Intravitreal Bevacizumab in Aggressive Posterior Retinopathy of Prematurity

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Abstract. The anatomic response to intravitreal bevacizumab injection in three patients with aggressive, posterior retinopathy of prematurity is described. In all cases, the worse eye was treated with a single intravitreal injection of 0.75 mg of bevacizumab as monotherapy or complementary to laser therapy. In 24 hours, all injected eyes showed regression of the tunica vasculosa lentis and iris vessel engorgement and disappearance of iris rigidity. In addition, plus disease and retinal proliferation began to regress. None of the eyes required additional treatment. Follow-up of up to 10 months showed good anatomic outcomes and no evidence of local or systemic adverse events. [Ophthalmic Surg Lasers Imaging 2007;38:233-237.]

INTRODUCTION
Retinopathy of prematurity is a proliferative vascular retinal disease that affects premature infants. Although prospective studies have proved the positive effect of ablative retinal treatment in retinopathy of prematurity, 30.8% of infants with stage 3, zone 1 retinopathy of prematurity had unfavorable visual outcome, even when treated early.

Oxygen-induced retinopathy models showed an association of elevated intraocular levels of vascular endothelial growth factor (VEGF) with pathologic retinal neovascularization. Further, VEGF mRNA was expressed in the avascular zone of the human infant eye with threshold retinopathy of prematurity. Published data revealed elevated subretinal fluid VEGF levels in human eyes with advanced retinopathy of prematurity. Anti-VEGF treatment could become a valuable strategy to control retinopathy of prematurity.

Intravitreal injection of bevacizumab, an anti-VEGF antibody, has been used to treat ocular neovascular disease with good results and no apparent toxicity. We decided to offer off-label, intravitreal injection of bevacizumab to infants with progressive retinopathy of prematurity as salvage treatment.

CASE REPORTS
Three premature infants were treated with a single injection of intravitreal bevacizumab in the worse eye as a salvage treatment for aggressive posterior progressive retinopathy of prematurity. In each case, the off-label use of bevacizumab was approved by the neonatology team and the Ethics Committee. The parents were fully informed about potential local and systemic risks and complications and signed an informed consent.

Case 1 was born at a gestational age of 25 weeks + 2 days and a birth weight of 510 g. Case 2 was born
at a gestational age of 25 weeks + 3 days and a birth weight of 650 g. At a post-menstrual age of 35 weeks, screening revealed bilateral, high-risk posterior zone 2 prethreshold retinopathy of prematurity. Laser treatment in the left eyes of both infants was complicated by anterior segment involvement, especially in the left eye. Two weeks later, as the disease progressed, a supplemental laser treatment was done bilaterally. Retinopathy of prematurity in the right eye regressed, but the left eye showed further progression at a post-menstrual age of 37 weeks. Intravitreal injection of bevacizumab was then performed in the left eye without complications.

The injections for all cases were performed in the operating room under sterile conditions. The infants were sedated, and anesthetic and betadine drops were used. To lower the intraocular pressure, gentle massage with a depressor was performed before the injection. A 30-gauge needle was used to intravitreally inject 0.75 mg of bevacizumab (0.03 mL of commercially available Avastin [Genentech, Inc., San Francisco, CA]) at the inferior temporal quadrant, 1.5 mm from the limbus.

Intraocular pressure and arterial blood pressure were checked 1 and 2 hours after treatment. Prophylactic topical antibiotics were given for 3 days. The infants were examined at days 1, 3, and 6, as well as weekly during the first 2 months and monthly thereafter.
RESULTS

In cases 1 and 2, the right eyes experienced an almost complete regression of the tunica vasculosa lentis, iris vessel engorgement, and iris rigidity 24 hours after intravitreal bevacizumab injection (Fig. 1). In addition, the extent of plus disease decreased and the extraretinal neovascularization had a gray appearance. Neovascularization regressed further within 1 week and showed only remnants of fibrous tissue after 3 weeks (Fig. 2). At 6 months following injection, physiologic retinal vessels had developed up to peripheral zone 2, leaving zone 3 avascular.

In case 3, the tunica vasculosa lentis had almost regressed and there was no iris rigidity in the left eye within 24 hours of the injection (Fig. 3). In addition, plus disease and the retinal proliferation began to regress (Fig. 4). Complete regression took 15 days in the injected (left) eye compared to 30 days in the eye that received only laser treatment (right eye).

