

## Review Article

# Bevacizumab in Retinopathy of Prematurity : Concerns and adverse effects

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### Abstract

Retinopathy of prematurity (ROP) ranks as one of the leading causes of blindness in the paediatric age group, the incidence of which is increasing in developing countries as the economy strengthens and healthcare practices improve. As a vaso-proliferative disorder affecting premature neonates VEGF is said to play a vital role in the pathogenesis of ROP. Evidence of the efficacy of anti-VEGF agents in treatment of ROP have been seen in literature since early 2007 with most published reports being either case studies or small case series. The only randomised controlled trial in this regard was the BEAT-ROP study which was published in 2011. However, even in that study the adverse effects of Bevacizumab were not analysed. This review aims to discuss the complications prior to the blanket administration of intravitreal bevacizumab in the management of ROP.

**Key words:** Bevacizumab, Retinopathy of Prematurity, Neuro-developmental delay, BEAT-ROP.

### Manuscript

VISION 2020 program put forth by the World Health Organisation puts emphasis on counteracting major ocular diseases posing a significant public health problem. Childhood blindness occupies a special mention amongst this group of ocular disorders with retinopathy of prematurity (ROP) being a leading cause of blindness among them (Augestad et al 2012). ROP is a serious vasoproliferative disorder that affects premature infants, which when

significant can lead to lifelong disabilities for survivors of neonatal intensive care units. Gilbert (2008) reported that at least 50,000 children globally were blind due to ROP or its sequelae. In India, the incidence of ROP is reported to vary from 24% to 47%. (Murthy et al., 2013)

The world is currently in the midst of the third epidemic of ROP. Financial resources in the developed nations of the world have allowed for a high standard of care and improved survival rates among preterm neonates. A similar increase in survival rates in preterm births has also been noted in countries with a developing economy (Sankar et al., 2016). However, this increase does not have a corresponding increase in the standard of care meted out to these patients. Hence, the rate of co-morbidities in such cases increases. This is

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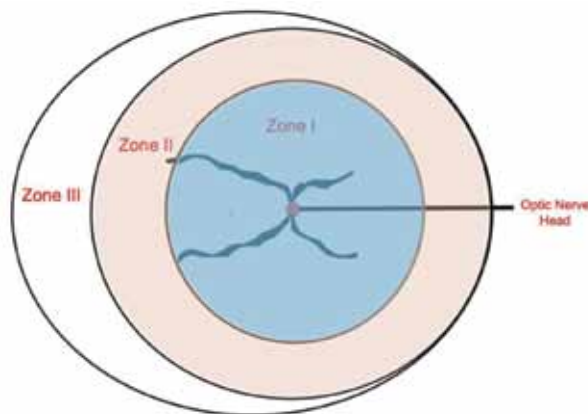
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noted in the case of ROP where the prevalence in the developed nations ranges around 10% while that in the developing nations is around 25 - 30% (Fleck and Dangata, 1994; Taqui et al., 2008; Murthy et al., 2006).

The classification of ROP was initially put forth as the International Classification of Retinopathy of Prematurity (ICROP) in 1984 (An International Classification of Retinopathy of Prematurity, 1984). The terminology was based on location, extent and severity of the condition. The retina of the neonate was divided into 3 zones centred on the optic nerve head (Fig. 1). A posterior location of the disease is usually associated with a more severe clinical course. The extent of the disease is expressed in terms of clock hours with each clock hour corresponding to 30 degrees of the retina. The severity of ROP was divided into 4 stages from demarcation line (Stage 1), ridge (Stage 2), extra-retinal fibrovascular proliferation (Stage 3), and retinal detachment (Stage 4).



**Figure 1** - The ICROP classification divided the neonatal retina into 3 distinct zones so as to accurately describe the location of ROP

A revision of the ICROP classification (The International Classification of Retinopathy of Prematurity Revisited, 2005) divided Stage 4 disease into partial retinal detachment, extra-foveal (4a) and foveal (4b) and total retinal detachment (Stage 5). The presence of vascular

dilatation and tortuosity involving all the four quadrants at the posterior pole, vitreous haze and vessel engorgement at the iris contribute to presence of plus disease which is an active and progressive state of ROP. The revised classification in 2005 introduced the concept of pre-plus disease which is a state of active ROP wherein the vascular changes are more marked than normal but insufficient to be labelled as plus disease.

The concept of aggressive posterior ROP (APROP) was also put forward by the revised classification. This type of ROP, previously labelled as “Rush disease” is posterior pole vascular dilatation and tortuosity which is out of proportion to the peripheral retinopathy. APROP is usually confined to the posterior zones and does not follow the classical stages of ROP.

