Intravitreal Bevacizumab

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Angiogenesis is a highly complex, dynamic process regulated by a number of pro and antiangiogenic molecules. The vascular endothelial growth factor (VEGF) and its receptors play a vital role in normal and pathologic angiogenesis. Activation of the VEGF receptor pathway triggers a network of signaling processes that promote endothelial cell growth, migration and survival from pre-existing vasculature, differentiation, and mobilization of endothelial progenitor cells from the bone marrow into the peripheral circulation. In addition, VEGF increases vascular permeability leading to deposition of proteins in the interstitium that facilitate the process of angiogenesis.

There are many ocular diseases in which angiogenesis plays a major role; for example, proliferative diabetic retinopathy, age-related macular degeneration (ARMD), retinal vascular occlusion, sickle cell retinopathy and retinopathy of prematurity. VEGF has been identified in neovascular membranes in both diabetic retinopathy and ARMD and intraocular levels of the factor correlate with the severity of neovascularization in diabetic retinopathy. Therapeutic antagonism of VEGF in animal models result in significant inhibition of both retinal and choroidal neovascularization as well as a reduction in vascular permeability.\(^1\),\(^2\).

**Bevacizumab** (Avastin; Genentech Inc, South San Francisco, CA) is a full length humanized murine monoclonal antibody against the VEGF molecule. The amino acid sequence of this monoclonal antibody is 93% of human origin and 7% murine.\(^3\) Bevacizumab is approved by the Food and Drug Administration for treatment of metastatic colorectal cancer in 2004 and is in phase III trial for advanced breast cancer and advanced renal cancer. VEGF selectively stimulates endothelial cells by binding to two receptors, VEGFR-1 and VEGFR-2, which respond in a typical fashion to ligand binding by activation of signal transduction cascades. Bevacizumab can theoretically inhibit the activity of both receptors.

The labelled indication of Avastin is for the treatment of colon cancer. Its use in the eye is therefore off-label; no robust scientific data exist on its safety and efficacy, all the positive reports have short follow-ups. Off-label use of drugs is not illegal. Physicians and surgeons are allowed to do this. The fact that it is a common practice does not make it safe. There may be a risk of unexpected adverse outcomes, but this is also true of labelled use of new drugs.

Bevacizumab is a clear to slightly opalescent, colorless to pale brown solution with a pH of 6.2. It is supplied in 100 mg and 400 mg preservative free single use vials to deliver 4 ml or 16 ml of Bevacizumab (25 mg/ml). It is formulated in trehalose dihydrate, sodium phosphate (monobasic, monohydrate), sodium phosphate polysorbate and water for injection. The most commonly used dose for intravitreal injection currently is 1.25 mg (0.05 ml) although up to 2.50 mg (0.1 ml) may be used.\(^4\) The stability and anti VEGF activity of bevacizumab that was drawn up from the vial and refrigerated or frozen for later use is currently not known. The question as to how long the withdrawn samples can be stored in a syringe, without affecting the stability of the product, is relevant to our clinical
practices. In addition, as clinical trials are designed, it is important to maintain consistency between samples of bevacizumab, to assess its efficacy and establish the optimum dose for each disease. Studies have shown that there is minimal change in concentration of bevacizumab in the samples at 3 months and minimal further change from 3 months to 6 months. Given the potential error in accurately dosing 0.05 mL of drug in a clinical setting, a 10% change in drug concentration at 3 months is insignificant. It is interesting to note that at 3 months and 6 months, bevacizumab in both the vial and stored syringes degrades minimally. The manufacturer's guidelines state that bevacizumab vials must be refrigerated at 2°C to 8°C (36°F to 46°F), should be protected from light, and should be stored in the original carton until time of use. The manufacturer recommends that bevacizumab be used within 8 hours of being opened when diluted for intravenous administration and that it should be neither frozen nor shaken.

