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Bevacizumab (Avastin) for Ocular Disorders

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Abstract

Abnormal ocular neovascularization is major cause of loss of vision. The newly formed vessels are dysfunctional which can leak fluid, cause hemorrhage, or are associated with fibrous proliferation, resulting in potentially catastrophic loss of vision. Anti VEGF have come as a boon to cure ocular neovascularization. This paper will describe the attempted uses of bevacizumab, humanized monoclonal antibody to VEGF, for various ocular disorders and its efficacy in addition to discussing safety. Comments regarding appropriate use of this treatment are based on our current level of knowledge and large ,randomized control studies are required to expand the use of this wonderful drug.

Key words: neovascularization, VEGF, anti VEGF, bevacuzimab

1. Introduction

AntiVEGF drugs came as a boon for management of ocular neovascular disorders. Pegaptanib (Macugen, OSI Eyetech, 2005) was the first intravitreal Anti VEGF drug for the treatment of choroidal neovascularization associated with exudative age-related macular degeneration (AMD). Its widely expanding use was curtailed later that year as reports began to surface of the successful use of off-label intravitreal bevacizumab (IVB) (Avastin, Genentech) for the treatment of exudative AMD. Bevacizumab is a humanized monoclonal antibody to VEGF that is Federal Drug Administration (FDA)-approved for adjunct antiangiogenic treatment of metastatic colorectal cancer. It was initially studied for the treatment of exudative AMD with intravenous delivery (2 or 3 injections 5 mg/kg at 2-week intervals) with promising results[1,2]. Because of systemic side effects of intravenous bevacuzimab studies on intravitreal administration of bevacizumab (IVB) for the treatment of exudative AMD were undertaken.[3] The adverse side effects associated with intravenous bevacizumab treatment appeared to be avoided with intravitreal administration. The visual acuity and anatomical results were sufficiently compelling to lead to a tremendous increase in the use of off-label IVB as a first-line therapy for exudative AMD by early 2006. During the same time period, intravitreal ranibizumab (Lucentis, Genentech), a fab fragment of the bevacizumab humanized monoclonal antibody, was undergoing FDA clinical trial testing. Results from these clinical trials suggested that treatment of exudative AMD with intravitreal ranibizumab was superior to those reported in the pegaptanib phase III trials. July, 2006, marked the release of the FDA-approved ranibizumab for treatment of exudative AMD. Since its release there has been continual debate on the preferred treatment medication for exudative AMD, focusing on the effectiveness, safety, and cost differences between bevacizumab and ranibizumab. Bevacuzimab being less expensive than ranibizumab is being extensively used ,though off label.

2. Pharmacology

Bevacizumab (molecular weight 149 kD) is a recombinant humanized monoclonal IgG1 antibody that binds to Flt-1 and KDR receptors on endothelial cells and hence inhibits the biologic activity of human vascular endothelial growth factor (VEGF) (Figure 1,2) i*n vitro* and *in vivo*. It is produced in a mammalian cell (Chinese Hamster Ovary) expression system in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Figure 1 VEGF: centeral factor in angiogenesis

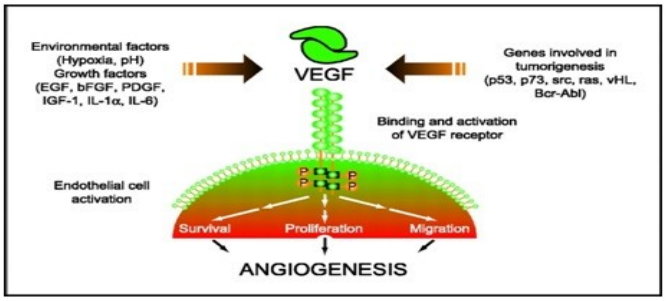
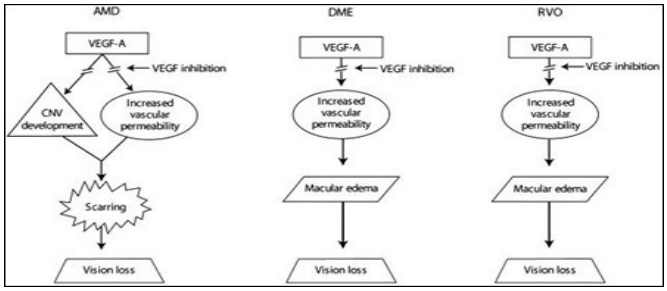


