**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 al2 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-

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**Figure.** Fluorescein angiograms before the intravitreous injection of 0.25 mg of bevacizumab (A) and 24 hours after the intravitreous injection of bevacizumab (B) in a 56-year-old diabetic patient with traction foveal detachment. A, Fluorescein leakage from active neovascularization was seen. B, Fluorescein leakage substantially decreased after the intravitreous injection of bevacizumab.

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reous hemorrhage or traction foveal detachment. There were no statistically significant differences between the 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 all eyes.

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.

Hidetaka Yamaji, MD
Fumio Shiraga, MD
Chieko Shiragami, MD
Hiroyuki Nomoto, MD
Tomoyoshi Fujita, MD
Kouki Fukuda, MD

Author Affiliations: Department of Ophthalmology, Kagawa University Faculty of Medicine, Kagawa, Japan.

Correspondence: Dr Yamaji, Department of Ophthalmology, Kagawa University Faculty of Medicine, 1750-1 Ikenobe, Miki-cho, Kita-gun, Kagawa 761-0793, Japan (proceed@kms.ac.jp).

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