Antivascular endothelial growth factor in the treatment of retinopathy of prematurity

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Purpose of review
To review the most recent literature regarding the clinical experience of antivascular endothelial growth factor (anti-VEGF) therapies in the treatment of retinopathy of prematurity (ROP).

Recent findings
Anti-VEGF agents in stage 3+ and aggressive posterior ROP have been shown to induce rapid ROP regression. However, significant reoccurrence rates can require repeat injections and thus longer term and more frequent follow-up. Initial studies reflect conflicting evidence regarding significant systemic side effects of these treatments, and outcomes in these patients past the first few years of life are yet to be definitively determined.

Summary
Although anti-VEGF therapies show promise in the treatment of ROP, frequent reoccurrences and lack of thorough data about long-term side effects of pharmacologic intervention necessitate further research before anti-VEGF agents become the mainstay of ROP management.

Keywords
anti-VEGF, bevacizumab, ranibizumab, retinopathy of prematurity

INTRODUCTION

Retinopathy of prematurity (ROP) is a devastating vascular proliferative disorder that causes a spectrum of clinical disease in preterm infants and can result in blindness. Until the 1990s, cryotherapy was the first-line therapy for the management of ROP. The multicenter trial of cryotherapy for ROP demonstrated that cryotherapy produced less adverse outcomes as compared with controls, and the impact was sustained at 10-year follow-up [1].

In the late 1990s and 2000s, cryotherapy was replaced by laser photocoagulation. Studies comparing cryotherapy with laser photocoagulation found that patients treated with cryotherapy had significantly higher myopia compared with patients treated with laser [2]. This research led to a shift in primary therapy, and laser photocoagulation became the gold standard of ROP treatment. Although better tolerated than cryotherapy, laser photocoagulation has side effects, including reduction of the visual field, retinal hemorrhage, myopia, and cataract formation [3]. More recently, antivascular endothelial growth factor (VEGF) agents, which pharmacologically modify the course of this pathologic retinal vascularization, have shown significant promise. The 2011 hallmark study of anti-VEGF therapy in ROP, the efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity (BEAT-ROP), found that in infants with zone 1 stage 3+ disease, the recurrence rate of ROP in patients treated with bevacizumab was 4% compared with 22% with traditional laser therapy, lending support to the use of this new treatment modality [4].

ANTIVASCULAR ENDOTHELIAL GROWTH FACTOR VERSUS CONVENTIONAL LASER THERAPY

As the introduction of anti-VEGF therapy for ROP, studies of the potential benefits and risks of anti-VEGF treatments are ongoing. A recent retrospective study by Isaac *et al.* evaluated outcomes in infants

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KEY POINTS

- Recent studies have shown promise regarding the use of anti-VEGF therapies in the treatment of stage 3+ ROP.
- The frequent rate of reoccurrence of ROP after treatment with anti-VEGF agents necessitates frequent and prolonged follow-up with the possible need for retreatment or laser therapy.
- There are insufficient data regarding the long-term ocular and systemic side effects of anti-VEGF therapy for ROP.
- Further research regarding lasting results and side effects is needed before anti-VEGF agents become the mainstay of the management of ROP.

with ROP in zone 1 or 2 posterior treated with laser therapy in comparison with intravitreal bevacizumab (IVB). The study reported a favorable outcome in 12/15 eyes in the IVB arm and 18/18 eyes in the laser arm, with a higher prevalence of myopia in the laser treatment arm [5].

Hwang *et al.* compared the efficacy and complication rates of IVB with laser photocoagulation. The investigators treated both zones 1 and 2 posterior ROP with either IVB or laser and found that the rate of recurrence of ROP between the treatment modalities was similar [6▪]. Notably, this outcome differs considerably from the results of the original BEAT-ROP study, which reported a higher recurrence rate with laser therapy [4]. In contrast to Issac *et al.*, Hwang *et al.* did not find a significant difference in refractive error between the two treatment groups. It should be noted that the average postgestational age of refraction was 22 months in the IVB group compared with 37 months in the laser group [6▪]. Perhaps, this discrepancy in follow-up interval, as well as the potential for myopia to develop later in life, could affect these results.