Figure 2 Pathophysiology of vision loss in AMD (Age related macular degeneration), DME (Diabetic macular edema), RVO (Retinal Vein Occlusion)



2.1 Ocular indications: Ocular conditions commonly treated with IVB are choroidal neovascularization, retinal neovascularization, macular edema, neovascular glaucoma and many other .

2.1.1 Choroidal Neovascularization

a. Exudative age related macular degeneration: Intravitreal bevacizumab has been widely used off-label for treatment of exudative AMD since early 2006. Following initial successful administration for exudative AMD (2005)[3] numerous case series were published illustrating the effectiveness of this treatment in high proportion of patients[4,5,6,7,8,9,10,11,12]. The most effective treatment regimen of IVB is still being explored. A greater visual acuity effect has been reported in naïve eyes compared to those that have received previous treatment.[13] However, those with longstanding exudative AMD have also been shown to improve with treatment. One retrospective study showed that 25% of those with exudative AMD for 5 months or longer (mean 17.9 months) improved at least 3 lines with treatment.[14]

The frequency of treatment and duration required are also being evaluated. Current treatment regimens vary with some clinicians treating as needed based on OCT findings and clinical examination, whereas others administer treatment on a monthly basis for a preset time period.[15,16,17]As prolonged courses of treatment are often necessary, combination therapy with PDT (Photodynamic therapy)and intravitreal dexamethasone has been studied in an effort to maintain good visual acuity results with less overall intervention.

b. Retinal Angiomatous Proliferation: Retinal angiomatous proliferation (RAP) is a variant of neovascular AMD that can exhibit intraretinal neovascularization, subretinal neovascularization, and choroidal neovascularization (CNV).[18,19,20] One series evaluated 23 eyes with RAP (11 with previous treatment) that were treated with IVB. At 3-month follow-up, five eyes (29.4%) had 2 or more lines improvement, one eye (5.9%) had worse vision, and 11 (64.7%) remained unchanged (six did not complete follow-up). Successful combination therapy with IVB and intravitreal triamcinolone has also been reported.[21]

c. CNV secondary to pathologic myopia: The prognosis of CNV secondary to pathologic myopia is quite poor.[22] Prior to anti-VEGF treatment, PDT was the most successful treatment modality for myopic CNV. Although follow-up is limited , the initial results with IVB appear promising.[23,24,25] A prospective study of 22 eyes evaluated the results of three consecutive monthly IVB injections with an additional three monthly injections in eyes with persistent CNV leakage. Only 2/20 eyes (10%) required the second series of injections. BCVA improved from 20/80 at baseline to 20/45 at 6 months. Sixty-eight percent improved 2 lines or more at 6 months.[26]

d. Other rare Choridal neovascularization: Various case series have documented positive response with intravitreal bevacuzimab in treatment of CNV secondary to Angioid Streaks[27], Best Disease[28], Adult Vitelliform Dystrophy[29], Central Serous Chorioretinopathy[30], Punctate Inner Choriodopathy[31], Multifocal Choroiditis[32], Presumed Ocular Histoplasmosis Syndrome[33], Choroidal Osteoma[34], Toxoplasmosis[35], Uveitis[36], Pseudotumor Cerebri[37], Peripapillary CNV[38] and Idiopathic CNV[39].

