ORIGINAL ARTICLE

INTRAVITREAL BEVACIZUMAB: INDICATIONS AND COMPLICATIONS

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Background: Bevacizmab is still an unlicensed drug for intraocular use in spite of the fact that it has shown comparable efficacy to other anti-vascular endothelial growth factors (anti-VEGF) medications in some large sample randomized control trails. Although repackaged bevacizumab has got safety concerns but its use is growing because of easy availability and low cost. Our study focuses on the diverse and growing indications of intravitreal bevacizumab (IVB) and its ocular complications in our geographical setting. **Method**: This interventional case series was carried out at my private practice in Said Anwar Medical Complex, Dabgari, Peshawar, from January 2008 to July 2015. Total of 6107 injections were given to 4352 eyes. Intravitreal bevacizumab was injected in proper operating room setting. Bevacizumab injections were prepared from same vial by multiple withdrawals taking care of aseptic precautions. Follow up was done at 1 week and 20 days and adverse effects were noted. **Results:** Diabetic macular oedema (36%), central retinal vein occlusion (17.6%) and branched retinal vein occlusion (11%) were the top three indications of IVB. Other common indications were proliferative diabetic retinopathy (9.6%), neo-vascular glaucoma (5.9%), proliferative diabetic retinopathy with vitreous bleed (4.4%), proliferative diabetic retinopathy with tractional retinal detachment (3.7%), neo-vascular age related macular degeneration (2.9%), central serous retinopathy (1.48%) and Eale's disease (1.48%). Endohthalmitis occurred in 3 eyes (0.069%) while retinal detachment was found in only 2 eyes (0.046%).**Conclusion:** Common indications of bevacizumab are diabetic macular oedema, central retinal vein occlusion and branched retinal vein occlusion. Complications like endophthalmitis and retinal detachment are rare.

Keywords: Intravitreal bevacizumab, Avastin, Endophthalmitis,

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INTRODUCTION

The introduction of anti-vascular endothelial growth factors (anti-VEGF) into ophthalmic care has revolutionized the management of various posterior segment diseases.[1] Pegaptanib, ranibizumab and aflibercept are all FDA approved drugs for the treatment of neo-vascular age related macular degeneration (ARMD).[2] Recently ranibizumab, aflibercept have also been approved for diabetic macular oedema (DME)and for retinal vein occlusion (RVO) related macular edema.[3,4] Bevacizumab on the other hand is FDA approved only for colorectal carcinoma but because of low cost and easy availability, its off label use in eye care is more than the licensed anti-VEGF drugs especially in the developing countries.[5] Many large sample prospective control trails have shown that bevacizumab has equal efficacy to ranibizumab in ARMD and DME.[6,7] Macular oedema secondary to retinal vein occlusion is another pathology where IVB has shown great promise.[8] Because of almost similar mechanism of action of bevacizumab to other anti-VEGFs, it is being increasingly used and found to be effective in many of the posterior segment diseases characterized by neo-vascularization and/or macular edema.[9]

Bevacizumab still remains an unlicensed ophthalmic medication and debate continues with regard to IVB safety in clinical practice.[10] Intravitreal bevacizumab is used either by multiple withdrawals from same bevacizumab vials by ophthalmologist or by preparing single use IVB syringes from bevacizmab vial by compounding pharmacy.[10] Such repackaging of medication has got safety issues due to possible risk of microbial contamination.[11]

Our study focuses on the diverse and growing indications of IVB and its ocular complications in our geographical setting. To our knowledge such large sample study has not been conducted so far in Pakistan on similar topic.

MATERIAL AND METHODS

Total of 4352 eyes of both genders were included in the study. The decision of IVB was made after thorough ophthalmic examination which included measurement of best corrected visual acuity and thorough anterior and posterior segment eye examination on slit lamp. Gonioscopy was done in selected cases. Ocular ultrasound was performed in cases with no visibility of posterior segment details. Cases with active surface infections like conjunctivitis, dacryocystitis and severe blephritis were deferred till resolution of these conditions.

