



## Anti-Vascular Endothelial Growth Factor Therapy for Primary Treatment of Type 1 Retinopathy of Prematurity

*A Report by the American Academy of Ophthalmology*

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**Purpose:** To review the available evidence on the ocular safety and efficacy of anti-vascular endothelial growth factor (VEGF) agents for the treatment of retinopathy of prematurity (ROP) compared with laser photocoagulation therapy.

**Methods:** A literature search of the PubMed and Cochrane Library databases was conducted last on September 6, 2016, with no date restrictions and limited to articles published in English. This search yielded 311 citations, of which 37 were deemed clinically relevant for full-text review. Thirteen of these were selected for inclusion in this assessment. The panel methodologist assigned ratings to the selected articles according to the level of evidence.

**Results:** Of the 13 citations, 6 articles on 5 randomized clinical trials provided level II evidence supporting the use of anti-VEGF agents, either as monotherapy or in combination with laser therapy. The primary outcome for these articles included recurrence of ROP and the need for retreatment (3 articles), retinal structure (2 articles), and refractive outcome (1 article). Seven articles were comparative case series that provided level III evidence. The primary outcomes included the effects of anti-VEGF treatment on development of peripheral retinal vessels (1 article), refractive outcomes (1 article), or both structural and refractive or visual outcomes (5 articles).

**Conclusions:** Current level II and III evidence indicates that intravitreal anti-VEGF therapy is as effective as laser photocoagulation for achieving regression of acute ROP. Although there are distinct ocular advantages to anti-VEGF pharmacotherapy for some cases (such as eyes with zone I disease or aggressive posterior ROP), the disadvantages are that the ROP recurrence rate is higher, and vigilant and extended follow-up is needed because retinal vascularization is usually incomplete. After intravitreal injection, bevacizumab can be detected in serum within 1 day, and serum VEGF levels are suppressed for at least 8 to 12 weeks. The effects of lowering systemic VEGF levels on the developing organ systems of premature infants are unknown, and there are limited long-term data on potential systemic and neurodevelopmental effects after anti-VEGF use for ROP treatment. Anti-VEGF agents should be used judiciously and with awareness of the known and unknown or potential side effects. *Ophthalmology* 2017;124:619-633 © 2017 by the American Academy of Ophthalmology

The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an Ophthalmic Technology Assessment is to review systematically the available research for clinical efficacy and safety. After review by members of the Ophthalmic Technology Assessment Committee, relevant subspecialty societies, and legal counsel, assessments are submitted to the Academy's Board of Trustees for consideration as official Academy statements. The purpose of this assessment by the Ophthalmic Technology Assessment Committee Pediatric Ophthalmology/Strabismus Panel is to

compare the ocular efficacy and safety of intravitreal injection of anti-vascular endothelial growth factor (VEGF) medications with those of laser photocoagulation therapy for treatment of type 1 retinopathy of prematurity (ROP).

### Background

Retinopathy of prematurity is a retinal vascular disorder found in premature infants, who have an increased risk of severe disease consistently associated with low gestational age (GA) at birth and low birth weight. Retinopathy of

prematurity is at least in part an oxygen-regulated retinopathy, and it is thought to develop in 2 phases. Exposure to relative hyperoxia in phase I causes downregulation of growth factors, resulting in retinovascular growth attenuation and vasocessation that leads to hypoxic ischemia and vasoproliferation in phase II.<sup>1-3</sup> Retinopathy of prematurity can progress from vasoproliferation to exudation and to cicatricial traction retinal detachment. Current estimates suggest that of the 13 million premature children born worldwide each year who survive the neonatal period, vision-threatening ROP will develop in more than 50 000.<sup>4</sup>

Although many efforts can be made to prevent ROP, most current treatments target the second phase, after abnormal fibrovascular proliferation occurs. The Cryotherapy for Retinopathy of Prematurity randomized trial demonstrated the efficacy of cryotherapy (vs. observation) as a treatment for threshold ROP (defined as 5 contiguous or 8 interrupted clock hours of stage 3 ROP with plus disease in zone I or II), and it showed a marked reduction in the rates of unfavorable retinal structural outcomes and blindness.<sup>5</sup> The Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial found improved retinal structural and visual outcomes when laser photocoagulation therapy was used for high-risk prethreshold ROP; current clinical treatment guidelines for ROP are based on ETROP recommendations.<sup>6</sup> The ETROP clinical guideline for the ROP severity at which treatment should be considered is defined as type 1 ROP, and it includes any ROP with plus disease or stage 3 without plus disease in zone I, and stage 2 or 3 with plus disease in zone II. However, any retinal ablative treatment is not always effective for type 1 ROP, as reflected in the 6-year ETROP outcomes showing an unfavorable visual acuity outcome (recognition visual acuity of  $\leq 20/200$ ) in 25.1% of eyes and an unfavorable structural outcome (retinal fold or detachment involving the macula, retrolental mass, or vitrectomy or scleral buckling surgery) in 8.9% of eyes. Furthermore, both laser treatment and cryotherapy are retinal ablative (destructive) treatments that can be stressful for the infant, require sedation or general anesthesia, and have potentially unwanted ocular side effects.

Although there are many factors involved in the normal growth and protection of retinal blood vessels, VEGF is required for normal angiogenesis, and it plays an important role in the development of ROP.<sup>7</sup> Vascular endothelial growth factor is modulated by relative tissue hypoxia or hyperoxia<sup>8</sup> and is potentiated by insulin-like growth factor 1,<sup>9</sup> which typically rises in the third trimester of fetal development but often is deficient after premature birth. Infants undergoing vitrectomy for severe ROP with retinal detachment have shown elevated intravitreal VEGF levels.<sup>10,11</sup> Similarly, adult eyes with proliferative retinal vascular disorders arising from retinal ischemia, such as diabetic retinopathy, also have elevated VEGF levels.<sup>12</sup> In recent years, there has been increased interest in, and use of, anti-VEGF therapy by intravitreal injection for several retinal vascular disorders, including ROP. In the premature infant population, however, there are concerns about systemic side effects of anti-VEGF agents because VEGF is important for angiogenesis not only in the eyes, but also in

other vital organs such as the lungs, kidneys, and brain.<sup>13</sup> Although off-label use of anti-VEGF agents for ROP treatment has been reported, either as monotherapy, in combination with laser photocoagulation therapy, or as salvage therapy, only a few studies provide a direct comparison of ROP treatment methods, and they generally provide limited follow-up data.

## Question for Assessment

The purpose of this assessment was to address the following question: How does the efficacy and safety of anti-VEGF therapy compare with that of standard laser photocoagulation for type 1 ROP, specifically with respect to retinal structural outcomes, visual and refractive outcomes, ocular complications, and systemic morbidity?

