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REVIEW ARTICLE

Avastin: Therapeutic Potential in Vascular Retinopathy due to Retinal Vein Occlusion

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ABSTRACT

Avastin (bevacizumab) is a recombinant humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF) and it is FDA-approved for the treatment of colorectal cancer. Though other VEGF inhibitors are being developed or already licensed to treat ocular diseases, the anticancer drug, bevacizumab, found its way into ophthalmology and clinical practice all around the world.

Vascular retinopathy due to retinal vein occlusion (RVO) causes retinal injury, resulting in the growth of new, inappropriate blood vessels that cause vision loss and more serious complications. Release of vascular endothelial growth factor (VEGF) contributes to increased vascular permeability in the eye and inappropriate new vessel growth. It is believed that anti-VEGF treatment may help decrease vascular permeability and edema and prevent the inappropriate growth of new blood vessels in the retina in patients with RVO.

The objective of this review is to evaluate the evidence and discuss the rationale behind the recent suggestions that intravitreal pharmacotherapy by Avastin as an anti-vascular endothelial growth factor may be useful in the treatment of retinal vein occlusion.

Keywords*: vascular endothelial growth factor inhibitors, avastin, Vascular retinopathy, retinal vein occlusion*

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INTRODUCTION

Avastin (Bevacizumab) is a full-length, humanized monoclonal antibody directed against all the biologically active isoforms of vascular endothelial growth factor (VEGF) –A [1]. It is a recombinant IgG1 antibody with a molecular weight of about 149kD that is produced in a Chinese Hamster Ovary mammalian cell expression system in a nutrient medium containing the antibiotic gentamicin [2].

Bevacizumab binds to the receptor-binding domain of all VEGF-A isoforms. Consequently, it prevents the interaction between VEGF-A and its receptors (Flt-1 and KDR) on the surface of endothelial cells which starts the intracellular signaling pathway leading to endothelial cell proliferation and new blood vessel formation [1].

Avastin was primarily designed to inhibit angiogenesis in the treatment of a variety of solid tumors [3-5]. In 2004, the FDA approved bevacizumab for the treatment of metastatic colorectal cancer in combination with standard chemotherapy [4].

Angiogenesis is a complex multifaceted process influenced by several factors. Inducers and inhibitors balance the angiogenic switch which finally turns the process on or off. Though the number of known factors is steadily increasing, VEGF-A seems to play a very pivotal role and is the primary target of recent anti-angiogenic strategies. An extensive number of experimental studies have established that VEGF plays a central role in the development of several ocular pathologies characterized by neovascularization and increased vascular permeability [6].

The concentration of VEGF is increased in all ocular diseases that involve neovascularization and/or inflammation, such as proliferative diabetic retinopathy [7], neovascular glaucoma [8,9], uveitis [10], age-related macular degeneration [11], retinal vein occlusion [12-14].

Vascular endothelial growth factor plays an important role in the pathophysiology of several light-threatening retinal disorders such as age-related macular degeneration, diabetic macular edema and proliferative diabetic retinopathy and retinal vein occlusion and contributes to increased permeability across both the blood-retinal and blood-brain barriers.

The logical consequence was a therapeutic regimen specifically targeting VEGF. Though other VEGF inhibitors are being developed or already licensed to treat ocular diseases, the anticancer drug, bevacizumab, found its way into ophthalmology and clinical practice all around the world.
Avastin was not intended and therefore not formally studied or approved for intraocular use, but Dr. Rosenfeld's pioneering work [15,16] and the unavailability of a related ocular drug, ranibizumab, and the need for a potent drug led to rapid and wide off-label use of bevacizumab . After initial studies were done with IV injections, this route of administration was not generally accepted due to higher costs and due to a more conceivable risk of systemic side-effects [17,18].
Retinal vein occlusion (RVO) is one of the most common causes of acquired retinal vascular abnormality in adults and a frequent cause of visual loss. In a recent analysis of pooled data from population studies worldwide, the overall RVO prevalence was 0.52% (0.44% branch retinal vein occlusion (BRVO), 0.08% central retinal vein occlusion (CRVO), translating to approximately 16 million individuals worldwide affected by RVO [19].
Despite being recognized at least as early as 1855 [20] its management is still controversial. Vascular retinopathy due to retinal vein occlusion causes retinal injury and loss of vision. The retina can also become "ischemic" (starved for oxygen), resulting in the growth of new, inappropriate blood vessels that can cause further vision loss and more serious complications. Release of vascular endothelial growth factor (VEGF) contributes to increased vascular permeability in the eye and inappropriate new vessel growth. It is believed that anti-VEGF treatment may help decrease vascular permeability and edema and prevent the inappropriate growth of new blood vessels in the retina in patients with RVO.
The objective of this review is to evaluate the evidence and discuss the rationale behind the recent suggestions that intravitreal pharmacotherapy by Avastin as an anti-vascular endothelial growth factor may be useful in the treatment of retinal vein occlusion.