Normal retinal vascularisation begins in the form of a superficial and deep capillary plexus emerging from the optic nerve head around the 16th week of gestation (Fruttiger, 2007). These retinal vessels growing out of the optic disc reach the nasal ora serrata around 32 weeks of gestation while the temporal ora serrata is vascularised shortly after birth. Multiple angiogenic molecules such as insulin like growth factor (IGF-1), basic fibroblast growth factor (FGF), platelet derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) have been isolated and attributed specific roles during this process of normal vasculogenesis (Saint-Geniez and D’amore, 2004).

VEGF is a hypoxia inducible vasoactive cytokine which acts as a mitogen for vascular endothelial cells and is necessary for normal angiogenesis. The secretion of VEGF from astrocytes and mesenchymal spindle cells is regulated by tissue hypoxia; hypoxia stimulates transcription of the VEGF gene whereas hyperoxia decreases it (McColm, Geisen and Hartnett, 2004). Further research has shown that

VEGF can be further divided into 5 sub-groups: VEGF-A, VEGF-B, VEGF-C, VEGF-D and Placental growth factor. VEGF-A has been found to be a key regulator of physiological and pathological angiogenesis (Ferrara, Gerber and LeCouter, 2003). It acts on the vascular endothelial cells and has both angiogenic and vasopermeable properties.

Retinal development in-utero progresses in an otherwise hypoxic condition as compared to room air, being supported by the foetal haemoglobin. A premature delivery of the infant poses the challenge of retinal development in an altered environment. ROP is considered as a biphasic disease; the first phase is characterised by hyperoxic vessel obstruction followed by a phase of hypoxic neovascularisation (Chen et al., 2011). The first phase lasts from birth to around 31-32 week post-gestational age. Neonatal hyperoxia results in vasoconstriction and obliteration of sections of the developing retinal vasculature, ultimately leading to tissue ischemia. The second phase begins around 31-32 weeks of gestation. Increasing metabolic demands of the retina results in increasing hypoxia due to the present vascular obliteration. This hypoxia results in production of angiogenic factors especially VEGF which stimulates neovascularisation or in severe cases unregulated vascular growth (Fruttiger, 2007).

However, VEGF is not the only mediator that may play a role in the development of retinopathy of prematurity. Smith (2005) evaluated the role of Insulin like growth factor -1 (IGF-1) in the development of ROP and concluded that IGF-1 acts by controlling VEGF activation. High levels allow for maximal stimulation of VEGF driven vascular proliferation while inadequate levels inhibit vessel growth despite the presence of VEGF.

Initially only prematurity was considered as a risk factor in the development of ROP however further investigation has noted other factors which may lead to an unfavourable clinical

outcome. Lee and Dammann (2012) reported that prenatal, perinatal and postnatal systemic inflammation is an additional risk factor for ROP beyond immaturity. Other notable risk factors include neonatal sepsis, oxygen exposure, and low gestational age which are not only independent risk factors but may even interact in an additive pattern as noted by Chen et al (2011).

The local concentration of VEGF in the vitreous cavity and the sub-retinal fluid has been found to be elevated in patients who had undergone surgery for late stages of ROP as compared to control eyes who underwent surgery for congenital cataract (Ma et al., 2014; Sonmez et al., 2008). A correlation has also been noted between the elevated levels of VEGF and the vascular activity of the disease and neovascularization by Sato et al (2009).

Bevacizumab is a humanised recombinant antibody which binds all iso-forms of VEGF-A (Mintz-Hittner, 2010). VEGF as previously mentioned is a potent mitogen for both pathological and physiological angiogenesis, the production of which is regulated by tissue hypoxia. The standard of care in ROP treatment is ablation of the peripheral avascular retina with laser photocoagulation to abolish tissue hypoxia and thus reduce the levels of VEGF in the retina and vitreous (Smith, 2008). This leads to destruction and permanent damage to the peripheral retina which may manifest in advanced cases as a constriction off the visual field. Anti-VEGF agents have a distinct advantage in this context; they help to reduce VEGF levels without causing structural damage to the retina; thereby preserving peripheral visual fields when the ROP regresses. Furthermore, the chances of development of refractive errors and progressive myopia are low (Tan, Christiansen and Wang, 2019).

In a preterm neonate both growth and development continue at an increased pace. Early development at this phase is marked

by periods of susceptibility to environmental factors and drugs. Tampering with internal body milieu and the fine balance between systemic cytokines at this stage can have far reaching consequences.

Hellgren et al (2016) noted that the mean concentration of VEGF at birth in premature infants (cord blood) was noted to be similar between infants who ultimately developed ROP and those that did not.