## Description of Evidence

A literature search was conducted last on September 6, 2016, in the PubMed and Cochrane Library databases without date restrictions and was limited to studies published in English. The following search terms were used:

*(Pegaptanib OR Macugen OR Bevacizumab OR Avastin OR Ranibizumab OR Lucentis OR Aflibercept OR vegf trap OR Eylea OR vegf inhibitor OR vegf inhibitors OR anti-vegf OR anti-vegfs OR vascular endothelial growth factor inhibitor OR vascular endothelial growth factor inhibitors) AND (prematurity retinopathies OR prematurity retinopathy OR retrolental fibroplasia OR retrolental fibroplasias OR ROP OR retinopathy of prematurity [Mesh] OR retinopathy of prematurity) AND (Laser Therapy [Mesh] OR laser therapy OR laser therapies OR laser ablation OR tissue ablation OR laser tissue ablation OR laser ablative) NOT (Child [Mesh] OR Child, Preschool [Mesh] OR Adolescent [Mesh] OR Adult [Mesh] OR Aged [Mesh] OR Aged, 80 and over [Mesh] OR Middle Aged [Mesh] OR Frail Elderly [Mesh] OR Young Adult [Mesh]) AND (Infant, Newborn [Mesh]).*

The search resulted in 311 potentially relevant citations. The first author (D.K.V.) reviewed the abstracts and marked those that potentially met the following inclusion criteria: the research was original; the study population consisted of infants with ROP; the study was a comparative case series or randomized trial; intervention group patients (eyes) were treated with bevacizumab, ranibizumab, or pegaptanib sodium (possibly in combination with laser); control group patients (eyes) underwent laser photocoagulation therapy; patients were followed up until retinal status after acute ROP could be determined; and retinal structure was included as an outcome. Each article was reviewed with respect to severity of ROP, based on the International Classification for ROP<sup>14</sup> considering zone, stage, and presence or absence of plus disease, as well as whether the ROP met contemporary treatment criteria. Some studies analyzed the effectiveness of an anti-VEGF agent as primary therapy for type 1 or threshold ROP, whereas others evaluated the effectiveness of these agents in combination with laser therapy, as salvage therapy after laser

treatment, or in conjunction with planned surgery for repair of retinal detachment. The first author reviewed prospective randomized trials and comparative case series that used anti-VEGF treatment as monotherapy or as a combined therapy compared with laser therapy. Noncomparative case series, single case reports, and commentaries were not included. Review articles were not considered in this assessment.

Thirty-seven articles were selected for full-text review. Most articles ( $n = 22$ ) were eliminated because they were not comparative case series or randomized trials, and 2 comparative case series were eliminated because the comparison group was not standard laser therapy. The remaining 13 studies were determined to be relevant for the assessment objectives, and they are listed in [Table 1](#).

The methodologist (M.M.) assigned levels of evidence ratings to the studies according to the strength of evidence. A level I rating was assigned to well-designed and well-conducted randomized clinical trials, a level II rating was assigned to well-designed case-control and cohort studies and lower-quality randomized studies, and a level III rating was assigned to comparative case series. No studies met the criteria for level I evidence, 6 articles (from 5 randomized trials) met the criteria for level II evidence, and 7 articles met the criteria for level III evidence. The predefined standardized criteria for rating all Ophthalmic Technology Assessments involving treatment comparisons requires masking when the outcome is subjective for a level I strength of evidence rating. Although it is clear that masking is not possible for this particular Ophthalmic Technology Assessment, having no masking is a source of possible bias in the treatment comparison, regardless of whether masking is possible, and the level of evidence reflects this.

## Published Results

### Prospective Randomized Trials

All prospective randomized studies were assigned a rating of level II.

In 2011, Mintz-Hittner et al<sup>15</sup> (United States) reported results of the Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) study.<sup>28</sup> This multicenter study randomized infants who had bilateral stage 3 ROP with plus disease in zone I or posterior zone II to intravitreal bevacizumab (0.625 mg in 0.025 ml) monotherapy or to laser photocoagulation therapy. In this study, 150 infants (300 eyes) were enrolled and 143 infants survived to 54 weeks' postmenstrual age (PMA). The primary outcome was recurrence of ROP that required retreatment by 54 weeks' PMA. RetCam (Clarity Medical Systems, Pleasanton, CA) images were used to document the ROP, and at recurrence, these images were reviewed by the treating and consulting ophthalmologist (without masking) before deciding on additional treatment. Recurrence that required treatment occurred in 4% (6/140 eyes) of the bevacizumab group and in 22% (32/146 eyes) of the laser group. Analysis stratified by zone of ROP showed a significant treatment effect for zone I ROP (recurrence of 6% [2/31 infants] in the bevacizumab group vs. 42% [14/33 infants] in the laser group), but not for zone II ROP. After treatment for zone I disease with bevacizumab, recurrence was

seen in 1 eye of 2 patients, and macular dragging occurred in 1 of these eyes. After laser treatment for zone I disease, recurrence was seen in 23 eyes (9 bilateral); macular dragging occurred in 16 eyes and retinal detachment in 2 eyes. After treatment for zone II disease with bevacizumab, recurrence was seen in both eyes of 2 patients, and both eyes of 1 patient showed retinal detachment. After laser treatment for zone II disease, recurrence was seen in 9 eyes of 5 patients, with macular dragging in 6 eyes, but no retinal detachments. This trial was rated level II evidence because of a lack of masked outcome determination. Additional concerns include the following: (1) a change in the primary study outcome from lack of recurrence to a need for retreatment by 54 weeks' PMA; (2) a lack of standardized laser protocol or assessment of the quality of laser treatment and pattern; (3) a higher level of treatment failure (a requirement for retreatment for zone I eyes) compared with other study populations, thus potentially biasing the primary outcome in favor of bevacizumab; and (4) concern about generalizability to all populations because of a high percentage of Hispanic infants in this study (85/150 [56.6%]). Furthermore, this study ended without follow-up for most zone I eyes that never met retreatment criteria in the bevacizumab group, but probably never fully vascularized.

In 2012, Atrata et al<sup>16</sup> (Czech Republic) reported the results of a prospective comparative study in which 76 infants (152 eyes) with stage 3 ROP with plus disease in zone I or posterior zone II were randomized to receive either intravitreal pegaptanib (0.3 mg in 0.02 ml) and conventional diode laser photocoagulation (group 1; 68 eyes of 34 infants), or diode laser photocoagulation with or without cryotherapy (group 2; 84 eyes of 42 infants). Thus, this study reports results of combination therapy (anti-VEGF treatment plus diode laser photocoagulation) compared with diode laser photocoagulation alone. Outcomes were categorized as retinal anatomic status and rate of recurrence requiring retreatment by 55 weeks' PMA. RetCam images were obtained by the treating ophthalmologist at the time of treatment or retreatment and were reviewed by 2 other ophthalmologists before treatment decisions were made. An unfavorable outcome was defined as the development of stage 4A or worse ROP. Recurrence of stage 3 ROP in at least 1 eye was seen in 14.6% (5/34) of infants in group 1 and in 50% (21/42) of infants in group 2; a favorable anatomic outcome was seen in 89.7% (61/68) of eyes in group 1 and 60.7% (51/84) of eyes in group 2. There was faster resolution of plus disease for eyes in group 1 compared with those in group 2 (mean, 1.3 weeks vs. 2.6 weeks, respectively), shorter time to the growth of retinal vessels into the peripheral retina treated with laser for eyes in group 1 compared with group 2 (mean, 2.2 weeks vs. 3.6 weeks, respectively), and a longer time to recurrence (mean  $\pm$  standard deviation, 15.1 $\pm$ 4.1 weeks for 6 eyes in group 1 vs. 5.9 $\pm$ 4.8 weeks for 26 eyes in group 2). Although the rate of recurrence, the rate of the need for retreatment, and the percentage of eyes with unfavorable anatomic outcomes are all higher in this study compared with most cohorts, the added benefit of anti-VEGF therapy is notable. Other limitations of the trial include a lack of standardized laser protocol and assessment of laser quality as well as a lack of a standard reading protocol for images used in making treatment decisions. This trial was rated level II because of its small sample size and a lack of masked outcome determination.

