

Review of effects of anti-VEGF treatment on refractive error

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Abstract: To examine the effect of anti-vascular endothelial growth factor (anti-VEGF) agents on refractive error in the setting of retinopathy of prematurity (ROP) through a review of the literature, a PubMed search was performed of appropriate search terms, and the results of all relevant studies were extracted and compiled. Eleven relevant articles were identified in the literature, totaling 466 eyes, treated with varied anti-VEGF agents (bevacizumab, ranibizumab, and aflibercept) with mean spherical equivalent refractions ranging from +0.75 D to -3.57 D, with prevalence of high myopia ranging from 0 to 35%. Anti-VEGF monotherapy for ROP leads to low levels of myopia, and there may be a differential effect of specific anti-VEGF agents utilized on refractive outcomes.

Keywords: retinopathy of prematurity, ROP, refraction, myopia, bevacizumab, ranibizumab, aflibercept

Introduction

Advances in treatment for retinopathy of prematurity (ROP) are allowing better anatomical and functional outcomes, with further prevention of blindness from retinal detachment. Perhaps the most recent addition to the ROP-treatment armamentarium are anti-VEGF agents. Anti-VEGF agents have considerable clinical benefits, including reduction in the rate of high and very high myopia following treatment, compared with peripheral ablation.¹

Previously, as seen following cryotherapy and laser ablative therapy, these eyes would often develop high and very high myopia, which was attributed to the severity of ROP and not to the treatment modality itself.²⁻⁴ Similar, though much lower degrees of myopia, termed “myopia of prematurity”, are also seen in children born prematurely without ROP,^{2,5-8} as well as in children with ROP that spontaneously regresses, called “myopia of spontaneously regressed ROP”.^{2,5-12} In all of these cases, the myopia is nonaxial in nature with a steepened cornea, shallow anterior chamber, and thickened crystalline lens.^{9,10,13-15} These features are thought to be due to an arrested state of development of the immature eye.^{12,16}

The myopia associated with prematurity and ROP develops along a spectrum, with myopia of prematurity of the lowest order, followed by myopia of spontaneously regressed ROP, with myopia of laser ablation creating the highest myopia.^{1-12,16-19} These factors alone are suggestive of an effect of severity of ROP on the development of myopia. However, with increasing research and recent data,^{1,16-19} it seems the myopia seen in the face of prematurity and ROP is multifactorial in etiology, with three main causative

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factors: 1) prematurity, 2) the severity of ROP, and 3) changes related to the treatment administered for ROP (ie, peripheral retinal ablation or anti-VEGF administration). Peripheral retinal ablation causing increased myopia has been described in several reports,¹⁶⁻¹⁹ including a recent report of the refractive outcomes of the BEAT-ROP clinical trial at age 2.5 years.¹ The purpose of this review is to investigate the contributions of these causative factors to the resulting refractive error seen in children treated by anti-VEGF agents for ROP.

Materials and methods

A PubMed search was performed of several combinations of the following search terms: retinopathy of prematurity, ROP, refraction, refractive error, myopia, bevacizumab, ranibizumab, aflibercept, pegaptanib, anti-vascular endothelial growth factor, and anti-VEGF. The last search update was performed on January 13, 2016. The reference list of each identified article was also reviewed to ensure completeness. Extracted information from each relevant article included the first author's name, year of publication, country in which the study was conducted, average gestational age of each cohort, average birth weight of each cohort, percentage of eyes treated for zone I ROP, specific treatment modalities utilized, average adjusted age

(gestational age + number of weeks of life) at time of treatment, average age at time of refraction, average spherical equivalent (SE) refractive error in diopters, prevalence of myopia (SE > -0.25 D), and prevalence of high myopia (SE > -5 D).

Results

After a thorough PubMed review, eleven articles^{1,20-29} were identified relevant to the topic. In total, this amounted to 466 eyes (the number of infants was not consistently reported) treated with anti-VEGF agents for ROP: 378 eyes with intravitreal bevacizumab monotherapy (dosage ranging from 0.375 to 1.25 mg, with the majority administered 0.625 mg), 31 eyes with intravitreal ranibizumab monotherapy (0.25 mg), and 26 eyes with intravitreal aflibercept monotherapy (1 mg). The extracted information from each article is compiled in Table 1. The average SE refractive error reported after anti-VEGF monotherapy ranged from +0.75 D to -3.57 D. The average age at time of refraction in these studies ranged from 11.4 months to 5 years.

