Review Article

An Update on Anti-Vascular Endothelial Growth Factor Treatment for Retinopathy of Prematurity

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Abstract

Purpose: To present updated information on the role of anti-vascular endothelial growth factor (anti-VEGF) therapy for treating retinopathy of prematurity (ROP).

Methods: We searched through PubMed and Scopus databases using the keywords of this article and gathered relevant published articles from the year 2005 to December 2022. The selected articles were classified and summarized, and reasonable conclusions were made accordingly.

Results: Considering the current evidence, anti-VEGF agents are superior to laser therapy for the initial treatment of type 1 ROP in zone 1 or posterior zone 2. However, there is a substantial risk of reactivation or persistent avascular retina after solo treatment with anti-VEGFs, and many cases may require laser therapy within the following weeks or months. Thus, vigilant follow-up examinations are mandatory.

Conclusions: The role of anti-VEGF agents in the treatment of ROP is indispensable. However, future studies are required to improve indications and dosage and determine long-term ocular and systemic safety.

Keywords: Aflibercept, Bevacizumab, Intravitreal, Ranibizumab, Retinopathy of prematurity, Vascular endothelial growth factor

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Introduction

The ocular advantages of anti-vascular endothelial growth factor (anti-VEGF) agents became widely understood in 2005 when off-label intravitreal bevacizumab (IVB) was successfully used to treat macular neovascularization and diabetic macular edema. In 2007, IVB was used with promise in neonates with aggressive posterior retinopathy of prematurity (ROP).[1,2] A landmark study by Mintz-Hittner *et al*. (BEAT-ROP study) established anti-VEGF injections as the first-line therapy for stage 3 zone 1 ROP.[3] Since then, several studies have investigated anti-VEGF treatment for different manifestations of ROP. This review focuses on new updates on the efficacy and safety of anti-VEGF agents for managing ROP.

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Methods

We searched through PubMed and Scopus databases using the following keywords: "retinopathy of prematurity" AND "vascular endothelial growth factor" OR "anti-VEGF" OR "bevacizumab" OR "ranibizumab" OR "pegaptanib" OR "aflibercept". The relevant articles were collected from 2005 to December 2022. The articles were reviewed by two authors (MHN and ES) considering the methodology and content. Finally, the selected articles were classified and summarized, and reasonable conclusions were made.

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Results

Eyes with type 1 ROP (a more severe form than type 2) have been shown to get more benefits than risks from treatment compared to observation.[4] Anti-VEGF agents can be used as monotherapy or supplemental treatment alongside laser. Cases with type 1 ROP in zone 1 (or aggressive posterior zone 2) are ideal for anti-VEGF monotherapy as anti-VEGF injections have been associated with a better outcome than laser therapy.[3] In addition, neonates with media opacity precluding effective laser (for example, eyes with vitreous hemorrhage or anterior segment media opacity) or unstable systemic conditions (who cannot tolerate lengthy anesthesia for laser therapy) may be initially treated with anti-VEGF agents.[5,6] Eyes that received anti-VEGF therapy may require additional injection or supplemental laser treatment a few weeks after the injection (because of failure, recurrence, or persistent avascular retina [PAR]),[7] or they may respond well to the monotherapy and need no further intervention.

Anti-VEGF agents can also be used as an adjuvant to laser treatment. They may be administered before, at the same time, or after laser therapy. IVB plus deferred or simultaneous less-dense/zone 1-sparing laser treatment is an effective alternative treatment for zone 1 ROP.[8,9] Cases with type 1 ROP in the anterior zone 2 can be successfully treated with laser therapy alone. However, for eyes with florid ROP (neovascularization of the iris, engorged iris vessels, severe plus disease, and extensive extraretinal neovascularization), an adjuvant anti-VEGF injection could be performed at the conclusion of the laser therapy, which may enhance ROP regression and decrease laser-associated complications such as hyphema and vitreous hemorrhage.[9] In some cases of ROP that had received proper laser therapy, the ROP and new vessels may not regress as expected (typically, within 2–3 weeks).[10] The supplemental anti-VEGF treatment may help to induce rapid regression in these cases. Figure 1 summarizes the indications for anti-VEGF therapy in ROP.