Arambulo *et al.* reported a series of 57 patients treated with either intravitreal ranibizumab (IVR) alone or a combination of IVR and laser. Eyes treated with IVR alone had favorable outcomes in 87.5%; however, all of these eyes remained with peripheral avascular retina up to 6 months after treatment. Eyes treated with a combination of laser and IVR had successful outcomes in 70.7% of eyes. Authors note that optimal time for treatment is very important for ROP outcomes. Eyes treated with IVR underwent treatment at a mean postconception age of 36.6 weeks, although those receiving combination treatments were treated at a mean of 38.2 weeks. Therefore, although the IVR group had a higher percentage of favorable outcomes, it could be suggested that the difference in outcomes is affected by the timing of treatment [7].

ANTIVASCULAR ENDOTHELIAL GROWTH FACTOR TREATMENT

Recent data regarding anti-VEGF therapy continue to offer mixed evidence. Several studies examine the efficacy of anti-VEGF treatment both alone and in conjunction with traditional laser photocoagulation.

Yetik *et al.* from Turkey report a series of 122 patients including patients with prethreshold (type 1), threshold, and aggressive posterior ROP (APROP) treated with IVB. They found total regression was achieved in 95.4% of eyes after the first injection, whereas the remaining 11 eyes resolved with subsequent injections. The APROP group resulted in more cases of recurrence that occurred somewhat earlier, and a more frequent rate of and shorter time period to reinjections was seen in the threshold and APROP groups. Complete retinal vascular maturation was achieved without any significant complications in all cases [8].

Similarly, Nicoara *et al.* reported a series of 74 eyes in Romania of which 52 had APROP and 22 had zone 1 stage 3+ ROP, all of which were treated with a single injection of bevacizumab. One week after IVB, ROP regressed in 63 eyes with a 100% rate of resolution in zone 1 stage 3+ ROP. The authors note that their study included patients with ROP who were bigger and older in gestational age than would have met screening criteria as per the US guidelines [9]. This raises the question as to whether differences in neonatal care in various countries result in higher rates and more aggressive forms of ROP than are typically seen in the United States, and caution must be taken when generalizing these results to all patients.

No serious complications, such as retinal detachment, cataract, endophthalmitis, or contraction of ROP-associated vitreoretinal proliferations were observed in any of these studies.

Despite these promising results, definitive data on the effectiveness of anti-VEGF treatment is inconsistent. Issac *et al.* reported that, in eyes treated with IVB, the frequency of regression of plus disease was 100% by day 8, and regression of both stage 3 and plus disease was 100% by week 4. They subsequently noted that 17/28 eyes developed recurrence to stage 1 or 2 after regression. By 3 months of follow-up, only 18% of eyes vascularized into zone 3, and by 2 years, 39% of eyes were not vascularized into zone 3 as seen on fluorescein angiography [10▪▪]. This high rate of reoccurrence highlights the need for significantly more frequent follow-up

and the potential need for repeat treatment in eyes treated with anti-VEGF agents.

FOCUS ON RANIBIZUMAB VERSUS BEVACIZUMAB

Because of the molecular structure and size of IVR, it has been theorized to achieve a less significant extraocular concentration and has greater activity with less half-life in the vitreous as compared with the bevacizumab [7]. However, some studies seem to indicate that IVR may require more subsequent treatments than IVB.

Zhou *et al.* obtained blood samples collected before IVR, and at 1 day, 1, 2, and 4 weeks postinjection to analyze systemic absorption of the ranibizumab. The authors reported that plasma VEGF levels were reduced 1 day after injection, but that effect disappeared by 1 week. In contrast to prior reports that IVB induces suppression of systemic VEGF activity for at least 2 weeks postinjection, it can be suggested that IVR has a shorter influence on systemic VEGF levels and therefore may have fewer systemic side effects [11▪].

With attention to efficacy, in a study comparing IVB and IVR, Chen *et al.* described 72 eyes that received treatment with either IVB or IVR for type 1 ROP. All but one eye in the IVB group and all patients in the IVR group had retinal neovascularization and plus disease regression after treatment. There were no reports of reoccurrence in any treated patients. The authors concluded that IVB and IVR have similar efficacy in the regression of ROP [12].

Similarly, Erol *et al.* found that IVR and IVB showed comparable efficacy in the treatment of type 1 ROP. They noted that the incidence of disease relapse was higher in eyes that received ranibizumab, and subsequent laser treatment was performed in 6 of 15 eyes treated with IVR compared with 2 of 21 eyes that received IVB [13].

