Anti-vascular endothelial growth factor therapy in retinopathy of prematurity: An updated literature review

Asma K. Alzuabi[1], Ola M. Alshammari[2], Abdullah N. Almousa[3], Marwan A. Abouammoh[3]

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Abstract:

Laser photocoagulation can still be considered the gold standard for treatment for retinopathy of prematurity (ROP). However, anti-vascular endothelial growth factor (anti-VEGF) therapy has increasingly become an important option that plays a significant role in the treatment of ROP. Major clinical trials have been published regarding the anti-VEGF use in ROP, along with multiple other studies looking into the different agents, doses, techniques, and possible complications. Anti-VEGF therapies can be considered as a safe and effective option for managing ROP. More longitudinal randomized clinical trials are necessary to evaluate the preferred treatment agent, the appropriate dose, best follow-up protocol, and the long-term ocular and systemic outcomes following treatment.

Keywords:

Anti-vascular endothelial growth factor, follow-up, retinopathy of prematurity

Introduction

Retinopathy of prematurity (ROP) is considered one of the primary causes of pediatric visual impairment.[1] ROP pathophysiology involves two distinctive stages, in which vascular endothelial growth factor (VEGF) levels markedly differ. Phase 1 (vaso-obliterative) extends approximately over 22–30 weeks' postmenstrual age (PMA), where the levels of VEGF are suppressed and Phase 2 (vasoproliferative), from around 31–44 weeks' PMA, where there is an overproduction of VEGF.[2]

Several updates regarding ROP definitions have been recently added in the third edition of the International Classification of ROP. Due to the increase of anti-VEGF agents utilization in the treatment of ROP, the committee has recommended using the terms regression and reactivation to describe later ROP outcomes.[3]

The treatment of ROP has been introduced by Cryotherapy for ROP Cooperative and the Early Treatment for ROP Cooperative Group studies, where ablative therapy by cryotherapy or laser photocoagulation is applied over the avascular retina.[4-6] However, since the recognition of VEGF's role in ROP pathogenesis, anti-VEGF therapy with intravitreal injection has increasingly become a treatment option in some ROP cases.[7]

The purpose of this review is to summarize and provide an update on the role of anti-VEGF therapy in ROP management, including trials, agents, dosing, and side effects.

Anti-Vascular Endothelial Growth Factor Agents Currently Used in Retinopathy of Prematurity

Anti-VEGF therapy is increasingly recognized as a treatment option for ROP. Current agents that have been studied for use in ROP include bevacizumab, ranibizumab, aflibercept, conbercept, and pegaptanib.[8-11] However, other recently released agents such as brolucizumab and faricimab are not yet tested for use in premature infants with ROP.

Bevacizumab

Bevacizumab is a monoclonal antibody that functions by VEGF inhibition with a molecular

[1]Department of Ophthalmology, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, [2]Department of Medical Education, King Khaled Eye Specialist Hospital, [3]Department of Ophthalmology, College of Medicine, King Saud University, Riyadh, Saudi Arabia

Address for correspondence: Prof. Marwan A. Abouammoh, Department of Ophthalmology, College of Medicine, King Saud University, P.O. Box 245, Riyadh 11411, Saudi Arabia. E-mail: dr.abouammoh@gmail.com

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weight: 148 kDa. It is FDA approved for colon cancer. It is the most recognized intravitreal anti-VEGF agent in the treatment of ROP to date. In premature infants, bevacizumab serum half-life can reach up to 21 days.[10-20]

Bevacizumab Eliminates the Angiogenic Threat of ROP trial (BEAT-ROP) was one of the early trials that demonstrated the effectiveness of intravitreal bevacizumab (IVB) in the management of Zone I or posterior Zone II ROP and showed that it significantly decreases the recurrence of disease in Zone I compared to laser treatment.[21]

Ranibizumab

Ranibizumab is a monoclonal antibody fragment (Fab) with a molecular weight of 48 kD. It has an advantage over other agents in premature infants due to its shorter serum half-life.

