

Treatment of retinopathy of prematurity with vascular endothelial growth factor inhibitors

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ABSTRACT

ROP remains a major cause of childhood blindness worldwide. The smallest, sickest infants develop the most severe forms of zone 1 ROP. Such eyes may not be successfully treated by near confluent laser to the avascular retina (current standard of care).

With an understanding of ROP pathogenesis, vascular endothelial growth factor inhibitors (anti-VEGF) are being given only when VEGF is elevated in retina and vitreous. Careful screening allows proper timing of administration. Ideal dose (perhaps different for mild and severe cases) and drug (interrupting only pathologic neovascularization and not normal angiogenesis) remain unproven.

The author discusses controversial use of anti-VEGF with documented efficacy, observed local complications, and potential systemic toxicities (none observed in six years) to allow retention of vision for severe zone 1 ROP. The benefits have been demonstrated, however, local and systemic risks in these developing premature infants must be carefully studied (both short and long term).

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1. Three epidemics of ROP

There have been three epidemics of ROP [1]. ROP first occurred for about a decade from 1943 to 1953 when it became possible to deliver concentrated oxygen to an infant in a closed incubator. In industrialized countries, many infants developed ROP before it was recognized that oxygen was the primary factor causing the disease (first epidemic). In this epidemic, infants were relatively large (> 1000 g) since medical practice had not advanced sufficiently to save very small preterm infants.

Thereafter, there was complete curtailment of oxygen, and ROP virtually disappeared. However, when preterm infant mortality and morbidity rates were recognized to have increased and when suitable ventilators for these infants became available, oxygen was again administered in neonatal intensive care units in industrialized nations, but with great care (initially by blood gas analyzers and more recently by adding skin monitors). Gradually, with increasing survival rates of very small preterm infants (mean birth weight of approximately 700 g), ROP cases have increased despite careful oxygen monitoring. At the current time, there is a persistence of small numbers of blind infants due to increased survival of very small preterm infants in industrialized nations (second epidemic).

In the early 2000s, severe ROP cases began to occur in large numbers of preterm infants in developing countries. The number of neonatal intensive care units has gradually increased with rapidly escalating

survival of small preterm infants (mean birth weights of approximately 1400 g), and ever-increasing numbers of infants blind due to severe ROP. However, due to lack of availability of many of the most recent technical advances in neonatal intensive care units, specifically equipment to monitor oxygen, and because of the inadequate numbers of ophthalmologists trained to screen and treat ROP, this blinding disorder has recently become a very serious problem in small preterm infants in developing countries (third epidemic).

The continued small numbers of blind infants from industrialized nations (second epidemic) and the emergence of large numbers of blind infants from developing countries (third epidemic) have continued to make ROP a serious clinical problem affecting large numbers of infants worldwide. Additionally, especially in severe zone 1 cases, (1) appropriate laser therapy may not be efficacious; (2) significant local side effects (decrease in field of vision, development of myopia, etc.) are unavoidable; (3) uncommon serious local complications (recurrence, retinal detachment, leucoma, cataract and other anterior chamber problems including anterior and posterior synechiae and angle closure glaucoma, hemorrhage in both the anterior and posterior portions of the eye, and phthisis) have been documented, and (4) systemic complications related to general anesthesia (vocal cord damage following intubation, diminished central nervous system function, etc) are significant risks. This makes it desirable from a clinical standpoint to find a better means of treating ROP (if it cannot be prevented). Thus, vascular endothelial growth factor inhibitors (anti-VEGF) have been given in an attempt to establish a treatment that is more efficacious with fewer local side effects and complications and systemic toxicities. Anti-VEGF use is extremely controversial at this time.

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2. Current classification, screening and treatment of ROP

Clinically, knowledge of the most recent classification of ROP [2,3], the rules guiding screening for the development of treatment warranted ROP [4,5], and the recommendations for treatment of ROP [6] are essential for obtaining optimal visual outcomes.