2.2 Retinal Neovascularization: Retinal neovascularization is a potential sequel of vascular compromise of retina in multitude of diseases. Neovascularization can lead to vision loss from vitreous hemorrhage (VH) or tractional retinal detachment (TRD).

a. Proliferative diabetic retinopathy: The standard of care for management of proliferative diabetic retinopathy is panretinal photocoagulation (PRP), which reduces the chance of severe vision loss by 50%. However, some patients will have persistent neovascularization despite PRP. Others have media abnormalities precluding the administration of PRP (e.g., corneal edema, VH, cataract). Many case reports and series have shown rapid regression of neovascularization of iris, disk, and retina following IVB treatment[40,41,42] between 1 and 3 weeks after injection with some reporting regression as early as 24 hours after treatment.

IVB treatment in conjunction with PRP for PDR has been evaluated. One retrospective case control study

reviewed 30 patients with symmetrical bilateral severe PDR. The control eye underwent PRP in two sessions separated by 2 weeks. The treatment eye received the same laser protocol, preceded by an IVB injection 1 week earlier. At 24-week follow-up, the treatment group had a statistically significant improvement in BCVA and CRT (VA = 0.039 [20/22], CRT = 264 microns) when compared to the control group (VA = 0.149 [20/28], CRT = 298 microns) ($p < 0.001$). Twenty-three percent of control eyes had a decrease in BCVA by 2 lines or greater at 24 weeks, whereas none of the IVB group had worsening of vision.[43] It was postulated that pretreatment with IVB may prevent secondary macular edema that is occasionally associated with PRP administration.

Preoperative IVB has been administered prior to pars plana vitrectomy (PPV) to assist in management of PDR-related complications such as vitreous hemorrhage and tractional retinal detachment.[44]The goal of pretreatment is to induce vessel regression and thereby reduce intraoperative bleeding and facilitate membrane peeling.

b. Sickle cell neovascularization: Evidence support value of IVB for sickle cell neovascularization if vitreous hemorrhage precludes sectoral PRP or for persistent neovascularization despite complete PRP.[45,46]

c. Retinopathy of prematurity: The standard treatment for ROP involves either sectoral laser photocoagulation or cryotherapy. Treatment of ROP with IVB has been reported.[47,48,49] A retrospective case series describes 22 eyes of 11 infants without previous treatment with moderate and severe stage 3 ROP in zone I or posterior zone II, treated with bilateral single IVB at 9 to 15 weeks of age. All eyes had regression of tunica vasculosa lentis, reduction of iris vessel engorgement, decreased plus disease (reduction of retinal vascular engorgement), and regression of peripheral retinal neovascularization. Successful treatment of ROP with IVB combined with laser has also been reported.[50]

There is extensive uncertainty regarding potential ocular and systemic side effects of IVB in premature infants. These concerns may preclude routine use of IVB treatment of ROP.

2.3 Macular Edema

a) Diabetic macular edema: Diabetic macular edema (DME) is leading cause of vision loss in working-aged population. IVB has been studied for treatment of DME[51,52,53] A multicenter, multinational retrospective study evaluated 78 eyes of 64 patients with DME treated with either 1.25 mg or 2.5 mg of IVB .Approximately 20% required a second injection at a mean of 13.8 weeks and 8% needed a third injection at a mean of 11.5 weeks later. Final visual acuity analysis demonstrated that 41.1% of eyes remained stable, 55.1% improved 2 or more lines, and 3.8% decreased 2 or more lines.CRT decreased to a mean of 275 microns at the end of follow-up ($p < 0.0001$).[54]

Attempts have been made to compare IVB to intravitreal triamcinolone acetonide (IVT) in treatment of DME.[55,56] Although both treatment modalities have shown short-term benefits in terms of reduced CRT and improved visual acuity, long-term results are unknown. The superiority of one treatment over other or in combination with other is uncertain. One noted advantage of IVB was avoidance of cataract progression and glaucoma commonly associated with IVT.

