7. Beer PM, Wong SJ, Hammad AM, Falk NS, O'Malley MR, Khan S. Vitreous levels of unbound bevacizumab and unbound vascular endothelial growth factor in two patients. Retina 2006;26:871-6.
8. Moisseiev E, Waisbourd M, Ben-Artsi E, et al. Pharmacokinetics of bevacizumab after topical and intravitreal administration in human eyes. Graefes Arch Clin Exp Ophthalmol 2014;252:331-7.
9. Zhu Q, Ziemssen F, Henke-Fahle S, et al., Tübingen Bevacizumab Study Group. Vitreous levels of bevacizumab and vascular endothelial growth factor-A in patients with choroidal neovascularization. Ophthalmology 2008;115:1750-75.
10. Krohne TU, Eter N, Holz FG, Meyer CH. Intraocular pharmacokinetics of bevacizumab after a single intravitreal injection in humans. Am J Ophthalmol 2008;146:508-12.

Refractive outcomes following the treatment of retinopathy of prematurity in the anti-VEGF era: a literature review

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A growing body of evidence indicates that antivascular endothelial growth factor (VEGF) therapy is effective in the treatment of retinopathy of prematurity (ROP). We conducted a comprehensive literature review on refractive outcomes of anti-VEGF treatments compared to laser treatment or a combination of laser therapy and anti-VEGF injections. Of the 9 studies analyzed, the final mean refractive error was myopic in 3 studies (37%) with IVB monotherapy, 7 studies (87.5%) with laser photocoagulation, and 1 study (50%) with combined therapy. In comparing IVB with laser monotherapy, 6 of 7 studies (86%) reported that final refractive error was significantly more myopic (>1 D) after laser treatment. No study was graded as high quality, and only a single article provided moderate quality of evidence.

Currently, laser photocoagulation of the avascular retina is the standard treatment for eyes with high-risk retinopathy of prematurity (ROP). Severe myopia has been reported as a possible adverse effect of laser photocoagulation.[1] Recent studies have shown less myopia after intravitreal bevacizumab (IVB) injections in eyes with ROP, which seems to contradict reports of the higher prevalence of myopia in patients who have undergone laser photocoagulation or cryotherapy.[1-4] This study reviewed the current literature regarding the refractive outcomes of eyes with ROP that underwent anti-VEGF therapy compared to those treated with laser or combined laser and anti-VEGF treatment.

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Methods

A comprehensive search of PubMed and Scopus databases for English-language publications on ROP covering the period January 2005 to April 2016 was conducted by 2 authors (JK, KGF). Search terms included the following: *retinopathy of prematurity*, *ROP*, *anti-VEGF*, *intravitreal bevacizumab*, *ranibizumab*, *aflibercept*, *refractive error*, *refraction*, *myopia*, and *hyperopia*. Original articles comparing anti-VEGF treatment with a control group were extracted. Case reports and noncomparative case series were excluded. Only articles reporting refractive outcomes were analyzed. The quality of evidence was rated by 2 authors (KGF, JK) according to the Scottish Intercollegiate Guidelines Network (SIGN) guidelines[5] and GRADE[6] criteria, considering the refractive error as the main outcome measure.

Results

Of 3,568 articles retrieved, 122 articles discussed anti-VEGF therapy. Of these, 19 reported refractive outcomes of intravitreal anti-VEGF injections in ROP, and 9 studies met inclusion criteria (eTable 1).[1-4,7-11] All studies used bevacizumab for intravitreal injections; all but 2 were retrospective.[1,2] With IVB monotherapy, final mean refractive error was emmetropic (range, −1 to +1 D) in 5 studies and myopic (≤−1 D) in the 3 remaining reports. With laser monotherapy, final mean refractive error was hyperopic (≥+1 D) in 1 study and myopic in the remaining reports. In patients treated with combined IVB and laser treatment group, final mean refractive error was emmetropic in one study and myopic in another.

Comparison of IVB with Laser Monotherapy

Seven studies compared IVB with laser treatment alone. Six studies reported that final refractive error was significantly more myopic after laser treatment.[1-4,8,9] In these reports, the mean final refractive error ranged from +0.42 to −3.70 D for the IVB group and from −4.41 to −10.1 D for the laser group. The difference of the refractive error between the two groups was 2.82–7.08 D.

