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A review of treatment for retinopathy of prematurity

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Abstract

Introduction: Retinopathy of prematurity (ROP) is a leading cause of childhood blindness worldwide.

Areas covered: Recent methods to identify and manage treatment-warranted vascularly active ROP are recognized and being compared to standard care by laser treatment in prospective large-scale clinical studies. Pharmacologic anti-angiogenic (anti-VEGF) treatment has changed the natural history of vascularly active ROP by reducing stage 3 intravitreal neovascularization and extending physiologic retinal vascularization in many infants. Tractional retinal detachments in stage 4 ROP after treatment with anti-VEGF agents show additional fibrovascular complexity compared to eyes treated with laser only. We review current management and outcomes for vascularly active and fibrovascular retinal detachment in ROP (stages 3, 4, 5 ROP), highlighting the evidence from recent clinical studies. Included are technical details important in surgery for retinal detachment in ROP. Literature searches were employed through PubMed.

Expert opinion: Methods in pediatric imaging, safer pharmacologic treatments, and surgical techniques continue to advance to improve future ROP outcomes.

Keywords

retinopathy of prematurity (ROP); vascular endothelial growth factor inhibitors (anti-VEGF); stage 4 or 5 ROP; lens-sparing; vitrectomy; scleral buckle; laser; angiogenesis; surgical outcomes; retinal detachment

1 Introduction

Retinopathy of prematurity (ROP) is a leading cause of vision loss worldwide and is increasing in incidence in developing and developed countries[1, 2]. ROP is strongly associated with prematurity[3] and remains a concern in the US as well as throughout the world, having been estimated as causing 32,200 cases of blindness and visual impairment worldwide [4, 5, 6].

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Declaration of interest

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Besides extreme prematurity, ROP is linked to high oxygen at birth[7, 8], fluctuations in oxygenation[9] including hypoxemic desaturations[10], and poor postnatal growth[11]. At the level of development when premature infants at risk of ROP are born, many vascular beds, neurons and glia within the eye are immature. Their ongoing development and differentiation may be affected by events surrounding prematurity. High oxygen, or fluctuations in oxygenation due to pulmonary or cardiac factors and the transition from fetal to adult hemoglobin, can affect ongoing development of retinal and choroidal vascular beds as well as the hyaloid system, which may be incompletely regressed[12]. Differentiation of retinal neurons and neural connectivity are also incomplete. Oxygen stresses, such as fluctuations in oxygenation can affect the expression of vascular endothelial growth factor (VEGF) [13] and immature vascular beds and neural retina. Oxygen stresses also create areas of avascular retina due to vaso-oblivation[14] and delay in physiologic retinal vascular development[15]. These broad areas of avascular retina later stimulate aberrant growth from existing blood vessels, known as angiogenesis, into the vitreous that can lead to complex fibrovascular tractional retinal detachments. Detached retina, which occurs in late stages of ROP[16, 17], is the most recognized cause of blindness in ROP [17A]. However, other components of poor vision in premature infants include abnormalities in the central nervous system with cortical visual impairment and neurovascular interactions within the retina that potentially affect retinal function[[17B]. It is known that 25% of infants successfully treated to prevent fibrovascular retinal detachments still have only 20/60 or worse visual acuity[18]. Finally, extremely premature infants who never developed ROP were found to have reduced dark-adapted amplitudes of a-waves and 30-Hz flicker electroretinograms at age 6.5 years[19]. In this Expert Review article, focus will be on prevention and treatment of fibrovascular retinal detachments.

2 Pathophysiology and classification of ROP

It is not ethical or possible to study molecular mechanisms of pathophysiology of ROP in human infants. Yet, understanding the pathophysiology is important in determining a treatment course for an infant. Therefore, in order to study ROP, animal models of oxygen-induced retinopathy (OIR) are used. These models exploit the fact that several newborn animals (rodents, cats, and beagle) have incompletely vascularized retinas at birth. However, this is also a limitation since OIR models do not recapitulate all of the stresses of premature infants. Based on OIR models, a two-phase hypothesis was developed by Ashton in 1950's[14]. Since the 1950's, advances in neonatal care and technology have led to a refinement of the two-phase hypothesis[15]. Phase I includes insufficient physiologic angiogenesis resulting from high oxygen-induced vaso-oblivation, compromised physiologic vascularity, and fluctuations in oxygenation that lead to delayed physiologic retinal vascular development. Once the animals are removed from oxygen stresses, the areas of avascular retina become hypoxic and angiogenic factors are upregulated, most notably, vascular endothelial growth factor (VEGF). Excessive signaling of VEGF through VEGF receptor 2 (VEGFR2) causes aberrant angiogenesis and vessel growth outside the plane of the retina during Phase II. Regulation of signaling through VEGFR2 normalized the orientation of dividing vascular cells to inhibit aberrant intravitreal angiogenesis and also to extend physiologic retinal vascular development[20]. Human clinical trials in which VEGF

is reduced using intravitreal antibodies against VEGF also show that aberrant angiogenesis can be inhibited and normal vascularization extended in some infants[21]. OIR models best show Phases I and II, but in human infants with ROP, there can be a third phase associated with fibrovascular tractional retinal detachments, which are not fully modeled in OIR models[22]. The third phase occurs when angiogenic vessels interact with collagen and other components within the vitreous. Once fibrovascular changes occur, inhibition of angiogenesis may not be sufficient to prevent complex retinal detachments.

2.1 From phase to stage and zone: classification of ROP

Phases of OIR describe the hypothesis of how ROP develops. Decades after the initial two-phase hypothesis by Ashton, the International Committee for the Classification of ROP (ICROP) published a classification of ROP[16, 17]. The classification underwent revisions in 1987[17] and most recently in 2005[23] to include pre-plus disease and aggressive posterior ROP (APROP). The classification system delineates ROP by location of disease (zone), severity of disease (stage), extent and plus disease.

Three zones centered on the optic nerve define the region where the ROP stage exists. Zone 1 is a circle with a radius twice the distance from the optic disc to the fovea. Clinically, temporal zone 1 is the visible retina within the image obtained with indirect ophthalmoscopy using a 28-diopter condensing lens when the optic nerve is at the nasal edge of the field of view[23]. Zone 2 begins at the edge of zone 1 and extends with equal radius in all directions to the nasal ora serrata. Zone 3 is the temporal crescent remaining. Zone 3 is defined as vascularization to the two clock hours abutting the horizontal meridian at the nasal ora serrata.