While ranibizumab (Lucentis) is derived from bevacizumab, the 2 molecules have quite different pharmacokinetics and VEGF–binding affinity. Ranibizumab (48 K Da)\(^2\) is an antibody fragment approximately one–third the size of bevacizumab (148 K Da)\(^3\) that penetrated the retina much better than a full sized antibody after intravitreal injection in monkeys. In June 2006, the FDA approved Lucentis for the treatment of patients with neovascular AMD. Ranibizumab has also been modified to increase 100 times its affinity for the VEGF-A receptor binding domain. The vitreous and serum half lives of bevacizumab are much longer than those of ranibizumab (5.6 Vs 3.2 days ; < 21 days Vs 15 hours respectively) raising the possibility of both local and systemic over dosage if bevacizumab is used in the same way as ranibizumab. Because subretinal neovascularisation causes breakdown of blood retinal barrier, it is inevitable that drugs injected into the eye will appear to inhibit important physiological functions of VEGF such as wound healing and the formation of collateral circulations in myocardium and peripheral vascular ischemia.

The last two years heralded the use of intravitreal anti-VEGF injections especially the use of intravitreal Bevacizumab (Avastin) injection in the management of ocular neovascularization arising from diverse etiologies. Age Related Macular Degeneration (ARMD) is a common cause of blindness that has a pathogenic link to neovascularization. The tell tale signs of AMD include the presence of drusen, thickening of Bruch's membrane and hypo and hyper pigmented areas of RPE cells. The development of choroidal neovascular membrane in the form of wet AMD leads to the growth of incomplete vessels. Leakage from these vessels cause accumulation of subretinal exudates and hemorrhages and brings about cell death and reactive gliosis with severe vision loss. Excellent results of regression of choroidal neovascular membranes associated with age related macular degeneration\(^5,\)\(^6\) following intravitreal Bevacizumab has been reported by various authors. Age related macular degeneration is the leading cause of irreversible vision loss among the elderly and macular neovascularisation is the most common cause of severe vision loss\(^7\). Photodynamic therapy is one current treatment for neovascular AMD patients with subfoveal neovascularisation. Although photodynamic therapy (PDT) is superior to placebos for preventing moderate vision loss in patients with relatively small minimally classic and occult lesions, there is little chance of visual improvement in these patients. Of all the angiogenic factors, VEGF is implicated as the major stimulus responsible for neovascularisation in AMD. Once injected into the eye, the proposed mechanism of action of anti VEGF agents involve penetration of the drug through the retina followed by competitive inhibition of VEGF in the extra cellular space\(^8\).

In a recent off-label study, patients with neovascular ARMD were treated systematically with bevacizumab (5 mg/kg)\(^9\). An open label prospective clinical study, the systemic Avastin for Neovascular AMD (SANA) study, proposed that systemic (B) could leak from CNV and blind extra cellular VEGF and that inhibition of extracellular VEGF could improve visual outcomes. Systemic (intravenous) bevacizumab was associated with a significant increase is visual acuity and decrease in central retinal thickness by OCT 1 week after therapy. These preliminary results are promising\(^9\). In addition to the ocular side effects, there were some systemic disadvantages associated with systemic administration of bevacizumab; the most significant disadvantage was
the possibility of life threatening adverse events. There was an increased risk of potentially fatal thromboembolic events in patients with advanced metastatic colorectal cancer receiving concomitant chemotherapy and bevacizumab when compared to patients receiving chemotherapy alone. Other potential systemic side effects included hypertension, epistaxis, hemoptysis, proteinuria, wound healing complications and gastrointestinal haemorrhage.

Another study has enrolled more than 250 patients to date for intravitreal Avastin therapy and data for the first 53 patients with 3-month follow-up is now available. The first set of data released in this ongoing study shows similar efficacy to that of Lucentis with notably 44% of patients gaining greater than or equal to three lines of visual acuity.

