Reduction in Dose of Intravitreous Bevacizumab Before Vitrectomy for Proliferative Diabetic Retinopathy

Bevacizumab (Avastin) is a full-length recombinant humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF). It has been approved by the US Food and Drug Administration for the treatment of metastatic colorectal cancer.

Intravitreous (IV) injection of bevacizumab, 1.25 mg/0.05 mL, has been studied in patients with age-related macular degeneration, macular edema associated with retinal vein occlusion, and diabetic macular edema. Recently, bevacizumab administered prior to vitrectomy for proliferative diabetic retinopathy (PDR) was reported to reduce intraoperative bleeding.\(^1\) Sawada et al\(^2\) showed that IV bevacizumab blocked all free VEGF in the aqueous humor.

However, IV bevacizumab may cause systemic adverse effects such as thromboembolic diseases or increases in systolic blood pressure.\(^3\) Moreover, the rapid progression of traction retinal detachment after IV injection of bevacizumab was reported.\(^4\) Therefore, we need to consider an appropriate dose of bevacizumab to be injected intravitreally. The purpose of this study is to elucidate whether a reduced dose (0.25 mg) of IV bevacizumab has an effect equally strong as the widely administered dose (1.25 mg) when IV bevacizumab is used as a surgical adjunct to treat PDR.

**Methods.** Thirty-eight eyes of 36 diabetic patients with PDR were studied. This study of the off-label use of bevacizumab and the collection of aqueous humor before and after IV injection were approved by the institutional review board of Kagawa University Faculty of Medicine.

All patients had vitreous hemorrhage or traction foveal detachment due to PDR. All patients underwent vitrectomy after IV injection of bevacizumab. Either 1.25 mg/0.05 mL or 0.25 mg/0.01 mL of bevacizumab was injected into the vitreous as a preoperative adjunct. Twenty-four consecutive eyes were treated with IV injection of 1.25 mg of bevacizumab between October 1, 2006, and February 29, 2008, and 14 consecutive eyes were treated with IV injection of 0.25 mg of bevacizumab between March 1, 2008, and September 30, 2009. Vitrectomy was performed 1 to 5 days after the injection. An aqueous humor sample was obtained just before IV injection of bevacizumab and just before vitrectomy. The concentration of free VEGF in the aqueous humor was measured with an enzyme-linked immunosorbent assay for human VEGF (Quankine VEGF enzyme-linked immunosorbent assay kit; R&D Systems, Minneapolis, Minnesota). Results were analyzed using SPSS version 12.1 statistical software (SPSS Inc, Chicago, Illinois).

**Results.** No statistically significant differences were found between the dose groups in baseline characteristics such as patient age, duration of diabetes, and presence of vit-

reous hemorrhage or traction foveal detachment. There were no statistically significant differences between both groups in the frequency of intraoperative hemostasis (high infusion pressure or diathermy) (1.25-mg group, 13%; 0.25-mg group, 7%) and the incidence of postoperative vitreous hemorrhage (1.25-mg group, 13%; 0.25-mg group, 14%). No local complications or systemic adverse effects were observed in any eye.

The mean (SD) free VEGF concentration in the aqueous humor before IV injection of bevacizumab was 349.0 (255.8) pg/mL in the 0.25-mg dose group and 359.5 (231.7) pg/mL in the 1.25-mg dose group. There were no significant differences between the groups. The VEGF levels in the aqueous humor 2 to 5 days after IV injection of bevacizumab were less than the limit of detection (31.0 pg/mL) in all eyes of both groups. Fluorescein angiography was performed before and 24 hours after the 0.25-mg IV injection of bevacizumab in 3 cases. Twenty-four hours after IV injection of bevacizumab, fluorescein angiography showed dramatic regression of retinal neovascularization with marked resolution of the leakage from active neovascularization seen before the injection (Figure).

**Comment.** The free VEGF concentration in the aqueous humor is different from that in the vitreous. However, the VEGF level in the aqueous humor has been reported to be significantly correlated with the VEGF level in the vitreous and is correlated with the severity of diabetic retinopathy and the activity of PDR. Both 1.25-mg and 0.25-mg IV injections of bevacizumab blocked all free VEGF in the aqueous humor. Nevertheless, 1.25 mg has been widely administered as the standard dose of IV bevacizumab. This study suggests that a lower dose (0.25 mg) of IV bevacizumab may be effective as a preoperative adjunct before vitrectomy in the treatment of PDR.

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**Ultra-High-Resolution Optical Coherence Tomographic Findings in Commotio Retinae**

Commotio retinae is a self-limited opacification of the retina secondary to direct blunt ocular trauma. Histologic studies of monkeys and humans relate this clinical observation to damaged photoreceptor outer segments and receptor cell bodies. Reports using time-domain optical coherence tomography (OCT) and spectral-domain OCT support the involvement of the photoreceptor layer, but these techniques lack the resolution necessary to confirm results of histologic analysis. Prototype high-speed ultra-high-resolution OCT (hs-UHR-OCT) images demonstrate these anatomical changes in a patient with acute commotio retinae.

**Report of a Case.** A 46-year-old man visited the emergency department with pain and blurry vision in the right eye after blunt ocular trauma. Uncorrected visual acuities were 20/30 OD and 20/25 OS. External examination showed periorbital ecchymosis and laceration. Pupillary examination results were normal with relative afferent pupillary defect. Intraocular pressures were 14 mm Hg OD and 13 mm Hg OS. Slitlamp examination revealed a subconjunctival hemorrhage in the right eye. Orbital computed tomography demonstrated fracture of the right infero-lateral and medial orbital walls. Dilated examination of the right eye showed a central, annular area of opacification of the retina surrounding the fovea consistent with commotio retinae (Figure 1). Retinal imaging was performed using spectral-domain OCT (Cirrus HD-OCT, software version 3.0; Carl Zeiss Meditec, Dublin, California) and prototype hs-UHR-OCT.

**Comment.** The spectral-domain OCT image suggests hyperreflectivity at the level of the photoreceptors (Figure 2A). However, the hs-UHR-OCT image better demonstrates increased backscattering at the level of the photoreceptors.

**Figure 1.** Color fundus photograph of the right eye showing annular opacification surrounding the macula of commotio retinae after blunt trauma. Corresponding spectral-domain and ultra-high-resolution optical coherence tomographic images are shown in Figure 2A and C.