The severity of ROP is classified by 5 stages. Stage 1 is a demarcation line between vascular and avascular retina. Stage 2 is a ridge with volume and is identifiable outside the retinal plane between vascular and avascular retina. Neovascular tufts, known as popcorn vessels, can be identified posterior to the ridge. Stage 3 is characterized by extraretinal neovascular proliferation into the vitreous from aberrant intravitreal angiogenesis and can appear flat along the retinal plane in zone 1, posterior zone 2 or aggressive posterior ROP. Stage 4 is subtotal retinal detachment, which can be exudative and/or tractional and is separated into stage 4a (extrafoveal) and stage 4b (fovea-involving) (Figure 1). Stage 5 ROP is a total retinal detachment that may have peripheral retina attached taking on the appearance of a trough. The funnel configuration of stage 5 ROP can be further characterized as open, closed, or a combination of both[24].

The extent of ROP present is determined by the number of 30 degree sectors, or clock hours, affected by the pathology at the junction of vascular and avascular retina, and is mainly used to characterize the extent of traction in progressive stage 4 ROP.

Plus disease refers to vascular activity and is identified as marked dilation and tortuosity of the retinal vasculature that occurs with treatment-warranted ROP (Figure 1A, 1B). In 2005, the ICROP added the designation of pre-plus disease in which abnormally engorged and tortuous retinal vasculature do not meet criteria for plus disease. Efforts are ongoing to

establish quantitative, objective determinants of plus disease, which remains a subjective criterion.

2.2 Treatment-warranted ROP

The Early Treatment for Retinopathy of Prematurity (ETROP) study defined type 1 ROP as zone 1, stage 3 ROP; zone 1, any ROP with plus disease; or zone 2, stage 2 or 3 ROP with plus disease. Within this definition is an aggressive form of ROP that was defined by ICROP as aggressive posterior retinopathy of prematurity (APROP)[23]. APROP represents a severe form of ROP characterized by posterior location in zone 1 or posterior zone 2 and posterior plus disease out of proportion to peripheral vascular changes at the junction of the vascular/avascular border. In APROP, the neovascularization appears lacy and flat without an associated ridge or demarcation line at the junction of vascular and avascular retina. APROP occurs in the smallest, youngest, sickest infants and does not follow the typical progression from stage 1 to stage 3 ROP. It often portends poor outcomes, especially without timely recognition and treatment.

Treatments for ROP

Preventive strategies of ROP include methods to optimize prenatal nutrition, maternal fetal health, monitor and regulate oxygenation and infant nutrition. Once ROP develops, strategies for treatment include ones that address Phase I or Phase II pathophysiology.

2.3 Phase I strategies

Methods to extend physiologic vascular development may prevent ROP by reducing the stimulus for unwanted aberrant intravitreal angiogenesis from hypoxia-induced VEGF. Several strategies in the OIR model looked promising, including: providing growth factors like vascular endothelial growth factor (VEGF)[25], placental growth factor[26], erythropoietin[27, 28], or insulin like growth factor 1[29][29A]; inhibiting oxidative compounds[30, 31]; or reducing inflammatory mechanisms[32]. However, clinical trials to date have not shown benefit. Other studies include using prolyl hydroxylase inhibitors to stabilize hypoxia inducible factors that increase the transcription of angiogenic factors[33]. Studies to treat anemia in adults using prolyl hydroxylase inhibitors show promise[34] and theoretically may be beneficial in ROP. However, consideration must be given to the timing of treatment so as not to increase intravitreal angiogenesis, and this is not as straightforward in the individual infant as in reproducible animal models. Also, it remains unknown the potential systemic effects on the premature infant.

2.4 Phase II strategies

2.4.1 Historical treatment (cryotherapy)—Most studies have focused on inhibiting aberrant intravitreal angiogenesis to prevent fibrovascular retinal detachments. Early studies involved the use of laser[35] or cryotherapy[36] to treat avascular retina and reduce the stimulus of hypoxia-driven angiogenesis. The Cryotherapy for Retinopathy of Prematurity study was the first multicenter clinical trial (NCT00000133) that demonstrated a reduction in unfavorable outcomes, such as posterior retinal detachment, from 43% in control eyes to 21.8% in eyes following treatment of the peripheral avascular retina with cryotherapy[37].

2.4.2 Laser treatment—Once laser delivery systems were available to treat the avascular retina with an indirect ophthalmoscopic delivery approach, laser treatment was tested. Laser provided easier access to eyes with large areas of avascular retina (i.e., zone I and posterior zone II eyes) that required conjunctival peritomy to advance the cryoprobe sufficiently posteriorly to treat avascular retina. Laser also caused less inflammation than cryotherapy. The Early Treatment for Retinopathy of Prematurity (ETROP, NCT00027222) study showed a reduction in unfavorable structural outcomes from 15.4% to 9.1% at two years[35] when implementing earlier treatment for high-risk prethreshold ROP, i.e., type 1 ROP. At 6 years, early treatment remained significantly better for structural outcomes (19.8% conventional vs. 14.3% early treatment[18]. However, the early treatment arm experienced greater systemic complications such as apnea, bradycardia and reintubation following treatment compared to the conventional arm with laser treatment for threshold ROP. Even then, mortality and morbidity at 6 years of follow up demonstrated no statistical difference between the two arms. Currently, in the US, laser treatment is considered within 72 hours for type 1 ROP (see Treatment-warranted ROP). In one study, cryotherapy was associated with significantly worse structural and visual outcomes[38] and more myopia at 10 years than was laser (mean diopters: -7.65D after cryotherapy vs. -4.48D after laser) [39]. The development of high myopia is a concern for any type 1 ROP requiring ablative therapy. ETROP showed no difference in the rate of high myopia at 6 years with early vs. conventional management, although nearly a third of infants developed myopia greater than 5.00D spherical equivalent after treatment[40].

Laser is important to add to skip areas in order to reduce vascular activity and potentially obviate the need for surgery for fibrovascular tractional retinal detachment. In eyes with APROP and flat neovascularization, a two-stage laser procedure is successful and was reported to have fewer complications[41]. Distinction of flat neovascularization overlying avascular retina from normal retinal vasculature is difficult, and direct treatment increases the risk of vitreous hemorrhage. Now, eyes with APROP and flat neovascularization are considered for treatment with anti-VEGF agents[42].

