Ocular Complications after Intravitreal Bevacizumab (Avastin) in Patients with Diabetic Retinopathy

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Abstract: Objective: To evaluate the results of intravitreal bevacizumab (IVB) in patient with diabetic retinopathy (DR) highlighting the rate of ocular complications encountered during the follow up period. **Methods:** 553 consecutive patients (940 injections) who suffered complications of DR and received one or repeated IVB were enrolled in this non-comparative retrospective descriptive study. They were intravitreally injected between April 2008 and August 2011 in one center (Dr Soliman Fakeeh Hospital, Jeddah, Saudi Arabia). **Results:** Significant improvement in best corrected visual acuity (BCVA) was seen in 60.2% patients after IVB. Patients with proliferative diabetic retinopathy (PDR) demonstrated 87.2% significant regression of retinal neovascularization (RN). Significant reduction of central macular thickness (CMT) measurements was demonstrated within one month after IVB in 73.6% patients with diabetic macular edema (DME). Patients with dense non-clearing vitreous hemorrhage, only 12% (14 patients out of 102 patients) who received IVB required vitrectomy. Significant complications were observed in 15 (2.7%) patients after IVB injection. Vitreous hemorrhage was observed in 2 (0.63%) patients, severe intraocular inflammation was observed in 3 (0.54%) patients, progression of preexisting traction retinal detachment (TRD) to involve the macula was observed in 4 (0.72%) patients after IVB and 5 (0.9%) patients developed retinal brake and subsequent combined tractional-rhegmatogenous retinal detachment (TRRD). The most serious complication is acute loss of vision due to central retinal artery occlusion (CRAO) after 4 weeks of IVA in one (0.18%) patient presented with severe PDR and ocular ischemic syndrome (OIS). Insignificant complications were seen in 51 (9.2%) patients included subconjunctival hemorrhage 36 (6.5%) patents, corneal abrasion 6 (1.0%) patents, transient mild uveitis 2 (0.63%) patients, extramacular TRD 4 (0.72%) patients, peripheral crystalline lens Injury 1 (0.18%) patients and raised IOP 2(0.63%) patients. **Conclusion:** Although the procedure of IVB is generally safe, there are some rare drug related complications that need careful attention in terms of patient selection and appropriate post injection monitoring.
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1. Introduction

Among more than 20 known growth factors, vascular endothelial growth factor (VEGF) and angiopoietin-1 (Ang1) are the only ones that are endothelial cell-specific. [1] These two factors have strong effects on angiogenesis and vasculogenesis.[2] VEGF is homodimeric glycoprotein not only acts as a potent angiogenic factor, whose specific activities include endothelial cell survival, proliferation, migration, and tube formation, but it also causes conformational changes of tight junctions of vascular endothelial cells leading to increased vascular permeability.[1], [2, 3] Advances in understanding of pathogenesis of choroidal and retinal neovascularization (RN) have facilitated the development of drugs specifically directed against VEGF. [4] Currently, there are four anti-VEGF agents which have been used in the management of diabetic retinopathy (DR), including pegaptanib (Macugen; Pfizer, Inc., New York, USA), ranibizumab (Lucentis; Genentech, Inc., South San Francisco, California, USA), bevacizumab (Avastin; Genentech Inc., South San Francisco, California, USA), and aflibercept (VEGF Trap-Eye; Regeneron Pharmaceuticals, Inc.,Tarrytown, New York, USA).

Bevacizumab is a full length recombinant humanized monoclonal IgG1 antibody that binds all isoforms of VEGF, was approved by the Food and Drug Administration in 2004 for systemic administration in patients with metastatic colon cancer in combination with chemotherapy. The drug works by reducing the size and number of new vessels feeding metastases. Off-label use of intravitreal bevacizumab (IVB) therapy for ophthalmologic neovascular disorders began shortly thereafter in 2005 for choroidal neovascularization (CNV) caused by age-related macular degeneration (AMD). [5, 6]

Intravitreal injection of bevacizumab has been administered off-label intravitreally in other VEGF mediated diseases, including retinal vein occlusion[7], proliferative diabetic retinopathy (PDR) [8, 9], diabetic macular edema (DME) [10] anterior segment neovascularization with PDR [11, 12], CNV caused by

pathological myopia[13], idiopathic CNV [14], pseudophakic cystoid macular oedema[15] and retinopathy of prematurity. [16] The number of patients who have undergone this therapy for ocular disease has increased markedly in the last few years. The dose used for intravitreal administration of bevacizumab for ocular diseases is about 1⁄ 400th of that administered intravenously, and the injection target is an intraocular site instead of the blood vessels. Therefore, the systemic effects caused by intravitreal injection of bevacizumab are considered to be much less than those resulting from intravenous injection. That is one reason why focal administration, instead of systemic administration, of this drug spread worldwide so rapidly. [17] Systemic administration of bevacizumab has a significant risk of thromboembolism in patients with cancer. [18] However, these potential systemic adverse events (including hypertension and cerebral vascular accidents) have been reported [18-20] when the drug is administered intravitreally. [17] Possible drug-related ocular adverse events after IVB have been reported [19- 24] and because of the wide-spread use of bevacizumab, the purpose of the present study is to evaluate the results of IVB in patient with DR highlighting the rate of ocular complications encountered within the follow up period in a single center.

2. Methods

Five hundred fifty three consecutive patients (940 injections) who suffered complications of DR and received one or repeated IVB were enrolled in this non-comparative retrospective descriptive study. They were intravitreally injected between April 2008 and August 2011 in one center (Dr Soliman Fakeeh Hospital, Jeddah, Saudi Arabia). Exclusion criteria included history of trauma, ocular inflammatory disease, vitrectomized eyes and patient who had been followed-up for a period of less than six months. The ‘‘off-label’’ status of this medication, and possible systemic and ocular complications, were discussed in detail and informed consent was obtained from all patients. Institutional review board/ethics committee approval was obtained for this study. All eyes underwent full pre-injection and post-injection assessment included best corrected visual acuity (BCVA) using Snellen visual acuity chart, intraocular pressure (IOP) with Goldman applanation tonometer, anterior segment examination using a slit lamp, dilated fundus biomicroscopy using slit lamp with +78 diopters lens and indirect ophthalmoscopy. Further investigation routinely used are ocular coherent tomography (OCT/SLO; OTI, Toronto, ONT, Canada) and fluorescein angiography (FA) when the ocular media are clear and B-scan ultrasonography in eyes with opaque media. Each patient received one or repeated IVB which was prepared by the hospital pharmacy as 1.25mg (0.05 ml) injections in an insulin syringe for each patient from commercially available 4 ml vial of bevacizumab (25mg/ml) under aseptic techniques. After the application of topical anesthesia using proparacaine hydrochloride 1% ophthalmic drops, the eye and lids were disinfected with 10% povidone iodine. 1.25mg/0.05ml of bevacizumab was injected intravitreally through the pars plana 3.5–4 mm posterior to the corneal limbus into the vitreous cavity using a 27 or 30 gauge needle. The injection site was compressed for several seconds to avoid reflux when the needle was removed. The IOP was assessed and the patients were instructed to use topical gatifloxacin eye drops 0.3% Q6H for 5 days. All enrolled eyes in this study were injected by one vitreoretinal surgeon. When informed consent was obtained, patients also were informed of their responsibility to report any ocular changes and systemic clinical episodes after treatment. Patients were instructed to call or visit the hospital if they experienced ocular or systemic pain or unexpected visual deterioration. All patients were asked to visit our clinic within 1 week, at 1 month and at 2 or 3 months after the injection. During the follow-up period, the patients are asked if there were visual symptoms or systemic changes and when they occurred, the BCVA was measured, and slit-lamp and fundus examinations were performed with special emphasis on ocular complication. OCT and FA were performed if needed. Subsequent injections were given at monthly intervals (4-6 weeks) depending upon response of macular edema and RN. Statistical analysis where appropriate, the Chi-square test, Fisher exact test, and analysis of variance tests were used to get correlations between baseline ocular characteristics and the anatomical and functional outcomes. Statistical analyses were performed using STATA for Windows version 8.0 (StataCorp Inc, College Station, Texas, USA).