Moran et al<sup>17</sup> (Ireland) reported outcomes of 14 infants with type 1 ROP, all with bilateral stage 3 with plus disease in zone I

Table 1. Studies Meeting Criteria for Ophthalmic Technology Assessment

Author(s), Year	Level of Evidence	Design	No. Infants/Eyes Included for Anti-Vascular Endothelial Growth Factor Treatment and for Laser Treatment	Anti-Vascular Endothelial Growth Factor Agent and Dose	Mean Gestational Age and Birth Weight (Postmenstrual Age at Treatment)	Retinopathy of Prematurity Stages Included in Study	Length of Follow-up	Outcome(s)/Results for Each Outcome by Treatment (% or Mean/Median and Range, Depending on Type of Outcome)	Comments
Mintz- Hittner et al, <sup>15</sup> 2011  (BEAT- ROP)	II	RCT	150 infants/300 eyes initially enrolled Infants randomized to: IVB (n = 75) or laser (n = 75)  143 infants survived to 54 weeks' PMA; zone I: 64 infants (31 IVB, 33 laser); zone II: 79 infants (39 IVB, 40 laser)	Bevacizumab 0.625 mg (0.025 ml)	Zone I IVB: GA, 24.2±1.3 wks BW, 615.2±139.5 g (34.5±1.4 wks) Zone I laser: GA, 24.3±1.6 wks BW, 657.9±159.5 g (33.7±1.6 wks) Zone II IVB: GA, 24.5±1.2 wks BW, 689.2±111.3 g (35.7±2.1 wks) Zone II laser: GA, 24.5±1.4 wks BW, 680.7±156.8 g (35.8±2.0 wks)	Stage 3+ ROP in zone I or posterior zone II in each eye	54 wks' PMA	Primary outcome was recurrence requiring retreatment by 54 weeks' PMA: Zone I: IVB, 6% (2/131 infants) Laser, 42% (14/33 infants) P = 0.003 Zone II: IVB, 5% (2/39 infants) Laser, 12% (5/40 infants) P = 0.27	Graded as lower- quality RCT primarily because there was no masking and the outcome was subjective. Also, (1) changed primary outcome during the trial but before data analysis; (2) reported subgroup results (zone I/zone II) without performing a test for interaction.
Autrata et al, <sup>16</sup> 2012	II	RCT	Total: 76 infants/152 eyes Anti-VEGF + laser: 34 infants/68 eyes Laser: 42 infants/84 eyes	Pegaptanib and laser 0.3 mg (0.02 ml)	Anti-VEGF + laser: GA, 24.9±1.3 wks BW, 773±158 g (33.7±1.6 wks) Laser: GA, 25.2±1.4 wks BW, 795±166 g (34.1±1.7 wks)	Stage 3+ ROP; zone I and posterior zone II	Anti-VEGF + laser: mean follow-up, 19.3 mos (5–37 mos) Laser: mean follow-up, 21.5 mos (4–38 mos)	Primary outcome was absence of recurrence of stage 3+: Anti-VEGF + laser, 85.4% (29/34 infants) Laser, 50% (21/42 infants) P = 0.0197 Secondary outcome was unfavorable structural outcome at final examination: Anti-VEGF + laser, 10.3% (7/68 eyes) Laser, 39.2% (33/84 eyes) P = 0.0149	Combination anti-VEGF + laser (group 1) compared with conventional laser therapy (group 2). Lower-quality RCT. Primary and secondary outcomes not masked. No formal sample size reported. Random assignment method not clear. Study reporting does not meet CONSORT* criteria.

Table 1. (Continued.)

Author(s), Year	Level of Evidence	Design	No. Infants/Eyes Included for Anti-Vascular Endothelial Growth Factor Treatment and for Laser Treatment	Anti-Vascular Endothelial Growth Factor Agent and Dose	Mean Gestational Age and Birth Weight (Postmenstrual Age at Treatment)	Retinopathy of Prematurity Stages Included in Study	Length of Follow-up	Outcome(s)/Results for Each Outcome by Treatment (% or Mean/Median and Range, Depending on Type of Outcome)	Comments
Moran et al, <sup>17</sup> 2014	II	RCT	14 infants/28 eyes; eyes were randomized to receive IVB in one eye and laser treatment in fellow eye (4 infants bilateral zone I/10 infants bilateral zone II)	Bevacizumab 1.25 mg (0.1 ml)	Mean PMA at treatment, 35 wks	Bilateral stage 3+ ROP in zone I (n = 4) or posterior zone II (n = 14)	2 yrs	Recurrence with retreatment: IVB, 21.4% (3/14 eyes) Laser, 7.1% (1/14 eyes) ( <i>P</i> value not reported)	Lower-quality RCT with small sample size and no masking.
Geloneck et al, <sup>18</sup> 2014  (BEAT-ROP)	II	RCT	150 infants/300 eyes (BEAT-ROP): 131 infants/255 eyes eligible for analysis  Cycloplegic refractions performed on 109 (83%) infants/211 (83%) eyes	Bevacizumab 0.625 mg (0.025 ml) (BEAT-ROP)	Zone I IVB: GA, 24.3±1.3 wks BW, 625±150 g (34.5±1.5 wks) Zone I laser: GA, 23.9±0.8 wks BW, 648±89 g (33.6±1.6 wks) Zone II IVB: GA, 24.4±1.2 wks BW, 699±116 g (35.5±1.8 wks) Zone II laser: GA, 24.5±1.5 wks BW, 681±150 g (35.8±2.1 wks)	Stage 3+ ROP or aggressive posterior ROP; zone I and posterior zone II (BEAT-ROP RCT)	Mean PMA, 2.5 (0.9) yrs	Cycloplegic refraction, mean (SD): Zone I: IVB, -1.51 (3.42) D (52 eyes) Laser, -8.44 (7.57) D (35 eyes) <i>P</i> < 0.001 Zone II: IVB, -0.58 (2.53) D (58 eyes) Laser, -5.83 (5.87) D (66 eyes) <i>P</i> < 0.001 Very high myopia (≥-8.0 D): Zone I: IVB, 3.8% (2/52 eyes) Laser, 51.4% (18/35 eyes) <i>P</i> < 0.001 Zone II: IVB, 1.7% (1/58 eyes) Laser, 36.4% (24/66 eyes) <i>P</i> < 0.001	Lower-quality RCT. Outcome assessment (cycloplegic refractive error by retinoscopy) not masked.

Table 1. (Continued.)