The use of intravitreal ranibizumab (IVR) has been established to be effective in the Ranibizumab versus Laser Therapy for the Treatment of Very Low Birth Weight Infants with ROP study (RAINBOW).[12,13,15,19,20,22-25]

Aflibercept

Aflibercept is a soluble fusion protein composed of the Fc portion of IgG fused to VEGF receptors' extracellular ligand-binding elements, with a molecular weight of 115 kDa. It has a greater affinity to bind to VEGF receptors compared to other anti-VEGF agents. Although it is a well-established and widely used treatment in adults, the popularity of aflibercept for ROP is low. However, good outcomes with its administration have been demonstrated by multiple publications.[13,20,23,25-27]

Conbercept

Conbercept is a soluble fusion protein which combines the second Ig-like domain of VEGF receptor 1 and the third and fourth Ig-like domains of VEGF receptor 2 to the Fc portion of human IgG1, blocking both VEGF-A and VEGF-B isoforms.[28] It has 50 times higher binding affinity for VEGF than bevacizumab and a longer half-life in the vitreous.[29] Intravitreal conbercept was found to be an effective therapy for the treatment of ROP with similar or probably better results than ranibizumab.[8,30-32]

Pegaptanib

Pegaptanib is a pegylated oligonucleotide that binds selectively to the VEGF-A165 isomer responsible for most of VEGF-A pathological actions in the eye. A lower rate of progression to advanced ROP stages was found with its combined use with laser therapy.[23,33-35]

Anti-Vascular Endothelial Growth Factor Dose

A lower intravitreal anti-VEGF dose is theoretically more desired to decrease systemic absorption and serum concentration, leading to fewer systemic complications. However, the ideal therapeutic dose of intravitreal anti-VEGF for ROP treatment is still controversial.[36,37]

In regard to bevacizumab, 0.625 mg in 0.025 ml is the current standard dose used in ROP management.[21] Pediatric Eye Disease Investigator Group has compared different dosing regimens of IVB in treating Type 1 ROP. Doses of 0.25, 0.125, 0.063, or 0.031 mg were used. Successful treatment outcome was determined as recovery in Type 1 ROP by 5 days after injection with no treatment-requiring relapse in 4 weeks. Moreover, it was achieved in 100%, 100%, 88%, and 100% eyes, respectively, concluding that lower doses could replace the standard dose with similar outcomes.[38]

Another study published by Hillier *et al*. assessed 0.16 mg of IVB. Of the 29 eyes included, 79% have achieved total regression of retinopathy after only one injection; 93% achieved complete regression of retinopathy with an additional injection or supplemental laser.[39]

Akdogan *et al*. have also assessed a 0.16 mg dose of IVB where 7% of the included infants showed persistence of the disease. To prevent disease relapse, 44% of the infants received additional peripheral photocoagulation over the avascular retina at 70 weeks of GA.[40]

These studies' results could indicate that lower IVB doses can be considered and result in good therapeutic responses in ROP.

The minimum therapeutic dose of IVR for ROP treatment is still undetermined. The widely applied dose is half the dose of an adult (0.20 mg in 0.025 ml).[41,42] Lower doses have been studied by Stahl *et al*. where 0.12 and 0.20 mg were compared. Additional treatments were not needed in 94% of the 0.12 mg group and in 93% of the 0.20 mg. Both doses of IVR were evenly effective in regressing ROP. Moreover, systemic VEGF levels were similar in both groups. However, the 0.12 mg dose group demonstrated superior physiologic vascularization of the retina.[43]

Although limited studies have been published regarding aflibercept in ROP, a dose of 1 mg/0.025 ml is considered standard and has achieved good regression in ROP.[26,44,45] A recently published study compared 0.4 mg/0.01 and 1 mg/0.025 ml IVA dose in ROP. The treatment success was found in 94% and 100%, respectively. However, a longer time was required for the plus disease improvement in the lower dose group than in the standard-dose group. Recurrence was observed in 28% and 24% of eyes in the lower and standard-dose groups, respectively. At 6 months, a statistically significant difference in vascularization was noticed, as it reached Zone III in 38% in the lower dose group compared to 57% in the standard-dose group.[46] This outcome contradicts previous experimental studies that showed superior physiological vascularization with lower doses of aflibercept.[47]