3. Results

A total of 553 consecutive patients (669 eyes) who suffered complications of diabetic retinopathy were enrolled in this non-comparative retrospective study. Mean age of patients was 51.6 ±12.7 years, (range 28–79 years) and 52 % (288 patients) were male. The mean follow-up time was 23.6 ±8.6 months (range 6–28 months). All eyes received IVB of 1.25mg at the initial treatment; however, in case of recurrence, retreatment was decided at the discretion of the treating surgeon. There were a total of 940 IVB injections performed. The mean number of IVB injections per eye was 2.2 (range 1 - 7 injections) at a

mean interval of 3.5 ± 2. 3 months. The indication of IVB were diffuse diabetic macular edema (DDME) 151 (27.37%) patients, severe PDR with DME 175 (31.88%) patients, dense non-clearing diabetic vitreous hemorrhage 102 (18.47%) patients, early diabetic vitreous hemorrhage 75 (13.58%) patients , preoperative use in diabetic tractional retinal detachment (TRD) involving or threatening the macula 48 (8.69%) patients and one (0.18%) patient who diagnosed as severe PDR with ocular ischemic syndrome (OIS) (Table 1). Within 1-4 weeks after the initial IVB, improvements in BCVA, reduction of central macular thickness (CMT) measurements, regression of RN, enhancement of clearance of vitreous hemorrhage and remarkable regression of new vessels in fibrovascular membranes (which necessitated minimum intra-operative haemostasis) were observed. Significant improvement in BCVA was seen after IVB. Out of 553 patients improvement was seen in 333 (60.2%) patients which is significantly high (p-value < 0. 005), decreased in 43 (7.8%) patients while 177 (32%) patients remained stable (Table 1).

Out of 250 patients with PDR (Severe PDR with DME 175 patients and early vitreous hemorrhage 75 patients), 215 (87.2%) patients demonstrated significant regression of RN (P-value <0.005). Regression of RN was complete in 155(62%) patients and partial in 63(25.2%) patients (Table 2). The remarkable regression of RN was observed as early as few days after injection and lasted for 1-3 months.

OCT results of patients with DME (326 patients: severe PDR with DME 175 patients and DDME 151 patients, table 1) showed significant reduction of CMT measurements within one month after IVB in 240 (73.6%) patients (Table 3). The mean CMT measurements decreased from 443.3 ±161.2 µm to 341.5±120.2µm ((P < 0 .001), and this overall improvement continued for 4-8 weeks. Recurrence of DME (as diagnosed by decrease of BCVA associated with an increase of CMT on OCT after complete or partial resolution in previous follow up visits), required the patients to receive reinjection of IVB. The overall mean number of IVB injections per eye in the study was 2.2 (range 1-7 injections) at a mean interval of 3.5 ± 2. 3 months.

In patient with dense non-clearing vitreous hemorrhage, only 12% (14 patients out of 102 patients) who received IVB required vitrectomy and the hemorrhage cleared anywhere from 2-20 weeks (average 12 weeks).

In patients who received IVB as an adjunctive therapy prior to vitrectomy for severe PDR with TRD involving or threatening the macula, the time of IVB was planned to be 5-7 days as maximum before the scheduled day of surgery. However in 9 (18.7%) patients (out of 48 patients, 1.6% of total patients), who missed or preferred to defer the planned date of surgery by 2-4 weeks, they developed progression and modification of both the extent and pattern of the retinal detachment. In five (0.9%) patient of this group the pattern of TRD changed to combined traction rhegmatogenous detachment (TRRD). The overall surgical procedure difficulties as evaluated by recording operative times, number and severity of intraoperative bleeding, the need to use intraoperative endodiathermy, dissection techniques, and iatrogenic retinal breaks were reduced. However because this study is not a comparative study, these findings are considered a personal view of the author although it is supported by other studies.

Complications: Table 4, 5

Of the 553 patients, complications were seen only in 66 (11.93%) patients after IVB injection. Insignificant complications were seen in 51 (9.2%) patients. Subconjunctival hemorrhage was the most frequent complication observed in 36 (6.5%) patents, corneal abrasion found in 6 (1.0%) patents, transient mild uveitis was seen in 2 (0.63%) patients, extramacular TRD was seen in 4 (0.72%) patients, peripheral crystalline lens Injury was seen in 1 (0.18%) patients and raised IOP was seen in 2(0.63%) patients, (Table 4). All of the above mentioned complications were transient events that not affected the visual outcome and most of them resolved by 1-2 weeks without any consequences.

Significant complications (Table 5) were observed in 15 (2.7%) patients after IVB. Vitreous hemorrhage was observed in 2 (0.63%) patients. Both of them were injected because of severe PDR. Only one of them needed pars plana vitrectomy while the other patient demonstrated clearing of vitreous hemorrhage within 2 weeks.

Severe intraocular inflammation was observed in 3 (0.54%) patients (case report 3). This complication was observed between 3 to 5 days after IVB. The inflammation was mainly affecting the anterior segment and one of them demonstrated anterior chamber hypopion (figure 4). All patients were managed by vitreous tap, culture & Gram stain, intravitreal and topical antibiotics, topical steroid and cycloplegic. Culture results and Gram stain of the vitreous tap of all patients were negative (sterile endophthalmitis). One of the three patients had received previous IVB. All three patients regained preinjection BCVA.

