Journal of Pharmacy and Alternative Medicine
ISSN 2222-5668 (Paper) ISSN 2222-4807 (Online)
Vol. 2, No. 2, 2013

Review Article

Branch Retinal Vein Occlusion in the Light of Anti-angiogenic Therapy

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Accepted Date: 17 April 2013

Abstract

Branch retinal vein occlusion (BRVO) is one of the most common causes of acquired retinal vascular abnormality in adults and a frequent cause of visual loss. This circulatory disorder leads to retinal ischemia, which then induces up regulation of various inflammatory factors, including vascular endothelial growth factor (VEGF). VEGF is a major regulator of angiogenesis and vascular permeability in the eye for physiologic as well as pathologic processes. Tissue hypoxia due to primary vascular occlusive disease is the most common driver of VEGF synthesis and as branch retinal vein occlusion is associated with increased levels of VEGF, therapy by anti-angiogenics or vascular endothelial growth factor inhibitors (anti-VEGF) was proposed to be a promising strategy for branch retinal vein occlusion. Consequently, several anti-angiogenics have been developed for the treatment of vasocclusive disease of retinal vein.

The objective of this review is to evaluate the efficacy of pharmacotherapy by vascular endothelial growth factor inhibitors as a therapeutic solution for branch retinal vein occlusion.

Keywords: Branch Retinal Vein Occlusion, Vascular Endothelial Growth Factor, Vascular Endothelial Growth Factor Inhibitors, Pharmacotherapy

1. Introduction

Branch retinal vein occlusion (BRVO) is one of the most common causes of acquired retinal vascular abnormality in adults and a frequent cause of visual loss (Rogers et al., 2010). By using pooled data involving approximately 50,000 participants from the United States, Europe, Asia, and Australia, study by Rogers et al. (2010) shows that BRVO affects 4 per 1000 persons .On the basis of these rates, projected to the world population, approximately 16 million adults are affected by retinal vein occlusion (RVO). The prevalence of BRVO increases significantly with age but does not differ by gender. Possible racial/ethnic differences in the prevalence of BRVO may reflect differences in the prevalence of RVO risk factors. Application of current understanding of pathophysiology of branch retinal vein occlusion is important for proper intervention for this most common visually disabling disease affecting the retina after diabetic retinopathy (Cugati et al., 2006; Klein et al., 2008).

Branch retinal vein occlusion is associated with increased levels of vascular endothelial growth factor (VEGF), therapy by anti-angiogenics or vascular endothelial growth factor inhibitors (anti-VEGF) was proposed to be a promising strategy for branch retinal vein occlusion. Consequently, several anti-angiogenics have been developed for the treatment of vasocclusive disease of retinal vein.

The objective of this review is to evaluate the efficacy of pharmacotherapy by vascular endothelial growth factor inhibitors as a therapeutic solution for branch retinal vein occlusion.

2. Pathophysiology of the branch retinal vein occlusion

The first case of BRVO was reported by Leber in 1877. There are still gaps in understanding the aetiology and pathogenesis of circulatory disorders of the branches of central retinal vein. Possible causes of BRVO include external vascular compression, disease of the vein wall, or intravascular thrombus formation (Klein et al., 2000). Hypertension and atherosclerosis are known risk factors for BRVO, and both cause thickening

of arteriole walls. BRVO occurs at sites where retinal arterioles cross over veins and it appears that thickening of the arteriole wall compresses the vein, causes turbulent flow, damages endothelium, and promotes thrombosis. 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 (Rehak and Rehak, 2008).

The obstruction in venous outflow after BRVO increases intraluminal venous pressure and causes transudation of plasma and blood, resulting in edema, including macular edema and hemorrhages throughout the drainage area of a branch retinal vein. Severe edema appears to increase interstitial pressure and compromise arterial perfusion resulting in variable amounts of capillary occlusion and cotton wool patches. It is likely that a difference in the amount of pre-existent arterial insufficiency from atherosclerosis determines differences in the amount of capillary nonperfusion. Extensive nonperfusion is associated with a poor prognosis. In some patients, ischemia increases over time and they are viewed as undergoing a transition from nonischemic to ischemic. Severe retinal ischemia can be complicated by retinal neovascularization, neovascular glaucoma, and a very poor visual outcome.