RETINAL VEIN OCCLUSION

Retinal vein occlusion as a vasooclusive disorder of the retinal vein is the most common visually disabling disease affecting the retina after diabetic retinopathy, and is a frequent cause of vision loss and even blindness [21-23]. Although it is more common in the middle-aged and elderly population, no age group is immube to it [24]. The pathogenesis of RVO is multifactorial with both local factors and systemic diseases being etiologically important. Many case-control studies have examined the clinical features and risk factors in this disorder [23,26-30]. Known risk factors for RVO include systemic vascular disease, hypertension, diabetes mellitus, hyperlipidemia and glaucoma. Hypercoagulable states are associated with RVO. These include primary hypercoagulable states with a defect in the physiological anticoagulant mechanism [31-34] and secondary hypercoagulable states, which are conditions, associated with an increased risk of thrombosis [35-43].
Depending on the location of the obstruction, the RVOs can be divided into central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO). In CRVO the obstruction is located in the central vein, at the level of the optic nerve, so most of the retina is affected. Anatomic features make the central retinal vein vulnerable to occlusion at this location. As the optic nerve and the accompanying central retinal artery and vein pass through the sieve-like connective tissue of the lamina cribrosa, the central retinal vein normally narrows, and the dense connective tissue of the lamina cribrosa limits any expansion of the traversing optic nerve and vessels within. Any thickening of the central retinal artery, which shares a common fibrous tissue sheath with the vein, might easily compress the lumen of the adjacent central retinal vein and start in motion the sequence of events that lead to thrombus formation [44]. In BRVO, the obstruction is located in one of the branches of the central vein, affecting only part of the posterior pole and the portion of the peripheral retina drained by occluded branch [45].

VASCULAR ENDOTHELIAL GROWTH FACTOR IN THE PATHOPHYSIOLOGY OF THE RETINAL VEIN OCCLUSION

VEGF contributes to increased permeability across both the blood-retinal and blood-brain barriers.
In central retinal vein occlusion there is increased intraluminal and interstitial pressure throughout the retina drained by the obstructed vessels, resulting in reduced arterial perfusion, which is exacerbated by preexistent arterial insufficiency, and in variable amounts of retinal ischemia. Retinal ischemia causes increased production of vascular endothelial growth factor , which causes vascular

leakage and macular edema. High levels of VEGF also promote retinal hemorrhages and exacerbate capillary nonperfusion [46].

Human eyes with CRVO showed evidence of intraretinal upregulated expression of VEGF mRNA [47]. Indeed, raised levels of VEGF have been reported in both the aqueous and vitreous fluid of patients with ischemic CRVO, and are responsible for the increase in vascular permeability that leads to ME [48] .

Branch retinal vein occlusion also leads to retinal ischemia that induces the production of cytokines such as VEGF by retinal cells such as glial cells and vascular endothelial cells in the occluded region affected by anoxia. These cytokines interact with each other (cytokine network) and this results in impairment of the blood-retinal barrier and an increase of vascular permeability, considered important in the development of macular edema associated with BRVO [49]. Lee et al. [50] ischaemic insult may play a central role in the development of BRVO-ME.

Aqueous and vitreous levels of VEGF were significantly correlated with the severity of ME [51,52] .

The logical consequence was a therapeutic regimen specifically targeting VEGF.

AVASTIN

Avastin(bevacizumab (Avastin, Roche)), is FDA-approved for the treatment of colorectal cancer. Though other VEGF inhibitors are being developed or already licensed to treat ocular diseases, the anticancer drug, bevacizumab, found its way into ophthalmology and clinical practice all around the world, because the agent costs substantially less per dose than Lucentis. It has been widely used off-label since 2004 to treat several retinal diseases, including retinal vein occlusion.