The reported efficacy rates of anti-VEGF agents for ROP were different across various studies. This difference was primarily due to disparities in study design, inclusion criteria, type and dose of anti-VEGF used, and the definition of effective treatment (short-term vs. long-term regression). Huang *et al*. reported a 94% initial response for 0.25-mg intravitreal ranibizumab (IVR) in type 1 ROP.[11] In a study by Stahl *et al*.,[12] 0.2-mg IVR was more effective than laser for treating type 1 ROP (treatment success [at 24 weeks], 80% vs. 68%; odds ratio: 2.19, 95% confidence interval (CI) 0.99–4.82; $P = 0.051$), and with fewer unfavorable ocular outcomes (1 vs. 7 cases). However, a 2021 meta-analysis concluded comparable efficacy (regression rate) for intravitreal injection (IVI) versus laser therapy.[13] Compared to laser treatment, IVI induces a faster regression in aggressive posterior ROP (AP-ROP), stage 3 ROP, and plus disease.[10] This finding might be linked to the mechanism of action of anti-VEGF agents, which leads to a rapid decrease in intraocular VEGF levels. Another meta-analysis reported comparable visual outcomes for IVI and laser.[13]

Most studies reported an overall higher rate of retreatment for ROP cases with IVI compared to laser therapy, particularly for the zone 2 disease;[13,14] whereas the rate of retreatment was lower with IVI than laser in zone 1 ROP.[14] The indications of retreatment could be due to initial failure of IVI, recurrence of the disease, or persistence of the PAR. The characteristics of

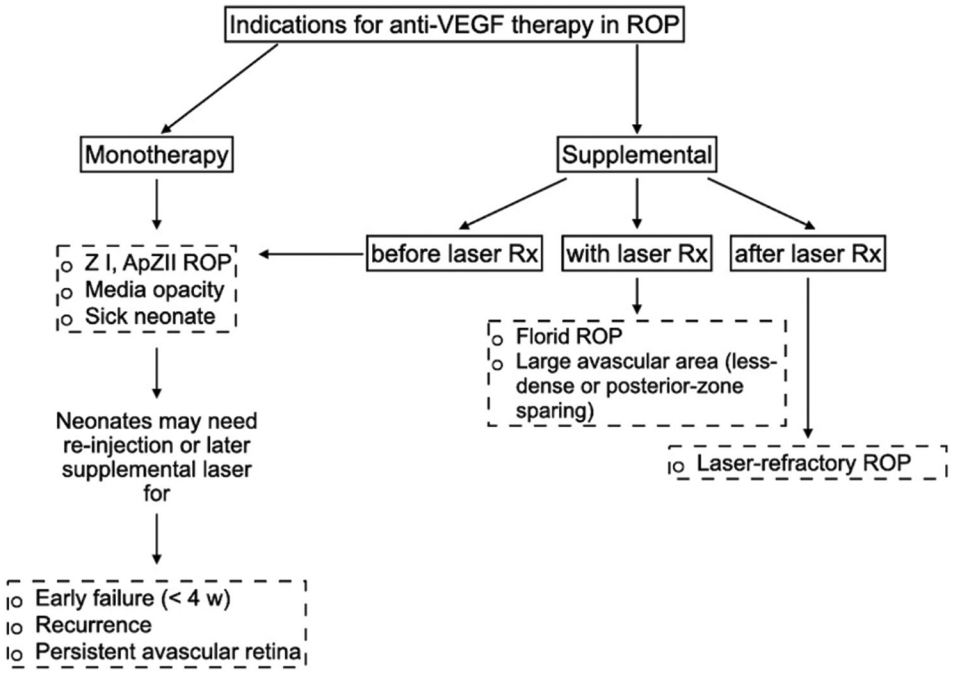

Figure 1: The indications for anti-vascular endothelial growth factor therapy in retinopathy of prematurity

different indications for retreatment after IVI for type 1 ROP are summarized in Table 1.

Treatment failure is defined as incomplete regression of ROP after IVI or reactivation of the disease <4 weeks after therapy. Compared to laser therapy, anti-VEGFs have been associated with fewer incomplete regressions in the short term.[10] Treatment failure on IVI usually prompts switching treatment to laser; however, reinjection of anti-VEGF agents may be indicated in some cases as unsuitable candidates for laser therapy.

Recurrence refers to the reactivation of ROP (after initial regression and response to treatment) >4 weeks after IVI. Treatment with anti-VEGF medications has been associated with a higher recurrence rate than laser therapy (relative risk [RR] =2.16, 95% CI: 1.26–3.73, $P = 0.005$).[13] Compared to laser, eyes treated with anti-VEGF therapy typically show recurrence at older ages (IVB, 43.4 ± 3.5 weeks; IVR, 42.3 ± 2.0; laser, 39.5 ± 2.8; $P = 0.0058$) and over broader time periods from the first treatment (IVB, 8.8 ± 3.9 weeks; IVR, 8.3 ± 1.6; laser, 3.6 ± 1.4; $P = 0.0001$).[15] Similarly, in the meta-analysis by Popovic *et al*., the interval between treatment and recurrence was more for IVI than laser (mean difference = 6.43 weeks, 95% CI: 2.36–10.51, $P = 0.002$).[13]

The recurrence rate after IVB therapy for posterior zone ROP was reported as 7% in the study by Mintz-Hittner *et al*. They concluded that the recurrence usually happens between 45 and 55 weeks of adjusted age (around 4 months after the first injection) and usually presents with both plus disease and retinal neovascularization.[16] In a large series by Roohipoor *et al*. (n = 493 patients), IVB was associated with a higher recurrence rate than laser therapy for zone 2 ROP (12.3% vs. 7.9%, respectively; $P = 0.017$), but the difference was not significant for zone 1 ROP. [17]