Branch retinal vein occlusion as was mentioned earlier leads to retinal ischaemia, which then induces upregulation of various inflammatory factors, including vascular endothelial growth factor (VEGF) (Noma et al., 2012), which is also known to play a role in macular edema (ME) secondary to retinal vein occlusion (Campochiaro et al.,2008). Observations by Noma et al. (2006, 2012) suggest that in patients with BRVO, vascular occlusion induces the expression of vascular endothelial growth factor (VEGF) and Interleukin-6 (IL-6), resulting in blood-retinal barrier breakdown and increased vascular permeability. Thus, VEGF and IL-6 may contribute to the development and progression of vasogenic (ME) in BRVO. The involvement of cytokines in the aqueous humour is also important in the development and progression of ME due to branch retinal vein occlusion the latest results results suggest that ischaemic insult may play a central role in the development of macular edema in BRVO (Lee et al., 2012).

Vascular endothelial growth factor is a major regulator of angiogenesis and vascular permeability in the eye for physiologic as well as pathologic processes (Pieramici and Rabena, 2008) is implicated in the pathogenesis of BRVO (Brand. 2012). Consequently, several anti-VEGF agents have been developed for the treatment of this disease.

3. Anti-angiogenic Therapy in Branch Retinal Vein Occlusion

The term anti-angiogenic therapy was born more than 35 years ago by J. Folkman, who hypothesized that cancer may be treated by abolishing the nutrients and oxygen-providing blood vessels (Stewart,2012) and bevacizumab became the first therapy approved by the US Food and Drug Administration (FDA) designed to inhibit angiogenesis in tumors. As retinal vein occlusion is associated with increased levels of VEGF, anti-VEGF therapy was proposed to be a promising strategy for retinal vein occlusion.

Intraocular injections of a VEGF-binding protein reduce vascular leakage, resulting in improvement in macular edema, accelerate resorption of retinal hemorrhages, and prevent worsening of capillary nonperfusion (Campochiaro, 2012; Stewart, 2012).

There are 3 anti-VEGF agents that are either approved or in common use in ophthalmology for BRVO treatment, namely ranibizumab (Lucentis, Novartis), bevacizumab (Avastin, Roche), pegaptanib (Macugen, Pfizer).

3.1 Ranibizumab

In June 2006, Lucentis (ranibizumab, Roche/Genentech) has first received FDA approval for the treatment of macular edema due to BRVO. Ranibizumab is a humanized, affinity-matured VEGF antibody fragment that binds to and neutralizes all isoforms of VEGF. One phase III multicenter, prospective clinical trial assessing the safety, tolerability and efficacy of intravitreal ranibizumab injections in the treatment of macular edema secondary to BRVO was finished. It was called BRAVO (study of the efficacy and safety of ranibizumab injection compared with sham in patients with macular edema due to BRVO) (Campochiaro et al., 2010).

In the BRAVO study, 397 patients with macular edema following branch retinal vein occlusion (BRVO)

were randomized to receive monthly intraocular injections of 0.3 mg (n = 134) or 0.5 mg (n = 131) of ranibizumab or sham injections (n = 132). Patients were eligible if they had foveal-involved macular edema from a BRVO occurring within 12 months of study entry, best corrected visual acuity (BCVA) of 20/40 to 20/400, and center subfield thickness (CST) ≥250 μm (Stratus OCT3). Patients were excluded if they had a brisk afferent pupil defect, had scatter laser photocoagulation within 3 months, an intraocular injection of steroid or a VEGF antagonist within 3 months, or had an improvement of ≥10 ETDRS letters in BCVA between screening and baseline. Baseline characteristics were well balanced among the three groups; mean BCVA was 20/80, the mean time from diagnosis of BRVO was 3.5 months, and the mean center point thickness (CPT) was 520 μm. Starting at month 3, patients were eligible for grid laser treatment if hemorrhages had cleared sufficiently to allow safe application of laser and the following criteria were met: Snellen equivalent BCVA ≤ 20/40 or mean CST ≥ 250 μm, and compared with the visit 3 months before the current visit, the patient had a gain of <5 letters in BCVA or a decrease of <50 μm in mean CST. If rescue laser was not given at month 3, the same criteria were applied at month 4, and if rescue laser was not given at month 4, the criteria were applied at month 5.

