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Ocular and developmental outcomes of a dosing study of bevacizumab for retinopathy of prematurity

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Abstract

Purpose—To report 2-year ocular and developmental outcomes for infants receiving low doses of intravitreal bevacizumab for type 1 retinopathy of prematurity (ROP).

Methods—A total of 120 premature infants (mean birthweight, 687 g; mean gestational age, 24.8 weeks) with type 1 ROP were enrolled in a multicenter, phase 1 dose de-escalation study. One eye per infant received 0.25 mg, 0.125 mg, 0.063 mg, 0.031 mg, 0.016 mg, 0.008 mg, 0.004 mg, or

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0.002 mg of intravitreal bevacizumab; fellow eyes when treated received one dosage level higher. At 2 years, 70 of 120 children (58%) underwent ocular examinations; 51 (43%) were assessed using the Bayley Scale of Infant and Toddler Development.

Results—Correlation coefficients for the association of total dosage of bevacizumab with Bayley subscales were −0.20 for cognitive (95% CI, −0.45 to 0.08), −0.15 for motor (95% CI, −0.41 to 0.14), and −0.19 for language (95% CI, −0.44 to 0.10). Fourteen children (21%) had myopia greater than −5.00 D in one or both eyes, 7 (10%) had optic nerve atrophy and/or cupping, 20 (29%) had strabismus, 8 (11%) had manifest nystagmus, and 9 (13%) had amblyopia.

Conclusions—In this study cohort, there was no statistically significant correlation between dosage of bevacizumab and Bayley scores at 2 years. However, the sample size was small and the retention rate relatively low, limiting our conclusions. Rates of high myopia and ocular abnormalities do not differ from those reported after larger bevacizumab doses.

Anti-VEGF drugs are increasingly used to treat type 1 retinopathy of prematurity (ROP), especially zone I disease. We previously conducted a multicenter, phase 1 dose de-escalation study and found that initial doses of intravitreal bevacizumab (IVB) as low as 0.004 mg were effective in small cohorts of infants.[1,2] This dose de-escalation study design allowed us to assess short-term efficacy of several doses. It also provided an opportunity to explore whether total IVB dosage may be associated with ocular or developmental outcomes. Specifically, because IVB injection has been associated with reduced circulating VEGF levels,[3] we hypothesized that infants receiving low doses would have better neuro-developmental outcomes than those receiving higher doses. Many of these infants were followed to 24 months' adjusted age. The purpose of the present study was to report results of their ocular examinations and performance on the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley III).

Subjects and Methods

The study was conducted at ten academic health centers and approved by the institutional review board of each. A parent or guardian of each study participant provided written informed consent. Study information is provided on ClinicalTrials.gov (NCT02390531), and the complete study protocol is available on the Pediatric Eye Disease Investigator Group (PEDIG) website (www.pedig.net).

The phase 1, masked study was conducted by PEDIG. A total of 120 infants were treated for ROP with an IVB injection in the study eye, using a dose level (in mg) of 0.25, 0.125, 0.063, 0.031, 0.016, 0.008 0.004, or 0.002; 109 fellow eyes were also treated, receiving a dose one level higher than in the study eye (the dose in the fellow eye was 0.625 mg if the study-eye dose was 0.25 mg). Details of drug dilution, injection, and 4-week outcomes were reported previously,[1] as were reactivations, additional treatments, and 12-month outcomes.[4–6]

On completion of the examination at 12 months' corrected age, the parents of 72 participants (60% of the original cohort) consented to return for an additional office examination at 24 ± 3 months corrected age (henceforth, "24-month examination"). The examination included assessment of vision, ocular alignment, cycloplegic refractive error, and the anterior and

posterior segments of the eye. Neurological development was assessed by trained examiners at each site, including the cognitive, motor, and language domains of the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley III).[7]

Statistical Methods

The total dosage of IVB, which included the initial injections in one or both eyes plus any repeat injections, was used for participant-level outcomes such as strabismus, nystagmus, anisometropia, and Bayley composite (domain) scores. The total dosage of IVB in an eye, which included the initial injection plus any repeat injections, was used for eye-level outcomes, such as refractive error, optic atrophy, optic nerve cupping, and abnormal anterior or posterior segment findings. For analyses, including refractive error, eyes with aphakia (both eyes of one child) were excluded.