Despite regression of neovascularization, progression of preexisting TRD to involve the macula was observed in 4 (0.72%) patients after IVB and 5 (0.9%) patients developed retinal brake and subsequent combined tractional rhegmatogenous

retinal detachment (TRRD) (case report 2). These 4 (0.72%) patients who developed TRD were presented by PDR and TRD threatening the macula. The other 5 (0.9%) patients who developed combined TRRD were presented by PDR with macular TRD and all of them were intravitreally injected with bevacizumab to prepare the eye for pars plana vitrectomy (PPV) (to reduce the risk of intraoperative bleeding facilitating the removal of fibrovascular membranes). The interval between IVB and PPV was unintentionally extended either due to patient declined surgery or patient's preference to postpone surgery. Eventually these patients underwent PPV with delamination of the epiretinal fibrovascular tissue. The most serious complication is acute loss of vision due to central retinal artery occlusion (CRAO) after 4 weeks of IVB in one (0.18%) patient presented with severe PDR and OIS (case report 1).

Selected case reports

Case report 1

A 60-year-old woman presented with deterioration of vision in both eyes specially the right eye of about 2 weeks duration. Her previous general medical history revealed diabetes mellitus type 2 diagnosed 12 years before, hypertension and hyperlipidemia. She was under therapy with oral hypoglycemic agents. BCVA was 0. 4 Snellen equivalent at right eye and 0.5 Snellen equivalent in the left eye. IOP) was 16 mm Hg in both eyes. Slit-lamp examination of the anterior segment revealed incipient cataract with no rubeosis iridis. Fundus examination revealed bilateral neovascularization at disc and elsewhere (NVD & NVE) with right preretinal and mild vitreous hemorrhage and clinically significant macular edema (CSME) (Fig. 1A). Central macular thickness (CMT) on OCT was 233 μm and 201 μm in right and left eye, respectively. Fluorescein angiography (FA) (Figures 1 B) demonstrated the presence of NVD and NVE with mid peripheral retinal nonperfusion. The patient was advised to undergo right IVA injection followed by bilateral PRP. Informed consent was obtained and the patient was treated with right IVA (1.25 mg) on September 2008 and PRP started few days after injection. One month later she experienced right vision loss to light perception (LP) only. Examination revealed right central retinal artery occlusion (Fig. 1C).The patient underwent a thorough investigation. Her erythrocyte sedimentation rate (ESR) was elevated (80 mm/hr, Westergren method) and she had positive antiphospholipid IgG (51.3 GPL-U/ml). Bilateral carotid Doppler ultrasound revealed 60-79% stenosis of the origin of the right internal carotid artery with spectral broadening in Doppler waveform. The patient was referred for neurological and vascular consultation and three months later, she developed rubeosis iridis and NVD with elevated IOP. She received augmentation of PRP along with antiglaucoma eye drops and the eye calmed down. Final BCVA remained at the level of LP only.

Case report 2

A 36-year-old man with a history of poorly controlled type 1 DM since age 7 years presented with bilateral visual loss. He had no history of any eye procedures. At presentation, his BCVA was counting figure (CF) at one meter in right eye and hand motion (HM) in the left eye. Fundus examination revealed right dense premacular and moderate vitreous hemorrhages with focal retinal traction caused by epiretinal fibrovascular membranes (Figure 2A). Left fundus examination revealed TRD involving the macula due to extensive widespread epiretinal fibrovascular membranes with broad vitreoretinal adhesions associated with underlying macular folds and retinal and preretinal hemorrhages (Figure 3A). Bilateral IVB at a dose of 1.25 mg was injected into the vitreous cavity in preparation for a vitrectomy. Right PPV, peeling, endo- PRP was performed 6 days later and silicone oil (1000 cSt) was left as intraocular tamponade. Sequential silicone oil removal was performed and BCVA recovered to 0.5 Snellen equivalent at the final follow-up examination (6 months) (Figure 2B). The patient preferred to defer left eye operation until he recovers from the right eye operation. During the interval (3 weeks) between left IVB and PPV, the patient developed a retinal break as a result of the increased traction, and a combined total TRRD was apparent despite regression of neovascularization (Figure 3B). The patient underwent left PPV with delamination of the fibrovascular tissue, perfluorocarbon liquid (PFCL) injection, endo-PRP and silicone oil (1000 cSt) was left as intraocular tamponade. The retina was successfully reattached (Figure 3C) and the patient recovered BCVA of 0.4 Snellen equivalent after sequential silicone oil removal and at his final follow-up examination (6 months) (Figure 3D).

Case report 3

A 59-year-old man pseudophakic with DME received two doses of IVB 10 weeks apart in the right eye. Four days after the second injection, the patient reported excessive eye tearing, light sensitivity, and painless rapid drop in vision from 0.2 Snellen equivalent to finger counting. Slit lamp biomicroscopy revealed severe anterior chamber reaction, hypopion with mild vitreitis (Figure 4). On the same day the patient underwent vitreous tap with simultaneous intravitreal antibiotics (ceftazidime 2.25

mg/0.1 ml and vancomycin 1 mg/0.1 ml) injections along with topical 0.3% gatifloxacin ophthalmic solution (Zymar; Allergan, Inc.), prednisolone acetate 1% solution and cyclopentolate 1%. Culture results and Gram stain of vitreous tap were negative. Ten days later, the BCVA improved to the preinjection level and hypopion disappeared.

Table 1 Diagnosis and post-injection BCVA (n=552)

Diagnosis	No. of patients n (%)	Improved BCVA n (%)	Decreased BCVA n (%)	Stable BCVA n (%)
Severe PDR with DME	175 (31.6)	114(65.1)	9 (5.1)	52 (29.7)
DDME	151 (27.3)	106 (70.1)	13 (8.6)	32 (21.2)
Dense non-clearing vitreous hemorrhage	102 (18.4)	61 (59.8)	7 (6.8)	34 (33.3)
Early vitreous hemorrhage	75 (13.5)	52 (69.3)	8 (10.6)	15 (20)
Traction retinal detachment	48 (8.6)	-	5 (10.4)	44 (91.6)
Severe PDR with ocular ischemic syndrome	1(0.18)	-	1(100)	-
Total	553 (100)	333 (60.2)	43 (7.8)	177 (32.0)

PDR: proliferative diabetic retinopathy, DME: diabetic macular edema, DDME: diffuse diabetic macular edema.

Table 2 Neovasularization regression

Diagnosis	Number of patients	Complete regression of RN, n (%)	Partial regression of RN, n (%)	Persistent RN, n (%)
PDR	250	155(62%)	63(25.2%)	32(12.8%)

RN: retinal neovascularization.

Table 3 Central macular thickness (CMT) reduction.

