Original Article

Visual Outcome Following Intra-vitreal Bevacizumab Injection in Neovascular Age-related Macular Degeneration

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Purpose: To assess the visual outcome after intravitreal Bevacizumab (Avastin) injection in eyes with choroidal neovascularization due to age–related macular degeneration (ARMD).

Material and Methods: This study was conducted in Isra Post-graduate Institute of Ophthalmology / Al-Ibrahim Eye Hospital, Karachi from February 2007 to January 2008. Forty – two eyes of 30 patients with neovascular ARMD received 3 intravitreal injections of Bevacizumab (1.25 mg / 0.05 ml) at 4-weeks interval and were followed up for 12 weeks after the initial treatment. Best – corrected visual acuity (BCVA), complete ophthalmic examination, and fluorescein angiography were done at baseline and on follow up visits. Main outcome measures were changes in Snellen's acuity, and change in angiographic characteristics of the lesions.

Results: The mean age ± SD of patients was 65.33 ± 8.32 years. The mean BCVA ± SD at baseline was 20/178 ± 4.6 lines on Snellen's quotations which improved to 20/142 ± 4.9 lines and 20/138 ± 4.9 lines at 4 and 12 weeks, respectively ($p<0.001$). Visual acuity (VA) improved or remained stable in thirty-seven (88%) eyes. Improvement of 1 or more lines was seen in 17 (40%) eyes. In majority of the patients, fluorescein angiography showed decreased leakage and regression of choroidal neovascularization (CNV). No patient had severe vision loss or significant ocular or systemic side effects.

Conclusion: Intravitreal Bevacizumab injection is effective in improving and stabilizing the visual acuity in patients with neovascular ARMD.

Age – related macular degeneration (ARMD) is the leading cause of irreversible blindness in patients over the age of 60 years in developed nations[1] and from a worldwide prospective, it has been estimated to cause 8.7% of total blindness[2]. The vast majority of severe vision loss occurs in patients with the exudative ('wet') form of the disease, which is caused by the growth of abnormal blood vessels under the central part of the retina[3]. Several angiogenic factors have been identified as likely stimuli for choroidal neovascularization (CNV). Among them, vascular endothelial growth factor (VEGF) has proven to be a major stimulus for the development of neovascularization. Not only does it promote the growth and survival of vascular endothelial cells, but also causes conformational changes of tight junctions of retinal vascular endothelial cells leading to increased vascular permeability[4].

A full – length monoclonal antibody that binds all isoforms of VEGF, Bevacizumab (Avastin, Genentech) was developed for the treatment of colorectal cancer. It has been used systemically as well as intravitreally for the treatment of choroidal neovascularization secondary to ARMD. Significant improvements in visual acuity and decreased retinal thickness on

optical coherence tomography (OCT) were seen. However, systemic administration of Bevacizumab has a small but significant risk of thromboembolism in patients with cancer[6]. Contrary, short-term effects of intravitreal Bevacizumab has shown to be well tolerated[7].

The purpose of this study is to investigate the short-term effect of intravitreal Bevacizumab on the visual acuity of patients with neovascular ARMD.

MATERIAL AND METHODS

This study was conducted in Isra Post-graduate Institute of Ophthalmology/Al-Ibrahim Eye Hospital, Karachi from February 2007 to January 2008. The design of the study was Quasi experimental with purposive sampling.

Forty two eyes of 30 patients with neovascular ARMD with clinical and angiographic evidence of CNV, age 50 years or older, ability to comply with the study protocol, and without any previous treatment for neovascular ARMD were enrolled for the study. Patients with a history of thromboembolic events within the past 3 months, presence of ocular conditions other than ARMD in the study eye that can affect the vision and/or safety, previous intraocular surgery within last 3 months and a history of fluorescein allergy were excluded from the study.

Patients were selected from Retina clinic at Al-Ibrahim eye hospital according to the inclusion and exclusion criteria. The off-label use of the drug and its potential risks and benefits were discussed extensively with all patients. All patients signed a comprehensive consent form before administration of bevacizumab. Baseline assessment included: best corrected visual acuity (BCVA) using Snellen's chart; biomicroscopic examination of anterior segment; intraocular pressure measurement with Goldman applanation tonometer; dilated fundus examination with +90 diopters lens and indirect ophthalmoscope; and colored photograph of the retina with the help of digital fundus camera. Fluorescein angiography was performed to identify the location and subtype of the lesions and to verify the presence of active choroidal neovascular leakage.

