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Editorial

Present Pharmacological Treatment for Macular Edema Secondary to Central Retinal Vein Occlusion

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Central retinal vein occlusion (CRVO) is a common sight-threatening retinal vascular disorder, in which macular edema is the main cause of visual impairment [1]. The pathophysiology of macular edema involves both the presence of inflammation and angiogenic stimulant regarding vascular endothelial growth factor (VEGF) [2,3]. Intravitreal injections of anti-VEGF, including ranibizumab [4,5] bevacizuamb [6], pegaptanib [7], aflibercept [8,9] are proven to be effective for treating macular edema resulting from CRVO. Intravitreal injections of corticosteroids, potent anti-inflammatory agents, such as dexamethasone implants [10-12] and triamcinolone acetonide [13] have been shown to have a beneficial effect on macular edema associated with CRVO. The Food and Drug Administration (FDA) of US have approved intravitreal injections of dexamethasone implants, ranibizumab, and aflibercept for treating macular edema secondary to CRVO.

Ozurdex™ (Pharm Allergan Inc., Irvine California) was the first intraocular implant that could slowly release dexamethasone. Ozurdex showed an anti-edematous effect between 4 to 6 months [10-12]. The GENEVA study, a randomized controlled trial, collected 136 eyes with CRVO receiving Ozurdex 0.7 mg, 154 eyes in Ozurdex 0.35 mg, and 147 eyes in sham injections [10]. Following single intravitreal injection of Ozurdex 0.7 or 0.35 mg, maximal response was found two months after the injection with visual improvement in 8 to 10 letters, comparing to non-improved vision in the sham group [10]. The effect of Ozurdex diminished six months after the injection. The same response for macular edema was noted after repeated injections of Ozurdex during 12-month follow-up [11]. Over 12 months, cataract progression occurred in nearly one third of phakic eyes, and a 10-mmHg intraocular pressure increase from baseline was observed in 15.4% of all patients receiving two injections of Ozurdex 0.7 mg [11]. The IOP increases were usually transient and controlled with medication or observation. The SHASTA study was a multicenter retrospective study collected 132 patients with macular edema secondary to CRVO [12]. patients with macular edema secondary to CRVO [12]. The patients received intravitreal Ozurdex 0.7 mg injection as monotherapy or with adjunctive treatments [12]. Mean reinjection interval was 5.6 months. Two third of the patients achieved more than 2-line visual improvement in the peak response [12]. Intraocular pressure increase more than 10 mmHg occurred in one third of patients, but only 1.7% of patients required incisional glaucoma surgery [12]. In eyes with CRVO in the GENEVA study, longer macular edema duration at the time of first Ozurdex treatment was associated with a significantly lower likelihood of achieving clinically meaningful improvements in vision or macular thickness 6 or 12 months after treatment [14]. This suggests that prompt Ozurdex treatment may be associated with improved clinical outcomes [14]. The proportion of CRVO eyes with active neovascularization increased from baseline to day 180 in the sham group, but stayed relatively constant in the Ozurdex-treated group in the GENEVA study [15]. It is hypothesized that corticosteroids are associated with the down-regulation of the VEGF and inhibition of ocular neovascularization.

Ranibizumab (Lucentis™, Genentech, Inc., South San Francisco, CA, and Novartis Pharma AG, Basel, Switzerland) is an antibody fragment with a high binding affinity towards all forms of VEGF. The CRUISE study included 392 patients with macular edema after CRVO, who were randomized 1:1:1 to receive 6 monthly then PRN intraocular injections of 0.3mg or 0.5mg of ranibizumab or sham injections during 12-month follow up [4]. At month 12, ranibizumab 0.3 mg or 0.5 mg resulted in a gain of 13.9 letters, significantly better than 7.3 letters in the sham group [4]. No significant ocular or nonocular safety events

were identified [4]. In the RETAIN study, 32 CRVO eyes treated with ranibizumab according to the protocol of the CRUISE study completed 4-year follow up [5]. Most (56%) of the patients required frequent injections, 44% of them had edema resolution without further treatment [5].The patients with resolved macular edema had greater visual improvement in 25.2 letters, compared with those with unresolved edema in visual gain of 4.3 letters [5]. The retrospective analysis of the CRUISE study suggest that initiating ranibizumab injection immediately after diagnosis of CRVO provides greater vision gain than the patients receiving delayed treatments [16]. Another analysis of the patients with CRVO in the CRUISE study found 71.2% (0.3 mg) and 78.5% (0.5 mg) having central foveal thickness less than 250 μm 3 months after treatment, and therefore was categorized as early ranibizumab responders [17]. The early ranibizumab responder demonstrated better visual outcome at months 6 and 12, comparing to late or incomplete responder [17].

Aflibercept (Eylea™, Regeneron Pharmaceuticals, Inc., and Bayer Pharma AG, Berlin, Germany) is a decoy receptor fusion protein, composed of the second domain of human VEGF receptor 1 and the third domain of VEGF receptor 2, which are fused to the Fc domain of human IgG1. Recent two large-scale studies demonstrated the efficacy of intravitreal aflibercept 2 mg for macular edema associated with CRVO [8,9]. The authors used monthly injections for the first 6 months and then PRN in the following 6 months [8,9]. The 12-month results of the GALILEO study showed the aflibercept group gained 16.9 letters, better than the sham group having only 3.8-letter improvement [8]. The COPERNICUS study extended the follow-up period to 24 months [8]. The visual gains still maintained at months 24 in the aflibercept group (+ 16.2 letters), which was higher than the sham group (+ 3.8 letters) [8]. Prominent decrease of macular thickness was noted in two studies, without accompanying serious ocular and systemic adverse events [8,9].

At present, The FDA-approved therapies for macular edema secondary to CRVO compose of intravitreal injections of corticosteriods (dexamethasone implants) and anti-VEGF (ranibizumab and aflibercept). These pharmacological treatments require repeated injections to achieve long-term visual and anatomical improvement. Ocular and systemic adverse events are rarely reported followin treatments require repeated injections to achieve long-term visual and anatomical improvement. Ocular and systemic adverse events are rarely reported following intravitreal anti-VEGF. Intravitreal dexamethasone implant (Ozurdex) is probably complicated with cataract progression and/or intraocular pressure increase.

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