Original Article

Effectiveness of Intravitreal Bevacizumab in Various Ocular Diseases

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Purpose: To evaluate the efficacy of monthly intravitreal bevacizumab injections (1.25 mg/.05 ml) in improving or stabilizing visual outcomes measured by Snellen's visual acuity charts for diverse ocular diseases.

Material and Methods: This was a prospective hospital based study in which a total number of 108 eyes of 80 patients were included with various ocular diseases. Maximum three intravitreal bevacizumab injections 1.25mg in 0.05ml each was given over a period of 3 months and follow up for 06 months after the first injection was carried out. The criteria for improvement was a gain of at least one line on Snellen's visual acuity chart, compared to the baseline while stabilization was considered if the visual acuity was unchanged relative to the baseline.

Results: A total number of 108 eyes of 80 patients were included in the study. Males were 40 and females were also 40 with an age range of 32-70 years. They were subjected to intravitreal injection of bevacizumab. Ten eyes (62.5%) with neovascular age related macular degeneration (ARMD) showed improvement while visual acuity was stabilized in 06 eyes (37.5%). In diabetic macular edema (DME) 30 eyes (68.1%) showed improvement, 10 eyes (22.7%) were stabilized and in 04 eyes (9%) visual loss continued. In patients with proliferative diabetic retinopathy (PDR) with vitreous hemorrhage 30 eyes (93.7%) showed improvement while stabilization of visual acuity was noted in 02 eyes (6.2%). In central retinal venous occlusion (CRVO) 04 eyes (80%) showed improvement and stabilization occurred in 01 eye (20%). Out of the 08 eyes of branch retinal venous occlusion (BRVO) all eyes showed visual improvement (100%). All 03 eyes (100%) of myopic choroidal neovascular membrane (CNV) patients also showed improvement. No systemic side effects of the given treatment were observed.

Conclusion: The treatment with Bevacizumab is beneficial in improving and stabilizing visual acuity not only in neovascular ARMD but also in other chorioretinal vascular disorders.

Anti-VEGF therapy, has fast become a mainstay of managing diseases such as age-related macular degeneration and the indications for its use have increased considerably ever since.

The role of vascular endothelial growth factor in the growth of blood vessels was identified in the 1980s, and agents that could block the angiogenic cascade first came for cancer treatments in the early 1990s.[1]

After exhaustive research on the pathogenesis of abnormal blood vessels and exudation of fluid, investigators were convinced of the role of Anti-VEGF therapy to curb the effect of these abnormalities. First came Macugen (pegaptanib sodium, Eyetech/Pfizer) and later Avastin (bevacizumab, Genentech) followed by Lucentis (Ranibizumab, Genentech).[2]

The recent results of two studies; study of efficacy and safety of Ranibizumab injections in patients with macular edema secondary to Central retinal vein

occlusion (CRUISE) and study of efficacy and safety of Ranibizumab injections in patients with macular edema secondary to Branch retinal vein occlusion (BRAVO), indicated that anti-VEGF therapy is effective in reducing macular edema secondary to branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO). In those studies, patients experienced rapid vision gain, some within the first 12 to 24 hours after injection. Imaging with optical coherence tomography (OCT), indicated a higher degree of anatomical resolution of edema compared with placebo.

After the availability of the Anti-VEGF drugs and the encouraging results on the visual functions of the patient, some physicians are skeptic about the future role of photocoagulation treatment, as the gold standard therapy.[1]

Bevacizumab prevents VEGF from binding to its receptors and subsequently inhibits receptor signaling pathways.[3] Interestingly, studies using magnetic resonance imaging showed decreased microvascular permeability as early as 24 hours after anti-VEGF treatment.[4] Bevacizumab was first used off-label in 2005 for neo-vascular age related macular degeneration.[5]

The purpose of the study is to evaluate the efficacy of monthly intravitreal bevacizumab injections (1.25 mg/.05 ml) in improving or stabilizing visual outcomes; best corrected visual acuity (BCVA), as measured by snellen's visual acuity charts, for diverse ocular diseases.

MATERIAL AND METHODS

It was a hospital based, Quasi experimental and prospective study. It was conducted at Baqai Medical University and Taj Eye Hospital, Federal B Area, Karachi from 18th Feb. 2010 to 27th Feb. 2011.

A total number of 108 eyes from 80 patients were selected on the basis of non-probability, purposive sampling. Patients diagnosed with the following ocular diseases were included in the study. Neo-vascular AMD, classic / occult CNV confirmed on fundus fluorescein angiography (FFA) and without macular scarring, clinically significant diabetic macular edema, proliferative diabetic retinopathy with vitreous hemorrhage, BRVO and CRVO (non-ischemic) with macular edema and myopic choroidal neovascular membrane (CNV) on FFA.