Patients were called for intravitreal injections on pre-scheduled date. An informed verbal consent was taken from the patients. Patients were specifically informed about the off-label use of bevacizumab and its comparable efficacy to ranibizumab (only other available licensed drug, Lucentis® in Pakistan by Novartis, at the time of our study). They were also told about cost difference between these options. After dilating the pupil with tropicamide 1% eye drops patients were taken to operating room. Periocular skin, eye lashes, upper and lower lids were carefully swabbed with povidone iodine 10%. Affected eyes were anaesthetized with proparacaine0.5% and 1 drop of povidone iodine 5% was instilled into the conjunctival cul-de-sac. Surgeon wearing sterile gloves opened the lids with sterile speculum. Another drop of proparacaine 0.5% was instilled and patients were asked to look supeonasally to expose infero-temporal area of the globe. Bevacizumab0.05 ml was taken aseptically from the vial into 30G insulin syringe and was injected infero-temporally (3.5mm from limbus in aphakic/pseudophakic eyes and 4mm in phakic eyes). Needle was withdrawn and injection site was pressed with cotton tipped applicator to stop IVB regurgitation. Topical chloramphenicol eye drop was instilled at the end of the procedure. Initially we checked IOP in 200 eyes, 30 minutes after injection. Later this practice was stopped as no case of raised IOP was detected with given dose of IVB.

Patients were advised chloramphenicol eye drops four times a day for 3 days. Intravitreal bevacizumab injections for the other patients booked for that day were prepared by withdrawing from the same bevacizumab vial. Patients were followed at 1 week and 20 days to check for any ocular complications.

SPSS version 17 was used for data analysis. Data was presented in simple tabulated form.

RESULTS

Total of 6107 injections were given to 4352 eyes. Total of 3570 patients were included. Male were 2236(62.6%) and 1334 (37.4%) were female. Mean age was 43 years (age range 5–81 years). Bilateral disease was found in 1755 (40.3%) patients while 2597 (59.7%) had unilateral diseases. Common indications of IVB are summarized in table-1. Table-2 has summed up relatively rare indications of IVB. All the 6 patients (12 eyes) with RP associated CME received 3, monthly injections in each eye and showed no visual improvement. Similarly 5 patients (10 eyes) of congenital retinoschisis with bilateral CME showed no visual improvement after 3, monthly bevacizumab injections in each eye. Five patients (10 eyes) of bilateral PFT received 5, monthly injections in each eye with no visual benefit at the end. One patient with post buckling CME received 5, monthly injections which were initiated 6 months post-operatively showed no visual improvement. Three patients had post cataract surgery CME. Two eyes received 5, monthly injections while 1 eye received 6, monthly injections of bevacizumab and all eyes showed visual improvement on Snellen's chart. Complications of IVB are shown in table-3.No other ocular complications were found beside them.

Table-1: Common indications of intravitreal bevacizumab

Indications	n	%
Diabetic macula oedema	1568	36
Central retinal vein occlusion	768	17.64
Branch retinal vein occlusion	480	11
Proliferative diabetic retinopathy (PDR)	416	9.6
Neo-vascular glaucoma	256	5.9
PDR with vitreous bleed	192	4.4
PDR+Tractional retinal detachment	160	3.7
Neo-vascular ARMD	128	2.9
Central serous retinopathy	64	1.48
Eale's Disease	64	1.48
Miscellaneous	256	5.9
Total	4352	100

Table-2: Rare Indications of intravitreal bevacizumab

Indications	n	%
Cystoid macular oedema(Uveitis)	52	20.3
Parafovealtalangeactasia	50	19.5
Choroidal neo-vascularization (Angiod Streak)	42	16.4
Cystoid macular oedema (Retinitis pigmentosa,)	36	14
Cystoid macular oedema (Congenital Retinoschisis)	30	11.7
Coats Disease	22	8.6
Cystoid macular oedema (Post Cataract Surgery)	16	6.3
Cystoid macular oedema (Post Buckling)	5	2
Choroidal neo-vascularization (Myopia)	3	1.2