The major reservation for the off-label use of Avastin in treatment of CNV continues to be debate over the possible systemic side effects. During the initial investigational studies of Avastin for the treatment of colon cancer, patients were found to have significant side effects including increases in blood pressure and doubling of the risk for thromboembolic events including myocardial infarctions and cerebral vascular accidents. Proponents of Avastin contend that those complication rates were based on systemic administration of much larger dosages every 2 weeks for up to a year or longer. The use of Avastin intravitreally with a substantially lower dose would result in lower systemic peak levels and monthly dosing would have lower total dosage, both of which can reasonably be expected to induce fewer systemic side effects. Moreover, the reported risk of thromboembolism with Avastin therapy is based on a cancer population receiving concomitant chemotherapy, clearly at great risk for such events. An increase in thromboembolic events has not been observed in the intravitreal study thus far; however, further studies are needed to provide more conclusive data on the safety and efficacy of Avastin. In February 2008, the National Eye Institute (NEI) announced the start of a multicenter clinical trial to compare the relative safety and effectiveness of Lucentis and Avastin to treat advanced AMD.

Recent studies show that intravitreal bevacizumab leads to rapid regression of iris and angle neovascularization and should be investigated thoroughly as an adjunct in the management of neovascular glaucoma. These studies have demonstrated the safety and efficacy of intravitreal Bevacizumab in causing regression of ocular neovascularization. Kahook MY et al and Davidorf FH et al have, in 2006, proved the efficacy of intravitreal Avastin injection as an adjunct in the management of neovascular glaucoma. In these studies rapid regression of iris neovascularization and clearing of corneal oedema occurred within 48 hours giving symptomatic relief to the patient along with short term IOP control. Thus IVB as an adjuvant in the management of neovascular glaucoma may offer a more scientific rationale for the treatment of the causative neovascular trigger, might prevent further PAS formation and extension of secondary angle closure. It also facilitates early initiation of PRP, further dampening the neovascular trigger. Prospective randomized trials are required to validate the efficacy of IVB alone as monotherapy and its use in conjunction with maximal anti glaucoma medications, ARC, CPC and cyclo cryotherapy. Long term results, chances of recurrence and the options to manage them can only be answered by a prospective trial in a larger series with longer follow up data.

Recalcitrant diabetic macular edema is characterized by the accumulation of plaques of hard exudates in a grossly oedematous retina not amenable to the standard modalities such as photocoagulation, intravitreal injection of triamcinolone acetonide or vitrectomy and showing a very poor visual potential. These patients usually have a poorly controlled glycemic status of long duration with associated co-morbid conditions such as systemic hypertension, dyslipidemia and chronic renal failure. Studies reveal reduction in central retinal thickness by OCT scan and improvement in visual acuity in these patients after intravitreal injection of bevacizumab.

Intravitreal bevacizumab results in significant decrease in macular edema due to central retinal vein occlusion. Retinal vein occlusion is associated with increased intravitreal levels of VEGF, particularly in cases complicated by neovascularisation. Eyes with CRVO show evidence of intraretinal VEGF mRNA expression. Inhibition of VEGF by anti sense oligo deoxy nucleotide or anti VEGF monoclonal antibody resulted in reduction or complete prevention of iris
neovascularisation in animal models of CRVO. Since intraocular injection of VEGF causes retinal microvascular abnormalities and retinal ischemia, and since retinal vein occlusion itself causes increased intraocular VEGF that varies with disease severity, inhibition of VEGF in human CRVO has therapeutic potential.