The studies that used IVR generally reported higher rates of recurrence, which tended to occur in shorter intervals after IVI. In a retrospective study (n = 50 eyes; IVR, 0.25 mg/0.025 mL), the recurrence rate was 64% and occurred on average at 7.9 weeks (standard deviation = 2.7) after injection (94% between 2.5 and 12.0 weeks). They noted that the recurrence could affect both the initial extraretinal fibrovascular proliferation site (4.5 ± 1.4 weeks) and the new advancing vascular edge (9.1 ± 2.0 weeks; $P < 0.001$).[18] Arámbulo *et al*.[7] reported on 43 infants (85 eyes) with zone 1 or posterior zone 2 ROP who were treated with IVR (0.25 mg) monotherapy. All eyes initially responded well; however, the recurrence rate was 53.6% (mean interval after first IVR, 7.1 ± 3 weeks, range, 3–15) (postmenstrual age, 43 ± 3.2 weeks, range, 35.5–54.5). Huang *et al*. assessed IVR treatment for type 1 ROP[11] and reported that the recurrence rate was as high as 48% in cases with the initial response.

Several risk factors have been associated with an increased recurrence rate of ROP after IVI. In the study by Huang *et al*. (IVR), lower gestational age (GA) (<29.5 w) and more severe ROP were associated with a greater likelihood of reactivation.[11] Iwahashi *et al*. confirmed that lower corrected age at the time of anti-VEGF therapy (≤35 weeks; $P = 0.014$) and AP-ROP ($P = 0.044$) were associated with a higher rate of recurrence.[19] Another study (n = 92 eyes; IVB; recurrence rate, 18%) found lower GA, greater avascular area, AP-ROP, and Asian ethnicity as predictors of ROP reactivation ($P < 0.01$ for all).[20] Extensive extraretinal fibrovascular proliferation ($P = 0.005$) and continued oxygen therapy after injection ($P = 0.016$) were independent risk factors for recurrence in the study performed by Lyu *et al*.[18] In addition to the patient factors, the type of anti-VEGF (IVR > IVB) and lower injected doses may also increase the risk of recurrence (without compromising the initial response).[14,21]

The recurrence could be managed with both reinjections of IVB and laser therapy; however, the latter should be preferred.[14]

Table 1: Characteristics of different indications of retreatment after intravitreal injection for type 1 retinopathy of prematurity

	Treatment failure	Recurrence	Persistent avascular retina
Definition	Incomplete regression or reactivation <4 weeks after IVI	Reactivation >4 weeks after IVI	>2 DD avascular retina in temporal quadrant or >1 DD in nasal quadrant
Typical time	<4 weeks after IVI	IVB: 45–55 weeks adjusted age (typically equal to 16 weeks after injection) IVR: Typically, several weeks earlier Lower doses → earlier reactivation	>60 weeks GA (>6 months after IVI)
Risk factors	Not widely investigated Possibly the same as recurrence	Lower GA; lower PMA at the time of treatment; more severe ROP; greater avascular area	Not widely investigated Possibly greater avascular area and higher doses of IVI
Management	Laser photocoagulation, followed by reinjection if inadequate response	Laser photocoagulation, followed by reinjection if inadequate response	Observe: Zone 3, as well as those with no high-risk characteristics at the border Laser: Zone 2, as well as those with high-risk characteristics at the border*

*High-risk characteristics referred to peripheral tortuosity, abnormal branching, circumferential vessels, and vascular leakage on fluorescein angiography. DD: Disc diameter, GA: Gestational age, IVI: Intravitreal injection, IVB: Intravitreal bevacizumab, IVR: Intravitreal ranibizumab, PMA: Postmenstrual age, ROP: Retinopathy of prematurity

The ROP usually regresses with (type 1) or without (type 2) treatment, and the retinal vessels are expected to grow and reach ora serrata within several weeks. This process may be halted or delayed in some cases, referred to as PAR. There is no consensus on the exact definition of PAR. Some investigators define PAR as the presence of avascular retina (for example, >2 disc diameter (DD) avascular area in the temporal retina or >1 DD in the nasal side) persisting for >60 weeks of GA (or at least 6 months after IVI).[7,22] PAR is usually described by its extent and location.[23] Compared to laser therapy, anti-VEGFs promote PAR (both in frequency and extent),[17] which may be explained by the positive role of VEGFs on normal retinal vascularization.

