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Review Article

Treating the Central Retinal Vein Occlusion: The Latest Option

Marianne L. Shahsuvaryan*

Yerevan State Medical University, 7Ap, 1Entr, 26 Sayat-Nova Avenue, Yerevan, 0001, Republic of Armenia

*E-mail of the corresponding author: mar_shah@hotmail.com , Tel: (37410) 523 468

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Abstract

After diabetic retinopathy, central retinal vein occlusion (CRVO) is the most common visually disabling disease affecting the retina. CRVO is caused by obstruction of the central retinal vein that leads to a backup of blood and fluid in the retina. This causes retinal damage and loss of vision. Release of vascular endothelial growth factor (VEGF) contributes to increased vascular permeability in the eye and macular edema. It is believed that anti-VEGF treatment may help decrease vascular permeability and edema in the retina in patients with CRVO. EYLEA (Regeneron Pharmaceuticals) is the latest anti-VEGF agent received FDA approval for the treatment of CRVO .The goal of this review is to evaluate the therapeutic potential of EYLEA in the management of CRVO.

Keywords: Eye, Central Retinal Vein Occlusion, Vascular Endothelial Growth Factor Inhibitor, Pharmacotherapy

1. Introduction

After diabetic retinopathy, central retinal vein occlusion (CRVO) is the most common visually disabling disease affecting the retina (Shahid et al., 2006). In a recent analysis of pooled data from population studies worldwide, the overall CRVO prevalence was 0.08%, translating to over 100,000 people in the United States and more than 66,000 people in key European countries affected by CRVO (Rogers S, et al., 2010). Although it is more common in the middle-aged and elderly population, no age group is immune to it (Hayreh et al., 1994).

In spite of the fact that the clinical entity of CRVO has been known since 1878 (Michel J.,1878), 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 (The Eye Disease Case-Control Study Group, 1996; Lang and Spraul, 1997; Sperduto et al., 1998; Shahsuvaryan and Melkonyan, 2003; Koizumi et al., 2007; Arakawa et al., 2011). Known risk factors for CRVO include systemic vascular disease, hypertension, diabetes mellitus, hyperlipidemia and glaucoma. Hypercoagulable states are associated with CRVO.

CRVO is caused by obstruction of the central retinal vein that leads to a backup of blood and fluid in the retina. This causes retinal injury and loss of vision. CRVO presents with hemorrhagic changes in all four quadrants of the retina and dilated and tortuous retinal veins, often described as a “blood and thunder” fundus, associated cotton wool spots, optic disc edema, and neovascularization may also be present. In CRVO the obstruction is located in the central vein, at the level of the optic nerve, so most of the retina is affected. Anatomic features make the central retinal vein vulnerable to occlusion at this location. As the optic nerve and the accompanying central retinal artery and vein pass through the sieve-like connective tissue of the lamina cribrosa, the central retinal vein normally narrows, and the dense connective tissue of the lamina cribrosa limits any expansion of the traversing optic nerve and vessels within. Any thickening of the central retinal artery, which shares a common fibrous tissue sheath with the vein, might easily compress the lumen of the adjacent central retinal vein and start in motion the sequence of events that lead to

thrombus formation (Green et al., 1981).

Once an obstruction has occurred, increased vascular pressure behind the occlusion can cause fluid and small molecules to leak across the vascular wall and into the surrounding retinal tissue, causing macular edema. Macular edema is a common complication of CRVO.

The retina can also become "ischemic" (starved for oxygen), resulting in the growth of new, inappropriate blood vessels that can cause further vision loss and more serious complications. Retinal ischemia causes increased production of vascular endothelial growth factor, which causes vascular leakage and macular edema. High levels of VEGF also promote retinal hemorrhages and exacerbate capillary nonperfusion (Campochiaro, 2012).

Human eyes with CRVO showed evidence of intraretinal upregulated expression of VEGF mRNA (Pe'er, 1998). Indeed, raised levels of VEGF have been reported in both the aqueous and vitreous fluid of patients with ischemic CRVO, and are responsible for the increase in vascular permeability that leads to macular edema (ME) (Noma et al., 2010).

Application of vascular endothelial growth factor (VEGF) inhibitors represents a treatment option for macular edema secondary to central retinal vein occlusion (CRVO) that targets the disease at the causal molecular level.

After 2 decades of extensive research into the VEGF families and receptors, specific molecules have been targeted for drug development, and several medications have received US Food and Drug Administration (FDA) approval. Eylea (Regeneron Pharmaceuticals) is the latest anti-VEGF agent received FDA approval for the treatment of CRVO. The goal of this review is to evaluate the therapeutic potential of Eylea in the management of CRVO.