Which Needle to Use

While a standardized technique for the injection of intravitreal anti-VEGF in ROP is still lacking, major considerations are important while delivering the injection. While a standardized technique for the injection of intravitreal anti-VEGF in ROP is still lacking, major considerations are important when delivering the injection. This is due to the fact that the immature

infant's eye is small in size, has immature pars plana, and larger crystalline lens relative to the volume of the eye.[48]

A 31-gauge, 7.93-mm needle was utilized in the anti-VEGF injection protocol in the BEAT-ROP study.[21] While in the RAINBOW study, a 30-gauge (12.7 mm) needle was utilized.[15] Wright *et al*. have published a study demonstrating the safety of 32-gauge, 4-mm needle using pathological specimens. They showed that standard ½-inch needles could lead to penetration of the retina or injury to the lens. The 4-mm needle, in contrast, penetrated the vitreous cavity efficiently with no damage to the retina or the lens.[49] A published follow-up chart review has demonstrated the safety of this needle clinically with no reported complications, such as cataract or vitreous hemorrhage.[50] The authors of the study have suggested using the 30-gauge needle with care if the 4-mm 32-gauge needle is unavailable and advised inserting roughly one-third of the needle length to avoid these complications.[50]

Follow-Up

There is no clear consensus up to this point about the scheduling time and length of follow-up following anti-VEGF injections for ROP. However, it is very rational, as has been reported by multiple resources, to perform the first examination after 48–72 h following the procedure and then 1 week later looking for any signs of endophthalmitis or other procedure-related complications.[51,52] In addition, follow-ups every 1–2 weeks are recommended to evaluate for signs of disease regression and monitor for any signs of reactivation and need for re-treatment.[52,53] RAINBOW trial protocol for follow-up consisted of patients re-evaluation at 1 and 3 days following the treatment, then at 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24 weeks after treatment.[15] However, other resources are recommending regular follow-ups up to 65 weeks' PMA, and additional regular follow-ups are also recommended beyond that in the presence of significant areas of persistent avascular retina.[52,53] The American Academy of Pediatrics Section on Ophthalmology recommended close follow-ups until at least 65 weeks' PMA following anti-VEGF injections and can be stopped if one of the endpoints has been reached, including full vascularization in close proximity to the ora serrata for 360° or successful treatment with laser performed over the avascular retina with no skip areas.[54]

Major Clinical Trials

In the BEAT-ROP trial, IVB (0.625 mg) was randomly compared with laser photocoagulation as the main intervention for Zone I or posterior Zone II Stage 3+ ROP. Follow-up was up to 54 weeks' PMA. The primary measured outcome was determined as disease recurrence necessitating treatment. The study reported that 4% of infants in the IVB group required additional treatment, in contrast to 22% in the photocoagulation therapy group. This contrast was valid for ROP present in Zone I only.[21]

Kennedy *et al*., in 2018, enrolled 16 infants from the original BEAT-ROP trial. The study aimed to assess the nonophthalmic outcomes of bevacizumab at 2 years. There was no significant difference in head circumference, length, weight, incidence of cerebral palsy, or Bayley scores between the laser and bevacizumab groups. However, both groups showed lower growth percentiles and Bayley developmental scores compared with healthy infants.[55]

Autrata *et al*., in a prospective randomized trial, compared intravitreal pegaptanib (0.3 mg) and laser combination therapy for Zone I and posterior Zone II, Stage 3+ ROP versus combined laser and cryotherapy. The absence of ROP recurrence by 55 weeks' PMA was considered successful treatment. An adverse outcome was determined as progression to advanced ROP (Stage 4A or more). When anti-VEGF and laser combination treatment was administered, lower rates of negative anatomic outcome with no ROP recurrence were noted.[33]

Lepore *et al*. compared the structural outcomes following the treatment of Type 1 ROP in Zone I. Each infant's eyes were randomized to receive either IVB (0.5 mg) or laser therapy. The retina and choroid were evaluated with fluorescein angiography for the presence of any structural anomalies. In 2014, their first report was published about the outcomes at 9 months' PMA; FA demonstrated abnormalities for all the eyes treated with IVB such as peripheral avascular areas, anomalous vascular shunting, and posterior pole findings, including the absence of FAZ. However, in the majority of eyes managed with laser, these findings were not present. These findings have persisted into childhood, when those infants were re-evaluated at the age of 4 years, according to their report that was published in 2018.[56,57]