One study reported similar refractive outcomes in IVB and laser groups (−1.53 and −1.71 D, resp.).[10]

Comparison of IVB and Combined IVB and Laser Treatment

One study compared IVB monotherapy with combined IVB and laser treatment.[7] The authors reported greater myopia after combined treatment. The difference between groups was 1.42 D.

Comparison of Combined IVB and Laser Therapy and Laser Monotherapy

One study compared combined IVB and laser treatment with laser monotherapy and found emmetropia in combined group and hyperopia (+1.43 D) in the laser monotherapy group.[11]

Quality of Evidence

Based on the SIGN and GRADE criteria, none of the studies specifically designed to evaluate refractive outcomes was of high quality (eTable 1).

Discussion

Among articles supporting the idea that less myopia develops after anti-VEGF for ROP compared with laser therapy, we found that while 9 articles met our inclusion criteria, sample sizes were small, and all but 2 studies were retrospective, with short follow-up time and no randomization. Furthermore, there were issues in comparing the data as a whole, such as the heterogeneity of ROP presentation and variation in patient management.

The discrepancies can be accounted for in part by comparing infants with similar stages of ROP at the time of treatment; however, the articles included ROP of different severity and risk factors. Six articles described type 1 prethreshold ROP, 2 articles described threshold ROP, and 1 described APROP at the time of treatment.

Although most of the articles reported IVB or laser monotherapy as the as first-line treatment, others reported simultaneous IVB plus laser therapy, anti-VEGF as rescue therapy, or laser ablation as rescue treatment. Only the BEAT-ROP clinical trial reported a randomization protocol for the study.[1]

The most striking limitation of these studies is that none of them were specifically conducted to compare the refractive outcomes in a randomized design. Age at time of refraction ranged from 7 to 76 months. Moreover, any definite conclusion needs comparison of the refractive changes in each group in relation to the baseline measurements and the concern for any potential observer bias in the refraction data should be considered.

The only randomized, prospective study comparing IVB with conventional laser therapy is the BEAT- ROP clinical trial.[1] The authors reported higher degree of myopia in laser treated eyes than infants received IVB. In each arm of their study, zone I and posterior zone II ROP demonstrated no significant difference in myopia severity. Regarding the IVB-treated eyes only, there was little difference in myopia between zone I (−1.51 D) and zone II eyes (−0.58 D). Therefore, the authors suggested severity of disease (zone I vs zone II posterior) is not the primary contributing factor to severity of myopia. The loss to follow-up in the BEAT-ROP study is a limitation of refractive error results.

Of the 9 papers analyzed, 2 found that anti-VEGF compared to laser leads to a lesser degree of myopia. Kou and colleagues reported that refractive outcome were clinically similar between the IVB monotherapy and laser monotherapy groups (mean of −1.53 vs −1.71 D, resp.).[10] The mean spherical equivalent of the untreated eyes was 0.69 D in the laser group and −1.8 D in the IVB group. The difference between eyes is apparently toward developing myopia in the laser monotherapy group. In the second paper,[11] which found emmetropia (mean, −0.15 D) after anti-VEGF injection and hyperopia (mean, 1.43 D) after laser treatment, the injections were given at the same time as laser; nevertheless, this study did not observe development of myopia after anti-VEGF injections.

In conclusion, the included studies supported the concept that anti-VEGF for ROP leads to less myopia than does laser therapy. However, the studies included in this analysis are limited by, for example, variation in inclusion criteria, variation in standard of care, and small sample size. Further studies are needed to elucidate the effect of IVB on refractive error of eyes with ROP.

