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REVIEW ARTICLE

Aggressive posterior retinopathy of prematurity: a review on current understanding

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Abstract

A review of literature was performed, focused on the etiopathogenesis of aggressive posterior retinopathy of prematurity (APROP), the characteristic and atypical clinical features, management strategies, anatomical and visual outcomes. Characteristically APROP has zone I/posterior zone II involvement with prominent plus disease, featureless junction, large vascular loops, flat extra-retinal fibrovascular proliferation, and a rapidly progressive course. The risk factors for APROP are extreme prematurity (birth weight ≤1000 gram and/or gestational age ≤28 weeks), dysregulated oxygen supplementation, intrauterine growth retardation, sepsis, and thrombocytopenia. The uncommon presentations include small zone I disease, a hybrid disease with additional ridge tissue, and APROP in bigger babies with birth weight greater than 1500 g. Laser photocoagulation role is limited by the resultant visual field loss and high refractive error. Although anti-vascular endothelial growth factor injection allows peripheral retinal vascularization; reactivation of disease, systemic absorption of the drug and long-term safety are the chief concerns. Early vitrectomy is required when tractional retinal detachment develops. The visual outcome depends upon the morphology and vascular development of the macula. With the limited yet emerging new understanding of the pathophysiology, a multifaceted rational and individualized treatment strategy is suggested for APROP. Best practices in neonatal intensive care may prevent the occurrence of APROP. Further studies need to be performed for the prevention and safe, effective management of APROP.

Introduction

Aggressive posterior retinopathy of prematurity (APROP) is a rapidly progressive form of retinopathy of prematurity (ROP). The clinical features are characteristic and different from the classical ROP. If not treated in time, the disease may rapidly progress to stage 5 ROP. The optimal management approach is debatable with the pros and cons of both laser photocoagulation and intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections. A comprehensive review of the pathophysiology, clinical features, and continuously evolving management options for APROP is being presented.

The relevant literature was searched on PubMed Medline and Google Scholar databases using the terms "aggressive posterior retinopathy of prematurity" and "APROP." The search was performed for articles published till 30 September 2019. A total of 175 articles were screened. For non-English articles without translated text, only abstracts were reviewed. The papers on severe non-APROP disease were excluded. All original studies or case series or case reports were included. The references of these articles were also searched for any other articles of interest. In the end, 129 articles were included in the review.

Terminology

In 2005, the International Classification of ROP (ICROP) introduced the term "APROP" [1]. "APROP" was described as "a severe variant of ROP, which includes zone I or posterior zone II with increased dilation and tortuosity of the posterior pole vessels in all four quadrants out of

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Table 1 Reported incidence of aggressive posterior retinopathy of prematurity.

Author, year	Country	Screened cohort	Incidence of ROP	Incidence of treatable ROP	Incidence of APROP
Hungi, 2012 [13]	India	118 babies (236 eyes)	38.5%	–	5.0%
Holmstrom, 2012 [8]	Sweden	3488 babies	30.3%	5.2%	0.43%
Gunay, 2016 [9]	Turkey	5920 ROP records	–	0.51%	0.11%
Ahn, 2017 [7]	Korea	770 babies	–	13.63%	3.12%
Dwivedi, 2019 [12]	India	763 babies	30%	14.2%	3.9%

ROP Retinopathy of prematurity, *APROP* aggressive posterior retinopathy of prematurity.

proportion to the peripheral retinopathy with flat extra-retinal fibrovascular proliferation and a rapidly progressive course" [1]. Previously APROP was referred to as "type II ROP" [2] or "fulminate ROP" [3] or "Rush disease" [4].

Demography

There is a varied incidence of ROP and APROP due to different standards of care and screening criteria in various health-care facilities (Table 1) [5–9]. A Korean study reported the incidence of treatment-requiring ROP and APROP of 13.63% and 3.12% respectively in a cohort of 770 infants screened for ROP [7]. In a nationwide survey of 3488 infants from Sweden, the incidence of ROP, treatment-requiring ROP, and APROP was 30.3%, 5.2%, and 0.43%, respectively [8]. In a study from a tertiary care referral centre in Turkey, the incidence of treatable ROP and APROP was 0.51% and 0.11%, respectively [9]. The incidence of ROP in Indian settings is reported to range from 24% to 47% [10–13]. The incidence rates of APROP are higher as compared to other countries, reported around 4–5% [12, 13].

Among the treatment-requiring ROP, the percentage of infants reported to have APROP is 8.3% in Sweden [8], 10% in Thailand [14], 20% in Turkey [9], and 24.2% in Korean population-based studies [7]. The incidence is increasing in developing countries due to improving neonatal care leading to increased survival of extremely premature babies [15]. To the best of our knowledge, there is no data on APROP incidence from the developed countries.

Pathophysiology and predisposing factors

ROP is a vasoproliferative disorder of the retinal vasculature in the preterm babies. The development of retinal vasculature depends on a complex interplay of growth factors secreted by the retinal astrocytes and microglial cells [16]. The key factors involved are VEGF and insulin-like growth factor-1 (IGF-1). Disturbance in the arterial oxygen levels, both hyperoxia and hypoxia adversely affect the retinal vasculature in the preterm babies. ROP occurs in two phases [16]. In the first phase (from birth till 4 weeks after birth or till 31–32 weeks post-conceptional age), there occurs relative environmental hyperoxia, which leads to vaso-obliteration. In the second phase, the hypoxic peripheral retina secretes VEGF and IGF-1 in abundance, which causes neovascularization at the junction of the vascular and avascular retina.

The usual neonatal risk factors for severe ROP includes gestation age (GA) < 30 weeks, birth weight (BW) < 1000 g, and other co-morbidities like respiratory distress syndrome, apnea of prematurity, hypotension, patent ductus arteriosus, necrotizing enterocolitis (NEC), sepsis including pneumonia and meningitis, intraventricular haemorrhage, unmonitored oxygen exposure through continuous positive airway pressure or positive pressure ventilation, surfactant use and packed cell transfusion [17, 18]. Apart from the GA and BW, which are the two most important known risk factors for ROP development, supplemental oxygen use is also a significant risk factor [18].

The pathophysiology of APROP remains an enigma [16, 18]. Perhaps the clinical presentation of ROP varies depending upon whether the vasculogenesis phase or the angiogenesis phase is disturbed [19]. In the vasculogenesis phase, the retinal vessels develop de novo at the area of optic disc by transformation of the vascular precursor cells. The major arcades develop in the phase of vasculogenesis. In the angiogenesis phase, new retinal vessels grow from the existing vessels by the process of budding. If the insult occurs early in the vasculogenesis phase (due to low GA and early hyperoxia), then the vasculogenesis gets disturbed resulting in a severe zone I aggressive disease [19].

The independent risk factors reported for the development of APROP include extreme prematurity, thrombocytopenia, multiple infectious episodes, sepsis, intrauterine growth retardation, and the presence of chorioamnionitis [1, 7, 19–21].

Studies from the West and Japan have shown extreme prematurity (BW < 1000 g and GA < 30 weeks) to be a significant risk factor for APROP development [1, 22, 23].

Borroni et al. reported GA < 24 weeks as a significant factor predisposing to APROP development in the Italian population [24]. Infants who are born small for gestational age i.e BW < 10th percentile for GA develop APROP more frequently [7]. However in some settings, APROP has been reported to develop in older and heavier babies as well [21, 25–28]. In a large series of patients reported by Sanghi et al. from North India, nearly half of the patients with APROP had BW > 1250 g, and GA > 30 weeks and around 16% of the patients had BW > 1500 g [26]. Perhaps risk factors other than the GA and BW, such as supplemental use of high concentration oxygen for a prolonged duration may play a more significant role in older and heavier babies. Shah et al. reported the use of unblended supplemental oxygen as an additional risk factor for the development of APROP in heavier and older babies [25].

Chorioamnionitis-positive infants also show higher incidence rate of APROP [7]. Maternal infection with Ureaplasma urealyticum or Mycoplasma hominis may induce production of pro-inflammatory cytokines in the foetal brain [29] and decrease the levels of serum IGF-1 [30], which is a critical non-oxygen-regulated factor in ROP. This pro-inflammatory situation, in turn, prevents retinal vascular growth and leads to severe proliferative ROP [31, 32]. Also, the neonates with APROP often have associated NEC and sepsis [20, 24], which also highlights the role of perinatal infection in worsening of the retinal proliferative disease.

Although thrombocytopenia is a common condition in new-borns, especially those with low GA and BW, the incidence of thrombocytopenia is more frequent in babies with APROP than those with classical ROP [7, 20, 21]. The occurrence is higher in zone I disease than posterior zone II disease [7]. Platelets store and transport angiogenic regulatory proteins like VEGF within the alpha granules and thereby regulate the extracellular VEGF levels [33, 34]. Low platelet levels lead to insufficient quenching of the VEGF from the retina, which in turn may cause unregulated retinal neovascularization [20].

Lundgren et al. suggested a “multiple-hit” hypothesis for the pathogenesis of APROP wherein thrombocytopenia and infectious episodes occurred twice in all of their cases, with the first episode occurring during the first month of life and the second episode at the time of diagnosis of APROP [20]. Both APROP and non-APROP cases had episodes of infection and thrombocytopenia during the first phase of ROP, but only APROP cases develop the second episode during the second phase of ROP [20]. This highlights the possibility of extremely poor health and recurrent, multiple co-morbidities being responsible for the development of APROP.

Genetics has long been thought to play a role in ROP [35]. Mutations in the genes related to retinal vascular formation have been implicated to cause advanced ROP [35]. These include Frizzled-4 (*FZD4)* or lipoprotein receptor-related protein 5 (*LRP5)* genes, the mutation of which adversely affects the Wnt-signal transduction [35]. Drenser et al. had reported that compound heterozygous mutation in the *FZD4* gene may be responsible for APROP development as compared to classical ROP [36].

Screening

Screening preterm babies for ROP is the only way to detect ROP, and more importantly APROP, in time. A majority of nations have their own defined ROP screening criteria [37]. The American Academy of Pediatrics and American Academy of Ophthalmology advocate screening of all infants born at ≤30 weeks of gestation or with ≤1500 g BW as well as certain older and heavier infants based on the clinical course as assessed by the paediatrician [38]. The Royal College of Ophthalmologists, United Kingdom advise screening of all infants born at <32 weeks of gestation or with <1501 g BW [39].

The screening guidelines differ considerably in the low-middle income countries where bigger babies with BW greater than 1500 g also develop severe ROP due to poor neonatal intensive care unit (NICU) care [37]. The Indian guidelines recommend screening of all infants born at ≤34 weeks of gestation or with ≤2000 g BW or higher with risk factors at one month of birth [40]. The Chinese Expert group also recommends screening infants with GA ≤ 34 weeks or BW ≤ 2000 g or any infant, irrespective of the GA and BW, if risk factors are present [41].

There are no definite guidelines for screening at-risk APROP cases. The Royal College of Ophthalmologists guidelines suggest early screening at 30–31 weeks post-menstrual age (PMA) for infants born at <27 weeks GA, perhaps to detect APROP early [39]. Similarly, the Indian guidelines recommend screening of preterm infants born <28 weeks or <1200 g earlier than usual (within 2–3 weeks rather than at 4 weeks) to detect APROP [40, 42].