O'Keeffe *et al*. conducted a randomized clinical study on 15 preterm infants with Zone I or posterior Zone II ROP to compare outcomes of IVB versus diode laser. The investigators followed ROP regression and recurrence, associated ocular or systemic side effects, and later visual and refractive outcomes 5 years following the intervention. Treatment-requiring reactivation occurred in three eyes of the bevacizumab group and in only one eye of the laser group. At 1-year follow-up, no systemic complications or neuroimaging abnormalities related to bevacizumab were detected with similar refractive status among the two groups. At a 5-year follow-up, IVB and laser treatment groups were maintaining satisfactory outcomes. However, eyes managed with laser photocoagulation showed a significant myopic shift compared to eyes treated with IVB.[58]

In 2016, Karkhaneh *et al*. published a randomized controlled trial comparing the outcome of IVB (0.625 mg) and laser therapy in infants with Zone II Stage 2+ or 3+ ROP. Failure of treatment was determined as persistence or recurrence of ROP by 90 weeks PMA. The study showed that in infants with Type 1, Zone II ROP, recurrence of the disease among eyes treated with IVB was higher (10.5%) compared to the conventional laser group (1.4%).[59] Nevertheless, reinjection causes regression in most of the cases that developed recurrence.

Zhang *et al*. published in 2016 a randomized controlled trial of 50 premature infants with Zone II Stage 2+ or 3+ ROP. Patients were randomly distributed to receive IVR (0.3 mg) or photocoagulation monotherapy, with a minimum follow-up period of 6 months. The primary measurements included plus disease and neovascularization resolution, ridge disappearance, disease recurrences, and occurrence of ocular or systemic side effects. Initial response to treatment occurred in all eyes that received IVR, and in all eyes treated with laser treatment but two belonging to the same infant. However, in the IVR group, 52% of eyes later developed treatment-requiring recurrence.[60]

In the Comparing Alternative Ranibizumab Dosage for Safety and Efficacy in ROP (CARE-ROP) study, Stahl *et al*. compared 0.12 mg versus 0.20 mg of IVR in the treatment of ROP. Nineteen infants with bilateral aggressive posterior ROP; ROP Stage 1 with plus disease, 2 with plus disease, or 3 with or without plus disease in Zone I; or ROP Stage 3 with plus disease in posterior Zone II were enrolled. Three infants died during the follow-up, and of the surviving infants, nine patients were in the 0.12 mg and seven were in the 0.20 mg group. Recurrence was found in two infants of each group (21%) and more prevalent in the 0.20 mg group. Progression of full physiological vascularization was found in 55% of the 0.12 mg group and in only 16.7% of the 0.20 mg group. Mean serum VEGF levels and rate pf systemic complications were similar between the two groups.[43]

The RAINBOW trial was published in 2019 where 225 premature infants with either Type 1 ROP, except for Zone II Stage 2+, or Aggressive Posterior ROP were randomly distributed into three groups. Group 1 received 0.2 mg IVR; Group 2 received 0.1 mg IVR, and Group 3 was treated with conventional laser therapy. The follow-up interval was up to 24 weeks post treatment. The objective was to evaluate whether IVR is superior to laser, as defined by the absence of active ROP, unfavorable ocular outcomes, or retreatment requirement. Treatment success occurred in 80% receiving ranibizumab 0.2 mg versus 75% infants receiving ranibizumab 0.1 mg and 66% after laser photocoagulation. Adverse ocular outcomes were found in one infant following IVR 0.2 mg, compared with five following IVR 0.1 mg, and seven after laser treatment. No differences were found between the three groups concerning death rates or ocular side effects.[15]

In a recently published randomized clinical trial in 2021, Wu *et al*. compared the use of intravitreal conbercept and ranibizumab in the treatment of ROP. Sixty eyes of 30 infants with the diagnosis of aggressive posterior ROP, Zone I or Zone II treatment-requiring ROP, were included in each group. One group underwent intravitreal injection of 0.25 mg of conbercept and 60 eyes and the other one underwent intravitreal injection of 0.25 mg of ranibizumab. The treatment-requiring recurrence rate was found in 16.67% versus 23.34% in the IVC and IVR groups, respectively, with no statistically significant difference between the two.[30]

A summary of the major clinical trials regarding anti-VEGF use in ROP is provided in Table 1.