The Diabetic Retinopathy Clinical Research Network (DRCR) reported phase II findings comparing IVB and standard laser treatment for center-involving DME in 121 subjects. Differing doses of IVB (1.25 mg and 2.5 mg), differing interval dosing (once vs twice), and combined treatment (IVB followed by focal laser at 3 weeks followed by IVB at 6 weeks) were evaluated. Twelve-week results showed greater improvement in visual acuity with IVB (both 1.25 mg and 2.5 mg), with an average 1 line gain, compared with no vision difference in the laser treated groups. However, the study was not powered to determine superiority of treatment groups. Whereas the CRT improved more quickly in the IVB only groups, the improvement found at 12 weeks was matched by the laser group. There were no meaningful differences between IVB 1.25 mg and 2.5 mg in CRT reduction or visual acuity improvement. Combined focal laser and IVB did not achieve results equal to IVB monotherapy, but follow-up was too limited to make conclusions regarding combination therapy. Of interest, the effects of IVB on retinal thickening appeared to plateau at 3 weeks, indicating that injections may need to be administered every 4 weeks rather than every 6 weeks in future clinical trials.[57] Electrophysiology testing in eyes with DME treated with IVB found an improvement in the multifocal electroretinography tracings 2 months following IVB treatment.[58]

At this juncture, IVB is reasonable as an adjunct to focal laser treatment for refractory cases, or for use in situations that preclude focal laser (e.g., microaneurysm too close to fovea, media opacity).

b) Central retinal vein occlusion: No proven therapy exists for patients with macular edema from central retinal vein occlusion (CRVO).[59,60] The Central Retinal Vein Occlusion Study (CVOS) showed that laser treatment was not effective in treating macular edema following CRVO[61] .The first report of IVB for treatment of macular edema secondary to CRVO was published in 2005[62]. Within 1 week of IVB treatment, BCVA improved from 20/200 to 20/50 and OCT showed resolution of cystic retinal edema. Improvements were maintained for at least 4 weeks. Subsequent reports have been published regarding successful experiences with this treatment.[63,64]

The optimal timing to initiate treatment with IVB is another issue requiring further study. One retrospective series

studied 23 eyes treated with IVB within 3 months of diagnosis compared to another 23 eyes treated after 3 months of diagnosis. The study showed no statistical significant difference in the mean number of ETDRS letters gained between the two groups at 6 months (<3 months = 15.8 letters; >3 months = 13.4 letters). However, the <3-month group had a better baseline visual acuity and post treatment outcome. It is uncertain whether the baseline difference in BCVA was due to duration of disease. The same study also indicated that there was no statistical difference in the number of letters gained for ischemic versus nonischemic CRVO (ischemic = 13.1 letters; nonischemic = 13.9 letters). However, the baseline visual acuity was worse in the ischemic group. An average of three injections were needed over the course of 6 months for all patients. No eyes needed PRP for neovascularization[65].

c) Branch retinal vein occlusion: Macular edema is a common complication of branch retinal vein occlusion (BRVO). The standard of care at present is grid laser photocoagulation (Branch Retinal Vein Occlusion Study).[66] Recently, anti-VEGF treatments have been investigated for this disorder. A number of studies describe improved retinal thickness and visual acuity following IVB[67,68]. It is reasonable to use IVB after a 3-month period of observation in situations where standard laser treatment cannot be applied (severe retinal hemorrhages, media opacity) or when the edema is refractory to laser treatment.

d) Uveitis-induced CME: CME develops in approximately 30% of HLA B27-positive patients with anterior uveitis and is commonly found with posterior or panuveitis. Considering pathophysiology of this disorder, anti-inflammatory agents remain the mainstay of treatment. Although the visual acuity benefit following IVB treatment for uveitic CME remains controversial, it may be considered for refractory CME or in eyes with a glaucomatous steroid response.

e) Pseudophakic cystoid macular edema: Pseudophakic cystoid macular edema (CME) following cataract removal can result in persistent decreased visual acuity despite aggressive treatment.[69] However, resolution of CME often occurs without treatment. Standard treatment for persistent pseudophakic CME consists of topical NSAIDs plus topical steroids, followed by subtenons steroid injection for resistant cases. Limited retrospective case series report conflicting results for management with IVB. The potential role of IVB treatment for refractory pseudophakic CME remains uncertain.

f) Retinitis pigmentosa macular edema: Two patients with persistent CME due to retinitis pigmentosa were treated with IVB. Neither patient experienced an improvement in visual acuity or retinal edema.[70] No apparent benefit was found in this limited report.