Author(s), Year	Level of Evidence	Design	No. Infants/Eyes Included for Anti-Vascular Endothelial Growth Factor Treatment and for Laser Treatment	Anti-Vascular Endothelial Growth Factor Agent and Dose	Mean Gestational Age and Birth Weight (Postmenstrual Age at Treatment)	Retinopathy of Prematurity Stages Included in Study	Length of Follow-up	Outcome(s)/Results for Each Outcome by Treatment (% or Mean/Median and Range, Depending on Type of Outcome)	Comments
Lepore et al, <sup>19</sup> 2014	II	RCT	13 infants/26 eyes with zone I ROP (3 infants stage 3+, 10 stage 3 no plus) Eyes were randomized to receive IVB in one eye and laser in the other eye 1 infant died; 1 eye progressed to complete retinal detachment before outcome measure (n = 23 study eyes)	Bevacizumab 0.5 mg (0.02 ml)	Infants with zone I stage 3 with plus disease: GA, 25 wks BW, 693 g Infants with zone I stage 3 without plus disease: GA, 25.7 wks BW, 705 g	Type 1 ROP; zone I, stage 3 with or without plus disease	9-mo follow-up Digital fundus photographs (every 3 days after treatment) and FA imaging (every 2 wks until discharge and at 9 mos)	Presence of retinal or choroidal abnormalities on digital fundus photographs or FA imaging All IVB-treated eyes demonstrated abnormalities in the retinal periphery (avascular areas, atypical branching, shunts) or posterior pole (hyperfluorescent lesion, absence of foveal avascular zone), whereas most laser-treated eyes did not	Lower-quality RCT. Small sample size, no masking.
Zhang, et al, <sup>20</sup> 2016 [Epub ahead of print]	II	RCT	50 infants/100 eyes Infants were randomized to receive IVR monotherapy or diode laser therapy	Ranibizumab 0.3 mg (0.03 ml)	IVR: GA, 29.0±1.6 wks BW, 1220±320 g Laser: GA, 28.3±1.8 wks BW, 1060±240 g	Type 1 ROP; zone II (stage 2 or 3 with plus disease)	6 mos	Regression of plus disease and ROP, recurrence of ROP, complications Significantly greater recurrence rate in IVR group (26 eyes of 13 infants [52%]) vs. laser group (2 eyes of 1 infant did not show initial regression and required retreatment [4%]); P = 0.001 No complications in either group	Lower-quality RCT. No sample size justification, no masking. Potential lack of generalizability; all zone II eyes and all patients were Han Chinese.
Lee et al, <sup>21</sup> 2010	III	Comparative case series	Total: 15 infants/30 eyes IVB + laser: 8 infants/16 eyes Laser: 7 infants/14 eyes	Bevacizumab 0.5 mg (0.02 ml)	IVB + laser: GA, 25.7 wks BW, 820.6±190.5 g (39 1/7 wks) Laser: GA, 26.9 wks BW, 933.1±355.9 g (36 3/7 wks)	Moderate to severe stage 3+ ROP	8-wk follow-up after treatment	Effects on development of peripheral retinal vessels: Time to resolution of plus disease (wks): IVB + laser, 1.0±0 (n = 8 infants) Laser, 2.3±0.8 (n = 7 infants) P = 0.002 Time to vascularization of peripheral retina (wks): IVB + laser, 2.0±0.5 (n = 8 infants) Laser, 2.9±0.7 (n = 7 infants) P = 0.02 No significant or systemic complications in either group	Combination therapy (IVB and laser) compared with laser alone. Comparative case series with small sample size and noncomparable treatment groups.

Table 1. (Continued.)

Author(s), Year	Level of Evidence	Design	No. Infants/Eyes Included for Anti-Vascular Endothelial Growth Factor Treatment and for Laser Treatment	Anti-Vascular Endothelial Growth Factor Agent and Dose	Mean Gestational Age and Birth Weight (Postmenstrual Age at Treatment)	Retinopathy of Prematurity Stages Included in Study	Length of Follow-up	Outcome(s)/Results for Each Outcome by Treatment (% or Mean/Median and Range, Depending on Type of Outcome)	Comments
Harder et al, <sup>22</sup> 2013	III	Comparative case series	Total: 25 infants/49 eyes IVB: 12 infants/23 eyes Historical laser cohort: 13 infants/ 26 eyes	Bevacizumab 0.375 mg (n = 9) or 0.625 mg (n = 3)	IVB: GA, 25.2±1.6 wks BW, 622±153 g Laser: GA, 25.3±1.8 wks BW, 717±197 g	Stage 3+ ROP in zone I or posterior zone II	1 yr (11.4±2.3 mos corrected age)	Cycloplegic refraction, mean (SD): IVB, -1.04±4.24 D (n = 23 eyes) Laser, -4.41±5.50 D (n = 26 eyes) P = 0.02	Comparative case series with small sample size. Treatment groups reasonably well matched; analysis adjusted for BW, GA, and gender. Seems laser group taken from period just before IVB use began. IVB = consecutive cases.
Hwang et al, <sup>23</sup> 2015	III	Comparative case series	Total: 28 infants/54 eyes IVB: 11 infants/22 eyes Laser: 17 infants/32 eyes	Bevacizumab 0.625 mg (0.025 ml)	IVB: GA, 24.2±1.0 wks BW, 668.1±127.3 g (35.1 wks) Laser: GA, 24.8±1.2 wks BW, 701.4±118.8 g (36.1 wks)	Type 1 ROP; zone I or posterior zone II	At least 6 mos IVB: 21.7 wks Laser: 34.5 wks	Rate of recurrence: IVB, 14% (3/22 eyes) Laser, 3% (1/32 eyes)  Complications: Retinal detachment (1 laser eye); macular ectopia (5 laser eyes)  Refraction at last follow- up/after GA: Overall: IVB, -2.4±3.5 D at 22.4 mos (n = 20 eyes) Laser, -5.3±5.4 D at 37.1 mos (n = 29 eyes) Zone I: IVB, -3.7±3.3 D (n = 14 eyes) Laser, -10.1±10.5 D (n = 4 eyes) P = 0.41	Comparative case series with small sample size.

(Continued)

Table 1. (Continued.)

Author(s), Year	Level of Evidence	Design	No. Infants/Eyes Included for Anti-Vascular Endothelial Growth Factor Treatment and for Laser Treatment	Anti-Vascular Endothelial Growth Factor Agent and Dose	Mean Gestational Age and Birth Weight (Postmenstrual Age at Treatment)	Retinopathy of Prematurity Stages Included in Study	Length of Follow-up	Outcome(s)/Results for Each Outcome by Treatment (% or Mean/Median and Range, Depending on Type of Outcome)	Comments
Isaac et al, <sup>24</sup> 2015	III	Comparative case series	Total: 25 infants/45 eyes IVB: 13 infants/23 eyes Diode laser: 12 infants/22 eyes	Bevacizumab 0.625 mg (0.025 ml)	IVB: GA, 25.2±1.4 wks BW, 722±131 g (37.6±1.7 wks)  Laser: GA, 25.0±1.1 wks BW, 674±175 g (36.7±2.6 wks)	Type 1 ROP; zone I or posterior zone II	At least 6 mos	Zone II: IVB, 0.6±1.7 D (n = 6 eyes) Laser, -4.7±4.6 D (n = 25 eyes) P = 0.002  Structural outcome at 1 yr corrected age: neither group developed unfavorable structural outcomes. VA (mean ± SD logMAR) at corrected age: IVB, 0.99±0.38 (n = 15 eyes) at 11.1 mos Laser, 0.71±0.36 (n = 18 eyes) at 12.1 mos P = 0.34  Refractive error (mean ± SD) at corrected age: IVB, -3.57±6.19 D (n = 23 eyes) at 10.8 mos Laser, -6.39±4.41 D (n = 22 eyes) at 11.3 mos P = 0.33  Number of follow-up visits 9 mos after treatment: IVB, 16±6 Laser, 6±3 P < 0.0001	Comparative case series with small sample size. Treatment groups were reasonably comparable on measured characteristics; no apparent severe confounding.
Gunay et al, <sup>25</sup> 2016	III	Comparative case series	134 infants/264 eyes IVB: 55 infants IVR: 22 infants Laser: 57 infants	Bevacizumab 0.625 mg (0.025 ml) or Ranibizumab 0.25 mg (0.025 ml)	IVB: GA, 27.3±2.2 wks BW, 1005±411 g (34.8±1.9 wks)  IVR: GA, 28.0±2.9 wks BW, 1196±467 g (35.6±1.6 wks)  Laser: GA, 28.2±2.5 wks	Type 1 ROP	IVB: 19.4±6.4 mos IVR: 19.0±4.8 mos Laser: 20.7±6.9 mos	Resolution after single treatment: 100% in all groups Recurrence of ROP: IVB, 5.5% IVR, 50% Laser, 1.8% Retreatment of ROP: IVB, 5.5% IVR, 13.6%	Comparative case series, noncomparable groups.

Table 1. (Continued.)

