·Review·

Therapeutic potential of intravitreal pharmaco – therapy in retinal vein occlusion

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Abstract

• Retinal vein occlusion (RVO) is the most common visually disabling disease affecting the retina after diabetic retinopathy. Although the disease entity has long been known, its management is still controversial. Macular edema is the main reason for decreased visual acuity (VA) in this retinal vascular disorder. Recently the vitreous cavity has increasingly been used as a reservoir of drugs for the direct treatment of macular edema through intravitreal injection route. The most widely injected drugs so far have been triamcinolone acetonide (TA) and bevacizumab. The objective of this review is to evaluate the evidence and discuss the rationale behind the recent suggestions that intravitreal pharmacotherapy by corticosteroids and anti-vascular endothelial growth factors may be useful in the treatment of retinal vein occlusion.

• KEYWORDS: retina; retinal vein; occlusion; medical treatment; intravitreal injections
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INTRODUCTION

Retinal vein occlusion (RVO) is the most common visually disabling disease affecting the retina after diabetic retinopathy [1]. Although it is more common in the middle-aged and elderly population, no age group is immune to it [2]. In spite of the fact that the clinical entity of RVO has been known since 1878 [3], its management still remains suboptimal. 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 [4-9]. 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 [10-13] and secondary hypercoagulable states, which are conditions, associated with an increased risk of thrombosis [14-22]. There are still gaps in understanding the aetiology and pathogenesis of circulatory disorders of the central retinal vein and its branches. Macular edema is the main reason for decreased visual acuity in RVO. Macular edema is a common sight-threatening response of the retina. It involves the breakdown of the inner blood-retinal barrier due to a restriction of the flow of blood leaving the retina with increased pressure and consists of an abnormal vascular permeability resulting in fluid accumulation and macular thickening, detectable by optical coherence tomography (OCT). Recently the vitreous cavity has increasingly been used as a reservoir of drugs for the direct treatment of macular edema through intravitreal injection route. Until the past few years, when pharmacologic treatments for central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) became available, the standard of care for macular edema secondary to CRVO was observation and the only treatment for BRVO was grid laser photocoagulation, which reduces edema very slowly and provides benefit in some, but not all patients. Since US Food and Drug Administration (FDA) approval of the dexamethasone intravitreal implant (Ozurdex, Allergan Inc.) and ranibizumab (Lucentis, Genentech) for treatment of CRVO and BRVO, physicians have been presented with expanded treatment options. Within the past year, clinical trials have demonstrated the effects of new pharmacologic treatments, VEGF TRAP, ranibizumab, and dexamethasone implants. Ophthalmology has witnessed an explosion in the number of intravitreal injections delivered to patients over the past 10 years.

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

INTRAVITREAL PHARMACOTHERAPY

Intravitreal Injections Intravitreal injections of air were first used in 1911 for the purpose of repairing retinal detachments [23]. Since that time, intravitreal injections have

been used for treatment of a variety of conditions, including endophthalmitis, intraocular lymphoma, cytomegalovirus (CMV) retinitis, submacular hemorrhage, vitreous hemorrhage, and neovascular age-related macular degeneration (AMD). The primary benefit of intravitreal injection is that the therapeutic agent is targeted in the eye while minimizing systemic absorption. In 1998, the U.S. Food and Drug Administration (FDA) approved the use of the first agent for intravitreal injections, fomivirsen sodium (Vitravene; Isis Pharmaceuticals, Carlsbad, CA), for the treatment of CMV retinitis.

Intravitreal injections of various agents have been studied extensively [23,24]. The overall risk of complications is low when the injection is administered by experienced ophthalmologists. Known risks of intravitreal injections can be vision threatening and require prompt diagnosis and treatment, possibly surgical intervention. The most serious but rarely occurring injection-related complications include acute-onset endophthalmitis [25-27], pseudo-endophthalmitis, cataract development/progression, retinal detachment, and hemorrhage [23]. The latest study [27] revealed that endophthalmitis following intravitreal injection was associated with an increased incidence of Streptococcus spp. infection, earlier presentation and poorer visual outcomes when compared with endophthalmitis following cataract surgery. Irigoyen *et al* [28] concluded that the overall numbers of patients with endophthalmitis following intravitreal injections has risen dramatically over the past years. In contrast to earlier reports of multicentre studies, outcome of patients is relatively poor in the current treatment settings.