Table-3: Complications of Intravitreal Bevacizumab

Complications	n	%
Subconjunctival Bleed	743	17.1
Corneal Epithelial Defects	22	0.51
Endophthalmitis	3	0.069
Retinal Detachment	2	0.046

DISCUSSION

In our study DME stands out to be the top most indication of IVB. This is quite logical and evident from the fact that nearly one in 20 people on the planet has diabetes mellitus and DME being the most common cause of visual impairment in diabetics.[12] Moreover, related indications like PDR, PDR with vitreous bleed, PDR and TRD makes diabetic eye disease as most common indication for IVB. This again is in agreement with literature published everywhere.[13] In diabetic patients with PDR and vitreous bleed and or TRD bevacizumab was injected

to reduce risk of further bleed during vitrectomy and in post-operative period. It is now a well-accepted indication of anti-VEGF worldwide and studies have shown very promising results.[14] In patients with PDR the definitive treatment of pan retinal photocoagulation (PRP) was given and additionally bevacizumab was injected to reduce the risk of imminent bleed from neo-vessels during PRP sessions and subsequent follow up. At present the role of anti VEGF therapy for PDR either as primary treatment or adjunct to laser is less clear but answer is being sought in an ongoing trail by DRCRnet.[15]

Macular oedema secondary to retinal vein occlusion, i.e., CRVO and BRVO constitute second most common indication for IVB in our study. Worldwide retinal vein occlusion is the most common retinal vascular disease after diabetic retinopathy.[16] Although ranibizumab and recently aflibercept have been licensed for use in RVO related macular edema but bevacizumab, despite showing promising results in many large sample studies, is still being used as an off label drug.[3,4]

Neo-vascular ARMD constitutes third most common indication of IVB in our study. Recently a large sample, multicentre, prospective trail proved that bevacizumab has equal efficacy to ranibizumab in neo-vascular ARMD.[6] Despite being an off label drug the bevacizumab use in neo-vascular ARMD is far more than other anti-VEGF drugs. Its low price, easy availability and importantly comparable efficacy to other anti-VEGF makes it most used drug both in developed and developing countries.[5]

Chronic CSR is a relatively common retinal cause of visual loss and offers great therapeutic challenge. Anti-VEGF therapy is an addition to the existing treatment options of observation, argon laser photocoagulation and photodynamic therapy. A recently published meta-analysis and review concluded that IVB did not have any significant effect on visual outcome in chronic CSR.[17]

Eale's disease is idiopathic, occlusive peri-vasculitis occurring in younger age group. Although argon laser photocoagulation is used as definitive treatment for proliferative stage of the disease but recently bevacizumab has been introduced as an adjuvant for quick regression of neo-vessels and prior to vitrectomy (in eyes with fibro-vascular proliferation and tractional retinal detachment) to reduce risk of bleed during surgery.[18]

The beneficial role of anti-VEGF therapy in DME and RVO related macular oedema has led to its use in macular oedema with various other ocular conditions. We also used it in macular oedema associated with PFT, RP, cataract surgery, uveitis and buckling for retinal detachment. Among these we noted visual acuity improvement of 2–3 lines on Snellen's chart only in cases of post cataract surgery cystoid macular oedema. One of the largest recent trails conducted by Pan-American Collaborative Retina Study Group demonstrated 2 or more lines of visual improvement on ETDRS chart in 72% of patients with post-cataract surgery macular oedema after 2–6 intravitreal injections of bevacizumab, which favours the outcome of our study.[19]Visual benefit was not observed in other cases of macular oedema. In few reported case series antiangiogenic therapy was found ineffective in macular telangiectasia despite positive angiographic and tomographic effects.[20] The limited available data shows promising results of bevacizumab in RP associated macular oedema with the apprehension of enhancing retinal ischemia.[21] This contradicts our study result. Majority of the studies have shown promising role of IVB in uveitic macular oedema refractory to therapy. The visual benefit which is usually transitory and hence requires multiple injections is dependent mainly on the chronicity of the disease.[22] The use of bevacizumab in congenital retinoschisis is not mentioned in literature. The splicing of sensory retina leading to schitic cavities in macular region is disease hallmark and is not a true form of oedema as evident by the absence of leakage on fluorescein angiography. The absence of any visual improvement in our study is probably because of the same reason. OCT would have been valuable to document changes in macular thickness.