In a study by Roohipour *et al*., zone 3 PAR was identified in 82.8% of eyes in the IVB (0.625 mg) group in the 1st year and 53.4% in the 2nd year after treatment.[17] Chen *et al*. reviewed the outcomes of 46 ROP patients (92 eyes) treated with IVB and assessed with fluorescein angiography (FA). Only three eyes (3.3%) achieved full vascular maturity; 39 eyes (43.8%) had PAR, and 34 (38.2%) had PAR plus persistent tortuosity.[20] In another study by Arámbulo *et al*., of 85 eyes treated with IVR, 12 eyes (29.2%) showed complete vascularization in both eyes, while 6 infants (11.6%) had avascular retina in zone 2, persisting >6 months after IVR injection.[7]

There is also no consensus on the management of PAR. Some investigators recommend laser ablation of the avascular retina in eyes with PAR involving zone 2 while observing those in zone 3. Others suggest concomitant findings as being important in the treatment decision process. For example, eyes with peripheral vascular tortuosity, abnormal branching, circumferential vessels in the border of the vascular and avascular area, or peripheral vascular leakage on FA may benefit from treatment,[24,25] while those with taper-ending straight vessels may be observed. It is important to note that PAR might be the cause of the reactivation of ROP several years after birth with tractional or exudative retinal detachments.[26,27] The avascular retina may also be prone to develop holes and subsequently rhegmatogenous retinal detachment.[23,28]

The ocular early safety issues of IVI for ROP could be technique-related or drug-related.

Similar to adults, IVI in neonates can be associated with severe but rare injection-related complications such as endophthalmitis, lens rupture, and vitreous hemorrhage. Proper injection techniques should be applied to prevent such complications, and different sources of anti-VEGF drugs should be used in bilateral cases.

One study reported that the rate of short-term retinal detachment (>stage 4A, within 8 weeks) was lower in ROP cases that had received IVI than those treated with laser in eyes that had their treatment before 36 weeks of postmenstrual age (0% vs. 7.9%; $P < 0.001$). For eyes that had received their treatment at or after 36 weeks postmenstrual age, the retinal detachment rate was similar between the IVI and laser groups (1.4% vs. 3.1%, respectively; $P = 0.27$).[29]

Eyes with ROP are subjected to late-onset ocular complications because of both disease and treatment-induced changes in ocular growth and homeostasis. Although both laser therapy and anti-VEGFs medications mainly act by decreasing intraocular VEGF, each method has its specific mechanism of action. Therefore, the effects on ocular growth and health may differ.

In a randomized clinical trial by Lepore *et al*., 42 eyes of 21 neonates with zone 1 ROP randomly received 0.5 mg IVB in one eye and laser ablation in the fellow eye. Twenty patients had FA performed at 4 years of age, which revealed significantly more frequent changes in the eyes treated with IVB. Specifically, all previous IVB-treated eyes had peripheral (avascular area, vascular leakage, shunts, or tangles) or macular (hyperfluorescence or the absence of foveal avascular zone [FAZ]) changes.[30]

An observational study on 131 neonates used handheld optical coherence tomography devices and found that IVB monotherapy was associated with more rapid outer retinal thickening at the foveal center, in contrast, laser therapy revealed earlier extrusion of the inner layers (to form foveal pit) and delayed development of the ellipsoid zone at the central fovea.[31] The clinical relevance of such findings is yet to be determined. Chen *et al*.[32] compared macular morphologic features in children with previously treated ROP ($n = 47$ eyes; 22 lasers, 25 anti-VEGF) and found more favorable macular anatomy (including microvasculature) in eyes that received anti-VEGF agents, despite similar visual acuity outcome.

Another study noted that IVR might induce microvascular changes in the macula (decreased vessel length and perfusion density), whereas the laser might contribute to a smaller FAZ area and a thicker central fovea in children with previously treated ROP.[33] Other surveys found no significant difference between IVB and laser in foveal thickness of preschool children with previously treated ROP.[34]

The 2-year report of the RAINBOW study showed that IVR (0.2 mg) for ROP treatment (compared to laser) was associated with a decreased rate of high myopia with better vision-related quality of life.[35] In a 2021 meta-analysis,[13] eyes that were treated with IVI (bevacizumab or ranibizumab) had less astigmatism (mean difference, 0.25 D) and a higher likelihood of emmetropia compared to eyes that had laser therapy (risk ratio [RR], 1.96).

Anti-VEGFs can leave the neonatal eye and be present in systemic circulation for several weeks (peaks at 2 weeks) after injection, with an associated decrease in systemic VEGF levels.[36-38] It has been shown that injection doses as low as 0.002 mg of bevacizumab can suppress plasma VEGF levels.[39] Ranibizumab has been reported to affect systemic VEGF levels less than bevacizumab.[40]

The neonates undergoing laser therapy typically require more prolonged general anesthesia than those treated with intravitreal injections. Therefore, the systemic instability associated with laser treatment is more severe and lengthy than intravitreal injections. For example, it was shown that the return to respiratory baseline is impaired in laser-treated neonates compared to injection monotherapy up to 7 days after the procedure.[41] The treatment-associated systemic stress may have early or late clinical implications for some children.