In the foetus expression of VEGF is noted in a number of tissues. In the lung the alveoli first appear around 29 weeks of gestation and become progressively thin-walled till around 36 weeks of age. In mice it has been noted that VEGF administration helps increase surfactant synthesis (Compernelle et al., 2002). In a similar manner it is stated that VEGF helps in the normal alveolar development in the neonate and that inhibition of VEGF during this critical period may lead to development of brocho-pulmonary dysplasia (Thebaud, 2007). Secretion of VEGF has also been noted from both the foetal and adult kidney. It is believed to have a role in the normal development of glomeruli with a strong dose response relationship to VEGF-A administration (Simon et al., 1995). Dysregulation of VEGF may lead to a pathological change in glomerular development. VEGF is also reported to play an important role in neurological development and its expression in different areas of the brain in the immediate post-natal period has been noted (Sentilhes et al., 2010).

Kong et al (2015) evaluated the effects of intravitreal bevacizumab on serum levels of free VEGF and Insulin like growth factor - 1 (IGF-1); which has noted to be of importance in post-natal weight gain in premature infants (Stahl et al., 2010). They divided their patients in three groups: group 1 received conventional laser therapy, group 2 received intravitreal bevacizumab (IVB) 0.625mg per eye per dose and group 3 received IVB 0.25mg per eye per

dose. The patients were followed up for 2 months post treatment. They concluded that reduction in serum VEGF levels were observed in both the laser and IVB treated groups. They also noted that bevacizumab remained detectable in circulation for 60 days post injection. However, the magnitude of decrease in levels of VEGF were noted to be almost double to that noted in the laser treated groups. The level of IGF-1 was noted to increase in both the groups following treatment of ROP however the levels were noted to be lower in the IVB treated group as compared to the laser treated group.



**Figure 2** - The presence of extra-retinal fibrovascular proliferation is noted in Zone II with evidence of pop-corn vessels and a haemorrhage in the supero-temporal quadrant of the left eye 34 week neonate with ROP.

The first reports favouring the use of Bevacizumab in ROP started to appear in research papers around 2007. These were majorly retrospective case series stating the beneficial effect of Bevacizumab in aggressive posterior ROP (AP-ROP) (Mintz-Hittner and Kuffel, 2008). AP-ROP, also referred to as Rush disease due to its relentless and rapidly progressive clinical course, is usually associated with a poor prognosis when treated with laser; hence people stood up and took notice of this new treatment alternative for ROP. A similar and encouraging result was also reported in

a prospective case series in Mexico (Quiroz-Mercado et al., 2008). They examined 18 eyes of 13 neonates with either Stage 4a or 4b ROP with no response following laser treatment, or threshold ROP wherein visualisation of the media was poor, and in high-risk pre-threshold or threshold ROP. A follow-up of 6 months was noted with a decrease in neovascularization in all but 1 eye which progressed to a retinal detachment.

With these encouraging results in mind investigators went ahead with a randomised controlled trial to ascertain the beneficial role of bevacizumab. This randomised control trial was aptly entitled 'Bevacizumab eliminates the angiogenic threat of Retinopathy of Prematurity' (BEAT-ROP) (Mintz-Hittner, Kennedy and Chuang, 2011). The study evaluated the effect of single injection of 0.625mg bevacizumab given bilaterally versus bilateral conventional laser therapy in 300 eyes of infants with zone I or posterior zone II ROP with stage 3+. The patients were randomly assigned to receive either bevacizumab or laser therapy with the primary outcome being ROP recurrence in one or both eyes requiring re-treatment before 54 weeks. 286 eyes were evaluated as a part of the final analysis which noted an recurrence of ROP in 6 eyes (4.29%) in the bevacizumab group as compared to 32 eyes (21.91%) of the laser group. This beneficial effect of Anti-VEGF injection was more pronounced in Zone I disease wherein only 2 eyes of the bevacizumab group noted a recurrence as compared to 23 eyes of the laser group (laser failure rate of 42.4%). The investigators reported complications in four patients all treated with laser for posterior Zone II disease.

The results mentioned in the trial are quite overwhelmingly in favour of bevacizumab. However, the results of this study should be scrutinised thoroughly before their implementation in the clinical scenario.

First and foremost as mentioned in the abstract of the study, the trial was not sufficiently powered to ascertain the systemic complications and adverse effects related to the Anti-VEGF agent. In fact, of the 7 deaths that have been reported in the study, 5 were noted in the bevacizumab group as compared to 2 in the laser group. The need of intubation following laser therapy was also reported to be suspiciously high at 30%.

A note should also be made of the fact that study population of the trial was majorly Hispanic in origin. Clinical experience has shown that these patients usually require more than one sitting of laser treatment for ROP. This was however not allowed as per the BEAT-ROP treatment protocol.