The preparation of the intravitreal injection site with topical povidone-iodine is the preferred prophylactic method to minimize the risk of endophthalmitis. There is no need for topical antibiotic use after intravitreal injection[26]. Additional infrequent complications include hypotony, sustained increase in IOP after injection with triamcinolone acetonide, angle closure, hemiretinal vein occlusion, retinal pigment epithelial tears, iritis/uveitis, optic disc atrophy, corneal epitheliopathy, maculopathy, and anaphylactic reaction to the agent injected in the vitreous [23,29]. A 2006 national survey in USA Complications reported following complications rate associated with intravitreal injections: endophthalmitis - 31%, increased IOP - 26%, cataract - 11%, other - 16% [30].

A 2007 national survey in the United Kingdom found that the rate of severe IOP increase following intravitreal injection of triamcinolone acetonide was 1.1% (45/3899), necessitating either laser or surgery to control IOP [31].

In conclusion, the overall risk of complications is low when the injection is administered by experienced ophthalmologists [23,24].

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 [32]. Patients should discuss the potential risks and benefits of intravitreal pharmacotherapy with their physicians before receiving treatment.

Intravitreal tissue plasminogen activator In a retrospective review of 17 eyes with BRVO, Murakami *et al* [33] treated subjects with the fibrinolytic agent intravitreal tissue plasminogen activator (tPA) and claimed that visual acuity (VA) significantly improved and foveal thickness significantly decreased. They concluded that intravitreal tPA injection may be an effective treatment for resolving macular edema and improving the VA in BRVO. This report is based on retrospective collection of information and on limited personal experience.

Corticosteroids Glucocorticosteroids have multiple specific and non-specific effects. They are used in particular for their anti-inflammatory, anti-edemic, antiproliferative and anti-angiogenic properties. In ophthalmology, steroids are administered topically, as periocular injections, or systemically. However, the problem with topical application of drugs is that it does not allow for sufficient delivery to the posterior segment of the eye as in case of retinal vein occlusion, while long term systemic administration of steroids is often associated with serious side effects. The rationale for using steroids to treat macular edema secondary to RVO is that corticosteroids provide stabilization of the blood-retinal barrier, thereby reducing macular edema. Steroids may also have an anti-angiogenic effect, reducing the vascular endothelial growth factor (VEGF) mediated increase in vascular permeability.

Intravitreal corticosteroids Given that the eye constitutes only 0.01% of body volume, that its sclerotic membrane makes it a relatively self-containing organ and that a substance works best when directly administered to the target area. Intravitreous local administration by injection recommends itself as a means of high dosage local corticosteroids treatment.

Intravitreal triamcinolone acetonide Triamcinolone acetonide is a crystalline, synthetic glucocorticoid with potency approximately five times that of cortisol. Since soluble triamcinolone is washed out of the eye within 24 hours of intravitreous injection, the crystalline form is preferable. Jonas reported that, after intravitreal injection, triamcinolone acetonide can be detected in the aqueous humor up to 1.5 years [34] with earlier findings [35] indicating up to 6 months. That may be responsible for the reported high incidence of markedly elevated intraocular pressure following intravitreal triamcinolone acetonide intravitreal triamcinolone acetonide (IVTA), as well regression of iris neovascularization [36]. Some authors have advocated the use

of intravitreal triamcinolone acetonide in patients with macular edema due to CRVO, claiming significant anatomic improvement in the majority of patients confirmed by OCT [37-41].