2.4.3 Treatment with Anti-VEGF agents—Clinical trials have demonstrated superior short-term outcomes with intravitreal anti-VEGF agents compared to laser for treatment-warranted ROP, particularly in eyes with zone 1 disease[21]. Inclusion criteria varied among these studies[21] [43] [44]. Prior to clinical trials, a number of clinical series were published on the use of intravitreal anti-VEGF agents for treatment-warranted ROP[45]. The first clinical trial tested bevacizumab, a humanized monoclonal antibody to full-length VEGFA, vs. laser for infants with a severe form of ROP: zone I or posterior zone II, stage 3 ROP with plus disease (BEAT-ROP [NCT00622726]) [21]. In this study, 0.625 mg of bevacizumab in 0.025 mL reduced recurrence at 54 weeks post-menstrual age (gestational age+chronologic age in weeks) to 4% compared to laser-treated eyes, in which 22% recurred [21]. Another large series showed treatment-warranted ROP recurred in 8.3% of infants on average 16.2 weeks after the initial anti-VEGF treatment[46]. Despite being an angiogenic inhibitor, treatment with bevacizumab permitted physiologic retinal vascular development in some infant eyes. Studies also reported that myopia was reduced in bevacizumab treated eyes. In one study, spherical equivalence was divided into grades of high myopia (-5 to -8D) and

very high myopia ($-8D$). Very high myopia occurred in 3.8% of bevacizumab-treated vs. 51.4% of laser treated in zone I eyes and 1.7% of bevacizumab-treated vs. 36.4% of laser treated in posterior zone II eyes [46A]. Another study reported mean spherical equivalents of $-2.4 D$ in bevacizumab-treated eyes compared to $-5.3D$ in laser treated eyes at a mean follow up of 22.4 months [46B].

It has become increasingly recognized that anti-VEGF agents like bevacizumab change the natural history of ROP and that recurrence can be seen a year or more after injection in some infants[47, 48]. In addition, arrest of vascular growth has also been reported as a potential prognostic indicator of eyes that experience recurrent treatment-warranted ROP[49]. There are several reasons for the variability in the literature. It remains unknown the correct dose of anti-VEGF agent for an individual infant eye, and there is likely variability in the amount of VEGF that needs to be neutralized in an individual infant eye depending on the pathophysiologic stage of ROP [50]. Also, the volume of the premature infant eye is estimated to be about 1/3 to 1/4 that of the adult eye [50A] (Figure 2). Even if a standard dose of anti-VEGF were selected, there is currently not a way to reproducibly and accurately determine a dose by diluting adult doses and to deliver it in a sufficiently small enough volume so as not to excessively increase the intraocular pressure. There is a need for more accurate methods to deliver appropriate doses to infant eyes. In addition to the difficulty with anti-VEGF dose, dilution, and delivery, bevacizumab can enter the blood stream and neutralize VEGF for up to 2 months[51, 52]. VEGF is potentially an important modulator of vascular development in other organs in the premature infant and is also neuroprotective. Several reports have not found an association of bevacizumab and neurocognitive delay[53], but at least one retrospective study reported an association of bevacizumab with neurocognitive delay[54] compared to laser. However, the authors indicated this was potentially due to the increased sickness of the infants treated with bevacizumab, making them more likely to have developmental delays. Nonetheless to address safety concerns, a number of studies were performed testing de-escalating doses of bevacizumab (ROP1 (NCT02390531)[44]) or ranibizumab (RAINBOW (nct02375971), CARE-ROP (NCT02134457)[43]). It should be noted that the indications for treatment differed among the studies. ROP1 enrolled infants with type 1 ROP, whereas CARE-ROP enrolled infants with more severe forms of ROP: zone 1, stage 3; zone 1, any ROP with plus; posterior zone 2, stage 3 with plus; or APROP, and RAINBOW enrolled infants with type 1 ROP but excluded eyes with zone II, stage 2+ ROP.

Although direct comparison of trials is inappropriate, some observations can be made. Ranibizumab has a shorter half-life than bevacizumab, and some trials allowed different numbers of retreatments within 6 months. In RAINBOW, failure was considered to be vascular activity or stage 3 ROP within 28 days of injection. Ranibizumab at 0.12 mg vs. 0.2 mg resulted in much more persistent peripheral avascular retina at 6 months (45% and 84%, respectively), whereas bevacizumab reported 18% persistent avascular retina and a 23% failure rate[44].

When injecting an anti-VEGF agent into the infant eye, several points are important to consider. The dose is critical and should be obtained through a compounded pharmacy under sterile conditions. The volume delivered should be small (10[44]-25[21] microLiters) to

prevent high intraocular pressure. The eyelids are prepped with povidone-iodine, and tetracaine is placed into the eye, followed by 5% povidone-iodine. A sterile lid speculum is used. Injections are ideally made 0.5 mm from the limbus to avoid the lens and retina, although wider distances have been reported[21]. Injections are directed toward the posterior pole to avoid the lens. If the needle is long (e.g., 8 mm), it is important not to insert the full length of the needle and to inject slowly to avoid damaging the retina. Some recommend a 32 gauge, 4 mm needle to provide a safe injection [54A]. We have success performing intravitreal injections under conscious sedation to reduce the risk of injury to the lens or retina during the procedure.

2.5 Retinal detachment in ROP (Stage 4 and 5)

2.5.1. Exudative retinal detachment—Retinal detachment can occur as a result of exudation or fibrovascular contraction and often involves both processes. Exudation is believed to occur from leaky blood vessels or inflammation related to ROP. Increased exudation also occurs after laser or cryotherapy. Exudative detachments can resolve spontaneously although use of subconjunctival steroids may be considered. One study suggested consideration of systemic corticosteroids in infants with exudative detachments without identifiable traction and who had received laser treatment at 40 weeks post-menstrual age.[55] Once exudation resolves, pigmentary changes often occur in the affected retina and can be associated with reduced visual acuity if there is macular involvement.

2.5.2. Fibrovascular phase

2.5.2.1. Description and indications for treatment: When vascular activity, i.e., plus disease or aberrant intravitreal angiogenesis, is present in the presence of stage 4 or 5 ROP with tractional retinal detachment, surgical outcomes are poorer than when vascular activity is absent[56]. Many investigators treat vascular activity before or concurrently with surgery for retinal detachment[57, 58]. We often perform fill-in laser treatment to new avascular retina following regression of flat neovascularization or to areas of untreated avascular retina to reduce the hypoxic drive that is postulated to increase vascular activity. Laser treatment may be sufficient to prevent further progression of tractional progressive Stage 4 ROP. If an anti-angiogenic treatment is considered, the eyes must be monitored closely for intense fibrous contraction with complex retinal detachments that can involve the temporal vascular arcades, sometimes referred to as a “crunch” phenomenon. Some have reported intense fibrosis from anti-VEGF around 70 days after injections, although 50% of eyes experienced fibrous contraction within 35 days[59]. The configuration of fibrovascular contraction following anti-VEGF treatment differs from conventional appearances after laser. After laser, fibrovascular contraction often occurs at the ridge, and vitreoretinal contractile forces extend from the ridge to anterior retina, from the ridge to the lens, circumferentially from ridge to ridge and from the ridge to the optic nerve[60] (Figure 3). However after anti-VEGF, fibrovascular contraction can also occur at the previous junction of vascular and avascular retina (Figure 4) that existed prior to extension of physiologic retinal vascular development. These patterns can progress and take on a circumferential pattern. In addition, a prepapillary fibrotic configuration can form[59]. In all cases, membranes can be tightly adherent to underlying retina and often require bimanual dissection to relieve traction.