2. EYLEA

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. EYLEA (Regeneron Pharmaceuticals) also known as Aflibercept VEGF Trap-Eye, is the latest anti-VEGF agent received FDA approval for the treatment of CRVO. EYLEA is a recombinant fusion protein, consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 and formulated as an iso-osmotic solution for intravitreal administration. EYLEA acts as a soluble decoy receptor that binds VEGF-A and placental growth factor (PlGF) and thereby can inhibit the binding and activation of these cognate VEGF receptors. EYLEA is specially purified and contains iso-osmotic buffer concentrations, allowing for injection into the eye.

Bayer HealthCare and Regeneron are collaborating on the global development of VEGF Trap-Eye for the treatment of the neovascular form of age related macular degeneration (wet AMD), central retinal vein occlusion (CRVO), diabetic macular edema (DME), and other eye diseases and disorders. Aflibercept (Eylea, Regeneron) acts as a decoy receptor binding-free VEGF (Pieramici and Rabena, 2008). Aflibercept was approved for macular edema following CRVO in September 2012. 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 (Boyer , 2011; Boyer et al., 2012) 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.

Dr. Korobelnik presented the results on behalf of the GALILEO investigators at the annual meeting of the American Academy of Ophthalmology (Campochiaropa, 2011). 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 2 mg 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 six-months results of the Phase 3 from COPERNICUS Study - multicenter, randomized, prospective, controlled trial (Boyer, 2011; Boyer et al., 2012) evidenced 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. In 1-Year Results From the Phase 3 COPERNICUS Study Brown et al. (2013) revealed a statistically significant improvement in visual acuity at week 24, which was largely maintained through week 52 with intravitreal aflibercept as needed (PRN) dosing. Intravitreal aflibercept injection was generally well tolerated.

The results of GALILEO and COPERNICUS are encouraging for patients with central retinal vein occlusion. In conclusion, while efficacy and safety appear similar to other anti-VEGF treatments, the higher potency, binding affinity, and duration of action make EYLEA an appealing new option (Evoy and Abel , 2013). 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 (Brown et al., 2013). In 1-Year Results From the Phase 3 COPERNICUS Study Brown et al. (2013) concluded that monthly injections of 2 mg intravitreal EYLEA for patients with macular edema secondary to CRVO resulted in a statistically significant improvement in visual acuity at week 24, which was largely maintained through week 52 with intravitreal aflibercept as needed (PRN) dosing. Intravitreal aflibercept (EYLEA) injection was generally well tolerated.

In Shapiro et al.(2012) and Hahn and Fekrat (2013) opinions it is clear that anti-VEGF therapies may be only the beginning, since the therapeutic landscape for retinal disease is continually expanding with interesting developments in the near future.

Following the introduction of anti-VEGF treatment for RVO, there was a consequent rise in the number of these patients, potentially suitable for treatment as well as the number (frequency) of follow-up appointments. The associated increase in clinical workload has been substantial and there is concern that the introduction of anti-VEGF treatments for CRVO could further exacerbate pressure on clinic capacity in

the hospital eye service.

Brand (2012) evidenced that it is already possible to begin to consider a patient-centred approach based on an individual's disease characteristics. It may be possible to use vision loss, visual acuity (VA) instability, or other signs of an active disease state as markers for requiring treatment, rather than using fixed dosing schedules. This type of approach should reduce the risks associated with over-treatment and under-treatment, thereby optimising the risk/benefit profile of the treatment and the efficient use of National Health Service resource.

Individualised treatment allows the identification of patients who are most likely to benefit from the treatment. Tailoring treatment to the individual patient in this way should increase the chance of treatment success, while sparing patients from unnecessary drug exposure and risk of adverse events. Furthermore, avoiding unnecessary treatment also has the potential to improve the cost-effectiveness of treatment (Brand , 2012) but further advances are needed in order to improve quality of life and reduce the burden to healthcare systems (Figueroa and Contreras, 2012) .

3. Conclusion

The available evidence suggests that repeated early frequent treatment of CRVO with the anti-VEGF agent EYLEA, gives the best chance of achieving and stabilizing both optimal anatomical and visual outcomes in the short to medium term. There is no standard protocol regarding the optimal timing of initial treatment with EYLEA and subsequent retreatment is yet to be formulated. Where multiple injections are likely to be required, the effectiveness and safety over longer periods has yet to be determined. With more research and experience into exploring the frequency and safety of currently available agent- EYLEA, it is also likely that clinicians would achieve the best protocol when dealing with patients suffering from vasocclusive disorder of the retinal vein.

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