

## Treatment Strategy for Macular Edema with Ischemic Retinal Vein Occlusion

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In recent years, with unhealthy eating habits and aging of society, there has been an increase of lifestyle-related diseases such as hypertension, hyper lipidemia, and diabetes, which are important risk factors for retinal vein occlusion (RVO), including branch RVO (BRVO) and central RVO (CRVO). Affecting an estimated 180,000 eyes per year in the United States, BRVO and CRVO comprise the second most-common type of retinal vascular disorder after diabetic retinopathy [1] BRVO accounts for approximately 80% of cases, but both types of RVO contribute to significant loss of vision, mostly as a result of macular edema [1,2]. The macula is the important part of the retina for detailed vision, especially the fovea that consists entirely of cones [3]. Therefore, BRVO and CRVO are potentially serious retinal diseases that can lead to severe visual impairment.

In BRVO and CRVO patients, vascular endothelial growth factor (VEGF) and several inflammatory factors have been reported to have an important role in the development of macular edema [4-6]. Several major studies, including BRAVO (Ranibizumab for the treatment of macular edema following Branch Retinal Vein Occlusion), [7] CRUISE (Ranibizumab for the treatment of macular edema after Central Retinal Vein Occlusion Study), [8] and SCORE (Standard Care vs Corticosteroid for Retinal Vein Occlusion study), [9,10] have shown that anti-VEGF therapy or intravitreal injection of triamcinolone acetonide (IVTA) improves macular edema in patients with BRVO or CRVO. However, most of the subjects of those studies had nonischemic RVO and the above-mentioned therapies are less effective for macular edema in patients with ischemic RVO [11,12]. This is probably because production of VEGF and inflammatory factors is higher in ischemic RVO, and because both anti-VEGF therapy and IVTA only have a temporary effect and do not improve the underlying retinal ischemia.

Unfortunately, there is no current therapy that is known to improve retinal ischemia. However, pars plana vitrectomy (PPV) was recently reported to achieve greater improvement of retinal sensitivity (measured by the Micro Perimeter 1 [13]) in ischemic RVO patients compared with nonischemic RVO patients, [14,15] suggesting that PPV may indirectly alleviate retinal ischemia in patients with ischemic RVO. Elevation of the oxygen tension in the inner retina could be important for the efficacy of PPV [16,17]. That is, transport of oxygen from well-perfused to ischemic retinal regions by fluid currents might increase after PPV, leading to better oxygenation of the ischemic inner retina and improvement of macular edema because an increase of oxygen tension would reduce VEGF production and decrease vascular permeability. An increase of retinal oxygen tension would also improve autoregulatory arteriolar vasoconstriction and reduces pressure in the retinal capillaries and venules. When water flux from the vascular compartment to the tissue compartment decreases, edema will improve according to Starling's law. PPV seems to achieve long-term elevation of the oxygen tension in the inner retina. This surgical procedure may reduce the intraocular levels of various inflammatory factors along with VEGF, [18] which could be another mechanism leading to the alleviation of macular edema. In short, an increase of inner retinal oxygen tension after PPV could restore photoreceptor cell function, resulting in improvement of retinal sensitivity, with a better response

of retinal sensitivity in patients who have ischemic RVO than in those with no ischemic RVO. In contrast, it has been reported that there was no significant difference in the trend profile of retinal sensitivity between patients with nonischemic and ischemic BRVO after IVTA [19]. Therefore, if RVO patients have severe retinal ischemia, PPV should be considered to improve retinal sensitivity rather than anti-VEGF therapy or IVTA. However, PPV does not completely abolish retinal ischemia. In the future, more effective medical treatment for retinal ischemia is needed, because ischemic RVO not only causes macular edema but also vitreous hemorrhage and rubeotic glaucoma, which are associated with a risk of blindness.

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