PERSPECTIVE

Retinopathy of Prematurity: Evolving Treatment With Anti–Vascular Endothelial Growth Factor

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• PURPOSE: To discuss the evolution in retinopathy of prematurity since its first description as retrolental fibroplasia in the United States, including the changes in the understanding of pathophysiology; methods of diagnosis; destructive, anti–vascular endothelial growth factor (anti-VEGF), and supportive treatments; and differences in retinopathy of prematurity manifestations worldwide. The overall goal is to clarify retinopathy of prematurity currently and formulate questions to optimize future care.
• STUDY DESIGN: Literature review and synthesis.
• METHODS: Critical review and consideration of the literature with inclusion of historical articles and those regarding pathophysiologic risk factors, retinopathy of prematurity worldwide, basic and clinical science particularly regarding anti-VEGF mechanisms and agents tested in clinical trials.
• RESULTS: Retinopathy of prematurity has evolved from affecting infants approximately 2 months premature to affecting extremely premature infants. Worldwide, retinopathy of prematurity differs and, in emerging countries, has features similar to that experienced in the United States when retinopathy of prematurity first manifested. Treatments have evolved from destruction of the peripheral avascular retina to inhibit angiogenic stimuli to anti-VEGF agents, which inhibit pathologic angiogenesis but also extend normal intraretinal angiogenesis by ordering the development of intraretinal vessels. Clinical trial evidence is accruing with the goal to develop less destructive treatments to optimize vision and that are protective to the retina and infant.
• CONCLUSIONS: Goals for retinopathy of prematurity are to optimize prenatal and perinatal care, improve diagnostic acumen worldwide and refine treatment strategies, including with anti-VEGF agents, to inhibit intravitreal angiogenesis and facilitate vascularization of the previously avascular retina, which include supporting neural and vascular development of the premature infant and retina. (Am J Ophthalmol 2020;218:208–213. © 2020 Elsevier Inc. All rights reserved.)

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RETINOPATHY OF PREMATURITY (ROP) WAS ORIGINALLY described as retrolental fibroplasia (RLF) in the United States in the 1940s[1] and, despite advances in neonatal care, continues to be a leading cause of childhood vision loss worldwide.[2] Complex retinal detachment from uncontrolled blood vessel growth into the vitreous termed as extraretinal or preretinal neovascularization and, (henceforth, referred to as preretinal neovascularization) remains a cause of blindness, but the risk profile of infants with this "treatment-warranted" retinopathy of prematurity has changed in the United States[2,3] and differs from countries worldwide, which have the resources and means to save premature infants but not to optimize care.[4] There is also a shortage of trained ophthalmologists who are skilled in screening premature infants using indirect ophthalmoscopy or tele-imaging to diagnose treatment-warranted retinopathy of prematurity,[5] administer treatment, and identify reactivation or progressive disease. In this perspective, the current understanding of how anti–vascular endothelial growth factor (anti-VEGF) treatment not only reduces the development of uncontrolled preretinal neovascularization into the vitreous but also facilitates ongoing intraretinal "vascularization of previously peripheral avascular retina" will be presented based on basic and clinical research. Ongoing concerns of anti-VEGF agents and traditional treatments in the developing preterm infant and retina will be discussed as will future directions and questions, including the differences in retinopathy of prematurity risk profiles worldwide.

CHANGES IN RETINOPATHY OF PREMATURITY EVOLUTION AND DIFFERENCES IN RISK PROFILE WORLDWIDE

RETINOPATHY OF PREMATURITY IS A RETINOVASCULAR disease in which blood vessels grow into the vitreous rather than into the retina. At the time Terry described

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retinopathy of prematurity in 1942,[1] premature infants at risk were more developmentally mature being born on average 2 months premature compared to 4 months premature today. Infants were also born at larger birth weights. The retinal vasculature, which does not extend to the ora serrata until approximately 40 weeks' gestation, was also likely more completely developed then compared with today. The ability to examine the peripheral retina was limited, so the understanding of the causes of retinopathy of prematurity was based largely on experimentation in newborn animals exposed to similar conditions that preterm infants experienced in early incubators that were less sophisticated than today. Experimentation led to the observations that high, unregulated oxygen damaged newly formed retinal capillaries, leaving areas of avascular retina. This avascular retina was postulated to become hypoxic when the animal was moved out of high supplemental oxygen into ambient air and induced fulminant angiogenesis into the vitreous as well as tortuous retinal vessels.[6] A multicenter clinical prospective study by Patz and Kinsey[7] provided evidence that high oxygen exposure at birth was related to clinical RLF. At that time, the ability to monitor and regulate oxygen had not been developed, and with technologic advances, regulation of oxygen virtually abolished RLF. However, retinopathy of prematurity re-emerged with the ability to save extremely premature infants. The process of high oxygen–induced retinal capillary damage may still occur in some infants where there are insufficient resources to monitor and regulate oxygen.[2]