Coat's disease is an idiopathic retinal telangiectasia that occurs generally in early childhood and is associated with intraretina, subretinal exudation and frequently exudative retinal detachment.[23] Limited studies with small sample size and limited follow up have shown promising effect of IVB in coat's disease.[23] The remarkable effect of IVB in neo-vascular ARMD is proven beyond doubt and this has led to its extensive usage in other diseases characterized be choroidal neo-vascularization (CNV).Degenerative myopia and angiod streaks are sometimes complicated by CNV.[24,25] IVB and other anti-VEGF have shown promising results and have largely replaced lasers in these conditions.[24,25]

The main complication in our study was subconjunctival haemorrhage at the injection site (17%). It resolved in couple of weeks and patients anxious feeling was relieved by proper reassurance. Reported incidence of subconjunctival haemorrhage is nearly 10% which rises to 35% in those using asprin.[1]We did not collect data regarding blood thinners use. Incidence of 17% in our study is reasonably within reported limits. Epithelial defects occurred in 22 cases (0.51%). Mostly these epithelial defects were induced by speculum and occurred in earlier cases in our study. With awareness and

cautious speculum removal technique epithelial defects did not occur in further cases.

Endophthalmitis occurred in 3 cases (0.069%) in our study. The incidence of endophthalmitis reported in large, multicentre trails with anti-VEGF therapy ranges from 0.019–1.6%.[9] Fung AE, *et al*, in an internet based survey found the infectious endophthalmitis rate after IVB to be 0.01%.[26] The rate of endophthalmitis seems to be the same with different anti-VEGF agents and geographical locations.[1]We adopted most of the precautions for reducing the incidence of endophthalmitis like deferral of patients with surface infections, use of 5% povidone iodine in conjunctival cul de sac as a recommended universal precaution, draping the eye, use of lid speculum to avoid contact with lashes and post-operative antibiotic drops. Most importantly we focused on aseptic preparation of bevacizumab syringes. All withdrawals from bevacizumab vial were done in one setting. Fingers contact with rubber septum was avoided.

Retinal detachment occurred in 2 cases (0.046%) in our study. The reported incidence of rhegmatogenous retinal detachment after intravitreal injection is very low and varies from 0–0.067%.[1]
No other complications were noted besides discussed above. Initially we checked IOP in all the patients 30 minutes after injection. Later this practice was stopped as no case of raised IOP was detected with given dose of IVB. No case of lens touch was seen. Vitreous haemorrhage did not occur in any case. On follow up visit at 7th day eyes were quiet and sterile inflammation was not detected in our patients.

There were some limitations of our study. Optical coherence tomography findings were not included in our study regarding any changes in macular thickness because it was not available at time of initiation of our study. Systemic complications were not recorded. Moreover, detailed record of all patients was not kept e.g. BCVA, co-morbidities, which would have been more helpful in defining patient's response to therapy. A strong scientific discussion is not possible as we did not gather data which might affect and determine visual outcome in most of our patients.

CONCLUSION

Intravitreal bevacizumab was used in variety of ocular conditions in our study. Most common indications are diabetic macular oedema and macular oedema associated with vascular occlusions. Our study in addition has shown that repackaged bevacizumab is safe to use as the incidence of endophthalmitis was very low. However, aseptic precautions that we mentioned must be taken into account during process of drug withdrawal from vial and its injection into vitreous cavity.

AUTHOR'S CONTRIBUTION

SJ: Conceptualized the study, study surgeon and consultant. MN, SK, ZH: All assisted in patient assessment, preparing injections in operation theatre, follow up and data collection and analysis.

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