2.4 Neovascular Glaucoma: Neovascular glaucoma (NVG) can result from numerous causes of ocular ischemia and can be a cause of significant visual morbidity. The standard treatment for neovascular glaucoma remains PRP with IOP-lowering medications . IVB is useful in those who are unable to undergo PRP, or as bridge therapy until PRP can be performed (e.g., media opacities). In cases of severe pressure elevation despite maximal medical therapy, IVB may be administered in conjunction with PRP in an attempt to achieve rapid regression of neovascularization thereby preventing permanent angle synechiae and more quickly achieving pressure control.

2.5 Other

a) Coats disease: Limited case reports show modest improvement in two of three eyes treated with IVB.[73,74]A 14-year-old boy with Coats disease unresponsive to laser treatment was treated with IVB and intravitreal triamcinolone acetonide. Following treatment, the superior bullous exudative retinal detachment and subfoveal serous fluid collection dramatically improved. The visual acuity improved from 20/400 to 20/125 and remained stable 6 months after injection. Further study in cases that have failed standard therapy is required prior to making treatment recommendations.

b) Juxtapapillary capillary hemangioma: Conflicting results exist in two case reports. A 58-year-old patient presented with right peripapillary hemangioma and visual acuity of 20/200. IVB 1.25 mg was administered. Two days later a decrease in exudation was observed and visual acuity improved to 20/40. Two weeks later, PDT was administered. Within 1 month, the tumor regressed markedly and visual acuity improved to 20/25. One year after therapy, the macula remained free of edema and visual acuity was 20/25.[75] In contrast, a second case report of a 23-year-old man with a Von Hippel-Lindau-associated capillary hemangioma of the optic nerve received three treatments of IVB with no effect on tumor size or exudation[76]. The eye that derived a benefit received PDT following the IVB. There was no apparent benefit from IVB monotherapy in this condition.

c) Idiopathic Macular Telangiectasia: Idiopathic macular telangiectasia (IMT) is a developmental retinal vascular abnormality associated with incompetence and ectasia of perifoveal capillaries[77]. Associated macular edema and subretinal neovascularization are the most common causes of visual loss. Laser photocoagulation and intravitreal injection of triamcinolone acetonide have been described for treatment of the macular edema, but no consistently effective treatment has been found.[78]

Several case reports describe regression of retinal and subretinal neovascularization due to IMT when treated with IVB.[79,80] In one series, six eyes of six patients with subretinal neovascularization were treated with IVB. Mean BCVA improved from 20/200 to 20/100, with a mean follow-up of 4.2 months. At the final visit, visual acuity had improved 2 or

more lines in five eyes (83%) and remained the same in one eye (17%). Mean CRT improved from 263 microns to 201 microns. Only one eye received more than one (two) IVB injection.[81]

d) Polypoidal Choroidal Vasculopathy: Initial reports suggest a positive effect on vascular leakage due to PCV but minimal effect on the choroidal vascular abnormality. An initial case report appeared to show marginal benefit of IVB in treatment of polypoidal choroidal vasculopathy (PCV).[82] A retrospective comparative series of 15 eyes showed a logMAR BCVA improvement from 0.61 (20/81) to 0.51 (20/65)($p = 0.014$) and CRT improvement from 347 to 247 microns after 3 months of monthly IVB treatment. The underlying polypoidal vascular abnormalities persisted on ICG testing. The study suggested that patients receiving subsequent PDT were less likely to have persistent polypoidal lesions.[83] A second retrospective series confirmed visual acuity improvement of previous study, but reported no benefit of adding PDT to IVB treatment. 58% of eyes had an improvement of BCVA of 2 lines or greater (average 2.2 injections).[84]

