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EDITORIAL

Approved pharmacotherapy for macular edema secondary to branch retinal vein occlusion: A review of randomized controlled trials in dexamethasone implants, ranibizumab, and aflibercept

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Abstract

There are three approved pharmacotherapies for treating macular edema secondary to branch retinal vein occlusion (BRVO), including corticosteroids (dexamethasone implants) and anti-vascular endothelial growth factor (VEGF) (ranibizumab and aflibercept). They all show superior ability to improve vision and reduce macular thickness, comparing with sham injections or macular grid laser treatment. There is no severe ocular or systemic adverse reaction reported in studies associated with anti-VEGF for macular edema after BRVO. Intraocular pressure elevation and cataract aggravation should be addressed after intravitreal dexamethasone implants. Single intravitreal dexamethasone implant had effective duration as long as four to six months. Intravitreal anti-VEGF requires six monthly injections as loading doses, and then PRN regimen needed according to functional and anatomical changes. Ozurdex and ranibizumab reduce not only macular edema, but also the probability of retinal ischemia and neovascularization in patient s with BRVO. Prompt treatment with these agents can lead to a better outcome.

Key words: Branch retinal vein occlusion; Intravitreal injection; Aflibercept; Ranibizumab; Macular edema; Ozurdex

Core tip: There are three approved pharmacotherapies

for treating macular edema secondary to branch retinal vein occlusion (BRVO), including corticosteroids (dexamethasone implants) and anti-vascular endothelial growth factor (VEGF) (ranibizumab and aflibercept). They all show superior ability to improve vision and reduce macular thickness, comparing with sham injections or macular grid laser treatment. There is no severe ocular or systemic adverse reaction reported in studies associated with anti-VEGF for macular edema after BRVO. Intraocular pressure elevation and cataract aggravation should be addressed after intravitreal dexamethasone implants. Single intravitreal dexamethasone implant had longer effective duration than two anti-VEGFs.

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Branch retinal vein occlusion (BRVO) 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[4-7], bevacizumab[8], pegaptanib[9], aflibercept[10] are proven to be effective for treating macular edema resulting from BRVO. Intravitreal injections of corticosteroids, potent anti-inflammatory agents, such as dexamethasone implants[11-13] and triamcinolone acetonide[14], have been shown to be beneficial to macular edema associated with BRVO. The Food and Drug Administration of United States and European Medicines Agency have approved intravitreal injections of dexamethasone implants, ranibizumab, and aflibercept for treating macular edema secondary to BRVO. Herein the clinical outcome of the randomized controlled studies in these approved pharmacotherapies will be reviewed.

Ozurdex™ (Pharm Allergan Inc., Irvine California) was the first intraocular implant that could slowly release dexamethasone. Ozurdex showed an anti-edematous effect as early as 7 d after implantation[14]. The effect can persist as long as four to six months after single injection[11,12]. The GENEVA study, a randomized controlled trial, collected 291 eyes with BRVO receiving Ozurdex 0.7 mg, 260 eyes in Ozurdex 0.35 mg, and 279 eyes in sham injections[11]. 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 nearly ten letters, significantly better than five-letter gain in the sham group. The central retinal thickness also showed significant decrease in the treatment group than in the sham group 90 d after Ozurdex implantation. 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-mo follow-up[12]. Over 12 mo, 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. The intraocular pressure increases were usually transient and controlled with medication or observation. A laser or surgical procedure to reduce intraocular pressure was required for only 14 study eyes. IOP required specific time for clinical monitoring[15]. The dexamethasone implants were reported migration into the anterior chamber, causing permanent corneal edema[16]. Absence of lens capsule and prior vitrectomy were risk factors for Ozurdex anterior migration[16]. In eyes with BRVO 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 mo after treatment[17]. This suggests that prompt Ozurdex treatment may be associated with improved clinical outcomes[17]. The proportion of BRVO 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[18]. It is hypothesized that corticosteroids are associated with the down-regulation of the VEGF and inhibition of ocular neovascularization.

The SHASTA study was a multicenter retrospective study collected 157 patients with macular edema secondary to BRVO[19]. The patients received intravitreal Ozurdex 0.7 mg injection as monotherapy or with adjunctive treatments. Mean reinjection interval was 5.6 mo. Two third of the patients achieved more than 2-line visual improvement in the peak response. Intraocular pressure increase more than 10 mmHg occurred in one third of patients, but only 1.7% of patients required incisional glaucoma surgery. Another randomized multicenter study compared clinical outcome of Ozurdex monotherapy and Ozurdex combined with macular grid laser in patients with macular edema associated with BRVO[20]. The combination of Ozurdex implant and macular grid laser was synergistic for visual improvement and lengthening the time between Ozurdex injections.

