Guest Editorial

Use of intravitreal anti-VEGF: Retinopathy of prematurity surgeons' in Hamlet's dilemma?

There is an increasing concern regarding the use of intravitreal anti-VEGF (Vascular endothelial growth factor) drugs for the treatment of retinopathy of prematurity (ROP).[1-5] General ophthalmologists, especially pediatric ophthalmologists and retinal surgeons are at a loss to understand the utility of anti-VEGF agents in ROP. The important issues are the short- and long-term ocular and systemic safety of these drugs and their role vis-à-vis laser retinal ablation in ROP. Laser ablation is the currently accepted, safe, and effective therapy for ROP. Frequently data regarding the use of anti-VEGF in ROP are being published and presented at scientific meetings. There are no prospective studies with adequate data regarding the use of anti-VEGF in ROP. Hence, the use of the drug either as a primary monotherapy, or as rescue therapy, is a burning question, akin to Hamlet's dilemma, "To be, or not to be, that is the question".

The recent publication of the BEAT-ROP (Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematuritytrial) by Mintz-Hittner *et al.*,[6] and the correspondence thereafter,[1-5] warrants an urgent discussion. The report credits a definite role for bevacizumab as a primary therapy in ROP, in lieu of laser treatment. In the latter, the non-regression rates are reported to be high. Apparently this trial seems to have given a green signal for the use of anti-VEGF monotherapy treatment in ROP, for the zone I threshold disease. However, before accepting the veracity of these results, one ought to study this trial and other reports critically.

In the BEAT-ROP trial, eyes treated with bevacizumab did exceptionally well, with preservation of peripheral retina, completion of retinal vascularization, and lower recurrence rates. The comparison of bevacizumab with laser treatment outcomes in the trial are however difficult to accept. The title of the published trial does not mention that this is a randomized controlled trial, and hence, violates the Consolidated Standards of Reporting Trials (CONSORT) statement guidelines[7] for randomized controlled trials. Similarly, the abstract clearly mentions that it is a trial assessing bevacizumab monotherapy and that it was too small to assess the safety of the treatment. The laser methodology and assessments and outcomes in the trial were not as per current standards of laser treatment for ROP.[8-12] The authors chose not to treat at high-risk prethreshold disease (in spite of starting early screening), which is the current standard of care recommended by the early treatment of retinopathy prematurity (ETROP) study, but waited until the threshold disease developed, especially for Zone 1, which is known to have a poorer outcome with laser treatment. The laser recurrence rate (which is actually more of a persistence rate based on the assessment and treatment protocol followed in the trial) was reported to be as high as 42% for Zone I disease and occurred at a mean of 6.2 ± 5.7 days, that is, less than a week after treatment. Recent trials using rigorous laser protocols show complete ROP regression with very good anatomic outcomes in 70 – 87.5% of the cases of Zone I disease, treated as per ETROP guidelines.[8-12] Besides, late recurrence of the disease (mean 16.0 ± 4.6 weeks)[6] was seen in the bevacizumab group as well, raising the concern that frequent and relatively long-term follow-up will be required. Details of the site of recurrence and characteristics of such recurrences are not described in the study.

Of great importance is the fact that VEGF is essential for the developing brain, lung, and kidneys, and the anti-VEGF effects on these organs in the newborn are not known. In spite of a prospective study design, developmental and other systemic evaluations were not part of the protocol, and so, long-term systemic safety issues have not been addressed in most reports. In the BEAT-ROP study more deaths (five) were reported in the bevacizumab group than in the laser group (two).[6] Systemic intubation rates (37.5%)[6] were far more than those reported in the current literature on ROP laser treatment. In the combined data from two recent studies by Jalali *et al.*,[11] and Sanghi *et al.*,[12] a total of only three babies had apnea during or after laser treatment.

In a recent uncontrolled, small sample, non-randomized, retrospective study from Mexico,[13] bevacizumab was claimed as a wonder drug for all stage 3 + ROP. However, a close scrutiny of the results revealed that safety was still an issue and indications and follow-up were not vigorously decided. Therefore, before the ROP managers of the world jump onto the band wagon of believers, more scientific study is essential. As we receive more reports of usage and success stories of the anti-VEGF therapy, adverse outcome reporting must be routine and all physicians using these drugs need to monitor actively and look out for any adverse systemic, ocular or developmental events related to the procedure or the drug. For example, choroidal rupture has been reported with injection of bevacizumab and the authors are also concerned that bevacizumab may have an adverse influence on the development of choroidal vessels.[14]

An important aspect of the use of anti-VEGF in ROP is assessing its adjunctive role. Some reports find good results with a combination therapy, as areas of retinal non-perfusion and vascular loops persist longer in cases where intravitreal bevacizumab has been used as a primary monotherapy. Anti-VEGF drugs have no effect on mature vessels once pericytes have been laid down, suggesting that a combination of anti-VEGF therapy (which neutralizes the pre-existing VEGF in the vitreous cavity) and laser (which reduces the hypoxic stimulus to VEGF production) would be a logical mode of treatment. However, systemic and ocular safety issues still need to be addressed.