At month 6, the primary endpoint, mean change from baseline BCVA letter score was 16.6 and 18.3 in the 0.3 mg and 0.5 mg ranibizumab groups and 7.3 in the sham group P (< 0.0001). The percentage of patients who gained ≥ 15 letters in BCVA was 55.2% (0.3 mg) and 61.1% (0.5 mg) in the ranibizumab groups and 28.8% in the sham group (P < 0.0001). The percentage of patients with a Snellen equivalent BCVA of 20/40 or better was 67.9% (0.3 mg) and 64.9% (0.5 mg) compared with 41.7% in the sham group (P < 0.0001). The percentage of patients with a Snellen equivalent BCVA of 20/200 or worse was 1.5% (0.3 mg) and 0.8% (0.5 mg) compared with 9.1% in the sham group (P < 0.01). Based upon the 25-item National Eye Institute Visual Function Questionnaire NEI VFQ-25 survey, patients who received ranibizumab felt they had greater improvement (improvement from baseline in NEI VFQ score: 9.3, 0.3 mg; 10.4, 0.5 mg: 5.4, sham). There was greater reduction of macular edema in the ranibizumab groups because CPT was reduced by 337.3 μm (0.3 mg) and 345.2 μm (0.5 mg) compared to 157.7 μm in the sham group. The percentage of patients with CPT ≤ 250 μm at month 6 was 91% (0.3 mg), 84.7% (0.5 mg), and 45.5% (sham, P < 0.0001). More patients in the sham group (54.5%) received rescue grid laser therapy than in the 0.3 mg (18.7%) or 0.5 mg (19.8%) ranibizumab groups. There were no safety signals identified in this trial.

After the primary endpoint in the BRAVO trial, patients were evaluated every month and if study eye Snellen equivalent BCVA was ≤20/40 or mean CST was ≥250 μm, they received an injection of ranibizumab; patients in the ranibizumab groups received their assigned dose and patients in the sham group received 0.5 mg. In patients with BRVO, the mean number of ranibizumab injections during the observation period was 2.9, 2.8, and 3.8 in the 0.3 mg, 0.5 mg, and sham/0.5 mg groups; and the percentage of patients that did not receive any injections during the observation period was 17.2, 20.0, and 6.5, respectively (Brown et al.,2011). At month 12 in the ranibizumab groups, the improvement from baseline in ETDRS letter score was 16.4 (0.3 mg) and 18.3 (0.5 mg), very similar to the month 6 results, indicating that vision is well maintained when injections are given only if there is recurrent or residual macular edema. Patients in the sham group showed substantial improvement during the observation period when they were able to receive ranibizumab; improvement from baseline in letter score was 7.3 at month 6 and 12.1 at month 12. The percentage of patients who had an improvement from baseline BCVA letter score ≥ 15 at month 12 was 55.2% (0.3 mg) and 61.1% (0.5 mg) in the ranibizumab groups, almost identical to the month 6 results. In the sham group, 43.9% of patients improved from baseline ≥ 15 in letter score at month 12 compared to 28.8% at month 6. At month 12, 67.9% (0.3 mg) and 64.4% (0.5 mg) of patients in the ranibizumab groups had a Snellen equivalent BCVA of 20/40 compared to 56.8% in the sham/0.5 mg group. Thus, in BRAVO study, patients in the sham groups showed a substantial improvement in vision during the second 6 months when they were able to receive ranibizumab as needed, but their vision at month 12 was not as good as that in patients in the ranibizumab groups (Varma et al.,2012). This raises a question as to whether delay in treatment carries a visual penalty.

