

Current and Future Trends in Treatment of Severe Retinopathy of Prematurity

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KEYWORDS

- Retinopathy of prematurity • Type 1 • Laser photocoagulation • Bevacizumab
- Clinical trials • Side effects

KEY POINTS

- Treatment for retinopathy of prematurity (ROP) is indicated when type 1 disease is present.
- The Early Treatment for Retinopathy of Prematurity (ETROP) clinical trial established that laser treatment of severe ROP has a high rate of visual and anatomic success.
- Recently, anti-vascular endothelial growth factor (VEGF) drugs, such as bevacizumab, have been used in lieu of or in addition to laser treatment.
- Results with bevacizumab are promising, but long-term outcomes and systemic side effects are unknown.
- Future studies are needed to determine whether anti-VEGF treatment is superior to laser and, if so, which drug and dose are safe and effective.

INTRODUCTION

The Early Treatment for Retinopathy of Prematurity (ETROP) study established the guidelines currently in use for optimal timing of laser treatment for severe retinopathy of prematurity (ROP).¹ The ETROP study concluded that ROP should be treated when type 1 ROP is present, which is defined as: (1) Zone I, any stage with plus disease, or (2) Zone I, stage 3 without plus disease, or (3) Zone 2, stage 2 or 3 with plus disease. Because Zone I, stage 3 ROP without plus disease is uncommon, most cases of type 1 ROP have plus disease. Treatment for disease less severe than type 1, including type 2 prethreshold ROP, is not indicated. Type 2 ROP is defined as Zone I, stage 1 or 2 without plus disease, or Zone II, stage 3 without plus disease. Eyes with type 2 ROP should not be treated, but instead should be observed for development of

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type 1 ROP. In the ETROP study, the rate of unfavorable visual acuity at age 6 years for type 2 prethreshold eyes was 23.6% for eyes treated as high risk prethreshold and 19.4% for those managed conventionally ($P = .37$).² In addition, many eyes recover without treatment. Even among high-risk prethreshold eyes in the ETROP study, 52% regressed without treatment.¹

LASER TREATMENT FOR SEVERE ROP

Laser photocoagulation is a time-tested, very successful treatment for severe ROP. Before the advent of laser treatment, cryotherapy was the first treatment shown to be effective for severe ROP. In the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study, eyes of 291 infants with threshold ROP were randomized to cryotherapy or observation. After 12 months, the rate of unfavorable anatomic outcome (defined as a macular fold or detachment, a retrolental mass, or surgery for a retinal detachment) was 47% in the untreated eyes and 26% in the treated eyes.³ Over time, laser replaced cryotherapy as the preferred method for treating peripheral avascular retina.

ETROP study investigators hypothesized that eyes treated earlier than threshold (ie, high-risk prethreshold) would have a better outcome. In this study, an unfavorable visual acuity outcome was defined as greater than 4 standard deviations from the mean for age by Teller Acuity Cards. The rates of unfavorable visual acuity at 9 months were 14.5% in eyes treated at high risk prethreshold, and 19.5% in conventionally managed eyes. Unfavorable retinal structure at 9 months was even better. Eyes treated at high risk prethreshold had an unfavorable visual acuity outcome rate of 9.1%, and those managed conventionally had a 15.6% unfavorable rate.¹ Six-year outcomes from the ETROP study confirmed that eyes with type 1 ROP benefited from treatment at high risk prethreshold. Twenty-five percent of those eyes had an unfavorable outcome (defined as visual acuity of 20/200 or worse) using Early Treatment Diabetic Retinopathy Study acuity.²

Laser treatment has several advantages. It has a very high success rate in terms of favorable visual outcome and avoiding retinal detachment. However, for many children, a favorable outcome does not mean normal vision.⁴ There may be effects of ROP or its treatment on the developing macula that are not seen by indirect ophthalmoscopy. For example, spectral-domain optical coherence tomography has shown cystoid structures and epiretinal membranes that are not detectable by routine examination.⁵ Laser treatment of ROP has been used successfully for many years, and the treatment itself has no systemic side effects. Sedation or intubation, sometimes required for treatment, may have systemic effects. Laser treatment does have some disadvantages. It is more time-consuming than is giving an intravitreal injection. It is more expensive than an injection of bevacizumab, which is the most commonly used anti-vascular endothelial growth factor (VEGF) treatment for ROP. There is a learning curve with delivery of effective laser treatment, and the necessary equipment and trained personnel are not available in all countries. Retreatment with laser is needed in approximately 10% of cases, but varies by practice, as some physicians deliver a higher number or intensity of laser spots during the initial treatment session. Prolonged laser treatment can cause upper back and neck pain for treating physicians. Possible ocular side effects of laser include cataracts, inflammation, hyphema, and phthisis.