Throughout the follow-up, retinopathy of prematurity did not recur in any of the eyes, no more treatment was necessary, and no evidence for local or systemic adverse events was found (Fig. 5).

Figure 3. Case 3. (Left) Anterior segment involvement of the left eye on the day of intravitreal injection of bevacizumab, presenting a persistence of tunica vasculosa lentis, engorgement of iris vessels, and iris rigidity. (Right) All signs of anterior segment involvement disappeared 24 hours after the intravitreal injection of bevacizumab.

Figure 4. Case 3. Progression of retinopathy of prematurity (left top) and extensive peripheral neovascularization (left bottom) of the left eye on the day of intravitreal injection of bevacizumab. Twenty-four hours later, plus disease had regressed (right top) and the extraretinal proliferation had a gray appearance (right bottom).

Figure 5. Case 3. Posterior pole and peripheral retina of the left eye 5 months following intravitreal injection of bevacizumab.
DISCUSSION

It is well known that VEGF, a hypoxia-induced cytokine, plays an important role in the normal development of retinal vasculature, in involution of the hyaloid vascular system, and in retinopathy of prematurity.\textsuperscript{6,12,24-26} In phase 1 or the ischemic phase of retinopathy of prematurity, VEGF is down-regulated by hyperoxia leading to vessel occlusion via apoptosis of endothelial cells. In phase 2 or the proliferative phase of retinopathy of prematurity, retinal ischemia induces increased levels of VEGF leading to retinal neovascularization.\textsuperscript{24-26} In addition, high levels of VEGF may not only limit regression of hyaloid vasculature but may also lead to persistence of the tunica vasculosa lentis, iris vessel engorgement, and iris rigidity. This anterior segment involvement reflects proliferative activity of the retinal vasculature and is a prognostic factor in retinopathy of prematurity screening.\textsuperscript{26,27} The regression of the anterior segment involvement within 24 hours following intravitreal bevacizumab injection may reflect the strong dependence of the described anterior retinopathy of prematurity findings on VEGF.

VEGF is not the only cytokine involved in angiogenesis or vasculogenesis, but it is probably the most relevant.\textsuperscript{24} Similar to the oxygen-induced retinopathy model, human infant eyes with retinopathy of prematurity show up-regulated intraocular levels of VEGF.\textsuperscript{13,14} Up to now, approved therapies indirectly affect VEGF by destruction of the ischemic peripheral retina. Anti-VEGF drugs offer the major advantage of limiting tissue destruction by directly blocking the mediator VEGF. However, it appears that optimal timing and dosing of anti-VEGF drugs is most important to obtain the most favorable outcomes.

Bevacizumab, a humanized recombinant antibody that binds all isoforms of VEGF-A, is a relatively large molecule (approximately 150 kD). The molecule size might limit bevacizumab reaching the systemic circulation following intravitreal injection and is likely to have a longer intravitreal half-life time. Binding all isoforms could potentially be a disadvantage because physiologic vascular development could be suppressed.\textsuperscript{26,28} The follow-up of the two infants who received bevacizumab monotherapy (cases 1 and 2) showed that normal vascular development was “frozen” within the first 3 months following injection. Thereafter, normal retinal vasculature progressed along the avascular retina up to zone 3, which remained avascular. This finding could also indicate that the currently used dose was slightly too high and that a lower dose of bevacizumab might be advantageous.

We have to be most careful when treating premature infants with an invasive procedure that potentially can have local complications or systemic side effects. Although there is currently no evidence for an increased risk of systemic adverse events in adult humans who received intravitreal bevacizumab,\textsuperscript{23} the risk profile might be different in a developing infant. However, we also have to keep in mind the devastating outcomes in eyes with progressive retinopathy of prematurity that are refractory to or not suitable for the current standard of care, which can lead to blindness. The pros and cons must be evaluated and both parents and specialists should be involved in the decision-making process.

Preliminary results with intravitreal injection of bevacizumab may suggest it as an alternative therapy in the management of aggressive retinopathy of prematurity, and we anticipate the need for controlled studies to further examine this.

REFERENCES