To evaluate the efficacy of IVTA, the National Eye Institute (NEI) sponsored randomized, controlled clinical trials-the SCORE Study. The SCORE (Standard care *vs* Corticosteroid for Retinal vein occlusion) study, was consisted of 2 multicentere randomized, controlled clinical trials comparing the safety and efficacy of standard care with IVTA in either a 1 or 4mg dose for vision loss associated with macular edema secondary to CRVO or BRVO [42,43]. In the CRVO trial, standard care therapy is observation. Re-treatments are considered for persistent or new macular edema at 4 months intervals. The SCORE-CRVO study [42] showed that both triamcinolone groups were superior to observation with respect to VA. The visual benefit of IVTA was demonstrated as early as 4 months and continued to 24 months; although there was less power at this point, the benefit appears to persist. However, in all 3 groups, 1mg IVTA, 4mg IVTA or observation, there was a reduction of central retinal thickness from baseline to 24 months. Therefore, the visual benefit of IVTA may be due not only to macular edema decrease, but also to other effects, such as anti-inflammatory or neuroprotective effects. The study reported 5 also evidenced the superior safety profile of the 1mg dose compared with the 4mg dose, particularly with respect to glaucoma and cataract, rendering in the preferred dose in CRVO [42]. In SCORE-BRVO [43], IVTA injections were not found to be associated with improved VA outcomes compared with grid photocoagulation, being the standard care. The rates of adverse events were highest in the 4mg triamcinolone group. The rates of adverse events in the 1mg TA group were similar, with respect to surgical intervention for cataract and glaucoma, to the laser group, but laser treatment excluded any possibility of injection-related adverse events. The SCORE Study Investigative Group concluded that grid photocoagulation should remain the benchmark against which other treatments are compared in clinical trials for eyes with vision loss associated with macular eedema secondary to BRVO.

Although systemically safe, intravitreal steroids have significant ocular side effects. Among the side effects mentioned are development of ocular hypertension (requiring antiglaucoma therapy including surgery) in about 50% of eyes after about 1 month to 2 months [38-40,44-47], progression of cataract in some [38,45,46] and rarely endophtha-lmitis. In the elderly population of patients with RVO, intravitreal injection of TA leads to clinically significant posterior subcapsular cataract and nuclear cataract in about 15% to 20% of eyes within one year of the intravitreal injection [38]. Repeated intravitreal injection of TA could also result in primary open angle glaucoma, particularly since, in patients with RVO there is already high incidence of glaucoma and ocular hypertension [38,40,45,46]. Gregori *et al*[48] have found that patients with pre-existing open angle glaucoma had an IOP elevation at a higher rate than eyes without glaucoma, suggesting that this population may be at a higher risk for glaucoma surgery after intravitreal TA treatment. The authors stated that this potential risks need to be seriously considered and discussed with the patient given the transient and modest visual benefit of steroids.

Moreover, the intravitreal method of delivery poses injection-related risks [23] of vitreous haemorrhage, retinal detachment and infections such as endophthalmitis with a rate of about 1:1000 [29,33] and also conjunctival necrosis [49] and macular hole [50]. Recently more prevalent are non-infectious endophthalmitis and pseudoendophthalmitis with TA crystals appearing in the anterior chamber [51].

Dexamethasone intravitreal implant Dexamethasone (DEX) is a potent, water-soluble corticosteroid that can be delivered to the vitreous cavity by the dexamethasone intravitreal implant (DEX implant; OZURDEX, Allergan; Irvine, Calif dexamethasone drug delivery system, DDS). A dextramethasone implant is composed of a biodegradable copolymer of lactic acid and glycolic acid containing micronized dexamethasone. The drug-copolymer complex gradually releases the total dose of dexamethasone over a series of months after insertion into the eye through a small pars plana puncture using a customized applicator system. The GENEVA Trials were two Phase III trials comparing the effects of intraocular injection of 0.7mg or 0.35mg DEX implants to sham injections in patients with macular edema due to CRVO or BRVO [52]. The trials were identical and therefore the pooled results were reported: 0.7mg (n= 427), 0.35mg (n= 414), sham (n= 426). Patients were eligible if they had foveal-involved macular edema from a CRVO (1.5-9 months) or BRVO (1.5-12 months), BCVA of 20/50 to 20/200, and CST $\geqslant$300μm (Stratus OCT2 or OCT3). Patients were excluded if they had glaucoma or ocular hypertension requiring more than one medication. Twice as many BRVO (n= 830, 66%) as CRVO (n= 437, 34%) were enrolled. The design of this study is unusual. In particular, data from the entire population which combines outcomes for CRVO and BRVO are difficult to interpret because of differences in their natural history; BRVO has a higher rate of spontaneous improvement of macular edema, lower rates of vitreous hemorrhage and neovascular glaucoma which can adversely affect visual outcomes, and there are potential confounding effects from rescue grid laser. Therefore, the subgroup analyses provide the information most relevant to patient care.

