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PHARMACOTHERAPY IN VASCULAR RETINOPATHY

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ABSTRACT

Visual impairment is a major health issue at present. The number of people of all ages visually impaired is 285 million, of whom 39 million are blind. People 50 years and older represent 65% and 82% of visually impaired and blind, respectively. Vascular retinopathy is the consequence of vascular disease, and the retina is the only place where the arteries and veins can be visualized directly. Central 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. Although it is more common in the middle-aged and elderly population, no age group is immune to it. The central retinal vein occlusion pathogenesis has varied systemic and local implications that make it difficult to elaborate treatment guidelines. The disease entity has long been known, but there is a great deal of confusion regarding its management. Various new therapeutic approaches have been developed in the past few years.

The objective of this review is to evaluate the treatments commonly advocated, emphasizing evidence-based ones, in the light of our current scientific knowledge of central retinal vein occlusion.

Keywords: retina, central retinal vein occlusion, therapy, visual impairment.

1.INTRODUCTION

Visual impairment is a major health issue at present. The number of people of all ages visually impaired is 285 million, of whom 39 million are blind. People 50 years and older represent 65% and 82% of visually impaired and blind, respectively [1]. Vascular retinopathy is the consequence of vascular disease, and the retina is the only place where the arteries and veins can be visualized directly.

Central retinal vein occlusion (CRVO) is the most common visually disabling disease affecting the retina after diabetic retinopathy [2]. Although it is more common in the middle-aged and elderly population, no age group is immune to it [3].

In spite of the fact that the clinical entity of CRVO has been known since 1878 [4], its management still remains highly controversial. The pathogenesis of CRVO 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 [5-10]. Known risk factors for CRVO include systemic vascular disease, hypertension, diabetes mellitus, hyperlipidemia and glaucoma. Hypercoagulable states are associated with CRVO. These include primary hypercoagulable states with a defect in the physiological anticoagulant mechanism [11-14] and secondary hypercoagulable states, which are conditions, associated with an increased risk of thrombosis [15-23].

There are still gaps in understanding the aetiology and pathogenesis of circulatory disorders of the central retinal vein and its branches.

Over the years, many treatments have been advocated enthusiastically and success has been claimed. Except for a few prospective studies, all the reports are based on retrospective collection of information or on limited personal experience. Most of the reported studies have a variety of limitations, which make it hard to evaluate the claimed benefits.

Macular edema is the main reason for decreased visual acuity in CRVO. Macular edema is a common sight –threatening response of the retina. It involves the breakdown of the inner blood-retinal barrier and consists of an abnormal vascular permeability resulting in fluid accumulation and macular thickening, detectable by optical coherence tomography (OCT).

Various new therapeutic approaches have been developed in the past few years.The objective of this review is to evaluate the treatments commonly advocated, emphasizing evidence-based ones, in the light of our current scientific knowledge of CRVO.

2. PHARMACOTHERAPY

2.1 Dexamethasone

The Ozurdex (Allergan Inc., Irvine, CA, USA) dexamethasone drug delivery system (DDS) was recently developed and approved by the FDA as a biodegradable intravitreal implant to provide sustained delivery of 0.7 mg dexamethasone for the treatment of macular edema associated with CRVO [24,25].

Haller et al.[24] concluded that for patients who have relatively short duration of macular edema, Ozurdex should be considered a viable treatment option. Increases in IOP were generally transient and similar following each treatment. Cataract adverse events occurred in 26% of patients treated with two injections and in 5% of patients who received no treatment over the 12-month study.

2.2 Posterior sub-Tenon injection of triamcinolone acetonide

Some authors [26,27] have recently advocated the posterior sub-Tenon (PST) injection of 40 mg TA under topic anesthesia, based on claims that IOP elevation may be less common after PST injection than after intravitreal injection, however Iwao et al. [27] have found that PST TA injection is associated with high rates of steroid-induced IOP elevation in eyes with previously normal IOP.

Lin et al. [26], in a prospective study of 18 eyes with CRVO treated by three biweekly PST TA injections, claimed that this treatment is effective in reversing cystoid macular edema (CME) and improving VA in recent-onset CRVO in the first 9 months before longstanding macular edema results in irreversible photoreceptor damage. No cataract progression or other complications were observed. They stated that patients with nonischaemic CRVO may respond more favourably than patients with ischaemic CRVO and further study with longer follow-up period is necessary.

Recently Mizumo et al. [28] in the experimental study have found that the periocular injection of TA effectively decreased retinal thickness and inhibited leukocyte-endothelium interactions in the retina after ischemia. Down regulation of adhesion molecules of retinal vascular endothelium induced by TA may play a role in the course.

2.3 Complex medical therapy

Taken into account that pathogenesis of CRVO is multifactorial with both local factors and systemic diseases being etiologically important we used the combination of different drugs named the therapeutic complex [29] in treatment of CRVO. Each of used drugs influences the specific link in the chain of pathologic changes resulted in RVO. The treatment included mix of Heparin and Dexamethason followed by Emoxypin and Dexamethason local in peribulbar injections, and Doxium, Solcoseryl [30], Diamox [31], Troxerutin, Vitamin E systemic during 15 days. The treatment is directed towards normalization the rheologic factors, resorbtion of blood clot in occluded vein, restoration of blood circulation, reducing vascular hyperpermeability and macular edema, activating of retinal oxygen metabolism and decreasing ischemic processes to prevent neovascularization. In CRVO patients with systemic hypertension also were used vasodilating drug to control blood pressure. To evaluate the efficacy of the therapeutic complex treatment we conducted a case-control study. A group of 20 patients treated after 2 weeks of the onset of occlusion was compared with controls without treatment after 1 month of the onset of occlusion. The groups were comparable for age, sex, systemic diseases (mainly presented systemic hypertension, less diabetes mellitus, myocardial infarction, atherosclerotic vascular disease). A statistically significant improvement in visual acuity was found in treated patients compared with control ($t=2.66$, $p<0.01$).