Ocular Complications

Ocular complications after anti-VEGF administration are fortunately unusual and are mostly related to the injection procedure itself. Reported side effects include endophthalmitis, retinal detachment, vitreous hemorrhage, high intraocular pressure, cataract, and corneal opacification.[23,61]

Other less commonly reported ocular adverse events following anti-VEGF therapy include optic atrophy, choroidal rupture and ischemia, retinal pigment epithelium tear, and retinal vascular sheathing.[21,22,62]

Pertl *et al*. have conducted a systematic review and meta-analysis on the safety of anti-VEGF for the treatment of ROP. One thousand four hundred fifty-seven eyes from 24 studies were included. Ocular complications were calculated for 882 eyes, and the complications were divided based on treatment requirements. Of the included cases, 55 eyes (6.2%) had treatment-requiring ocular complications, which were consistent with ROP advancement in all of them. Nontreatment-requiring complications reported in 11 cases (1.2%) out of 882 eyes, including cataract, macular dragging with exotropia, and spontaneously resolved hemorrhages.[62]

In the BEAT-ROP trial, ROP progression-requiring treatment was 4% following IVB administration in Zone I or posterior Zone II disease. However, other procedure-related complications such as vitreous hemorrhage or cataracts were not reported.[21]

Bazvand *et al*., in a recently published study, reported ocular complications following IVB for ROP. It included 865 eyes from 441 infants who received IVB for ROP. The most common complication was ROP progression which was reported in 2% of the cases, and it was significantly more prevalent in Zone I ROP and in those with iris neovascularization. Other reported complications included cataract in two infants and vitreous hemorrhage in one case.[63]

Other reported long-term ocular complications related to intravitreal anti-VEGF injections included persistent peripheral vascular anomalies and refractive errors.[23,56,64-66] However, lower myopia and astigmatism rates are consistently reported compared to laser therapy, as was shown in the randomized control trial published by Geloneck *et al*. in 2014, where very high myopia (≥−8.00 D) occurred in Zone I-treated disease in 3.8% of eyes that received IVB compared to 51.4% of eyes that received laser photocoagulation and in 1.7% of eyes that received IVB compared to 36.4% of eyes that received laser treatment in posterior Zone II disease. This outcome was supported by many other studies later, as shown in the recently published meta-analysis where 13 studies involving 1850 eyes were assessed, and statistically

Table 1: A summary of major clinical trials on anti-vascular endothelial growth factor use in retinopathy of prematurity