Diagnosis	Number of patients	Reduction of CMT n (%)	No reduction of CMT n (%)
DME	326	240 (73.6%)	86 (26.3%)

Table 4 Insignificant complications

Insignificant complications	Number of patients
Corneal abrasion	6 (1.0%)
Subconjunctival hemorrhage	36 (6.5%)
Transient mild uveitis	2 (0.63%)
raised IOP	2 (0.63%)
Lens Injury	1 (0.18%)
Extramacular TRD	4 (0.72%)
Total	51 (9.2%)

IOP: intraocular pressure, TRD: traction retinal detachment.

Table 5 Significant complications

Significant complications	Number of patients
Vitreous hemorrhage	2 (0.63%)
Severe intraocular inflammation	3 (0.54%)
Macular TRD	4 (0.72%)
Combined TRRD	5 (0.9%)
CRAO	1 (0.18%)
Total	15 (2.7%)

TRD: traction retinal detachment, TRRD: traction rhegmatogenous retinal detachment,
CRAO: central retinal artery occlusion.

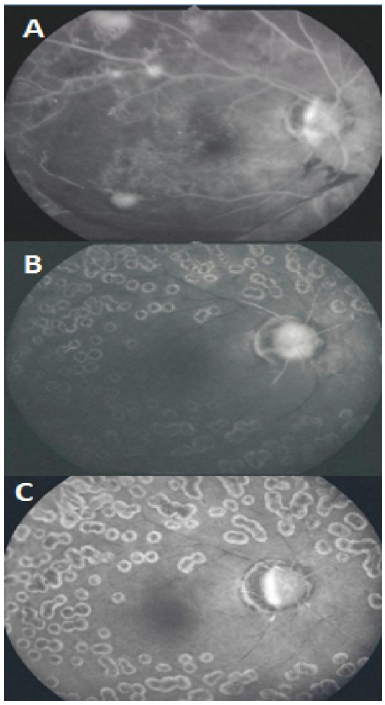

Figure 1 Case 1. (A) Fluorescein angiogram in late venous phase demonstrating the presence of NVD and NVE with mid peripheral retinal nonperfusion and preretinal hemorrhage. (B) Fluorescein angiogram in late venous phase showing central retinal artery occlusion one month after intravitreal avastin. (C) Fluorescein angiogram in late venous phase showing delayed arterial filling (central retinal artery occlusion) with NVD three months after intravitreal avastin.

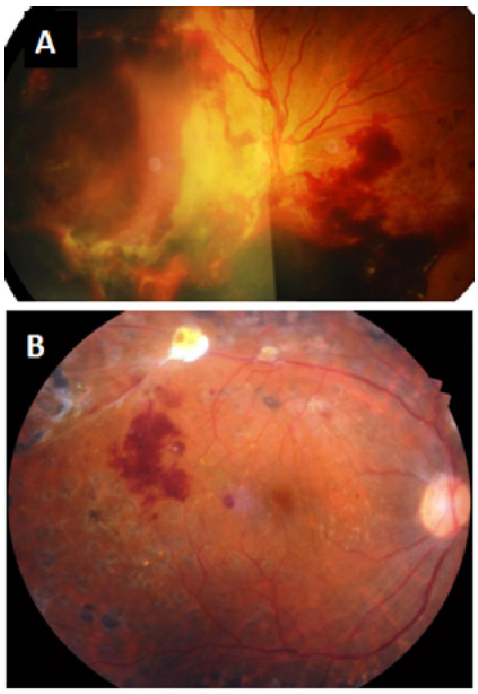

Figure 2 Case 2. (A) Preoperative composite colored picture of right fundus revealed dense premacular and moderate vitreous hemorrhages with focal retina traction caused by epiretinal fibrovascular membranes. (B) Postoperative colored picture of the same fundus demonstrating flat retina with minimal residual hemorrhage, scars of scatter photocoagulation and residual membrane stump at the superior arcade. BCVA is 0.5 at 6 months.

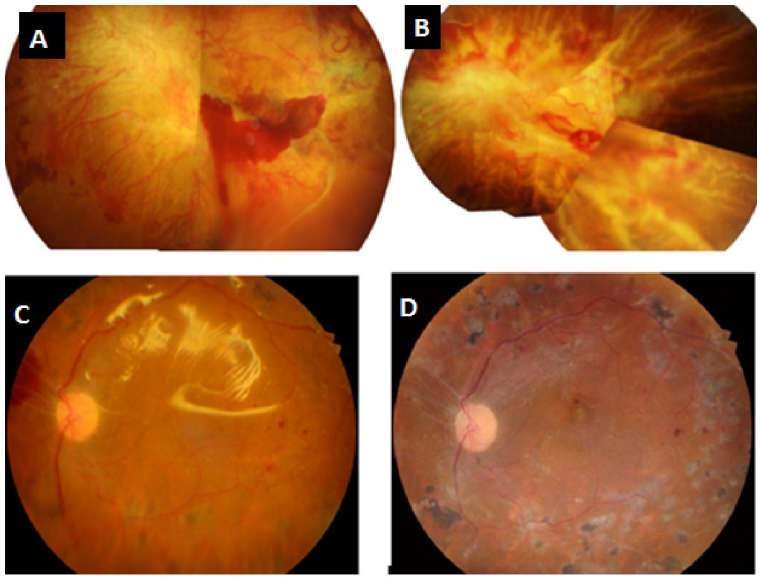

Figure 3 Case 2. (A) Preoperative and pre-avastin injection composite colored picture of left fundus revealed extensive widespread epiretinal fibrovascular proliferation, traction retinal detachment involving the macula with broad vitreoretinal adhesions associated with retinal and preretinal hemorrhages. (B) 3 weeks post-avastin injection composite colored picture of the same fundus demonstrating total combined tractional-rhegmatogenous retinal detachment with regression of neovascularization. (C) 2weeks postoperative colored fundus picture of the same eye after PPV and silicone oil tamponade demonstrating successfully reattached retina. (D) 6 months postoperative colored fundus picture of the same eye after sequential silicone oil removal. BCVA is 0.4 at 6 months.

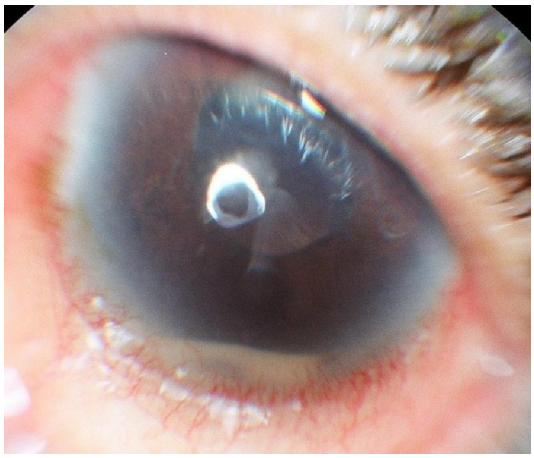

Figure 4 Case 3. Colored picture of anterior segment revealed mild ciliary injection with small hypopion at the bottom of anterior chamber 4 days after intravitreal avastin.