All patients with the above mentioned entities, but who had received prior treatments with other modalities like laser photocoagulation, photodynamic therapy (PDT), intravitreal Ranibizumab, intravitreal or posterior sub tenon triamcinolone, were excluded from the study.

Pre-operatively detailed history was taken, visual acuity was measured using snellen's acuity chart, complete anterior segment and posterior segment examination was done using slit lamp, +90D lens, indirect ophthalmoscopy and intraocular pressure (IOP) was measured using Goldman applanation tonometer. Fundus Fluorescein Angiography, Optical Coherence Tomography and B-scan ultrasound examinations were ordered where necessary.

Patients were informed beforehand about the off-label status of the drug, risks and benefits of treatment were discussed and informed consent was taken on Avastin (bevacizumab) specific consent forms.

All the patients included in the study received intravitreal bevacizumab 1.25mg in 0.05ml dispensed by a well reputed pharmacy of the city and given by the same surgeon. Pre- operative topical antibiotic moxifloxacin QID started 03 days before. Tropicamide and topical anesthetic proparacaine were started ½ hour before injection and repeated as necessary. All the injections were given in the operating room (OR), with strict sterile technique.

Patients were advised to continue pre-operative antibiotic drops for 07 days more after the intravitreal injection. Follow up was scheduled after 1 week, 4 weeks and every month till the end of follow up at 6 months. Follow up visits included checking visual acuity by snellen's chart and complete ocular examination. The primary end point of the treatment was functional or symptomatic rather than anatomic i.e. a change in best corrected visual acuity from baseline over 06 months. The maximum number of injections given was three for each eye and they were given four weeks apart.

The criteria for improvement was a gain of at least one line on snellen's visual acuity chart , compared to the baseline while stabilization was considered if the visual acuity on the snellen's chart was unchanged relative to the baseline.

RESULTS

A total number of 108 eyes of 80 patients 40 males and 40 females with an age range of 32-70 years were subjected to intravitreal injection of bevacizumab even in table 1.

Table 1: Patient's characteristics

Age Range	32 - 70 Years
Males	40
Females	40
No. of patients	80
No. of eyes	108
Duration of study	1 Years
Average follow up	6 Months

Sixteen patients (20%) had neovascular AMD, 26 patients (32%) had DME, PDR with vitreous hemorrhage was noticed in 24 patients (30%), 4 patients (05%) had CRVO, 8 patients (10%) had BRVO and 2 patients (2.5%) with myopic CNV were included in the study.

Out of the total 108 eyes, 16 eyes (14.8%) had neovascular age related macular degeneration, 44 eyes (40.7%) diabetic macular edema, 32 eyes (29.6%) proliferative diabetic retinopathy, 05 eyes (4.6%) with central retinal vein occlusion, 08 eyes (7.4%) branch retinal vein occlusion and 03 eyes (2.7%) had myopic CNV.

Ten eyes (62.5%) with neovascular AMD showed improvement while visual acuity was stabilized in 06 eyes (37.5%). 30 eyes (68.1%) with DME showed improvement, 10 eyes (22.7%) were stabilized and in 04 eyes (9%) with DME visual loss continued. In patients with PDR with vitreous hemorrhage 30 eyes (93.7%) showed improvement while stabilization of visual acuity was noted in 02 eyes (6.2%). In CRVO patients 04 eyes (80%) showed improvement and stabilization occurred in 01 eye (20%). Out of the 08 eyes of BRVO patients all showed visual improvement (100%). All 03 eyes (100%) of Myopic CNV patients also showed improvement. All of the preinjection visual acuities are given in table 2. Gradual improvement in visual acuities of all the diseases after one month, then 3rd month and at 6th month post injection are given in table 3, 4 and 5 respectively.

No systemic side effects of the given treatment were observed.

However amongst the local side effects sub-conjunctival hemorrhage was the most frequent; occurred in 05 eyes (4.5%), traumatic corneal abrasion in 01 eye (0.9%). Complications like endophthalmitis, retinal detachment or traumatic cataracts were not seen in any case.

DISCUSSION

The discovery of Anti-Angiogenic agents and its clinical application has opened new avenues for the treatment of retinal vascular disorders. The first anti-angiogenic agent to be approved by the US Food and Drug Administration (FDA), bevacizumab, was originally developed to inhibit tumorigenisis. Bevacizumab is used off-label intravitreal to treat ocular diseases with high VEGF levels, such as choroidal neovascularization (CNV), Proliferative diabetic retinopathy, diabetic maculopathy and retinal vein occlusion.

