



Anti-vascular endothelial growth factor treatment for retinopathy of prematurity

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Abstract: Retinopathy of prematurity (ROP) is a proliferative disorder of the developing retina in premature and low birth weight infants. Recently, the role of vascular endothelial growth factor (VEGF) in the pathophysiology of ROP has been well studied and anti-VEGF drugs have been used in phase 2 to treat ROP patients in many ways. At first, ophthalmologists began to give intravitreal bevacizumab (IVB) or ranibizumab off-label to treat ROP as a salvage treatment after failure in laser photocoagulation or in combination with laser as an adjuvant treatment for patients had media opacity or rigid pupil. Now anti-VEGF drugs are also used as monotherapy in type I ROP or perioperative use in stage 4/5 ROP. Questions remain regarding long-term safety, dose, timing, visual outcomes and long-term effects, including systemically.

Keywords: Retinopathy of prematurity (ROP); vascular endothelial growth factor (VEGF); bevacizumab; ranibizumab; treatment

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Retinopathy of prematurity (ROP) is a proliferative disorder of the developing retina in premature and low birth weight infants that continues to be a major cause of blindness of children worldwide (1-3). Randomized trials CRYO-ROP (4) and ET-ROP (5) have established cryotherapy for threshold disease and laser photocoagulation for type 1 prethreshold ROP, respectively. Although cryotherapy and laser treatment can cure most ROP disease, they may cause complications such as peripheral visual field defect. Recently, the role of vascular endothelial growth factor (VEGF) in pathophysiology of ROP has been well studied and anti-VEGF drugs have been used to treat ROP patients in many ways. This article reviews pathogenesis, indication, timing, dose, ocular and systemic complications of this treatment for ROP patients.

Pathogenesis of ROP

Now we know that ROP is a biphasic disease: a vaso-obliterative phase and a vaso-proliferative phase (6-8). Phase 1 is from premature birth to at least 30 weeks post menstrual age (PMA). Following preterm birth, the infant enters a hyperoxic environment due to relatively higher levels of PaO₂ in extrauterine environment as well as supplemental oxygen. The normal PaO₂ in utero is 30 mmHg, while a normal infant breathing room air will have a PaO₂ of 60–100 mmHg. This change suppresses hypoxia-driven factors and VEGF as seen by the arrest of retinal vessel growth, and the constriction and retraction of already formed vessels. In this phase, anti-VEGF drugs are contraindicated. Therapeutic interest has focused on the

physiological replacement of insulin-like growth factor-1 (IGF-1) (9,10), which in utero is produced by placenta, appears to be required for VEGF signalling and vessel growth and survival.

Phase 2 commences around 31 weeks PMA. In this vaso-proliferative phase, further growth of the neural retina and its high metabolic rate causes relative hypoxia. The hypoxic peripheral avascular retina stimulates secretion of VEGF. Thus, abnormal inner retinal vessels (neovascularization) form at the junction of the avascular and vascular retina (traditional ROP going through stages 1 to 3) or in the posterior retina as an especially aggressive posterior ROP (APROP). This phase of ROP is similar to the neovascularizations in other proliferative retinopathies such as diabetic retinopathy. Over time, this pathological growth of vessels produces a fibrous scar extending from the retina to the vitreous gel and lens. Retraction of this scar tissue can separate the retina from the retinal pigment epithelium, resulting in a retinal detachment and likely blindness. In this phase, the therapeutic interest is direct inhibition of VEGF.

Current anti-VEGF drugs

Currently there are four main anti-VEGF drugs: pegaptanib (Macugen[®]; Eyetech Pharmaceuticals Inc., FL, USA and Pfizer Inc., New York, NY, USA), ranibizumab (Lucentis[®], Genentech Inc., San Francisco, CA, USA), bevacizumab (Avastin[®], Genentech Inc. and Roche, Basel, Switzerland) and aflibercept (Eylea[®]; Regeneron Pharmaceutical Inc., Tarrytown, NY, USA and Bayer, Basel, Switzerland).

Pegaptanib is a small pegylated RNA fragment aptamer (a 28-nucleotide RNA oligonucleotide) developed in the 1990s (11). It was the first VEGF inhibitor approved by the United States Food and Drug Administration (FDA) in December 2004 (12-14). It is an aptamer which specifically binds VEGF₁₆₅ and it was proven to be less effective than other “pan-VEGF” compounds. For this reason, it is no longer widely used in most countries.

Ranibizumab is the other drug approved by FDA for the treatment of wet AMD in 2006. It is a humanized recombinant G1 kappa isotype antibody fragment. It is structurally derived from the light chains of bevacizumab but has approximately ten times greater affinity for VEGF (15). Each ranibizumab molecule has one VEGF binding site, meaning that two molecules of ranibizumab bind each VEGF dimer. Its binding with the main VEGF-A isoforms (VEGF110, VEGF121, and VEGF165) is strong, stable,

and shows slow dissociation.