The Aga Khan University hospital pharmacy prepared 1.25mg (0.05 ml) injections in a 30-guage insulin syringe for each patient from commercially available 4 ml vial of Bevacizumab (25mg/ml) under aseptic techniques. The eyes to be treated were prepared with 5% povidone-iodine solution. Topical anesthesia was administered using proparacaine hydrochloride 1% ophthalmic drops (Alcaine, Alcon-Belgium). The site of the injection was measured with the help of a caliper. Using a 30 –gauge needle, 0.05ml of Bevacizumab (Avastin; Roche Basel, CH; Genentech, Inc, South San Francisco, California, USA) was injected intravitreally through the pars plana 3.5 mm from the limbus. Intravitreal injection of Bevacizumab was repeated in all eyes at four and eight weeks of follow-up.

After the injection, intraocular pressure was measured along with the slit lamp examination of anterior segment. Patients were instructed to use topical ciprofloxacin 0.3% (Ciloxan, Alcon-Belgium) four times a day for three days.

Patients were examined at one week and four weeks after each injection. At each visit, BCVA was measured along with the slit lamp examination of the anterior segment, intraocular pressure measurement and dilated fundus examination. Fluorescein fundus angiography was repeated at 12th week follow-up.

The main outcome measures were changes in Snellen's acuity, and change in angiographic characteristics of the lesions. Snellen's acuities were converted to the logarithm of the minimum angle of resolution (log MAR) to facilitate statistical analysis. The paired Student *t*-test was used to compare the mean visual acuity at week's four to 12 after treatment with mean baseline measurements. The level of statistical significance was set at $P< 0.05$ with a 95% confidence interval. Statistical analysis was done through statistical package for social sciences (SPSS) 10.0.

RESULTS

Forty-two eyes of 30 patients with choroidal neovascularization due to ARMD were treated with an intravitreal injection of Bevacizumab. There were 19 men and 11 women. The average age was 65.3 years, ranging between 54 to 83 years. Out of 30 patients, 12 (40%) patients of neovascular ARMD had active CNV component in both eyes while the rest of the patients had unilateral lesion.

Baseline characteristics of CNV lesions on fluorescein angiography showed predominantly classic lesion in 8(19%) eyes, minimally classic in 18(43%) eyes and occult in 16(38%) eyes (Fig. 1).

Thirty-one (74%) eyes had subfoveal location of CNV while the rest were juxtafoveal except for 2 (5%), which were extrafoveal (Fig. 2).

The mean BCVA ± SD at baseline was 20/178 ± 4.6 lines (LogMAR values= 0.95±0.46). Most significant improvement was seen at 4th and 8th week with mean BCVA ± SD of 20/142 ± 4.9 lines (LogMAR values = 0.85±0.49) and 20/138 ± 4.9 lines (LogMAR values= 0.84±0.49) [p < 0.0001], respectively (Tables 1, 2).

Overall, 20 eyes (47.6%) had stabilization of visual acuity at the final follow-up. This was defined as no gain or loss in visual acuity. Seventeen eyes (40.5%) had improvement in visual acuity (Fig. 3).

Mean IOP ± SD at baseline was 13.7± 3.3. Insignificant increase was seen in IOP after injecting Bevacizumab (P-value = 0.096) (Table 3).

After 12 weeks, 26 eyes (62%) showed regression of CNV along with reduced leakage on fluorescein angiogram while the rest had stabilization of CNV after three injections of Bevacizumab (Fig. 4).

DISCUSSION

There is increasing evidence that medications targeting vascular endothelial growth factor (VEGF) are effective in the treatment of choroidal neovascularization (CNV) associated with age-related macular degeneration (ARMD). Pegaptanib (Macugen), and more recently, Ranibizumab (Lucentis), have been subjected to large randomized clinical trials and have been proven safe and effective[8-10]. Bevacizumab (Avastin) is also an anti-VEGF drug which is Food and Drug Administration (FDA) approved for intravenous use in patients with colorectal cancer. In patients with ARMD, systemic administration of the drug has been shown to improve vision and decrease retinal thickness[11]. Preliminary laboratory studies have demonstrated the drug to be well tolerated as an intravitreal injection[12]. Avery et al [13]reported a retrospective case series of 81 eyes that had intravitreal Bevacizumab for CNV associated with ARMD, showed promising results and supports the continued exploration of Bevacizumab as a treatment option.