Discussion

The use of anti-VEGF agents in the treatment of ROP is being increasingly studied and utilized. The average SE

Table 1 Reports of refractive error after the use of anti-vascular endothelial growth factor agents for the treatment of retinopathy of prematurity

| Study | Location | Mean GA (weeks) | Mean BW (g) | Mean AA at Tx (weeks) | Refracted eyes, n | Refraction age (months) | Anti-VEGF, dose (mg) | Mean SE ± SD (D), anti-VEGF Tx | Mean SE ± SD (D), laser Tx |
|--|----------|----------------------|------------------------|-----------------------|------------------------|-------------------------|-------------------------|---|---|
| Wu et al ²⁰ | Taiwan | 26.3 IVB | 930.1 IVB | 36.6 IVB | 53 IVB 14 IVB + CLT | 17.8 | IVB, 0.625 | -0.1±1.8 | NA |
| Martinez-Castellanos et al ²¹ | Mexico | 29.3 IVB | 1,233.3 IVB | 25.2 IVB | 9 IVB | 60 | IVB, 1.25 | -1.75 | NA |
| Harder et al ²² | Germany | 25.2 IVB 25.3 CLT | 622 IVB 717 CLT | 25.2 IVB 25.3 CLT | 23 IVB 26 CLT | 11.4 | IVB, 0.375 or 0.625 | -1.04±4.24 | -4.41±5.5 |
| Chen et al ²³ | Taiwan | 26.4 IVB | 882.2 IVB | 35 | 40 IVB 17 IVB + CLT | 24 | IVB, 0.625 | -0.98±4.05 | IVB + CLT: -2.4 |
| Geloneck et al ¹ | USA | 24.4 IVB 24.2 CLT | 652.1 IVB 669.3 CLT | 35.1 IVB 34.8 CLT | 110 IVB 101 CLT | 30 IVB 30 CLT | IVB, 0.625 | Zone I: -1.51±3.42 Zone II: -0.58±2.53 | Zone I: -8.44±7.57 Zone II: -5.83±5.87 |
| Salman and Said ²⁴ | Egypt | 26.3 IVA | 991 IVA | NA | 26 IVA | 12 | IVA, 1 | 0.75 | NA |
| Isaac et al ²⁵ | Canada | 25.2 IVB 25 CLT | 722 IVB 674 CLT | 37.6 IVB 36.7 CLT | 23 IVB 22 CLT | 12 | IVB, 0.625 | -3.57±6.19 | -6.39±4.41 |
| Kuo et al ²⁶ | Taiwan | NA | NA | NA | 14 IVB 15 CLT | 36 | NA | -1.53±2.2 | -1.71±1.27 |
| Chen et al ²⁷ | Taiwan | 26.5 IVB 26.2 IVR | 869.1 IVB 848.8 IVR | 36.8 IVB 36.4 IVR | 41 IVB 31 IVR | 12 | IVB, 0.625 IVR, 0.25 | -0.3 IVB +0.1 IVR | iVB + CLT: -2.4 |
| Hwang et al ²⁸ | USA | 24.2 IVB 24.8 CLT | 668.1 IVB 701.4 CLT | 35.1 IVB 36.1 CLT | 22 IVB 32 CLT | 22.4 IVB 37.1 CLT | IVB, 0.625 | -2.4 (zone I, -3.7; zone II, 0.6) | -5.3 (zone I, -10.1; zone II, -4.7) |
| Gunay et al ²⁹ | Brazil | 26.4 IVB 27.3 CLT | 901.4 IVB 941 CLT | 34.0 IVB 33.9 CLT | 43 IVB 35 CLT | 24 | IVB, 0.625 | 0.42±3.42 | -6.66±4.96 |

Abbreviations: CLT, conventional laser therapy; IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; IVA, intravitreal aflibercept; GA, gestational age; BW, birth weight; AA, adjusted age; Tx, treatment; SD, standard deviation; SE, spherical equivalent refractive error; NA, not available.

Table 2 Cycloplegic retinoscopic refractive error at age 2.5 years in the Bevacizumab Eliminates the Angiogenic Threat for Retinopathy of Prematurity clinical trial¹

| Spherical equivalent refractions, D | Intravitreal bevacizumab | | Laser | |
|-------------------------------------|--------------------------|--------------------|---------------------|----------------------|
| | Without recurrence | With recurrence | Without recurrence | With recurrence |
| Zone I (87 eyes)* | 50 eyes | 2 eyes | 26 eyes | 9 eyes |
| Mean (SD) | -1.36 (3.34) | -5.25 (4.6) | -7.34 (7.44) | -11.61 (7.42) |
| Median (range) | -0.50 (-8 to 6) | -5.25 (-8.5 to -2) | -4.69 (-24.88 to 2) | -10 (-22 to 0.75) |
| Zone II posterior (124 eyes)** | 56 eyes | 2 eyes | 58 eyes | 8 eyes |
| Mean (SD) | -0.63 (2.56) | 0.88 (0) | -5.2 (5.77) | -10.42 (4.58) |
| Median (range) | 0 (-13 to 2.5) | 0.88 (0.88-0.88) | -4 (-19 to 3.5) | -11.5 (-15 to -2.63) |