A major concern with the use of bevacizumab in preterm neonates is with reference to the dosage that should be administered. Investigators in the BEAT-ROP trial utilised 0.625 mg of bevacizumab via intravitreal injection per eye stating that since bevacizumab is a large molecule it cannot penetrate the intact retina or can only enter the systemic circulation in small amounts. The pharmacokinetics of the drug were not taken into account before deciding the dosage. A dosage that is half of what is administered to adults was given to infants who had a body surface area around 9 times less than that of an average adult. Furthermore, the vitreous volume in a neonate is considerably less than that compared to an adult. Both these factors would favour chances of systemic absorption and toxicity of the drug. In fact, as previously mentioned, Kong et al (2015) using a dosage similar to that used in the BEAT-ROP study showed that levels of bevacizumab were still detectable in the blood even after 60 days of administration. They also noted a persistent and marked depression in the levels of systemic VEGF in these cases. Harder et al (2014) evaluated the effect of 0.375 mg of bevacizumab injected via an intra-vitreous injection in 57 eyes of 29 infants with ROP and

found a regression of Type I ROP in both Zone I and Zone II disease. A recent study carried out by the Pediatric Eye Disease Investigator Group found that a dose as low as 0.004mg was effective in 90% of the cases to prevent recurrence of Type I ROP in the 4 weeks of follow-up of the study (Wallace et al., 2020).

One of the major controversies surrounding the BEAT-ROP study is the higher failure rate with laser therapy. The authors had noted a recurrence rate as high as 42% with respect to Zone I disease. The methodology for the laser was not as per the current rigorous guidelines of the Early Treatment of Retinopathy of Prematurity (ET-ROP) study (Early Treatment For Retinopathy Of Prematurity Cooperative Group, 2003) . The authors of BEAT-ROP had chosen to treat only threshold disease while as per the current standard of care high-risk pre-threshold disease is also treated. ET-ROP trial noted an unfavourable clinical outcome in only 30% of zone I treated infants. Furthermore the time period to treatment failure was noted as  $6.2 \pm 5.7$  days; however it usually takes more than a week for a response in ROP treated with laser. Thus the trial labelled the laser treatment as ineffective even before it could start acting.



**Figure 3** - The left eye of a pre-term neonate who presented at 36 weeks post-conceptual age with stage 4b ROP. The other eye had a macula sparing retinal detachment and was planned for pars plana vitrectomy.

There was a late recurrence of the disease in the Bevacizumab treated group as well. A resurgence in the disease activity was noted at  $16.0 \pm 4.6$  weeks in the eyes that were treated with bevacizumab. Thus, the infant cannot be labelled successfully cured till the vascularisation of the far periphery is complete with absence of all traction elements. This thereby underlines the fact that these infants require a more comprehensive and closer follow-up. The late recurrence may be attributed to the persistently lowered IGF-1 levels that are associated with bevacizumab treatment as noted by Kong et al (2015).

Scattered reports of toxicity following bevacizumab have been noted on a literature search. Experimental evidence in mice has shown that postnatal VEGF blockade results in stunted growth, impaired organ growth and an increased mortality due to renal failure (Gerber et al., 1999; Kitamoto, Tokunaga and Tomita, 1997). Wu et al (2016) first reported a case of hypotension associated with intravitreal bevacizumab injection in a 26 week old premature infant which persisted for 22 hours after therapy. This was associated with shortness of breath, apnoea and feeding intolerance. The condition of the infant was noted to stabilise 6 days post therapy.

A retrospective study carried out in Canada (Morin et al., 2016) noted an increase in motor defects at 18 months in premature infants who were treated with intravitreal injection of Bevacizumab given for ROP. The authors stated that bevacizumab-treated infants were 2 to 3 times more likely to display unfavourable developmental outcomes compared with those who had received laser, but after adjusting for confounders, only risk of severe neuro-developmental disability remained statistically significant. The odds of neuro-developmental disabilities was 3.1 times higher with Bevacizumab as compared to laser photocoagulation. Lien et al (2016) noted



detrimental effects on neurodevelopment at 2 years of age when patients were treated with a combination of intravitreal bevacizumab and laser photocoagulation for ROP during infancy.

Chhablani et al (2013) have reported a case of choroidal ischemia with hypotony and exudative detachment in a 6 week old pre-term infant, with a post-conceptual age of 34 weeks, who was administered intravitreal bevacizumab for Zone I APROP. This was resolved with the administration of topical steroids and cycloplegics.

Keeping in mind the aforementioned reports it is important to study the long term effects of Bevacizumab particularly when used in a vulnerable population, as in pre-term infants, before administering it as a blanket therapy for retinopathy of prematurity.

Bevacizumab does have a promising future in the management of retinopathy of prematurity. The potential for development of a peripheral vascularised retina with full visual fields is an exciting prospect. However, a lot of uncertainty regarding the dosage and long-term safety still clouds its usage as a first line agent. More clinical research in the form of randomised control trials are needed to answer these questions before it can become a more accepted intervention. Results from newer trials such as the RAINBOW trial (Stahl et al., 2019) looking at Ranibizumab and its role in ROP will provide some of the answers to these problems and further open the gates for the medical management of ROP but till then laser photocoagulation remains the primary mode of treatment.

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