Clinical features

APROP occurs in zone I or posterior zone II with large vascular loops at the junction of the vascular and avascular retina [1, 22]. Prominent plus disease with tortuous retinal arteries and dilated retinal veins at the posterior pole is characteristic. Within the vascular loops, the retina is devoid of the vasculature and has capillary non-perfusion (Fig. 1). Intraretinal shunting of the blood occurs not only at the junction but also posteriorly in the apparently vascularised

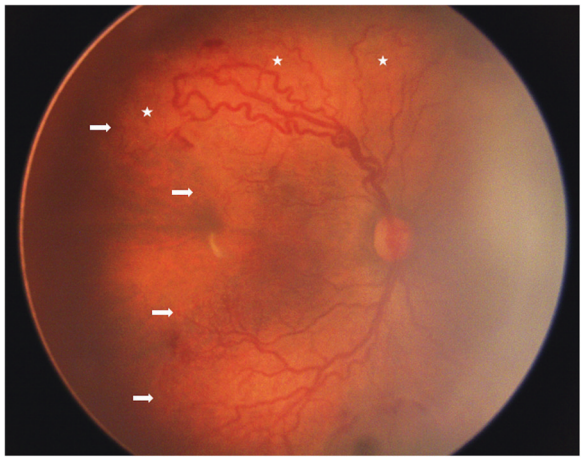

Fig. 1 Fundus imaging of zone I APROP. The colour fundus photograph shows prominent dilation of retinal veins and tortuosity of retinal arteries at the posterior pole, vascularization till zone I with indistinct margins (white arrows), and vascular shunting loops (white stars).

retina. The retinal vasculature may have a four-lobed topography with more vascular development temporally than nasally, hypoplastic/absent major arcades and hypoplastic macular vessels.

The iris may have prominent, persistent tunica vasculosa lentis (TVL) leading to pupillary rigidity and poor pupillary dilatation in these eyes. If dense, TVL may also obscure the retinal view. Vitreous haze is another important clinical feature of APROP, but may precede the development of APROP.

The neovascularization is clinically less evident as the growth of abnormal vessels is along the retinal surface instead of into the vitreous cavity. Less often the neovascularisation may be brush-fire like and grows into the vitreous cavity [43]. The friable neovascular tissue tends to bleed, and it is common to find preretinal and vitreous haemorrhage in such cases. The classical stages of ROP (from demarcation line to the ridge to extra-retinal neovascularisation) may not occur in APROP. If not treated in time, the extensive flat neovascularisation may progress to partial or total tractional retinal detachment (TRD) within a few days [1].

The characteristic clinical presentation may not always be present, and variations in the morphological features do exist. APROP may develop in bigger babies (defined by BW greater than 1000 g [25] or 1500 g [43] and/or gestational age greater than 28 weeks [25]) as well. The vascularization may not be restricted to zone I or posterior zone II. Sometimes it may be limited to the area of optic disc or may even reach up to the nasal ora serrata in the form of large vascular loops. The vascularization is not always flat and may have components of the ridge tissue at or behind the junction of the vascular and avascular retina. The current ICROP classification does not mention about these features [1].

APROP in bigger babies

Unblended oxygen therapy results in hyperoxia and resultant obliteration of retinal capillaries and large vessels in preterm infants [25, 43]. This is believed to cause APROP in bigger preterm babies (BW greater than 1000 g [25] or 1500 g [43] and/ or gestational age greater than 28 weeks) [25]. Such cases often have posterior zone II disease as compared to zone I disease in extremely premature infants [27, 43]. They often have mature central vessels (Supplementary Fig. 1). The nasal retina is apparently vascularised for a considerable distance with large vascular loops and enclosed capillary non-perfusion areas [43]. The fibrovascular tissue (FVT) is not as relentless as that seen in typical APROP cases [43].

Small zone I APROP

In these cases, there is poor macular development, and temporally a wedge-shaped avascular area distal to the fovea known as “temporal notch” can be seen [19]. Sometimes the retinal vascularization may be entirely short of the macular area and is termed as “posterior zone I disease” (Supplementary Fig. 2) [44].

Recently an atypical and severe type of ROP has been described by Tadashi et al. wherein the fibrovascular proliferation arises directly from the optic disc rather than the flat or brush-fire like neovascularisation seen at the junction of the avascular and vascular retina in APROP [45]. These patients had extreme prematurity (GA 24–25 weeks and BW < 1000 g). The features of this disease are similar to those seen in oxygen-induced retinopathy in animal models except that in the induced retinopathy, retinal detachment somehow does not occur despite neovascularization [46]. It is hypothesized that vaso-obliteration occurs in all retinal vessels except those at the optic disc from which abnormal proliferation occurs later. The prognosis remains dismal in such cases despite multimodal treatment with laser, intravitreal anti-VEGF injection and vitrectomy due to extensive retinal ischaemia and rapidly progressive retinal traction [45].

Hybrid APROP

When the eye develops both the ridge tissue (a feature of classical ROP) and flat neovascularization (a feature of APROP) then such a presentation is termed as hybrid ROP (Supplementary Fig. 3a) [47]. It is challenging to characterize them by ICROP. The general four-lobe topography of APROP is not seen due to considerable vascularization in

the nasal retina. Majority of the cases have posterior zone II disease. Usually it starts with flat neovascularization but as it reaches zone II, a ridge starts developing in the vascular area adjacent to the flat neovascularization, generally in the nasal retina [47]. The BW and GA of babies with hybrid ROP is usually higher (mean 1380 g and 29.6 weeks) [47].

Sanghi et al. first reported this entity in around one-fifth of their APROP cases [47]. Different patterns may occur depending upon the arrangement of avascular retina and ridge tissue: type 1 pattern with the ridge at the junction (most common and favourable), type 2 pattern with ridge posterior to the junction in vascularised retina (less common but also favourable), and type 3 pattern with a mat-like fibrovascular proliferation and poorly defined ridge close to the optic disc (least common and unfavourable) [47]. The type 1 and 2 patterns behave more like classical staged ROP with complete regression after laser treatment. Type 3 pattern often develops stage 4 ROP despite adequate laser photocoagulation due to its more posterior location and extensive flat neovascularisation.

Another type of hybrid APROP has been described by Flynn et al. with normal and abnormal temporal vessels demarcated by the horizontal meridian [19]. In the ordinary course of retinal vascular development, the major retinal arcades form during the initial vasculogenesis phase which is followed by the late angiogenesis phase with further vessel development from the existing vasculature. Flynn et al. proposed that there occurs an overlap between the two phases and it is this overlapping period when an insult leads to disrupted vasculogenesis (flat new vessels) and disrupted angiogenesis (ridge tissue development) together leading to a hybrid picture of disease [19].

Role of fundus fluorescein angiography

Fundus fluorescein angiography (FFA) is a useful investigative modality which helps in diagnosis and appropriate management of APROP [48–50]. APROP presentation is very atypical with an indistinct vascular–avascular junction, large vascular shunting loops enclosing capillary non-perfusion areas and flat neovascularization along the retina, which may not be visible otherwise.

The most significant advantage of FFA over colour fundus imaging is a better delineation of the capillary non-perfusion areas within the vascular loops (Supplementary Fig. 3b) [49, 50]. The capillary non-perfusion areas are often multiple, isolated islands of hypoperfusion surrounded by the retinal vasculature. FFA guided laser treatment allows a more complete treatment of the avascular retina in a single sitting in such cases.

Certain other FFA features have also been described in APROP (Supplementary Fig. 4) [49, 50]. The apparently quiet junction on clinical examination may have angiographic evidence of neovascularization which leaks fluorescein profusely. The popcorn lesions present posterior to the junction are better appreciated on FFA as hyperfluorescent lesions. Anomalous vessel branching may be seen near the junction at various levels—large arterioles, small arterioles, and at pre-capillary level. However, these do not leak, unlike neovascularisation. Another feature of the junction that is better appreciated on FFA is the presence of circumferential intraretinal shunt vessels.

Clinically hypoplastic/absent macular vessels appear as an area of macular hypoperfusion on FFA. FFA also allows monitoring of the change in the size of capillary non-perfusion areas [51] and development of macular vascularization following intravitreal anti-VEGF treatment [49].

Management

The identification of flat neovascularization in the presence of poorly dilating pupil and featureless junction remains a difficult task which may lead to delay in the diagnosis and treatment of APROP. The treatment options for APROP include laser photocoagulation, intravitreal anti-VEGF injection, vitrectomy, and a multipronged combination of these individual options. Once used to treat acute threshold ROP, cryotherapy gave way to laser treatment in 1990s due to its adverse effects and better long-term safety and efficacy of laser [52]. Cryotherapy is no longer used for the treatment of ROP.

Laser photocoagulation

The retinal laser acts by destroying the cellular retinal elements producing VEGF. Although laser photocoagulation has long been performed in APROP eyes, there are no standard guidelines regarding the timing, pattern, and follow-up of the cases (Table 2) [22, 26, 27, 48, 53–57]. The 810 nm diode laser was commonly used previously, but currently, 532 nm green laser is preferably used with no comparative studies between the two in APROP.

The laser procedure involves near-confluent treatment of the entire avascular retina anterior to the vascular retina till the ora serrata. Since the junction between the vascular and avascular retina is featureless and often not picked up, the posterior extent of the laser is often variable in different studies. The variations in the standard laser procedure include laser in the posterior tongue-shaped extensions of the avascular retina temporally [26, 53, 55], laser in the avascular loops in the clinically vascularized retina (Fig. 2) [26, 48, 56], and laser over the flat neovascular fronds [54, 55]. The posteriorly pointing temporal tongues of the avascular retina or “temporal notch” are often not

Table 2 Review of literature on laser treatment of aggressive posterior retinopathy of prematurity.

Author, year	Number of eyes/ infants	Mean BW (g)	Mean GA (weeks)	Laser type	PMA at laser (weeks)	Pattern and area of laser	Retreatment- *n* (%), timing after primary treatment	Average follow-up-PMA	Favourable primary outcome (%)	Unfavourable outcome
Sanghi, 2009 [26]	81/44	1259.6	29.75	Diode, 810 nm	34.6	Near—confluent; Anterior, clinical loops and posterior tongues	11 eyes (13.58%), 10.4 days	12.8 months	71.4%	2.6% stage 5 2.6% macular fold 23.4% peripheral TRD
Drenser, 2010 [22]	44/22	627	24	Diode	34	Near—confluent	14 eyes (31.8%), <2 weeks	4 months to 4 years	81.8%	18.2% stage 4a/b
Ahn, 2013 [48]	12/6	1432	30.5	–	35.2	Near—confluent; Anterior, clinical loops	4 eyes (33.3%), 2–3 weeks	25.2 months	58.3%	33.3% stage 4 8.3% macular fold
Sanghi, 2013 [53]	109/61	1392	30.2	Diode, 810 nm	35.3	Near— confluent; Anterior, posterior tongues	12 eyes (11%), 7–10 days	6 months	82.6%	7.3% stage 4a 3.7% stage 4b 3.7% stage 5 2.7% falciform fold
Gunn, 2014 [54]	15/8	634	24.2	Diode	34.1	Near—confluent; Anterior, Ridge	5 eyes (33.3%), <1 week	56 months	86.7%	6.7% stage 4b 6.7% stage 5
Pandya, 2015 [57]	6/3	704	24.3	–	34	Near—confluent	None	7 months	50%	50% stage 4a
Vinekar, 2015 [55]	48/29	1276	30.1	Green, 532 nm	34.2	Near—confluent; Gp1: Anterior, tongue, plus over fronds, Gp2: Anterior, tongue	Gp1: 6 eyes (20.69%), 2–3 weeks Gp2: All cases re-laser in exposed areas after 7 days, third sitting-7 eyes (24.14%)	Minimum 12 months	100%	None
Gunay, 2015 [56]	30/15	941	27.3	Diode, 810 nm	33.9	Near—confluent; Anterior, clinical loops	4 eyes (13.3%), 1 week	64.7 weeks	93.3%	6.7% stage 4a
Nicoara, 2016 [27]	12/6	1198	29.8	Diode, 810 nm	36.3	Near—confluent	2 eyes (16.66%), 1 week	60 weeks after laser	75%	25%

BW birth weight, *GA* gestational age, *PMA* post-menstrual age, *TRD* tractional retinal detachment.

