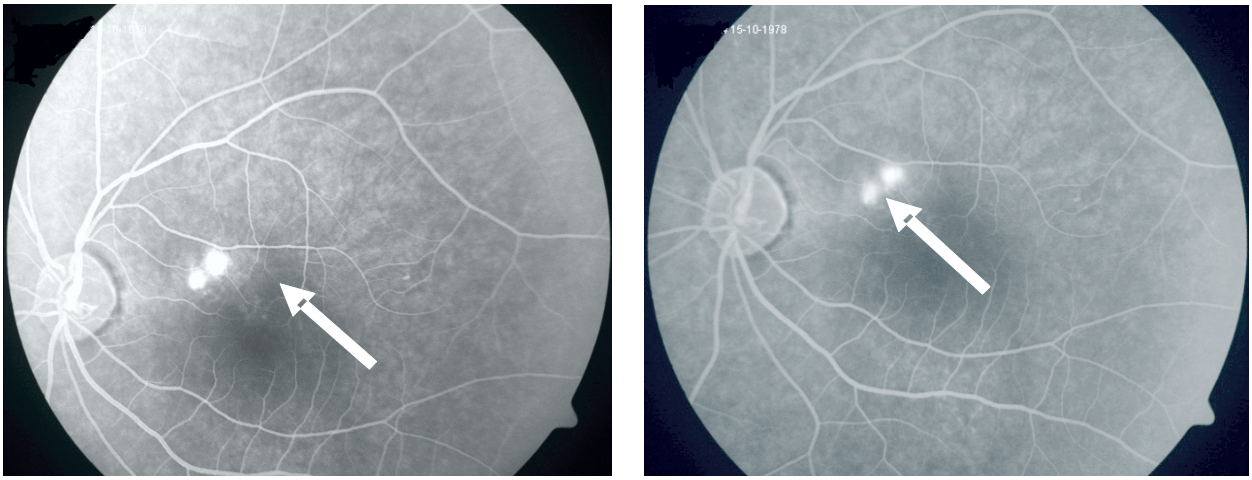

Fig. 2: Typical INK BLOT LEAK (marked by arrow head) in superonasal quadrant at 04:00 mins in a young Male patient on FFA& and shows improvement in area as well as decrease of leak in same patient at 5:05 mins, at 08 weeks follow up post Lucentis

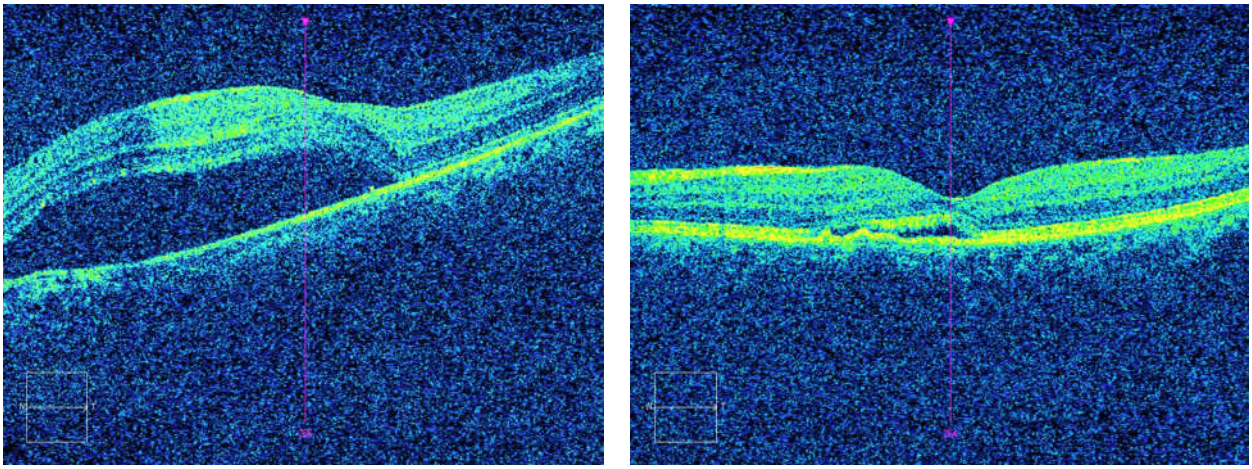

Fig. 3: CMT (central macular thickness) of 380 μm and post injection shows CMT of 250 μm of same patient at 08 weeks follow up post Inj Ranibizumab