In this study, 30 patients were included. The gender distribution (63% males against 37% females) shows a male preponderance. This was in contrast with studies done in developed countries, where either female preponderance[13] or similar [14] distributions were seen. The difference in gender distribution in our study could be attributed to our rural social system where problems of female members of the family are usually overlooked. Additionally, they have less access to any kind of treatment and the least is spent on their health as compared to males however it could not be stated with certainty as the collection of socioeconomic status and locality data of these patients was not carried out.

The study found the baseline characteristics of CNV lesions on fluorescein angiography as predominantly classic lesion in 19%, minimally classic in 43% and occult in 38% of the eyes which was similar to a case series reported by Yoganathanet al[15].

Laic R et al[16] reported 74.8 years as mean age of patients in his study. However, in our study the average age of the patients was 65.4 years. The discrepancy could be due to the fact that most of the (74%) eyes had subfoveal location of CNV in the current study and subfoveal CNV causes more severe and more rapid loss of vision than juxtafoveal or extrafoveal lesions, as fovea has the highest concentration of photoreceptors which could get damaged early due to the sub-retinal CNV. Therefore, these patients presented at an earlier stage of the disease.

Results of this study support the hypothesis that there is significant improvement of visual acuity in eyes with choroidal neovascularization due to age-related macular degeneration after giving intravitreal Bevacizumab injection. Mean Snellen's acuity improved from 20/178 to 20/145 at 3 months after administrating 3 intravitreal Bevacizumab injections 1 month apart. Most significant improvement in mean visual acuity, 20/142 and 20/ 138, was seen at 4 and 8 weeks respectively with a slight but significant decline at 12th week follow-up. These results are less impressive than those of Rich et al[14] and Spade et al[17] that described ≥ 3 lines of vision improvement in 38.3% to 44% of treated patients, respectively. This may represent short-term variability of visual acuity measurements or differences in baseline features of the respective patient populations. More over Bari et al[18] reported the vitreous half-life of 1.25 mg of intravitreal Bevacizumab in a rabbit eye as 4.32 days. This also explains the necessity for frequent intravitreal injections of Bevacizumab in exudative ARMD to persistently neutralize the VEGF in these patients.

Smith and his collegues[19] combined the photodynamic therapy with intravitreal injection of Bevacizumab for the treatment of neovascular ARMD.

Table 1. Best corrected visual acuity pre and post bevacizumab injection, (n=42)

Best Corrected Visual Acuity (BCVA)	Mean ± SD	P-Value
Baseline	20/178± 4.6 lines	< 0.0001
First Week	20/158± 4.6 lines	
Fourth week	20/142± 4.9 lines	
Eighth week	20/138± 4.9 lines	
Twelfth week	20/145± 4.9 lines	

Table 2. Comparison of baseline best corrected visual acuity (BCVA) with each post-injection follow-up, (n=42)

Factors	BCVA	Mean ± S.D	Comparisons	p-value
I	Baseline	20/178± 4.6 lines		
II	After 1 week	20/158± 4.6 lines	I vs. II	0.058
III	After 4 weeks	20/142± 4.9 lines	I vs. III	0.001
IV	After 8 weeks	20/138± 4.9 lines	I vs. IV	0.003
V	After 12 weeks	20/145± 4.9 lines	I vs. V	0.029

Table 3. Comparison of intra ocular pressure pre and post bevacizumab injection, (n=42)

Best Corrected Visual Acuity (BCVA)	Mean ± SD	P-Value
Baseline	13.7± 3.3	0.096
First Week	14.1± 2.6	
Fourth week	14.9± 1.9	
Eighth week	14.1± 2	
Twelfth week	14.45± 2.3	

Seventy-three percent of patients showed improvement in visual acuity. Mean improvement in visual acuity of 1.73 lines in this study is similar to findings of other studies[13,20] in, which patients received Bevacizumab injection as monotherapy. However, they witnessed complete resolution of CNV in 65% of eyes after a single combination treatment while in this study 62% showed regression of CNV along with reduced leakage on fluorescein angiogram while the rest had stabilization of CNV after three injections of Bevacizumab. Only one case showed complete resolution of CNV component at 3 month. It was a small, (< ½ disc diameter) subfoveal and occult type of CNV in a 54 year old male.