Bevacizumab is a humanized function-blocking monoclonal murine full-length antibody, which binds to all VEGF isoforms and received the FDA approval for the systemic treatment of metastatic colorectal cancer in 2004 (16). Each bevacizumab can simultaneously bind two VEGF dimers (17). Bevacizumab is approximately three times larger than ranibizumab (149 *vs.* 48 kDa), and its higher molecular weight results in an intravitreal half-life that is 36% higher than that of ranibizumab (18). The smaller dimensions of ranibizumab enable it to diffuse through the vitreous, into the retina and choroid; however, it is also rapidly eliminated from the blood stream (19).

Aflibercept, also named VEGF Trap-Eye, is the most recent member of the anti-VEGF family. It is a full human recombinant fusion protein of 115 kDa. This drug has been recently developed to afford a more potent and prolonged anti-VEGF effect and was approved by the FDA in 2011 (20). Aflibercept tightly binds VEGF-A and placental growth factor dimers in a 1 to 1 ratio with a powerful “two-fisted grasp”. Based on its high binding affinity and estimated intraocular half-life, mathematical modeling suggests that intravitreally administered aflibercept should have a longer duration of clinical action (possibly as long as 2.5 months) than either ranibizumab or bevacizumab (21).

Ranibizumab and bevacizumab have been reported to treat ROP patients off-label from 2007 (22). The other two are seldom used for ROP.

Salvage treatment for laser photocoagulation

Given the experience in treating exudative AMD, some ophthalmologists began to give intravitreal bevacizumab (IVB) or ranibizumab off-label to treat ROP, as a salvage treatment after failure in laser photocoagulation or in combination with laser as an adjuvant treatment for patients had media opacity and rigid pupil (22-26). Shah *et al.* reported a case with favorable outcome of intravitreal injection of bevacizumab treating anterior segment ischemia after aggressive posterior laser treatment (22). Lalwani *et al.* reported three cases unable to receive laser treatment due to miosis, hyphemas, vitreous hemorrhages or exudative retinal detachments and concluded that bevacizumab can improve dilation, quiet the disease when visibility is difficult, and temporize the disease until laser can be supplemented. In contrast to other ocular pathologic angiogenesis conditions, ROP is a self-limited condition. Based on this, he also raised the question as to whether intravitreal injections of anti-

VEGF agents at the appropriate time window could abort the need for laser entirely (23).

Anti-VEGF monotherapy for ROP

The BEAT-ROP trial was the only prospective, controlled, randomized, stratified, multicenter trial to assess IVB (0.625 mg/0.025 mL) versus conventional laser therapy as the primary treatment for zone 1 or posterior zone II stage 3+ ROP (27). One hundred and fifty infants were enrolled. The primary outcome was ROP recurrence needing treatment before 54 weeks PMA. The study concluded that when considering both zone I and posterior zone II ROP together, bevacizumab treatment was more effective than laser ablation. When considering the prospectively stratified subgroups separately, this benefit held for zone I ROP eyes but not for posterior zone II ROP eyes. Several authors have drawn attention to design and other problems with this trial. The treatment criteria included only a subset of type 1 ROP, the primary outcome was not masked and was assessed at the early age of 54 weeks PMA by non-impartial observers, visual outcomes were not reported and important adverse outcomes were not assessed thoroughly (28-30).

Apart from stage 3+ ROP, IVB was also reported to be effective and well-tolerated method of treating other prethreshold ROP and APROP (31-33). Laser therapy or vitrectomies may still be required as a backup treatment for patients who do not respond to an IVB injection or for those in whom ROP worsens after an IVB injection (34,35).

Ranibizumab has similar responses as bevacizumab in neovascularization and plus disease regression in ROP eyes (36). However, given the smaller molecular sizes and shorter half-lives, ranibizumab is considered to be a safer option for premature infants but has higher recurrence rate (24,25,37,38). In a study, Wong *et al.* compared these two drugs and found ROP reactivation occurred in 83% (5/6) eyes treated with ranibizumab, on average 5.9 weeks after treatment; whereas none of the four eyes treated with bevacizumab experienced reactivation (38). Also, it is reported that high myopia was more prevalent in the bevacizumab-treated eyes (36).

Perioperative use in ROP patients

For stage 4 or 5 ROP, anti-VEGF treatment before or during vitrectomy can reduce the neovascular activity (32). Xu and Zhao *et al.* found that the bevacizumab group has less intraoperative bleeding, reduced use of endodiathermy

during the surgery, less surgery time, higher percentage of lens preservation, higher percentage of anatomical reattachment, less postoperative complications and better vision recovery (39).

Besides, it is observed that Stage 4 ROP regressed after bevacizumab injection without the need for subsequent vitrectomy (32,37), which enlightened us that anti-VEGF agents may be effective either as a monotherapy or as supplement to laser treatment for some stage 4 ROP without additional surgical intervention.