Table 1: Baseline and Post Ranibizumab BCVA, CMT & Leaks on FFA

	Baseline	Post INJ Ranibizumab
BCVA (decimal)	0.8	0.5
MEAN CMT (um)	375	259
LEAKS on FFA	20 patients showed leaks	13 showed improvement in size and intensity

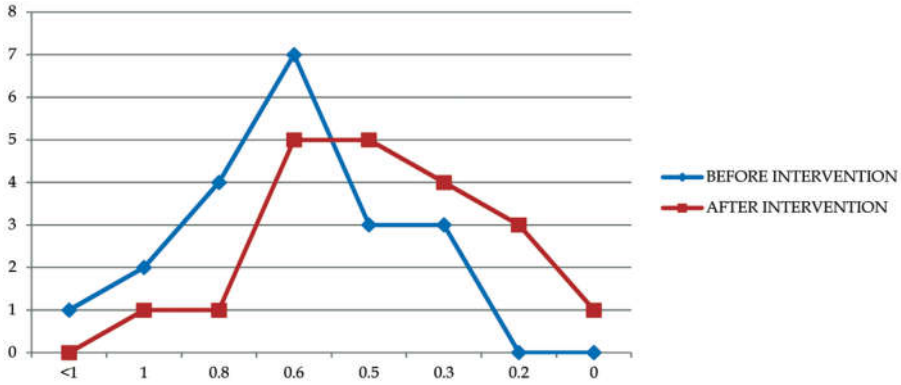

Fig. 4: Showing improvement in BCVA over a period of 02 months

um at baseline and decreased to 259 um. There was significant improvement in CMT of 70% ($p < 0.001$).

Half fluence PDT was kept as a rescue option for all patients of chronic CSCR who did not respond to Anti VEGF therapy.

Discussion

In this prospective study, the effect of intravitreal injection of Ranibizumab on ink blot leaks on FFA and CMT on OCT in 20 cases CSCR was evaluated. The precise pathophysiology of CSCR remains unclear. There is no standard treatment for it. Various medical treatments have been attempted to treat it, including acetazolamide, beta-blockers, vitamins and non-steroidal anti-inflammatory medicines.

There was reduction in intensity and time of onset of leak in all patterns observed during study after 02 months of single injection of Ranibizumab. The leaks which appeared in early phases on FFA before intervention were delayed and reduced in intensity as well as area. There was improvement in BCVA and CMT on OCT noted at all follow-up visits.

Median CMT at baseline was 375 µm and at 2 month was 259 µm. Difference between baseline and 2 month CMT was statistically significant, $p<0.001$. The BCVA showed improvement from 0.8 to 0.5 on decibel scale. These results show anatomic and functional improvement following intravitreal Ranibizumab injections, which suggest that VEGF may be involved in fluid leakage in patients with CSCR.

Ranibizumab is a recombinant humanized full-length monoclonal antibody that binds VEGF- A isoform. The Ranibizumab molecule can penetrate the retina and is transported into the RPE, the choroid and photoreceptors outer segments after intravitreal injection [19]. Intravitreal Ranibizumab has been utilized to treat ocular disorders, which are associated with neovascularization or vascular leakage as a result of an underlying disease. In this study, it was demonstrated that intravitreal Ranibizumab injection in patients with CSCR could bring resolution of subretinal fluid, which was accompanied by improvement in BCVA. The mechanism by which the intravitreal Ranibizumab 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 [1.20]. Therefore, theoretically reduced levels of VEGF may improve choroidal ischemia.

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].

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 Ranibizumab for CSCR patients in controlled randomized large number of patients with longer follow-up period are necessary to confirm the efficacy and safety of Ranibizumab and to determine the ideal protocol for this new promising treatment.

It would be helpful if a larger cohort be included in the study with longer follow up duration to assess the role of Intravitreal Ranibizumab, FFA changes & CMT on OCT in CSCR.

Conclusion

Intravitreal Ranibizumab injection was associated with improvement in ink blot leaks on FFA and CMT (central macular thickness) on OCT in chronic CSCR, in the majority of patients. All patients who had reduction in CMT did not necessarily manifest with visual improvement. It was observed that 65% improvement in BCVA, ink blot leaks reduction in 65% and decrease in CMT on OCT in 80% patients. These short-term results suggest that intravitreal Ranibizumab injection may constitute a promising therapeutic option in central serous chorioretinopathy.