4. Discussion

Diabetic retinopathy remains the major threat to sight in the working age population in both the developed and developing countries.[25] Although visual loss secondary to proliferative changes is more common in patients with type 1 diabetes, visual loss in patients with type 2 diabetes is more commonly due to macular edema.[26] Hypoxia is the main trigger of VEGF release. VEGF, also known as vascular permeability factor, has been demonstrated to increase retinal vessel permeability in DME and the growth of new vessels from the retina or optic nerve in PDR. [27–30] Since 2005, the intravitreal applications of anti-VEGF have markedly increased in frequency as therapy of many VEGF mediated diseases including intraocular neovascular and edematous diseases. [6] Several electrophysiologic and histologic studies have shown the lack of ocular toxicity of IVB in cell cultures, animal and human eyes at least in the short term. [3, 31–34] The widespread use of anti-VEGF molecules in clinical practice is so far limited by their short-lived effects and the lack of established protocols. Another concern has to do with the fact that bevacizumab is not manufactured or labeled for intravitreal injection.[21]

The current study reported the results of IVB in patient with DR highlighting the ocular complications encountered during the follow up period.

Given that most eyes with DME that are treated with laser photocoagulation do not have an improvement in visual acuity, there has been an interest in other pharmacological treatment modalities such as intravitreal anti-VEGF. [10] The current study showed significant reduction of CMT measurements within one month after IVB in 73.6% patients, and this overall improvement continued for 4-8 weeks. All reported studies about IVB for DME therapy, have demonstrated transient beneficial effects with a requirement for repeated injections. [35-38] The overall mean number of IVB injections per eye in the current study were 2.2 (range 1-7 injections) at a mean interval of 3.5 ± 2. 3 months. After the first IVB, the improvement of visual acuity and reduction of CMT lasts for 4 - 6 weeks with deterioration of visual acuity and recurrence of macular edema 8 to 12 weeks later necessitating another injection. [38, 39] It was reported that both the improvement in visual acuity and reduction of CMT were maintained for 8 weeks after the first injection, and for 2–4 weeks after repeated injection. [37] This recurrence of macular edema following IVB is a quite common finding which represents a major limit in anti VEGF treatment that needs further work to provide longer acting agents. Recent studies determined the clinical effectiveness of cataract surgery combined with IVB for the management of the postoperative increase of CMT in patients with DME. The short-term results suggest that IVB has the potential not only to prevent the increase in CMT, but also reduce the CMT of eyes with DME after cataract surgery. [40-42]

Several studies demonstrated that IVB injection resulted in marked regression of retinal and iris neovascularization, and rapid resolution of vitreous hemorrhage in patients with PDR. [43-45] Other studies demonstrated the effectiveness of IVB as an adjunctive treatment to PRP in the management of high-risk PDR. [46, 47] The current study demonstrated significant regression of RN in 87.2% patients. The remarkable regression of RN was observed as early as few days after injection and lasted for 1-3 months. IVB injection before PRP was found to be beneficial in preventing PRP-induced visual dysfunction due to macular edema as compared with PRP alone in patients with high-risk PDR. [40, 46, 47]

In patients with diabetic vitreous hemorrhage, the current study supports the results of previous studies demonstrated that IVB injection was effective in inducing rapid regression and reduce the need for vitrectomy in eyes with PDR complicated with vitreous hemorrhage.[43, 48] In patient with dense non-clearing vitreous hemorrhage,the current study showed only 12% (14 patients out of 102 patients) who received IVB required vitrectomy during the follow up period.

It is obvious that using an unlicensed off-label drug is less safe than using a licensed one where the quality control of the manufacturer is monitored by the regulatory authority. Although the rates for ocular safety outcomes were low, it has to be kept in mind

that the cumulative risk will increase with repeated injections. Along with its therapeutic effect on ocular neovascularization and macular edema, IVB may be accompanied by a number of side effects. The insignificant ocular complications were encountered in 66 (11.93%) patients after IVB and included corneal abrasion, subconjuctival hemorrhage, mild uveitis, extramacular TRD, peripheral crystalline lens injury and raised IOP. These complications were transient events that did not lead to any visual consequences.

Vitreous hemorrhage is a risk that might follow IVB .The mechanism is uncertain. It was probably attributable either to the procedure or the underlying pathologic condition for which the injection was administered like in cases of PDR. [49] Khan et al [49] reported 1% of their series suffered the complication of vitreous hemorrhage after IVB which was managed by PPV. The current study reported vitreous hemorrhage after IVA in 2 (0.63%) patients. Both of them were injected because of severe PDR and only one of them needed PPV. Lihteh Wu et al [50] have reported this complication in only 0.02% cases.

It has been observed that during diabetic PPV there is severe bleeding which obscures the surgical field and prolongs the surgical time, resulting in an increased number of complications and difficulty in handling the situation. IVB has become a common practice as a preoperative adjuvant in cases of severe PDR.[51, 52] IVB remarkably attenuates the activity of fibrovascular membrane at one week post-administration. Results of the current study correlate with these findings. Intraoperative observation showed less bleeding in surgical excision of fibrovascular membrane in eyes operated 4-7 days after IVB. However the development of strong adhesion between fibrovascular membrane and retina was observed and delaying the surgical interference may lead to some difficulty of peeling and delimitation of fibrovascular epiretinal membrane from the retina and sometimes it was impossible to separate posterior hyaloid membrane. Furthermore, progression of preexisting TRD or development of tractional retinal breaks may occur as a result of delayed intervention. [53- 57]

The current study reported progression of preexisting TRD to involve the macula and/or development of retinal breaks with subsequent combined tractional-rhegmatogenous retinal detachment in 4 (0.72%) patients and 5 (0.9%) patients respectively after IVB prior to PPV for the management of PDR. The etiology was unclear; however, this unfavorable response could be related to the natural history of the disease or rapid neovascular involution with accelerated fibrosis and posterior hyaloidal contraction as a response to decreased levels of VEGF. [57] Several studies investigated the appropriate timings of vitrectomy after IVB. They found that shorter period (less than 7 days) may be preferable [53, 58- 60]. However Further studies are required on this subject to determine the appropriate timings. Risk factors for TRD after IVB identified in the study of Arevalo et al., [53] included, more than 15 years from the diagnosis of diabetes mellitus (DM) (P = .009), more than 13 days from injection to vitrectomy (P = .0001) and the use of a higher dose (2.5mg) of bevacizumab.