Classification now places plus disease as the most important observation to be made. Many systems are being developed to provide computer assisted analysis of plus disease. However, none of these systems has been adopted as a standard of care and no software is readily available, especially integrated into a digital imaging system.

Screening should be done in industrialized nations on infants who are less than or equal to 30 weeks gestational age at birth or whose birth weight was less than or equal to 1500 g. In developing nations, screening can be done on infants who are less than or equal to 34 weeks gestational age at birth or whose birth weight was less than or equal to 2400 g. Screening should begin at 4 weeks post natal age or at 31 weeks post menstrual age, whichever ever comes earlier. Follow-up examinations are determined by the presence and severity of the ROP noted on the initial examination [4,5].

Treatment is still evolving. For many years, there was no recommended therapy for ROP and infants were simply diagnosed and observed while the disease advanced to blindness. In 1988, a large, multi-center clinical trial, CRYO-ROP, made recommendations for treatment with cryotherapy in what are now considered advanced ROP cases based on a threshold requiring severe plus disease and five continuous or eight cumulative clock hours of Stage 3 [7]. Gradually, over the next decade, cryotherapy was replaced by laser therapy without a large multi-center clinical trial. In 2003, another large, multi-center clinical trial, ET-ROP, changed the recommendations for treatment with laser therapy to a much less advanced threshold requiring less plus disease and no specific number of clock hours of Stage 3 [6].

3. Normal intra-uterine inner retinal vascular development

Differentiation of the cellular components of the retina occurs from the optic disc toward the ora serrata and from the vitreal surface toward the sclera surface of the eye. There are two processes that underlie the development of normal inner retinal vascularization. The first process is vasculogenesis which occurs from approximately 12 to 21 weeks gestational age from the optic nerve to the ora serrata and involves vascular precursor cells. These cells do not migrate into the future fovea. Posterior to the leading edge of these vascular precursor cells form vascular cords which ultimately become patent. Anterior to the leading edge of vascular precursor cells, astrocyte precursor cells are also detected from 12 to 26 weeks gestation from the optic nerve to the ora serrata. These cells surround new vessels and contribute to the formation of the blood–retinal barrier.

The second process is angiogenesis which involves the development of new vessels from already existing vessels, and generates the perifoveal vessels, the peripheral vessels, the deep plexus of retinal vessels, the capillary system, and the peripapillary radial vessels. This process occurs from 17 to about 40 weeks gestational age and is thought to be stimulated by “physiologic hypoxia”.

4. Pathogenesis of ROP—abnormal extra-uterine inner retinal vascular development with neovascularization

ROP is a neovascularization of the inner retinal vessels that progresses in a small percentage of high risk infants in a predetermined timeline that has some variability, but is rather predictable. ROP occurs in two phases: a vaso-obliterative phase and a vaso-proliferative phase [8].

4.1. Pathogenesis of ROP—phase I

From premature birth to at least 30 weeks post menstrual age. Phase I is the vaso-obliterative phase. With preterm birth, the infant enters a hyperoxic environment. This occurs even without supplemental oxygen because the in utero levels of PaO₂ are 30–35 mm Hg and the extrauterine levels of PaO₂ are from 55–80 mm Hg. This change causes hypoxia-driven angiogenic factors to be down regulated. Thus, VEGF decreases as seen by the cessation of the anterior migration of astrocyte precursor cells, the cessation of new vessel growth, and the constriction and retraction of already formed vessels. In this vaso-obliterative phase, anti-VEGF drugs are contra-indicated. Thus, in a few cases where clinicians tried to preemptively treat zone 1 cases before the development of intravitreal neovascularization with plus disease (Stage 3 + ROP), the results were vaso-oblation of normal vessels of the inner retina and the development of marked macular abnormalities with pigment dispersion and severe loss of vision.