Author(s), Year	Level of Evidence	Design	No. Infants/Eyes Included for Anti-Vascular Endothelial Growth Factor Treatment and for Laser Treatment	Anti-Vascular Endothelial Growth Factor Agent and Dose	Mean Gestational Age and Birth Weight (Postmenstrual Age at Treatment)	Retinopathy of Prematurity Stages Included in Study	Length of Follow-up	Outcome(s)/Results for Each Outcome by Treatment (% or Mean/Median and Range, Depending on Type of Outcome)	Comments
Gunay et al, <sup>25</sup> cont.					BW, 1119±337 g (36.0±1.4 wks)			Laser, 0% Presence of high myopia (zone I, zone II): IVB, 23.8%, 5.9% IVR, 14.3%, 12.5% Laser, 71.4%, 6% P = 0.019, P = 0.77	
Gunay et al, <sup>26</sup> 2016 [Epub ahead of print]	III	Comparative case series in infants with BW >1500 g and high-risk characteristics	36 infants/71 eyes IVB: 15 infants Laser: 21 infants	Bevacizumab 0.625 mg (0.025 ml)	IVB: GA, 32.3 wks BW, 1908 g (36.9 wks) Laser: GA, 32.0 wks BW, 1816 g (38 wks)	Zone II stage 3+ or aggressive posterior disease	IVB: 18 mos (range, 11–33 mos) Laser: 20 mos (range, 8–47 mos)	Unfavorable structural outcome: no eyes in either group had unfavorable structural outcome	Comparative case series with small sample size.
Mueller et al, <sup>27</sup> 2016 [Epub ahead of print]	III	Comparative case series	54 infants/108 eyes IVB: 37 infants/74 eyes Laser: 17 infants/34 eyes	Bevacizumab 0.625 mg (0.025 ml)	Posterior zone I (n = 4 infants):† GA, 24.0 wks BW, 461 g (33.7 wks) Posterior zone II (n = 29 infants):† GA, 24.9 wks BW, 642.5 g (35.4 wks) Peripheral zone II (n = 21 infants):† GA, 25.4 wks BW, 575 g (40.1 wks)	Type 1 ROP; posterior zone I, posterior zone II, or peripheral zone II stage 3+	12–15 mos of age	Time to complete regression of active ROP (median days): Posterior ROP: IVB, 12 (IQR, 9–15) Laser, 57 (IQR, 28–63) P = 0.002 Peripheral ROP: IVB, 25 (IQR, 13.5–34.5) Laser, 24 (IQR, 12–45) P > 0.05 Recurrence of ROP: IVB, 12% of infants Laser, 0% of infants Visual acuity (cycle/degree) and refractive error (SE diopters). No statistically significant differences between IVB and laser for posterior or peripheral ROP	Comparative case series with small sample size.

BEAT-ROP = Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity study; BW = birth weight; CONSORT = Consolidated Standards of Reporting Trials; D = diopter; ERG = electroretinography; FA = fluorescein angiography; GA = gestational age; IQR = interquartile range; IVB = intravitreal bevacizumab; IVR = intravitreal ranibizumab; logMAR = logarithm of the minimum angle of resolution; MRI = magnetic resonance imaging; PMA = postmenstrual age; RCT = randomized controlled trial; ROP = retinopathy of prematurity; SD = standard deviation; SE = spherical equivalent; VA = visual acuity; VEGF = vascular endothelial growth factor; VEP = visual evoked potential.

\*Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c332.

†Median values.

or posterior zone II ROP, who were randomized to receive bevacizumab (1.25 mg in 0.1 ml) in 1 eye and diode laser therapy in the other eye. In addition to early retinal status after treatment, these infants had complete eye and pediatric medical and developmental examinations at 1 and 2 years of age. Pediatric examinations included assessment of systemic diagnoses and developmental status, and magnetic resonance imaging of the brain was obtained for all infants. When possible, visual evoked potentials and electroretinography were performed. Recurrence requiring retreatment occurred for 3 eyes in the bevacizumab group and for 1 eye in the laser group; all eyes had a favorable structural outcome. Retreatment occurred earlier for the eye that received laser (at 37 weeks) than for the eyes that received bevacizumab (at 50, 51, and 52 weeks). The authors concluded that the pediatric and ophthalmic assessments at 2 years of age showed no adverse ocular or systemic events that could be attributed to bevacizumab therapy. No details of functional outcome measures were reported. Limitations of this study include small sample size, lack of distinction between zone I and II disease, and recurrence that was not well defined. This trial was rated level II because of its small sample size and a lack of masked outcome determination.

In 2014, Geloneck et al<sup>18</sup> (United States) published the refractive outcomes for eyes of infants enrolled in the BEAT-ROP study. Of the 150 infants enrolled, 137 survived (there were 6 deaths in the bevacizumab group and 7 deaths in the laser photocoagulation group). Eyes undergoing intraocular surgery were excluded from analysis (19 eyes, 6 bilateral), leaving 255 eyes of 131 infants for analysis. Refractions determined by cycloplegic retinoscopy were available for 83% of the eyes, and infants were examined at a mean age of  $2.5 \pm 0.9$  years. For eyes treated for zone I disease, the mean spherical equivalent (SE) was  $-1.51 \pm 3.42$  diopters (D) for the group of 52 eyes that received bevacizumab compared with  $-8.44 \pm 7.57$  D for the group of 35 eyes that received laser treatment. For eyes with zone II disease, the mean SE was  $-0.58 \pm 2.53$  D for the group of 58 eyes that received bevacizumab compared with  $-5.83 \pm 5.87$  D for the group of 66 eyes that received laser treatment. Very high myopia ( $\geq -8.0$  D) was seen more frequently among eyes undergoing laser treatment (51.4% zone I, 36.4% zone II) compared with eyes receiving bevacizumab (3.8% zone I, 1.7% zone II). Because high myopia after laser therapy is attributed in part to alterations in anterior segment development, the authors concluded that less impact on ocular growth may be seen with bevacizumab therapy. This trial report was rated level II evidence because it lacked a masked outcome determination.

In a 2014 publication, Lepore et al<sup>19</sup> (Italy) reported on retinal structural outcomes based on digital fundus photography and fluorescein angiography of 13 infants with type 1 ROP in zone I who were randomized to receive 0.5 mg (0.02 ml) bevacizumab in one eye and laser photocoagulation therapy in the other eye, using digital fundus photographs and fluorescein angiography. All infants had stage 3 ROP in zone I at the time of treatment. Plus disease was present in 6 eyes of 3 infants, and all other eyes had stage 3 ROP without plus disease. Infants were followed up for 9 months after treatment, except for 1 infant who died at 3 months of age. Two eyes that received laser therapy progressed to retinal detachment (1 at stage 5, 1 at stage 4A). At 9 months, all eyes receiving bevacizumab had a favorable anatomic outcome, but showed 1 or more of the

following abnormalities on fluorescein angiography: abnormal retinal vascular branching, peripheral retinal shunt vessels, a persistent avascular retina, the absence of a foveal avascular zone, posterior hyperfluorescent lesions, or a linear choroidal filling pattern. Some of the laser-treated eyes also demonstrated these abnormalities as well as the expected peripheral atrophic retinochoroidal lesions. This trial was rated level II because of its small sample size and a lack of masked outcome determination.