Bacterial endophthalmitis is an expected and dreaded complication of any intravitreal injection. The reported incidence of endophthalmitis after IVB ranging from 0.014% to 0.082%.[61, 62] Recently, there have been a few reports of toxic anterior segment syndrome (TASS)-like culture-negative sterile endophthalmitis after IVB injection for diverse etiologies. [63-65] In the current study severe intraocular inflammation was observed in 3 (0.54%) patients between 3 to 5 days after IVB and one of them demonstrated anterior chamber hypopion (figure 4). culture results and Gram stain of the vitreous tap of all patients were negative (sterile endophthalmitis). According to the author's knowledge, this is the first report of anterior chamber hypopion formation after IVB. Retrospective review of 2,500 consecutive IVB performed at a single center revealed eight cases of post-injection inflammation. All eight patients had a marked anterior chamber reaction with increased flare and cells, but no hypopyon. Onset was within two days of injection and microbiological findings were negative. Patients responded to systemic or topical cortisone treatment, without any permanent retinal damage. [66] The cause of intraocular inflammation remains to be determined. However this response could be related to the endotoxin or breakdown product due to the faulty storage of bevacizumab or related to an immune-mediated response to bevacizumab, following repeated injections. [36, 66] In the current study only one patient of the 3 (0.54%) patients who developed severe intraocular inflammation had repeated IVB. Negative microbiological findings of the vitreous tap of all patients makes the infective etiology is less likely. There are different options in management of intraocular inflammation after IVB. Sato et al[65], have performed vitrectomy in all their cases of sterile endophthalmitis, Whereas Yamashiro et al., [64], have done vitrectomy in the most severely affected eyes and managed conservatively the less severely affected eyes with topical and systemic medications. In the current study all patients were managed by vitreous tap, culture & Gram stain, intravitreal and topical antibiotics, topical steroid and cycloplegic. All three patients regained preinjection BCVA.

Acute vision loss secondary to CRAO was reported in the current study in one (0.18%) patient with severe PDR and OIS after IVB. Von Hanno et al., [67] reported 2 cases of CRAO after IVB for treatment of macular edema secondary to CRVO. Both patients experienced visual loss within days of the injections while in the current study the patient developed CRAO after one month of IVB. Huang et al., [68] reported a case of acute vision loss associated with OIS and acute stroke after IVB in a patient with neovascular glaucoma. On the other hand, Amselem et al. reported encouraging results after the use of IVB in OIS. [69]

Mansour et al., [70] reported 8 patients of retinal vascular events after IVB. They documented CRAO in four patients, branch retinal artery occlusion, capillary occlusion, central retinal vein occlusion and branch retinal vein occlusion in one patient each within 0–55 days (median 2 weeks) of IVB. In a retrospective review of 707 patients undergoing IVB, Shima et al., [17] described one patient of acute visual loss in a patient with PDR 1–3 weeks after the injection with no further details given. Yokoyama et al., [71] described combined retinal arterial and venous occlusions 4 weeks after IVB in a 60-year-old vitrectomized pseudophakic patient with diabetic neovascular glaucoma. Kim et al., [72] noted a conversion of non-ischaemic CRVO into ischaemic CRVO in a 65-yearold diabetic man at 3 weeks after IVB. The mechanism of acute vision loss associated with IVB is complicated. [68] Increased IOP after IVB was noted, but the IOP spike normalized over 30 min, so that the evidence of retinal damage due to the IOP elevation may not be convincing. [73] Falkenstein et al., [74] concluded that bevacizumab injections caused a predictable rise in IOP; however, this rise never occluded the central retinal artery. Analysis of risk factors of CRAO after IVB suggested underlying systemic vasculopathy to be the main contributing factor for CRAO. [70]

Conclusion

Intravitreal bevacizumab injection seems to be safe, promising and effective in both treatment and prevention of further complications of DR. Although the procedure of IVB is generally safe, there are some rare drug related complications that need careful attention in terms of patient selection and appropriate post injection monitoring. The current study and most of the recent reports are restricted by lack of randomization, lack of controls and their retrospective nature which preclude any estimation of the long-term safety of IVB. Further long term large prospective randomized control trial is recommended to clarify short- and long-term ocular and systemic adverse effects associated with the IVB.

Conflict of Interests

The author has no financial or proprietary interest in any of the products or techniques mentioned in this paper.

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References

1. Yancopoulos GD, Davis S, Gale NW, Rudge JS, Wiegand SJ, Holash J. Vascular-specific growth factors and blood vessel formation. Nature 2000; 407, 242–248
2. 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
3. Shahar J, Avery RL, Heilweil G, et al., Electrophysiologic and retinal penetration studies following intravitreal injection of bevacizumab (Avastin). Retina 2006; 26: 262–269.
4. Khan A, Mahar PS, Hanfi AN, Qidwai U. Ocular complications after intravitreal bevacizumab injection in eyes with choroidal and retinal neovascularization. Pak J Ophthalmol 2010;26:205 209.
5. Rosenfeld PJ, Fung AE, Puliafito CA. Optical coherence tomography findings after an intravitreal injection of bevacizumab (Avastin) for macular edema from central retinal vein occlusion. Ophthalmic Surg Lasers Imaging 2005; 36: 336–339.
6. Rosenfeld PJ, Moshfeghi AA, Puliafito CA. Optical coherence tomography findings after an intravitreal injection of bevacizumab (Avastin) for neovascular age-related macular degeneration. Ophthalmic Surg Lasers Imaging 2005; 36: 331–335.
7. Iturralde D, Spaide RF, Meyerle CB, et al., Intravitreal bevacizumab (Avastin) treatment of macular edema in central retinal vein occlusion: a short-term study. Retina. 2006; 26(3):279-84.
8. Avery RL, Pearlman J, Pieramici DJ, et al., Intravitreal bevacizumab (Avastin) in the treatment of proliferative diabetic retinopathy. Ophthalmology 2006; 113: 1695.
9. Chen E, Park CH. Use of intravitreal Bevacizumab as a preoperative adjunct for tractional retinal detachment repair in severe