Surgery is performed for progressive stage 4a ROP before stage 4b occurs if at all possible, but determining which eyes will progress is also challenging[60]. With the advent of optical coherence tomography (OCT), it is recognized that retinoschisis, rather than retinal detachment, can occur in the region posterior to the ridge and is likely tractional in nature[61]. Retinoschisis and retinal detachment are difficult to distinguish with indirect ophthalmoscopy alone. It is helpful to recognize retinoschisis as an area vulnerable for retinal tears during vitreoretinal dissection. If vitreoretinal traction is recognized as a major component of a retinal detachment and retinoschisis, then surgical segmentation of the tractional forces is carefully performed during a vitrectomy.

Surgery can be performed with a scleral buckle or lens-sparing vitrectomy (LSV). However, multiple studies have shown that for zone 2, stage 4 ROP following laser, outcomes are better with lens-sparing vitrectomy than primarily with scleral buckle. Outcomes will be presented below.

2.5.2.2. Determining the timing for surgery: Indications for surgical intervention in stage 4 ROP have evolved with the advent of anti-VEGF treatment. Advancement of a retinal detachment can be rapid and careful monitoring is indicated. Once progression is determined, vitreous surgery is considered. However, there is more in the literature about features associated with progressive stage 4 ROP after laser. Fibrovascular contraction, vitreous haze, and vitreous hemorrhage are recognized as predictive features of Stage 4 ROP[62, 63, 64]. In one retrospective review of features following laser treatment, a logistic regression was used to assess the contribution of these features with progressive stage 4 ROP two weeks after laser treatment for then “threshold” ROP[63]. The features were stage 3 ROP; vitreous haze, condensation or hemorrhage; clock hours of ridge thickening or elevation; and clock hours of plus disease. The presence of two or more of the following: vitreous condensation/haze/hemorrhage, 2 or more clock hours of plus disease, or 6 or more clock hours of ridge elevation was significantly associated with progressive stage 4 ROP, whereas stage 3 ROP as intravitreal angiogenesis was not. In this study, vitreous haze and condensation occurred mainly over the ridge or at the optic nerve. With hemorrhage over the ridge, concern exists for underlying fibrovascular traction that cannot be visualized or adequately assessed for progression. These areas are carefully monitored, and surgery may be indicated earlier[62]. Even one clock hour of vitreoretinal traction can lead to dragging of much of the retina into a complex fold. One group reported fibrovascular contraction associated with recurrent retinal detachment following successful vitrectomy for stage 4b ROP[64].

Indications for surgery following anti-VEGF and tractional detachments have evolved and continue to do so[65]. Initially scleral buckles were performed until lens-sparing vitrectomy was developed to release vitreoretinal traction more effectively[66]. The initial reports of lens-sparing vitrectomy were encouraging mainly for posterior vitreoretinal pathology [67]. However, scleral buckles still have a role in certain types of retinal detachment associated with ROP.

After scleral buckling, success has been reported in the literature between 46% and 75% [68, 69, 70, 71, 72, 73, 74], whereas anatomical success after lens-sparing vitrectomy is reported

from 80–90% [60, 71, 75, 76, 77] but varies in some reports based on whether stage 4a or 4b is present and the extent of concurrent vascular activity. Since original reports prior to the recognition of the importance of treating vascular activity to improve prognosis, outcomes with lens-sparing vitrectomy for stage 4a and 4b ROP have improved. Scleral buckling, especially the use of radial elements, was and still is considered for some cases with peripheral traction or folding. Other potential factors associated with outcomes include characteristics and comorbidities of premature infants.

2.5.2.3. Surgical approaches for retinal detachments in ROP

2.5.2.3.1. Scleral buckle: Scleral buckles have been proposed in stage 4 ROP to reduce traction and stabilize vascular activity [78]. Several studies have reported that circumferential scleral buckling for stage 4 ROP does not reduce the progression of retinal detachment and results in lower success than vitrectomy with or without removal of the lens [71, 79].

However, scleral buckling performed concurrently with anti-VEGF or laser was reported to slow progression of stage 4a ROP detachments [58] or bring outcomes for vascularly active stage 4b ROP to that of vascularly inactive cases [57]. In eyes with peripheral detachments, in which it is difficult to address tractional forces without removing the lens, we and many advocate a scleral buckle [80]. Eyes with open peripheral folds limited to fewer than 6 clock hours, a meridional or radial element may create a local indentation to allow for retinal attachment and prevent progressive contraction [72] (Figure 5) more successfully than a circumferential band. The circumferential extent of elevation of the retina increases the risk of progression of stage 4 ROP or reduces the prognosis for macular attachment after scleral buckle surgery [63, 72].

Scleral buckling procedures are also considered for eyes with rhegmatogenous retinal detachments from peripheral breaks. These holes may occur in the locations adjacent to atrophic laser spots or from traction on thin retina.

As an external surgical approach, performing a scleral buckle carries less theoretical risk of cataract or endophthalmitis. However, the infant sclera is thinner than adult sclera so there is a risk of perforation. In addition, scleral buckles induce anisometropia, even up to 12 diopters, which increases the risk for amblyopia. Therefore, scleral buckles require a second surgery to divide the buckle as the eye grows, often by 3 to 6 months of age, in order to reduce the risk of anisometropia and induced myopia. One approach to scleral buckling is provided. A limbal-based 360-degree conjunctival peritomy is performed, and the rectus muscles are carefully isolated with 4–0 silk ties to allow exposure of the 4 quadrants of sclera. The choice of an encircling band or buckle is made based on the size of the eye and age of the infant as well as the location of pathology to be treated. A 2.5mm band (240 style) or a 41 or 42 band (4.0 mm wide by 1.25 mm thick) is considered. If there is sufficient subretinal fluid, a careful scleral cutdown with a 64 blade, diathermy of the scleral and choroidal beds and release of subretinal fluid are performed while the globe is not firm and prior to closure of scleral sutures. If a retinal break is present, it is treated with transcleral cryotherapy prior to placement of the band; the use of cryotherapy can soften the globe. If there is insufficient subretinal fluid to safely release, the intraocular pressure can be lowered by a careful and controlled anterior chamber paracentesis. We use spatulated 5–0 Mersilene

(Ethicon) sutures to secure the band in each of 4 quadrants, but nylon can also be used to make intrascleral passes. Sequential tying of the sutures is performed while monitoring the intraocular pressure tactilely. The ends of the band are often secured with a clove hitch knot of Mersilene suture or a silicone sleeve of the appropriate size in wide bands.

Division of the scleral buckle is performed at about 3–6 months to reduce myopia and the risk of anisometropic amblyopia. In infants or children, a partial limbal-based conjunctival peritomy is performed exposing the quadrant and adjacent rectus muscles where the connection of the band ends had been made. A pseudo-capsule present around the band can be easily incised with a perpendicular incision using a 64 blade after confirming the presence of a hard silicone band abutting the knife blade. The incision will expose the silicone band. The band can then be easily identified, lifted and divided. We prefer to segment the band in the region of the connection between ends.