4.2. Pathogenesis of ROP—phase II

From approximately 31 to at least 42 weeks post menstrual age. Phase II is the vaso-proliferative phase and is caused by a hypoxic environment due to an increased need of vessels in the peripheral retina which cannot be provided by damaged vessels in the posterior retina. Over the weeks following preterm birth (from 4 to 20 weeks chronological age), the peripheral avascular retina becomes hypoxic due to its increased size without any accompanying formation of inner retinal vessels. This hypoxic peripheral avascular retina becomes metabolically active and stimulates new vessel growth. Thus, VEGF increases and normal inner retinal vessel formation (angiogenesis) does not continue. Instead, there is an overgrowth of abnormal inner retinal vessels (neovascularization) 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).

4.3. Advancement or Regression (Formation of Tractional Elements or Resolution of ROP)

From approximately 43 to at least 54 weeks post menstrual age. Following the increase of VEGF in the vaso-proliferative phase of ROP, there is either an advancement of ROP with increasing membrane formation or a regression of ROP with resolution of extraretinal fibrovascular proliferation. At this time, in severe cases of ROP neovascularization is replaced by cicatrization and VEGF decreases while TGF- β increases. Thus, there is an end to the significance of VEGF in the pathogenesis of ROP. At this time, anti-VEGF drugs are only used to decrease hemorrhage and inflammation immediately prior to vitrectomy surgery. Great care must be used when administering VEGF to patients with Stage 4A (peripheral retinal detachment). In some Stage 4A cases, with few membranes, anti-VEGF therapy may be effective in inducing regression of ROP pathogenesis. However, in some Stage 4A cases, anti-VEGF will accelerate the progression of retinal detachment causing a crunch syndrome. In Stages 4B and 5, anti-VEGF therapy will always accelerate the progression of retinal detachment and should only be administered immediately prior to vitrectomy surgery.

5. Current treatments

Near confluent laser therapy is the current standard of care and ideally can be performed in Phase II (Type 1—ETROP). Unfortunately, the therapy is destructive and the retinal vessels never advance beyond the original point of treatment (see Fig. 1).

Anti-VEGF therapy is a controversial treatment which also ideally can be employed in Phase II (Type 1—ETROP). Although VEGF is not the only driving force in the pathogenesis of ROP, it is a very