In the BRVO subgroup at the 6 months primary endpoint, the mean change from baseline BCVA letter score was 7.5

in the two DEX implant groups compared to 5.0 in the sham group (P= 0.008). The percentage of patients who gained ≥15 letters in BCVA was 23% (0.7mg) and 21% (0.35mg) in the implant groups and 20% in the sham group. In the CRVO subgroup, the mean change from baseline BCVA letter score was 0 (0.7mg) and 2 (0.35mg) in the two DEX implant groups, not significantly better than sham (-2). The percentage of patients who gained ≥15 letters in BCVA was 18% (0.7mg) and 17% (0.35mg) in the implant groups and 12% in the sham group (NS). Thus, 6 months after injection there was little evidence of benefit in patients with BRVO and no benefit in CRVO. However, both patient populations showed some evidence of benefit at earlier time points. Peak effects were at 60 days. In the CRVO subgroup, the mean change from baseline BCVA letter score was 9 (0.7mg) and 10 (0.35mg) in the two DEX implant groups, significantly better than sham (0), and 29% and 33% of patients gained ≥15 letters in BCVA compared to 9% for sham. At 3 months, the mean change from baseline BCVA letter score was 4 (0.7mg) and 6 (0.35mg) in the two DEX implant groups, significantly better than sham (0), and 18% and 24% of patients gained ≥15 letters in BCVA compared to 10% for sham. In the BRVO subgroup, the mean change from baseline BCVA letter score was 10 (0.7mg) and 9 (0.35mg) in the two DEX implant groups, significantly better than sham (5), and 30% and 26% of patients gained ≥15 letters in BCVA compared to 13% for sham. At 3 months, the mean change from baseline BCVA letter score was 9 (0.7mg) and 8 (0.35mg) in the two DEX implant groups, significantly better than sham (5), and 24% and 23% of patients gained ≥15 letters in BCVA compared to 15% for sham. The dexamethasone implant was well tolerated, producing generally transient, moderate, and readily managed increases in IOP in less than 16% of eyes. Cataract adverse events occurred in 26% of patients treated with two injections and in 5% of patients who received no treatment over the 12 months study. Haller *et al* [52] concluded that for patients who have relatively short duration of macular edema, Ozurdex should be considered a viable treatment option. In addition, in subgroup analysis of data from the GENEVA trial [53], patients who had macular edema for a shorter period of time had a greater chance of gaining vision. London *et al* [54] and Chan *et al* [55] also evidenced that the dexamethasone DDC was one of the most recent additions to the armamentarium against macular edema, specifically associated with retinal vein occlusion and was intriguing for its potency, dose consistency, potential for extended duration of action, and favorable safety profile. Reibaldi *et al* [56] have recently advocated Dexamethasone intravitreal implant use in vitrectomized eyes with ME secondary to CRVO. Kiss [57] have found that for many patients with chronic edema from BRVO, the best choice may be the dexamethasone implant.

Anti-Vascular Endothelial Growth Factor Inhibitors Therapy The development of therapy with anti-angiogenics or vascular endothelial growth factor inhibitors (anti-VEGF) has marked the beginning of a new era in eye diseases treatment. Application of vascular endothelial growth factor (VEGF) inhibitors represents a treatment option for macular edema secondary to RVO that targets the disease at the causal molecular level. Over the past years, ophthalmologists have attempted to treat RVO-associated edema triggered by hypoxia-induced expression of VEGF with ranibizumab (Lucentis®), bevacizumab (Avastin®), and pegaptanib sodium (Macugen®) and recently by VEGF Trap.