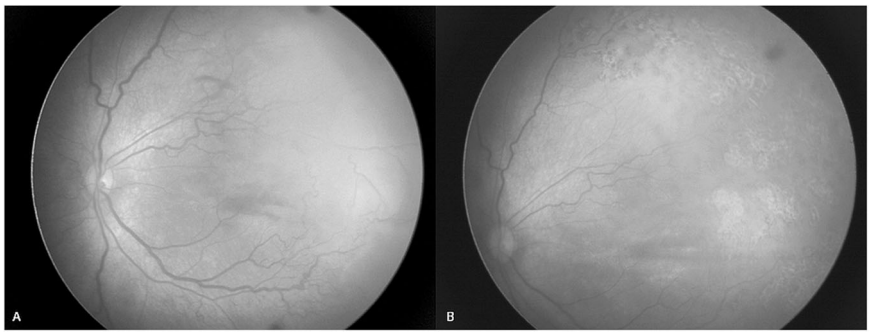

Fig. 2 Fundus images of a case of posterior zone II APROP treated with laser monotherapy. A The fundus image shows prominent arteriolar tortuosity, venous dilation, flat neovascularization at the junction of vascular–avascular retina inferotemporally and large vascular shunting loops temporal to the macula. **B** Three weeks after near-confluent laser photocoagulation of the entire avascular retina including vascular loops, the vessel tortuosity and dilation has significantly reduced, and the flat neovascularization has regressed.

treated fully due to the fear of spread of the laser reaction posteriorly towards the macula. However, Pandya et al. did not report posterior creep phenomenon in six APROP cases treated with laser [57]. Instead these eyes had an anterior displacement of the laser scars over time due to possible transverse retinal growth [57]. Another problem faced during laser treatment is difficult visualization and disrupted laser penetration due to the presence of TVL.

Vinekar et al. compared the standard treatment involving the neovascular fronds in 48 eyes with APROP in one vs. two sittings [55]. In group 1 where the complete laser was performed in a single sitting, regression with primary treatment was noted in 79.3% eyes, and the rest were retreated. In group 2, the neovascular fronds were not targeted primarily, and the exposed areas were treated in the second sitting in all eyes. Retreatment was required in 24% of the eyes in group 2. The two-stage laser procedure produced fewer and smaller retinal haemorrhages and no fibrosis at the area of apparent demarcation as compared to the single staged procedure [55]. Similar to the two-stage procedure, based on the retrospective review of digital fundus imaging, the Photographic Screening for Retinopathy of Prematurity study group also suggested a close follow-up at 7–10 days following laser to identify and treat previously avascular areas hidden by extensive flat neovascularization [55, 58].

Since the VEGF load is very high in the vitreous cavity in APROP cases, the laser treatment may often not lead to complete regression of the disease. Following laser treatment, the regression of neovascularization takes 2–3 weeks. The existing VEGF in the vitreous cavity and new VEGF expression from the vitreal macrophages may lead to progression of ROP till the effect of laser starts [59]. The retreatment rates with laser monotherapy in APROP vary between 11 and 33.3% [22, 26, 27, 48, 53, 54, 56]. The retreatment, when performed is often required within 7–10 days.

Anatomical outcomes

A favourable outcome in the form of complete disease regression with laser monotherapy ranges from 50–100% with most of the studies reporting it to be between 70 and 85% [22, 26, 27, 53]. This is less than the laser treatment success rates of above 90% in type 1 ROP cases [60, 61]. The progression of APROP can occur despite laser treatment leading to unfavourable outcomes such as peripheral TRD (stage 4a) and rarely stage 4b/stage 5/falciform fold formation. Macular drag/ectopia may also develop [1]. Sanghi et al. studied the risk factors for unfavourable outcomes despite laser treatment in APROP and found GA < 29 weeks, presence of retinal haemorrhages, posterior zone I disease, extensive fibrovascular proliferation (>3 clock hours), need for multiple laser treatment, and development of new fibrovascular proliferation following laser to be significant factors for development of retinal detachment [53]. The more posterior the junction is, the less is the chance of favourable outcome. In the study by Sanghi et al. from North India, the rates of a favourable outcome with laser were 98%, 68%, and 0% for posterior zone II disease, anterior zone I disease (vessels anterior to fovea), and posterior zone I disease (vessels not reaching fovea), respectively [53].

Limitations

Severe constriction of the visual field and induction of myopic refractive error are the common occurrences while late angle-closure glaucoma and cataract development are rare adverse effects of laser treatment in APROP [1, 62, 63]. Extensive confluent laser treatment may cause necrosis of the treated retina and resultant vitreous and anterior segment inflammation. Altered anterior segment development following extensive laser in APROP cases is responsible for the development of high myopia [64].

Anti-VEGF treatment

VEGF plays a vital role in the pathogenesis of APROP, and VEGF inhibition is an alternative treatment to laser photocoagulation. While laser treatment aims to prevent further VEGF release, the existing VEGF can only be targeted with anti-VEGF therapy. Anti-VEGF drugs also target the VEGF expressed from the vitreal macrophages [19, 59]. Anti-VEGF treatment permits the peripheral growth of the retinal vessels and thereby avoids the extensive visual field loss observed with laser monotherapy [65–67].

The initial reports by Mintz-Hittner et al. [68] and Travassos et al. [69] highlighted disease regression with no untoward consequences in cases of APROP treated with intravitreal Bevacizumab (BCZ). The efficacy of anti-VEGF agents was later proved in BEAT-ROP trial in zone I disease [70]. Further studies on anti-VEGF therapy in APROP have shed light on the treatment outcomes of this disease (Table 3). There have been numerous reports/series of the use of anti-VEGF therapy in APROP as primary monotherapy, as a combination with laser, as rescue therapy after laser treatment failure, or as an adjunctive agent before vitrectomy [49, 65–67, 71–76]. Till date, the use of BCZ for intraocular purposes remains off-label.

Drug and dosage

To date, the Food and Drug Administration, United States has not approved any anti-VEGF agent for the treatment of ROP. The choice of agent in reviewed studies remains BCZ commonly and Ranibizumab (RBZ) less frequently. Although some studies have reported a similar effect of these two drugs in classical ROP with type 1 disease [77], some have reported longer VEGF suppression and less reactivation with BCZ in type 1 ROP [78]. There is no head-on comparative trial of these drugs in APROP. Aflibercept (AFL) has also been used for treatment-requiring ROP and has been reported to have the advantage of less frequent and more delayed recurrences than other anti-VEGF agents, but there are no studies reporting outcomes with intravitreal AFL separately in APROP [79, 80].

BCZ is commonly used off-label in a dosage of 0.625 mg (half the adult dosage) as recommended by the BEAT-ROP study [70]. Recent research has shown that the vitreous cavity size-adjusted dose of BCZ in neonates should be 0.4 mg [81]. Also, the classical type 1 ROP has been shown to regress with even lower doses of 0.16 mg and 0.031 mg of BCZ [82, 83]. Isolated reports of successful treatment of APROP with 0.16 mg or 0.375 mg of BCZ exist [71, 84]. While the use of lower dosage may need additional treatments for early failure of treatment/late recurrence of disease; larger dosage may cause vascular arrest and thereby increase the need for longer follow-up [66]. In a drug dose de-escalation study, Wallace et al. reported that with low dose BCZ, the anatomical outcomes may be good but often additional treatment is required [85]. Dikci et al. did a comparative trial of two doses of BCZ (0.625 and 0.5 mg) and found that although primary regression of disease was same between the two groups, late reactivation occurred in 50% of the cases with the lower dosage [66]. Similar to BCZ, RBZ is often used in the dose of 0.25–0.3 mg and AFL in the dose of 1 mg (half the adult dosages).

The timing of intravitreal injection is of prime importance [86]. If injected early in the course of the disease (phase 1 of disease), it may delay the normal retinal vascularization. If delayed (beyond phase 2 of disease), the interplay of VEGF and other fibrotic growth factors (transforming growth factor and connective tissue growth factor) gets unbalanced and acute fibrosis, and tractional detachment occurs (Crunch phenomenon) [76, 87].

The effect of an intravitreal anti-VEGF drug appears within 24 hours of the injection with regression of TVL, decrease in iris engorgement, better pupillary dilation, and decrease in the vitreous haze, venous dilation and arterial tortuosity (Fig. 3) [69]. The vascular changes (better visualized on FFA) occur in three phases: an initial phase of rapid quietening (within 1 week), the second phase of slow vascularization (over 1–10 weeks), and the last phase of regression (between 10 and 16 weeks) in which features of classical ROP such as demarcation ridge develop [88]. The non-perfusion areas within the vascular loops gradually shrink with capillary refill and eventually resolve in 5–6 weeks [48, 50].

The regression rates with a single injection in APROP ranges from 62.5% to 100% [49, 65–67, 71–75]. However, the failure of regression and disease reactivation are two significant limitations of anti-VEGF monotherapy, and these require retreatment. The retreatment rates vary from 7.8% to 75% [49, 67, 72–76]. Nicoara et al. [73] and Lorenz et al. [49] reported early failure in 26.16% ($n = 11/52$) and 37.5% ($n = 3/8$) eyes which had to be treated within 7–10 days with repeat injection and laser, respectively.

Reactivation occurs once the effect of anti-VEGF drug present in the vitreous cavity wanes off. Reactivation commonly occurs between 40 and 52 weeks post-conceptional age, i.e., between 2 and 10 weeks post injection [49, 65, 67, 72, 74, 75]. As compared to the classical type 1 ROP, APROP eyes have a five-fold increased risk of recurrence [74]. While the recurrence rates with BCZ vary between 30% and 40% [49, 66, 74, 89], Huang et al. reported a high recurrence rate (46.9%) in eyes with APROP treated with 0.25 mg RBZ monotherapy [90]. The risk factors for recurrence include lower BW and the presence of retinal haemorrhages [76]. The recurrence in APROP often occurs only at the advancing edge, unlike classical ROP where it involves both the advancing edge

Table 3 Review of literature on anti-vascular endothelial growth factor treatment of aggressive posterior retinopathy of prematurity.