proliferative diabetic retinopathy. Retina. 2006; 26:699-700.
10. Simo R, Hernandez C. Intravitreous anti-VEGF for diabetic retinopathy: hopes and fears for a new therapeutic strategy. Diabetologia 2008; 51:1574-80.
11. Avery RL. Regression of retinal and iris neovascularization after intravitreal bevacizumab (avastin) treatment. **Retina**. 2006;26(3):352–354.
12. Oshima Y, Sakaguchi H, Gomi F, Tano Y. Regression of iris neovascularization after intravitreal injection of bevacizumab in patients with proliferative diabetic retinopathy. Am J Ophthalmol.2006; 142:155–158.
13. Sakaguchi H, Ikuno Y, Gomi F, et al., Intravitreal injection of bevacizumab (Avastin) for subfoveal choroidal neovascularistaion associated with pathological myopia.Br J Ophthalmol. 2007; 91:161–5
14. Gomi F, Nishida K, Oshima Y, et al., Intravitreal bevacizumab for idiopathic choroidal neovascularization after previous injection with posterior subtenon triamcinolone. Am J Ophthalmol. 2007; 143(3):507-10.
15. Mason III JO, Albert Jr MA, Vail R. Intravitreal bevacizumab (Avastin) for refractory pseudophakic cystoid macular edema. **Retina** 2006; 26: 356–357.
16. Chung EJ, Kim JH, Ahn HS, Koh HJ. Combination of laser photocoagulation and intravitreal bevacizumab (Avastin) for aggressive zone I retinopathy of prematurity. Graefes Arch Clin Exp Ophthalmol 2007; 245:1727-30.
17. Shima C, Sakaguchi H, Gomi F, et al., Complications in patients after intravitreal injection of bevacizumab. Acta Ophthalmol 2008; 86:372–376.
18. Salesi N, Bossone G, Veltri E, et al., Clinical experience with bevacizumab in colorectal cancer. Anticancer Res. 2005; 25: 3619-23.
19. Rich RM, Rosenfeld PJ, Puliafito CA et al. et al., Short-term safety and efficacy of intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. Retina 2006; 26: 495–511.
20. Fung AE, Rosenfeld PJ, Reichel E. The International Bevacizumab Safety Survey: using the internet to assess drug safety worldwide. Br J Ophthalmol 2006; 90: 1344–1349.
21. Wu L, Martinez-Castellanos MA, Quiroz-Mercado H, et al., Twelve-month safety of intravitreal injections of bevacizumab (Avastin): results of the Pan- American Collaborative Retina Study Group (PACORES). Graefes Arch Clin Exp Ophthalmol 2008; 246:81–87.
22. Avery RL, Pieramici DJ, Rabena MD, Castelliarin AA, Nasir MA, Giust MJ. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. Ophthalmology 2006b; 113: 363–372.
23. Spaide RF, Laud K, Fine HF, et al., Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. Retina 2006; 26: 383–390.
24. Meyer CH, Mennnel S, Schmidt JC , Kroll P. Acute retinal epithelial tear following intravitreal bevacizumab (Avastin) injection for occult choroidal neovascularization secondary to age related macular degeneration. Br J Ophthalmol 2006; 90: 1207–1208.
25. Zimmet P, Alberti K G M, Shaw J. Global and societal implications of the diabetes epidemic. Nature, 2001; 414 (6865), 782–787.
26. . Wormald R, Smeeth L, Henshaw K. Medical interventions for diabetic retinopathy, in Evidence-Based Ophthalmology, Wormald R, Smeeth L, Henshaw K, Eds., p. 331, BMJ Books, London, UK, 2004.
27. Adamis A P, Miller J W, Bernal MT, et al., Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. Am J Ophthalmology1994; 118 (4): 445–450.
28. Aiello L P, Avery R L, Arrigg P G, et al., Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Eng J Med. 1994; 331(22):1480-1487.
29. Pe'er J, Shweiki D, Itin A, Hemo I, Gnessin H, Keshet E. Hypoxia-induced expression of vascular endothelial growth factor by retinal cells is a common factor in neovascularizing ocular diseases. Lab Invest. 1995; 72(6):638-45.
30. Malecaze F, Clamens S, Simorre-Pinatel V, et al., Detection of vascular endothelial growth factor messenger RNA and vascular endothelial growth factor-like activity in proliferative diabetic retinopathy. Arch Ophthalmol. 1994; 112(11):1476-82.
31. Manzano RP, Peyman GA, Khan P, Kivilcim M. Testing intravitreal toxicity of bevacizumab (Avastin). Retina (2006) 26:257–261.
32. . Maturi RK, Bleau LA, Wilson DL. Electrophysiologic findings after intravitreal bevacizumab (Avastin) treatment. Retina (2006) 26:270–274.
33. Luthra S, Narayanan R, Marques LE, et al., Evaluation of in vitro effects of bevacizumab

(avastin) on retinal pigment epithelial, neurosensory retinal, and microvascular endothelial cells. Retina 2006 26:512–518.
34. Luke M, Warga M, Ziemssen F, et al., Effects of bevacizumab on retinal function in isolated vertebrate retina. Br J Ophthalmol (2006) 90:1178–1182.
35. Arevalo JF, Sanchez JG, Fromow-Guerra J, et al., Pan-American Collaborative Retina Study Group (PACORES). Comparison of two doses of primary intravitreal bevacizumab (Avastin) for diffuse diabetic macular edema: results from the Pan-American Collaborative Retina Study Group (PACORES) at 12-month follow-up. Graefes Arch. Clin. Exp. Ophthalmol. 2009; 247 (6), 735–743.
36. Lam DS, Lai TY, Lee VY, et al., Efficacy of 1.25 MG versus 2.5 MG intravitreal bevacizumab for diabetic macular edema: six-month results of a randomized controlled trial. Retina 2009; 29 (3), 292–299.
37. Fang X, Sakaguchi H, Gomi F, et al., Efficacy and safety of one intravitreal injection of bavacizumab in diabetic macular oedema. Acta Ophthalmol 2008; 86 (7), 800–805.
38. Roh MI, Byeon SH, Kwon WO. Repeated intravitreal injection of bevacizumab for clinically significant diabetic macular edema. Retina 2008; 28 (9), 1314–1318.
39. Paccola L, Costa RA, Folgosa MS, Barbosa JC, Scott IU, Jorge R. Intravitreal triamcinolone versus bevacizumab for treatment of refractory diabetic macular oedema (IBEME study). Br J Ophthalmol. 2008; 92 (1), 76–80.
40. Abu El-Asrar AM, Al-Mezaine HS. Diabetic retinopathy update. Advances in the treatment of diabetic retinopathy. Saudi Journal of Ophthalmology 2011; 25, 113–122.
41. Lanzagorta-Aresti A, Palacios-Pozo E, Menezo Rozalen JL, Navea-Tejerina A. Prevention of vision loss after cataract surgery in diabetic macular edema with intravitreal bevacizumab: a pilot study. Retina 2009; 29 (4), 530–535.
42. Takamura Y, Kubo E, Akagi Y. Analysis of the effect of intravitreal bevacizumab injection on diabetic macular edema after cataract surgery. Ophthalmology 2009; 116 (6), 1151–1157.
43. Arevalo JF, Wu L, Sanchez JG, et al., Intravitreal bevacizumab (Avastin) for proliferative diabetic retinopathy: 6-months followup. Eye 2009; 23 (1), 117–123.
44. Wakabayashi T, Oshima Y, Sakaguchi H, et al., Intravitreal bevacizumab to treat iris neovascularization and neovascular glaucoma secondary to ischemic retinal diseases in 41 consecutive cases. Ophthalmology 2008; 115 (9), 1571–1580.
45. Jiang Y, Liang X, Li X, Tao Y, Wang K. Analysis of the clinical efficacy of intravitreal bevacizumab in the treatment of iris neovascularization caused by proliferative diabetic retinopathy. Acta Ophthalmol. 2009; 87 (7), 736–740.
46. Cho WB, Oh SB, Moon JW, Kim HC. Panretinal photocoagulation combined with intravitreal bevacizumab in highrisk proliferative diabetic retinopathy. Retina 2009; 29 (4), 516–522.
47. Tonello M, Costa RA, Almeida,FP, Barbosa JC, Scott IU, Jorge R. Panretinal photocoagulation versus PRP plus intravitreal bevacizumab for high-risk proliferative diabetic retinopathy (IBeHi study). Acta Ophthalmol. 2008; 86 (4), 385–389.
48. Huang YH, Yeh PT, Chen MS, Yang CH, Yang CM. Intravitreal bevacizumab and panretinal photocoagulation for proliferative diabetic retinopathy associated with vitreous hemorrhage. Retina 2009; 29 (8), 1134–1140.
49. Khan A, Mahar PS, Hanfi AN, Qidwai U. Ocular Complications after Intravitreal Bevacizumab Injection in Eyes with Choroidal and Retinal Neovascularization. Pak J Ophthalmol 2010; 26:205- 209.
50. Lihteh Wu, Maria A, Martinez-Castellanos MA, et al., Twelve- month safety of intravitreal injection of bevacizumab (Avastin): results of the Pan- American Collaborative Retina Study Group (PACORES). Graefes Arch Clin Exp Ophthalmol. 2008; 246: 81-7.
51. Chen E, Park CH. Use of intravitreal bevacizumab as a preoperative adjunct for tractional retinal detachment repair in severe proliferative diabetic retinopathy. Retina 2006; 26:699–700. 20.
52. . Avery RL, Pearlman J, Pieramici DJ, et al., Intravitreal bevacizumab (Avastin) in the treatment of proliferative diabetic retinopathy. Ophthalmology 2006; 113:1695.e1–15.
53. Arevalo JF, Maia M, Flynn HW Jr, et al., Tractional retinal detachment following intravitreal bevacizumab (Avastin) in patients with severe proliferative diabetic retinopathy. Br J Ophthalmol. 2008; 92(2):213-6.
54. Torres-Soriano M E, Reyna-Castelán E, Hernández-Rojas M. Tractional retinal detachment after intravitreal injection of bevacizumab in proliferative diabetic retinopathy. Retinal Cases & Brief Reports 2009; 3(1), 70–73.