Notes: *For zone I, the mean (SD) spherical equivalent refractions for the intravitreal bevacizumab group were -1.51 (3.42) D (median [range], -0.56 [-8.56 to 6] D), and for the laser group were -8.44 (7.57) D (median [range], -8.00 [-24.88 to 2] D) ($P < 0.001$); ** for zone II posterior, the mean (SD) spherical equivalent refractions for the intravitreal bevacizumab group were -0.58 (2.53) D (median [range], 0 [-13 to 2.5] D), and for the laser group were -5.83 (5.87) D (median [range], -4.88 [-19 to 3.50] D) ($P < 0.001$). Reproduced with permission from *JAMA Ophthalmol.* 2014;132(11):1327-1333. Copyright©2014 American Medical Association. All rights reserved.¹

Abbreviation: SD, standard deviation.

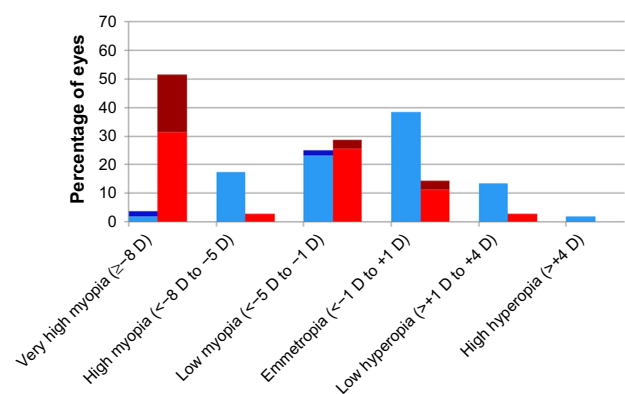
refractive error following the administration of anti-VEGF agents is in the low-myopia range (mean ranging from +0.1 to -3.57 D).^{1,20-29} There is some suggestion, however, that different anti-VEGF agents may yield different prevalence of high myopia (defined as SE ≤ -5 D), with intravitreal bevacizumab yielding high myopia in 8%–35% of eyes^{1,20-23,25-27} versus in 0 following intravitreal ranibizumab treatment.²⁷ However, more data are needed to better establish any differential effects on refractive error.

In the BEAT-ROP study, infants with stage 3+ or aggressive posterior ROP in zone I or zone II posterior were randomized to receive peripheral retinal laser ablation or intravitreal bevacizumab monotherapy.³⁰ In the 2.5-year refractive outcome results of the BEAT-ROP cohort, eyes matched for severity of ROP receiving anti-VEGF therapy were found to have significantly lower myopia on average than those receiving peripheral laser ablation (Table 2).¹ Mean SE refractions for those with zone I disease were -1.51±3.42 D in eyes treated with anti-VEGF and -8.44±7.57 D in eyes that received laser treatment. Mean SE refractions for those with zone II posterior disease were -0.58±2.53 D after treatment with anti-VEGF and -5.83±5.87 D after treatment with retinal laser. Specifically, very high myopia (≥ -8 D) occurred in significantly fewer eyes treated with anti-VEGF (3.8% zone I, 1.7% zone II posterior) than in those treated with peripheral laser (51.4% zone I, 36.4% zone II posterior). These findings suggest a possible significant contribution of laser ablation to the increased myopia seen in these infants (Figures 1 and 2).

In eyes treated for recurrence of ROP with additional anti-VEGF, as was done in the BEAT-ROP clinical trial, there was a further increase in myopia. This increased myopia was also seen in the control arm (laser ablation) of BEAT-ROP.¹ This increased myopia in eyes treated for recurrence of ROP is likely due to two of the three main etiological factors responsible for myopia in the premature population: increase in sever-

ity of ROP, and changes related to the treatment administered. Recurrence of ROP causes an equivalent reexposure to the disease process in both arms, and should therefore be expected to cause an equivalent increase in resultant myopia. However, there was a much higher incidence of very high myopia in eyes receiving additional laser (76.5%) for recurrence than in those receiving additional anti-VEGF (25%), suggestive of an added contribution from the treatment modality itself.¹ Increase in myopia and high myopia (defined in this study as SE ≤ -5 D) in eyes (n=17) treated with laser for recurrence following initial anti-VEGF therapy was also seen in a recent study by Chen et al, suggesting again the role of both severity and possibly treatment modality in the development of increased myopia in eyes treated for recurrent ROP.²³