ANTI-VEGF TREATMENT FOR SEVERE ROP

VEGF is important in the pathogenesis of ROP. Retinal ischemia causes excessive accumulation of VEGF, which results in the neovascularization that characterizes

severe ROP.⁶ As such, anti-VEGF drugs are a more direct approach than laser in blocking the effects of VEGF on the retina. Laser destroys peripheral avascular retina, which results in less VEGF production, but the effect is less rapid than with anti-VEGF treatment. Four anti-VEGF drugs are bevacizumab (Avastin), ranibizumab (Lucentis), pegaptanib (Macugen), and aflibercept (VEGF trap); of these, bevacizumab has been used the most in premature infants. An injection of bevacizumab is less time-consuming and less expensive than laser treatment. **Fig. 1** shows both eyes of a premature infant with type 1 ROP in Zone I, before bevacizumab injection and then 1 day after injection. Several case series have reported rapid resolution and high rates of success after bevacizumab,⁷⁻¹¹ and there has been one randomized trial (BEAT-ROP study) suggesting that anti-VEGF treatment is superior to laser for severe ROP in Zone I.¹² **Table 1** summarizes results from studies published to date on the treatment of severe ROP with anti-VEGF injections.

BEAT-ROP STUDY

There has been one published randomized trial comparing bevacizumab with laser for severe ROP. The BEAT-ROP (Bevacizumab Eliminates the Angiogenic Threat of ROP) study randomized infants to receive laser or bevacizumab, 0.625 mg in 0.025 mL. All infants had Zone I or posterior Zone II, stage 3 ROP with plus disease. The primary outcome was "recurrence of neovascularization in 1 or 2 eyes requiring retreatment by 54 weeks postmenstrual age." The study found that 6 of 140 eyes (4%) receiving bevacizumab had recurrence of neovascularization, compared with 32 of 146 lasered eyes (22%, $P = .002$). For Zone I, there was a statistically significant difference in recurrence rate between groups ($P = .003$), and for Zone II, there was no difference

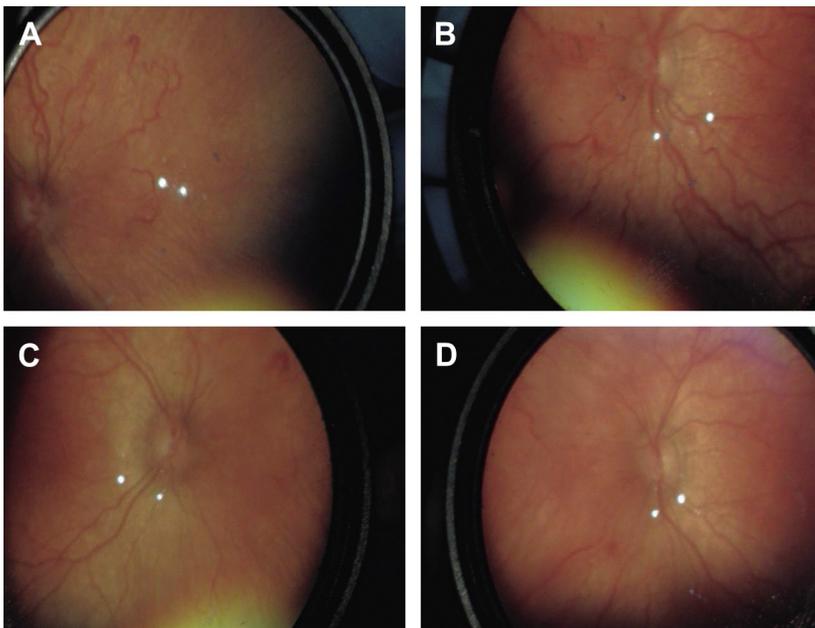


Fig. 1. Pre-injection of (A) Right eye of premature infant and (B) Left eye of premature infant. 1 day after intravitreal injection of 0.625 mg bevacizumab of (C) Right eye and (D) Left eye.