Authors (year)	Participants		Intervention	Length of follow-up	Outcome(s) and results for each outcome
	Total number of infants/eyes included	ROP stages included			
Mintz-Hittner, *et al*. (2011)[21] BEAT-ROP clinical trial	150 infants were initially included, but only 143 infants survived 143 infants/286 eyes	Stage 3+ ROP in Zone I or posterior Zone II	Group 1: Bevacizumab 0.625 mg (70 infants/140 eyes); 31 infants with Zone I Stage 3+ ROP and 39 infants with posterior Zone II Stage 3+ ROP Group 2: Laser (73 infants/146 eyes); 33 infants with Zone I Stage 3+ ROP and 40 infants with posterior Zone II Stage 3+ ROP	Until 54 weeks PMA	The rate of recurrence (P=0.002), and the interval from treatment to recurrence Group 1: 4/70 infants (6%), 6/140 eyes; 16.0±4.6 weeks Group 2: 19/73 infants (26%), 32/146 eyes; 6.2±5.7 weeks Complications requiring intraocular surgery Group 1: 0/140 eyes Group 2: 4/146 eyes; one case of corneal opacity and three of lens opacity
Kennedy, *et al*. (2018)[55]	16 infants	Stage 3+ ROP in Zone I or posterior Zone II	Group 1: Bevacizumab 0.625 mg (7 infants) Group 2: Laser (9 infants)	2 years	Growth parameters (weight [P=0.27] length [P=0.39] and head circumference [P=0.46]) There were no significant differences between the two groups. Poor growth was common in each group Developmental assessment (Bayley Scales of Infant and Toddler Development III; cognitive composite score [P=0.06] language composite score [P=0.18] and motor composite score [P=0.22]) There were no significant differences between the two groups. The medians for Bayley scores were all <100 for each group None of the infants was assigned a low score because of severe impairment Gross motor performance (P=0.85) and cerebral palsy (P=1) There were no significant differences between the two groups
Autrata, *et al*. (2012)[33]	76 infants/152 eyes	Stage 3+ ROP in Zone I or posterior Zone II	Group 1: Pegaptanib 0.3 mg combined with laser (34 infants/68 eyes); 36 eyes with Zone I Stage 3+ ROP and 32 eyes with posterior Zone II Stage 3+ROP Group 2: Laser (42 infants/84 eyes); 44 eyes with Zone I Stage 3+ ROP and 38 eyes with posterior Zone II Stage 3+ ROP	Until 55 weeks PMA	The rate of recurrence in one eye (P=0.0274), the rate of recurrence in both eyes (P=0.0385), and the interval from treatment to recurrence (P=0.0172) Group 1: 4/34 infants (11.7%), 1/34 infants (2.9%); 15.1±4.1 weeks Group 2: 16/42 infants (38%), 5/42 infants (12%); 5.9±4.8 weeks Decrease in signs of plus disease ROP after treatment (P=0.0043) Group 1: 1.29±0.24 weeks Group 2: 2.61±0.73 weeks Peripheral retinal vascularization after treatment (P=0.0172) Group 1: 2.23±0.51 weeks Group 2: 3.57±0.84 weeks Unfavorable final structural outcome (Stage 4a, 4b) (P=0.0149) Group 1: 7/68 eyes (10.3%) Group 2: 33/84 eyes (39.2%)
O'Keeffe, *et al*. (2016)[58]	15 infants/30 eyes	Stage 3+ ROP in Zone I or posterior Zone II	Group 1: Bevacizumab 1.25 mg (15 infants/15 eyes)	5 years	The rate of recurrence, and the mean PMA at time of recurrence Group 1: 3/15 eyes (21.42%), 51 weeks Group 2: 1/15 eyes (7.14%), 37 weeks

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Table 1: Contd...

Authors (year)	Participants		Intervention	Length of follow-up	Outcome(s) and results for each outcome
	Total number of infants/eyes included	ROP stages included			
			Group 2: Laser (15 infants/15 eyes)		Ocular assessment (dilated ocular examination, VEP, and ERG) and pediatric assessment (pediatric examination, and MRI brain scan) at 1 year and 2 years follow up There was no difference in refraction and VEP/ERG in both groups. Pediatric assessment (including MRI brain scans) showed no abnormality that could be attributed to bevacizumab Ocular assessment and pediatric assessment performed at 5-years follow up Group 2 demonstrated significant myopic shift compared to Group 1. The retina remained flat in both groups. There was no systemic adverse effects associated with bevacizumab
Karkhaneh, *et al*. (2016)[59]	79 infants/158 eyes	Stage 2+, or 3+ ROP in Zone II	Group 1: Bevacizumab 0.625 mg (43 infants/86 eyes) Group 2: Laser (36 infants/72 eyes)	Until 90 weeks PMA	The rate of recurrence (P=0.018) and the interval from treatment to retreatment (P=0.290) Group 1: 9/86 eyes (10.5%), 5.07±1.66 weeks Group 2: 1/72 eyes (1.4%), 3 weeks The need for surgery (P=0.54) Group 1: 1/86 eyes (1.2%) Group 2: 0/72 eyes The situation of the retinal periphery in Group 1 At 54 weeks PMA, 65/86 eyes (79.3%) had avascular areas in Zone III. At 90 weeks PMA, 37/86 eyes (45%) had avascular areas in Zone III
Lepore, *et al*. (2018)[56,57]	21 infants were initially included, but only 20 infants survived 20 infants/40 eyes	Stage 3, or 3+ ROP in Zone I	Group 1: Bevacizumab 0.5 mg (20 infants/20 eyes) Group 2: Laser (20 infants/20 eyes); one eye progressed to a complete retinal detachment 4 weeks after treatment. Therefore, only 19 eyes were included in the analysis	Until the age of 4 years	Number of eyes with abnormal fluorescein angiographic findings before treatment, and 4 years after treatment Group 1 showed more significant vascular and macular abnormalities compared with Group 2 Irregular branching (starting at various distances from the optic disk): Group 1: 20/20, 17/20|Group 2: 19/19, 0/19 Arteriolar-venular shunts (frequently running along the avascular-vascular junction): Group 1: 18/20, 17/20|Group 2: 19/19, 2/19 Leakage in the area of avascular-vascular junction: Group 1: 19/20, 13/20|Group 2: 18/19, 1/19 Vascular tangles: Group 1: 18/20, 15/20|Group 2: 18/19, 1/19 Macular abnormalities (absence of foveolar avascular zone or hyperfluorescent lesions): Group 1: 18/20, 10/20|Group 2: 19/19, 3/19 Capillary bed loss (central or peripheral) Group 1: 20/20, 15/20|Group 2: 19/19, 2/19 Linear choroidal filling pattern: Group 1: 19/20, 11/20|Group 2: 17/19, 1/19
Stahl *et al*. (2018)[43] CARE-ROP study	19 infants were initially included, but only 16 n infants survived	Bilateral aggressive posterior ROP; ROP-requiring treatment in Zone I or posterior Zone II	Group 1: 0.12 mg ranibizumab (9 patients) Group 2: 0.20 mg ranibizumab 7 patients)	24 weeks	Recurrence was found in 2 infants of each group (21%) and more prevalent in the 0.20 mg group Progression of full physiological vascularization was found in 55% of the 0.12 mg group and in only 16.7% of the 0.20 mg group Mean serum VEGF levels and rate pf systemic complications were similar between the two groups