Analyses were performed to evaluate whether there was any relationship between IVB total dosage and each 24-month outcome measure. The relationships between continuous 24-month outcomes and the logarithm base 2 ($\log_2$) of the total dosage were evaluated using a linear mixed model, adjusting for correlation between eyes (if eye level) or a linear regression model (if participant level). For categorical 24-month outcomes, a logistic regression model with generalized estimating equations or the Fisher exact test was used to evaluate the relationship between total dosage and each binary outcome, as appropriate. The analysis window for 24-month outcomes was 639–912 days' adjusted age.

For Bayley III developmental testing at the 24-month examination, analyses were performed separately for each of the three composite scores: cognitive development, language development, and motor development, analyzed as continuous outcomes. Bayley scores were also tabulated as categorical outcomes as follows: normal (scores ≥85), slightly impaired (70–84), and severely impaired (<70), because these cut points have been described previously,[8] but we refer to scores below 70 as "severely" rather than "significantly" impaired, to avoid confusion with statistical significance. Participants with cerebral palsy who were unable to complete Bayley testing were assigned scores as follows: cognitive development, 54; motor development, 46; and language development, 46.[9] Spearman correlation coefficients and 95% confidence intervals were calculated for the relationship between each composite Bayley score and $\log_2$ total dosage and gestational age. A positive correlation coefficient indicates a direct relationship (higher Bayley score with higher IVB dose), whereas a negative value indicates an inverse relationship (higher Bayley score with lower IVB dose, which was our hypothesis). Because Bayley scores typically increase with age, the analysis window for Bayley scores was tighter than the 24-month analysis window for ocular outcomes; the Bayley analysis window was 639–821 days' adjusted age.

A linear mixed model, adjusted for the correlation between eyes, was used to test for (1) an association between laser treatment (yes vs no) and refractive error and (2) an association between zone at baseline (I vs II) and refractive error. Laser treatment was at investigator discretion beginning 4 weeks after initial bevacizumab treatment or sooner if failure criteria were met.

To control for type I error due to multiple comparisons, outcomes with *P* values ≤0.01 were considered suggestive of associations. Analyses were conducted using SAS version 9.4 (SAS Inc, Cary, NC).

Results

A total of 70 participants completed the 24-month examination within the analysis window of 639–912 days. Baseline birthweight was lower in the participants completing versus not completing the 24-month examination, and participants completing had a higher proportion of Hispanic or Latino and unknown or unreported race, whereas those not completing had a higher proportion of white race. Otherwise, baseline characteristics appeared similar between those completing the 24-month examination versus not (eSupplement 2, available at jaapos.org), and those completing the Bayley outcome examination versus not (Table 1). Also, 12-month outcomes appeared similar between those completing the 24-month examination versus not, except there was a higher incidence of strabismus at 12 months (30% vs 14%) in those completing the 24-month examination (eSupplement 3, available at jaapos.org). Between the 12-month and 24-month examinations, 40% of participants had been rehospitalized at least once, 33% required a gastrostomy and/or feeding tube, and 20% required supplemental oxygen (eSupplement 4, available at jaapos.org).

Among the 70 participants completing the 24-month examination, 51 (73%) completed Bayley testing within the analysis window. Cognitive, motor, and language scores were severely impaired for 20 (39%), 26 (51%), and 26 (51%) of participants, respectively (Tables 2–3 and eSupplement 5, available at jaapos.org). Spearman correlation coefficients for $\log_2$ total dosage of IVB and Bayley subscales were −0.20 for cognitive (95% CI, −0.45 to 0.08), −0.15 for motor (95% CI, −0.41 to 0.14), and −0.19 for language (95% CI, −0.44 to 0.10). See Figure 1. Sensitivity analysis excluding imputed values for cerebral palsy patients who were unable to complete testing yielded similar results.

Cycloplegic refractive error was measured by retinoscopy in 68 participants. Twenty-one eyes (16% [95% CI, 9%−25%]) of 14 participants (21% [95% CI, 13%−32%]) had myopia more than −5.00 D spherical equivalent, and 12 (17%) participants had anisometropia >1.50 D SE (Table 4). No significant relationship was identified between total IVB dosage in the eye and cycloplegic refractive error at 24 months ($P = 0.31$). Mean refractive errors for eyes with ROP in zone I (n = 65) and zone II (n = 69) at the time of initial bevacizumab injection were −1.72 D and −1.77 D, respectively (difference = 0.06 D; 99% CI, −3.30 to 3.41 D). Mean refractive error for eyes receiving laser after bevacizumab (n = 69) was −2.23 D, compared with −1.23 D for those eyes not having laser (n = 65) (difference = −1.70 D; 99% CI −5.00D to 1.62 D). Figure 2 shows refractive error at age 2 versus age at time of laser.