The results from open-label extension trial of the 12-month Ranibizumab assessing long-term safety and efficacy in BRAVO trial (Heier et al., 2012) evidenced that in patients who completed month 12, the mean number of injections (excluding month 12 injection) in the sham/0.5-, 0.3/0.5-, and 0.5-mg groups

was 2.0, 2.4, and 2.1 (branch RVO) . The incidence of study eye ocular serious adverse events and systemic adverse events potentially related to systemic vascular endothelial growth factor inhibition across treatment arms was 2% to 9% and 1% to 6%, respectively. The mean change from baseline BCVA letter score at month 12 in branch RVO patients was 0.9 (sham/0.5 mg), -2.3 (0.3/0.5 mg), and -0.7 (0.5 mg), respectively. The authors concluded that no new safety events were identified with long-term use of ranibizumab; rates of systemic adverse events potentially related to treatment were consistent with prior ranibizumab trials. Results suggest that during the second year of ranibizumab treatment vision in branch RVO patients remained stable, follow-up and injections should be individualized .In addition, the subanalyses in BRAVO study (Ho, 2010; Campochiaro ,2010) generally confirmed that patients with BRVO who were younger or who had worse vision and greater retinal thickness at baseline fared better. Patients with BRVO fared better if time from diagnosis to treatment was less than 3 months.

In general, then, in BRVO, patients who needed fewer therapies, such as laser or other previous treatments, probably had milder RVO requiring less treatment. Patients who were younger did better than those who were older (Fung, 2011).

3.2 Bevacizumab

Bevacizumab(Avastin) is a recombinant humanized monoclonal antibody directed against VEGF. Avastin is FDA-approved for the treatment of colorectal cancer. However, 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 neovascular age-related macular degeneration (AMD) and retinal vein occlusion.

Recently, various clinical studies demonstrated beneficial effects of anti-VEGF therapy on both ME and BCVA in patients with BRVO.

Rabena et al. (2007) reported a significantly increased VA and reduced macular thickness after treatment with 1.25 mg bevacizumab in a retrospective study of 27 patients with BRVO. Recurrent ME was observed in 6 (22%) patients an average of 2.1 months after the initial injection. These patients were reinjected and all showed moderate to complete reduction in ME. The limitations of this retrospective study are short follow-up and lack of control group. Additionally, most of the eyes in the study were previously treated and thus failed standard treatment, and perhaps represent a group unlikely to benefit from any treatment. All published reports provide evidence that this treatment is well tolerated. The most common adverse events were conjunctival hyperemia and subconjunctival hemorrhage at the injection site. However, the duration of reduced ME after bevacizumab administration is currently unknown. Frequent repeated injections are required to prevent a rebound effect with no clearly defined endpoint (Matsumoto et al.,2007). In the retrospective study of 37 eyes of patients with BRVO treated with bevacizumab and followed up for more than 24 weeks, Yunoki et al. (2012) revealed that mean VA, central retinal thickness, and mean retinal thickness in a circular region of 1-mm diameter at the fovea improved significantly with treatment. Final VA was correlated with baseline VA and integrity grade of the photoreceptor inner and outer segment (IS/OS) line beneath the fovea, concluding that baseline VA and IS/OS line grade at 4 weeks may be predictive factors for final VA.

Jaissle et al.(2011) also investigating the predictive factors for functional improvement after intravitreal bevacizumab therapy for ME due to BRVO highlighted that treatment resulted in a significant improvement of BCVA and reduction of ME. Baseline BCVA, patient's age, and duration of BRVO were found to be of prognostic relevance for visual improvement. A less favorable outcome of the bevacizumab therapy in eyes with longstanding BRVO would advocate initiation of treatment within 12 months after onset.

In the systematic review based on four clinical trials Yilmaz and Cordero-Coma (2012) also assessed the effectiveness of intravitreal bevacizumab versus a comparison group in the treatment of BRVO-associated macular edema, and concluded that Avastin was effective in improving VA and CMT values in the long-term (12 weeks), but statistically significant improvements in VA in the short-term (4 weeks) could also be seen.

