Commentary: Are we there yet? Role of anti-vascular endothelial growth factor and laser in the management of retinopathy of prematurity

Retinopathy of prematurity (ROP) remains one of the most important preventable causes of childhood blindness. The treatment for ROP has evolved over time from the use of cryotherapy, to laser, to the more recent advent of intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections. Laser is the gold standard for ROP management, but is destructive, limits visual field, and induces significant refractive error. In cases with the very posterior disease in zone 1, treatment with laser can itself destroy the area where a fovea would develop, thereby severely limiting visual potential. The use of intravitreal anti-VEGF injections for ROP gained interest with the aim to preserve central vision. The groundwork for use of intravitreal bevacizumab (IVB) was laid by the "bevacizumab eliminates the angiogenic threat for retinopathy of prematurity" (BEAT-ROP) trial,[1] with more recent evidence on use of intravitreal ranibizumab (IVR) from the "RAnibizumab compared with laser therapy for the treatment of INfants BOrn prematurely With retinopathy of prematurity" (RAINBOW) trial.[2] Currently, intravitreal anti-VEGF injections are used in the management of very

posterior forms of ROP and aggressive posterior ROP (APROP). In the study "Outcomes of early versus deferred laser after intravitreal Ranibizumab in aggressive posterior retinopathy of prematurity," the authors present valuable data on response of APROP to IVR with laser performed after either 1 week or 6 weeks.[3] They found comparable anatomical outcomes after early or differed laser.

Babies in the differed arm of this study required fewer laser spots, and those who were evaluated at 6 months also showed lesser refractive error as compared to babies who received early laser treatment.[3] During intrauterine development, vascular precursors migrate into the retina, with cessation of their development after premature birth. Use of anti-VEGF leads to regression of disease signs and allows vascular growth to progress up to the point where the precursors are formed.[1,4] By differing laser, this natural vascular development can progress; thereby the babies in the differed arm of the study required less laser.[3]

Use of anti-VEGF in premature babies is not bereft of controversy. Prolonged suppression of systemic VEGF levels is seen in babies following IVB, as compared to IVR.[5] Concerns over systemic anti-VEGF absorption and potential effect on lung maturation and neurodevelopment in premature babies have been raised in many studies,[6] but not systematically evaluated in any prospective trial. Anti-VEGF causes a transient blockade of VEGF, as against long-term downregulation seen with laser, making a recurrence of disease possible. BEAT-ROP showed that the rate of recurrence with bevacizumab was significantly lower as compared to laser for zone 1 disease (6% vs 26%). The recurrence occurred much earlier in babies treated with laser (6.4 ± 6.7 weeks) than in those receiving bevacizumab (19.2 ± 8.6 weeks).[1] In the RAINBOW trial, the median time to retreatment was 55–57 days. The retreatment was in the form of repeat IVR as well as additional laser therapy.[2] In the current study, early disease recurrence was seen in the differed laser arm in 43.75% of babies at 4 weeks. The evidence indicates disease recurrence occurred much earlier in babies treated with IVR than in those treated with IVB.

Following anti-VEGF therapy regression of plus disease occurs earlier than that of stage 3 ROP.[7] Isaac *et al*.[7] showed vascularization to zone 3 in 18% of babies treated with IVB, by 3 months, which increased to 61% by 24 months. Full peripheral vascularization, by indirect ophthalmoscopy, was seen in 27–38% of babies treated with ranibizumab in RAINBOW trial, at about 169 days.[2] This raises the vital question of necessity of laser immediately after anti-VEGF injection. As a certain subset of babies are likely to have complete vascularization of retina, with more showing development of vasculature into zone 3, laser may not be required as a default following anti-VEGF therapy. A feasible management option would be to follow up the babies to allow maximal vascular development. Laser ablation can be performed at the first sign of type 1 disease recurrence. Potentially one can minimize the need for laser, preserve visual field and reduce refractive error.

While the utopia of ROP treatment is yet to be found, advent of anti-VEGF use has opened up newer avenues of management. The drug of choice for ROP remains elusive as yet, with IVB showing a better ocular profile and IVR being systemically safer. Laser may not be necessary immediately following anti-VEGF therapy. The optimum timing and requirement of laser in eyes treated for ROP needs to be determined. The journey toward optimal ROP treatment continues, and we are not there yet.

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