Wong *et al.* [14] reported ROP reactivation in 5/6 eyes treated with IVR, whereas none of four eyes treated with IVB experienced reactivation. The reports by Wong and Erol seem to contradict the conclusion presented by Chen suggesting that IVB and IVR are equally effective, despite the fact that all three studies utilized the same dosage of anti-VEGF agents. Wong *et al.* [14] note that although the shorter half-life and decreased systemic absorption of ranibizumab may make it an attractive option, it may translate into a higher chance of reactivation when compared with infants treated with bevacizumab necessitating even closer follow-up for reoccurrences.

Yi *et al.* reported 66 eyes treated with IVR. Over a mean 12.9 months follow-up interval, eight eyes had to receive additional treatments with a mean time to recurrence of 6.9 weeks. The authors report that compared with their prior experiences with IVB, a higher incidence and shorter time to reoccurrence were observed after IVR treatment, thus enforcing the need for longer and more frequent follow-up [15].

A small series of eight eyes of four infants by Baumal *et al.* resonates this point. All eight eyes treated with IVR showed resolution of plus disease within 48 h after injection and complete resolution of stage 3 ROP within 1 week. However, recurrent stage 2 or 3 ROP in mid-to-anterior zone 2 was noted 8–11 weeks after injection in all eyes and subsequent treatment with peripheral laser led to complete ROP regression.

Interestingly, the authors demonstrated anterior retinal growth during the time between IVR and laser treatment [16]. Although the potential for recurrent ROP after anti-VEGF treatment for posterior ROP requires vigilant monitoring, there may be an emerging role for anti-VEGF as a bridging modality to subsequent peripheral laser for recurrences in an effort to spare the posterior retina from photocoagulation effects.

Although much research has been conducted on anti-VEGF treatment in stage 3+ ROP, a case series by Cheng *et al.* sought to determine the effect of IVB and IVR on stage 4 ROP. Although one eye required a second IVB injection because of persistence of disease, all 13 eyes included in this report attained retinal reattachment and full vascularization [17]. As standard therapy for stage 4 ROP may include scleral buckling and vitrectomy, which is a more involved surgery requiring general anesthesia, this case series offers the possibility that anti-VEGF therapy may provide a promising nonsurgical option for disease treatment in the future.

STRUCTURAL CHANGES

Although many studies have reported on the clinical regression of ROP following anti-VEGF treatment, others have reported more subtle structural changes associated with this therapy. Padhi *et al.* examined changes in retinal vasculature after IVB for APROP in zone 1 and showed a rapid decrease of disease activity within a week of injection followed by a low phase of vascular development. On continued observation, ROP in eyes treated with laser regressed in an expected pattern within 3 weeks, as compared with bevacizumab-treated eyes where peripheral vascular abnormalities persisted even up to 1 year [18]. Lepore *et al.* reported a series of 12 infants with type 1, zone 1 ROP who were treated with IVB in one eye and conventional laser in the fellow eye. All eyes treated

with IVB had persistent peripheral and *posterior pole* abnormalities, such as hyperfluorescent lesions or absence of the foveal avascular zone, at 9 months of age [19]. Another series of three cases of IVB and IVR use in the setting of APROP revealed that a single round of anti-VEGF injection was sufficient to prevent disease recurrence in only one case as determined by serial fluorescein angiography [20].

Additionally, Erol *et al.* examined subclinical macular changes associated with IVR injection for ROP using spectral domain-optical coherence tomography, performed before and after injection. The authors reported a significant decrease in mean central foveal thickness before and 2 months after IVR. They note 16 eyes had macular edema before treatment, which had regressed in all patients [21].

Fortunately, advances in neonatal care have limited the development of APROP and thus the need for frequent treatment; however, these smaller studies suggest that disease regression after anti-VEGF therapy, as noted by indirect ophthalmoscopy, may be missing more subtle signs of macular change or persistent disease activity.

REFRACTIVE OUTCOMES

One of the major purported benefits of anti-VEGF therapy over laser therapy is that it offers a decreased incidence of myopia; however data on refractive outcomes after anti-VEGF treatment are mixed.

Kuo *et al.* compared patients who were treated with laser therapy or IVB to those with nontype 1 ROP under conservative follow-up and premature babies without ROP. Patients who received treatment for ROP were more prone to myopia, regardless of treatment modality. The results suggest that treatment-demanding ROP eyes are susceptible to more severe myopia with age compared with eyes without ROP or those with spontaneously regressed ROP [22].

In contrast, Gunay *et al.* [23] who examined 48 eyes treated with IVB compared with 30 eyes treated with traditional laser therapy, found that refractive errors were significantly less myopic with lower rates of anisometropia and strabismus at 2 years in those treated with IVB compared with laser.