At the same time Hanada et al. (2012) emphasized that retreatment with Avastin because of recurrence of macular edema is common, and the probability of retreatment was approximately 70% after each individual

bevacizumab injection, indicating that 4 injections is maximum for three-quarters of eyes with BRVO macular edema.

The International Intravitreal Bevacizumab Safety Survey gathered adverse events from doctors around the world via the internet (Fung et al.,2006)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. (2006) 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. Campbell et al.(2012) 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.

The latest study (Sharma et al., 2012) 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.

Inhibition on VEGF in Age-related Choroidal Neovascularization (IVAN) Study Investigators wrote a letter on August 2012 –Important statement on safety, and action required stated that there was no difference in arteriothrombotic adverse events (ATE) between the drugs. However, a slight excess of other serious adverse events (other SAE) was observed in the Avastin arm (Chakravarthy et al., 2012). The combined Comparison of Age-related Macular degeneration Treatments Trials (CATT) and IVAN data on the numbers of patients who had experienced at least 1 other systemic SAE showed an excess of these events in patients who received Avastin compared to those who received Lucentis. The magnitude of the increase in risk was consistent with previous analyses and was statistically significant (Martin et al., 2012).

The worldwide use of intravitreal application of anti-vascular growth factor (a-VEGF) 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 (Binder, 2012). In 2007, two papers suggested for the first time possible tachyphylaxis/tolerance with chronic ranibizumab (Keane et al., 2008) and bevacizumab treatment (Schaal et al., 2008). Binder S. (2012) 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).

3.4 Combined therapy

3.4.1 Bevacizumab and Dexamethasone Intravitreal Implant

To determine whether dexamethasone intravitreal implant 0.7 mg (Ozurdex; Allergan, Inc.) with bevacizumab (Avastin; Genentech, Inc.) therapy can be synergistic, providing further improvements in visual acuity, sustainability, and macular thickness when compared with dexamethasone intravitreal implant 0.7 mg alone the authors of the following prospective, interventional case series intended to monitor changes in visual acuity and macular thickness in patients diagnosed with retinal vein occlusion (RVO), after injection of bevacizumab followed by a scheduled dexamethasone intravitreal implant (Singer et al., 2012). This prospective, interventional case series consisted of 34 eyes of 33 patients with ME

associated with RVO who were injected with bevacizumab, followed by dexamethasone intravitreal implant injection 2 weeks later. These patients were reexamined monthly and retreated with bevacizumab when ME recurred during the 6-month study period. The primary outcome measure was the time to reinjection based on OCT and vision criteria. Thirty-five percent of patients had central RVO (CRVO) and 65% had branch RVO (BRVO); 82% (28 of 34) needed at least 1 more injection before month 6, while 18% (6 of 34) did not need an additional injection of bevacizumab.97% of patients gained vision during the study, and mean visual acuity improved from initially 11 letters to a maximum of 25 letters during the study period. OCT showed macular thickness decreased with the combination treatment, and the effect continued an average of 126 days from the initial bevacizumab treatment.Eighteen percent (6 of 34) of patients had an IOP of 23 mmHg or greater. Five of these 6 subjects were controlled with drops alone, while one required an additional selective laser trabeculoplasty. This study demonstrates efficacy and the duration of effect using a combination of bevacizumab and dexamethasone vs dexamethasone alone. The combination is synergistic, increasing visual acuity and prolonging the time between injections, compared with either medication alone. Therefore, the combination of a VEGF inhibitor and a dexamethasone implant may be a valuable option for RVO treatment.

4. Conclusion

The efficacy of antiangiogenics as a therapeutic solution for BRVO is shorter in duration than desired and is incomplete. Not all patients benefit, and among those who do, efficacy is not always maintained, perhaps because of tachyphylaxis or due to poor compliance with the need for maintenance injections. Application of current and future understanding of pathophysiology of the branch retinal vein occlusion will be important for proper guiding the best intervention in this vasooclusive disorder.

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