Bevacizumab is a recombinant humanized monoclonal antibody directed against VEGF. There have been several studies with bevacizumab and RVO, retrospective or prospective, all showing improvements in visual acuity (VA) and optical coherence tomography (OCT) outcomes, but also short-term efficacy and high recurrence rate. The dosage varies between 1 and 2.5 mg, there are no different outcomes [53-62]. The Pan-American Collaborative Retina Study group concluded that intravitreal injections of bevacizumab at doses up to 2.5 mg were more effective in improving VA and reducing macular edema at 6 months (compared to 1.25 mg), but the study had no control group [59]. By contrast, no statistically significant differences were found between the doses, when the group presented the results at 24 months [63]. In addition, Ach et al. [64] found that CRVO patients who benefit from therapy were significantly younger and had lower central retinal thickness at baseline, while BRVO patients showed no predictive factors for effectiveness of bevacizumab therapy. Recently, Axel-Siegel et al. [65], in a retrospective study of 35 eyes with CRVO-induced macular edema treated with 3-4 loading doses (1.25 mg) of intravitreal bevacizumab, repeated injections as necessary and followed for at least 6 months, claimed that visual acuity gain was positively correlated with central macular thickness reduction and treatment improves vision, especially in patients with good initial VA. Recently, Ghayoor et al. [66] evaluated the effect of Avastin (mean 2.8 injections) in 8 eyes with CRVO- and 22 with BRVO-associated macular edema and claimed that significant improvement in best corrected VA was observed at 6th week of follow-up. At 6th month more than 60% showed improvement in best corrected visual acuity, similarly 70% patients had complete resolution of macular edema. The authors concluded that anti-VEGF therapy should be further evaluated in large, prospective, controlled clinical studies.

At the latest prospective study Dallen et al. [67] evaluating the 12-month outcome and predictive factors of visual acuity (VA) changes following bevacizumab therapy for CRVO concluded that early injections of bevacizumab in young patients in whom VA is relatively preserved leads to a significant improvement in VA. Ischaemic CRVO and poor baseline VA are associated with nonresponse to such therapy [67].

Epstein et al. [68] conducted the latest prospective double-masked clinical trial of 60 patients with macular edema secondary to CRVO randomized 1:1 to receive intraocular injections of bevacizumab or sham injection every 6 weeks for 6 months. Results evidenced that the treatment improve VA and reduce macular edema significantly compared with sham.

Potential Hazards of Avastin Therapy

Local adverse events

The International Intravitreal Bevacizumab Safety Survey gathered adverse events from doctors around the world via the internet [69] and showed all ocular and systemic side effects to be under 0.21% including corneal abrasion, lens injury, endophthalmitis, retinal detachment, inflammation or

uveitis, cataract progression, acute vision loss, central retinal artery occlusion, subretinal haemorrhage, retinal pigment epithelium tears, blood pressure elevation, transient ischaemic attack, cerebrovascular accident and death. Fung. et al. [69] concluded that self-reporting of adverse events after intravitreal bevacizumab injections did not show an increased rate of potential drug-related ocular or systemic events and these short-term results suggest that intravitreal bevacizumab seems to be safe.

The latest study [70] on the rate of serious adverse effects in a series of bevacizumab and ranibizumab injections revealed that subjects who received bevacizumab were 12 times more likely to develop severe intraocular inflammation following each injection than were those who received ranibizumab (OR = 11.71; 95% CI 1.5-93). The 1 case of acute intraocular inflammation following ranibizumab injection was mild and not associated with vision loss. No other serious ocular complications were noted. A trend was also noted toward an increased risk for arterial thromboembolic events in patients receiving bevacizumab, although the confidence interval was wide (OR = 4.26; 95% CI 0.44-41). In conclusion, authors stated that significant concern still exists regarding the safety of off-label use of intravitreal bevacizumab. Patients receiving bevacizumab should be counselled regarding a possible increased risk for serious adverse events. Anti-VEGF therapy may therefore have adverse effects on ocular blood flow. Von Hanno et al. [71] presented two cases of retinal artery occlusion after intravitreal injection of bevacizumab (Avastin) and ranibizumab (Lucentis) respectively and concluded that the therapeutic principle may be associated with an increased risk of retinal arterial occlusions.