Results of this study revealed that the complex medical therapy in RVO may be more effective than ordinary treatment or spontaneous regression [32] and suggest that a randomized double-masked study should be conducted.

2.4 Anti-VEGF therapy

Application of vascular endothelial growth factor (VEGF) inhibitors represents a treatment option for macular edema secondary to CRVO 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®).

Ranibizumab

Ranibizumab has received FDA approval for the treatment of macular edema due to both CRVO and BRVO, and it is the only available FDA-approved therapy.

With ranibizumab, Pieramici et al .[33] 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 is 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. [34] and Rouvas et al. [35] demonstrated in two prospective studies that the patients with RVO have an improvement in VA, but with a mean of 7.4–8.5 injections in 1 year of follow-up.

Nowadays two phase III multicenter, prospective clinical trial are under way, assessing the safety, tolerability and efficacy of intravitreal ranibizumab injections in the treatment of macular edema secondary to CRVO [36]. It is called CRUISE (study of the efficacy and safety of ranibizumab injection compared with sham in patients with macular edema due to CRVO). During the first 6 months, the patients monthly received either 0.3 or 0.5 mg of ranibizumab or sham injection. During the second 6-month period, the patients were evaluated monthly and treated on an as-needed basis; meanwhile, patients in the sham group received 0.5 mg ranibizumab. For the first 6 months, results are available. Regarding efficacy, at the primary endpoint (mean change from baseline BCVA at month 6), there is a rapid and sustained improvement in BCVA in patients with macular edema due to CRVO. They show a statistically significant number of patients who gained ≧15 letters from baseline at month 6, in the study group compared to the control group, as well as a change from baseline central foveal thickness over time to month 6. Besides, intravitreal ranibizumab seems to have a safety profile consistent with previous phase III trials, and low rates of ocular and nonocular safety events [36-38]. Moreover, this trial demonstrates that the duration of the disease does not matter for taking the decision of treating. Treated patients did always better than sham-treated patients. Therefore, treatment for RVO can also be delayed by 3 months [39,40]. The latest results from open-label extension trial of the 12-month Ranibizumab assessing long-term safety and efficacy in CRUISE trial [40] 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 2.9, 3.8, and 3.5 in central 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 at month 12 in central RVO patients was -4.2 (sham/0.5 mg), -5.2 (0.3/0.5 mg), and -4.1 (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. Reduced follow-up and fewer ranibizumab injections in the second year of treatment were associated with a decline in vision in central RVO patients. 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.

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 2.5 mg, there are no different outcomes [41-50]. 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 [46]. By contrast, no statistically significant differences were found between the doses, when the group presented the results at 24 months [51]. In addition, Ach et al. [52] found that CRVO patients who benefit from therapy were significantly younger and had lower central retinal thickness at baseline.

Epstein et al.[53] 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.

Pegaptanib Sodium The pegaptanib sodium is a selective anti-VEGF and it is still not well studied in RVO. Bennet [54] 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..

VEGF Trap

The VEGF trap is another novel anti-VEGF agent. It is essentially a small fully human, soluble VEGF receptor that acts as a decoy receptor binding-free VEGF [55]. The VEGF trap eye is currently under evaluation in two phase 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 [56] 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 2 mg 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 457.2 μm in eyes treated with VEGF Trap-Eye versus 144.8 μm 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 2 mg 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.

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 [57-66]. 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.

The International Intravitreal Bevacizumab Safety Survey gathered adverse events from doctors around the world via the internet and showed all ocular and systemic side effects to be under 0.21% [67] 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. 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

The latest studies [68-69] revealed that endophthalmitis following intravitreal injection is associated with an increased incidence of Streptococcus spp. infection, earlier presentation and poorer visual outcomes when compared with endophthalmitis following cataract surgery.

CONCLUSIONS

In conclusion, studies evaluating interventions for macular edema secondary to CRVO have lacked sufficient sample size and power, lack an adequate control using placebo or best practice intervention, did not have insufficient follow-up times for long-term assessment of outcomes, or a combination thereof. Therefore, definitive conclusions cannot be reached.

In spite of enthusiastic claims of success for various therapies, the reality is that the currently available treatments are associated with visual improvement in only a subset of patients and the approach to treatment of macular edema secondary to CRVO is not evidence-based yet. The benefits and risks of therapy should be weighted in all treatment decisions. There is a need for large well-designed prospective randomized controlled trials with a long-term follow-up of new drugs taken in a non-invasive way.

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List of Abbreviations

CRVO – central retinal vein occlusion

CME – cystoid macular edema

IOP – intraocular pressure

OCT – optical coherence tomography

PST – posterior sub-Tenon injection

RVO – retinal vein occlusion

TA – triamcinolone acetonide

VEGF - Vascular Endothelial Growth Factor