The treatment of branch retinal vein occlusion with bevacizumab

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Current Opinion in Ophthalmology 2008, 19:234–238

Purpose of review

New treatment modalities for branch retinal vein occlusion have recently been introduced. The role of intravitreal bevacizumab injections will be discussed and compared with laser photocoagulation and other novel intravitreal pharmacotherapies.

Recent findings

Argon laser photocoagulation is the single treatment for branch retinal vein occlusion that has been shown to reduce vision loss in a randomized controlled clinical trial. The effectiveness of this treatment is limited though. Currently, increasing data support the role of intravitreal bevacizumab as an effective treatment for patients with macular edema secondary to branch retinal vein occlusion. Multiple injections seem to be necessary in order to achieve visual stabilization, favorable and durable macular changes. The effect of a single injection seems to last 6–8 weeks. The most common treatment protocol is two to three injections over the first 5–6 months. Patients who had minimal or no response to laser therapy appeared to benefit from bevacizumab. No significant complications have been associated with its use but only short-term data are available.

Summary

Intravitreal bevacizumab appears to be a safe and effective treatment for macular edema associated with branch retinal vein occlusion, at least in the short term. Further randomized, controlled investigations are needed to assess long-term safety and efficacy of intravitreal bevacizumab.

Keywords

avastin, bevacizumab, branch retinal vein occlusion, macular edema

Curr Opin Ophthalmol 19:234–238

1040-8738

Introduction

Branch retinal vein occlusion (BRVO) is a common retinal vascular disorder affecting mostly subjects over 50 years of age [1•,2]. This condition is characterized by sectoral intraretinal hemorrhages, retinal ischemia, retinal exudates and macular edema. The site of occlusion is typically located at an arterio-venous crossing site. Vision is usually decreased by a variety of mechanisms: capillary nonperfusion and increased hydrostatic pressure that results in hemorrhages and fluid exudation. The presence of fluid within the macula (macular edema) is the most common cause of vision loss in this group of patients [3].

Current standard of care: laser photocoagulation

Treatments in BRVO have two main goals: to reduce macular edema and to prevent retinal neovascularization caused by ischemia. Currently the only evidence-based therapy for BRVO is argon laser photocoagulation. This is the single treatment that has been shown to reduce vision loss in a randomized controlled clinical trial [1•].

The BRVO study evaluated whether macular grid laser photocoagulation could improve vision in patients with macular edema secondary to BRVO and vision between 20/40 and 20/200. One hundred and thirty-nine eyes were randomized to either treatment or observation. After an average follow-up of 3.1 years, treated eyes presented with a mean visual acuity of 20/40 to 20/50, in which the mean visual acuity among controls was 20/70 (the difference was statistically significant with $P < 0.0001$). Further data analysis suggested that the smaller the interval between the onset of symptoms and treatment, the better the visual outcome: two or more lines of vision were gained by 70% of patients treated within the first 12 months compared with only 32% of patients treated after 1 year.

Unfortunately patients with acute symptoms (less than 3 months of onset) were not evaluated in the study on the basis of the assumption that they will spontaneously improve during that period. This leaves an important question unanswered: whether starting treatment

immediately after development of symptoms could make any impact on the outcome.

Two interesting studies by Battaglia-Parodi and colleagues attempted to address this issue. One study [4] compared the efficacy of macular grid laser photocoagulation versus observation in patients with less than 15 days of symptoms. Seventy-seven eyes were randomized to either treatment or no treatment and after 12 months of follow-up both groups showed improved visual acuity without significant difference among the two groups.

The second study [5] evaluated whether in cases of acute BRVO (less than 15 days of symptoms) the visual outcome could be influenced by treatment timing. One-hundred and thirty-seven eyes were randomized to either early grid laser photocoagulation (3 months after diagnosis) delayed photocoagulation (6–18 months after diagnosis) or no treatment. After 2 years of follow-up the visual acuity improved in all groups without significant differences among them. The authors of these two studies conclude that grid laser photocoagulation of the macular region does not significantly impact the natural course of the disease. Since the authors of these reports did not perform pre-study power calculations it remains uncertain whether the studies where sufficiently powered to detect a difference.