Table 1
Summary of results from studies published to date on treatment of severe ROP with anti-VEGF injections

Authors, ^{Ref.} Year	Study Design	No. of Patients	ROP Severity of Patients	Treatment	Outcome	Retreatment	Complications	Follow-up
Quiroz- Mercado et al, ⁹ 2008	Noncomparative, prospective, interventional case series	13 patients (18 eyes)	<i>Group I:</i> Stage 4a or 4b ROP that had no response to conventional treatment (3 patients, 4 eyes) <i>Group II:</i> Patients with threshold ROP and poor visualization of the retina (5 patients, 5 eyes) <i>Group III:</i> Patients with high- risk prethreshold or threshold ROP (5 patients, 9 eyes)	1 intravitreal injection of 1.25 mg bevacizumab as initial therapy	Neovascular regression in all patients	Not applicable	None	Mean follow-up of 6 mo after injection

Roohipoor et al, ¹⁰ 2011	Interventional case series	10 patients (12 eyes)	<p><i>Group 1:</i> Threshold ROP that did not respond to laser or had complications after laser (8 eyes)</p> <p><i>Group 2:</i> Aggressive Posterior ROP (APROP) with no prior treatment (4 eyes)</p>	<p><i>Group 1:</i> 1 intravitreal injection of 0.625 mg bevacizumab after laser</p> <p><i>Group 2:</i> 1 intravitreal injection of 0.625 mg bevacizumab as initial therapy</p>	<p><i>Group 1:</i> All eyes had regression of neovascularization (NV), resorption of vitreous hemorrhage (VH), and disappearance of hyphema in first week</p> <p><i>Group 2:</i> 1 patient had regression of ROP and complete peripheral vascularization; 1 patient had regression in plus disease, incomplete vascularization</p>	<p><i>Group 1:</i> Not applicable</p> <p><i>Group 2:</i> 1 patient required laser treatment 1.5 mo after bevacizumab</p>	None	At least 1 y
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Table 1
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Authors, ^{Ref.} Year	Study Design	No. of Patients	ROP Severity of Patients	Treatment	Outcome	Retreatment	Complications	Follow-up
Wu et al, ¹¹ 2011	Multicenter, retrospective case series study	27 patients (49 eyes)	<p><i>Stage 3 ROP:</i> 23 patients (41 eyes, 9 of which are Zone 1 and 32 are Zone 2)</p> <p><i>Stage 4A ROP:</i> 3 patients (6 eyes)</p> <p><i>Stage 5 ROP:</i> 1 patient (2 eyes)</p>	<p><i>Stage 3 ROP:</i> 36 eyes (88%) received 1 intravitreal injection of 0.625 mg bevacizumab as initial therapy</p> <p>5 eyes (12%) received 0.625 mg bevacizumab as salvage therapy after no response to laser</p> <p><i>Stage 4 and 5 ROP:</i> 0.625 mg Becavizumab was used to reduce chance of bleeding during vitrectomy</p>	<p><i>Stage 3 ROP:</i> 37 of 41 eyes (90%) regressed</p> <p><i>Stage 4a ROP:</i> 2 eyes (33%) regressed without need for vitrectomy</p> <p><i>Stage 5 ROP:</i> 2 eyes displayed decreased vascular tortuosity after treatment</p>	<p><i>Stage 3 ROP:</i> 4 eyes (10%) required additional laser</p> <p><i>Stage 4a ROP:</i> 4 eyes (67%) regressed after bevacizumab + vitrectomy</p> <p><i>Stage 5:</i> 2 eyes had retina fail to reattach after multiple vitrectomy surgeries</p>	<p>Vitreous or preretinal hemorrhage in 4 eyes (8%). Eventually resolved in all eyes</p> <p>Transient vascular sheathing in inferior venous branch in 2 eyes (4%)</p>	At least 6 mo following treatment

Mintz-Hittner et al, ¹² 2011	Prospective, controlled, randomized, stratified, multicenter trial	143 patients (286 eyes)	Zone I or posterior Zone II stage 3+	1 intravitreal injection of 0.625 mg bevacizumab, bilaterally, as initial therapy OR Conventional laser therapy, bilaterally, as initial therapy	<i>Bevacizumab group:</i> *Recurrence of NV with Zone I disease in 4 of 62 eyes *Recurrence of NV with Zone II disease in 4 of 78 eyes <i>Laser group:</i> *Recurrence of NV with Zone I disease in 28 of 66 eyes ($P = .003$) *Recurrence of NV with Zone II disease in 10 of 80 eyes ($P = .27$)	Need for additional treatment was the primary outcome	1 case of corneal opacity, 3 cases of lens opacity with laser therapy	54 wk postmenstrual age
Hu et al, ¹⁴ 2012	Retrospective review	9 patients (17 eyes) Only patients that had recurrence of ROP after bevacizumab were included	Type 1 ROP	1 intravitreal injection of 0.625–0.75 mg bevacizumab	Initial regression of ROP 5 eyes progressed to retinal detachment (RD) (mean age of RD was 58.4 wk postmenstrual age, minimum = 49 wk, maximum = 69 wk)	Mean age at treatment requiring recurrence was 49.3 wk postmenstrual age Retreatment consisted of repeated injections, and/or laser, and/or surgical repair	1 eye had cataract presumably associated with injection	56–104 wk