In 2016, Zhang et al<sup>20</sup> (China) reported outcomes of a prospective randomized trial for 50 infants who had bilateral type 1 ROP in zone II who were randomized to receive either intravitreal ranibizumab (0.3 mg in 0.03 ml) or diode laser photocoagulation. All infants had stage 2 or 3 ROP with plus disease. The main outcomes assessed were regression of ROP and plus disease, recurrence requiring treatment, and complications. All infants were followed up for 6 months. In the ranibizumab group, all eyes showed initial regression, but 26 eyes of 13 infants (52%) demonstrated a recurrence and underwent laser photocoagulation. The mean time to retreatment for this group was  $12.6 \pm 7.9$  weeks. At the last follow-up, eyes treated with ranibizumab still did not show complete vascularization to the ora serrata. In the laser group, both eyes of 1 patient did not show an initial response; the patient was considered to have experienced a recurrence (4%) and received ranibizumab injections 1 week after the laser treatment. There were no complications in either group. The difference in recurrence rates was statistically significant ( $P = 0.001$ ), so the authors did not endorse ranibizumab therapy for type 1 ROP in zone II. They also mention that the outcomes may not be generalizable to other populations because all infants were of Han Chinese ethnicity. This study was rated level II because: (1) it lacked information on randomization administration, including whether it was concealed; (2) the outcome determination was unmasked; and (3) there was no sample size calculation to justify the choice of sample size.

### Comparative Case Series

All comparative case series were rated as providing level III evidence.

In 2010, Lee et al<sup>21</sup> (Korea) reported on the effects of combination therapy on the development of peripheral retinal vessels using bevacizumab (0.5 mg in 0.02 ml) and diode laser photocoagulation versus diode laser photocoagulation alone. This was a retrospective comparative case series of infants with bilateral moderate to severe ROP. Eight patients (16 eyes) with ROP that was considered to have more vascular activity received combination therapy, whereas 7 patients (14 eyes) with less-active disease received diode laser photocoagulation only. Patients who received combination therapy showed more rapid resolution of plus disease, faster regression of fibrovascular tissue, and earlier vascularization into the peripheral retina. There are several limitations to this study in addition to its retrospective nature and small sample size: (1) the severity of ROP was clinically dissimilar between groups; (2) no specific information was provided about the ROP zone or presence of plus disease; (3) the amount of laser treatment was not specified; and (4) the measurement of the response was not standardized. There were also clinical differences between the groups in terms of GA, birth weight, and age at treatment (the combination group had a lower GA and birth weight and an older age at the time of treatment).

Nonetheless, this was an early comparative case series that showed results of laser photocoagulation in combination with an anti-VEGF agent for treatment of patients that were considered to have more severe ROP.

In 2013, Harder et al<sup>22</sup> (Germany) performed a retrospective, nonrandomized, comparative study of refractive outcomes for a consecutive series of infants who had received intravitreal bevacizumab compared with a historical cohort of infants who underwent argon laser photocoagulation therapy. There were 12 children in the study group and 13 in the historical control group. There was no statistically significant difference between the groups in mean GA ( $25.2 \pm 1.6$  weeks vs.  $25.3 \pm 1.8$  weeks) or mean birth weight ( $622 \pm 153$  g vs.  $717 \pm 197$  g). In the study group, 9 infants received 0.375 mg bevacizumab and 3 children received 0.625 mg bevacizumab; the dosage was determined by the practice preference of the treating ophthalmologist. All eyes in this study met type 1 ROP treatment criteria. In the study group, 3 infants had acute posterior type 1 ROP and both eyes of the remaining 9 infants, as well as all of the control group eyes, had classic threshold ROP as defined in the Cryotherapy for Retinopathy of Prematurity study. One infant in the study group received intravitreal bevacizumab in 1 eye and argon laser therapy in the other eye; however, the eye that received laser therapy required retreatment with bevacizumab, so that eye was not included in the refractive analysis. The anatomic results were favorable in all bevacizumab-treated eyes; 1 eye in the control group showed a stage 4B retinal detachment (and the eye excluded from refractive analysis showed a macular fold). At a mean age of  $11.4 \pm 2.3$  months after birth, less myopia was seen in the study group ( $-1.04 \pm 4.24$  D) compared with the control group ( $-4.41 \pm 5.50$  D). Additionally, a higher degree of astigmatism was associated with laser treatment. Limitations of this study, in addition to the small sample size and retrospective analysis, include the use of a historic cohort with clinically dissimilar birth weights and dissimilar severities of ROP, the use of different bevacizumab doses, and a lack of detail about the laser protocol.

In 2015, Hwang et al<sup>23</sup> (United States) performed a retrospective review of all eyes that underwent primary treatment of type 1 ROP with either bevacizumab (0.625 mg in 0.025 ml) or diode laser treatment and had at least 6 months of follow-up. There were 22 eyes (11 patients) in the bevacizumab group and 32 eyes (17 patients) in the laser group. The groups showed similar GA at birth, birth weight, and age at treatment, but a longer follow-up period was noted for the infants treated with laser (34.5 weeks for the laser group vs. 21.7 weeks for the bevacizumab group). The main outcomes were rate of recurrence requiring retreatment or retinal detachment, complications, and refraction at last follow-up. In the bevacizumab group, recurrence was seen in 14% of eyes compared with 3% of laser-treated eyes; all recurrences were in zone I eyes in both groups. No complications were seen in the bevacizumab group, but in the laser group, 1 eye experienced stage 5 retinal detachment and 5 eyes demonstrated macular ectopia. Refraction data were available for 93% of the cohort. More myopia was seen in the laser group compared with the bevacizumab group (mean SE,  $-5.3$  D at 37.1 months vs.  $-2.4$  D at 22.4 months, respectively). Eyes treated with laser for zone I disease also demonstrated more myopia ( $-10.1$  D for the laser group vs.  $-3.7$  D for the bevacizumab group) compared with zone II eyes ( $-4.7$  D for the laser group and  $+0.6$  D for the bevacizumab group). Although the mean spherical power and degree of myopia were

significantly greater in zone II ROP eyes treated with laser compared with those treated with bevacizumab, there was no significant difference between the groups for zone I eyes. Limitations of this study include the small sample size, the retrospective nature of the study, the comparison of groups with dissimilar zones of ROP, and the dissimilar lengths of follow-up.

Isaac et al<sup>24</sup> (Canada) performed a retrospective review of infants undergoing treatment for type 1 ROP over a 4-year period that included patients with at least 6 months of follow-up. The primary outcome was retinal status at a corrected age of 1 year. Thirteen infants (23 eyes) received bevacizumab (0.625 mg in 0.025 ml) and 12 infants (22 eyes) received diode laser therapy. A favorable anatomic result was obtained in all eyes. No statistically significant difference was found in visual acuity measures, and although a higher prevalence of myopia in the laser-treated eyes was found, this did not reach statistical significance. There was a significant increase in the number of examinations required for infants who had bevacizumab injection compared with the infants who had diode laser therapy (mean,  $16 \pm 6$  visits vs.  $6 \pm 3$  visits, respectively). Although this small retrospective study has limitations, the demonstration of the significant difference in follow-up examinations that were needed, even with successful treatment, is noteworthy.

Gunay et al<sup>25,26</sup> (Turkey) published 2 comparative case series in 2016. The first study<sup>25</sup> included 264 eyes of 134 infants with type 1 ROP or aggressive posterior ROP at 2 large referral centers. It evaluated resolution and recurrence rates after anti-VEGF therapy using either bevacizumab (55 infants; dose, 0.625 mg), ranibizumab (22 infants; dose, 0.25 mg), or diode laser photocoagulation (57 infants). Patients were followed up for up to 1.5 years adjusted age for refractive and biometry measurements. Eyes that received supplemental anti-VEGF therapy for failed laser treatment were excluded. All eyes in this study showed an initial response to treatment, but recurrence of ROP was seen in 3 of 55 infants in the bevacizumab group (5.5%), 11 of 22 infants in the ranibizumab group (50%), and 1 of 57 infants in the laser group (1.8%). Whereas all of the infants with recurrence in the bevacizumab group required bilateral retreatment, only 3 of the 11 with recurrence in the ranibizumab group required bilateral retreatment, so there was no significant difference in retreatment rates between the groups receiving anti-VEGF therapy. The mean time to recurrence was 14 weeks for bevacizumab-treated eyes and 9 weeks for ranibizumab-treated eyes. No complications were noted for any of the groups, but 1 eye of a patient treated with laser photocoagulation demonstrated a stage 4A retinal detachment that did not progress to require treatment. At the last follow-up, the prevalence of emmetropia was significantly higher in the groups that received anti-VEGF therapy compared with the laser-treated group (50.9% of the bevacizumab group, 45.5% of the ranibizumab group, and 16.3% of the laser group). The presence of zone I ROP at treatment was associated significantly with the presence of myopia and high myopia across the treatment groups.