e) Central Serous Chorioretinopathy: IVB has been studied in treatment of CSCR for subretinal fluid accumulation . A series of five eyes with CSCR (without CNV) were treated with a single injection of IVB. All eyes had improved visual acuity, decreased leakage on FA, and diminished neurosensory detachment on OCT.[85] Due to the limited series and lack of controls, it is difficult to distinguish between effect of treatment versus natural course of disease. However, a separate report of a patient with CSCR persistent for more than 4 months and visual acuity reduction to 20/40 showed complete resolution of the serous detachment and improved vision of 20/20 2 weeks following IVB treatment.[86]

The standard care for CSCR is observation, as great majority resolve without intervention. There is currently more evidence to support use of focal laser or PDT for refractory cases,[87,88] but potential treatment with IVB for persistent subretinal fluid with diminished visual acuity deserves further study.

f) Eales disease: Eales disease is an idiopathic obliterative perivasculitis of unknown etiology with extensive retinal nonperfusion, perivascular sheathing, and neovascularization of disk and retina that affects mainly healthy young adults.[89] A 27-year-old man with Eales disease had a vitreous hemorrhage that resolved spontaneously over 6 months. FA revealed multiple areas of retinal neovascularization for which PRP was performed. Despite the laser, further disk and retinal neovascularization developed over the next 6 months. IVB 1.25mg was administered. At 1 month, both the disk and retinal neovascularization had regressed. Follow-up at 4 months revealed no recurrence of neovascularization.[90]

The neovascularization associated with Eales disease appears to respond to intravitreal bevacizumab in a similar manner to retinal neovascularization associated with other etiologies (PDR, Sickle cell retinopathy). Although panretinal laser remains the treatment of choice for this complication, IVB can be considered for refractory cases or for those with media opacity precluding laser. IVB is not reported to influence the vasculitic process.

g) Macroaneurysm: Standard therapy for macroaneurysm remains observation or photocoagulation if visual acuity is threatened. A single case report of macroaneurysm in a type 2 diabetic treated with IVB has been reported. The macroaneurysm resolved along with associated macular edema and hard exudates 2 weeks after the second of two injections of IVB delivered 1 month apart. BCVA improved from 20/400 to 20/50. The duration of effect was not reported.[71]

h) Vasoproliferative tumor: A 59-year-old with a vasoproliferative tumor, previously treated with laser photocoagulation and cryotherapy presented with CME and visual acuity of 20/60. The tumor thickness was 2.6 mm. IVB 2.5 mg was administered. Twenty-four days after treatment, the visual acuity improved to $20/20^{-1}$, the tumor thickness decreased to 1.0 mm and the macular edema resolved.[72]A single report limits the ability to provide a recommendation.

i) Topical bevacizumab for corneal neovascularization: Topically administered bevacizumab limits corneal neovascularization following chemical injury in a rat model[91]. However, clinical evidence is limited. Topical bevacizumab 1% (10 mg/ml) has been used to treat corneal neovascularization due to herpes in one case and ocular cicatricial pemphigoid in another. Both eyes had corneal neovascularization resistant to topical corticosteroid treatment for many months. Within 1 month of q.i.d. application of topical bevacizumab, the superficial and deep stromal neovascularization had subsided markedly.[92] Subconjunctival injection of bevacizumab also led to regression of corneal neovascularization due to dry eye and corneal graft failure[93].

j) Glaucoma surgery: Adjunctive IVB at the time of trabeculectomy and valve implant surgery for neovascular glaucoma has been reported. All surgeries were reported to be successful without adverse events.[95,96] .Bevacizumab (1mg) has also been used in bleb needling revision in a patient with a failing bleb and at 6 weeks of follow-up, the patient had a mildly vascularized bleb and IOP remained controlled at 6 mm Hg.[94] Further investigation is warranted after this encouraging case report.