Another important conclusion of the BRVO study [6] was that peripheral scatter laser photocoagulation can effectively reduce development of neovascularization and vitreous hemorrhage. Four hundred and one eyes were assigned randomly to either a treated or an untreated control group. After an average follow-up time of 4 years the development of neovascularization and vitreous hemorrhage was significantly less in treated eyes. Even though the study was not designed to determine whether peripheral scatter treatment should be applied before rather than after the development of neovascularization, the authors suggested that peripheral scatter photocoagulation should be applied after the development of neovascularization rather than before.

New treatments: intravitreal pharmacotherapy

Laser photocoagulation has been the only evidence-based treatment for patients with macular edema secondary to BRVO since 1984 when the BRVO study was published. Recently there have been increasing data supporting intravitreal pharmacotherapies as a valid adjunct if not an alternative to standard laser photocoagulation.

Bevacizumab (Avastin; Genentech Inc., San Francisco, California, USA) is a monoclonal antibody to vascular endothelial growth factor (VEGF) that has been approved by the Food and Drug Administration (FDA) for intravenous use in metastatic colon cancer. Since 2005, it has been given off-label via intravitreal injections in patients with macular degeneration. Patients with retinal vein occlusion present increased intravitreal levels of VEGF [7]. Recently, intravitreal injections of bevacizumab have been documented to improve visual acuity and reduce macular edema in patients with retinal vein occlusion [8,9,10•,11•,12,13].

A few retrospective studies have reported short-term safety and efficacy of intravitreal bevacizumab injections in patients with macular edema secondary to branch retinal vein occlusion. In the case series from Rabena *et al.* [10•] the clinical course of 27 eyes treated with intravitreal bevacizumab 1.25 mg/0.05 ml is presented. During a mean follow-up of approximately 5 months patients received on average two injections. Visual acuity improved from 20/200 at baseline to 20/100 at 1 month, 3 months and last visit. The mean central macular thickness was 478 μm at baseline and decreased to 310, 336 and 332 μm at 1 month, 3 months and last visit. Interestingly, among these patients more than 80% had limited or no response to prior treatment with either macular grid laser (63%) or intravitreal triamcinolone acetonide injections (22%). The time between BRVO diagnosis and treatment with bevacizumab was approximately 2 years on average.

We reviewed our experience with 16 patients with macular edema secondary to BRVO treated with intravitreal bevacizumab 1.25 mg/0.05 ml and found similar results (F. Badala, *et al.* ARVO meeting 2007; personal communication). Over a mean follow-up of almost 5 months patients received 2.5 injections on average. Mean visual acuity improved from 20/230 at baseline to 20/70 and 20/50 at 1 month and last visit, respectively. Mean central macular thicknesses have been reduced from 505 μm at baseline to 267 and 273 μm at 1 month and last visit, respectively. Interestingly, 25% of our patients who failed to respond intravitreal triamcinolone or laser grid photocoagulation improved after intravitreal bevacizumab. The average time between BRVO diagnosis and treatment with bevacizumab was about 1 year.

To date there are three prospective studies published on the role of intravitreal bevacizumab after BRVO. Schaal and colleagues [11•] prospectively evaluated 40 patients [22 with BRVO, 18 with central retinal vein occlusion (CRVO)] with macular edema secondary to vein occlusion who received 2.5 mg of intravitreal bevacizumab. The injections were repeated every 6 weeks when persistent or recurring macular edema was noted. Over a mean follow-up of approximately 6 months each patient received on average 2.6 injections. On the last visit, 77% of patients with BRVO had significantly improved vision (at least three lines) and the mean central macular

thickness had significantly been reduced from an average of 678 μm at baseline to 236 μm.