2.5.2.3.2. Vitrectomy: The infant at birth does not have a mature pars plana. Therefore, entry into the vitreous without injuring retina or lens is safely done through the pars plicata, or iris root or limbus when the lens is removed. Specifically for LSV, we enter 0.5 mm posterior to the limbus perpendicularly to avoid the retina and lens. Several different approaches can be used. A two-port vitrectomy was originally described with the irrigating light pipe (20 gauge, Alcon[66]) and we have adapted this to use in combination with a 23 or 25 gauge vitrectomy probe. Surgery is also performed using a three or four port system with 23, 25 or 27 gauge vitrectomy[65, 81]. If ports are used, care must be taken not to injure the posterior retina or lens during insertion. Infant sclera can be difficult to enter and, therefore, an MVR blade can be used to make an opening into the sclera to insert the port. The infant eye is smaller than the adult eye (Figure 2). Therefore, to reduce the risk of injury of the posterior retina, a 42 band can be cut into a 2×2×1.25mm piece and the cannula placed through the silicone before entering the eye[81, 82]. Alternatively, pediatric ports that are shorter than adult can be used. A fourth port can be useful for a chandelier light source to permit bimanual technique to release traction from posterior adherent membranes associated with retinal detachments from APROP. The valved ports allow greater control of intraocular pressure during the procedure than direct entry into the eye from MVR blade incisions. The ports also support the more flexible, 27 gauge instruments that are useful to segment tight fibrous membranes in small areas adherent to the underlying retina^[65]. If ports are not used, plugs can be used to temporally close the sclerotomy sites when instruments are removed from the eye.

Vitreoretinal tractional forces are released by excising vitreous between the ridge and the ora serrata, the ridge and the lens (seen on preoperative OCT, Figure 3B), overlying the optic nerve, and the circumferential vitreous (Figure 3). Often there are vitreous tractional adhesions between the optic nerve and the ridge also that are carefully approached from the posterior pole to periphery. Here, it is helpful to have a preoperative OCT to detect retinoschisis (Figure 4B) [61].

Wide-angle viewing systems with the BIOM (Oculus) are useful. Contact lens systems are often cumbersome to use in small infant eyes that collapse readily. However, to aid with stereopsis of posterior pathology a contact lens can be helpful. There is interest in heads-up

3D visualization systems (NGENUITY, Alcon) in adult vitreoretinal surgery, and these can offer improved stereoptic visualization over other viewing systems without the disadvantages of a contact lens in small infant eyes.

Lens-sparing vitrectomy is performed ideally on stage 4 ROP in posterior zone II or zone I or in stage 5 eyes with open funnels in which the retina does not abut the lens. However, in cases with minimal space between the lens and elevated retina in which to enter the vitreous cavity, there can be several approaches. The eye is entered strategically at clock hours that do not overlie the elevated retina. While in the eye, the irrigating spatula is used to gently tease the vitreous away from the posterior lens capsule. The MVR blade can also be used to sever the connections between the vitreous and the posterior lens capsule.

In eyes with zone I ROP or APROP, plaque-like membranes form over the surface of the retina. These are best approached with bimanual dissection. An illuminated pic is helpful in combination with a pair of MaxGrip or ILM forceps (Alcon), which are especially useful if the main tractional forces are vitreous or thin membranes. For adhesive thick membranes, we use a chandelier light source and bimanual technique with forceps and curved scissors. Visualization is important. Ways to improve visualization include addressing cornea edema by assuring the intraocular pressure is tactilely normal and by using dispersive viscoelastics that assure long-term clarity, such as OcuCoat (Bausch + Lomb), Improvue (Oculus). Corneal scraping can also be judiciously used, and if lens opacities preclude visualization, a lensectomy may be performed. Contact lenses or the NGENUITY can be used to improve stereopsis for posterior dissection.

For anterior membranes, corneal haze, media opacities and to directly visualize difficult retroirideal, retrolental and anterior retinal structures, a lensectomy may be performed. If the lens is retained, a scleral buckle or endoscopy is considered[83].

2.5.2.3.3. Stage 5 considerations: Reattachment of the retina in stage 5 ROP is performed in infants and through 2 years of age. Besides some measureable level of visual acuity, the ability to perceive light and its projection may be measured and potentially help in the development of the child. Furthermore, with research into methods to restore vision and treat amblyopia in adults, there may be new opportunities for vision in the future not currently realized. Throughout life, complications related to earlier ROP can occur, including rhegmatogenous detachments and cataracts that require surgery to restore or preserve vision[84].

Ultrasonography with B-scan provides a preoperative tool when planning for surgery for stage 5 ROP in which a retrolental membrane prevents visualization of the retina. It helps to have an idea of the configuration of the funnel of the stage 5 ROP detachment and whether it is closed, open, or a combination of the two, the direction of the funnel and if it is pulled to a side[24].

Surgery for stage 5 ROP has better anatomic outcomes when vascular activity is reduced even if it requires monitoring for reduced vascular activity for a period of time after treatment. When the retina is adherent to a fibrovascular membrane abutting the posterior

lens capsule, there is no space to inject an anti-angiogenic agent. Treatment with topical anti-inflammatory drops may be considered but evidence is lacking regarding outcome.

Once the eye is quiet and the preoperative B-scan has been performed, most stage 5 detachments are approached through the limbus or pars plicata and through the lens. An anterior chamber maintainer is useful for infusion. The vitrector can enter through the iris and this helps stabilize the vitrectomy probe. The iris can be trimmed around the pupil when pupils are small to allow access to the retrolental space. Alternatively, perpendicular iridectomies can be made and later repaired with 10-0 or 9-0 Prolene (Ethicon). Iris hooks may also be useful. The lens is removed including the capsule. Once the retrolental tissue is identified it can be approached circumferentially or from the central region and extending peripherally.

There is often a peripheral trough under the retrolental membrane in which the retina is attached. Using bimanual technique, a strong forceps (e.g., Maxgrip or ILM, often 23 gauge, Alcon) is used to gently pull the membrane anteriorly and with curved scissors in the other hand, the plane between the membrane and retina is identified and circumcised temporally or nasally. Care is taken not to pull excessively to avoid creating a dialysis. The clock hour to start the incision is often where traction is believed to be greatest. The incision is carried out for 4 to 6 clock hours and then the membrane is approached from the opposite side in an identical fashion by switching the instruments between hands. The circumferential incision is completed. As the incision is created, the membrane is also dissected from the underlying retina, and the dissection is carried out toward the center of the eye approaching the center of the funnel. The membrane is removed in sections with the vitrector.