In developed countries, such as the United States, Canada, United Kingdom, Sweden, and Australia, as examples, retinopathy of prematurity occurs in extremely preterm infants born less than 28 weeks' gestational age or under 1000 g birth weight. In extremely premature infant eyes, the retinal vasculature has extended incompletely to the ora serrata, often leaving broad areas of avascular retina. Therefore, if treatment-warranted retinopathy of prematurity develops, it includes incomplete peripheral retinal vascularization and later preretinal neovascularization into the vitreous. Oxygen monitoring and regulation are now standard care in countries with resources to supply them, so besides high oxygen at birth, other factors have been associated with the pathophysiology of retinopathy of prematurity. These vary across regions of the world but include oxygen saturation targets, sepsis, ventilator-related factors, fluctuations in oxygenation, diseases associated with oxidative signaling, extreme prematurity, and poor postnatal growth.[8–13] Because the retinal vasculature is often incompletely developed in extremely premature infants, inhibiting abnormal blood vessel growth to treat preretinal neovascular growth into the vitreous may also interfere with normal retinal vascularization to the ora serrata, and treatments for retinopathy of prematurity, such as cryotherapy, laser, or anti-VEGF agents either destroy peripheral avascular retina or potentially interfere with peripheral retinal vascular growth to the ora serrata.

ADVANCES IN TREATMENTS

PRIOR TO ANTI-VEGF AGENTS FOR ADULT VITREORETINAL diseases, several seminal clinical trials tested methods that ablate the avascular peripheral retina to cause regression of preretinal neovascularization and prevent subsequent fibrovascular retinal detachments. Treatment-warranted retinopathy of prematurity was defined by a threshold of characteristics that together led to a 50% risk of an unwanted outcomes, and cryotherapy reduced the risk compared to no treatment (Multicenter Trial of Cryotherapy for ROP[14]). A later multicenter clinical trial found efficacy with laser treatment for a less severe form of treatment-warranted retinopathy of prematurity (ie, type 1 retinopathy of prematurity), in which the risk of an unwanted outcome was approximately 15% (Early Treatment for ROP study[15]). The ablation of the peripheral avascular retina was believed to reduce the hypoxic retina that expressed angiogenic factor(s) or to treat the cells that were expressing the angiogenic factors. Once laser or cryotherapy was performed, it was difficult to determine if the avascular retina could have supported intraretinal vascularization extending to the ora serrata. There is anecdotal evidence that retinal vessels grow in between treatment spots toward the ora serrata (personal observation), and stronger evidence from the natural history of comparison groups in the multicenter studies in which eyes underwent spontaneous regression of preretinal neovascularization and vascularization of the previously peripheral avascular retina.[16,17] Altogether, observations supported the thinking that if a treatment were developed to extend normal vascularization, the stimulus for abnormal preretinal neovascularization might be removed. Although remodeling of retinal vasculature had been reported in adult retinovascular diseases,[18,19] it requires vascular repair and regrowth as opposed to reinitiating a developmental process that had been stalled, as in some preterm infants.

When VEGF was discovered as an important growth factor largely responsible for adult retinovascular diseases associated with preretinal neovascularization, there was the concern that treating premature infants with anti-VEGF agents might halt normal retinal vascularization, because VEGF is also essential for the development of the retinal vasculature.[20,21] This potential interference with normal vascularization then might also result in later recurrences of preretinal neovascularization and, in fact, reactivation has now been reported in some infants treated with anti-VEGF agents.[22,23]

New approaches to facilitate vascularization of the previously peripheral avascular retina as a means to prevent preretinal neovascularization were tested experimentally

based on current pathophysiologic risk factors. Animal models were chosen that represent retinopathy of prematurity in which oxygen was a factor as was delayed normal vascular development of the peripheral retina. Several studies reported that inhibiting or regulating signaling mechanisms triggered by reactive oxygen species supported intraretinal vascular development but did not prevent preretinal neovascularization experimentally.[20] Later clinical trials also failed to find a benefit or found toxicity from antioxidants.[3,24] Downstream signaling of the JAK/STAT3 pathways in retinal endothelial cells through experimental approaches reduced preretinal neovascularization but did not promote intraretinal vascularization of the previously avascular retina.[25] However, innovative methods specifically knocking down, and thereby regulating but not abolishing, signaling through the angiogenic receptor of VEGF, VEGF receptor 2 (VEGFR2), specifically in retinal endothelial cells, provided strong evidence that regulation of the VEGF signaling pathway could both inhibit preretinal neovascularization and facilitate vascularization of the previously peripheral avascular retina.[25] Although it is counterintuitive that inhibiting an angiogenic factor would actually promote intraretinal angiogenesis, experimental evidence established the importance of VEGFR2 signaling in ordering the alignment of dividing retinal endothelial cells to form into vessels that could extend intraretinal vascularization to the ora serrata instead of allowing disordered growth into areas with few cells to encumber growth, such as the vitreous.[26]