Ranibizumab Ranibizumab is a humanized, affinity-matured VEGF antibody fragment that binds to and neutralizes all isoforms of VEGF. Ranibizumab has first received FDA approval for the treatment of macular edema due to both CRVO and BRVO. With ranibizumab, Pieramici *et al* [58] designed a study following the scheme of the PIER Study, *i.e.* the first 3 injections monthly and then after 6 and 9 months, if needed (persistent macular edema). They found that ranibizumab was generally well tolerated and may improve BCVA and decrease central retinal thickness in OCT. But the efficacy was lost after the loading phase, so an interval of 3 months between injections may be too long. In addition, Spaide *et al* [59] and Rouvas *et al* [60] demonstrated in two prospective studies that the patients with RVO had an improvement in VA, but with a mean of 7.4-8.5 injections in 1 year of follow-up. Two phase III multicenter, prospective clinical trials assessing the safety, tolerability and efficacy of intravitreal ranibizumab injections in the treatment of macular edema secondary to BRVO and CRVO[61] were finished. They were called BRAVO (study of the efficacy and safety of ranibizumab injection compared with sham in patients with macular edema due to BRVO)[62] and CRUISE (study of the efficacy and safety of ranibizumab injection compared with sham in patients with macular edema due to CRVO) [63].

In the BRAVO study [62], 397 patients with macular edema following branch retinal vein occlusion (BRVO) were randomized to receive monthly intraocular injections of 0.3mg (n=134) or 0.5mg (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, BCVA of 20/40 to 20/400, and CST ≥250μm (Stratus OCT3). Exclusion criteria were the same as those in the CRUISE trial. 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 CPT was 520μm. 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 ≥250μm, 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 <50μm 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 0.3mg and 0.5mg 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% (0.3mg) and 61.1% (0.5mg) 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% (0.3mg) and 64.9% (0.5mg) 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% (0.3mg) and 0.8% (0.5mg) compared with 9.1% in the sham group (P< 0.01). Based upon the NEI VFQ-25 survey, patients who received ranibizumab felt they had greater improvement (improvement from baseline in NEI VFQ score: 9.3, 0.3mg; 10.4, 0.5mg: 5.4, sham). There was greater reduction of macular edema in the ranibizumab groups because CPT was reduced by 337.3μm (0.3mg) and 345.2μm (0.5mg) compared to 157.7μm in the sham group. The percentage of patients with CPT ≤250μm at month 6 was 91% (0.3mg), 84.7% (0.5mg), and 45.5% (sham, P<0.0001). More patients in the sham group (54.5%) received rescue grid laser therapy than in the 0.3mg (18.7%) or 0.5mg (19.8%) ranibizumab groups. There were no safety signals identified in either trial.

In the CRUISE Study [63], 392 patients with macular edema following CRVO were randomized to receive monthly intraocular injections of 0.3mg (n=132) or 0.5mg (n=130) of ranibizumab or sham injections (n=130). Patients were eligible if they had foveal-involved macular edema from a CRVO occurring within 12 months of study entry, BCVA of 20/40 to 20/320, and center subfield thickness (CST) ≥250μm (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; the mean age was 68 years, mean BCVA was 20/100, the mean time from diagnosis of CRVO was 3.3 months, and the mean center point thickness (CPT) was 685μm. At 6 months, the primary endpoint, mean change from baseline BCVA letter score was 12.7 and 14.9 in the 0.3mg and 0.5mg ranibizumab groups and 0.8 in the sham group (P<0.0001). The percentage of patients who gained ≥15 letters in BCVA was 46.2% (0.3mg) and 47.7% (0.5mg) in the ranibizumab groups and 16.9% in the sham group (P<0.0001). The percentage of patients with a Snellen equivalent BCVA of 20/40 or better was 43.9% (0.3mg) and 46.9% (0.5mg) compared with 20.8% in the sham group (P< 0.0001). The percentage of patients with a Snellen equivalent BCVA of 20/200 or worse was 15.2% (0.3mg) and 11.5% (0.5mg) compared with 27.7% in the sham group (P<0.005). 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: 7.1, 0.3mg; 6.2, 0.5mg: 2.8, sham) [64]. There was greater reduction of macular edema in the ranibizumab groups because CPT was reduced by 433.7μm (0.3mg) and 452.3μm (0.5mg) compared to 167.7μm in the sham group. The percentage of patients with CPT ≤250μm at 6 months was 75.0% (0.3mg), 76.9% (0.5mg), and 23.1% (sham, P<0.0001). This study demonstrated that six sessions of monthly injections of 0.3mg or 0.5mg reduced macular edema and provided substantial visual benefit in patients with CRVO.