Since VEGF contributes to childhood neurodevelopment, there is concern that intravitreal anti-VEGF injection might interfere with normal growth. The outcomes of studies in this regard are controversial. Morin *et al*.[42] conducted a retrospective review on 125 infants with treated ROP (27 IVB and 98 laser) and found higher odds (3.1, 95% CI: 1.2–8.4) of severe neurodevelopmental disabilities (Bayley score <70) at 18 months for those who had received IVB. Natarajan *et al*.[43] assessed the effect of IVB versus laser on the systemic safety of ROP patients at the corrected age of 18–26 months ($N = 405$: 45% IVB, 55% laser); the two modalities were not different in causing severe neurodevelopmental impairment, but the odds of cognitive score <85 were slightly higher with the IVB (OR = 1.73, 95% CI: 1.04–2.88).

On the other hand, Fan *et al*.[44] assessed neurodevelopmental outcomes in type 1 ROP patients (mean age, 1.5 years) receiving IVB (0.625 mg) and found no significant difference compared to premature infants with untreated ROP. Stahl *et al*.[45] reported a comparable 24-month systemic safety profile for 0.2 mg IVR versus laser therapy. Likewise, Zayek *et al*.[6] (IVB, 61 infants; laser, 85) did not find any higher risk of death or neurodevelopmental impairment at 18–24 months corrected age attributable to bevacizumab injection. The follow-up report of the RAINBOW study at 2 years revealed that IVR (compared to laser) did not affect nonocular infant development.[35] In addition, magnetic resonance diffusion tensor imaging of white matter pathways did not show any difference in developmental outcomes at 18 months corrected age between infants with or without IVB therapy.[46]

A 2021 meta-analysis concluded that considering the current evidence, intravitreal anti-VEGF injections do not increase the rate of severe neurodevelopmental impairments in children with ROP compared to laser or no treatment. However, they noted that the overall quality of evidence used for the analysis was low.[47]

Table 2 summarizes the advantages and disadvantages of anti-VEGF therapy versus the standard laser for the treatment of ROP, primarily based on the 2017 American Academy of Ophthalmology report[4] and a 2021 meta-analysis.[13]

Most previous important studies used bevacizumab, followed by ranibizumab in the IVI arm [Table 3]. However, aflibercept is the first anti-VEGF agent that could receive US Food and Drug Administration approval to treat preterm infants with ROP. IVB often showed a lower recurrence rate than IVR.[10,14,16] However, IVR had less effect on systemic VEGF levels.[40] The aflibercept has not been used widely, and the available data are limited compared to IVB or IVR.[14] Chen *et al*. studied the effect of intravitreal aflibercept (IVA) on type 1 ROP[17] eyes of 9 patients; 1-year follow-up) and reported an 88.2% success rate. No significant ocular or systemic complications attributed to IVA were noted.[49] The study by Stahl *et al*. reported comparable efficacy and safety outcomes for IVA versus laser in cases with type 1 ROP but has failed to fulfill the predefined noninferiority criteria (1-sided 95% CI >−5% for the mean difference of treatment success at week 24).[48] In a 2022 network meta-analysis, the single treatment success rates for type 1 ROP were 89.3%, 87.0%, 80.7%, and 74.0% for laser, IVB, IVA, and IVR, respectively. The mean time to secondary treatment was 12.96 weeks for IVA, 11.36 weeks for IVB, and 9.29 weeks for IVR.[14] The duration of action was longer for IVB or IVA than for IVR.

As of drafting this review, no research has been published in MEDLINE regarding the effect of brolucizumab or faricimab

Table 2: Advantages and disadvantages of anti-vascular endothelial growth factor therapy versus the standard laser for the treatment of retinopathy of prematurity

	Advantages	Disadvantages
Anti-VEGF injection	Easier to administer and requires less anesthesia	A higher rate of recurrences in Z2 ROP
	More safe/effective regression in Z1 and AP-ROP	Need for more frequent and extended follow-up examinations
	Faster regression of severe or AP-ROP	Retinal vascularization is usually incomplete with PAR or macular vascular changes
	No destruction of the peripheral retina and long ciliary nerves (and associated complications)	Possible long-term systemic and neurodevelopmental safety issues
	Less chance for childhood refractive error	
	Could be delivered to critically ill neonates (who cannot tolerate the stress of laser treatment)	
Laser therapy	Lower rate of recurrence (especially in Z2 disease)	The procedure is more stressful for neonates
	Less frequent follow-up examinations	The rate of complications increases in cases with florid ROP or very large avascular areas (Z1 and pZ2)
	Less PAR and persistent abnormal vascular changes	More chance for childhood refractive error
		Ablation-related complications (adverse effects on visual field, night vision, pupillary response, corneal sensation)