References

1. Geloneck MM, Chuang AZ, Clark WL, et al., BEAT-ROP Cooperative Group. Refractive outcomes following bevacizumab monotherapy compared with conventional laser treatment: a randomized clinical trial. JAMA Ophthalmol 2014;132:1327-33.
2. Harder BC, von Baltz S, Schlichtenbrede FC, Jonas JB. Early refractive outcome after intravitreous bevacizumab for retinopathy of prematurity. Arch Ophthalmol 2012;130:800-801.
3. Harder BC, Schlichtenbrede FC, von Baltz S, Jendritza W, Jendritza B, Jonas JB. Intravitreal bevacizumab for retinopathy of prematurity: refractive error results. Am J Ophthalmol 2013;155:1119-24.
4. Hwang CK, Hubbard GB, Hutchinson AK, Lambert SR. Outcomes after intravitreal bevacizumab versus laser photocoagulation for retinopathy of prematurity: a 5-year retrospective analysis. Ophthalmology 2015;122:1008-15.
5. SIGN 50: A Guideline Developer's Handbook. Available at: http://www.sign.ac.uk/pdf/qrg50.pdf. Accessed December 11, 2015.
6. Guyatt GH, Oxman AD, Vist GE, et al., GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.
7. Chen YH, Chen SN, Lien RI, et al. Refractive errors after the use of bevacizumab for the treatment of retinopathy of prematurity: 2-year outcomes. Eye (Lond) 2014;28:1080-86.
8. Gunay M, Celik G, Gunay BO, Aktas A, Karatekin G, Ovali F. Evaluation of 2-year outcomes following intravitreal bevacizumab (IVB) for aggressive posterior retinopathy of prematurity. Arq Bras Oftalmol 2015;78:300-304.
9. Isaac M, Mireskandari K, Tehrani N. Treatment of type 1 retinopathy of prematurity with bevacizumab versus laser. J AAPOS 2015;19:140-44.
10. Kuo HK, Sun IT, Chung MY, Chen YH. Refractive error in patients with retinopathy of prematurity after laser photocoagulation or bevacizumab monotherapy. Ophthalmologica 2015;234:211-17.
11. Araz-Ersan B, Kir N, Tuncer S, et al. Preliminary anatomical and neurodevelopmental outcomes of intravitreal bevacizumab as adjunctive treatment for retinopathy of prematurity. Curr Eye Res 2015;40:585-91.

eTable 1. Comparative studies evaluating refractive outcome of antivascular endothelial growth factor therapy[a]

Study	Study design	Intervention	Mean BW, g	Mean GA, weeks	Follow-up, months	Zone	No. eyes	Final spherical equivalent, mean	Cylinder, mean (*P* value)	Conclusion, in terms of myopia (*P* value)	SIGN Scale	GRADE
Araz-Ersan et al[11]	Cohort case–control	Laser + IVB	1016.8 ± 285.1	27.26 ± 2.57	24	Zone I Zone II posterior	13 5	−0.15 ± 3.01	−1.26 ± 1.18	NSD (0.16)	3	Very low
		Laser	987.7 ± 321.9	27.68 ± 1.91		Zone I Zone II posterior	N/A (13 patients)	+1.43 ± 1.83	−0.57 ± 1.86			
Chen et al[7]	Retro	IVB IVB + laser	879.0 ± 212.5 732.4 ± 127.4	26.6 ± 1.7 24.7 ± 2.2	24	N/A N/A	40 17	−0.98 ± 4.05 −2.40 ± 3.13	2.23 ± 1.53 2.32 ± 1.10 (0.29)	IVB < laser + IVB (<0.001)	2−	Low
Geloneck et al[1]	Pro	IVB	N/A	N/A	30	Zone I Zone II posteror	52 58	−1.51 ± 3.42 −0.58 ± 2.53	N/A	IVB < laser (<0.001); no significant intergroup difference in zone and refraction	2+	Moderate
		Laser				Zone I Zone II posteror	35 66	−8.44 ± 7.57 −5.83 ± 5.87	N/A			
Gunay et al[8]	Retro	IVB	901.40 ± 304.60	26.40 ± 1.82	24	APROP Zone I Zone II posterior	 25 23	0.42 ± 3.42		IVB < laser (0.001)	2−	Low
		Laser	941.00 ± 282.48	27.30 ± 1.82		APROP Zone I Zone II posterior	 18 12	−6.66 ± 4.96				
Harder et al[2]	Pro	IVB	627 ± 116	24.8 ± 1.2	10.5	N/A	12	−0.27 ± 4.09 (OD) 1.54 ± 2.19 (OS)	1.13 ± 0.54 OD 0.92 ± 0.52 OS (0.2)	IVB < laser (OD, 0.03; OS, 0.02)	2−	Low
	Matched control group with previous history of laser therapy at the same center	Laser	732 ± 226	25.1 ± 1.9	11.5	N/A	20	−6.25 ± 5.31 (OD) −4.20 ± 5.92 (OS)	1.80 ± 1.49 OD 1.58 ± 0.88 OS (0.9)			