The second study by Gunay et al<sup>26</sup> reviewed outcomes for 36 infants with a birth weight of more than 1500 g who required ROP treatment. Treatment was performed for type 1 ROP in 30 infants and for aggressive posterior ROP in 6 infants. Diode laser photocoagulation was performed in 21 infants (58.3%), all of whom had anterior zone II ROP, and intravitreal bevacizumab treatment was given to 15 infants (41.7%), all of whom had either aggressive posterior ROP in zone I or type 1 ROP in

posterior zone II. Infants were followed up for a minimum of 8 months, and the mean follow-up was 19.9 months for the laser photocoagulation group and 17.9 months for the bevacizumab group. All eyes in both groups showed a good response to therapy, with no complications or recurrences reported, although treatment choice was influenced by the posterior location of ROP. Limitations of this study include the small sample size and the retrospective nature of the analysis, as well as the inclusion of clinically dissimilar treatment groups. However, the authors' focus was to show that in some countries, severe ROP can still develop in heavier preterm infants, sometimes as a result of underlying systemic conditions or variability in early neonatal care, which national ROP screening guidelines should take into consideration. The authors concluded that both anti-VEGF agents were useful for halting ROP; that recurrence of ROP after ranibizumab treatment was more common, but also more likely to regress spontaneously; and that both anti-VEGF agents allowed for more normal refractive development compared with eyes receiving laser therapy.

In 2016, Mueller et al<sup>27</sup> (Germany) reported on retinal, visual, and refractive outcomes for a cohort of German infants who underwent treatment for type 1 ROP. In this retrospective study, 54 patients were identified who underwent ROP treatment with either intravitreal bevacizumab (37 infants; dose, 0.625 mg) or diode laser photocoagulation (17 infants). There was some preference for eyes with posterior disease to be given anti-VEGF therapy; thus, 28 of 33 infants (56/66 eyes) with zone I or posterior zone II ROP received intravitreal bevacizumab and 5 of 33 infants (10/66 eyes) with zone I or posterior zone II ROP received laser photocoagulation. Of the 21 infants with more peripheral zone II ROP, intravitreal bevacizumab was given in 9 (18 eyes) and laser treatment was performed for 12 (24 eyes). Patients were followed up to 12 to 15 months of age, and retinal anatomic status, grating visual acuity, and refractions were obtained. The time to complete regression of ROP was significantly less for eyes with posterior ROP that received bevacizumab (median, 9 days) compared with laser-treated eyes (median, 57 days), although there was no difference for peripheral zone II eyes. Recurrence of ROP was noted in 7 infants (12%) at a median of 12.7 weeks after bevacizumab treatment, and 5 required retreatment (with laser). No recurrences were seen in laser-treated eyes. Ocular complications included exudative retinal detachment in both eyes of 1 patient who underwent laser photocoagulation for posterior zone II disease, macular dragging in 1 eye of another infant after laser treatment for posterior zone II ROP, and culture-negative keratitis with permanent corneal opacity in 1 eye of an infant who received bilateral bevacizumab injections. One child in the bevacizumab group died 3 weeks after ROP treatment as a result of cardiorespiratory failure with severe bronchopulmonary dysplasia. The ROP treatment method had no significant impact on grating visual acuity scores or refractive error. There was a lower SE (more myopia) in eyes treated for posterior disease compared with eyes treated for peripheral zone II disease. The main limitation of this study is the clinical dissimilarity of ROP between the groups, with anti-VEGF therapy preferred for posterior disease.

There have been a few large noncomparative case series using anti-VEGF monotherapy,<sup>29–31</sup> but these studies did not meet the criteria for full review for this Ophthalmic Technology Assessment.

## Conclusions

Anti-VEGF agents for ROP are an emerging treatment option that is becoming used more frequently,<sup>32,33</sup> and review of the recent literature suggests that the short-term efficacy and ocular safety are similar to those of laser photocoagulation therapy. The advantages of using anti-VEGF agents include less time to administer treatment (resulting in possibly less stress for the infant), faster improvement in plus disease and regression of ROP, less treatment-related destruction of the peripheral retina, and a lower likelihood of myopia, high myopia, and astigmatism. The disadvantages of anti-VEGF therapy include a longer required follow-up as a result of delayed or incomplete vascularization, significant rates of recurrence and the potential need for later retreatment, and the possibility of developmentally abnormal or atypical retinal vascular patterns. The long follow-up period required after anti-VEGF therapy also creates a burden on families and the medical system to ensure that late recurrences or complications do not arise.

With respect to the severity of ROP, there seem to be several potential advantages for primary treatment with anti-VEGF agents for eyes with zone I ROP or eyes with aggressive posterior ROP. However, there is no clear advantage over laser photocoagulation for eyes with more peripheral zone II ROP, and there is no clear advantage for first-line combination therapy. The rapid response and involution of ROP that can be obtained with anti-VEGF treatment compared with laser treatment can be of particular advantage for aggressive posterior ROP. Although treatment of zone I eyes with anti-VEGF treatment can allow some retinal vascular development over time, most zone I eyes treated with anti-VEGF will never completely vascularize and may still need retreatment after 55 weeks' PMA (the standard end point for several studies considered in this review).

The rate of ROP recurrence is not insignificant with anti-VEGF therapy, but it is somewhat variable among study populations. The BEAT-ROP study showed a lower recurrence rate for zone I eyes that received bevacizumab compared with laser therapy, but one criticism of this study was the unusually high retreatment rate for the eyes that had undergone laser therapy. Most other studies have shown that, when there is a difference, there is a higher recurrence rate with anti-VEGF therapy compared with laser therapy, though not all recurrences require retreatment. Recurrence after bevacizumab monotherapy was characterized by Mintz-Hittner et al<sup>34</sup> in a series of 241 infants who received treatment for zone I or posterior zone II ROP and who were followed up at least to 65 weeks' PMA. In this series, 8.3% of infants required retreatment for recurrence of ROP, with greater risk noted for babies with aggressive posterior ROP, lower birth weight, and extended duration of hospitalization (a surrogate for systemic illness). Recurrences occurred both from the fibrovascular complex present at the initial treatment and at the advancing edge, and were noted at up to 70 weeks' PMA. In a comparative case series reviewed for this report, Gunay et al<sup>25</sup> found a higher rate of ROP recurrence in eyes treated with ranibizumab compared

with bevacizumab, but there was no difference in retreatment rates. Chen et al<sup>31</sup> performed a comparative case series of 72 eyes (37 patients) treated with intravitreal bevacizumab (0.625 mg) or ranibizumab (0.25 mg) for type 1 ROP, and followed up the infants to 1 year of age. Recurrence was not defined except for the need to retreat, and only 1 eye in the bevacizumab group did not respond initially and underwent laser treatment. However, 2 other small comparative case series using intravitreal bevacizumab (0.625 mg) or ranibizumab (0.25 mg) reported high rates of ROP recurrence requiring retreatment in eyes treated with ranibizumab compared with those treated with bevacizumab (83% vs. 0%<sup>35</sup> and 40% vs. 9.5%<sup>36</sup>). It is clear from all of these studies that there is a significant risk of ROP recurrence after anti-VEGF therapy for ROP. There is also the risk of delayed and incomplete retinal vascularization (particularly for zone I eyes), which significantly prolongs the period needed to follow up and manage acute ROP after anti-VEGF treatment, compared with the follow-up time needed to manage acute ROP after laser photocoagulation therapy.