In the current study, overall post treatment visual acuity improved in 40.5% of cases while it remained stable in 47.6% of cases that was comparable with other studies. Rich et al[14] reported visual acuity improvement in 44% of eyes at 3 month and Cleary et al[21] found improvement or stabilization of vision in 76.5% of cases at 6 months.

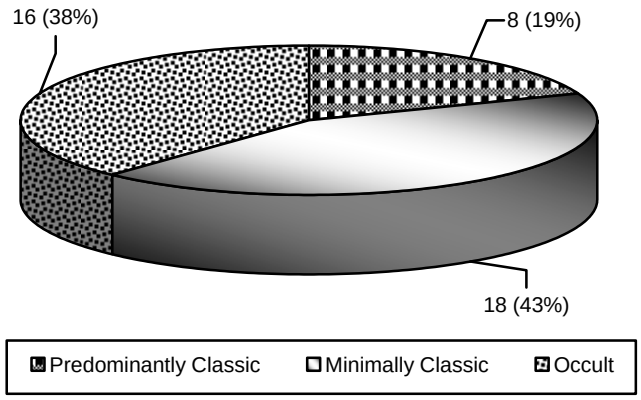

Fig. 1: Types of choroidal neovascular membrane on fundus fluorescein angiography (n = 42)

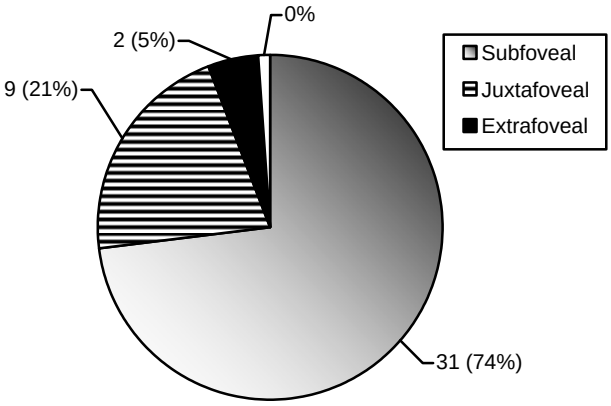

Fig. 2: Location of choriodal neovascular membrane on fundus fluorescein angiography (n = 42)

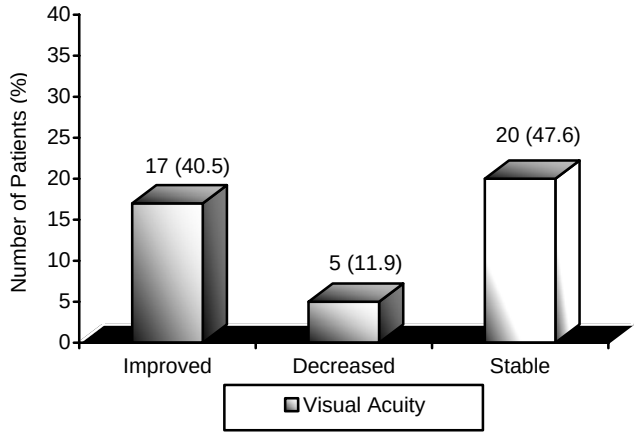

Fig. 3: Overall post-treatment visual acuity, (n = 42)

Theoretically, injecting any extra volume in the closed vitreous cavity can cause an increase in intraocular pressure. However, in this study we did not find any significant change in IOP pre and post injection. Similar results were also reported by Yoganathan and coworkers[15]. This could be due to the short half-life of intravitreal Bevacizumab as shown by Bari et al[18], who obtained data from 40 eyes of 20 rabbits showing a peak concentration of 400 µg/ml in the vitreous humor 1 day after the intravitreal injection of Bevacizumab. Vitreous concentrations of Bevacizumab declined steadily with a half-life of 4.32 days maintaining the concentrations of ≥ 10 µg/ ml for 30 days. Moreover, humans have a larger vitreous cavity then rabbits (4.5 ml and 1.5 ml respectively). In this study, after injecting intravitreal Bevacizumab, we recorded the IOP at 1st week and then at 4, 8 and 12 weeks. There might have been a transient rise in IOP during the first few days as shown by Fleckenstein et al [22] and Hollands et al[23] who reported a predictable volume related rise in IOP after injecting intravitreal Bevacizumab, which never occluded the central retinal artery and which spontaneously fell below 30 mmHg in all eyes within 15 minutes of injection.