VEGF, also known as VEGF-A or vascular permeability factor (VPF), was first identified in 1989 by Napoleon Ferrara[6]. Numerous effects on endothelial cells were found when VEGF was inhibited and without it endothelial cells in immature vessels could not survive. Endothelial cells were unable to grow and proliferate.

Increased vitreous VEGF levels were found in diabetic retinopathy, diabetic maculopathy, and retinal vein occlusions. This led to the development of a therapeutic armamentarium targeted at selective inhibition of VEGF with antibodies, fragments of antibodies and aptamers. The first designed for ocular use, pegaptanib and Ranibizumab demonstrated success in clinical trials for neovascular age-related macular degeneration.

Despite a large full length antibody, bevacizumab demonstrated full retinal penetration[7]. No evidence of a toxic effect was observed in patients treated with 1.25mg of bevacizumab for exudative AMD measured by full field and multifocal ERG[8].

Neovascular AMD is the most common indication for intravitreal bevacizumab. Publications regarding intravitreal bevacizumab for the treatment of exudative AMD include six prospective studies,[9-13] one uncontrolled randomized trial,[14] nine retrospective studies, and uncontrolled case series. The majority of the papers showed mean improvement in visual acuity and a reduction in macular thickness after intravitreal bevacizumab.

Avery RI, et al,[15] studied 79 patients with a diagnosis of exudative AMD, affected eyes were injected monthly with 1.25mg of intravitreal bevacizumab until there was no sign of CNV. They

Table 2: Baseline visual acuities.

Baseline Visual Acuity	AMD No. of Eyes	DME No. of Eyes	PDR No. of Eyes	CRVO No. of Eyes	BRVO No. of Eyes	Myopic CNV No. of Eyes
FC	–	–	08	–	–	–
3/60	–	04	–	–	–	–
6/60	10	10	04	–	02	–
6/36	–	02	06	01	–	–
6/24	02	06	06	–	04	03
6/18	04	08	02	04	02	–
6/12	–	06	–	–	–	–
6/9	–	08	06	–	–	–
6/6	–	–	–	–	–	–

Table 3: Visual outcomes of IVB: post injection improvement at 01 months.

Post Injection Visual Acuity	AMD No. of Eyes	DME No. of Eyes	PDR No. of Eyes	CRVO No. of Eyes	BRVO No. of Eyes	Myopic CNV No. of Eyes
6/6	01	04	01	–	–	–
6/9	–	–	05	02	01	01
6/12	01	07	02	01	02	–
6/18	02	08	04	01	01	01
6/24	04	09	04	–	02	01
6/36	02	04	06	01	02	–
6/60	06	12	10	–	–	–

Table 4: Visual outcomes of IVB: post injection improvement at 03 months.

Post Injection Visual Acuity	AMD No. of Eyes	DME No. of Eyes	PDR No. of Eyes	CRVO No. of Eyes	BRVO No. of Eyes	Myopic CNV No. of Eyes
6/6	01	07	02	–	04	–
6/9	–	02	04	01	02	01
6/12	03	06	–	02	01	01
6/18	02	01	06	02	01	01
6/24	01	07	04	–	–	–
6/36	04	09	06	–	–	–
6/60	05	12	10	–	–	–

Table 5: Visual outcomes of IVB: post injection improvement at 06 months.

Post Injection Visual Acuity	AMD No. of Eyes	DME No. of Eyes	PDR No. of Eyes	CRVO No. of Eyes	BRVO No. of Eyes	Myopic CNV No. of Eyes
6/6	02	10	04	–	04	01
6/9	–	04	06	02	–	02
6/12	02	08	06	02	02	–
6/18	04	02	06	01	02	–
6/24	–	10	04	–	–	–
6/36	04	04	–	–	–	–
6/60	04	06	06	–	–	–

were followed for eight weeks and showed an improvement in mean visual acuity from 20/200 to 20/80, however an average of 3.5 intravitreal injections were required.

The results of our study are comparable except that out of the 108 eyes 16 eyes(15%), were diagnosed with neovascular AMD, our follow up was however longer (24 wks), improvement in mean visual acuity from 6/60 to 6/12 was noted in 62.5% of the eyes.