It is well known that ROP is due to cessation of the normal process of angiogenesis, leading to ischemia, and angiogenesis needs VEGF. The fibrovascular proliferations are a result of ischemia. This raises a question regarding the use of pan anti-VEGF blockers and over time our 'ROP managers' have evolved their own criteria for screening,[15] showing excellent outcomes with timely and aggressive laser therapy, even in zone I ROP.[11,12] In our population we need to define and characterize the subset

of babies with ROP, where the benefits of bevacizumab may be most needed, provided the drug is proved to be safe. This will require prospective studies and good long-term follow-up. Unanswered questions in relation to bevacizumab administration are: which stage, when and how should it be given. What are the effects of a pan-VEGF blocking, on very severe Zone I ROP in bigger babies, where vasculogenesis has stopped around the optic disc and where VEGF levels are very high? What about systemic safety, especially long-term impacts on development and cognition? These are very vital and probing questions that need unbiased answers so that our decision-making is based on science and not just populism. The main issue continues to be the improved neonatal practice for prevention of ROP. This is possible when there is timely screening for earlier therapy, and working closely with neonatology colleagues.

We feel that anti-VEGF agents in ROP, both as monotherapy and as rescue therapy, need thorough investigation, using well-designed scientific protocols, with informed consent, and monitoring of the long-term ocular, systemic, and developmental outcomes. The purpose of this write-up is neither to negate nor propagate the results of the Mintz-Hittner trial, but to highlight some other pertinent questions that this trial raises. Thus, for those as yet undecided about the use of anti-VEGF, we advice caution, remembering that babies treated today have 50 or so years ahead of them. In a nutshell, it is time to address the questions that arise because of anti-VEGF therapies in ROP!

Rajvardhan Azad

Chief, Dr. R P Centre of Ophthalmic Sciences, Professor of Ophthalmology and Head,
Vitreo-Retina, Ocular Trauma & ROP services,
Immediate Past President, All India Ophthalmological Society, Regional Secretary,
Asia Pacific Academy of Ophthalmology, Chairman, Ophthalmic Education and Certification Committee,
Asia Pacific Academy of Ophthalmology and Former President, National Board of Examination
Ministry of Health and Family Welfare, Government of India.
E-mail: rajvardhanazad@hotmail.com

References

1. Good WV, Palmer EA. Bevacizumab for retinopathy of prematurity. N Engl J Med 2011;364:2359.
2. Gilbert CE, Zin A, Darlow B. Bevacizumab for retinopathy of prematurity. N Engl J Med 2011;364:2359-60.
3. Lim LS, Mitchell P, Wong TY. Bevacizumab for retinopathy of prematurity. N Engl J Med 2011;364:2360.
4. Gole GA, Camuglia JE, Ells AL. Bevacizumab for retinopathy of prematurity. N Engl J Med 2011;364:2360-1.
5. Moshfeghi DM, Berrocal AM. Retinopathy of Prematurity in the Time of Bevacizumab: Incorporating the BEAT-ROP Results into Clinical Practice. Ophthalmology 2011;118:1227-8.
6. Mintz-Hittner HA, Kennedy KA, Chuang AZ. BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med 2011;364:603-15.
7. Schulz KF, Altman DG, Moher D. CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med 2010;152:726-32.
8. Revised indications for the treatment of retinopathy of prematurity. Results of the early treatment for retinopathy of prematurity randomized trial. Arch Ophthalmol 2003;121:1684-94.
9. Hurley BR, McNamara JA, Fineman MS, Ho AC, Tasman W, Kaiser RS, *et al.*. Laser treatment for retinopathy of prematurity: Evolution in treatment technique over 15 years. Retina 2006;26:S16-7.
10. Jalali S, Azad R, Trehan HS, Dogra MR, Gopal L, Narendran V. Technical aspects of laser treatment for acute retinopathy of prematurity under topical anesthesia.Indian J Ophthalmol 2010;58:509-15.
11. Jalali S, Kesarwani S, Hussain A. Outcomes of a protocol based management for zone I retinopathy of prematurity. The Indian twin cities ROP screening program report number 2. Am J Ophthalmol 2011;151:719-24.
12. Sanghi G, Dogra MR, Das P, Vinekar A, Gupta A, Dutta S. Aggressive Posterior ROP in asian Indian babies: spectrum of disease and outcome after laser treatment. Retina 2009;29:1335-9.
13. Quiroz-Mercado H, Martinez-Castellanos MA, Hernandez-Rojas ML, Salazar-Teran N, Chan RV. Antiangiogenic therapy with intravitreal bevacizumab for Retinopathy of prematurity. Retina 2008;28:S19-25.
14. Atchaneeyasakul LO, Trinavarat A. Choroidal ruptures after adjuvant intravitreal injection of bevacizumab for aggressive posterior retinopathy of prematurity. J Perinatol 2010;30:497-9.
15. Jalali S, Matalia J, Hussain A, Anand R. Modification of screening criteria for retinopathy of prematurity in India and other middle income countries. Am J Ophthalmol 2006;141:966-8.

Access this article online	
Quick Response Code:	Website: www.ijo.in
	DOI: 10.4103/0301-4738.86305