Leung et al. [72] presented a series of three patients of the nearly 200 patients with CRVO who suffered apparent macular infarction within weeks of intravitreal administration of bevacizumab. The authors stated that this has not been described in the natural history of the disease and is associated with poor visual outcomes.

In Manousaridis and Talks [73] opinion worsening of macular ischaemia in the long term cannot be definitely excluded, particularly in eyes with significant ischaemia at baseline and after repeated intraocular anti-VEGF injections. The decision to offer prolonged anti-VEGF treatment in cases of significant coexisting macular ischaemia should not be based only on measurements of macular thickness; instead repeat fluorescein angiograms should be performed.

In conclusion, the overall risk of complications is low when the injection is administered by experienced ophthalmologists [74].

Tachyphylaxis/tolerance

The worldwide use of intravitreal application of anti-vascular growth factor and the realisation that regular applications over long periods of time are necessary to maintain vision in these eyes, has revealed the problem of tolerance/tachyphylaxy [75] . In 2008, the paper suggested for the first time possible tachyphylaxis/tolerance with chronic and bevacizumab treatment [76] . Binder S. [75] recommended different options to prevent tachyphylaxis/tolerance: (1) to increase the dosage or shorten treatment intervals if tolerance has developed; (2) to pause treatment if tachyphylaxis has occurred; (3) to combine drugs with different modes of action; or (4) to switch to a similar drug with different properties (bevacizumab and ranibizumab differ in molecular size, affinity and absorption).

Systemic adverse effects

While used intravitreally, the systemic absorption is minimal, however, a trend has been observed towards a higher risk of stroke among patients with a history of heart disease [77]. Campbell et al. [78] assessing the risk of systemic adverse events associated with intravitreal injections of vascular endothelial growth factor inhibiting drugs in the nested case-control study have found that intravitreal injections of bevacizumab and ranibizumab were not associated with significant risks of ischaemic stroke, acute myocardial infarction, congestive heart failure, or venous thromboembolism.

There is some evidence that intravitreal anti-VEGF injections may result in systemic absorption, with the potential for injury in organs that are reliant on VEGF, such as the kidney. Pellé et al. [79] reported the first case of a patient who developed an acute decrease in kidney function, nonimmune microangiopathic hemolytic anemia with schistocytes, and thrombocytopenia after 4 intravitreal injections of VEGF inhibitor. Light microscopy of a kidney biopsy specimen showed segmental duplications of glomerular basement membranes with endothelial swelling and several recanalized arteriolar thrombi. Because of the increasing use of intravitreal anti-VEGF agents, ophthalmologists and nephrologists should be aware of the associated risk of kidney disease. Early detection is crucial so that intravitreal injections can be stopped before severe kidney disease occurs. In Sorenson and

Sheibani [80] opinion perhaps baseline and renal function during treatment (serum creatinine and urinary protein levels, blood pressure) should be carefully monitored to ensure that the improved visual acuity is not at the expense of renal function.

In conclusion, major concerns with anti-VEGF therapy for ocular diseases include: repeat intravitreal injections; risk of cardiovascular complications; possible retinal and neural toxicity due to cumulative dosing; interference with physiologic functions of VEGF; and economic and cost-effectiveness concerns. Tailoring treatment to the individual patient should increase the chance of treatment success, while sparing patients from unnecessary drug exposure and risk of adverse events. Furthermore, avoiding unnecessary treatment also has the potential to improve the cost-effectiveness of treatment [81].

CONCLUSIONS

In conclusion, studies evaluating pharmacotherapy by Avastin in vascular retinopathy due to retinal vein occlusion have lacked sufficient sample size and power, did not have sufficient follow-up times for long-term assessment of outcomes, or a combination thereof. There are still many unclear points, such as: the correct time to start injections and the specific moment to finish them, the number of injections, the long-term efficacy and safety, ocular and systemic side effects. Therefore, definitive conclusions cannot be reached.

In spite of enthusiastic claims of success for anti-VEGF therapy in RVO, the reality is that the currently available treatment by Avastin is associated with visual improvement in only a subset of patients and the benefits and risks of therapy should be weighted in all treatment decisions.

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