Author, year	Number of eyes/ infants	Mean BW (g)	Mean GA (weeks)	Anti-VEGF type and dose	PMA at Injection (weeks)	Primary success with injection alone	Retreatment, mean timing	Reason for retreatment	Mean follow-up-PMA	Final outcome	Unfavourable outcome
Harder, 2011 [71]	8/4	642	26.5	BCZ 0.375 mg	35.75	100% regressed	None	–	66 weeks	100% regressed	None
Park, 2014 [72]	6/3	1747	31	BCZ 0.625 mg: 2 eyes, RBZ 0.3 mg:4 eyes	32, 35, 35	100% regressed	4 eyes, 2 eyes: BCZ, 40 wks PMA 2 eyes: LP, 43 wks PMA	Reactivation	56.7 weeks	Far peripheral retina not fully vascular	–
Yetik, 2014 [67]	62/31	–	27.7	BCZ 0.625 mg	34	92, 96.8, 100% success (1st/ 2nd/3rd inj)	5 eyes, 1.2 wks 2nd BCZ≫2 eyes, 2.5 wks 3rd BCZ	Inadequate regression (2nd inj), reactivation (3rd inj)	92.5 weeks	100% complete vascularization	–
Nicoara 2015 [73]	52/26	1218	28.9	BCZ 0.625 mg	35.2	41 eyes (78.84%) regressed	11 eyes (21.16%), LP 7–10 days	Failure to regress	60 weeks	50 eyes (96.2%) regressed	Stage 5 in 2 eyes
Mintz-Hittner, 2016 [74]	19/-	512	23.3	BCZ 0.625 mg	33.8	100% regressed	6 eyes (31.6%), BCZ PMA 52.1wks	Reactivation at advancing edge in zone II	65 weeks	18 eyes (94.7%) regressed	Stage 4a in 1 eye
Li, 2016 [75]	32/ 16: Z[j] I- 22 ZII- 10	1336	29.1	RBZ 0.3 mg	35.7	100% regressed	7 eyes (21.88%) 2–8 week, LP	Reactivation in zone I	At least 6 months after treatment	100% regressed	None
Lorenz, 2017 [49]	8/5	581	23	BCZ 0.312 mg	34.2	5 eyes (62.5%) regressed	6 eyes (75%) 3 (37.5%): BCZ, 10 days 3 (37.5%): LP, 10 wks	Early failure: 3; Reactivation: 3	–	100% regressed	None
Sukgen, 2017 [65]	26/13	1114	28	RBZ 0.25 mg	35.4	100% regressed	2 eyes (PMA 42 wks) 1 LP 1 RBZ	Reactivation in 7 eyes, 2 retreatment	–	100% regressed, vascularization complete in 24 eyes	None
Dikci, 2018 [66]	15/ 8 5/3: Gp1 10/ 5 Gp2	835, 724	26,25.2	BCZ Gp1: 0.625 mg Gp2: 0.5 mg	32–33	100% regressed	5 eyes (Gp2), LP	Reactivation in 5 eyes (Gp2)	61.5 wks	100% regressed, vascularization complete in 10 eyes	None
Tong, 2018 [76]	160/ 83	1340	30	RBZ 0.3 mg	36.6	36.25% regressed	29.4% (47 eyes) RBZ; 20.6% (33 eyes) LP; 13.75% (22	Failure to regress/ reactivation: 63.75%	17 months after treatment	78.125% regressed	21.8% developed TRD

Table 3 (continued)

Author, year	Number of eyes/ infants	Mean BW (g)	Mean GA (weeks)	Anti-VEGF type and dose	PMA at Injection (weeks)	Primary success with injection alone	Retreatment, mean timing	Reason for retreatment	Mean follow-up-PMA	Final outcome	Unfavourable outcome
							eyes) RBZ + PL				
Perente, 2019 [51]	116/58, Z I- 80 Z II- 36	1156	28.3	BCZ 0.625 mg	34.4	100% regressed	None (spontaneous regression of recurrence in 18 eyes)	–	95 wks	Vascularization: (FFA[1] based) 29.2% - zone II, 70.8%- zone III	Abnormal vasculature: 86.2%, leakage (FFA) 10.3%,
Ekinci, 2019 [89]	59/30 Z I- 45 Z II- 14	1145	28.4	BCZ 0.650 mg	34.9	100% regressed	6 eyes BCZ: 47wks PMA (spontaneous regression in 12 eyes)	Reactivation (18 eyes)	102 wks	100% regressed, vascularization complete in 8% eyes	Leakage (FFA) 15.3% eyes

BW birth weight, *GA* gestational age, *VEGF* vascular endothelial growth factor, *PMA* post-menstrual age, *BCZ* bevacizumab, *RBZ* ranibizumab, *LP* laser photocoagulation, *TRD* tractional retinal detachment, *FFA* fundus fluorescein angiography, *Z* zone.

and the initial ridge [74]. FFA may show leakage at the junction and help in picking up early recurrences. Recurrence may be treated with a repeat intravitreal injection [74] or laser photocoagulation of the anterior avascular retina [49, 65, 66, 73]. Although the plus disease gets controlled immediately with repeat injection, the retinal revascularization may proceed minimally after anti-VEGF retreatment [74]. The number of times an anti-VEGF agent may be used is not known. The systemic safety should be kept in mind before repeating intravitreal anti-VEGF injection.

Anatomical outcomes

With retreatment, a final favourable result is achieved in 78% to 100% of eyes (Table 2). Advanced ROP (stage 4 or rarely stage 5) develops in a minority of the cases [73, 74]. The risk factors for progression of the disease to TRD despite treatment include a higher post-conceptional age at treatment and low neutrophil count [76]. The neutrophils play an anti-angiogenic role by virtue of the production of Angiostatin which in turn inhibits the action of VEGF [91]. A low neutrophil count may, therefore, allow uncontrolled vascular proliferation and disease progression. Vascular arrest, i.e., the retinal periphery is not completely vascularized, and the vascularization stops growing further, is not an uncommon event post-anti-VEGF treatment [65, 66, 72]. The amount of retinal revascularization following anti-VEGF therapy is variably reported. Perente et al. recently reported that following a single intravitreal BCZ injection for APROP, FFA at 90–100 weeks post gestation showed vascularization in zone III in three-fourth of the cases, while the rest still had vascular arrest in zone II [51]. While Mintz-Hittner et al. hypothesized that the retinal vessels after anti-VEGF treatment advance only to a certain point at which the vascular precursors have ceased migration in the first place and therefore, the vascular arrest sets in [70], there is enough recent literature reporting complete vascularization with anti-VEGF monotherapy in cases of APROP [65–67]. RetCam assisted FFA may be useful for further treatment of cases with vascular arrest as it is superior to indirect ophthalmoscopy in determining the vascularization end limit, persistent capillary non-perfusion areas, and abnormal vascular shunts and leakage [51].

Limitations

The anti-VEGF treatment has its flaws. The possible adverse effects include systemic thromboembolic events, prolonged systemic VEGF suppression, impairment of systemic angiogenesis and organogenesis, intraocular inflammation, cataract, retinal vascular arrest, and worsening of the retinal detachment (Crunch phenomenon)

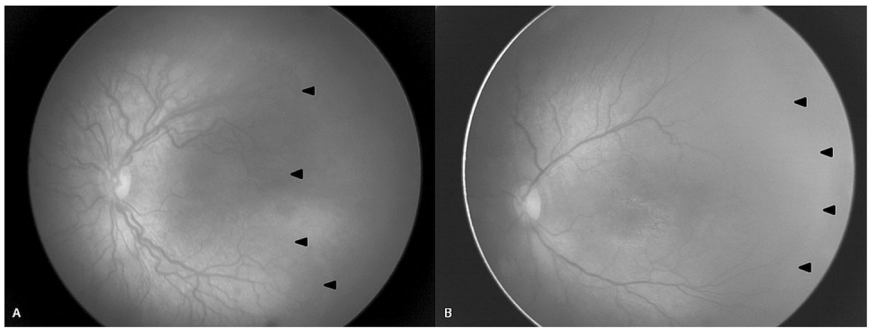

Fig. 3 Fundus images of a case of posterior zone II APROP treated with intravitreal Ranibizumab injection (0.25 mg). A The fundus image shows prominent arteriolar tortuosity, venous dilation, indistinct junction temporal to the macula (black arrowheads), and vascular shunting loops at the junction supero-temporally. **B** Four weeks post injection, the vessel tortuosity and dilation has significantly reduced, and normal vascularization has progressed anteriorly (black arrowheads).

[92–96]. VEGF is essential for the normal ongoing organogenesis in the lungs, brain, and kidney of the growing child [97]. The suppression of systemic VEGF due to systemic absorption of the intraocular anti-VEGF drug may thus have untoward neuro-developmental outcomes in the long run [98]. Some research networks have shown that preterm infants treated with anti-VEGF therapy especially BCZ as compared to laser treatment have higher likelihood of neuro-developmental disabilities [99, 100]. However, other studies report no difference in infant neurodevelopment with anti-VEGF therapy as compared to observation or laser treatment [101–103]. Injection procedure-related complications of anti-VEGF injection include lenticular injury, vitreous haemorrhage, and endophthalmitis [92, 95, 96, 104]. Since majority of the injection procedures are performed under topical anaesthesia in NICU settings, the risk of infection and lenticular injury in an awake and moving infant remains a concern.

Combined treatment

The combination treatment can be either simultaneous or sequential. The anti-VEGF agent provides immediate resolution of the TVL and 'plus' disease (as early as day one after injection), while laser treatment helps in complete regression of the new vessels and takes care of the avascular anterior retina permanently [14, 105, 106]. Wutthiworawong et al. did a retrospective study of 23 zone I APROP eyes treated with near-confluent diode laser photocoagulation in the avascular retina immediately followed by intravitreal BCZ 0.5 mg injection [14]. The mean PMA at treatment was 35.83 weeks (32–43 weeks). The proliferative disease regressed completely by a mean duration of 4.9 weeks in all the eyes. Only two eyes had disc-macular drag. The aggressive combination treatment prevented progression to advanced ROP in all eyes. The combination treatment takes care of certain factors that preclude a thorough laser treatment such as the presence of TVL, pupillary rigidity, and vitreous haemorrhage [107].

Another type of combination therapy is sequential or rescue treatment. The rescue treatment is often governed by the primary treatment and is often a modality different from the primary treatment, i.e., laser for babies primarily treated with an anti-VEGF injection and anti-VEGF injection for babies with disease progression despite adequate laser. Spandau et al. retrospectively reviewed records of 16 zone I APROP eyes of eight infants treated with different approaches (mean PMA at treatment was 34 weeks): laser alone (two eyes), laser followed by anti-VEGF salvage for lack of regression (four eyes) and anti-VEGF treatment (eight eyes) followed if required with additional laser if disease continued to progress (4 eyes) [108]. The disease regressed in all eyes and macular drag developed in only one eye treated with laser alone [108].

Intravitreal anti-VEGF can be an effective treatment for laser failure in APROP eyes such as those with increasing vascularity and those developing vitreoretinal traction following laser [86, 107]. Kara et al. studied seven eyes of four infants with zone I/posterior zone II APROP who had laser treatment failure and were retreated with intravitreal BCZ 0.625 mg injection [86]. The disease regressed in five eyes of three infants (within a week) but both eyes of an infant with zone I APROP progressed to stage 4a requiring vitrectomy. There were no complications noted till 6 months follow-up.

Intravitreal RBZ may be considered as the primary treatment of APROP associated with vitreous haemorrhage followed closely by laser treatment once the media clarity permits [107, 109]. Xu et al. reported the efficacy of anti-VEGF treatment in 37 eyes of 20 infants with APROP who had associated vitreous haemorrhage. RBZ (0.25 mg) was used which led to rapid resorption of the vitreous haemorrhage [109]. This was followed by laser photocoagulation at a mean follow-up of 4.8 weeks after RBZ injection. Second

laser treatment was required in ten eyes. With this approach, all eyes had disease regression with mild macular drag only in three eyes, and none of the eyes developed advanced-stage ROP. Garcia Gonzalez et al. reported the efficacy of FFA guided laser treatment in cases of reactivation of disease after intravitreal BCZ treatment for 16 eyes of 8 infants with APROP [110]. Reactivation was noted in 50% of the eyes for which laser was performed in the avascular anterior retina. The disease regressed finally in all eyes.