To better understand the impact of the refractive outcomes following anti-VEGF therapy, it is necessary to

**Figure 1** Zone I distribution of refractive error by treatment modality.

Notes: Distribution of spherical equivalent refractive error at age 2.5 years in eyes that received treatment for stage 3+ retinopathy of prematurity or aggressive posterior retinopathy of prematurity in the Bevacizumab Eliminates the Angiogenic Threat for Retinopathy of Prematurity clinical trial.¹ Data presented according to treatment modality: red, laser without recurrence; brown, laser with recurrence; light blue, intravitreal bevacizumab without recurrence; dark blue, intravitreal bevacizumab with recurrence. Reproduced with permission from *JAMA Ophthalmol.* 2014;132(11):1327-1333. Copyright ©2014 American Medical Association. All rights reserved.¹

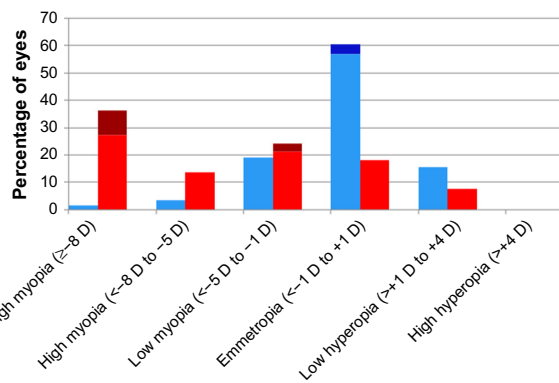


Figure 2 Zone II posterior distribution of refractive error by treatment modality. **Notes:** Distribution of spherical equivalent refractive error at age 2.5 years in eyes that received treatment for stage 3+ retinopathy of prematurity or aggressive posterior retinopathy of prematurity in the Bevacizumab Eliminates the Angiogenic Threat for Retinopathy of Prematurity clinical trial.¹ Data presented according to treatment modality: red, laser without recurrence; brown, laser with recurrence; light blue, intravitreal bevacizumab without recurrence; dark blue, intravitreal bevacizumab with recurrence. Reproduced with permission from *JAMA Ophthalmol.* 2014;132(11):1327–1333. Copyright © 2014 American Medical Association. All rights reserved.¹

appreciate them in the setting of the current standard of care for ROP derived from the ETROP clinical trial.³¹ A historical comparison of ETROP and BEAT-ROP was compiled to highlight some similarities and differences in the refractive outcomes of these studies (Figure 3). In the ETROP study,^{3,4} the control group (laser treatment at threshold ROP) had a slightly greater percentage of eyes with myopia of -5 D or higher than the experimental group (laser treatment at high-risk prethreshold ROP). The percentage of eyes with myopia of -5 D or greater following laser therapy in the BEAT-ROP trial (for high-risk prethreshold to threshold ROP) was between that seen following laser treatment for both the control and experimental eyes in the ETROP clinical trial.¹ In contrast, the percentage of eyes with myopia of -5 D or greater after intravitreal bevacizumab treatment in the BEAT-ROP cohort was far less than that seen following peripheral retinal ablation. The myopia following anti-VEGF monotherapy for ROP in eyes that received intravitreal bevacizumab in the BEAT-ROP trial was similar to the myopia of spontaneously regressed ROP seen in the ETROP trial.^{1,3,4}

Similar amounts of low myopia and a tendency for emmetropia following treatment with anti-VEGF agents were also reported in several other case series.^{20–29,32} Although purely speculative at this time, it is possible that intravitreal anti-VEGF agents allow for minimal disruption in the local growth-factor milieu and signaling pathways responsible for development of the anterior segment. As others have previously hypothesized, the incomplete development of the retina in prematurity with or without ROP may alter

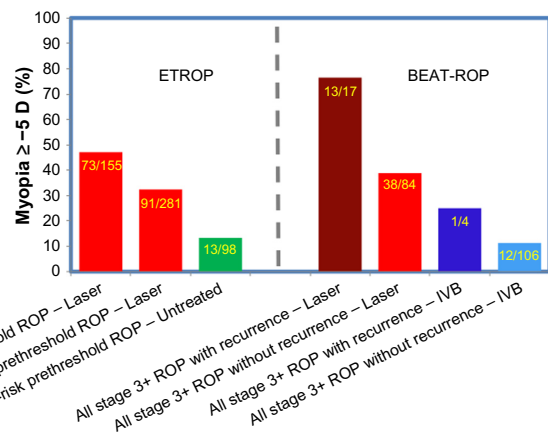


Figure 3 Percentage of eyes ≥ -5 D in ETROP and BEAT-ROP by ROP severity at treatment.