55. Kuiper EJ, Van Nieuwenhoven FA, de Smet MD, et al., The Angio-Fibrotic Switch of VEGF and CTGF in Proliferative Diabetic Retinopathy. PLoS ONE 2008; 3(7): e2675.
56. Yeh P T, Yang C M, Lin Y C, Chen M S, Yang C H. Bevacizumab pretreatment in vitrectomy with silicone oil for severe diabetic retinopathy. Retina2009; vol. 29(6), 768–774.
57. Jonas J B, Schmidbauer M, Rensch F. Progression of tractional retinal detachment following intravitreal bevacizumab. Acta Ophthalmologica 2009; 87(5), 571–572.
58. Sami AM, IhsanKM , Tayyib M. Role of adjunctive use of intravitreal bevacizumab for severe proliferative diabetic retinopathy before vitrectomy. Biomedica 2009; vol. 25, 163 – 165.
59. Ishikawa K, Honda S, Tsukahara Y, Negi A. Preferable use of intravitreal Bevacizumab as a pretreatment of vitrectomy for severe proliferative diabetic retinopathy. Eye 2009; 23: 108-111.
60. Moradian S, Ahmadieh H, Malihi M, Soheilian M, Dehghan MH, Azarmina M. Intravitreal bevacizumab in active progressive proliferative diabetic retinopathy. Graefe's Archive for Clinical and Experimental Ophthalmology 2008; 246(12), 1699–1705.
61. Jonas JB, Spandau UH, Rensch F, Von Baltz S, Schlichtenbrede F. Infectious and noninfectious endophthalmitis after intravitreal bevacizumab. J Ocul Pharmacol Ther. 2007; 23:240–2.
62. Shima C, Sakaguchi H, Gomi F, et al., Complications in patients after intravitreal injection of bevacizumab. Acta Ophthalmol. 2008; 86:372–6.
63. Wickremasinghe SS, Michalova K, Gilhotra J, Guymer RH, Harper CA, Wong TY, et al., Acute intraocular inflammation after intravitreous injections of bevacizumab for treatment of neovascular age related macular degeneration. Ophthalmology. 2008; 115:1911–5.
64. Yamashiro K, Tsujikawa A, Miyamoto K, et al., Sterile endophthalmitis after intravitreal injection of bevacizumab obtained from a single batch. Retina. 2010; 30:485–90.
65. Sato T, Emi K, Ikeda T, et al., Severe Intraocular Inflammation after intravitreal Injection of Bevacizumab. Ophthalmology. 2010; 117:512–6.
66. Georgopoulos M, Polak K, Prager F, Prünte C, Schmidt-Erfurth U. Characteristics of severe intraocular inflammation following intravitreal injection of bevacizumab (Avastin). Br J Ophthalmol 2009; 93:4 457-462.
67. Von Hanno T, Kinge B, Fossen K. Retinal artery occlusion following intravitreal anti-VEGF therapy. Acta Ophthalmol. 2010; 88(2):263-6.
68. Huang ZL, Lin KH, Lee YC, Sheu MM, Tsai RK. Acute vision loss after intravitreal injection of bevacizumab (avastin) associated with ocular ischemic syndrome. Ophthalmologica. 2010; 224(2):86-9.
69. Amselem L, Montero J, Diaz-Llopis M: Intravitreal bevacizumab (Avastin) injection in ocular ischemic syndrome. Am J Ophthalmol 2007; 144: 122–124.
70. Mansour AM, Bynoe LA, Welch JC, et al. Retinal vascular events after intravitreal bevacizumab. Acta Ophthalmol. 2010 Nov; 88(7):730-5.
71. Yokoyama K, Chochi T, Kimoto K, Shinoda K, Nakatsuka K. Retinal circulatory disturbances following intracameral injection of bevacizumab for neovascular glaucoma. Acta Ophthalmol 2008; 86: 927–928.
72. . Kim KS, Chang HR, Song S. Ischaemic change after intravitreal bevacizumab (avastin) injection for macular oedema secondary to non-ischaemic central retinal vein occlusion. Acta Ophthalmol 2008; 86: 925–927.
73. . Kim JE, Mantravadi AV, Hur EY, Covert DJ: Short-term intraocular pressure changes immediately after intravitreal injections of anti-vascular endothelial growth factor agents. Am J Ophthalmol 2008; 146: 930– 934.
74. Falkenstein IA, Cheng L, Freeman WR. Changes of intraocular pressure after intravitreal injection of bevacizumab (avastin). Retina 2007; 27: 1044–1047.

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