Timing and dose of anti-VEGF treatment

The timing of IVB or IVR as monotherapy is unknown yet. Due to unique two-phase characteristics of ROP pathogenesis, it is clear that the timing of the administration of anti-VEGF therapy is of utmost importance. The PMA and thus the likely proportion of angiogenic versus fibrotic growth factors present are the main considerations that ophthalmologists should take into account (40).

As for perioperative use in ROP 4 or 5 eyes, it is recommended that anti-VEGF therapy should be administered less than 1 week prior to vitrectomy surgery (7,32), which is similar to the use of anti-VEGF drugs in proliferative diabetic retinopathy with retinal detachment in adult patients (41,42). Anti-VEGF agents might exacerbate pre-existing fibrosis and retinal detachment (40,43). In patients with proliferative diabetic retinopathy, a decline in VEGF levels with active neovascularization due to anti-VEGF treatment may inhibit angiogenesis and promote fibrosis driven by connective tissue growth factor (44). In patients with ROP, there are several reports of vitreoretinal traction band formation and retinal detachment following anti-VEGF therapy (31,34,35,43,45). Thus, for stage 4A with membranes and stage 4B and 5, anti-VEGF drugs are only used to decrease hemorrhage and inflammation immediately prior to vitrectomy surgery.

The minimum effective dose of IVR for ROP infants remains undetermined. The dose most used is half of the dose administered intravitreally in adults for ocular neovascular diseases (27,36,38). However, it has been argued that this dose might be relatively high for infants with ROP, considering their vitreous volume and body weight, compared to adults (29). Case series have been reported where a low dose of 0.375 mg bevacizumab (0.03 mL) produced regression of retinal neovascular change (46,47). Moreover, bilateral effects of unilateral injections of both IVB and IVR have been described for both adults

and children (48,49). Future studies using a smaller dose of anti-VEGF drug or even unilateral anti-VEGF treatment in certain infants with ROP should be performed.

Anti-VEGF versus laser treatment

Currently, laser treatment is the standard treatment for ROP. However, it is to some extent destructive to the peripheral retina. Anti-VEGF treatment is not destructive and the inner retinal vessels will advance beyond the original point of treatment (50).

Compared with laser therapy, anti-VEGF agents may delay the recurrence of ROP (27,51). This delay in recurrence was reported by the BEAT-ROP study. In eyes with zone I disease, the mean (SD) time to recurrence was 6.5 (6.7) weeks after laser treatment but 19.2 (8.6) weeks after bevacizumab treatment. A Retrospective review study by Hu *et al.* reported the mean (SD) time of recurrence was 49.3 (9.1) weeks PMA. Additionally, anti-VEGF therapy may alter the pattern of recurrence. It is observed that reactivation of proliferative ROP after bevacizumab treatment may occur posteriorly at or near the original posterior site of extraretinal fibrovascular proliferation rather than more anteriorly at the junction of the vascular and avascular retina (51). The frequent rate and altered pattern of recurrence after treatment with anti-VEGF agents necessitates frequent and prolonged follow-up with the possible need for retreatment or laser therapy.

Lepore *et al.* (52) compared the structural outcome at 9 months of eyes treated with IVB with fellow eyes treated with conventional laser photocoagulation in zone I type IROP, found that all eyes treated with a bevacizumab injection were noted to have abnormalities at the periphery (large avascular area, abnormal branching, shunt) or the posterior pole (hyper-fluorescent lesion, absence of foveal avascular zone). These posterior and peripheral lesions were not observed in the majority of the lasered eyes.

Ocular and systemic complications

The major ocular complications following intravitreal anti-VEGF injections were vitreous or preretinal hemorrhage and cataract. Vitreous or preretinal hemorrhage may be caused by tractions from resolution of new vessels. These forces exerted on the neovascularization could lead to bleeding. In most cases, the hemorrhage can reabsorb a few weeks later. Cataract can be associated with both

anti-VEGF agents and injection. To avoid injection-related cataract and retinal tears, it is suggested that the injection should be performed with a smaller gauge (such as 30-gauge) needle, at about 2 mm posterior to the limbus directed almost perpendicularly to the globe initially and then slightly directed toward the center of the eyeball after the needle passed the lens equator (7,31). Transient retinal vessel sheathing and exotropia were also reported (31).

A meta-analysis of 24 studies by Pertl *et al.* concluded that anti-VEGF therapy has a low-risk profile in ROP treatment in the first 6 months (53). It is certain now that bevacizumab and ranibizumab can enter the systemic circulation following intravitreal injection in both animal models and humans (28,54-57). Although BEAT-ROP study and many other retrospective studies showed no certain systemic adverse events or higher mortality rate in ROP patients after IVB or IVR, ophthalmologists should still consider any damage that may occur from the small amount of drug that may get into the general circulation to the developing organs of the infant.

Overall, questions remain regarding long-term safety, dosage, timing, visual outcomes and long-term effects, including systemically. Although anti-VEGF treatment is well tolerated, and rapidly effective in initial stage, tempered optimism and further study is needed.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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