No level I studies have yet addressed the longer-term ocular, visual, systemic, or neurodevelopmental effects of anti-VEGF treatment. Bevacizumab used for ROP treatment can be detected in the serum within 1 day of intravitreal injection, and there is a corresponding decline in serum VEGF levels.<sup>37</sup> Intravitreal bevacizumab results in low VEGF serum levels for at least 8 weeks<sup>38</sup> and up to 12 weeks after the treatment.<sup>39</sup> Intravitreal ranibizumab also can lower serum levels of VEGF by 1 day after treatment, but this effect is short lived and serum VEGF levels recover to baseline within 1 week of treatment.<sup>39,40</sup> The potential effects of lowering systemic VEGF levels on other developing organ systems in a premature infant are unknown. Determining whether anti-VEGF therapy has a clinically evident effect would be difficult, because the presence of treatment-warranted ROP is known to be associated with comorbidities and poor neurodevelopmental outcomes in the first place. Hence, a very large patient population would be needed for such a study to be powered correctly to sort out confounding variables.

Nevertheless, systemic safety remains a concern, and neurodevelopmental outcomes at 2 years of age for children who received intravitreal anti-VEGF treatment have been measured by a few groups using the validated and standardized Bayley Scales of Infant Development (BSID) test. Araz-Ersan et al<sup>41</sup> evaluated series of 13 infants treated with combination intravitreal bevacizumab (0.625 mg) and laser therapy for ROP, compared with a birthweight- and gestational age-matched control group of children who had received laser treatment for ROP. They found no difference in the mean cognitive, language, or motor scores on the BSID III test. In another study, Lien et al<sup>42</sup> studied BSID scores at 24 months of age in 61 infants who had received either bevacizumab (0.625 mg) monotherapy, laser monotherapy, or a combination of bevacizumab and laser therapy (required for salvage therapy). The patients who required combination (salvage) therapy had a higher incidence of mental or psychomotor impairment, but there was no difference between the groups that had either modality as monotherapy. The authors

concluded that because of the retrospective nature and lack of randomization for this study, the cause for this difference could not be determined. However, they speculate that poorer outcomes could be related to exposure to more surgical procedures and anesthesia, earlier age at treatment, and more cases of zone I disease in the combination therapy group. Morin et al<sup>43</sup> evaluated neurodevelopmental data from infants in the Canadian Neonatal Network and Canadian Neonatal Follow-Up Network. The neurologic examination and the BSID III test results of 125 infants treated for ROP (27 with bevacizumab) were compared. The group of infants who had received bevacizumab showed a statistically lower median motor composite score, and the odds of having a severe neurodevelopmental disability (BSID score <70, severe cerebral palsy, hearing aids, or bilateral blindness) was 3.1 times higher with bevacizumab versus laser treatment. However, this comparison was adjusted for many infant variables but not ROP severity, and there was a significantly greater proportion of patients with zone I disease in the bevacizumab group. Additionally, aside from having zone I disease, treatment choice could have been biased toward using bevacizumab in those infants with a worse overall medical condition, which has been shown to be associated with greater neurodevelopmental impairment. Finally, in the BEAT-ROP trial,<sup>15</sup> there was concern that 5 of 7 early deaths (mostly resulting from respiratory failure) occurred in children treated with bevacizumab, although by the time of the 2-year follow-up publication,<sup>18</sup> this difference in mortality was no longer seen (there were 6 deaths in the bevacizumab group and 7 deaths in the laser group).

## Future Research

Evidence is lacking on the long-term safety of anti-VEGF agents, the best anti-VEGF agent to use for ROP treatment, the optimal dose for each agent, and the potential long-term systemic effects. For this Ophthalmic Technology Assessment, we found significant variability in or lack of standardized classifications of treatment, use of different agents and dosing, variable follow-up periods, lack of standardized and masked assessment of treatment outcomes, and significant variation in efficacy of treatment among populations. Other areas to consider for further study and when considering implementation of anti-VEGF treatment in clinical practice are the potential effects of ethnic or genetic background in different populations, differences in early exposures and neonatal care, and effects of regional bias toward treatment preference and need for close follow-up after treatment, particularly in areas with limited resources. The 13 articles reviewed for this assessment were from 9 different countries (United States, Czech Republic, Ireland, Italy, China, Korea, Germany, Canada, and Turkey), which demonstrates that there is likely significant diversity in the above-mentioned variables. This should be considered when applying study results to regional clinical practice.

Further evidence for efficacy, safety, and dosing of anti-VEGF agents is forthcoming. Most studies to date have used bevacizumab, perhaps because of wider availability and

lower cost, with various doses. The Pediatric Eye Disease Investigator Group, in collaboration with the National Eye Institute, currently is conducting a prospective phase 1 multicenter trial aimed at determining the lowest effective bevacizumab dose for treatment of type 1 ROP.<sup>44</sup> This study also will collect serum levels of VEGF and bevacizumab after intravitreal injection, which may aid in understanding the effects of dosing on systemic bevacizumab and VEGF circulation in the short term in premature infants. Ranibizumab is of interest because it has a vitreous half-life that approaches that of bevacizumab, but after reaching systemic circulation, the elimination half-life is a few hours rather than weeks and results in a negligible effect on serum VEGF levels. Although this could be a distinct advantage for the treatment of ROP, the efficacy of ranibizumab for ROP treatment with respect to recurrences or long-term ocular outcomes is not available. A prospective multicenter trial of ranibizumab for ROP is underway in Germany (Comparing Alternative Ranibizumab Dosages for Safety and Efficacy in Retinopathy of Prematurity [CARE-ROP]; [clinicaltrials.gov](http://clinicaltrials.gov) identifier, NCT02134457) and in the United States (RAnibizumab Compared With Laser Therapy for the Treatment of INfants BOrn Prematurely With Retinopathy of Prematurity [RAINBOW]; [clinicaltrials.gov](http://clinicaltrials.gov) identifier, NCT02375971).

Finally, questions remain about late systemic and neurodevelopmental effects.<sup>45</sup> Challenges will include following up a large cohort for long-term data collection to sort out the impact of this treatment within a population that is already at high risk of experiencing later neurodevelopmental abnormalities. Until these questions have been addressed more fully, clinicians should exercise caution and offer anti-VEGF therapy only for type 1 ROP treatment in patients with zone I or posterior zone II disease after carefully weighing the benefits and risks and discussing treatment options with parents.

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Abbreviations and Acronyms:

**BSID** = Bayley Scales of Infant Development; **CARE-ROP** = Comparing Alternative Ranibizumab Dosages for Safety and Efficacy in Retinopathy of Prematurity; **D** = diopter; **ETROP** = Early Treatment for Retinopathy of Prematurity; **GA** = gestational age; **PMA** = postmenstrual age; **RAINBOW** = RAnibizumab Compared With Laser Therapy for the Treatment of INfants BOrn Prematurely With Retinopathy of Prematurity; **ROP** = retinopathy of prematurity; **SE** = spherical equivalent; **VEGF** = vascular endothelial growth factor.

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