References

1. J.Gaudreault, D. Fei,J.C.Beyer, A.Ryan, L. Rangell,V.Shiu,L.A.Damico,"Pharmacokinetics and

Retinal Distribution of Ranibizumab, a Humanized Antibody Fragment Directed against VEGF-A, Following Intravitreal Administration in Rabbits," *Retina*. 2007; 27(9): 1260-1266.

2. Haimovici R, Koh S, Gangnon DR, Lehrfeld T, Wellik S. Risk factors for central serous chorioretinopathy. *Ophthalmology* 2004.
3. Jampo lLM,Weinreb R, Yannuzzi L.involvement of corticosteroids and catecholamines in the pathogenesis of central serous chorioretinopathy: a rationale of new treatment strategies. *Ophthalmology*. 2002; 109: 1765-6.
4. GassJD, editor. Stereoscopic atlas of macular diseases: diagnosis and treatment. 4th ed. St.Louis:*Mosby*; 1997.
5. P. J. Rosenfeld, J. S. Heier, G.Hantsbarger and N. Shams, "Tolerability and Efficacy of Multiple Escalating Doses of Ranibizumab (Lucentis) for Neovascular Age-Related Macular Degeneration," *Ophthalmology*. 2006; 113(4): 623-632.
6. StephenL, Perkins, JudyE, Kim, JohnS. Pollack, PaulineT .Clinical characteristics of central serous chorioretinopathy in women.*Ophthalmology*. 2002; 109: 262-6.
7. Tewari HK, Gadia R, Kumar D, VenkateshP. Sympathetic & parasympathetic activity and reactivity in central serous chorioretinopathy. *InvestOphthalmolVisSci*. 2006; 47: 3474-8.
8. Guyer DR, Yannuzzi LA,Slakter JS.Digital indocyaninegreen video angiography of central serous chorioretinopathy. *ArchOphthalmol*. 1994; 112: 1057-62.
9. Prunte C, Flammer J. Choroidal capillary and venous congestion in central serous chorioretinopathy. *AmJOphthalmol*. 1996; 121: 26-34.
10. SchaalK B, Hoeh AE, Scheuerle A, Schuett F, Dithmar S. intravitreal Bevacizumab for treatment of chronic central serous chorioretinopathy. *EurJOphthalmol*. 2009; 19: 613-7.
11. JalkAE, Jbbour N, Avila MP. Pigment epithelium decompensation, clinical features and natural course.*Ophthalmology*. 1984; 91: 1544-8.
12. Taban M, Boyer DS, Thomas EL, Taban M. Chronic central serous chorioretinopathy: photodynamic therapy. *AmJOphthalmol*. 2004; 137: 1073-80.
13. Pikkel J, BeiranI, Ophir A, Miller B. Acetazolamide for central serousretinopathy. *Ophthalmology*. 2002; 109: 1723-5.
14. Bujarborua D, Chatterjee S, Choudhury A, Bori G, Sarma AK. Fluorescene angiographic features of asymptomatic eyes in central serous chorioretinopathy. *Retina*. 2005; 25: 422-9.
15. Burumcek E, Mudun A, Karacorlu S, Arslan MO.Laser photocoagulation for persistent central serous retinopathy: results of long-termfollow-up.*Ophthalmology*. 1997; 104: 616-22.
16. Battaglia ParodiM, DaPozzoS, RavalicoG. Photodynamictherapy in chronic central serous chorioretinopathy. *Retina*. 2003; 23: 235-7.
17. ColuccielloM. Choroidal neovascularization complicating photodynamictherapy for central serous retinopathy. *Retina*. 2006; 26: 239-42.
18. Lee PY, Kim KS, Lee WK. Severe choroidal ischemia following photodynamic therapy for pigment epithelial detachment and chronic central serous chorioretinopathy. *JpnJOphthalmol*. 2009; 53: 52-6.
19. Heiduschka P, Fietz H, HofmeisterS, SchultheissS, Mack AF, Peters S. Penetration of Bevacizumab through the retina after intravitreal injection in the monkey.*InvestOphthalmolVisSci*. 2007; 48: 2814-3.
20. Mazhar PS, Hanfi AN, Khan A. Angiogenes is and role of anti VEGF therapy. *PakJOphthalmol*. 2009; 25: 169-73.