Limitations

Combination treatment also has its shortcomings. Rescue anti-VEGF treatment especially if delayed may acutely worsen the TRD [87, 107]. This occurs due to rapid neovascular tissue involution and cortical vitreous contraction. It is also believed that the rescue anti-VEGF therapy might have systemic side effects due to increased systemic absorption of the anti-VEGF agent from the inflamed ablated retina [105, 111]. Also, this may allow a greater washout/escape of the anti-VEGF drug from the eye and hence a higher risk for recurrences [74].

Comparison of laser and anti-VEGF treatment

There are a couple of studies that have performed a comparison between the laser and anti-VEGF therapy in APROP exclusively but all are retrospective in design [27, 56, 112].

Gunay et al. did a retrospective study comparing intravitreal BCZ 0.625 mg injection (48 eyes of 25 infants) with 801 nm diode laser photocoagulation (30 eyes of 15 infants) in zone I/posterior zone II APROP [56]. Although all eyes undergoing anti-VEGF therapy had initial disease regression, reactivation was noted in six eyes of three infants at a mean PMA of 39.6 weeks, which required repeat injection of intravitreal BCZ. In the laser treatment group, four eyes needed repeat laser at 1 week and two eyes developed stage 4A ROP, which remained stable till the last follow-up. Myopic refractive error was significantly higher in the laser treatment group (-6.66 ± 4.96 D) vs. anti-VEGF treatment group (0.42 ± 3.42 D) at 2 years ($P = 0.001$). Also, anisometropia and strabismus occurred significantly greater in the laser treatment group.

Nicoara et al. performed a retrospective study that included 12 eyes of 6 infants with APROP who underwent laser photocoagulation (followed up till 60 weeks post treatment) and 34 eyes of 17 infants with APROP who were treated with intravitreal BCZ 0.625 mg (followed up till 80 weeks post treatment) [27]. In the laser group, disease regression with one laser sitting was achieved in nine eyes (75%). Two of these three eyes in which laser retreatment was performed regressed further. In the intravitreal BCZ injection group, the disease regressed in 29 eyes (85.29%) and failed to regress in 5 eyes (14.71%) with a single injection. Three of these five eyes could be salvaged with laser retreatment. No late recurrences were noted until the last follow-up.

Shah et al. recently performed a historically controlled cohort study in South India comparing laser photocoagulation (performed in 168 eyes of 84 infants during the period 2002-2010) to anti-VEGF therapy (performed in 230 eyes of 115 infants during the period 2010–2018) for treatment of APROP [112]. The incidence of retinal detachment was 10% in the laser treatment cohort as compared to 1% in anti-VEGF cohort. Despite the babies being more preterm, with lower BW and having more oxygen exposure in the anti-VEGF cohort, the anti-VEGF treatment seemed to have better anatomical outcomes than laser. However, there could have been temporal difference in disease characteristics and management that may have biased the results. Also, the anti-VEGF cohort had additional laser treatment for disease recurrence in 21.4% infants and therefore the RD incidence data does not depict a true comparison of the laser vs. anti-VEGF monotherapy [112].

Surgery

Vitrectomy is required in cases of APROP with TRD and vitreous haemorrhage. Vitrectomy has multiple possible mechanisms by which it helps in the management: removal of the vitreous framework responsible for traction, removal of the vitreous gel which acts as a sink for VEGF, clearing–off the vitreous haemorrhage and prevention of the vascular re-proliferation by removing the traction and its consequent trophic effect on the new vessels [23, 113].

A greater area of avascular retina in zone I/posterior zone II disease leads to high VEGF load in the vitreous cavity. This, in turn, causes extensive fibrovascular proliferation at the junction. Also, the neovascular fronds are often close to the arcades and threaten the macula. If not treated aggressively in time, such cases progress to stage 4/5 disease. The results of vitrectomy in APROP cases have often been reported to be poor (Table 4) [23, 114, 115].

Surgical debulking of the vitreous and the extent of anterior growth of the FVT towards the vitreous base may be the deciding factor for the anatomical outcome [23, 114, 116, 117]. Azuma et al. did a retrospective study of 22 eyes of 15 infants who developed TRD despite timely laser treatment and underwent either lens-sparing vitrectomy (LSV, 6 eyes) or lensectomy vitrectomy (LV, 16 eyes) [23]. The surgery in LSV group was limited to core vitrectomy, and therefore the FVT continued to grow along the anterior vitreous skirt and led to progression to stage 5 disease. The LV group had thorough vitreous removal and may have therefore led to TRD regression in all eyes.

Table 4 Review of literature on the surgical management of aggressive posterior retinopathy of prematurity.

Author, year	Number of eyes/infants	Mean BW (g)	Mean GA (weeks)	Inclusion criteria	PMA at surgery (weeks)	Vitrectomy details	Follow-up	Favourable outcome	Unfavourable outcome
Azuma, 2006 [23]	22/15; Stage 4a: 15 Stage 4b: 7	773	25	Progressive stage 4 disease despite laser (FVP extends for ≥6 continuous clock hours)	38.6	25G LV 16 eyes, LSV 6 eyes	9 months	Retina flat in 100% of LV cases, 56% had normal foveal configuration	100% LSV eyes progressed to stage 5; even with re-surgery large peripheral TRD in all eyes Slight VC bleed in all eyes (resolved in 2–3 weeks)
Micelli, 2007 [116]	13/9	725.8	24.1	Progressive stage 3 disease despite laser but without TRD	–	20G LSV	13.5 months	Retina attached in all eyes	None
Nishina, 2009 [117]	11/7; Stage 4a: 10 Stage 4b: 1	734	25	Progressive stage 4 disease laser (FVP extends for 6–10 continuous clock hours)	38	25G LV	9.2 months	Markedly decreased vascular activity within 1–2 wks, regression in all eyes	Drag in 2 eyes
Yokoi, 2010 [115]	43/31	808.7	25.1	Well lasered stage 4 APROP[i]; FVP not attached to vitreous base	39.7	LV	At least 6 months	Initial regression in all eyes; dense LP was a significant factor in the decreased recurrence	Recurrence in 8 eyes (18%) at 2–8 weeks; Re-surgery in 3 eyes; only one had regression
Azuma, 2013 [114]	103/57	706	24	TRD despite laser	–	LV	–	In 39 of 58 eyes (67.2%), the FVP had not reached the vitreous base preoperatively, and foveal formation occurred postoperatively with nearly age-appropriate VA (range, 20/250 to 20/40).	In 17 of 58 eyes (29.3%), the FVP had reached the vitreous base, and no fovea formed (VA range, 20/2000 to 20/250).

BW birth weight, *GA* gestational age, *PMA* post-menstrual age, *FVP* fibrovascular proliferation, *LV* lensectomy vitrectomy, *LSV* lens-sparing vitrectomy, *TRD* tractional retinal detachment, *VC* vitreous cavity, *APROP* aggressive posterior retinopathy of prematurity, *LP* laser photocoagulation, *VA* visual acuity.

Nishina et al. also reported 100% TRD regression with early LV in 11 eyes of 7 infants with APROP with stage 4 disease [117]. This highlights the importance of prompt and thorough removal of vitreous around the FVT in TRD associated with APROP. In the largest of the series of 103 eyes with APROP associated TRD, Azuma et al. reported that when an early surgery is performed before the FVT grows into the vitreous base, the chance of regression of disease remains high [114]. While if the FVT grows into the vitreous base, then the anatomical and visual outcome remains poor [114].

Another category of cases, where surgical success is limited, are the cases with severe recurrent fibrovascular proliferation despite combined anti-VEGF and laser treatment [118]. It is possible that excess anti-VEGF suppression in the immature retina not only causes widespread capillary bed loss but also mal-development of retinal vessels in the form of aneurysms and loops [118]. This leads to persistent retinal ischaemia and severe recurrence of fibrovascular proliferation which may not have a favourable anatomical outcome with vitrectomy as well.

Peripapillary TRDs are a surgical dilemma since the retina along the arcades is pulled up towards the disc with tightly adherent hyaloid and extensive avascular peripheral retina [119]. Careful dissection of the hyaloid with 25G/27G instruments may open up the contracted retina without iatrogenic retinal breaks [119]. With retinal reattachment, the vascular development may progress and the attached tissues may perfuse and provide some functional vision.

The limitations of vitrectomy in APROP include post-operative vitreous cavity bleed, recurrence of disease, and rebleed [23, 115]. The extensive FVT if vigorously manipulated and not aggressively treated with diathermy, may have post-operative vitreous cavity bleed. Azuma et al. reported post-operative bleed in 100% cases undergoing LV, but the bleed was slight and resolved spontaneously within 2–3 weeks in all eyes [23]. However, persistent preretinal bleed may be detrimental. It acts as a source of fibrotic growth factors which may cause fibrosis within the residual cortical vitreous and lead to failure of reattachment or new-onset re-detachment. Rebleed may occur if the FVT fails to regress or new FVT develops because of persistent avascular retinal areas which continue to produce VEGF. Yokoi et al. studied the risk factors for recurrence of FVT after early LV in 43 eyes with APROP related TRD where the FVT had not grown initially into the vitreous base area [115]. The recurrence rate was 18% for the FVT, which developed between 2 and 8 weeks after surgery and led to irregular TRD between the disc and the FVT. On multivariate analysis, a thorough laser to the avascular retina and vascular loops preoperatively was the only factor significantly preventing recurrence of the disease.

Lensectomy may not be required in early cases without extensive TRD [22, 116]. With 20G LSV, Micelli et al. reported 100% regression rates and no complications. Similarly, Drenser et al. performed LSV in eight eyes with APROP with stage 4A/4B ROP and achieved 100% retinal reattachment [22]. Since in early cases, the FVT and the TRD are posterior to the equator, lens removal may not be required.

Apart from the operational difficulties involved in vitrectomy in small eyes of neonates with florid retinal neovascularization, there also exist general anaesthesia risks in such premature babies [120, 121]. Premature infants cannot tolerate repeated and long general anaesthesia sessions [121]; thus surgical intervention may have to be performed preferably in a single sitting in both eyes and completed within a shorter duration [122].

Long-term visual and refractive outcomes

The visual outcome depends upon the morphology of the macula. Besides anatomical attachment of the macula, the macular vascular development remains a prime factor. As compared to non-APROP cases, the visual outcomes in APROP cases are often poor.

Refractive errors commonly occur in ROP and more so after laser treatment [54, 123]. The most common refractive error noted after laser treatment of zone I APROP is astigmatism (with-the–rule more often than against-the-rule), which develops in around 90% of the treated cases [123]. The mean spherical equivalent and average astigmatism reach as high as −6 dioptres (D) and −2D, respectively [123]. Shah et al. reported a best-corrected Snellen visual acuity >20/40 at a mean follow-up of 6.9 years in around 80% of the laser treated zone I APROP cases [123]. Gunn et al. reported the development of moderate myopia (>−3D) in 40% of APROP eyes treated with laser [54]. The cause for poor visual outcome after laser treatment may include disc pallor, disc-macular dragging, hypoplastic macula, and development of cataract [123].

The visual outcome following treatment of small zone I APROP with VEGF monotherapy may be limited due to hypoplastic macular vessels and disturbed capillary-free zone in the macula [50]. Despite regression of the disease, the vascular abnormalities may persist, and the macular arcades may fail to develop [50].