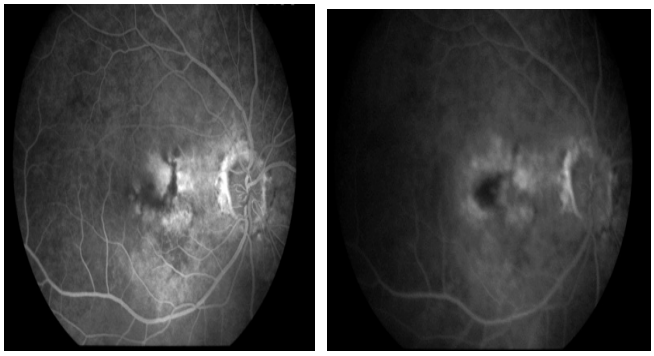

Fig. 4. Fluorescein angiographic changes in an eye with subfoveal occult choroidal neovascularization (CNV) due to age – related macular degeneration (ARMD) after three intravitreal injections of bevacizumab. Late – phase angiograms at baseline (left) and at 12 weeks of follow-up (right), showing considerable decrease in the leakage and size of the CNV.

The Bevacizumab preparation is unpreserved and contains no ingredients that are known to be toxic to the eye. Bevacizumab has been tested in rabbit eyes and no evidence of toxicity was seen by electro-retinogram (ERG) or visual evoked potential (VEP) testing[24]. These findings were consistent with those by Matura and associates[25], who demonstrated that no evidence of retinotoxocity noted in the short term use

of intravitreal bevacizumab in patients with neovascular ARMD. Adverse events observed during intravenous use of Bevacizumab (5mg/kg) for treating colorectal cancer include hypertension, impaired wound healing, hemorrhage, thromboembolic events, myocardial infarction, stroke and proteinuria[26]. Since, the intravitreal dose of Bevacizumab is approximately 1/400th that of the intravenous dose therefore the safety profile of intravitreal Bevacizumab appeared to be more favorable. In a study of Avery and associates[89] involving 79 patients, no significant systemic or ocular complications were noted. This finding was consistent with that of other investigators[17,14,15,19]. Similarly, in the present study intravitreal Bevacizumab at a dose of 1.25 mg (0.05 ml) appeared to be well tolerated by all patients. Systemic adverse events like hypertension, stroke, or myocardial infarction and ocular adverse events, like uveitis, raised IOP, endophthalmitis, vitreous hemorrhage or retinal detachment were not recorded. Few patients experienced a reduction in visual acuity which could be due to the disease progression rather than the drug toxicity.

The weaknesses of this study include absence of randomized controls, limited number of patients, nonstandard visual evaluation and short term follow-up. Lesion size and chronicity were not evaluated. Optical coherence tomography of these patients would have provided us with a better visualization of the retinal anatomy than fluorescein angiography. However, the OCT was unavailable in our set up and we could not subject our patients to an extra financial burden of going to a private setup. Nevertheless OCT is recognized as a superior tool to FFA in documenting anatomical outcome.

Furthermore, randomized trials should also compare intravitreal Bevacizumab with other available anti-VEGF agents, such as pegaptanib sodium and Ranibizumab because the much lower cost per dose of intravitreal Bevacizumab compared with that of pegaptanib and Ranibizumab, make it promising and cost effective treatment option for those who may not be able to afford the more expensive alternatives.

CONCLUSION

Intravitreal Bevacizumab injection is effective in improving and stabilizing the visual acuity in patients with neovascular ARMD. Large, randomized, controlled trial is warranted to evaluate the long term efficacy and safety of this treatment.

