Published in final edited form as:

Asia Pac J Ophthalmol (Phila). 2014 ; 3(6): 329–330. doi:10.1097/APO.0000000000000099.

Intravitreal anti-VEGF in Retinopathy of Prematurity: Several years on

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Retinopathy of prematurity (ROP) is a disorder of the developing retina, affecting premature infants of low birth weight and remains one of the leading causes of childhood blindness in the United States.¹ As advanced neonatal intensive care services become more prevalent and high risk neonates survive globally, ROP has become a significant cause of childhood blindness across the world with increasing numbers in Latin American, Eastern Europe, India and China.²

Although multifactorial in its pathogenesis, ROP typically follows a sequence of vascular obliteration induced by excess oxygen followed by hypoxia induced vessel proliferation³, that results in significantly high intraocular levels of vascular endothelial growth factor (VEGF).⁴ As with other retinal vascular diseases, VEGF figures prominently in the pathobiology of ROP.⁵ The ablation of avascular retina has been shown to induce regression of retinal neovascularization (NV). Based on results of controlled, prospective, randomized, multi-center clinical trials, the ablation of avascular retina by laser photocoagulation or cryotherapy has been long established as the standard of care treatment for ROP when retinal neovascularization develops.^{6–8}

In the last decade, numerous clinical trials examining the use of intravitreal injection of anti-VEGF agents for various retinal vascular disorders have shown excellent results in visual and anatomic outcomes.⁹ In the last several years, intravitreal anti-VEGF therapy for the treatment of ROP has also emerged as a potentially more effective treatment for certain stages of ROP whether used as monotherapy or in conjunction with laser or surgery.^{10–14}

In this issue of the Asia-Pacific Journal of Ophthalmology, Hapsari and Sitorus review the current body of clinical knowledge pertaining to the human intraocular administration of anti-VEGF therapy in the management of ROP since it was first used in 2007. Their article, “Intravitreal Bevacizumab in Retinopathy of Prematurity: Inject or Not?” specifically focuses on the off-label use of bevacizumab in ROP and comprehensively summarize past retrospective and prospective clinical studies. Although a detailed and agreed upon practice pattern for the use of bevacizumab in ROP has yet to be established, through their meta-analysis, the authors describe three recurrent scenarios where intravitreal bevacizumab appears to have utility in ROP. These include (1) type 1 ROP zone I and/or posterior zone II;

(2) aggressive posterior ROP with poor retinal visualization in which laser photocoagulation would be difficult to perform; and (3) stage 4 ROP before vitrectomy.¹⁵

Properly timed administration of intravitreal anti-VEGF therapy in ROP has the attractive effect of inducing rapid regression of NV. In successful cases, neonates have an opportunity to further develop their peripheral retina, when compared with the irreversible ablative property of cryotherapy or photocoagulation. In addition, less induced refractive error and amblyopia have also been reported. Intravitreal bevacizumab may also assist ophthalmologists in improving the intraocular environment in ROP prior to laser or surgery. It has become well recognized, however, that recurrences of neovascularization have been reported increasingly and these occurrences are not often predictable. Analogous to patients undergoing intravitreal anti-VEGF treatment for other retinal vascular diseases, neonates who receive intravitreal anti-VEGF therapy require vigilant long-term follow-up to check for recurrent neovascularization. The systemic side effect profile of intravitreal anti-VEGF agents in premature infants has yet to be studied in a systematic fashion. In trying to address these concerns, prospective studies such as the BEAT-ROP study by Mintz-Hittner et al¹³ have substantially improved our understanding to date. The use of anti-VEGF agents such as bevacizumab seems to hold promise for the treatment of ROP. Eight years on since the first report of its use in 2007, there remains uncertainty, significant controversy, and limited widespread acceptance in its use. As ROP becomes more prevalent globally, there is universal interest in the establishment effective guidelines and long-term ocular and systemic safety in the intraocular use of anti-VEGF therapy in ROP. Based on Hapsari and Sitorus' review article, there appears to be sufficient evidence and justification for further prospective randomized controlled trials to ascertain the safety and efficacy of the intravitreal use of anti-VEGF therapy in ROP.

Acknowledgments

Support:

Unrestricted Grant, Research to Prevent Blindness, New York, New York; National Institute of Health Core Grant (NIH P30EY010572)

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