The outcomes after vitrectomy in APROP not only depend upon the preoperative stage of ROP (stage 4A or 4B) but also on the preoperative extent of the fibrovascular proliferation [114]. If the FVT does not reach till the vitreous base, then a flat macula with foveal development is more likely to occur with resultant age-appropriate visual

acuity [114]. The post-operative visual acuity ranges from 20/250 to 20/40 in eyes with total reattachment [114]. Central steady fixation develops in majority of the eyes with clinical fovea formation with no macular drag [23].

Even if the anatomical outcomes are favourable, a long-term follow-up is necessary to detect refractive errors and associated strabismus. Late-onset rhegmatogenous retinal detachment has been reported after uneventful regression of APROP following laser treatment [124]. The visual rehabilitation may be performed with spectacles or aphakic contact lenses in children undergoing lensectomy. Amblyopia treatment with patching should be provided to those with anisometropia or ametropic amblyopia.

Prevention

Following the best neonatal care practices may prevent ROP and especially APROP [125, 126]. However, there is no high-level evidence to support any particular intervention aimed at reducing the risk of ROP [127]. Since APROP cases are often premature babies with multiple co-morbidities; the primary prevention will be through avoidance of preterm birth by good antenatal practices and through the provision of better neonatal intensive care services to prevent/manage the co-morbidities [126, 128]. This is supported by the clear disparity observed in the incidence of APROP between NICUs of tertiary care centres and the peripheral nurseries [10, 11]. Since dysregulated oxygen supplementation due to lack of oxygen saturation monitors and unavailability of oxygen blenders is a significant risk factor for APROP development [43], NICUs need to follow stringent guidelines regarding the need for oxygen supplementation, adequate levels of oxygen concentration, required arterial oxygen saturation and the duration of supplementation. The clinical studies are not conclusive regarding the adequate oxygen saturation that needs to be maintained for preterm infants requiring oxygen supplementation [129]. In a meta-analysis study, Chen et al. reported that in preterm infants during the first several weeks after birth, low oxygen saturation (70%–96%) should be kept to prevent hyperoxia and retinal capillaries obliteration [129]. Although by maintaining lower arterial oxygen saturation the risk of ROP and severe ROP decreases, there occurs an increase in neonatal mortality [127]. During and after 32 weeks PMA, high-oxygen saturation (94–99%) is desirable as it prevents progression of vaso-proliferation by mitigating the retinal ischaemia [129]. The NICU team needs to be educated, and good clinical practices relating to oxygen supplementation, nutrition, and management of sepsis should be enforced [126, 128].

The secondary prevention will include a timely screening of the at-risk infants for APROP. It may be advisable to screen the extremely premature infants with multiple co-morbidities a little earlier than usual (3 weeks post-natal rather than at 4 weeks, but not before 31 weeks) depending upon the age and timing of APROP noted in different healthcare settings [39, 40]. The tertiary prevention aims at avoiding progression to advanced stages of ROP (stage 4/5) and includes prompt treatment of APROP with laser/anti-VEGF monotherapy or combination therapy. A multidisciplinary approach involving the ophthalmologist, neonatologist and anaesthetist needs to be taken.

Future directions

APROP is a challenging disease, and it is imperative that every NICU should have a regular ROP screening programme to detect APROP in time. Although laser treatment remains the gold standard treatment for type 1 ROP, anti-VEGF agents are emerging as first-line treatment option for APROP with definite advantages in terms of preserved visual field and decreased myopic refractive error. With the rapidly increasing use of anti-VEGF agents for the treatment of APROP, there is a need to determine the ideal safe dosage, frequency, and type of agent with the help of randomized control trials. Newer longer acting anti-VEGF drugs need to be explored to prevent frequent recurrences with anti-VEGF monotherapy. Mutational analysis may provide further understanding regarding the genetic mechanisms for aggressive retinopathy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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References

1. International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol. 2005;123:991–9.
2. Morizane H. [Initial sign and clinical course of the most severe form of acute proliferative retrolental fibroplasia (type II) (author's transl)]. Nippon Ganka Gakkai Zasshi. 1976;80:54–61.
3. Shah PK, Narendran V, Saravanan VR, Raghuram A, Chattopadhyay A, Kashyap M, et al. Fulminate retinopathy of prematurity—clinical characteristics and laser outcome. Indian J Ophthalmol. 2005;53:261–5.
4. Nissenkorn I, Kremer I, Gilad E, Cohen S, Ben-Sira I. 'Rush' type retinopathy of prematurity: report of three cases. Br J Ophthalmol. 1987;71:559–62.
5. Darlow B, Cust A, Donoghue D. Improved outcomes for very low birthweight infants: evidence from New Zealand national population based data. Arch Dis Child Fetal Neonatal Ed. 2003;88:F23–F28.

6. Harper RG, Rehman KU, Sia C, Buckwald S, Spinazzola R, Schlessel J, et al. Neonatal outcome of infants born at 500 to 800 grams from 1990 through 1998 in a tertiary care center. J Perinatol J Calif Perinat Assoc. 2002;22:555–62.
7. Ahn YJ, Hong KE, Yum HR, Lee JH, Kim KS, Youn YA, et al. Characteristic clinical features associated with aggressive posterior retinopathy of prematurity. Eye. 2017;31:924–30.
8. Holmström G, Hellström A, Jakobsson P, Lundgren P, Tornqvist K, Wallin A. Five years of treatment for retinopathy of prematurity in Sweden: results from SWEDROP, a national quality register. Br J Ophthalmol. 2016;100:1656–61.
9. Gunay M, Celik G, Tuten A, Karatekin G, Bardak H, Ovali F. Characteristics of severe retinopathy of prematurity in infants with birth weight above 1500 grams at a referral center in Turkey. PLoS ONE. 2016;11. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4993354/. Accessed 16 Mar 2019.
10. Murthy KR, Murthy PR, Shah DA, Nandan MR, S NH, Benakappa N. Comparison of profile of retinopathy of prematurity in semiurban/rural and urban NICUs in Karnataka, India. Br J Ophthalmol. 2013;97:687–9.
11. Sivanandan S, Chandra P, Deorari AK, Agarwal R. Retinopathy of prematurity: AIIMS, New Delhi experience. Indian Pediatr. 2016;53:S123–S128.
12. Dwivedi A, Dwivedi D, Lakhtakia S, Chalisgaonkar C, Jain S. Prevalence, risk factors and pattern of severe retinopathy of prematurity in eastern Madhya Pradesh. Indian J Ophthalmol. 2019;67:819–23.
13. Hungi B, Vinekar A, Datti N, Kariyappa P, Braganza S, Chinnaiah S, et al. Retinopathy of prematurity in a rural Neonatal Intensive Care Unit in South India–a prospective study. Indian J Pediatr. 2012;79:911–5.
14. Wutthiworawong B, Thitiratsanont U, Saovaprut C, Subhangkasen I, Geyuraphun B, Ampornprut A, et al. Combine intravitreal bevacizumab injection with laser treatment for aggressive posterior retinopathy of prematurity (AP-ROP). J Med Assoc Thai. 2011;94:S15–21.
15. Padhi TR, Jain L, Behera UC, Pradhan L. Retinopathy of prematurity profile and trend over the years: experience from a two tier city in Eastern India. Indian Pediatr. 2016;53:S76–S79.
16. Hartnett ME. Advances in understanding and management of retinopathy of prematurity. Surv Ophthalmol. 2017;62:257–76.
17. Kumar P, Sankar MJ, Deorari A, Azad R, Chandra P, Agarwal R, et al. Risk factors for severe retinopathy of prematurity in preterm low birth weight neonates. Indian J Pediatr. 2011;78:812–6.
18. Kim SJ, Port AD, Swan R, Campbell JP, Chan RVP, Chiang MF. Retinopathy of prematurity: a review of risk factors and their clinical significance. Surv Ophthalmol. 2018;63:618–37.
19. Flynn JT, Chan-Ling T. Retinopathy of prematurity: two distinct mechanisms that underlie zone 1 and zone 2 disease. Am J Ophthalmol. 2006;142:46–59.
20. Lundgren P, Lundberg L, Hellgren G, Holmström G, Hård A-L, Smith LE, et al. Aggressive posterior retinopathy of prematurity is associated with multiple infectious episodes and thrombocytopenia. Neonatology. 2016;111:79–85.
21. Vinekar A, Hegde K, Gilbert C, Braganza S, Pradeep M, Shetty R, et al. Do platelets have a role in the pathogenesis of aggressive posterior retinopathy of prematurity? Retina. 2010;30:S20–S23.
22. Drenser KA, Trese MT, Capone A. Aggressive posterior retinopathy of prematurity. Retina. 2010;30:S37–40.
23. Azuma N, Ishikawa K, Hama Y, Hiraoka M, Suzuki Y, Nishina S. Early vitreous surgery for aggressive posterior retinopathy of prematurity. Am J Ophthalmol. 2006;142:636–43.
24. Borroni C, Carlevaro C, Morzenti S, De Ponti E, Bozzetti V, Console V, et al. Survey on retinopathy of prematurity (ROP) in Italy. Ital J Pediatr. 2013;39:43.
25. Shah PK, Narendran V, Kalpana N. Aggressive posterior retinopathy of prematurity in large preterm babies in South India. Arch Dis Child Fetal Neonatal Ed. 2012;97:F371–375.
26. Sanghi G, Dogra MR, Das P, Vinekar A, Gupta A, Dutta S. Aggressive posterior retinopathy of prematurity in Asian Indian babies: spectrum of disease and outcome after laser treatment. Retina. 2009;29:1335–9.
27. Nicoară SD, Ştefănuţ AC, Nascutzy C, Zaharie GC, Toader LE, Drugan TC. Regression rates following the treatment of aggressive posterior retinopathy of prematurity with bevacizumab versus laser: 8-year retrospective analysis. Med Sci Monit Int Med J Exp Clin Res. 2016;22:1192–209.
28. Jalali S, Kesarwani S, Hussain A. Outcomes of a protocol-based management for zone 1 retinopathy of prematurity: the Indian Twin Cities ROP Screening Program report number 2. Am J Ophthalmol. 2011;151:719–724.e2.
29. Silveira RC, Fortes Filho JB, Procianoy RS. Assessment of the contribution of cytokine plasma levels to detect retinopathy of prematurity in very low birth weight infants. Investig Ophthalmol Vis Sci. 2011;52:1297–301.
30. Chen J, Smith LEH. Retinopathy of prematurity. Angiogenesis. 2007;10:133–40.
31. Hellstrom A, Perruzzi C, Ju M, Engstrom E, Hard AL, Liu JL, et al. Low IGF-I suppresses VEGF-survival signaling in retinal endothelial cells: direct correlation with clinical retinopathy of prematurity. Proc Natl Acad Sci USA. 2001;98:5804–8.
32. Port AD, Chan RVP, Ostmo S, Choi D, Chiang MF. Risk factors for retinopathy of prematurity: insights from outlier infants. Graefes Arch Clin Exp Ophthalmol. 2014;252:1669–77.
33. Battinelli EM, Markens BA, Italiano JE. Release of angiogenesis regulatory proteins from platelet alpha granules: modulation of physiologic and pathologic angiogenesis. Blood. 2011;118:1359–69.
34. Radziwon-Balicka A, Moncada de la Rosa C, Jurasz P. Platelet-associated angiogenesis regulating factors: a pharmacological perspective. Can J Physiol Pharmacol. 2012;90:679–88.
35. Kondo H, Kusaka S, Yoshinaga A, Uchio E, Tawara A, Tahira T. Genetic variants of FZD4 and LRP5 genes in patients with advanced retinopathy of prematurity. Mol Vis. 2013;19:476–85.
36. Drenser KA, Vinikar A, Dailey W, Trese MT Jr. Aggressive posterior retinopathy of prematurity. Investig Ophthalmol Vis Sci. 2008;49:1388–1388. AC
37. Mora JS, Waite C, Gilbert CE, Breidenstein B, Sloper JJ. A worldwide survey of retinopathy of prematurity screening. Br J Ophthalmol. 2018;102:9–13.
38. Fierson WM. American Academy of Pediatrics Section on Ophthalmology, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus, American Association of Certified Orthoptist Screening examination of premature infants for retinopathy of prematurity. Pediatrics. 2013;131:189–95.
39. Wilkinson AR, Haines L, Head K, Fielder AR, Guideline Development Group of the Royal College of Paediatrics and Child Health, Royal College of Ophthalmologists. et al. UK retinopathy of prematurity guideline. Eye. 2009;23:2137–9.
40. Singh AK (ed). Guidelines for universal eye screening in newborns including retinopathy of prematurity. 1st Ed. (Rashtriya Bal Swasthya Karyakram, Ministry of Health & Family Welfare, Government of India, 2017).
41. Xu Y, Zhou X, Zhang Q, Ji X, Zhang Q, Zhu J, et al. Screening for retinopathy of prematurity in China: a neonatal units-based prospective study. Investig Ophthalmol Vis Sci. 2013;54:8229–36.
42. National Neonatology Forum. Evidence-based clinical practise guidelines, retinopathy of prematurity. India: National Neonatology Forum; 2010.

