Ranibizumab for Retinal Neovascularization

Dear Editor:

Proliferative diabetic retinopathy (PDR) is an important cause of severe vision loss in patients with diabetes mellitus.[1] Laser photocoagulation is the standard treatment for retinal or optic disc neovascularization, and approximately 60% of patients respond to panretinal photocoagulation (PRP) with regression of neovascularization within 3 months.[2] However, in some cases complete regression of neovascularization does not occur after PRP, but rather, persistent retinal neovascularization is present[3] and approximately 4.5% of patients require pars plana vitrectomy despite PRP. Such cases, as well as the demonstrated upregulation of intravitreal vascular endothelial growth factor (VEGF) in patients with retinal neovascularization, have prompted investigations about anti-VEGF drugs for management of this condition.

Based on the promising results using bevacizumab, [3]we evaluated the effects of another humanized anti–VEGF-A neutralizing drug, intravitreal ranibizumab (IVR), in diabetic patients with persistent new vessels (NV) unresponsive to PRP performed at least 4 months prior, [4]with best-corrected visual acuity (BCVA) of 20/32 or worse. Patients were not enrolled if they had a history of vitrectomy, thromboembolic event, surgery within the prior 6 months or planned within the next 28 days, uncontrolled hypertension, or known coagulation abnormalities. If both eyes were eligible for treatment, the eye with worse visual acuity was included.

Evaluations included Early Treatment Diabetic Retinopathy Study (ETDRS) BCVA, slit lamp biomicroscopy, indirect funduscopic examination, and fluorescein angiography (FA) (TRC-50IA; Topcon, Tokyo, Japan). Fluorescein leakage area (FLA) was measured using IMAGEnet software. Patients were scheduled for follow-up examinations at weeks 1, 6, 12(±1), 24(±2), 36(±2), and 48(±2) after IVR treatment, and were re-treated if any active new vessel was detected on FA. Three measures were used to evaluate the short-term effects of ranibizumab: (1) total area (measured in mm^2) of fluorescein leakage from active NV (NV at the disc and/or NV elsewhere); (2) changes in logMAR BCVA; and (3) central subfield macular thickness (CSMT). One-way analysis of variance for repeated measures (MANOVA) was used to evaluate differences in NV area, logMAR BCVA, CSMT and intraocular pressure between each visit. The significance level adopted was 0.05.

Twenty-two patients (9 women; mean age: 61±9 years; mean glycosylated hemoglobin: 9.4±1.7%; 21 with diabetes mellitus type II) completed the 24 weeks of follow-up (1 patient died and 1 missed 2 consecutive study visits after week 12), while 19 patients completed 36 and 48 weeks (1 patient missed 2 consecutive study visits after week 24). No clinical evidence of ocular toxicity was observed for the 22 patients treated in this study. Intraocular pressure and lens status did not change significantly throughout follow-up (data not presented).

On average, FLA was reduced to 4% of baseline 1 week after treatment, and although it returned to 45% of baseline at week 48, it remained statistically significantly lower than baseline throughout follow-up (Table 1, available at http://aaojournal.org). Eighteen patients were retreated with IVR at week 12, 16 patients at week 24, and 16 patients at week 36 (Figure 1 and Table 1; available at http://aaojournal.org).

Mean BCVA was 20/100 at baseline and showed improvement of 1 ETDRS line from the 1st until 12th after treatment. CSMT demonstrated significant, although modest, reduction compared with baseline at weeks 1, 6, 24, and 36 (Table 1; available at http://aaojournal.org). Eight of 22 eyes received focal/grid laser treatment for macular edema (CSMT >300 μm) during follow-up.

FLA reduction 1 week after IVR injection was similar to our previous findings in 15 patients, also with persistent new vessels, treated with 1.5 mg of intravitreal bevacizumab,[3] but interestingly, effects of bevacizumab injection were stronger than IVR at the 6th and 12th weeks after treatment (Figure 2, available at http://aaojournal.org), suggesting a longer lasting effect of bevacizumab on FLA reduction. This difference may be explained by the 2-times higher half-life of bevacizumab,[5] and consequently, fewer injections of bevacizumab may be necessary to control persistent retinal new vessels in the long term.

The relatively consistent number of patients needing IVR retreatment at weeks 12 (18 patients), 24 (16 patients), and 36 (16 patients), and the maintenance of mean FLA around 2 mm^2 on these visits (Figure 1, available at http://aaojournal.org), suggest that the persistent new vessels did not tend to regress after an IVR injection every 3 months during a 1 year follow-up and additional injections would likely be needed on subsequent follow-up visits.