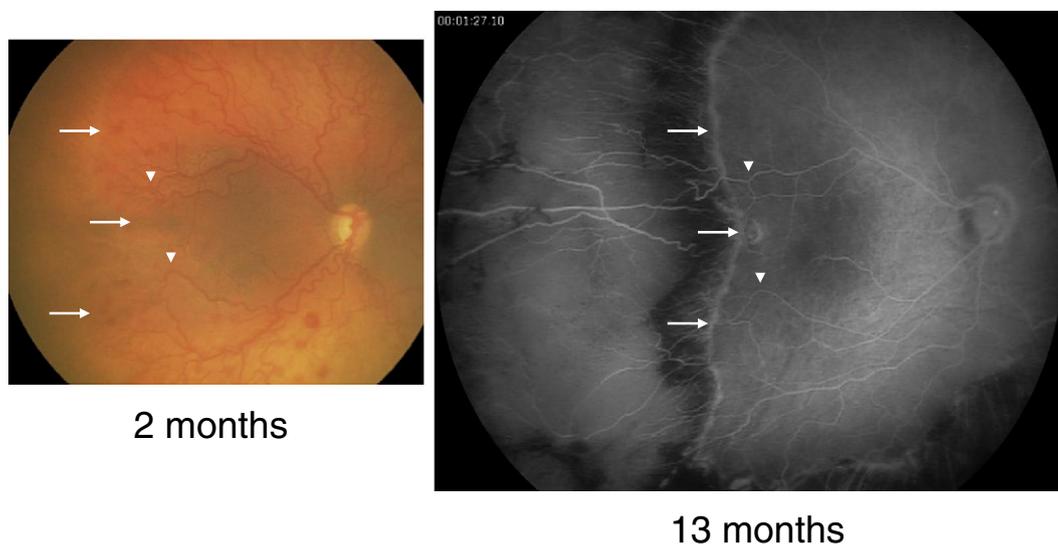


Fig. 1. Laser treatment for ROP. A. Temporal pretreatment fundus photograph of right eye of infant at age 2 months (born at 24 weeks gestational age weighing 760 g) with ROP Stage 3 in Zone 1; B. Temporal post-treatment fluorescein angiogram (of same area as Fig. 2A at age 13 months) following conventional laser therapy with full thickness destruction of peripheral retina. Identical retinal points (white \blacktriangle), and temporal extent of retinal vessels pre- and post-treatment with laser (A and B) (\rightleftharpoons) are delineated.

significant factor. The therapy is not destructive and the inner retinal vessels will advance beyond the original point of treatment (see Fig. 2).

6. Recurrence of ROP following ROP treatment

If near confluent laser therapy begins as early as 31 weeks, ROP can persist (resistant to ablative therapy) or it can regress and then recur as early as one week following therapy until at least 55 weeks post menstrual age (rarely). Recurrence is observed overlying the treated areas with the return of plus disease and the eventual formation of tractional membranes. Traditionally, recurrence is treated by laser therapy \pm vitrectomy as necessary. Anti-VEGF therapy may be used also, recognizing that previous laser will allow exit of any drug more rapidly, and thus, necessitate additional doses of anti-VEGF doses.

If anti-VEGF therapy begins as early as 31 weeks, ROP usually regresses initially, there is a period of slow advancement of inner retinal vascularization, and then recurrence can be observed as early as one month following therapy until at least 70 weeks post menstrual age (rarely). Recurrence is observed at two locations and usually with the return of plus disease: at the advancing edge of the newly formed inner retinal vessels, but also, at the site of the original extraretinal fibrovascular proliferation (see Fig. 3). Additional doses of anti-VEGF are indicated for recurrence cases identified early (before significant tractional elements form). Laser therapy/vitrectomy may be necessary in recurrence cases identified (when significant tractional elements exist).

7. Ocular benefits of anti-VEGF therapy

Anti-VEGF therapy may not only stop the advance of severe ROP, but have the added benefit of allowing the vasculature to develop