43. Sanghi G, Dogra MR, Katoch D, Gupta A. Aggressive posterior retinopathy of prematurity in infants ≥1500 g birth weight. Indian J Ophthalmol. 2014;62:254–7.
44. Kychenthal A, Dorta P, Katz X. Zone I retinopathy of prematurity: clinical characteristics and treatment outcomes. Retina. 2006;26:S11–15.
45. Yokoi T, Katagiri S, Hiraoka M, Nakayama Y, Hosono K, Hotta Y, et al. Atypical form of retinopathy of prematurity with severe fibrovascular proliferation in the optic disk region. Retina. 2018;38:1605–12.
46. Madan A, Penn JS. Animal models of oxygen-induced retinopathy. Front Biosci J Virtual Libr. 2003;8:d1030–1043.
47. Sanghi G, Dogra MR, Dogra M, Katoch D, Gupta A. A hybrid form of retinopathy of prematurity. Br J Ophthalmol. 2012;96:519–22.
48. Ahn SJ, Kim JH, Kim S-J, Yu YS. Capillary-free vascularized retina in patients with aggressive posterior retinopathy of prematurity and late retinal capillary formation. Korean J Ophthalmol. 2013;27:109–15.
49. Lorenz B, Stieger K, Jäger M, Mais C, Stieger S, Andrassi-Darida M. Retinal vascular development with 0.312 MG intravitreal bevacizumab to treat severe posterior retinopathy of prematurity: a Longitudinal Fluorescein Angiographic Study. Retina. 2017;37:97–111.
50. Yokoi T, Hiraoka M, Miyamoto M, Yokoi T, Kobayashi Y, Nishina S, et al. Vascular abnormalities in aggressive posterior retinopathy of prematurity detected by fluorescein angiography. Ophthalmology. 2009;116:1377–82.
51. Perente I, Eris E, Seymen Z, Cevik SG, Bekmez S. Aggressive posterior retinopathy of prematurity treated with intravitreal bevacizumab: late period fluorescein angiographic findings. Graefes Arch Clin Exp Ophthalmol. 2019;257:1141–6.
52. O'Keefe M, Kirwan C. Diode laser versus cryotherapy in treatment of ROP. Br J Ophthalmol. 2006;90:402–3.
53. Sanghi G, Dogra MR, Katoch D, Gupta A. Aggressive posterior retinopathy of prematurity: risk factors for retinal detachment despite confluent laser photocoagulation. Am J Ophthalmol. 2013;155:159–164.e2.
54. Gunn DJ, Cartwright DW, Gole GA. Prevalence and outcomes of laser treatment of aggressive posterior retinopathy of prematurity. Clin Exp Ophthalmol. 2014;42:459–65.
55. Vinekar A, Jayadev C, Mangalesh S, Kumar AK, Bauer N, Capone A, et al. Comparing the outcome of single versus multiple session laser photoablation of flat neovascularization in zone 1 aggressive posterior retinopathy of prematurity: a Prospective Randomized Study. Retina. 2015;35:2130–6.
56. Gunay M, Celik G, Gunay BO, Aktas A, Karatekin G, Ovali F. Evaluation of 2-year outcomes following intravitreal bevacizumab (IVB) for aggressive posterior retinopathy of prematurity. Arq Bras Oftalmol. 2015;78:300–4.
57. Pandya HK, Faia LJ, Robinson J, Drenser KA. Macular development in aggressive posterior retinopathy of prematurity. BioMed Res Int. 2015;2015:808639.
58. Vinekar A, Trese MT, Capone A. Photographic Screening for Retinopathy of Prematurity (PHOTO-ROP) Cooperative Group. Evolution of retinal detachment in posterior retinopathy of prematurity: impact on treatment approach. Am J Ophthalmol. 2008;145:548–55.
59. Naug HL, Browning J, Gole GA, Gobé G. Vitreal macrophages express vascular endothelial growth factor in oxygen-induced retinopathy. Clin Exp Ophthalmol. 2000;28:48–52.
60. Austeng D, Källen KBM, Ewald UW, Wallin A, Holmström GE. Treatment for retinopathy of prematurity in infants born before 27 weeks of gestation in Sweden. Br J Ophthalmol. 2010;94:1136–9.
61. Gunn DJ, Cartwright DW, Yuen SA, Gole GA. Treatment of retinopathy of prematurity in extremely premature infants over an 18-year period. Clin Exp Ophthalmol. 2013;41:159–66.
62. Trigler L, Weaver RG, O'Neil JW, Barondes MJ, Freedman SF. Case series of angle-closure glaucoma after laser treatment for retinopathy of prematurity. J AAPOS Publ Am Assoc Pediatr Ophthalmol Strabismus. 2005;9:17–21.
63. Quinn GE, Dobson V, Davitt BV, Wallace DK, Hardy RJ, Tung B, et al. Progression of myopia and high myopia in the Early Treatment for Retinopathy of Prematurity study: findings at 4 to 6 years of age. J AAPOS. 2013;17:124–8.
64. Hwang CK, Hubbard GB, Hutchinson AK, Lambert SR. Outcomes after intravitreal bevacizumab versus laser photocoagulation for retinopathy of prematurity: a 5-year retrospective analysis. Ophthalmology. 2015;122:1008–15.
65. Sukgen EA, Koçluk Y. The vascularization process after intravitreal ranibizumab injections for aggressive posterior retinopathy of prematurity. Arq Bras Oftalmol. 2017;80:30–34.
66. Dikci S, Ceylan OM, Demirel S, Yılmaz T. Which dose of bevacizumab is more effective for the treatment of aggressive posterior retinopathy of prematurity: lower or higher dose? Arq Bras Oftalmol. 2018;81:12–17.
67. Yetik H, Gunay M, Sirop S, Salihoglu Z. Intravitreal bevacizumab monotherapy for type-1 prethreshold, threshold, and aggressive posterior retinopathy of prematurity - 27 month follow-up results from Turkey. Graefes Arch Clin Exp Ophthalmol. 2015;253:1677–83.
68. Mintz-Hittner HA, Kuffel RR. Intravitreal injection of bevacizumab (avastin) for treatment of stage 3 retinopathy of prematurity in zone I or posterior zone II. Retina. 2008;28:831–8.
69. Travassos A, Teixeira S, Ferreira P, Regadas I, Travassos AS, Esperancinha FE, et al. Intravitreal bevacizumab in aggressive posterior retinopathy of prematurity. Ophthalmic Surg Lasers Imaging. 2007;38:233–7.
70. Mintz-Hittner HA, Kennedy KA, Chuang AZ. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med. 2011;364:603–15.
71. Harder BC, von Baltz S, Jonas JB, Schlichtenbrede FC. Intravitreal bevacizumab for retinopathy of prematurity. J Ocul Pharmacol Ther. 2011;27:623–7.
72. Park SW, Jung HH, Heo H. Fluorescein angiography of aggressive posterior retinopathy of prematurity treated with intravitreal anti-VEGF in large preterm babies. Acta Ophthalmol. 2014;92:810–3.
73. Nicoară SD, Nascutzy C, Cristian C, Irimescu I, Ştefănuţ AC, Zaharie G, et al. Outcomes and prognostic factors of intravitreal bevacizumab monotherapy in zone I stage 3+ and aggressive posterior retinopathy of prematurity. J Ophthalmol. 2015;2015:102582.
74. Mintz-Hittner HA, Geloneck MM, Chuang AZ. Clinical management of recurrent retinopathy of prematurity after intravitreal bevacizumab monotherapy. Ophthalmology. 2016;123:1845–55.
75. Li X-J, Yang X-P, Sun S, Lyu X-B, Jia H. Intravitreal ranibizumab for aggressive posterior retinopathy of prematurity. Chin Med J. 2016;129:2879–81.
76. Tong Q, Yin H, Zhao M, Li X, Yu W. Outcomes and prognostic factors for aggressive posterior retinopathy of prematurity following initial treatment with intravitreal ranibizumab. BMC Ophthalmol. 2018;18:150.
77. Chen S-N, Lian I, Hwang Y-C, Chen Y-H, Chang Y-C, Lee K-H, et al. Intravitreal anti-vascular endothelial growth factor treatment for retinopathy of prematurity: comparison between Ranibizumab and Bevacizumab. Retina. 2015;35:667–74.
78. Erol MK, Coban DT, Sari ES, Bilgin AB, Dogan B, Ozdemir O, et al. Comparison of intravitreal ranibizumab and bevacizumab