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-A, which can effectively inhibit intraocular level of VEGF-A. The BRAVO study included 397 patients with macular edema after BRVO, who were randomized 1:1:1 to receive 6 monthly intraocular injections of 0.3 or 0.5 mg of ranibizumab or sham injections[4]. At month 6, ranibizumab 0.3 or 0.5 mg resulted in a mean gain of 16.6 and 18.3 letters, significantly better than 7.3 letters in the sham group. The central foveal thickness also demonstrated significant decrease in the treatment group than in the

sham group. No significant ocular or nonocular safety events were identified. All the patients including the sham group received PRN ranibizumab injections from month 6 to month 12[5]. The mean number of intravitreal ranibizumab was nearly three injections in the treatment group between month 6 and month 12. At month 12, ranibizumab 0.3 mg or 0.5 mg resulted in a mean gain of 16.4 and 18.3 letters, significantly better than 12.1 letters in the sham group. In the HORIZON trial, 304 patients with BRVO treated with PRN ranibizumab administration according to the protocol of the BRAVO study completed 2-year follow up[6]. The mean number of intravitreal ranibizumab was 2.1 injections in the 0.5 mg ranibizumab group between month 12 and month 24[6]. At month 24, ranibizumab 0.5 mg injection caused a mean gain of 17.5 letters, which maintained the visual outcome comparing to the results at month 6 and month 12. Fewer ranibizumab injections were required to control the edematous condition from month 6 to month 24. In the RETAIN study, 34 BRVO eyes treated with ranibizumab according to the protocol of the BRAVO study completed 4-year follow up[7]. Half of the patients required frequent injections, and another half of them had edema resolution without further treatment. There was a trend that the patients with resolved macular edema had more visual improvement in 25.9 letters, compared with those with unresolved edema in visual gain of 17.1 letters. The retrospective analysis of the BRAVO study suggest that initiating ranibizumab injection immediately after diagnosis of BRVO provides greater vision gain than the patients receiving delayed treatments[21]. Another analysis of the patients with BRVO in the BRAVO study found 79.1% (0.3 mg) and 84.7% (0.5 mg) having central foveal thickness less than 250 μm 3 mo after treatment, and therefore was categorized as early ranibizumab responders[22]. The early ranibizumab responder demonstrated better visual outcome at months 6 and 12, comparing to late or incomplete responder[22]. After analysis of the data in the BRAVO trial, ranibizumab injections prevent the worsening of retinal nonperfusion area, and even promotes reperfusion of the ischemic area, comparing to the sham group[23].

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. Aflibercept can downregulate both VEGF-A and placental growth factor, which are synergistic for pathologic angiogenesis. The VIBRANT study, a randomized controlled trial, demonstrated the efficacy of intravitreal aflibercept 2 mg over the macular grid laser for 183 patients with macular edema associated with BRVO[10]. The authors used monthly injections for 6 mo[10]. The 6-mo results showed the aflibercept group gained mean 17.0 letters, significantly better than the laser group having only mean 6.9-letter improvement. Decrease of macular thickness was more prominent in the aflibercept group than in the laser group, without accompanying serious ocular and systemic adverse events.

Although there was no serious adverse effect reported in studies of ranibizumab and aflibercept for macular edema secondary to BRVO, some rare serious complications were found after use for other indications. Retinal pigment epithelium tears, macular ischemia, cataract progression, retinal breaks and detachment, endophthalmitis, macular hole, and intraocular inflammation were reported as ocular complications after intravitreal anti-VEGF for treating neovascular AMD[24]. Systemic adverse effects were uncommonly reported such as thromboembolic events (stroke and myocardial infarction) and gastro-intestinal bleeding[24].

In summary, there are three approved pharmacotherapy for treating macular edema secondary to BRVO, including intravitreal injections of corticosteroids (dexamethasone implants) and anti-VEGF (ranibizumab and aflibercept). They all show superior ability to improve vision and reduce macular thickness, comparing with sham injections or macular grid laser treatment. There is no severe ocular or systemic adverse reaction reported in studies associated with anti-VEGF for macular edema after BRVO. Intraocular pressure elevation and cataract aggravation should be addressed after intravitreal dexamethasone implants. Single intravitreal Ozurdex had effective duration as long as four to six months. Intravitreal anti-VEGF requires six monthly injections as loading doses, and then PRN regimen needed according to functional and anatomical changes. Ozurdex and ranibizumab reduce not only macular edema, but also the probability of retinal ischemia and neovascularization in patients with BRVO. Prompt treatment with these agents can lead to a better outcome.

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