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Authors (year)	Participants		Intervention	Length of follow-up	Outcome(s) and results for each outcome
	Total number of infants/eyes included	ROP stages included			
Stahl, *et al*. (2019)[15] RAINBOW clinical trial	225 infants were initially enrolled, but only 214 infants were included in the analysis 214 infants	Stage 1+, 2+, 3, or 3+ ROP in zone I Stage 3+ ROP in Zone II AP-ROP	Group 1: Ranibizumab 0.2 mg (70 infants) Group 2: Ranibizumab 0.1 mg (76 infants) Group 3: Laser (68 infants)	24 weeks	Treatment success Group 1: 56/70 infants (80%)|Group 2: 57/76 infants (75%)|Group 3: 45/68 infants (66%) OR of treatment success in Group 1 compared with Group 3 was 2·19 (*P*=0·051); hence, other significance testing was not undertaken Full peripheral vascularization in Group 1 and Group 2 after 24 weeks of initial treatment Group 1: 28/70 infants (38%)|Group 2: 21/76 infants (27%) Death, serious and nonserious AEs They were evenly distributed among the three groups Growth parameters (weight, body length, knee to heel length, and head circumference) and blood pressure readings There were no significant differences between the three groups
Zhang, *et al*. (2017)[60]	50 infants/100 eyes	Stage 2+, or 3+ ROP in Zone II	Group 1: Ranibizumab 0.3 mg (25 infants/50 eyes) Group 2: Laser (25 infants/50 eyes)	6 months	The rate of recurrence (*P*=0.001) Group 1: 26/50 eyes (52%) Group 2: 2/50 eyes (4%)
Wu, *et al*. (2021)[30]	60 infant/120 eyes	Aggressive posterior ROP, treatment-requiring ROP in Zone I or Zone II	Group 1: Ranibizumab 0.25 mg (30 infants/60 eyes) Group 2: Conbercept 25 mg (30 infants/60 eyes)	6 months	The rate of recurrence (*P*=0.36) Group 1: 23.34% Group 2: 16.67% Features of recurrence based on FFA: In 10 of the eyes with recurrent disease, FFA showed posterior pole vascular dilation and tortuosity, wide peripheral avascular areas, arteriovenous anastomosis, neovascularization and vascular leakage Complications: Three eye developed cataract as a complication following the injection (two in the IVC and one in the IVR group)