VEGF: Vascular endothelial growth factor, ROP: Retinopathy of prematurity, AP-ROP: Aggressive posterior ROP, PAR: Persisting avascular retina, Z2: Zone 2, pZ2: Posterior Z2, Z1: Zone 1

Table 3: Landmark studies of anti-vascular endothelial growth factor agents for retinopathy of prematurity

Study	Method	Participants	Intervention	Findings
Mintz-Hittner *et al*., 2011, BEAT-ROP study[3]	RCT	150 infants: 300 eyes Z1 or pZ2 with stage 3+	0.625 mg bevacizumab versus laser Rx	IVB was better than laser for Z1 ROP (*P*=0.003) and was equal to laser for Z2 ROP (*P*=0.27) The recurrence rate was 4% in the IVB and 22% in laser Rx groups (*P*=0.002)
Mintz-Hittner *et al*., 2016[16]	Retrospective case series	241 infants, 471 eyes Z1 or pZ2 with stage 3+ or AP-ROP	IVB monotherapy (0.625 mg)	Recurrence rate=7.2% of eyes Risk factors for recurrence: AP-ROP (*P*=0.006), duration of hospitalization (*P*=0.01), lower BW (*P*=0.024) Recurrence period: Mean, 51.2 weeks (AA); SD, 4.6 weeks; range, 45.7–64.9 weeks; 94.1% of eyes in between 45–55 weeks (AA) Mean interval between treatments, 16.2 weeks (SD, 4.4) Recurrence features: Plus (100%), EFP (85.7%) Retreatment → slow and minimal progression of retinal vascularization
Huang *et al*., 2017[11]	Retrospective case series	145 infants, 283 eyes Type 1 ROP	IVR monotherapy (0.25 mg)	Primary response rate: 94% Of 94% responsive cases: 48.6% no recurrence; 44.9% with recurrence Rate of recurrence For GA >29.5 weeks → 29.6% For GA ≤29.5 weeks → 61.6% (37.9% for Z2 stage 2+, and 80% for more severe forms)
Roohipoor *et al*., 2018[17]	Retrospective case series	493 infants, 986 eyes Type 1 ROP	0.625 mg bevacizumab (73.4%) versus laser Rx (26.5%)	Retreatment: IVB, 14.4%; laser, 8.8% (*P*=0.065) Retreatment for Z1: No difference (*P*=0.978) Retreatment for Z2: IVB, 12.3%; laser, 7.9% (*P*=0.017) Z3 PAR in IVB group: Year 1, 82.8%; year 2, 53.4% SE refraction: IVB, 1.26±3.19 D; laser, −2.84±2.77 D (*P*=0.007)
Stahl *et al*., 2019, RAINBOW study[45]	mcRCT (open-label)	225 infants Type 1 ROP	3-arm, 1:1:1 IVR 0.2 mg, *n*=74 IVR 0.1 mg, *n*=77 Laser, *n*=74	Treatment success (at 24 weeks): IVR 0.2 (80%); IVR 0.1 (75%); laser (66%) Unfavorable structural outcome: IVR 0.2 (1 infant); IVR 0.1 (5); laser (7) No difference in death, serious/nonserious adverse events up to 24 weeks
Popovic *et al*., 2021[13]	Meta-analysis	24 articles	IVI, 1289 eyes Laser, 2412 eyes	Regression rate: No difference (*P*=0.68) Retreatment: IVI > laser (OR, 2.16; 95% CI, 1.26–3.73; *P*=0.005) Interval between treatment and recurrence: IVI > laser (mean difference, 6.43 weeks; 95% CI, 2.36–10.51; *P*=0.002) Need for surgery: IVI < laser (RR, 0.45; 95% CI, 0.27–0.99; *P*=0.05 Astigmatism: IVI < laser (mean difference, −0.25 D; 95% CI, −0.45–−0.06; *P*=0.01) Proportion of emmetropia: IVB > laser (RR, 0.51; 95% CI, 0.27–0.99; *P*=0.05) Visual acuity: No difference Safety outcomes: No difference
Barry *et al*., 2021 2nd analysis of G-ROP 1 and 2[29]	Nonrandomized, comparative cohort study	640 infants; 1167 eyes Type 1 ROP	IVI, 164 eyes Laser, 1003 eyes	Short-term RD (stages 4A, 4B, or 5) within two months of first treatment 458 eyes treated before 36 weeks AA: IVI < laser (0% vs. 7.9%; *P*<0.001) 709 eyes treated at or after 36 weeks AA: IVI=laser (1.4% vs. 3.1%; *P*=0.27)
Fleck *et al*., 2022 RAINBOW study (*post hoc*)[10]	mcRCT (open-label)	225 infants Type 1 ROP	3-arm, 1:1:1 IVR 0.2 mg, *n*=74 IVR 0.1 mg, *n*=77 Laser, *n*=74	Median times to regression IVR (0.2 mg) versus laser Plus disease, 4 versus 16 days (*P*<0.001); stage 3 ROP, 8 versus 16 days (*P*=0.004); AP-ROP, 7.3 versus 22 days (*P*=0.03) Results for IVR 0.1 mg: Similar to IVR 0.2 mg (a median of 4, 9, and 8 days, respectively) Additional treatments: Laser, 25% IVR 0.2 mg 27%, IVR 0.1 mg 28% Incomplete regression (treatment failure): Laser 22% (median interval, 15 days), IVR 0.2 mg 8% (21 days), IVR 0.1 mg 6% (13 days)

Contd...