The lack of controlled studies leaves open questions regarding the safety of intravitreal injection of Bevacizumab. The literature to date suggests that IVB is relatively safe in the short term with few severe ocular and systemic side effects. The systemic risk from intravitreal injections of drugs in adults are relatively low because the amount of drug that is absorbed into the systemic circulation is then diluted substantially by blood volume. Nevertheless, beneficial cross over effects have been reported (eg; as a reduction in neovascularization of the disc in the fellow eye of an eye that received anti VEGF agent). Published ocular side effects include uveitis, subconjunctival haemorrhage, transient blurred vision, vitritis, lid irritation, ocular discomfort, foreign body sensation, corneal abrasion, elevated IOP, cataract, posterior vitreous detachment, endophthalmitis, subretinal haemorrhage, RPE tears, and retinal detachment. Anti VEGF agents act by reducing angiogenesis and arresting the CVNM. The same pathology of fibrovascular tissue contraction may be at work in RPE rips following anti-VEGF therapy. The risk of an RPE rip should be considered with treatment for anti VEGF agents in cases with fibrovascular PED. The lack of controlled studies leaves questions as to the frequency of the various reported side effects.

Kernt et al measured IOP in 45 patients undergoing IVB and reported 2 cases of elevated IOP (22 and 28 mm of Hg) immediately following injection, both of which resolved without therapy. Although the frequency of elevated IOP after IVB appears to be low, the long term consequences of transient IOP elevation could be significant not only for those with already compromised optic nerves, such as in patients with glaucoma, but also in terms of risk of vascular occlusive events, such as retinal venous or arterial occlusion. The mechanism for acute elevation in IOP has been postulated to be mechanical, secondary to increased vitreous volume. If this is the case, in high risk cases one might consider anterior chamber tap prior to injection. Certain precautions have to be taken to limit the risks and complications associated with intravitreal injection of anti-VEGF agents. So to reduce the risk of endophthalmitis associated with intravenous injections, 5% povidone iodine can be applied to the conjunctival cul de sac. To avoid cataract or possible injury should the patient move, forceps is used to stabilize the globe in the region anesthetised before administering the injection and ensure that the angle of the needle path into the vitreous cavity avoids the lens. After the injection, the intraocular pressure is measured and the patency of central retinal artery (CRA) is checked by indirect ophthalmoscopy. If there is loss of vision, or the patency of the CRA is compromised, a paracentesis has to be performed.

It should be explained to the patients that the drug is approved for use in the human body, but has either not been approved by intravitreal route or not for use in this particular disease. A large scale study has not been conducted, and therefore the data to support this use of the agent are limited and also there are small case series that suggest the agent may be benefit.

Intravitreal bevacizumab did not appear toxic to the retina in albino rabbits at a concentration of 2.5 mg based on electrophysiologic studies. Maturi R K et al in his study concluded that intravitreal use of Bevacizumab resulted in improvement of mf – ERG macular function responses and relatively stable G - ERG responses. The macular electrophysiologic response suggested that macular function improved with treatment. G -ERG suggested that there is no significant measurable photoreceptor toxicity with the use of IVB over short term.

The use of intravitreal bevacizumab for the treatment of chorioretinal diseases mediated by VEGF has spread throughout the globe in less than six months from the time of the first case reports. The most obvious reasons for the rapid adoption of intravitreal Avastin include the rational scientific basis of treatment, the overwhelming efficacy reported for the closely related drug known as Lucentis (Ranibizumab, Genentech Inc), the presence of an enormous unmet need to prevent blindness from VEGF–mediated diseases, the visual acuity and anatomic improvements appreciated by patients and treating physicians, the apparent short term safety and the affordable low cost of the drug.
Neovascularization is a key pathophysiologic mechanism of a wide variety of diseases, making the factors that mediate angiogenesis an attractive therapeutic target. Although the brunt of clinical research in the inhibition of ocular neovascularization has been on CNV related to AMD, researchers are exploring the potential for benefit from the utilization of these drugs in other diseases such as diabetic retinopathy, vascular occlusion, and macular edema. While the gamut of retinal and choroidal neovascular diseases varies greatly, the common source of pathogenesis, incompetent vessels and the compromise of the blood retinal barrier, has provided for significant advancement in the treatment of these diseases. Despite all the advancements in treatment discussed here, the collection of ocular diseases caused by neovascularization continues to create significant morbidity among patients.

References