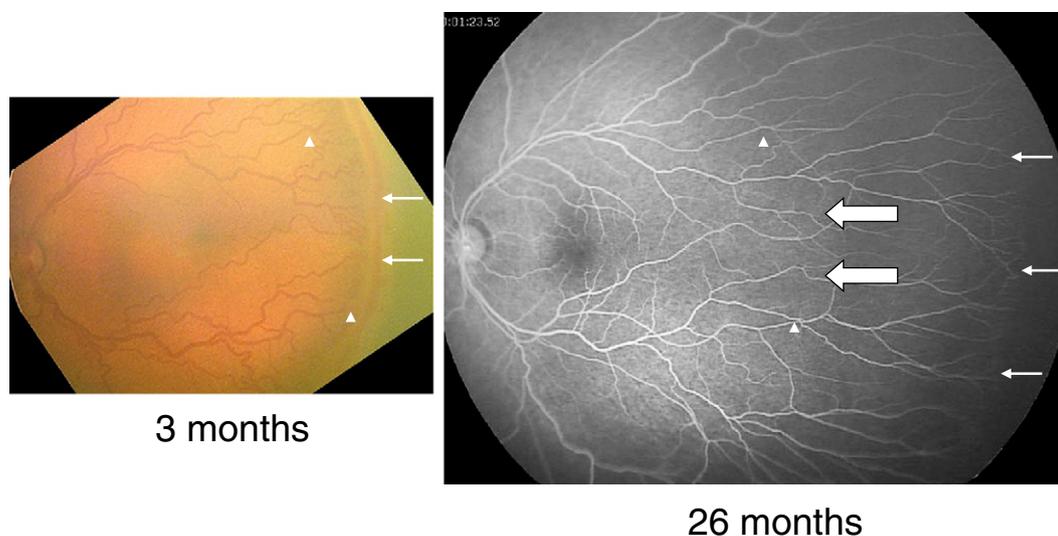


Fig. 2. Anti-VEGF monotherapy treatment for ROP. A. Temporal pre-treatment fundus photograph of left eye of infant at age 3 months (born at 24 weeks gestational age weighing 745 grams) with ROP Stage 3 in Zone 2; B. Temporal post-treatment fluorescein angiogram (of same area as Fig. 3A at age 26 months) following intravitreal bevacizumab monotherapy with continued retinal vascularization of the peripheral retina. Identical retinal points (white \blacktriangle), temporal extent of retinal vessels pre- and post-treatment with bevacizumab (A and B) (\rightleftharpoons), and temporal extent of retinal vessels pre-treatment with bevacizumab (B) (\rightleftharpoons) are delineated.

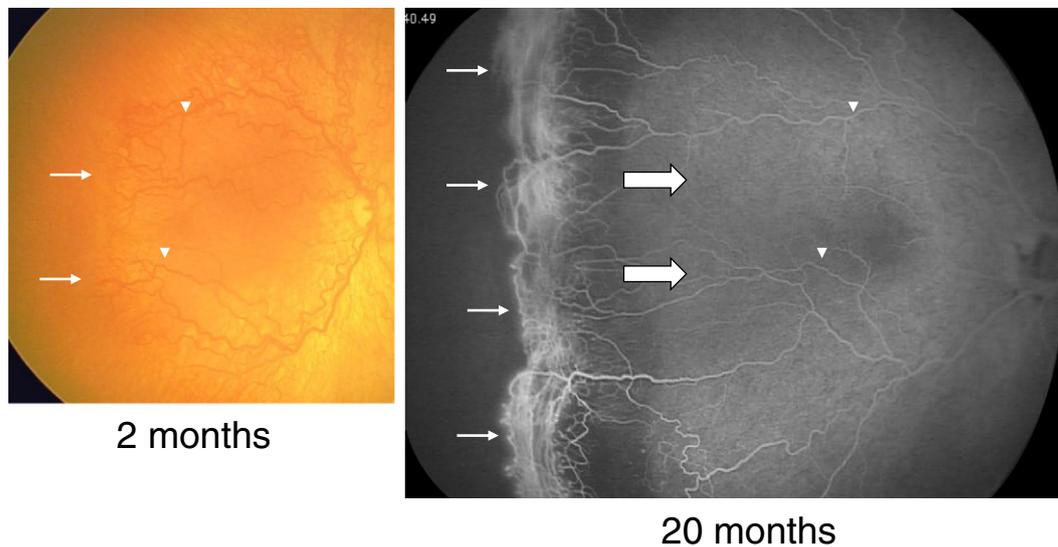


Fig. 3. Traction with recurrence following anti-VEGF treatment for ROP. A. Temporal pretreatment fundus photograph of right eye of infant at age 2 months (born at 26 weeks gestational age weighing 830 grams) with AP-ROP in zone 1. This eye was treated with bevacizumab at 35.0, 46.9, and 68.1 weeks post menstrual age. B. Temporal post-treatment fluorescein angiogram (of same area as Fig. 4A) at age 20 months with continued retinal vascularization of the peripheral retina but significant membrane formation causing traction. Identical retinal points (white \blacktriangle), temporal extent of retinal vessels pre- and post-treatment with bevacizumab (\rightleftharpoons), and temporal extent of retinal vessels following first treatment with bevacizumab (\rightleftharpoons) are delineated.

anteriorly as far as the precursors had migrated prior to preterm birth. Normally, the peripheral retina in very small infants never reaches the ora serrata, that is, an anterior avascular zone of the retina is a permanent marker of a former preterm infant [9].