ROP: Retinopathy of prematurity, BEAT-ROP: Bevacizumab eliminates the angiogenic threat for ROP, CARE-ROP: Comparing alternative ranibizumab dosage for safety and efficacy in ROP, RAINBOW: Ranibizumab versus laser for the treatment of very low birthweight infants with ROP, AEs: Adverse events, PMA: Postmenstrual age, VEGF: Vascular endothelial growth factor, AP-ROP: Aggressive posterior-ROP, FFA: Fundus fluorescein angiography, IVC: Injection of conbercept, IVR: Intravitreal injection of ranibizumab, ERG: Electroretinography, VEP: Visual-evoked potentials, MRI: Magnetic resonance imaging

significant lower rates of myopia were found in eyes receiving anti-VEGF therapy compared to eyes receiving laser treatment with a mean difference of 1.8 diopters.[67,68]

Systemic Complications

Despite the advantages of intravitreal anti-VEGF injections in ROP, there are still significant concerns regarding the systemic safety and long-term effects, as reported in 66% of participants in a survey recently conducted among pediatrics and retina specialists.[69]

These concerns are stemmed from the possibility of escape of anti-VEGF agents into the systemic circulation and their effect on organogenesis.[70]

In infants with ROP, multiple studies were done to estimate the effect of anti-VEGF therapy on systemic absorption and its impact on serum VEGF concentrations. A recent study found that a significant negative correlation was found between the IVB dose (0.25 mg and 0.5) and serum VEGF concentration in infants with ROP. However, this study was criticized as it measured the systemic absorption in infants who received IVB along with peripheral laser treatment, causing blood–retinal barrier breakdown and possibly increasing systemic IVB absorption.[17,18]

The CARE-ROP study showed that VEGF serum levels were not affected by IVR administration with 0.20 mg and 0.12 mg doses.[43] However, another study found lower levels of serum VEGF on the day following IVR injection, but this effect was short lived for only 1 week.[71] A paradoxical improvement in both eyes following unilateral IVR injection was also reported in one case series, supporting the systemic absorption and its effect on serum VEGF levels.[41]

In the systematic review and meta-analysis conducted by Pertl *et al*., 585 infants were investigated for systemic complications following intravitreal anti-VEGF injection, and they were reported in 8 patients (1.4%). However, none of these documented events were directly attributed to anti-VEGF treatment.[62]

In the BEAT-ROP study, death was reported in four infants in the IVB group and in one infant in the laser group. These deaths were attributed to pulmonary disease. It was nonstatistically significant but raised concerns over the anti-VEGF effect on lung maturation.[21]

Multiple groups have investigated neurodevelopmental outcomes following anti-VEGF intravitreal administration. A retrospective study by Morin *et al*. found that debilitating neurodevelopmental changes were 3.1 higher in infants managed with bevacizumab than patients managed with laser therapy. However, the study was retrospective and nonrandomized. The authors acknowledged that infants managed with IVB were more sick and had many systemic issues, so the difference between prematurity and the anti-VEGF effect was not distinguished.[72]

Likewise, in their comparative study, Natarajan *et al*. concluded that higher death rates and abnormal cognitive functions were found in extremely preterm infants with ROP who received IVB than in infants who received laser or cryotherapy. However, those findings again could be attributed to the health status differences between the groups, as the infants in the IVB group were more sick, requiring prolonged oxygen therapy.[73]

Lien *et al*. reported similar neurodevelopmental outcomes when comparing IVB and photocoagulation monotherapy. However, statistically significant higher rates of cognitive abnormalities were found in infants who received combination therapy.[74]

This outcome is supported by multiple other studies, including Fan *et al*., who concluded that there were no significant neurodevelopmental variations between infants receiving IVB or laser therapy.[75-77]

In conclusion, anti-VEGF therapy plays a major role in the treatment of ROP. All anti-VEGF agents used in treating ROP in major trails seem effective with a rather good safety profile. The dose of anti-VEGF for ROP treatment is much less than that for adult use, but the exact dose is yet to be determined. More randomized clinical trials are required to evaluate the preferred treatment agent, the appropriate dose, and the long-term ocular and systemic outcomes following the treatment.

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Conflicts of interest

There are no conflicts of interest.

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