

Anti-VEGF for ROP

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The role of VEGF in ROP: VEGF dysregulation in the premature infant occurs in two stages and an inverse concentration of endogenous VEGF is seen. In the first stage, retinal vascular maturation slows as intravitreal VEGF levels decrease in the presence of the relatively hyperoxic ex utero environment. In the second stage retinal vasculature grows aberrantly as endogenous and intravitreal VEGF levels increase secondary to prolonged persistence of avascular retina. Upon delivery, the newborn enters a relatively hyperoxic environment compared to the womb. Because complete retinal vascularization does not occur until full term, premature infants are delivered into a hyperoxic environment while the peripheral retina remains incompletely vascularized. Hyperoxia acts to down-regulate VEGF produced by the avascular peripheral retina, and the normal process of retinal vascularization is impeded. In some infants the prolonged tissue hypoxia induced by avascular retinal periphery causes an abnormal increase in VEGF production. Instead of resuming the normal maturation process pathologic angiogenesis occurs and intra-retinal shunting and extra-retinal neovascularization develops. Presumably, laser photocoagulation of peripheral avascular retina decreases VEGF production by ablating hypoxic tissue. However, in some cases complete laser ablation of avascular retina may be impossible, or disease progression may occur despite adequate treatment.

Anti-VEGF therapy for ROP: Peripheral ablation is not universally effective in eliciting regression of ROP. This is particularly true for APROP, which typically afflicts profoundly premature neonates. In this subset of infants, progression of ROP to bilateral retinal detachment and blindness may occur despite timely and complete peripheral retinal ablation. The advent of anti-VEGF drugs has raised the possibility of treating selected cases of ROP off-label with these medications. The rationale for this approach is drawn from intravitreal VEGF concentration data in human infants with ROP. Undiluted vitreous samples were taken at the time of surgical repair from the mid-vitreous of children who developed stage IV ROP despite standard of care laser. At the time of surgery the eyes were graded and divided into two groups - vascularly active and vascularly inactive - and compared to a control group consisting of children undergoing cataract surgery for uncomplicated congenital cataract. We measured all isoforms of VEGF by enzyme-linked immunosorbent assay (ELISA). Our findings confirmed that upregulation of VEGF occurs in ROP and that abnormally high levels are present in eyes developing retinal detachments with persistent vascular activity. Such eyes are potential candidates for anti-VEGF medications.

VEGF is required in the developing retina for normal angiogenesis, and therefore, the goal of treatment is to quench the excessive levels of VEGF in the vitreous while maintaining a normal vanguard of intraretinal VEGF. For this reason, bevacizumab is a more desirable drug than ranibizumab for treatment of ROP. While the two medications work through an identical mode of action, bevacizumab is a larger molecule than ranibizumab and may therefore penetrate the retina to a lesser degree. Several small case series in the literature have documented the use of intravitreal bevacizumab in eyes with APROP refractory to peripheral laser ablation. The largest experience to date of intravitreal bevacizumab for treatment of ROP is a combined series from Mexico, Portugal and New York City. Fifty-three eyes of 27 patients were injected with bevacizumab. The authors reported that all eyes responded favorably with respect to neovascularization, but five eyes with advanced ROP worsened anatomically. No serious systemic adverse events were appreciated. The next appropriate step would be a prospective clinical trial to evaluate the safety and efficacy of treatment with bevacizumab for improving structural outcomes in ROP. This is the mission of the BLOCK-ROP study, a multicenter prospective longitudinal cohort study including eleven clinical centers in the United States and Canada.