Additionally, anti-VEGF therapy may allow the vasculature of the posterior retina to develop more normally by allowing normal apoptosis to occur in the macula. Normally, the foveal avascular zone in the very smallest infants never develops, that is, an absent foveal avascular zone is a permanent marker of a former preterm infant [10]. This may have the benefit ultimately of better visual acuity.

Anti-VEGF therapy does not require anesthesia with intubation of infants for precise laser treatment in severe zone 1 cases, nor is there a requirement for dilation and steroid drops for acute inflammation following anti-VEGF therapy.

Anti-VEGF therapy acts more rapidly than near confluent laser therapy. The continued progression of ROP for at least a week following laser that results from VEGF already in the vitreous continuing to stimulate pathologic neovascularization is eliminated by intravitreal anti-VEGF injection.

Anti-VEGF therapy allows the preservation of visual field by allowing all potential peripheral retinal development. With both cryotherapy and laser therapy, the peripheral retina is ablated. Long term complications, especially in severe zone 1 ROP, include a significant loss of peripheral vision. Studies that demonstrate a minimal effect of laser on the visual field have been done on children who generally had zone 2 ROP. A comparison of visual fields in untreated ROP versus ROP treated by cryotherapy, laser therapy, and anti-VEGF therapy has not been done; however, the field of patients treated by anti-VEGF therapy will most likely to equate to the field of untreated ROP patients and not reflect ablated retina.

In patients treated by anti-VEGF therapy, the myopia is less than that following conventional ablative therapy and equates to the myopia of untreated ROP patients. Prematurity itself, severity of ROP and its location (zone) prior to regression or treatment, and treatment modality and number of treatments all contribute to myopia. ROP is well known to cause myopia with or without therapy. Cryotherapy and laser therapy, especially repeated treatments for zone 1 ROP, add to the baseline ROP myopia and myopia is generally more severe. This myopia following ablative therapy may be partially due to axial

myopia due to scleral weakening. ET-ROP does not decrease the near-sightedness that occurs following conventional laser for threshold ROP.

8. Evidence of local safety of anti-VEGF therapy

One *immuno-histopathologic case report* of both eyes of an infant who received two doses of anti-VEGF therapy (bevacizumab) prior to death has been published. This report makes several important points. Bevacizumab is not toxic to the very immature retina since all layers of the retina and the inner retinal and choroidal vessels developed normally after two, small, sequential doses of bevacizumab (0.050 mg in 0.02 mL). Anti-VEGF therapy is very successful even in treating APROP in the very smallest and sickest infants, as this infant was only 22 weeks gestational age and 350 grams at birth [11].

Fundus photography and fluorescein angiography have provided evidence of local safety and efficacy and give important clues regarding completion of vascularization versus recurrence when anti-VEGF therapy is utilized [12]. Anti-VEGF drugs are safe locally, and although they cannot repair the damage of the vaso-obliterative phase of the pathogenesis of ROP, they may permit the peripheral retina to advance further than it would after laser surgery and it may allow the macula to develop better than it would after laser surgery by avoiding cystoid macular edema which often develops following the extensive near confluent laser therapy required for severe zone 1 ROP.

9. Potential complications of local anti-VEGF therapy

Although infection is rare with intravitreal injections, extreme measures must be used to maintain sterility when administering anti-VEGF therapy for ROP to prevent endophthalmitis.

The lens is larger in the premature infant relative to the overall ocular volume and the lens/ocular volume ratio decreases with age. However, this knowledge emphasizes the need to avoid the lens by injecting about 2 mm posterior to the limbus and aiming posteriorly while injecting to avoid the formation of cataract or the dislocation of the lens.

Retinal tears and retinal detachment can occur by local trauma. Caution includes using a smaller gauge and shorter length needle for injection.

