Does Bevacizumab Alter Vascularization Potential in Retinopathy of Prematurity?

Off-label intravitreal injection of bevacizumab, an anti-vascular endothelial growth factor agent, has been shown to be an effective treatment for type 1 retinopathy of prematurity (ROP) in zone I.[1] One of the benefits of intravitreal bevacizumab (IVB) is continued peripheral retinal vascularization as opposed to the permanent ablation associated with laser.[1] Still, the development of late recurrence and retinal detachment requires extended and careful follow-up.[1,2] Reports on fundus fluorescein angiography (FFA) after bevacizumab treatment showed persistent avascular retina and abnormal vascular patterns indicating the possibility of long-term ocular effects.[3] To specifically address the question of the extent of retinal vascularization, we compared 5 unilaterally treated infants with IVB monotherapy for type 1 ROP in zone I or posterior zone II to their untreated fellow eyes. To our knowledge, there are no other reports that compared the vascular extent between treated and untreated eyes after unilateral IVB treatment of the same infant.

We performed a retrospective chart review of all infants treated for ROP with a single IVB injection of 0.625 mg (Avastin; Genentech Inc., San Francisco, CA) in 1 eye between March 2012 and April 2014. The research ethics board approved the study. Treatment was performed and structural outcomes were defined according to the Early Treatment for Retinopathy of Prematurity study criteria.[4] Follow-up and examination under anesthesia were scheduled for each treated infant as described by our group previously.[5] Vascular markings on color fundus and FFA images obtained with RetCam (Clarity Medical Systems, Pleasanton, CA) were reviewed to identify pre- and post-treatment vascularization extent in both eyes. A linear measurement, in disc diameters, of the extent of temporal vascularization was taken from the temporal edge of the optic disc through the foveal center to the border of vascular and avascular retina (Fig 1A and B, available at www.aaojournal.org). Measurements were performed by the nontreating ophthalmologist (MI), who was masked to treatment using ImageJ software (https://imagej.nih.gov/ij/).

Table 1 shows the demographics, indications of treatment, and vascularization extent before and after treatment in treated and untreated eyes. All treated eyes responded to a single injection of IVB and showed regression of disease activity. None have required further treatment. The extent of vascularization between the treated and untreated eyes was within 2 disc diameters on FFA performed at a mean of 10.2±2.9 months. In 2 patients (cases 2 and 3), there was leakage of fluorescein on images performed at 12 and 14.5 months after treatment in both eyes in the absence of neovascularization. Case 2 is a patient with Bartter syndrome type IV *BSND* gene mutation associated with electrolyte imbalance who remains under closer follow-up because the impact of his syndrome on the integrity of retinal vasculature is unknown. A repeat FFA at 36.4 months showed persistence of fluorescein leakage in both eyes (Fig 2A and B, available at www.aaojournal.org). Case 3 also has not required treatment at 30.9 months of follow-up. All treated eyes and 4 of the untreated eyes vascularized to the ora serrata nasally as documented with FFA and scleral indentation. One untreated eye (case 1) remained in anterior zone II at last follow-up 39.1 months after treatment and remains under close observation. All infants developed favorable structural outcomes at a mean follow up of 28.9±10.1 months (range, 14.0−39.1 months) after treatment.

In this report, we observed no difference in the extent of vascular growth after a single injection of bevacizumab for a subset of infants with asymmetric severe ROP. Vascularization of peripheral retina continued beyond the original disease similarly in both treated and untreated eyes of the same infant. At a mean follow-up of 29 months, all treated eyes had vascularized into zone III. Our results show that the extent of vascularization in the treated eye (with a high local dose of bevacizumab) was similar to that in the untreated eye (with a potential effect from systemic absorption). It is impossible to comment on whether the untreated eye might have been affected

Table 1. Demographics and Temporal Vascularization Extent in Disc Diameter before and after Treatment of Infants Unilaterally Treated for Type 1 Retinopathy of Prematurity with Single Intravitreal Injection of Bevacizumab