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Authors, ^{Ref.} Year	Study Design	No. of Patients	ROP Severity of Patients	Treatment	Outcome	Retreatment	Complications	Follow-up
Wu et al, ¹⁸ 2013	Multicenter, retrospective case series	85 patients (162 eyes)	Type 1 ROP	1 intravitreal injection of 0.625 mg bevacizumab as initial therapy	143 eyes (88%) exhibited ROP regression	14 eyes (9%) required additional laser treatment 2 eyes (1%) required 1 additional injection	2 eyes (1%) had vitreous or preretinal hemorrhage 1 eye (1%) had cataract	Until full vascularization of retina was observed (average of 13.7 mo)
Nazari et al, ¹⁹ 2010	Prospective, interventional case series	8 patients (14 eyes)	Severe ROP associated with VH or retinal hemorrhage (RH) 8 eyes had VH and/or RH precluding laser 6 eyes had VH develop after laser	1 intravitreal injection of 0.625 mg bevacizumab as initial therapy	In all eyes, plus disease disappeared completely within 2 wk and VH and/or RH was absorbed at last follow-up	Not applicable	None	3 mo after injection

Harder et al, ²⁰ 2011	Retrospective chart analysis	12 patients (23 eyes)	Threshold ROP	1 intravitreal injection of 0.375 mg bevacizumab as initial therapy 1 eye of 1 infant received laser then 0.375 mg bevacizumab owing to progression of disease	All eyes showed regression of plus disease within 2–6 d, decrease in pupillary rigidity, resolution of any tunica vasculosa lentis, if present before injection, and complete regression of retinal NV within 2–3 wk The eye that received laser and then bevacizumab developed a retinal fold and macular ectopia	Not applicable	None	Mean follow-up 30.4 wk
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Table 1
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Authors, ^{Ref.} Year	Study Design	No. of Patients	ROP Severity of Patients	Treatment	Outcome	Retreatment	Complications	Follow-up
Lee et al, ²¹ 2012	Retrospective review	3 patients (5 eyes) Patients were referred to tertiary care center for management of fibrous retinal traction band	Stage 3 ROP with plus	1 intravitreal injection of 0.75 mg bevacizumab as initial therapy (1 eye) 1 intravitreal injection of 0.75 mg bevacizumab + laser (4 eyes)	In all patients, initial regression of extraretinal fibrovascular proliferation and initial regression of plus disease In all patients, within 2.5–4 mo of initial ROP regression, atypical fibrous traction membrane developed Tractional RD in 3 of 5 eyes	Not applicable	None	19–31 mo after treatment (mean 23 mo)
Dorta and Kychenthal, ²² 2010	Noncomparative, consecutive case series	7 patients (12 eyes)	Type 1 ROP (9 eyes had Zone I, 3 had Zone II)	1 intravitreal injection of 0.625 mg bevacizumab as initial therapy	All eyes showed regression of disease	Not applicable	1 eye had an epiretinal hemorrhage due to injection procedure	Until vascularization reached Zone III
Salman, ²³ 2010	Prospective, nonrandomized study	9 patients (18 eyes)	Stage 3, threshold, or plus disease in Zone I/II	1 intravitreal injection of 0.625 mg bevacizumab as initial therapy	12 eyes had reduced neovascular activity after 1 injection	4 eyes required 2 injections 2 eyes needed 3 injections	None	1 y

between groups ($P = .27$).¹² This study had several important limitations. The primary outcome of recurrent neovascularization depended on treatment decisions by unmasked investigators. In addition, this outcome is considerably less relevant than visual acuity or retinal structure. Second, the laser “failure rate” of 22% was much higher than that reported in other studies, such as the ETROP study. Third, no safety data were provided.