(*Continued*)

eTable 1. Comparative studies evaluating refractive outcome of antivascular endothelial growth factor therapya (*Continued*)

Study	Study design	Intervention	Mean BW, g	Mean GA, weeks	Follow-up, months	Zone	No. eyes	Final spherical equivalent, mean	Cylinder, mean (*P* value)	Conclusion, in terms of myopia (*P* value)	SIGN Scale	GRADE
Harder et al[3]	Retro	IVB	622 ± 153	25.2 ± 1.6	11.4 ± 2.3	Zone I prethreshold ROP	5	−1.04 ± 4.24	−1.0 ± 1.04	IVB < laser (0.02)	2−	Low
						Posterior zone II or zone I threshold ROP	18					
		Laser	717 ± 197	25.3 ± 1.8		N/A	26	−4.41 ± 5.50	1.82 ± 1.41 (0.03)			
Hwang et al[4]	Retro	IVB	668.1 ± 127.3	24.2 ± 1.0	22.4 ± 8.1	Type 1 ROP				NSD (0.4); distribution of zone I and zone II disease differed between groups	2−	Low
						Total	22	−2.4 ± 3.5	1.0 ± 0.8			
						Zone I	16	−3.7 ± 3.3	1.2 ± 0.8			
						Zone II	6	+0.6 ± 1.7	1.6 ± 1.5			
		Laser	701.4 ± 118.8	24.8 ± 1.2	37.1 ± 19.8	Type 1 ROP						
						Total	32	−5.3 ± 5.4	0.6 ± 0.8			
						Zone I	5	−10.1 ± 10.5	2.1 ± 1.1			
						Zone II	27	−4.7 ± 4.6	1.6 ± 1.6 (0.1)			
Isaac et al[9]	Retro	IVB	722 ± 131	25.2 ± 1.4	10.81 ± 1.71	Zone I	8	−3.57 ± 6.19		NSD (0.33)	2−	Low
						Zone II posterior	15					
		Laser	674 ± 175	25.0 ±1.1	11.29 ± 2.58	Zone I	8	−6.39 ± 4.41				
						Zone II posterior	14					
Kuo et al[10]	Retro	IVB	1,079.6 ± 357.4	27.3 ± 2.9	36	N/A	15	−1.53 ± 2.20		NSD (1)	2−	Low
		Laser	1,006.7 ± 327.6	27.4 ± 2.9		N/A	14	−1.71 ± 1.27				

APROP, aggressive posterior retinopathy of prematurity; *BW*, birth weight; *GA*, gestational age; *GRADE*, Grading of Recommendations, Assessment, Development and Evaluation; *IVB*, intravitreal bevacizumab; *N/A*, not available; *NSD*, no significant difference; *OD*, right eye; *OS*, left eye; *Pro*, prospective; *Retro*, retrospective; *ROP*, retinopathy of prematurity; *SIGN*, Scottish Intercollegiate Guidelines Network.

[a]Continuous data are presented as mean ± standard deviation.

Table A1. Summary of Duane syndrome and synergistic divergence patients[a]

			BCVA			
Subject	Parents' relation	Siblings	Right eye	Left eye	Affected eye	Contralateral eye
1	2nd cousins	5th of 7	20/30	20/40	Left	Normal
2	Unknown	Unknown	20/30	20/40	Left	Slight adduction defect
3	1st cousins	None	20/20	20/40	Left	Normal
4	2nd cousins	6th of 8	20/400	20/25	Right	−2 adduction with retraction; −3 abduction

BCVA, best-corrected visual acuity.
[a]No patient had a known family history for strabismus. The affected eye had congenital large-angle exotropia (estimated 70^{Δ}-90^{Δ} in primary position), limited adduction (−4 or −5) in that eye, and paradoxical increased abduction during attempted adduction in that eye; vertical ductions were full in both eyes.