Will the BEAT-ROP Study Results Really Beat ROP?

Recently, many scientific journals have published articles regarding the role of intravitreal injection of anti-vascular endothelial growth factor (VEGF) in retinopathy of prematurity (ROP). The BEAT-ROP cooperative group have now reported their results. By far, their study seems to be the largest and best executed. In addition, the results are no less than spectacular, and if they can be repeated in other centers worldwide, it may lead to a paradigm shift in the present standard of care for ROP.

We are members of a team of vitreoretinal surgeons who oversee the ROP program in Kuwait. We would like to put forth some points that warrant researchers’ attention and may augment our understanding of the disease.

1. VEGF is a potent and critical regulator, and its equilibrium in the body should be carefully regulated to avoid vascular disasters. It has been reported that the disruption of both VEGF alleles in mice leads to complete absence of vasculature. Any perturbation of normal VEGF expression patterns destroys retinal vascularization patterns, with dire results for retinal function, and subsequent restoration of VEGF expression does not correct the problem. It has been reported that transient suppression of retinal VEGF results in the cessation of vessel growth and even causes vascular regression. The authors in the BEAT-ROP study reported that intravitreal bevacizumab leads to decreased epiretinal proliferation but allows development of peripheral vessels up to the periphery. This contrasting effect of intravitreal anti-VEGF injection must be explained physiologically.

2. The BEAT-ROP study group did not elaborate on the pathogenesis of ROP. VEGF is clearly important in angiogenesis, but it is not the only factor that controls blood vessel growth and stability. We do know that the etiology of ROP is multifactorial and that, apart from VEGF, there are other mediators such as insulin growth factors and erythropoietin (Epo) that play an important role in the disease process. Epo-1 and -2 are locally expressed and are upgraded together with VEGF, demonstrating a strong positive correlation in their levels. In a mouse model, hypoxia induced a ninefold increase in retinal Epo but only a threefold increase in VEGF. The relationship between anti-VEGF therapy and Epo levels has not had much investigation, although in one study, results showed that, in highly vascular ROP, after intravitreal injection of bevacizumab, levels of VEGF decreased but levels of Epo did not.

3. VEGF is a double-edged sword. Although VEGF and Epo have been implicated in pathologic neovascularization, they are also regarded as potent neuroproteective and neuroregenerative agents. Suppression of VEGFR-1 and -2 in vivo by the specific small-molecule tyrosine kinase antagonist SU5416 inhibits development of the nonvascularized immature retina, resulting in cell loss in the inner retina, including the inner nuclear layer containing Müller cells and the ganglion cell layer. There are reports published in the peer-reviewed literature that suggest that intravitreal anti-VEGF can lead to a worsening of tractional retinal detachment (TRD) in stage IV ROP. After injection of anti-VEGF, the vascular component of the fibrovascular membrane regresses, but acute fibrosis occurs, leading to a deterioration of the TRD.

4. Intravitreal injections in neonates are tricky; hence, we do not agree that it can be administered at the “bed side” by “any ophthalmologist” as stated in the BEAT-ROP report. There are two major concerns here. First, most of these premature neonates are in the neonatal ICU, are surrounded with equally sick infants, and at times harbor multiple infections. Giving an intravitreal injection in a nonsterile environment can be disastrous. Moreover, signs of inflammation and infection are difficult to assess in neonates. Second, the neonatal eye differs from the adult eye with respect to the spatial relationship of intraocular structures. The pars plana first develops during the second trimester of gestation. A rapid growth phase occurs between 26 and 35 weeks after conception. In the neonatal eye, the pars plana region is incompletely developed, and the anterior retina lies just behind the pars plicata. Hence, utmost care is needed in administering an injection, because it may cause inadvertent lens touching, traction on the vitreous base, and retinal damage, especially if the intravitreal injection is given in a condition of topical anesthesia, when the infant may move suddenly. In a recent editorial in *Ophtalmology*, the parameter used for intravitreal injection in the BEAT-ROP study was questioned when the injection was given approximately 2.5 mm posterior to the limbus. It was cautioned that in a premature infant, a pars plana injection greater than 1.5 to 2.0 mm posterior to the limbus may pass through the full thickness of the retina.

5. The pharmacokinetics and pharmacodynamics of bevacizumab have not been extensively studied in neonates, and because VEGF is involved in a wide variety of physiologic processes, the ocular and systemic safety of anti-VEGF agents is of prime concern in this age group. VEGF is essential for organogenesis and skeletogenesis. The systemic adverse effects of bevacizumab include hypertension, proteinuria, hemorrhage, and thromboembolic events. The BEAT-ROP group did not observe any systemic or ocular side effects after intravitreal bevacizumab, but did admit that the study was too small to address questions of safety. Further, they asserted that bevacizumab cannot penetrate the intact retina or escape the eye except in very small amounts, but there are several reports in the literature that counter this statement. In one study, it was reported that bevacizumab appears in the systemic circulation after intravitreal injection and results in up to a 42% decrease in circulating VEGF after the third injection. In another study, it was reported that in ROP cases, after intravitreal injection, bevacizumab escapes from the vitreous into the systemic circulation and reduces serum VEGF concentration, which warrants extensive evaluation of the patient.

In conclusion, although the initial results reported in some case series and by the BEAT-ROP group are promising, serious deliberations are needed before we label intravitreal bevacizumab as the preferred mode of treatment for ROP. We still do not have enough scientific data about bevacizumab regarding its maximum tolerable dose in the neonatal age group, its ocular and systemic safety profile, or its efficacy, mode of action, and bioactivity in a developing child. The current need is for a randomized, controlled trial with adequate long-term follow-up that can investigate these issues, a comparison with
better results for laser controls consistent with those published in the literature, and the power to assess the long-term safety and tolerability of intravitreal anti-VEGF for the treatment of ROP.

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References

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