After the primary endpoint in the CRUISE and BRAVO trials, patients were evaluated every month and if study eye Snellen equivalent BCVA was ≤20/40 or mean CST was ≥250μm, they received an injection of ranibizumab; patients in the ranibizumab groups received their assigned dose and patients in the sham group received 0.5mg. In patients with CRVO, the mean number of ranibizumab injections during the observation period was 3.9, 3.6, and 4.2 in the 0.3mg, 0.5mg, and sham/0.5 mg groups; and the percentage of patients that did not receive any injections during the observation period was 7.0, 6.7, and 4.3, respectively [65]. At month 12 in the ranibizumab groups, the improvement from baseline in ETDRS letter score was 13.9, 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 0.8 at month 6 and 7.3 at month 12. The percentage of patients who had an improvement from baseline BCVA letter score ≥15 at month 12 was 47.0% (0.3mg) and 50.8% (0.5mg) in the ranibizumab groups, almost identical to the month 6 results. In the sham group, 33.1% of patients improved from baseline ≥15 in letter score at month 12 compared to 16.9% at month 6. At month 12, 43% of patients in the two ranibizumab groups had a Snellen equivalent BCVA of 20/40 compared to 35% in the sham/0.5mg group.

In patients with BRVO, the mean number of ranibizumab injections during the observation period was 2.9, 2.8, and 3.8 in the 0.3mg, 0.5mg, and sham/0.5mg 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 [66]. At month 12 in the ranibizumab groups, the improvement from baseline in ETDRS letter score was 16.4 (0.3mg) and 18.3 (0.5mg), 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% (0.3mg) and 61.1% (0.5mg) 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% (0.3mg) and 64.4% (0.5mg) of patients in the ranibizumab groups had a Snellen equivalent BCVA of 20/40 compared to 56.8% in the sham/0.5mg group. Thus, in both CRUISE and BRAVO, 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. 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 and CRUISE trials [67] 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) and 2.9, 3.8, and 3.5 (central RVO), respectively. 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/0.5mg), -2.3 (0.3/0.5mg), and -0.7 (0.5mg), respectively. The mean change from baseline BCVA at month 12 in central RVO patients was -4.2 (sham/0.5mg), -5.2 (0.3/0.5mg), and -4.1 (0.5mg), 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. Reduced follow-up and fewer ranibizumab injections in the second year of treatment were associated with a decline in vision in central RVO patients, but vision in branch RVO patients remained stable. Results suggest that during the second year of ranibizumab treatment of RVO patients, follow-up and injections should be individualized and, on average, central RVO patients may require more frequent follow-up than every 3 months.

In addition, the subanalyses in BRAVO and CRUISE study [68-71] generally confirmed that patients with BRVO or CRVO 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. Patients with CRVO had similar results regardless of time to treatment. 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. And patients with CRVO had a more unpredictable course than those with BRVO, and therefore warrant even closer observation than those with BRVO [72].

Bevacizumab 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 VA and optical coherence tomography (OCT) outcomes, but also short-term efficacy and high recurrence rate. The dosage varies between 1 and 2.5mg, there are no different outcomes [73-82]. The Pan-American Collaborative Retina Study group concluded that intravitreal injections of bevacizumab at doses up to 2.5mg were more effective in improving VA and reducing macular edema at 6 months (compared to 1.25mg), but the study had no control group [79]. By contrast, no statistically significant differences were found between the doses, when the group presented the results at 24 months [83]. In addition, Ach *et al* [84] found that CRVO patients who benefited 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, Axer-Siegel *et al* [85], in a retrospective study of 35 eyes with CRVO-induced macular edema treated with 3-4 loading doses (1.25mg) 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. At the latest prospective study, Daien *et al* [86] 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 was relatively preserved leads to a significant improvement in VA. Ischaemic CRVO and poor baseline VA are associated with nonresponse to such therapy [86].