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REFERENCE

1. The Eye Diseases Prevalence Research Group. Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol. 2004; 122: 564-72.
2. **Resnikoff S, Pascolini D, Etya'ale D, et al.** Global data on visual impairment in the year 2002. Bull World Health Organ. 2004; 82: 844-51.
3. **Ambati J, Ambati BK, Yoo SH, et al.** Age-related macular degeneration: etiology, pathogenesis, and therapeutic strategies. Surv Ophthalmol. 2003; 48: 257–93.
4. **Otani A, Takagi H, Oh H, et al.** Vascular endothelial growth factor family and receptor expression in human choroidal neovascular membranes. Microvasc Res. 2002; 64: 162-9.
5. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials - TAP report 2. Arch Ophthalmol. 2001; 119: 198-207.
6. **Salesi N, Bossone G, Veltri E, et al.** Clinical experience with bevacizumab in colorectal cancer. Anticancer Res. 2005; 25: 3619-23.
7. **Lihteh Wu, Maria A, Martinez-Castellanos, et al.** 12 month safety of intravitreal injection of bevacizumab: results of the Pan- American Collaborative Retina Study Group (PACORES). Graefes Arch Clin Exp Ophthalmol. 2008; 246: 81-7.
8. **Gragoudas ES, Adamis AP, Cunningham ET Jr, et al.** VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group. Pegaptanib for neovascular age-related macular degeneration. N Engl J Med. 2004; 351: 2805–16.
9. **Rosenfeld PJ, Brown DM, Heier JS, et al.** Marina Study Group. Ranibizumab for neovascular age related macular degeneration. N Engl J Med. 2006; 355: 1419–31.
10. **Brown DM, Kaiser PK, Michels M, et al.** Anchor Study Group.Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med. 2006; 355: 1432-44.
11. **Michels S, Rosenfeld JR, Puliafito CA, et al.** Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration: twelve-week results of an uncontrolled open-label clinical study. Ophthalmology. 2005; 112: 1035–47.
12. **Manzano RP, Peyman GA, Khan P, et al.** Testing intravitreal toxicity of bevacizumab (Avastin). Retina. 2006; 26: 257–61.
13. **Avery RL, Pieramici DJ, Rabena MD, et al.** Intravitrealbevacizumab (Avastin) for neovascular age-related macular degeneration. Ophthalmology. 2006; 113: 363–72.
14. **Rich RM, Rosenfeld PJ, Puliafito CA, et al.** Short-term safety and efficacy of intravitrealbevacizumab (Avastin) for neovascular age-related macular degeneration. Retina 2006; 26: 495-511.
15. **Yoganathan P, Deramo VA, Lai JC, et al.** Visual improvement following intravitrealbevacizumab (Avastin) in exudative age-related macular degeneration. Retina. 2006; 26: 994-8.

16. **Lazic R, Gabric N.**Intravitreally administered bevacizumab (Avastin) in minimally classic and occult choroidal neovasculrization secondary to age – related macular degeneration. Graefes Arch Clin Exp Ophthalmol. 2007; 245: 68-73.
17. **Spaide RF, Laud K, Fine HF, et al.**Intravitrealbevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. Retina. 2006; 26: 383–90.
18. **Bakri SJ, Synder MR, Reid JM, et al.** Pharmacokinetics of intravitrealbevacizumab (Avastin). Ophthalmology. 2007; 114: 855-9.
19. **Smith BT, Dhalla MS, Shah GK, et al.** Intravitreal injection of bevacizumab combined with verteporfin photodynamic therapy for choroidal neovascularization in age-related macular degeneration. Retina. 2008; 28: 675-81.
20. **Chen CY, Wong TY, Heriot WJ.** Intravitrealbevacizumab (Avastin) for neovascular age – related macular degeneration: a short-term study. Am J Ophthalmol. 2007; 143: 510-2.
21. **Cleary CA, Jungkim S, Ravikumar K, et al.** Intravitrealbevacizumab in the treatment of neovascular age-related macular degeneration, 6- and 9-month results. Eye 2008; 22: 82-6.
22. **Falkenstein IA, Cheng L, Freeman WR.** Changes of intraocular pressure after intravitreal injection of bevacizumab (avastin). Retina. 2007; 27: 1044-7.
23. **Hollands H, Wong J, Bruen R, et al.** Short term intraocular pressure changes after intravitreal injection of bevacizumab. Can J Ophthalmol. 2007; 42: 807-11.
24. **Bakri SJ, Cameron JD, McCannel CA, et al.** Absence of histologic retinal toxicity of intravitrealbevacizumab in a rabbit model. Am J Ophthalmol. 2006; 142: 162–4.
25. **Maturi RK, BLeau LA, Wilson DL**. Electrophysiologic findings after intravitrealbevacizumab (Avastin) treatment. Retina. 2006; 26: 270-4.
26. **Hurwitz H, Fehrenbacher L, Novotny W, et al**. Bevacizumab plus irinotecan, fluorouracil and leucovorin for metastatic colorectal cancer. N Engl J Med 2004; 350: 2335-42.

Glaucoma

Considering the recent developments in imaging techniques and their applications to glaucoma, despite most of these still being research tools, the OCT is somewhat better than HRT and GDx as diagnostic help and has the most potential for long term detection of structural changes in glaucoma.

M Lateef Chaudhry

Editor-in-Chief