In central and branch retinal vein occlusions, macular edema is often treated with intravitreal bevacizumab. Grid pattern laser photocoagulation was the first widely accepted treatment.[16] This has been the standard treatment and has shown benefit in selected cases of branch retinal venous occlusion (BRVO).[17] intravitreal triamcinolone acetonide has also been used to treat BRVO, with several studies showing an improvement in visual acuity and decreased macular thickness assessed by OCT. As VEGF levels are elevated in patients with retinal vein occlusions[18] .However the side effects of triamcinolone including cataract formation and elevated intraocular pressure are much less common with anti VEGF.[18]

In a study conducted by Rabena M, et al, intravitreal bevacizumab in the treatment of macular edema secondary to branch retinal vein occlusion.[19] 27 patients with BRVO who received intravitreal Bevacizumab, visual acuity improved from 20/200 at baseline to 20/100 at three months. In our study of 08 eyes with macular edema secondary to BRVO, 6/6 vision was noted in 4 eyes (50%), 6/12 in 02 eyes (25%) and 6/18 in 02 eyes (25%), at the end of six months follow up.

In a study by Iturralde D, et al, intravitreal bevacizumab treatment of macular edema in central retinal vein occlusion, a short term study, 16 eyes with CRVO during a mean follow-up of three months, mean visual acuity improved from 20/600 to 20/138 at month three[20]. Out of the 05 eyes with CRVO in our study, visual acuity improved to 6/9 in 02 eyes(40%), 6/12 in 02 eyes (40%) and 6/18 in one eye (20%).

Intravitreal bevacizumab in diabetic retinopathy was first used in patients with advanced proliferative diabetic retinopathy with vitreous hemorrhage that obscured the view for panretinal photocoagulation.[21]

In a prospective study of patients with proliferative diabetic retinopathy treated with intravitreal injections of bevacizumab, Jorge R Costa RA, et al, found a rapid regression of actively leaking neovascularization, as well as significant improvement in mean visual acuity from 20/160 to 20/125 at three months follow up.[22] In this study, out of the 32 eyes with advanced proliferative diabetic retinopathy with vitreous hemorrhage, 6/6 vision was achieved in 04 eyes (12.5%), 6/9 in 06 eyes (18.7%), 6/12 in 06 eyes (18.7%), 6/18 in 06 eyes (18.7%), 6/24 in 04 eyes (12.5%) and 6/60 in 06 eyes (18.7%), at the end of 06 months of follow up.

The rationale for the use of a VEGF inhibitor in the treatment of Diabetic macular edema is strong, Funatsu and colleagues[23] found elevated levels of VEGF in the aqueous humor in eyes of patients with Diabetic macular edema.

In a non-comparative case series, Haritoglou C, et al[24] 51 patients with diffuse macular edema, refractory to other treatments were studied. OCT measurements showed central retinal thickness decreased signify-cantly from 501µm to 416µm at six weeks and 377µm

at 12 weeks follow up. Improvement in visual acuity of one line was reported at six weeks follow up.

In this prospective study, out of 44 patients with diabetic macular edema, 30 patients showed significant improvement (68.1%), however, 4 patients (9.09%), continued to show deteriorating visual acuity, all these patients had extensive hard exudates at macula. It is comparable to a local study which also showed significant improvement in visual acuity in patients with diabetic macular edema after intravitreal Avastin.[25] In these cases OCT of the macula was done to rule out vitreo- macular traction (VMT) component to the macular edema, however no such traction was noted in any of the case. These refractory cases may represent tachyphylaxis; however lipid profile was also deranged in all these cases. These were scheduled for combination treatment with bevacizumab and laser photocoagulation. Physician's help was also needed to manage the lipid derangement.

Intravitreal bevacizumab has been used in cases of CNV secondary to high myopia. Initially, the intravitreal bevacizumab dose was 1.25mg, and was reserved for cases of progression of CNV despite treatment with PDT, with or without intravitreal triamcinolone.[26] Initial results was positive, showing CNV regression as well as visual acuity improvement. In our study all the 03 patients (100%) with myopic CNV, showed an improvement in the visual acuity.

The basic limitation of our study was the non availability of the ETDRS (Early treatment diabetic retinopathy study) vision screening charts. That's why the visual acuity was measured on snellen's acuity charts. Other limitation was financial restraints which discouraged us to follow the progression of macular thickness by periodic OCT scans. Serial OCT revealed decrease in central macular thickness to normal or near – normal levels in eyes with choroidal neovascularization (CNV) secondary to age – related macular degeneration (AMD).[27]

CONCLUSION

The central role of VEGF in chorio-retinal vascular disorders is now well established. Results of our study conclude that the treatment with Bevacizumab is beneficial in improving and stabilizing visual acuity not only in neovascular ARMD but also in other chorioretinal vascular disorders. It is less expensive as compared to Ranibizumab. The findings of this important study will cut down the cost of treatment.

Standardized guidelines are needed for the commencement and conclusion of the treatment sessions, dosing regimens, frequency of treatment sessions and protocols of combination treatments for each ocular condition.

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