	GA (wks)	BW (g)	PMA at Treatment (wks)	Eye	Severity of Disease	Pretreatment Vascularization (Disc Diameter)	Post-Treatment Vascularization (Disc Diameter)
1	25.1	730	37.8	RE, treated	S3, plus, Z IIP	9.0	15.0
				LE	S2, no plus, Z II	10.0	14.0
2	27.7	920	38.4	RE, treated	S3, plus, Z IIP	7.0	10.0
				LE	S2, no plus, Z II	9.0	11.0
3	24.1	770	36.0	RE	S3, no plus, Z IIP	10.0	14.00
				LE, treated	S3, plus, Z IIP	10.0	16
4	26.3	770	39.3	RE, treated	S3, plus, Z IIP	10.0	13.0
				LE	S2, no plus, Z II	11.0	15.0
5	24	680	35.0	RE	S2, no plus, Z I	6.0	9.0
				LE, treated	S2, plus, Z I	5.0	10

BW = birth weight; GA = gestational age; LE = left eye; PMA = postmenstrual age; RE = right eye; S = stage; Z = zone; Z IIP = zone II posterior.

from systemic absorption of bevacizumab because the disease severity was always less on that side. However, our results may provide some information on 2 clinically relevant concerns about IVB-treated eyes. First, does IVB treatment impede full retinal vascularization? Tahija et al[3] reported incomplete peripheral vascularization to more than 2 disc diameters from the ora serrata in 11 of 20 eyes after bilateral treatment with a single injection of bevacizumab on FFA performed between 27 and 224 weeks after injection.[3] Our study compared the extent of vascular growth in treated and untreated eyes of the same infant and showed that there was a similar extent of vascularization in both eyes, and thus the "higher" local dose of bevacizumab did not appear to have a differential effect on vascularization. In fact, all treated eyes vascularized into zone III, whereas 1 untreated eye did not. It may be that ROP itself is a more significant factor than IVB treatment on the extent of retinal vascularization.

Second, does IVB treatment result in abnormal leaking peripheral vessels in the long term? Tahija et al[3] also reported that of the 11 eyes with incomplete vascularization, 9 had peripheral leakage on FFA at the vascular-avascular junction.[3] Of note, peripheral vascular leakage was seen in both treated and untreated eyes in 2 patients in our cohort without any adverse events. These eyes proceeded to vascularize into zone III. Leakage on FFA may represent inherent abnormalities associated with severe ROP rather than treatment with IVB.

In this small case series of 5 patients, the extent of vascular growth after unilateral single IVB injection was comparable between treated and untreated eyes. Leakage on FFA without frank neovascularization occurred in treated and untreated eyes. It is possible that the vascular abnormalities are related to prematurity rather than treatment with bevacizumab; however, larger studies are needed to ascertain the contribution of bevacizumab to retinal vascular development versus the ROP disease process. This study was neither designed nor statistically powered to determine whether intravenous bevacizumab is safe or effective in preventing ocular morbidity from ROP. We emphasize the need for diligent long-term follow-up of babies who receive anti-vascular endothelial growth factor injections until full retinal vascularization close to the ora serrata occurs for 360 degrees.[5]

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Retinal Dystrophy in 6 Young Patients Who Presented with Intermediate Uveitis

Inherited retinal dystrophies (RD) comprise a clinically and genetically heterogeneous group of inherited diseases characterized by progressive rod and cone dysfunction and degeneration. Intermediate uveitis (IU) is a clinical diagnosis characterized by bilateral intraocular inflammation located primarily in the vitreous and pars plana. Intermediate uveitis is the second most common uveitis entity among children. Most young patients with IU do not present with any apparent underlying disease.[1] Intermediate uveitis is frequently complicated by cystoid macular edema (CME), which may also occur in RD.

We describe 6 patients initially diagnosed with IU who visited the outpatient uveitis clinics of 3 university medical centers in Utrecht, Groningen, and Amsterdam between 2006 and 2015. During the course of the disease, these patients were diagnosed with RD.

At presentation, age of the patients ranged from 5 to 22 years. Five patients had a negative family history for consanguinity or retinal or immunologic disease and for 1 patient (patient 3; Table 1) it was unknown. They all had subnormal vision (range, 20/25–20/50 Snellen equivalent) and 1 patient complained of nyctalopia. Slit-lamp examination revealed minimal or no anterior segment inflammation and 1+ to 3+ cells with mild to moderate haze in the vitreous. Fundoscopy showed CME in all patients and several white peripheral lesions in 1 patient and some pigment