In comparing IVB with IVR, Chen at al found no significant differences in *mean* refractive errors between the 2 groups, but reported a significantly higher chance of high myopia (more than −5.00 diopters) in the IVB group [12].

The potential decreased incidence of early unfavorable refractive outcomes in the anti-VEGF groups compared with the laser group may represent a potential benefit of anti-VEGF therapy, but consistent supporting data need to be substantiated.

ADVERSE OUTCOMES

Few severe side effects of anti-VEGF treatment have been reported. One infant had a cardiopulmonary event requiring cardiopulmonary resuscitation several hours after a unilateral injection, though neither the neonatology nor ophthalmology teams believed the injection was related to the event [14]. In a series of six eyes successfully treated with IVR, one infant had an upper air way infection 2 days postinjection, and three eyes required paracentesis to reduce the intraocular pressure after injection and to restore central artery perfusion [24]. Others reported those eyes treated with IVB had a higher rate of preretinal or vitreous hemorrhage compared with eyes treated with laser [6▪].

Yetik *et al.* noted less significant complications at a rate of 5.9%, of which 4.7% were subconjunctival hemorrhage and 1.2% due to pinpoint choroidal incarceration to the injection site. They noted an incidental positive systemic course after IVB injections, such as decrease in oxygen dependency, more rapid advancement to oral nutrition, and weight gain [8].

A meta-analysis of 24 studies by Pertl *et al.* determined that the adjusted 6-month risk of developing an ocular complication requiring retreatment to be approximately 2.8% with a systemic complication rate of 1.4%. Most systemic complications were thought to be incidental and not caused by anti-VEGF injection. Overall, the meta-analysis concluded that anti-VEGF therapy has a low-risk profile in ROP treatment in the first 6 months [25].

Systemic side effects of intravitreal anti-VEGF therapy may be decreased by using a decreased dose of medication. Connor *et al.* [26] reported a single case that was successfully treated with 0.16 mg of bevacizumab, which opens the door for further studies exploring this concept.

Regarding the long term systemic side effect profile of anti-VEGF agents, Araz *et al.* conducted a longitudinal follow-up study of premature infants who received IVB therapy in addition to standard laser photocoagulation. These patients were compared with a control group of birth weight and gestational age-matched infants who were treated with laser therapy alone. No significant differences were noted mean cognitive, language, or motor test scores of the groups [27]. Lein *et al.* examined neurodevelopmental outcomes at 24 months of 61 infants who received conventional laser treatment, IVB, or a combination of IVB with laser for reoccurrence or failed treatment. Interestingly, there was no difference in neurodevelopmental outcomes when the IVB-only and laser-only group were compared. However, a significantly higher rate of mental and psychomotor impairment was seen in the combination

treatment group as compared with the IVB only group (odds ratio = 5.3). The authors note that it is difficult to determine if the poorer outcomes in the combination group are definitively due to the use of IVB due to lack of randomization and selection bias [28]. In contrast, a recent report by Morin *et al.* evaluated 125 infants at 18 months corrected age at the time of the study and found that those treated with IVB compared with laser for ROP had a higher incidence of severe neurodevelopmental disabilities, such as severe cerebral palsy, hearing aids, and bilateral blindness. Although the study only included infants who were less than 29 weeks at birth and had a significantly higher percentage of patients that received laser compared with IVB which could affect their results, the outcomes are certainly concerning [29]. Additional and longer term data are needed for definitive answers.

CONCLUSION

Recent studies consistently report that anti-VEGF injections work well in stopping ROP progression, and can be performed quickly without the need for the general anesthesia as is the case with conventional laser therapy. The rate of reoccurrence and need for repeat injections and thus longer, more frequent follow-up are definite obstacles to widespread implementation. However, questions remain that require further study. Is this new treatment truly better than the standard laser treatment? Are the intraocular vascular changes demonstrated on fluorescein angiography and OCT permanent? How will these changes affect the central and peripheral vision for the life of the child? Is there less myopic progression with these treatments in the long term? This current review reveals mixed answers in the short term. Does the need for recurrent injections in some children increase these risks? What are the long-term neurodevelopmental effects of these agents, knowing that their vascular and neurologic development continue for weeks after injection? Will longer term studies reveal late changes, either intraocular or systemic, that will make us reconsider its use? Although this treatment is well tolerated generally, and initially rapidly effective, tempered optimism and further study is needed.

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Conflicts of interest

There are no conflicts of interest.

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