treatment for retinopathy of prematurity. Arq Bras Oftalmol. 2015;78:340–3.
79. Sukgen EA, Koçluk Y. Comparison of clinical outcomes of intravitreal ranibizumab and aflibercept treatment for retinopathy of prematurity. Graefes Arch Clin Exp Ophthalmol. 2019;257:49–55.
80. Vural A, Perente İ, Onur İU, Eriş E, Seymen Z, Hergünsel GO, et al. Efficacy of intravitreal aflibercept monotherapy in retinopathy of prematurity evaluated by periodic fluorescence angiography and optical coherence tomography. Int. Ophthalmol. 2019;39:2161–9.
81. Spandau U. What is the optimal dosage for intravitreal bevacizumab for retinopathy of prematurity? Acta Ophthalmol. 2013;91:e154.
82. Micieli JA, Surkont M, Smith AF. A systematic analysis of the off-label use of bevacizumab for severe retinopathy of prematurity. Am J Ophthalmol. 2009;148:536–543.e2.
83. Wallace DK, Kraker RT, Freedman SF, Crouch ER, Hutchinson AK, Bhatt AR, et al. Assessment of lower doses of intravitreous bevacizumab for retinopathy of prematurity: a phase 1 dosing study. JAMA Ophthalmol. 2017;135:654–6.
84. Connor AJ, Papastavrou VT, Hillier RJ, Shafiq A. Ultra-low dose of intravitreal bevacizumab in the treatment of retinopathy of prematurity. J Pediatr Ophthalmol Strabismus. 2015;52:e20–21.
85. Wallace DK, Dean TW, Hartnett ME, Kong L, Smith LE, Hubbard GB, et al. A dosing study of bevacizumab for retinopathy of prematurity: late recurrences and additional treatments. Ophthalmology. 2018;125:1961–6.
86. Kara C, Hekimoğlu E, Petriçli İS, Akıl H. Intravitreal bevacizumab as rescue therapy following treatment failure with laser photocoagulation in retinopathy of prematurity. J Curr Ophthalmol. 2018;30:80–84.
87. Honda S, Hirabayashi H, Tsukahara Y, Negi A. Acute contraction of the proliferative membrane after an intravitreal injection of bevacizumab for advanced retinopathy of prematurity. Graefes Arch Clin Exp Ophthalmol. 2008;246:1061–3.
88. Padhi TR, Das T, Rath S, Pradhan L, Sutar S, Panda KG, et al. Serial evaluation of retinal vascular changes in infants treated with intravitreal bevacizumab for aggressive posterior retinopathy of prematurity in zone I. Eye. 2016;30:392–9.
89. Ekinci DY, Vural AD, Bayramoglu SE, Onur IU, Hergunsel GO. Assessment of vascular leakage and its development with FFA among patients treated with intravitreal anti-VEGF due to aggressive posterior ROP. Int. Ophthalmol. 2019;39:2697–705.
90. Huang Q, Zhang Q, Fei P, Xu Y, Lyu J, Ji X, et al. Ranibizumab injection as primary treatment in patients with retinopathy of prematurity: anatomic outcomes and influencing factors. Ophthalmology. 2017;124:1156–64.
91. Scapini P, Nesi L, Morini M, Tanghetti E, Belleri M, Noonan D, et al. Generation of biologically active angiostatin kringle 1-3 by activated human neutrophils. J Immunol. 2002;168:5798–804.
92. Wu A-L, Wu W-C. Anti-VEGF for ROP and pediatric retinal diseases. Asia-Pac J Ophthalmol. 2018;7:145–51.
93. Wu W-C, Yeh P-T, Chen S-N, Yang C-M, Lai C-C, Kuo H-K. Effects and complications of bevacizumab use in patients with retinopathy of prematurity: a multicenter study in taiwan. Ophthalmology. 2011;118:176–83.
94. Sankar MJ, Sankar J, Chandra P. Anti-vascular endothelial growth factor (VEGF) drugs for treatment of retinopathy of prematurity. Cochrane Database Syst Rev. 2018;1:CD009734.
95. Khokhar S, Chandra P, Gupta Y, Kumawat D, Dhull C. Bilateral total cataract after intravitreal bevacizumab injection in aggressive posterior retinopathy of prematurity. J Pediatr Ophthalmol Strabismus. 2019;56:e28–e30.
96. Vanathi M, Kumawat D, Singh R, Chandra P. Iatrogenic crystalline lens injury in pediatric eyes following intravitreal injection for retinopathy of prematurity. J Pediatr Ophthalmol Strabismus. 2019;56:162–7.
97. Haigh JJ. Role of VEGF in organogenesis. Organogenesis. 2008;4:247–56.
98. Lien R, Yu M-H, Hsu K-H, Liao P-J, Chen Y-P, Lai C-C, et al. Neurodevelopmental outcomes in infants with retinopathy of prematurity and bevacizumab treatment. PLoS ONE. 2016;11. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4729687/. Accessed 2 March 2019.
99. Morin J, Luu TM, Superstein R, Ospina LH, Lefebvre F, Simard M-N, et al. Neurodevelopmental outcomes following bevacizumab injections for retinopathy of prematurity. Pediatrics. 2016;137:e20153218.
100. Natarajan G, Shankaran S, Nolen TL, Sridhar A, Kennedy KA, Hintz SR, et al. Neurodevelopmental outcomes of preterm infants with retinopathy of prematurity by treatment. Pediatrics. 2019;144:e20183537.
101. Kennedy KA, Mintz-Hittner HA.BEAT-ROP Cooperative Group Medical and developmental outcomes of bevacizumab versus laser for retinopathy of prematurity. J AAPOS. 2018;22:61–65.e1.
102. Fan Y-Y, Huang Y-S, Huang C-Y, Hsu J-F, Shih C-P, Hwang Y-S, et al. Neurodevelopmental outcomes after intravitreal bevacizumab therapy for retinopathy of prematurity: a prospective case-control study. Ophthalmology. 2019;126:1567–77.
103. Rodriguez SH, Peyton C, Lewis K, Andrews B, Greenwald MJ, Schreiber MD, et al. Neurodevelopmental outcomes comparing bevacizumab to laser for type 1 ROP. Ophthalmic Surg Lasers Imaging Retin. 2019;50:337–43.
104. Chandra P, Kumawat D, Tewari R, Azimeera S. Post-ranibizumab injection endophthalmitis in aggressive posterior retinopathy of prematurity. Indian J Ophthalmol. 2019;67:967–9.
105. Chung EJ, Kim JH, Ahn HS, Koh HJ. Combination of laser photocoagulation and intravitreal bevacizumab (Avastin) for aggressive zone I retinopathy of prematurity. Graefes Arch Clin Exp Ophthalmol. 2007;245:1727–30.
106. Altinsoy HI, Mutlu FM, Güngör R, Sarici SÜ. Combination of laser photocoagulation and intravitreal bevacizumab in aggressive posterior retinopathy of prematurity. Ophthalmic Surg Lasers Imaging. 2010:42:1–5.
107. Law JC, Recchia FM, Morrison DG, Donahue SP, Estes RL. Intravitreal bevacizumab as adjunctive treatment for retinopathy of prematurity. J AAPOS. 2010;14:6–10.
108. Spandau U, Tomic Z, Ewald U, Larsson E, Akerblom H, Holmström G. Time to consider a new treatment protocol for aggressive posterior retinopathy of prematurity? Acta Ophthalmol. 2013;91:170–5.
109. Xu Y, Kang X, Zhang Q, Huang Q, Lv J, Zhao P. Combination of intravitreal injection of ranibizumab and photocoagulation for the treatment of aggressive posterior retinopathy of prematurity with vitreous hemorrhage. J Ophthalmol. 2016;2016:5029278.
110. Garcia Gonzalez JM, Snyder L, Blair M, Rohr A, Shapiro M, Greenwald M. Prophylactic peripheral laser and fluorescein angiography after bevacizumab for retinopathy of prematurity. Retina. 2018;38:764–72.
111. Sato T, Wada K, Arahori H, Kuno N, Imoto K, Iwahashi-Shima C, et al. Serum concentrations of bevacizumab (avastin) and vascular endothelial growth factor in infants with retinopathy of prematurity. Am J Ophthalmol. 2012;153:327–333.e1.
112. Shah PK, Subramanian P, Venkatapathy N, Chan RVP, Chiang MF, Campbell JP. Aggressive posterior retinopathy of prematurity in two cohorts of patients in South India: implications for primary, secondary, and tertiary prevention. J AAPOS. 2019;23:264.e1-264.e4.

113. Hinz BJ, de Juan E, Repka MX. Scleral buckling surgery for active stage 4A retinopathy of prematurity. Ophthalmology. 1998;105:1827–30.
114. Azuma N, Ito M, Yokoi T, Nakayama Y, Nishina S. Visual outcomes after early vitreous surgery for aggressive posterior retinopathy of prematurity. JAMA Ophthalmol. 2013;131:1309–13.
115. Yokoi T, Yokoi T, Kobayashi Y, Nishina S, Azuma N. Risk factors for recurrent fibrovascular proliferation in aggressive posterior retinopathy of prematurity after early vitreous surgery. Am J Ophthalmol. 2010;150:10–15.e1.
116. Micelli Ferrari T, Furino C, Lorusso VV, Dammacco R, Sborgia G, Sborgia L, et al. Three-port lens-sparing vitrectomy for aggressive posterior retinopathy of prematurity: early surgery before tractional retinal detachment appearance. Eur J Ophthalmol. 2007;17:785–9.
117. Nishina S, Yokoi T, Yokoi T, Kobayashi Y, Hiraoka M, Azuma N. Effect of early vitreous surgery for aggressive posterior retinopathy of prematurity detected by fundus fluorescein angiography. Ophthalmology. 2009;116:2442–7.
118. Tanaka S, Yokoi T, Katagiri S, Yoshida T, Nishina S, Azuma N. Severe recurrent fibrovascular proliferation after combined intravitreal bevacizumab injection and laser photocoagulation for aggressive posterior retinopathy of prematurity. Retin Cases Brief Rep. 2019 Jul 17. Epub ahead of print. PMID: 31339872.
119. De la Huerta I, Yonekawa Y, Thomas BJ, Capone A. A surgical technique for the management of tractional retinal detachment in aggressive posterior retinopathy of prematurity treated with intravitreal bevacizumab. Retina. 2019;39:S156–S159.
120. van der Griend BF, Lister NA, McKenzie IM, Martin N, Ragg PG, Sheppard SJ, et al. Postoperative mortality in children after 101,885 anesthetics at a tertiary pediatric hospital. Anesth Analg. 2011;112:1440–7.
121. Sinha R, Talawar P, Ramachandran R, Azad R, Mohan VK. Perioperative management and post-operative course in preterm infants undergoing vitreo-retinal surgery for retinopathy of prematurity: a retrospective study. J Anaesthesiol Clin Pharmacol. 2014;30:258–62.
122. Yonekawa Y, Wu W-C, Kusaka S, Robinson J, Tsujioka D, Kang KB, et al. Immediate sequential bilateral pediatric vitreoretinal surgery: an International Multicenter Study. Ophthalmology. 2016;123:1802–8.
123. Shah PK, Ramakrishnan M, Sadat B, Bachu S, Narendran V, Kalpana N. Long term refractive and structural outcome following laser treatment for zone 1 aggressive posterior retinopathy of prematurity. Oman J Ophthalmol. 2014;7:116–9.
124. Chandra P, Tewari R, Salunkhe N, Kumawat D, Kumar V. Giant retinal tear with retinal detachment in regressed aggressive posterior retinopathy of prematurity treated by laser. J Pediatr Ophthalmol Strabismus. 2017;54:e34–e36.
125. Chandra P, Tewari R, Jain S. The restless retina in aggressive posterior retinopathy of prematurity: prevention is better than cure. Community Eye Health. 2018;31:S27–S28.
126. Chow LC, Wright KW, Sola A, CSMC Oxygen Administration Study Group. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? Pediatrics. 2003;111:339–45.
127. Fang JL, Sorita A, Carey WA, Colby CE, Murad MH, Alahdab F. Interventions to prevent retinopathy of prematurity: a meta-analysis. Pediatrics. 2016;137:e20153387.
128. Vinekar A, Jayadev C, Kumar S, Mangalesh S, Dogra MR, Bauer NJ, et al. Impact of improved neonatal care on the profile of retinopathy of prematurity in rural neonatal centers in India over a 4-year period. Eye Brain. 2016;8:45–53.
129. Chen ML, Guo L, Smith LEH, Dammann CEL, Dammann O. High or low oxygen saturation and severe retinopathy of prematurity: a meta-analysis. Pediatrics. 2010;125:e1483–1492.