Another approach involves removing the membrane from the center where the funnel opening is believed to be present. Two 26 gauge needles can be used to create a vertical slit in the center of the membrane by pulling toward the periphery in cross-action fashion and this technique is especially useful when the membrane is not very dense and the retina can be visualized beneath the membrane. The membrane is dissected toward the periphery using curved scissors.

Dissecting the tissue from the funnel presents several challenges. The funnel can have a curved course as it extends to the optic nerve. If retinal adhesions are strong and the funnel is tight, it is helpful to use viscodissection with cohesive or cohesive-dispersive viscoelastics to gently separate and identify bridging membranes that can be incised. Using a foot activated pump at low pressure can be helpful to inject viscoelastic. The difficulty is providing sufficient light to dissect membranes as one dissects toward the posterior pole. The microscope light is useful in the anterior part of the dissection, but more posteriorly, it is helpful to use illuminated instruments or light pipe. Staged procedures are helpful in stage 5 ROP detachments. After dissection is safely completed, Healon (Johnson&Johnson) or Amvisc (Bausch&Lomb) can be used to keep the posterior retina away from the iris to prevent postoperative irido-retinal adhesions. It may become necessary to release subretinal fluid to facilitate dissection or maintain the retina from abutting the iris. The goal is to release traction safely without creating a retinal break and not to reattach the retina at the

end of the case. Postoperatively, subretinal fluid is reabsorbed. Bridging membranes may be identified and segmented in subsequent surgeries.

With mild cornea clouding, a lensectomy can be performed to create space between the iris and cornea allowing the cornea to clear for a later procedure. For extremely cloudy corneas, the open-sky vitrectomy involves corneal trephination, maintaining the cornea in OptiSol-GS (Bausch & Lomb), while vitreoretinal dissection is done using bimanual technique. If the anterior chamber is shallow or the intraocular pressure is elevated, subretinal fluid is drained before corneal trephination to reduce the risk of back pressure causing a break in the retina. The sclerotomy is temporarily closed to maintain pressure in the eye during further dissection. Once the cornea is removed and placed into media, the lens is removed with a cryoprobe and the retrolental membrane is more easily approached with bimanual dissection. To facilitate dissecting into the funnel, a glass contact lens is used over viscoelastic to improve visibility posteriorly, and curved scissors are used to dissect tissue. Once the posterior retina is visualized or membrane dissection has been safely achieved, the cornea is then replaced and sutured.

We often wait a month before considering additional surgery. Sutures can be removed from the cornea once adequate healing is identified, often by one month in infant eyes.

2.5.2.3.4. Adjuvants: Plasmin has been reported to release laminin and facilitate vitreoretinal surgery in stage 4 and 5 ROP[85]. However, there have been safety concerns as well as reduced electrophysiology in adult patients[86].

Steroids have also been used to identify vitreous membranes in the vitreous cavity or as postoperative adjuncts to improve surgical outcomes[87].

2.5.2.3.5. Bilateral sequential surgery: Within pediatric vitreoretinal surgery, immediate sequential bilateral surgery reduces the risks associated with repeat anesthesia in the most tenuous infants and offers timely intervention for advanced diseases. If bilateral surgery is performed, each eye is treated as a new case with resterilization and new drapes, new vitrectomy packs, media, instruments, drapes, instruments and tubing to reduce the risk of endophthalmitis. In addition, to reduce the risk of toxic anterior segment syndrome (TASS), any medications or fluids (viscoelastics, pharmacologics) should have different lot numbers. In one multicenter retrospective report of cases, no significant increases in adverse events were noted compared to the literature and aligned with the literature on bilateral simultaneous cataract surgery[88]. Considerations for simultaneous bilateral surgery are made for premature infants with progressive, bilateral, symmetric stage 4 or 5 ROP who have increased risk for anesthesia related complications.

2.5.2.4 Outcomes: Few prospective studies have been done and none that compared scleral buckling and lens-sparing vitrectomy; however, retrospective analyses have supported vitrectomy as having better anatomic outcomes. However, infants of young gestational ages with APROP are at risk of subretinal hemorrhage and later fibrovascular contraction even if treated to reduce vascular activity[89, 90, 91, 92].

Scleral buckle surgery for ROP has been evaluated both as a primary procedure and as an adjunct to LSV to improve reattachment rates. A retrospective study of 21 eyes of 15 infants found the addition of a scleral buckle in 12 of 21 eyes did not greatly affect the outcomes seen in patients treated with a lens-sparing vitrectomy[77], but other studies have supported using anti-angiogenic agents or laser to improve outcomes in scleral buckle surgery[57, 58]. Lens-sparing vitrectomy (LSV) offers advantages over primary scleral buckle surgery or vitrectomy with lensectomy. In contrast to scleral buckles, LSV does not induce significant anisometropia and does not require an additional surgery to transect the buckle as the eye grows. The advantages of maintaining the infant's natural lens are to allow for some development of vision and reduce the risk of glaucoma; however, sometimes it is necessary to remove the lens to release tractional components anteriorly. In all series, surgeon and surgical selection bias must be considered, as well as the wide variation in severity or extent of what can comprise retinal detachment in ROP.

Anatomic success with scleral buckle was reported as 46% to 70% in a number of small series based on whether treating stage 4a or 4b ROP[72, 74, 79, 93, 94]. One study reported greater anatomic success with LSV than scleral buckling and equal, if not greater, success to vitrectomy with lensectomy for most Stage 4 ROP[71], mainly noting that circumferential scleral buckling did not appear to prevent macular dragging. Others have also found that scleral buckling alone may not prevent progression of ROP[79]. However, another study reported that radial elements may have accounted for successes with peripheral folds[72].

Anatomic success in early studies using LSV ranged from 69–90% for stage 4 ROP with better outcomes for stage 4a than 4b generally and largely based on length of follow-up. In an early series, 90% retinal reattachment was reported after LSV in stage 4A ROP[60]. A later series reported 86% reattachment with LSV[75] and no significant difference in macular reattachment outcomes between stage 4a or 4b ROP[75]. Similarly, 85% reattached with one surgery using a 3-port LSV technique[95], and other studies have demonstrated similar outcomes with the 3-port technique. In 2015, a retrospective review included 496 eyes that had LSV for stage 4a, 4b, or 5 ROP between 1992 and 2013[96]. Reattachment after one procedure was 82% for stage 4a ROP, 69% for stage 4b ROP and 43% of stage 5 ROP. Additional retinal surgeries were performed in 20% of eyes, and 88% required a lensectomy. At the time of lensectomy, lens opacification was seen in 17% of eyes that had stage 4a ROP, 29% that had Stage 4b ROP, and 26% that had stage 5 ROP. Most eyes that required lensectomy had them within one year of lens-sparing vitrectomy[96]

Long-term outcomes published by from the ETROP Group were poorer. Only 30% of eyes that had vitrectomy for retinal detachments maintained macular attachment at 6 years of follow up. ETROP had longer-term follow up when compared to most previous studies, and some of the discrepancy with earlier studies may have been related to the difficulty achieving adequate examinations long-term following surgery for infants with stage 4 and 5 ROP.