10. Specific method of treatment to decrease complications of local anti-VEGF therapy

The specific method for administering anti-VEGF therapy for ROP is very important since their eyes are smaller and the lens is larger than that of the adult eye. In the smallest infants, the lens may occupy at least one third of the anterior-posterior length of the eye. The most important objective is to avoid complications. Sterility will avoid endophthalmitis. Avoiding the lens and its zonules will avoid cataract and lens dislocation. The following protocol has been followed for intravitreal bevacizumab injections in infants with ROP in the BEAT-ROP clinical trial:

The infant may or may not be premedicated with an oral, intramuscular, or intravenous sedative drug of choice, as preferred by the attending neonatologist. A drop of tetracaine hydrochloride 0.5% or proparacaine hydrochloride 0.5% ophthalmic solution is placed into the conjunctival sac between the lids of the infant for local analgesia. A sterile speculum for use in preterm infants is placed between the lids. Antisepsis is achieved with a drop of povidone iodine 5% ophthalmic solution placed between the lids of the infant, into the conjunctival sac and allowed to remain for one minute. Excessive povidone iodine 5% solution is removed with a sterile cotton tip applicator or sterile gauze from the temporal lid margin. The infant's eye is stabilized with a sterile toothed forceps, cotton tip applicator, or scleral depressor. A unit dose of bevacizumab (0.625 mg as 0.025 mL) is injected behind the lens into the vitreous, in a sterile manner. The medication is supplied by a compounding pharmacy as two 0.3 mL syringes that are single-use syringes with a 5/16th inch, 31 gauge needle attached (a 32 gauge needle would be even better). This prevents accidentally hitting the opposite side of the eye with a 1/2 inch needle and has less inadvertent leakage of the anti-VEGF drug through a needle that is ≤ 30 gauge. Following the injection, povidone iodine 5% antisepsis is again applied to the eye for one minute and removed with a cotton tip applicator or gauze. An ophthalmic antibiotic drop [gatifloxacin (0.35%) or moxifloxacin (0.5%) ophthalmic solution] is instilled into the conjunctival sac and subsequently is given every 8 hours for 5 days following the intravitreal injection. The sterile speculum is removed from between the lids. The same procedure is followed for the contra lateral eye injection.

11. Evidence of systemic safety of anti-VEGF Therapy

Many surveys have been done to identify cases of systemic toxicity of anti-VEGF drugs administered into the vitreous. To date these surveys have not uncovered any consistent systemic toxicity in the adult when the drug is given intravitreally. In considering use of anti-VEGF drugs for ROP, it is urgent that we 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. There are some organs that are particularly susceptible to damage because of their late development. Thus, the embryonal tumors (retinoblastoma, neuroblastoma, Wilm's tumor, etc.) suggest that the retina, brain, kidney, etc. will be the most vulnerable organs because of their late development. We must intently evaluate the continued development of the ocular system, central nervous system, renal system, etc. and all of the functions that they perform.

12. Multiple case series of anti-VEGF therapy for ROP with and without supplemental laser and/or vitrectomy

The literature provides many case reports using intravitreal injection of anti-VEGF therapy (primarily bevacizumab, but also pegaptanib, ranibizumab, and aflibercept) in combination with laser (with or without vitrectomy). Further, the literature provides multiple case series, and

randomized clinical trials [13–15] suggesting that intravitreal injection of anti-VEGF as monotherapy offers better efficacy, and fewer local side effects and complications. However, the use of intravitreal injection of this drug is still considered experimental requiring an IND (investigational new drug) number (from the FDA) and approval by individual IRBs (institutional review boards) to report clinical trials. Use of anti-VEGF therapy is used extensively for adult ocular neovascularization, such as, for age related neovascularization and diabetic retinopathy (different diseases)—often as an off-label drug. Importantly, use for retinopathy of prematurity (a different disease) in a different population (preterm infants) is considered an off-label, off-label use of this drug and an extensive informed consent form is warranted stressing that long-term consequences of anti-VEGF therapy use in former preterm infants is unknown.

Conflict of interest statement

The author has no conflicts of interest to declare.

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