Epstein *et al* [87] 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 improves VA and reduces macular edema significantly compared with sham.

The International Intravitreal Bevacizumab Safety Survey gathered adverse events from doctors around the world via the internet [88] 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* [88] 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* [89] 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 [90] 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.

Leung *et al* [91] 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. Inhibition of 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 serious adverse events, SAE) was observed in the Avastin arm [92]. 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 [93].

Dr. Kaiser observed data are emerging showing more systemic serious adverse events with bevacizumab compared with ranibizumab, which perhaps may be explained by significantly greater lowering of serum VEGF levels with bevacizumab. Lastly, bevacizumab for intravitreal injection is not commercially available, which raises concern about problems associated with compounding, and presented this interpretation at Retina Day at the annual meeting of the American Academy of Ophthalmology in Chicago, November 11, 2012 [94].

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, have revealed the problem of tolerance/tachyphylaxy [95]. In 2007, two papers suggested for the first time possible tachyphylaxis/tolerance with chronic ranibizumab [96] and bevacizumab treatment [97]. Binder S [95]. 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).

Pegaptanib sodium The pegaptanib sodium is a selective anti-VEGF and it is still not well studied in RVO. Bennet [98] performed a pilot study where Macugen treatment achieved a decrease in macular thickness and an improvement in VA and retinal perfusion. But this study had enrolled only 7 patients with 6 months of follow-up and it had no control group. On the other hand, Wroblewski *et al* [32] conducted a study where subjects with BRVO were randomized 3:1 to intravitreal injections of pegaptanib 0.3 or 1mg at baseline and at weeks 6 and 12 with subsequent injections at 6-week intervals at the discretion of the investigator until week 48. He also found improvements in VA and macular thickness in this study with a 54-week follow-up. Therefore, the authors consider that intravitreal pegaptanib offers a promising alternative for macular edema secondary to BRVO.

VEGF trap The VEGF trap is another novel anti-VEGF agent aflibercept (Eylea, Regeneron). It is essentially a small fully human, soluble VEGF receptor that acts as a decoy

receptor binding-free VEGF [99]. Aflibercept was approved for macular edema following CRVO in September 2012. The VEGF trap eye is currently under evaluation in two phases III studies on CRVO (GALILEO and COPERNICUS Studies) with 6-monthly injections of drug or sham-controlled injections. The latest six-months results of the Phase 3 from COPERNICUS Study - multicenter, randomized, prospective, controlled trial [100,101] assessing the efficacy and safety of intravitreal Trap-Eye in one hundred eighty-nine eyes with macular edema secondary to central retinal vein occlusion (CRVO) randomized 3:2 to receive VEGF Trap-Eye 2mg or sham injection monthly for 6 months evidenced that at week 24, 56.1% of VEGF Trap-Eye treated eyes gained 15 letters or more from baseline versus 12.3% of sham-treated eyes (P<0.001). The VEGF Trap-Eye treated eyes gained a mean of 17.3 letters versus sham-treated eyes, which lost 4.0 letters (P<0.001). Central retinal thickness decreased by 457.2μm in eyes treated with VEGF Trap-Eye versus 144.8μm in sham-treated eyes (P <0.001), and progression to any neovascularization occurred in 0 and 5 (6.8%) of eyes treated with VEGF Trap-Eye and sham-treated eyes, respectively (P=0.006). Conjunctival hemorrhage, reduced visual acuity, and eye pain were the most common adverse events. Serious ocular were reported by 3.5% of VEGF Trap-Eye patients and 13.5% of sham patients. Incidences of nonocular serious adverse events generally were well balanced between both groups. The authors concluded that at 24 weeks, monthly intravitreal injection of VEGF Trap-Eye 2mg in eyes with macular edema resulting from CRVO improved visual acuity and central retinal thickness, eliminated progression resulting from neovascularization, and was associated with a low rate of ocular adverse events related to treatment.