Notes: Percentage of eyes with myopia ≥ -5 D in the ETROP and BEAT-ROP clinical trials at ages 3 and 2.5 years, respectively. Data presented according to ROP severity at treatment (threshold, high-risk prethreshold, low-risk prethreshold, and all stage 3+) by treatment modality utilized (laser and IVB) in the respective clinical trials. Data from ETROP,³ and BEAT-ROP.¹

Abbreviations: ROP, retinopathy of prematurity; IVB, intravitreal bevacizumab.

local ocular growth signals,^{12,16,33} which may account for the anterior-segment changes seen in myopia of prematurity and in myopia of spontaneously regressed ROP. Intravitreal bevacizumab allows for continued development of the retinal vessels beyond the neovascular ridges, while this continuation is minimal following laser ablation.³⁰ The allowance of further migration of retinal vessels toward but not always necessarily to the ora serrata and the further maturation of photoreceptors may allow for more normal levels of the local growth factors required for proper signaling cascades in anterior-segment development.^{11,34} This would account for the lower amounts of myopia seen following anti-VEGF therapy. This is in contrast to the increased myopia and high myopia seen following treatment with laser, in which conceivably peripheral retinal ablation is more disruptive of the local growth-factor milieu and signaling pathways, leading to further impediment of anterior-segment development.

By potentially allowing more normal anterior-segment development in eyes treated with anti-VEGF agents, the cornea might be less steep, the anterior chamber deeper, and the lens less thickened. Thereby, these eyes may have the added benefit of also being at less risk of secondary long-term effects of high myopia, namely late angle-closure glaucoma, which is not uncommonly seen in eyes that have received prior laser therapy for ROP.^{35,36}

Most recently, questions regarding the most appropriate anti-VEGF agent to use for the treatment of ROP have arisen and received much attention. The main two anti-VEGF agents being discussed for use in ROP, which

have shown similar efficacy in the treatment of choroidal neovascularization in adults with age-related macular degeneration, are bevacizumab (Avastin; Genentech Inc, San Francisco, CA, USA) and ranibizumab (Lucentis; Genentech).³⁷ These two agents differ in biochemical structure, size and half-life, with bevacizumab having the longer half-life of 20 days versus ranibizumab's half-life of 2 hours.^{38,39} These differences in structure, size, and half-life are of particular interest in their systemic and ocular effects on neonates following treatment for ROP. Studies have shown systemic VEGF levels are blunted for several weeks following treatment with bevacizumab for ROP.^{40–42} However, this blunting of systemic VEGF is not as prolonged following treatment with intravitreal ranibizumab for ROP. Recent evidence has shown that systemic VEGF levels immediately following intravitreal ranibizumab administration for ROP are diminished (at 1 day), but this effect does not persist at 1 week or later.⁴³

The differential ocular effects of these two anti-VEGF agents in eyes with ROP are just now being elucidated. While the efficacy in treatment of ROP (ie, regression and recurrence patterns) has been reported as similar between bevacizumab and ranibizumab,²⁷ the refractive outcomes may differ. More high myopia was seen in eyes treated with bevacizumab than in those treated with ranibizumab at 1 year of age (14.6% versus 0, respectively; $P=0.03$).²⁷ Chen et al hypothesized that the longer half-life of bevacizumab may be responsible for these refractive differences, perhaps by allowing increased apoptosis of retinal structures responsible for developmental signaling cascades.²⁷ This theory is based on a murine model, in which inhibition of VEGF receptors led to loss of Müller cells, astrocytes, and ganglion cells from the inner retina.⁴⁴ While this was just a single retrospective review, it raises interest in the differential effects on anterior-segment development and subsequent refractive error, which deserve further investigation and longer-term outcome data.

Conclusion

As intravitreal anti-VEGF agents are still new in the treatment armamentarium for ROP, there are several aspects of this therapy requiring further investigation, specifically longer-term refractive and visual outcomes following anti-VEGF treatment, as well as establishment of the long-term safety and a refinement of the dose and best specific anti-VEGF agent. However, outcomes thus far have been exciting, and the lesser myopia and decreased incidence of high myopia seen following anti-VEGF treatment compared to that following retinal laser ablation is not trivial.

Disclosure

The authors report no conflicts of interests in this work.

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