When reviewing visual acuity outcomes, only two studies reported visual acuities of 20/60 or better on children who were on average 3.5 years old[95, 97], and one of these also reported reasonable visual acuity for stage 4b (mean of 20/200)[95]. In other studies, visual

acuity for stage 4a was reported at 20/189[98] and for stage 4b was 20/200 for 16 eyes following LSV; but other studies reported lower levels of visual acuity often at the 20/800 range[98, 99]. In the ETROP report, macular attachment was present in only 5 of 16 stage 4a eyes and only one of these had visual acuity of 20/200 or better[100], whereas only two treated stage 4b eyes had measurable visual acuity and no stage 5 ROP eye had vision[101]. A more recent report of long-term follow up from lensectomy-vitreectomy or LSV was reported in 88 eyes of 65 infants followed on mean 6.9 years. Anatomic success occurred in 89% of stage 4a, 63% of stage 4b and 42% for stage 5 ROP[102]. No eye had a previous scleral buckle or anti-VEGF injection. All patients were followed and received refractive correction. Visual acuity outcomes were best in stage 4a ROP but still were approximately 20/550 (20/500 for LSV and 20/650 lensectomy-vitreectomy). In a study of stage 5 ROP followed for one year and with at least partial retinal reattachment, the ability to discriminate stationary objects was present in 58%, whereas motion vision or light perception was present in 42%[103]. More recent reports of lensectomy-vitreectomy show visual outcomes below 20/4000[102].

The variability in outcomes, especially for LSV in stage 4a ROP, may be due to the age when children are tested for visual acuity and whether vision was tested with HOTV or recognition vision. Low Teller acuity vision at earlier ages is not as predictive of recognition vision in older children[104, 105]. Other variability may relate to the macular status. The degree of foveal dragging can be monitored as a change in the angle between the retinal veins in images from serial examinations. Also, in cases of previous macular detachment, loss of photoreceptor outer segments or the ellipsoid zone on optical coherence tomography (OCT) is often associated with poor visual acuity. Retinoschisis may adversely affect visual acuity outcomes, and it is unknown if this is present postoperatively in patients unless an OCT is performed. The initial oxygen insult to the macular capillaries is often unknown unless a fluorescein angiogram was performed at an earlier visit prior to the development of retinal detachment. Capillary nonperfusion can lead to loss of structural integrity and organization seen on OCT. However, even in poor visual acuity outcomes, children may still achieve levels of visual function. It is important to immerse the child at young ages in enriched environments.

Ongoing investigation into better approaches is warranted. In a study of 27–29 year olds who had been born <1500g, those with previous ROP had reduced visual acuity compared to those without and were less likely to drive a car[106]. Surgical techniques and methods to prevent and treat ROP continue to advanced and the future will determine if outcomes will be improved.

In addition to cataracts (reported in 17% of eyes following LSV), other ocular conditions are associated with ROP - before and after surgery[96]. Glaucoma is recognized to occur in eyes with ROP[107, 108]. In a prospective analysis of anterior chamber structures identified during Koepe gonioscopy in infant eyes with advanced ROP prior to surgical intervention, abnormalities in the angles were found and included a “Barkan-like” membrane. This study aligns with the thinking that an arrest or delay in development of the anterior chamber occurs in premature infants with advanced ROP [107]. A recent retrospective case series reported that 10% of eyes treated for advanced ROP (stage 4a, 4b or 5 ROP) developed

glaucoma and occurred in 33% of eyes treated for stage 5 ROP[108]. Lensectomy was an independent significant factor associated with developing glaucoma (hazard ratio 2.76, CI 1.371–5.581, $P=0.004$), but even LSV increased the risk of glaucoma[108]. Late rhegmatogenous retinal detachment can be seen in adolescent children and has been reported to have better outcomes with a scleral buckle than a vitrectomy[109, 110, 111].

3 Expert opinion

It is difficult to assess outcomes after surgery for advanced ROP because of wide variability in characteristics of infants in various series. Fibrovascular stage 4 and 5 ROP that developed from treatment-warranted ROP after laser has differences from eyes treated with anti-VEGF agents and is further different from eyes that were never treated. Decisions as to type of surgical intervention may vary based on initial management of vascularly active ROP. The degree of vascular activity when surgery was performed also adversely affects outcomes. Differences in long-term structural outcomes after surgery for retinal detachment in ROP between the ETROP study and case series also raise questions regarding variability in outcomes. Eye growth may lead to recurrent detachments at later ages. Older children are more challenging to examine in the clinic. Use of ultra wide angle imaging in the clinic may be helpful.

Outcomes from retrospective analyses are practical even though they have retrospective analyses have limitations. There are many challenges involved in designing studies to address surgical techniques for ROP. Often studies in the literature report on few patients. If studies enroll infants over long time periods to increase enrollment, surgical techniques have often been modified. Multicenter studies involve a number of surgeons, and enrolled infants may have had different gestational ages and birthweights, neonatal courses as to oxygen profiles and resources available for prenatal and perinatal care. These factors affect treatment outcomes and potentially the pathophysiology of ROP and severity of vitreous and fibrovascular interactions. Surgery for tight funnel stage 5 detachments in extremely preterm infants have poorer anatomic outcomes than open funnel detachments. When all factors are taken into account, the number of cases may be too small to derive meaningful analysis.

When assessing visual acuity outcomes, many factors come into play, including oxygen exposure at birth and during the neonatal course, health and structure of the retina including the presence of macular detachment, presence of retinoschisis or dragging, and development of neurocognitive pathways. Better awareness of ROP internationally and implementation of public health methods to reduce its incidence are important. Also, imaging methods to facilitate treatment consultations about eyes at various stages of pathophysiology; improved and targeted therapies for vascularly-active, treatment-warranted eyes; surgical innovations for the fibrovascular phases; and adequate follow up to maximize visual development are likely to improve outcomes. Ongoing research will be important in these steps.

In treatment-warranted ROP, pharmacologic methods to safely regulate the VEGF signaling pathway in endothelial cells may reduce the number of retinal detachments in ROP; however, close monitoring of eyes is necessary since some eyes treated with anti-VEGF agents will develop tractional retinal detachments from a few days to almost a year later[59].

Current methods involve inhibiting VEGF signaling broadly with an intravitreal antibody that affects endothelial cells but also has access to retinal neurons and glia. Since VEGF is neuro- and glial protective in experimental studies[112, 113, 114], there is concern. Clinical outcomes suggest benefit from anti-VEGF agents, especially for zone I eyes and APROP. Different anti-VEGF agents and doses have varying effects on ROP clinically. It will be important to assess safety not only systemically, but also for the retina. Studies reported differences in retinal structure by OCT based on whether eyes were treated with laser or the anti-VEGF agent, bevacizumab[115]. Additional studies using OCT to evaluate the structure of the retina may provide some insight.