Table 3: Contd...

Study	Method	Participants	Intervention	Findings
				Reactivation: Laser 2% (median interval, 43 days), IVR 0.2 mg 15% (53.5 days; maximum, 105), IVR 0.1 mg 17% (54.5 days; maximum, 128)
Freedman *et al*., 2022, PEDIG[21]	Masked, multicenter, dose de-escalation study	120 infants Type 1 ROP 12 months outcome	Two studies: Low-dose (0.25, 0.125, 0.063, and 0.031 mg) or very low-dose (0.016, 0.008, 0.004, and 0.002 mg) IVB The fellow eye received one higher dose level than the study eye	Additional treatment: Study eye, 55%; fellow eye, 56% Study eyes: 31 (27%), had additional treatment (6, initial treatment failure; 4, reactivation ≤4 weeks, 21, later reactivation), and 31 (27%) received prophylactic laser for PAR The fellow eye showed similar outcomes Time to reactivation: Very low-dose (mean 76.4 days) < low-dose (85.7 days) Poor retinal outcome at 12 months: 3%
Chang *et al*., 2022[14]	Network meta-analysis	30 articles Type 1 ROP	IVB, *n*=2081 IVR, *n*=727 IVA, *n*=326 Laser, *n*=1552	Type 1 ROP, Single treatment success rates: Laser, 89.3% (95% CI, 83.8–93.8); IVB, 87.0% (78.6–93.8); IVA, 80.7% (62.0–94.4); IVR, 74.0% (62.7–84.1) The mean time to secondary treatment: IVA, (12.96 weeks±0.47 SEM); IVB, (11.36±0.54); IVR, (9.29±0.43) Zone I ROP, single treatment success rates: IVB, 91.2% (83.6–96.9; *n*=231); IVR, 78.3% (61.4–91.9; *n*=100); and laser, 65.9% (41.4–87.2; *n*=158)
Stahl *et al*., 2022[48]	Noninferiority, phase 3 mcRCT	118 infants Type 1 ROP	Two arms, 2:1 IVA (0.4 mg): 75 Laser: 43	Treatment success (week 24) was 85.5% with IVA and 82.1% with laser (mean difference, 3.4% [1-sided 95% credible interval, −8.0% to ∞]); did not reach the predefined noninferiority criteria (1-sided 95% CI >−5%) Rescue treatment: IVA, 4.8%; laser, 11.1% Serious adverse event rates: Ocular: 13.3% (IVA) versus 7.9% (laser) Systemic: 24.0% versus 36.8%

AA: Adjusted age, ROP: Retinopathy of prematurity, AP-ROP: Aggressive posterior ROP, BW: Birth weight, CI: Confidence interval, EFP: Extraretinal fibrovascular proliferation, RCT: Randomized controlled trial, mcRCT: Multi-center RCT, PAR: Persistent avascular retina, RD: Retinal detachment, RR: Relative risk, Rx: Therapy, SE: Spherical equivalent, SD: Standard deviation, Z3: Zone 3, Z1: Zone 1, Z2: Zone 2, pZ2: Posterior Z2, IVB: Intravitreal bevacizumab, IVR: Intravitreal ranibizumab, IVI: Intravitreal injection, IVA: Intravitreal aflibercept, GA: Gestational age, SEM: Standard error of mean, OR: Odds ratio

on ROP. Because of the safety concerns and the age range of the ROP patients, conducting well-designed clinical trials are much more complex than for adult patients with macular conditions, precluding valid information on the ocular or systemic superiority (or noninferiority) of different anti-VEGF agents.

There have been considerably fewer studies conducted on the efficacy of pegaptanib for treating ROP compared to other commonly used anti-VEGF medications. In combination with laser therapy, intravitreal pegaptanib (0.3 mg per 0.02 mL) was observed to lower the risk of retinal detachment compared to laser/cryotherapy alone, as evidenced by a study of 152 eyes (RR = 0.26, 95% CI: 0.12–0.55). In addition, the incidence of recurrence of ROP by 55 weeks' postmenstrual age was lower in the group that received pegaptanib + laser therapy, based on a study of 76 infants (RR = 0.29, 95% CI: 0.12–0.7). The study did not show any difference in the risk of perioperative retinal hemorrhages between the two groups (152 eyes, RR = 0.62, 95% CI: 0.24–1.56). However, the quality of evidence supporting these findings is low.[50,51]