3. Safety

Both ocular and systemic side effects have been an area of debate for intravitreal anti-VEGF medications, especially so for the off-label use of IVB. Intravenous use of bevacizumab for the management of colorectal cancer is

associated with severe systemic side effects including arterial thromboembolism, gastrointestinal perforation, hemorrhage, hypertensive crisis and nephrotic syndrome. Of note, these patients were receiving concurrent chemotherapy. Initial studies using this therapy intravenously for ocular disease in a healthier population did not find nearly the same risks.[97,98] IVB is administered at 1/400th of the dose used for intravenous treatment and has not been found to result in unexpected systemic side effects.

The safety data for bevacizumab do not include controls, with the exception of a few clinical trials.[99,100] In these, the follow-up is too short to make firm conclusions regarding safety. There has been no apparent systemic safety concerns related to the administration of IVB in these studies.

A safety study evaluating ocular and systemic side effects of IVB followed 1,173 patients for 12 months. Systemic adverse events were reported in 1.5% patients. These included 0.59% cases of an acute elevation of blood pressure, 0.5% strokes, 0.4% myocardial infarctions, and 0.4% deaths. Ocular complications included 0.16% bacterial endophthalmitis, 0.16% TRD, 0.09% uveitis, and a 0.02% each of rhegmatogenous retinal detachment and vitreous hemorrhage. These results are similar to those found for the other anti-VEGF agents in registration trials. Of note, the series is retrospective and 92 patients were lost to follow-up. Also, there was no standard dosing regimen in terms of volume of administration or frequency of injection.[101]

Electrophysiology and histology studies have been conducted to evaluate retinal toxicity following IVB treatment. Twelve rabbits were injected with IVB with doses ranging from 0.5 mg to 5 mg. Histologic and electroretinography (ERG) results in all groups showed no retinal toxicity.[102] There was no difference in flash visual evoked potential in 10 rabbits 4 weeks after IVB 2.5 mg when compared to controls. ERG responses were similar between the two groups throughout the follow-up testing period of 3 hours to 4 weeks after injection.

Tissue cultures have been performed on ganglion and retinal pigment epithelial (RPE) cells to evaluate their response to bevacizumab. The intravitreal concentration of bevacizumab following a 1.25-mg injection is approximately 0.3 mg/ml, based on a typical vitreous volume of 4 ml. Tissue cultures showed no effect on ganglion cells at an intravitreal concentration of 2.5 mg/ml. There was no increase in the rate of RPE cell death after 48 hours of incubation in a bevacizumab concentration of 0.8 mg/ml, but this did occur if the concentration was increased to 2.5 mg/ml[103] The clinical significance of these results is uncertain, but it is important to note that no adverse findings were found for intravitreal concentrations three times that used for treatment.

One study evaluated the rate of inflammatory reaction, infectious, and noninfectious endophthalmitis following 1218 injections of IVB. Infectious endophthalmitis was reported in one patient and in no patients was a noninfectious response noted. There were no reported cases of cellular infiltration or amorphous opacification of the vitreous.[104] Fluorophotometry has been used to demonstrate the lack of an inflammatory response following IVB treatment.[105]

4. Summary

Intravitreal bevacizumab has been utilized to treat numerous ocular disorders, generally those associated with neovascularization or vascular leakage as a consequence of an underlying disease. In general, the results have been positive, with numerous case series describing regression of neovascularization or resolution of leakage in response to treatment.

This paper outlines many conditions that are sufficiently rare to have limited case reports describing bevacizumab treatment. As a summary for such conditions, IVB is reasonable to use for salvage therapy of neovascularization that has not responded to standard treatment.

As far as safety of this wonder drug remains (from histology to functional retinal testing to adverse event reporting in larger trials) ,there is no current evidence that bevacizumab differs from the other injectable anti-VEGF agents in its safety profile. In the next few years the role of bevacizumab treatment for multiple conditions will undergo more rigorous study, allowing more refined recommendations regarding the care of patients and also it may get FDA approval for ophthalmic use.

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