Many series tested anti-VEGF strategies, but only a few prospective comparative studies have been reported. It is important to recognize differences in the studies when making observations. There are differences in the enrollment criteria for treatment-warranted ROP and whether it is defined as type 1 ROP or a more severe form. An extremely premature infant or growth-restricted infant will have a lower blood volume than a less premature infant. The anti-VEGF, which enters the blood stream, may be less diluted in the extremely premature infant. That infant is also at a different developmental age than an older infant. These factors may allow the anti-VEGF to have a greater effect on developing organs and on safety outcomes. Also, regions throughout the world may have varying resources available for maternal nutrition, prenatal care and oxygen regulation and monitoring.

Although any level of visual acuity is important for developing infants and children, the outcomes in the literature support the goal to prevent retinal detachment. Indirect ophthalmoscopy and laser are difficult skills to learn. A pharmacologic intravitreal therapy that is safe may be a practical approach with education about the necessity for appropriate dose, sterile technique, entry into the eye to avoid the lens and retina, and close monitoring. Additionally, there is great need for an injection system that reliably and reproducibly delivers the dose in a small volume (~10 microLiters). Long-term visual acuity outcomes and safety will need to be measured, and this applies to anti-VEGF agents also. Research into more targeted approaches is warranted, and better treatments will have been developed. Avenues of research will include identifying neuroprotective and vasoprotective factors or pathways that improve overall infant development and the retina. Safer approaches targeting VEGF receptor regulation specifically in retinal endothelial cells and understanding the affected signaling mechanisms to inhibit pathologic and extend or restore physiologic retinal angiogenesis and that can be delivered into the vitreous may improve outcomes.

In the future, introduction of public health measures to regulate and monitor oxygen and promote prenatal care will have extended to developing countries. Education of the impact of ROP will be widespread to parents, governments and health systems. This will be especially necessary in developing countries where infants are treated with high oxygen or anti-VEGF agents but are not able to be monitored, and often show up with advanced retinal detachments. Telemedicine approaches may be more widely implemented for referral-warranted ROP[116, 117, 118], defined as the presence of plus disease, zone 1 ROP, or stage 3 ROP[118]. However, telemedicine still leads to false negatives, in which infants with ROP are missed. Cameras with higher quality images and use of OCT and other imaging modalities will provide greater ability to detect early traction. In many areas, anti-VEGF

injections will be used for treatment-warranted ROP. However, follow up will be important to identify traction early and permit early surgical intervention. Improvements in surgical techniques with more ergonomic heads-up displays will allow improved stereopsis and better visualization of vitreoretinal pathology. Better education on surgical techniques will have evolved through courses, videos and outreach programs.

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Article highlights

- Understanding of ROP pathophysiology has evolved to include compromised physiologic vascularity and delayed physiologic retinal vascular development in Phase I and intravitreal angiogenesis in Phase II.
- Humans have a third phase of ROP that involves retinal detachment from vitreoretinal traction occurring often at areas of former intravitreal angiogenesis.
- Both laser and intravitreal anti-VEGF agents inhibit stage 3 ROP and plus disease, but anti-VEGF agents offer the additional possibility of extending physiologic retinal vascular development.
- The fibrovascular patterns after anti-VEGF treatment differ from those following laser in infants who develop later retinal detachments.
- Close monitoring of early fibrovascular activity that portends retinal detachment is important to determine the window of opportunity for surgery and to best balance its risks and benefits Progression can occur within one week or up to one year after anti-VEGF treatment.
- Features associated with progressive fibrovascular retinal detachment in ROP include vitreous condensation centrally, at the ridge or over optic nerve, recurrent or persistent plus disease; and mid-peripheral contraction at the location of the former ridge in eyes treated with anti-VEGF agents.
- Anatomic success for posterior or mid-peripheral pathology is better with vitreoretinal surgery that addresses tractional forces causing retinal detachment than with circumferential scleral buckle.
- Meridional or radial scleral buckles are useful for open retinal folds of 3–4 clock hours, whereas circumferential scleral buckles are useful for rhegmatogenous detachments and peripheral traction.
- Combination techniques of circumferential elements for peripheral traction and vitrectomy techniques for posterior traction may be useful as adjuncts following anti-VEGF agents, which extend physiologic vascularization,.
- Even low levels of vision are important to developing children, but current studies with disappointing visual acuity outcomes emphasize the importance of continued research to prevent retinal detachment and improve neural pathways for visual development in ROP.

Figure 1.

Treatment-Warranted and Retinal Detachment in ROP

Retacam images of A. Type 1 ROP in zone II, stage 3+. B. Type 1 ROP in zone I- posterior zone II, stage 3+. C. Stage 4 ROP with a combination of exudative and tractional elements. Images by Melissa Chandler, CRA, OCT-C

Safe Zone

Figure 2.

Infant and Adult Eye

Artist drawing depicting estimated differences in A. Infant eye – Safe entry into the vitreous is through pars plicata, which is less than 1 mm wide; lens is more spherical; vitreous is about 1 mL, and B. Adult eye – Safe entry into vitreous is through pars plana – 3.5–4.0 mm posterior to the limbus; vitreous is ~4 mL.

Drawn by James Gilman, CRA, FOPS

Figure 3.

Tractional Forces in Stage 4 ROP Addressed in Lens-sparing Vitrectomy

A. Artist drawing of lens-sparing vitrectomy demonstrating vitreoretinal contractile forces from (1) ridge to ora serrata and anterior retina, (2) ridge and lens, (3) circumferentially from ridge to ridge, (4) ridge to the optic nerve, and (5) over the optic nerve. After anti-VEGF treatment, additional tractional components occur over the optic nerve and in the mid peripheral retina where previous ridge occurred. Drawn by James Gilman, CRA, FOPS
 B. Optical coherence tomogram (OCT) through ridge of stage 4 ROP showing retinal detachment and vitreoretinal tractional components. Image obtained by Glen Jenkins, CRA, OCT-C

Figure 4.

Fibrovascular Contraction after Anti-VEGF in Former APROP

A. Montage of mid-peripheral vitreoretinal traction in region of previous stage 3 ROP at posterior vascular/avascular junction prior to extension of physiologic vascularization after anti-VEGF treatment. Laser marks noted in periphery. B. OCT through superotemporal ridge shows evidence of tractional retinal detachment and retinoschisis. Images by Glen Jenkins, CRA, OCT-C.

Figure 4.

Meridional External Element

Artist drawing of an external element to support peripheral traction causing a localized retinal fold and reduce further macula dragging.

Drawn by James Gilman, CRA, FOPS