UNKNOWN/POTENTIAL DISADVANTAGES OF ANTI-VEGF TREATMENT

Disadvantages of anti-VEGF treatment include the risk for endophthalmitis with intravitreal injection, unknown neural retinal effects, the possible effects of anti-VEGF on developing organs in the systemic circulation,¹³ a possibly higher death rate,¹² and the need for extended follow-up in the outpatient setting because of late recurrence of severe ROP.¹⁴

Serum VEGF levels decrease significantly after intravitreal injection in infants with ROP. In one study, bevacizumab levels increased from 1 day to 1 week to 2 weeks after injection.¹⁵ The effects on developing organs in the fragile premature infant are unknown. Some investigators have presented case series of infants treated with anti-VEGF drugs and have stated that “there have been no systemic side effects,” but such a conclusion cannot be established without a randomized comparison group. In a cohort of premature infants, there is much comorbidity, including developmental delay and cerebral palsy. If, for example, an anti-VEGF drug adversely affects the brain, this can only be known by comparing the neurodevelopment of infants randomized to treatment with that in children without the study drug.

Late recurrence of ROP has been observed in some cases after bevacizumab injection.¹⁴ It is unknown how often this occurs, how it should be treated, and how long these infants need to be closely followed after anti-VEGF injection. Additional clinical studies, including randomized trials, are needed to address many of these unanswered questions.

OUR CURRENT APPROACH

The current approach is based on the fact that laser has a high success rate, and the failure rate reflects the ETROP experience. Therefore, most babies with Zone I or Zone II ROP will undergo laser treatment. Bevacizumab also seems to have a high success rate. Which of the two treatments is better for infants with type 1 ROP has not yet been established. Data from the BEAT-ROP study showed a lower rate of recurrent neovascularization requiring retreatment with bevacizumab in comparison with laser.¹² However, there are different types of Zone I eyes. For example, there are Zone I eyes with a ridge that is close to or straddling the border of Zone 2. These eyes tend to act like Zone II eyes and usually respond well to laser treatment. On the other hand, there are eyes that resemble a postage stamp, which have a very small amount of vascularization and no visible macula and whose vessels do not extend far from the optic nerve. Bevacizumab is a particularly promising treatment for these types of eyes.

FUTURE DIRECTIONS

A large clinical trial comparing anti-VEGF treatment with laser is needed, with data on outcomes of visual acuity, retinal structure, and nerve development. Clinicians need to know how these treatments compare for short-term and long-term outcomes of (1) visual acuity by blinded examiners and (2) retinal structure, which would ideally be based on grading of the images by blinded experts. Moreover, data are needed

to compare outcomes when the laser failure rate is similar to that shown by ETROP. In the BEAT-ROP study, the laser failure rate was much higher than that found by most investigators who treat severe ROP. A larger trial could include intensive monitoring for systemic side effects and information about rare events, such as death, that can only be gleaned from a large cohort.

Which Drug?

Which anti-VEGF drug is the best to use for ROP? When choosing which drug to use, factors to consider are efficacy, systemic effects, and cost. The amount of drug crossing the ocular-blood barrier is not just a function of molecular size, because there are receptors that can facilitate the transport of entire molecules of immunoglobulin G.¹⁶ In adults, ranibizumab has a shorter half-life than bevacizumab in the systemic circulation.¹⁷ Comparative data on pharmacokinetics and systemic side effects in premature infants are required.

Which Dose?

Once the best anti-VEGF drug is known, what is the best dose? Dosing studies can be done as part of the nonrandomized, phase 1 clinical trial. One strategy would be to start with an effective dose and then gradually reduce the dose, using preestablished criteria for success at each dose level.

Which Treatment Strategy?

There is a plethora of new information about anti-VEGF treatment, which must all be put together into an evidence-based treatment paradigm. Possible treatment paradigms include: (1) laser for all type 1 cases followed by anti-VEGF as salvage treatment if laser fails; (2) laser for most cases and then anti-VEGF for very posterior Zone 1, obstructed view for laser, or when laser is not available; (3) laser for some cases, anti-VEGF for all Zone 1 cases and Zone 2 cases with an obstructed view; or (4) anti-VEGF as the primary therapy for all cases. If anti-VEGF is used as primary therapy for all cases of type 1 ROP, it could be followed by laser in all cases, or it could be followed by additional treatment for cases with recurrent disease. Additional treatment might consist of laser photocoagulation or reinjection of anti-VEGF treatment. Regarding the best approach, uncontrolled observational data may suggest that anti-VEGF treatment is effective without causing significant systemic side effects, but only high-quality comparisons of different approaches will truly guide us. Although nonrandomized retrospective or prospective data can be helpful, randomized controlled trials are the gold standard for guiding future treatments.

Need for Additional Studies

There is a long way to go to before an evidence-based treatment paradigm for laser and anti-VEGF therapy is available. Even before we pursue large randomized trials we still need to know which drug, which dose, and which treatment strategies to compare. There are many opportunities for high-quality comparative studies to shape the future treatment of severe ROP.

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