CLINICAL EVIDENCE

CLINICAL EVIDENCE SUPPORTS EXPERIMENTAL OBSERVATIONS that regulating actions of VEGF not only inhibits preretinal neovascularization, but also extends intraretinal vascularization of the previously peripheral avascular retina toward the ora serrata. However, dose and type of anti-VEGF agent appear important. The first clinical trial, BEAT-ROP, found 0.625 mg of bevacizumab effective at reducing the need for retreatment at 54 weeks postconceptual age compared with laser in a subgroup of infants with retinopathy of prematurity in zone I or posterior zone II.[27] Subsequent reports using similar doses reported recurrent retinopathy of prematurity with progression to retinal detachment in infants of older postconceptual ages than reported in the natural history of disease or after laser treatment, or reduced serum VEGF for more than several months after injection.[28] These findings were concerning, because examination of the peripheral retina in older, more active preterm infants is difficult to perform without sedation in the clinic. Low serum VEGF may be harmful to developing organs, such as the brain, in the premature infant. Studies have reported either increased risk or no effect on neurocognitive outcomes in infants treated with intravitreal anti-VEGF agents.[29–31] However, the question whether reduced serum VEGF truly affects neurocognitive development in preterm infants is difficult. Extremely premature infants at the greatest risk of retinopathy of prematurity are also at the greatest risk of neurocognitive delay. The highest-risk infants are not always included in prospective clinical trials, and controlling for enrollment can lead to bias.[32] A recent example of this regards addressing the question whether erythropoietin administered to preterm infants can improve neurocognitive development. A meta-analysis of several clinical studies that addressed this question showed a benefit of erythropoietin for neuroprotection, but the recent PENUT clinical trial, which had stringent enrollment criteria, did not find value of early erythropoietin treatment on neurocognitive outcomes in children at 2 years of age.[33] The studies as of this writing testing anti-VEGF in preterm infants have been retrospective or may have excluded infants at the greatest risk.[32] Currently, few, if any, studies have evaluated the effect of anti-VEGF on the neural retina, including by optical coherence tomography. Considering the effect of VEGF on the developing retina is important, because VEGF is also a survival factor for other retinal cells besides endothelial cells.[34]

Drugs that regulate VEGFR2 specifically in retinal endothelial cells without inhibiting its beneficial effects in other retinal cells are not currently available. Experimental models used subretinal delivery of gene therapy to specifically knockdown VEGFR2 in endothelial cells,[25] but this is not safe in the human preterm infant eye. Current approaches for retinopathy of prematurity employ intravitreal agents that bind the ligand, VEGF, to reduce signaling through receptors, but the approach is not specific to the receptor or to endothelial cells. However, experimental methods that reduce the expression of VEGF in Müller cells where it was produced in a representative model of retinopathy of prematurity provided evidence that greater anti-VEGF effect thinned neural retina, but a lesser anti-VEGF effect reduced preretinal neovascularization and did not thin the neural retina.[34] These findings together suggest that an appropriate dose of the right anti-VEGF agent may safely extend intraretinal angiogenesis and inhibit preretinal neovascularization without adversely affecting developing organs or the brain.

Ideally, a dose of intravitreal anti-VEGF would neutralize excess VEGF and thereby regulate signaling through VEGFR2 specifically in retinal endothelial cells, but it is unknown what the concentration of intravitreal VEGF is in an eye of an infant with retinopathy of prematurity. Also the VEGF concentration may vary from infant to infant and eye to eye. Vitreous and blood volumes are small in premature infants, so errors in dose can have big effects. It is difficult to prepare and deliver small volumes and concentrations to preterm infant eyes. In addition, larger infants with retinopathy of prematurity, reported in some countries,[4] have bigger volumes of vitreous and blood. Injecting a similar dose of drug into a larger infant

may lead to a lower concentration of anti-VEGF in the bloodstream and a lesser deleterious systemic effect on the more developmentally mature infant. When reviewing the many studies throughout the world addressing anti-VEGF agents in retinopathy of prematurity, there are differences found, including in the definitions of treatment-warranted retinopathy of prematurity, in the size and developmental ages of infants who develop retinopathy of prematurity, and in the agents and doses used. For these reasons, it is not as helpful to compare agents or doses from different clinical studies. A previous Cochrane review of studies testing anti-VEGF agents for retinopathy of prematurity concluded that more evidence was needed.[35]

Recent prospective and randomized clinical studies and trials have been reported since the Cochrane review in 2018. The RAINBOW study used ranibizumab, which is cleared more rapidly from the blood and eye, compared to laser,[36] and the PEDIG ROP1 studies tested de-escalating doses of bevacizumab to find an effective and safe dose.[37] Studies through Regeneron are also testing the effect of aflibercept[38] to laser in type 1 retinopathy of prematurity.