No ocular adverse events including sight-threatening complications of PDR, such as vitreous hemorrhage or tractional retinal detachment, were observed. Future studies with larger sample sizes are warranted to more comprehensively evaluate the potential role of ranibizumab treatment in patients with persistent new vessels secondary to diabetic retinopathy.

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Table 1. Means and Standard Deviations for Fluorescein Angiography Leakage from Active New Vessels (FLA), Best-Corrected Visual Acuity (BCVA); Central Subfield Macular Thickness (CSMT) and Intraocular Pressure (IOP) for All Visits

Week	FLA (mm^2)	BCVA (LogMAR)	CSMT (μm)	IOP (mmHg)
Baseline	4.8±5.7	0.7±0.4	321.3±175.8	15.8±2.2
1	0.1±0.5 ($P = 0.0009$)	0.6±0.4 ($P = 0.0136$)	267.6±104.5 ($P = 0.0373$)	16.0±2.3 ($P = 0.4923$)
6	0.3±0.4 ($P = 0.0011$)	0.6±0.3 ($P = 0.0222$)	276.7±123.9 ($P = 0.0110$)	15.2±2.9 ($P = 0.2379$)
12	2.1±2.4 ($P = 0.0113$)	0.6±0.4 ($P = 0.0273$)	297.7±148.1 ($P = 0.1665$)	15.4±2.6 ($P = 0.4543$)
24	2.1±2.5 ($P = 0.0254$)	0.6±0.4 ($P = 0.1472$)	260.9±109.1 ($P = 0.0179$)	16.5±3.5 ($P = 0.5434$)
36	1.8±2.2 ($P = 0.0097$)	0.6±0.3 ($P = 0.1141$)	241.9±89.9 ($P = 0.0349$)	17.0±3.1 ($P = 0.1944$)
48	1.4±1.6 ($P = 0.0103$)	0.6±0.4 ($P = 0.3900$)	243.7±111.6 ($P = 0.0641$)	16.7±3.4 ($P = 0.3374$)

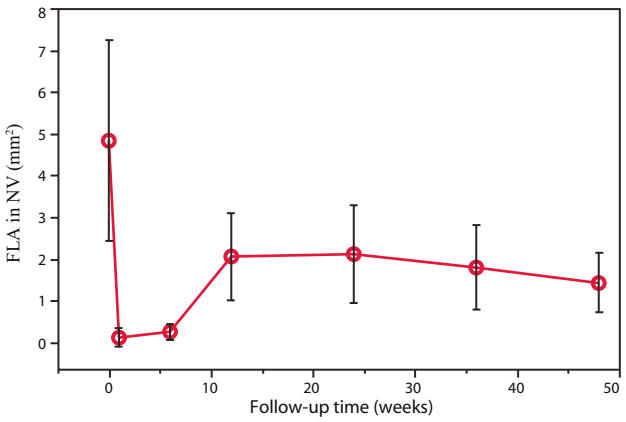

Figure 1. Mean FLA (mm^2) after intravitreal ranibizumab injection by visit in diabetic patients with persistent actively leaking new vessels. The bars indicate the range of 95% and the circles represent the mean. FLA = fluorescein leakage area; NV = new vessels.

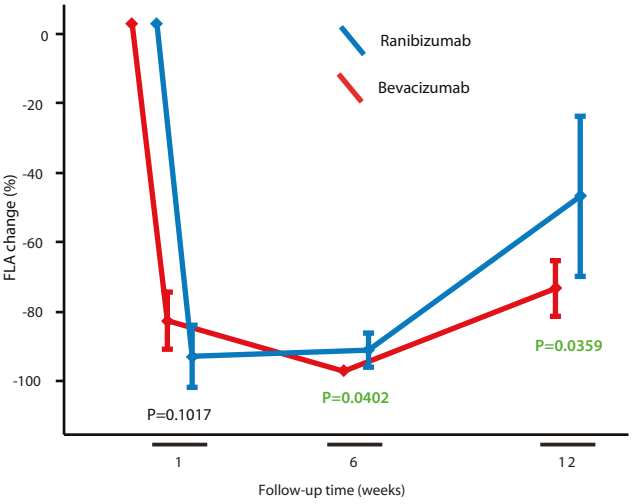

Figure 2. Mean FLA change (%) comparison between patients treated with intravitreal bevacizumab (blue line) (data from Jorge et al., 2006; n = 15) and patients from the present study treated with intravitreal ranibizumab (red line; n = 22). Points are the mean and error bars represent the standard error of the mean. FLA = fluorescein leakage area.