Conbercept is a soluble receptor decoy created in China, which selectively binds to various isoforms of VEGF-A, VEGF-B, and placental growth factor. Studies on the use of conbercept for ROP are limited and mostly focused on comparing its efficacy to laser therapy and ranibizumab. The dosage administered in these studies was half of the adult dose (0.25 mg/0.025 mL). In a retrospective study conducted in China, 1627 eyes of 862 patients with zone 1 or zone 2 and type 1 ROP were included, and the reactivation rate in the eyes treated with conbercept was lower than those treated with ranibizumab.[52] A recent meta-analysis compared the effectiveness of conbercept and ranibizumab in treating ROP. In the meta-analysis, seven studies (n = 989) were included, comprising 303 cases (594 eyes) receiving conbercept and 686 patients (1318 eyes) receiving ranibizumab. Primary cure rate was reported in three studies, and results showed that conbercept had a significantly higher primary cure rate than ranibizumab (OR = 1.91, 95% CI: 1.05–3.49, $P < 0.05$). Five studies reported on the rate of ROP recurrence, and there were no significant differences between conbercept and ranibizumab (OR = 0.62, 95% CI: 0.28–1.38, $P > 0.05$). Retreatment rates were reported in three studies, and there were no significant differences between conbercept and ranibizumab (OR = 0.78, 95% CI: 0.21–2.93, $P > 0.05$).[53]

There is a consensus that the dose of intravitreal anti-VEGFs in neonates with ROP should be less than in adults because

the neonate eyeball volume is considerably less. However, the exact dose has been the subject of debate. In principle, higher doses may have a greater effect on inducing initial regression, but the lower doses could have the advantages of enhancing normal peripheral vascularization and improving systemic safety. In an RCT (n = 19 infants), Stahl *et al*. compared 0.12–0.20 mg IVR (24%–40% of the standard adult dose) and found them equally effective in controlling zone 1 or posterior zone 2 ROP. They reported superior physiologic peripheral retinal vascularization in the 0.12 mg group than in the 0.20 mg group (complete vascularization, 55.0% vs. 16.7%, respectively).[12]

Bayramoglu *et al*. compared two doses of IVB (0.3125 vs. the standard 0.625 mg) on 259 eyes of 142 patients with type 1 or AP-ROP. The retreatment rate was similar for both groups (23% vs. 19%; $P = 0.362$). The results of the progression of normal vascularization were inconclusive.[54]

In a de-escalation dose RCT on 61 neonates, Wallas *et al*. could achieve positive outcomes with IVB doses as low as 0.031 mg (2.5% of adult dose).[55] Another study assessed very low doses of IVB (0.016, 0.008, 0.004, and 0.002 mg) for ROP and found that the IVB effect would not be notably compromised for doses as low as 0.004 mg per injection.[56]

A recent report described good retinal structural outcomes after low or very low-dose IVB for type 1 ROP. However, additional treatment was needed for many eyes. The rate of reactivation was not related to the dosage, but it occurred sooner with very low-dose IVB.[21]

Discussion

Currently, the anti-VEGF agents have their role in managing type 1 ROP. They are preferred as the first-line treatment for zone 1 or posterior zone 2 ROP. Compared to laser therapy, anti-VEGFs were associated with fewer incomplete regression instances but more ROP reactivation, mainly in zone 2 disease. The current standard dose of IVI for ROP is half of the adult dose. IVB is the most widely used anti-VEGF in ROP management, followed by IVR. The recurrence rate is higher in infants with lower GA, more posterior zones, more severe disease, and IVR compared to IVB. IVI is associated with less astigmatism and ametropia than laser therapy but more PAR and long-standing abnormal vascular changes. IVI eliminates long-term ablation-related complications. There is no solid evidence on the possible association between IVI and neurodevelopmental delay.

Table 3 summarizes the findings of landmark studies of anti-VEGF agents for ROP. A comprehensive 2018 Cochrane systematic review and meta-analysis found that at that time, the quality of evidence was low/very low for most efficacy or ocular/systemic safety outcomes.[51] Although there has been significant progress since then, the need for well-designed studies to address the controversies in the field remains. In addition, the possible long-term systemic/neurodevelopmental effects of anti-VEGFs require additional investigation. Future studies are needed to answer several topics, including whether there is an advantage of one anti-VEGF agent over another; the safest effective dose in a neonate; the effect of anti-VEGF agents on ocular structural and functional outcomes in childhood (compared to laser); the delayed systemic effects of intravitreal anti-VEGFs (including adverse neurodevelopmental outcomes); and when should laser be administered after an intravitreal anti-VEGF injection? Of note, updated treatment algorithms are needed to highlight the optimal use of anti-VEGF agents in the context of ROP.

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Conflicts of interest

There are no conflicts of interest.

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