Dr. Korobelnik presented the results on behalf of the GALILEO investigators at the annual meeting of the American Academy of Ophthalmology [102]. GALILEO is a double-masked study conducted at 62 centers in Europe and Asia. It randomly assigned 177 patients 3:2 to receive intravitreal aflibercept 2mg or sham every 4 weeks until week 24.

Between week 24 and 52, patients continued monthly monitoring, but the aflibercept eyes received treatment as needed while the sham group continued to receive sham treatment every 4 weeks. From weeks 52 to 76, the inter-visit interval was extended to 8 weeks and sham patients were eligible for aflibercept. Nearly three-fourths of sham eyes and 85% of the aflibercept eyes completed 76 weeks of follow-up.

During the first 24 weeks of GALILEO, monthly aflibercept treatment resulted in rapid and sustained gains in best-corrected visual acuity. The improvement was largely maintained through week 52, but declined some between weeks 52 and 76. Similar temporal patterns were seen in analyses of changes in central retinal thickness (CRT) and proportion of eyes without retinal fluid in the aflibercept treatment group.

After becoming eligible for aflibercept, eyes in the sham group gained vision and had decreased CRT. However, outcomes at week 76 were superior in the eyes that had been treated with aflibercept since entry. Results from follow-up to 76 weeks in the phase III GALILEO study show that intravitreal injection of aflibercept (Eylea, Regeneron Pharmaceuticals) provides marked improvement in visual acuity in treatment-naive eyes with macular edema secondary to central retinal vein occlusion. However, the data also suggest the value of close monitoring and early treatment. The results of GALILEO and COPERNICUS are encouraging for patients with central retinal vein occlusion.

It appears that VEGF production can be a long-term problem in many patients with RVOs. A period of aggressive pharmacologic blockade of VEGF may be one key to reducing the need for repeated injections. It is to be hoped that, as we gain more long-term experience with the use of anti-VEGF agents and other interventions for the treatment of BRVO and CRVO, we can identify regimens that will reduce edema and restore good vision to our patients relatively quickly [103].

COMBINATION THERAPY

The rationale for combination therapies with drugs with different modes of action was suggested by Schaal *et al*[97] and others [104,105].

Bevacizumab followed by panretinal and macular grid photocoagulation Long-term effect of early intervention with single intravitreal injection of 2.5mg (0.1mL) bevacizumab followed 3 weeks later by panretinal and macular grid photocoagulation in central retinal vein occlusion (CRVO) with macular edema was evaluated in a pilot study of 9 eyes [106] and evidenced that this therapy may provide visually and anatomically favourable results in a case of CRVO. It may also obviate the need for repeated injection, requires a large randomized study to substantiate the results.

Bevacizumab and Triamcinolone Acetonide To compare the efficacy and safety of intravitreal bevacizumab alone *versus* bevacizumab combined with triamcinolone acetonide in eyes with macular edema caused by central retinal vein occlusion (CRVO) in Chinese patients, seventy-five eyes of 75 patients were enrolled in this prospective, randomized, consecutive study [107]. Thirty-six patients in group 1 were treated with an intravitreal injection of bevacizumab (1.25mg/0.05mL), and 39 patients in group 2 were treated with intravitreal bevacizumab (1.25mg/0.05mL) combined with triamcinolone acetonide (2mg/0.05mL). The authors concluded that intravitreal injection of bevacizumab alone or

combined with triamcinolone acetonide has a short beneficial effect in Chinese patients with macular edema caused by CRVO, but there is no significant difference between the two groups.

Bevacizumab and Dexamethasone Intravitreal Implant To determine whether dexamethasone intravitreal implant 0.7mg (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 0.7mg 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 [108]. 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 23mmHg 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.

CONCLUSION

Medical management of retinal diseases has arguably come to dominate clinical practice and has resulted in better delivery of patient care. The general consensus is that the intravitreal injections turned out to be promising in recent clinical trials and appear to be an additional therapeutic option [109-120]. But there are limits in efficacy, need for multiple injections, rebound effect of macular edema and nonresponders. 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, but intravitreal pharmacotherapy in retinal vein occlusion is a clear breakthrough with exciting potential.

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