Pai *et al.* [12] prospectively studied 21 patients with macular edema secondary to vein occlusion (12 with BRVO, nine with CRVO). Patients received a single 1.25 mg bevacizumab injection and were followed for 3 months. Mean visual acuity improved from 20/381 at baseline to 20/135 and 20/178 at 1 and 3 months, respectively. The central macular thickness decreased from a mean of 647 μm at baseline to 293 μm at 1 month and 320 μm at the last visit. There was no significant difference in the visual outcome between the BRVO and the CRVO groups.

The German group of Schaal and collaborators [13] prospectively evaluated the response of a single bevacizumab treatment in 21 eyes with vein occlusion (14 with CRVO, seven with BRVO). Patients were followed for 9 weeks; the mean visual acuity improved by more than two lines compared with baseline. The peak visual acuity was reached between 3 and 6 weeks after injection, while a decrease in visual acuity was observed between weeks 6 and 9. The authors conclude that since the decrease of visual acuity was anticipated by macular thickness increase, OCT examinations between weeks 3 and 6 may be helpful in judging the appropriate time for reinjection. Subgroup analysis showed that patients receiving treatment within the first 3 months after onset of symptoms gained on average four lines of visual acuity compared with an average of 1.8 and 2.5 gain for patients who received treatment later in the course of the disease (4–6 months and more than 6 months after diagnosis, respectively). The latter finding may represent the natural tendency for visual acuity to improve early in the course of the disease, but also raises the question of whether early treatment may be associated with a more favorable outcome.

None of the above mentioned studies described significant complications after intravitreal bevacizumab injections including endophthalmitis, increased intraocular pressure, retinal tears, retinal detachments or retinal pigment epithelial rips. A restrospective case series from the group of Matsumoto and colleagues [14•] reported on rebound macular edema following intravitreal bevacizumab in three patients with retinal vein occlusion (1 BRVO, 2 CRVO). These patients presented with macular edema that initially responded to intravitreal bevacizumab but subsequently recurred in excess of that observed at baseline. The authors conclude that in some cases frequently repeated injections may be required to prevent a rebound phenomenon with no clearly defined endpoint and recommend caution with the use of anti-VEGF treatments until long-term safety is addressed.

The literature available seems to indicate that multiple injections are usually needed to achieve visual acuity stabilization, favorable and durable macular changes. Two to three injections over the first 5–6 months appear to be the most common treatment protocol [10•,11•]. Peak visual acuity appears to be reached during the first month after treatment [10•,13]. Six to eight weeks postoperative seems to be a critical interval for reinjection in order to stabilize vision [11•,13]. Some authors suggest performing OCT scans between 3 and 6 weeks after treatment to help decide on the best re-injection time [13]. The amount of medication injected does not seem to significantly impact the outcome (three different dosing regimens have been utilized: 1.25 mg [10•,12], 2.0 mg [15•] and 2.5 mg [11•]). There seems to be pivotal evidence that initiation of therapy early after the onset of symptoms is associated with a better visual outcome [13]. Theoretically, though, the use of anti-VEGF medications early after diagnosis could suppress the development of collateral vessels and have a negative impact on the long-term vision. After myocardial ischemia, for example, the expression of VEGF is critical for development of coronary collaterals [16,17]. So far, treatment with intravitreal bevacizumab does not seem to worsen perfusion dynamics after retinal vein occlusion [10•]. Moreover, bevacizumab appears to be effective also in patients who had minimal or no response to prior laser or intravitreal steroids [10•].

These results are encouraging and warrant further investigation. Short follow-up and the lack of a control group, however, are major limitations of all the studies on intravitreal bevacizumab after BRVO and limit generalizability of these results. Convincing evidence could only come from a randomized controlled clinical trial. Currently, a phase II, randomized controlled trial is recruiting patients with macular edema secondary to BRVO in Iran; the study will be comparing intravitreal injections of bevacizumab with sham controls.

