Commentary: Looking beyond anti-vascular endothelial growth factor – Novel therapeutic targets for retinopathy of prematurity

Retinopathy of prematurity (ROP) is a vaso-proliferative disease affecting the developing retina of premature infants. In developing countries like India, it is the leading cause of both preventable and treatable childhood blindness.[1] Therapy for ROP has come a long way ever since its description as 'retrolental fibroplasia' almost eight decades ago. Current understanding of the pathogenesis of ROP involves two distinct phases, wherein hyperoxia leads to vaso-obliteration is *phase 1* and relative hypoxia and increased vascular endothelial growth factor (VEGF) leads to vaso-proliferation in *phase 2*. The presently validated non-surgical treatment modalities for ROP (cryotherapy, laser photocoagulation and intravitreal anti-VEGF agents) are targeted mainly towards suppression of VEGF in phase 2 of the disease while vitrectomy remains the mainstay for advanced stages of ROP.[2,3] VEGF is required for normal vascularization of retina and also for organogenesis of infants. Hence, suppression of VEGF is not the final answer in our quest for the optimal treatment of ROP. Various therapeutic targets are being investigated for the prevention and treatment of ROP, namely:

1. Light – Light causes increase in free radicals, which may lead to increase in incidence of ROP. This formed the basis for the hypothesis that increase in ambient light may increase incidence and severity of ROP. LIGHT-ROP trial prospectively investigated the same and failed to find any proof.[4] On the contrary, light may have a protective role and further research is warranted to investigate the same.
2. Insulin-Like Growth Factor-1 – IGF-1 is vital to infant growth in utero and is primarily provided by the mother. Premature infants are incapable of producing IGF-1 adequately and this is thought to contribute to the development of ROP. IGF-1 supplementation is proposed to have a biphasic response in ROP, in phase 1 of ROP it promotes normal vascular growth while in phase 2 it promotes extra-retinal fibrovascular proliferation.[5]
3. Erythropoietin (EPO) and its derivatives – Similar to IGF-1, early administration of EPO is proposed to stabilize the retinal capillary bed and late administration promotes vaso-proliferation. Both EPO and its derivatives like darbepoietin have been studied for the prevention of ROP with conflicting results.[6]
4. Antioxidants – Antioxidant supplementation is proposed to counteract the increased reactive oxygen species in the pathogenesis of ROP. Various molecules including vitamin A, vitamin E, N-acetylcysteine, D-penicillamine, superoxide dismutase and lutein have been studied for the same. However questionable efficacy and serious side-effects like increased risk of sepsis have limited their use in clinical situations.[7]
5. Polyunsaturated fatty acids (PUFA) – Similar to antioxidants, PUFA are known to stabilize membranes and reduce oxidative stress. Omega-3 fatty acid supplementation has been shown to reduce the risk of severe ROP, but the same has not been validated in large, multicentre, randomized controlled trials.[8]
6. Propranolol – Propranolol is a beta-adrenergic receptor blocker that has been shown to reduce the severity of ROP. However, the unfavourable systemic side-effect profile, including hypotension and bradycardia in an already susceptible population, limits its clinical utility. More studies regarding the appropriate dose are required.[7]
7. Caffeine – Caffeine has been shown to inhibit VEGF and reduce endothelial cell apoptosis. This has a protective effect in development of severe ROP. However, further prospective trials are required to validate the same.[9]
8. Decorin – Decorin is a proteoglycan molecule which inhibits receptor tyrosine kinase leading to the inhibition of various growth factors like VEGF and IGF-1. It has been shown to have similar activity to anti-VEGF agents in reducing retinal neovascularization in an animal model.[10] However, its interaction with other growth factors, especially IGF-1, needs to be looked at in context of overall growth of premature babies.
9. Genetics (WNT Signalling) – Though no definite causal association has been established between genetic factors and ROP, members of the WNT signalling pathway are proposed to contribute to the severity of ROP. Epigenetic modifications by perinatal factors may be responsible for the variability of ROP severity amongst similar risk profile infants.[11]
10. Stem Cells – Endothelial colony-forming stem cells, harvested from the umbilical cord or bone marrow are being investigated for repair of damaged retinal vasculature in animal models.[12]

As our understanding of ROP improves, the therapeutic targets to prevent as well as treat this blinding disease are also evolving. The current management approaches give us good outcomes in a sizeable proportion of infants with severe ROP, if timely detected. But there is a long way to go before treatment stratergies can eliminate ROP as a major cause of preventable childhood blindness.

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