The RAINBOW STUDY was a multicenter international randomized, open-label study testing the superiority of ranibizumab (0.2 mg, 0.1 mg) to laser. The study did not achieve statistical significance as a superiority study, but the 0.2 mg dose of ranibizumab was concluded to be possibly superior to laser. The trial was performed for a more severe level of treatment-warranted retinopathy of prematurity than type 1 retinopathy of prematurity tested in the ETROP and ROP1 studies and mainly included eyes with zone II retinopathy of prematurity. Recurrences by 6 months were found in 31%, but there was no reduced serum VEGF from either dose of ranibizumab at 1 month.[36]

The PEDIG ROP1 study found that bevacizumab, even at a dose of 0.031 mg, was effective a small sample of infants with type 1 retinopathy of prematurity through 6 months. The number of infants is too small to make a firm conclusion about correct dose,[37] and future studies will compare a chosen dose to laser with outcomes of efficacy of treatment, extension of vascularization of the previously peripheral avascular retina, reactivation of retinopathy of prematurity, and neurocognitive outcomes.

ONGOING QUESTIONS

ALTHOUGH MUCH KNOWLEDGE HAS BEEN GAINED ABOUT retinopathy of prematurity since the first description in 1942, questions remain. It remains unclear what dose and what anti-VEGF agent can be delivered to safely inhibit preretinal neovascularization and facilitate vascularization of the previously avascular retina without injuring the neural retina or developing systemic organs, including the brain. The anti-VEGF treatment ideally would be an agent that would not require repeat injections, which also increase risk to the eye. If retinopathy of prematurity is misdiagnosed and treatment is performed too early, then the effect might be similar to delivering too high a dose. Therefore, accurate diagnosis is important. Telemedicine and methods employing artificial intelligence and machine-based learning are being evaluated.[39,40]

Controversy exists whether to treat persistent avascular retina with laser following anti-VEGF treatment. There is a risk of reactivation following anti-VEGF even over a year after treatment, and there is concern that persistent peripheral avascular retina may increase the risk of later retinal tears adjacent to vascularized \ retina. However, it has not been established that laser will prevent reactivation in all cases, and long-term study is needed to address the effect of laser to persistent peripheral avascular retina on risk of later retinal detachment. It is also unclear if anti-VEGF increases the risk of persistent avascular retina or later retinal detachment, or if persistent avascular retina in eyes that never develop retinopathy of prematurity or with regressed retinopathy of prematurity poses similar risks. Perhaps the retina of an extremely premature infant has not developed normally or fully and is unable to support complete intraretinal vascularization to the ora serrata. If persistent peripheral avascular retina is common after anti-VEGF even in zone II retinopathy of prematurity, perhaps laser would be optimal to anti-VEGF as a first-line treatment. Clinical trials are testing the effect of anti-VEGF compared to laser on refractive errors, including myopia, vascularization of the previously peripheral avascular retina, and neural structure of the retina, and these outcomes, in addition to future studies assessing risk of retinal detachment, are important.

Methods to vascularize the avascular retina through nutritional supplementation and growth factors, including IGF-1, are being tested. An initial study found infusion of IGF-1 did not reduce retinopathy of prematurity,[41] but future trials will test IGF-1 for other complications of prematurity, and retinopathy of prematurity will also be evaluated. In addition, it will be important to continue to test strategies to address neuroprotection and neurovascular effects on the developing neural and vascular retina, including the role of erythropoietin. In addition, other treatments designed to target more specifically the pathology of preretinal neovascularization and persistent avascular retina, are needed through ongoing research.

Throughout the world, more work is needed to understand the causes for differences in infants at risk of retinopathy of prematurity. Work in public health is needed to improve resources and to develop systems to optimize pre- and perinatal care including but not excluding implementing methods to regulate oxygen.[2] In addition, research to identify causes and test strategies to prevent premature birth, such as by reducing environmental pollutants and other factors,[42] and thereby reduce the number of infants at risk of retinopathy of prematurity is important.

CONCLUSION

IN CONCLUSION, MANY CHANGES HAVE OCCURRED SINCE retinopathy of prematurity was first described, including in our understanding of the pathophysiology of disease to find potentially better mechanisms to treat retinopathy of prematurity. There are different appearances and causes of retinopathy of prematurity worldwide, from extremely premature infants in developed countries to larger infants worldwide.[2] Studies have made great strides in the care of these fragile premature infants, who are true survivors, and there is still much to learn.

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