A comparison of intravitreal bevacizumab with laser treatment for macular edema secondary to branch retinal vein occlusion is difficult. Bevacizumab appears to be effective in patients with acute and chronic BRVO; some authors reported efficacy up to more than 3 years after diagnosis [10•] while apparently the best outcome is associated with early treatment. Likewise, laser treatment seems to be more effective when applied in the first year after BRVO, but the BRVO study did not evaluate patients with acute symptoms (patients included were at least 3 months after diagnosis) [1•]. In contrast with laser treatment, the use of bevacizumab is not limited by presence of macular hemorrhages. In addition to that, patients who had limited or no response to laser showed improvement after intravitreal bevacizumab [10•]. Whether bevacizumab can improve vision on a long-term basis still remains to be addressed,

while the efficacy of laser treatment has been documented well after 3 years of treatment. The inclusion criteria in the BRVO study [1•] did not permit entry of patients with less than 20/200 vision; intravitreal bevacizumab case series document reduced macular edema and improved visual acuity in patients with much worse vision (counting fingers) at baseline. The BRVO study [6] showed that peripheral scatter laser photocoagulation can effectively reduce development of neovascularization and vitreous hemorrhage; evidence of whether bevacizumab has a role in these regards remains anecdotal. Despite this, the short follow-up and limited numbers of all bevacizumab series preclude a direct comparison between the current standard of care of laser treatment and the new promising intravitreal pharmacotherapy.

Intravitreal triamcinolone acetonide (IVTA) has been shown to be effective in improving vision and reducing macular edema secondary to BRVO [18–21] but its use is often associated with cataract formation [22] and increased intraocular pressure [23–25]. The long-term safety and efficacy of IVTA are currently being investigated in a multicenter clinical trial known as the Standard Care Versus Corticosteroid for Retinal Vein Occlusion Study (SCORE). The study is recruiting over 400 patients that will be randomized to laser treatment, IVTA 4 mg or IVTA 1 mg. Another multicenter randomized trial is evaluating safety and efficacy of an intravitreal implant of dexamethasone (Posurdex; Allergan Inc., Irvine, California, USA) in patients with macular edema secondary to retinal vein occlusion.

Tissue plasminogen activator (TPA) has also been injected intravitreally to treat macular edema secondary to BRVO. One study by Murakami *et al.* [26] showed improved visual acuity and reduced macular edema following treatment, but other reports showed retinal toxicity to be associated with intravitreal use of TPA [27].

Conclusion

Argon laser photocoagulation is the only treatment for BRVO which has been shown to reduce vision loss in a randomized controlled clinical trial and still remains the standard of care [1•,28]. Increasing data, however, support the use of intravitreal bevacizumab as an effective adjunct, if not an alternative, for patients with macular edema secondary to BRVO. Multiple treatments appear to be necessary in order to achieve visual stabilization, favorable and durable macular changes. The effect of a single injection seems to last 6–8 weeks. The most common treatment protocol is two to three injections over the first 5–6 months. Patients who have minimal or no response to laser therapy or intravitreal steroids appear to benefit from bevacizumab. No significant complications, including endophthalmitis, increased intraocular pressure, retinal tears or detachments have been associated with the use of intravitreal bevacizumab after BRVO, but only short-term data are available. Bevacizumab seems to be safer than other intravitreal medications like triamcinolone and tissue plasminogen activator, which have been described to improve vision in patients with macular edema secondary to BRVO but carry potential side effects, such as increased intraocular pressure, cataract progression and retinal toxicity.

All the studies on bevacizumab and BRVO are noncontrolled and have a short follow-up, which limit generalizability of their results; nevertheless, preliminary data are encouraging and warrant further investigation. If a randomized controlled clinical trial confirms the long-term safety and efficacy of bevacizumab this intervention may replace laser therapy as the standard of care for BRVO treatment.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 267).

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