At the 24-month examination, constant or intermittent strabismus at distance or near was reported in 20 participants (29%), manifest nystagmus in 8 (11%), and amblyopia in 9 (13%). (eSupplement 6, available at jaapos.org) Amblyopia was treated by spectacles alone in 2, patching alone in 5, and both in 2. Abnormalities of the lens were reported in 4 eyes (3%) and included 2 with aphakia and 2 with visually insignificant lens opacities. Optic nerve atrophy was present in 8 eyes (6%) and optic nerve cupping (cup:disk ratio >0.5) was

present in 10 eyes (7%). Seven children (10%) had optic atrophy and/or cupping in one or both eyes (Table 4).

Visual acuity was assessed using Teller Acuity Cards in 18 children, of whom 13 (72%) scored within normal range for age[10] (better than 3.7 cycles/degree in one or both eyes). Forty-five participants had vision assessed by fix-and-follow instead of Teller Acuity Cards, and all 45 could fix and follow with each eye. There were no relationships identified between any ocular findings with total dosage of IVB (Table 4).

Discussion

In this 2-year extension of a study evaluating de-escalating doses of bevacizumab for ROP, we investigated whether total intravitreal bevacizumab (IVB) dosage was associated with ocular or developmental outcomes. We were particularly interested in neurodevelopmental outcomes assessed by the Bayley scales at 2 years' corrected age. We observed no associations between dosage of bevacizumab and Bayley scores at 2 years. However, small sample size and the relatively low retention rate limit our conclusions. Based on confidence intervals, we cannot exclude a weak-to-moderate inverse correlation (higher scores with lower doses, consistent with our study hypothesis) or a weak direct correlation (higher scores with higher doses). Regarding ocular outcomes, we did not observe any relationships between total dose and any specific ocular findings.

Although our study data support that there is not a strong correlation between higher dose and lower Bayley scores, this study was unable to determine whether or not higher doses of bevacizumab contribute to worse developmental outcomes, for several reasons. First, treatment after 4 weeks was at investigator discretion, and it is possible that infants likely to have worse developmental outcomes were also more likely to have worse ROP and receive a higher total dose of bevacizumab. This could bias toward finding an association between higher doses and worse developmental outcome. Second, we did not have Bayley scores for 58% of the original cohort, and there were some differences between those who completed the Bayley tests and those who did not. Finally, our modest sample size of 51 who completed Bayley testing resulted in relatively wide confidence intervals, limiting our conclusions. In general, the greater the sample size, the more precise the estimate (ie, the narrower the confidence interval), and the more informative the observed data.

A large proportion of our cohort had significant neurodevelopmental impairment at 24 months (39%, 51%, and 51% for cognitive, motor, and language, resp.), which is expected for low-birth weight infants with ROP requiring treatment who often have several comorbidities. IVB injection has been associated with a reduction in circulating VEGF concentrations,[3] and VEGF is necessary for normal development of many tissues of premature infants, including the brain.[11] It is unclear whether use of IVB may have a detrimental effect on development. Morin and colleagues[12] analyzed data from a Canadian national registry and reported that motor development was delayed in infants receiving bevacizumab versus laser (composite score of 81 vs 88), although the authors acknowledged that sicker infants were more likely to receive bevacizumab. Another study utilizing registry data in the United States reported that ROP treatment modality (bevacizumab or laser) was

not associated with differences in their composite outcome of death or neurodevelopmental impairment, but the bevacizumab group had higher mortality and poor cognitive outcomes in early childhood.[13] It has been hypothesized that a lower dose of IVB will reduce the risk of systemic adverse effects, which was one of the primary reasons we initiated this dose de-escalation study. However, despite using much lower than standard doses, we did not observe less reduction of plasma VEGF in our cohort.[14]

Fourteen of 68 participants (21%) had high myopia (≥5 D) in one or both eyes, and 21 of 136 eyes (16%) had high myopia. Mean and median refractive errors were mildly myopic, which is consistent with other studies of refractive error after treatment with IVB.[15,16] For comparison, 25.5% of eyes treated with laser for high-risk prethreshold ROP in the Early Treatment for ROP Study had developed high myopia by 9 months of age.[17] In our study, eyes that received laser after IVB had more myopia on average (−2.23 D) than eyes not receiving laser (−1.23 D), but the 95% confidence interval for difference was wide and not statistically significant. It is noteworthy that most of the eyes developing high myopia after IVB with subsequent laser treatment had laser before 56 weeks' postmenstrual age (Figure 2), but this could be due to factors other than timing of laser, such as more severe ROP, or simply chance.

Our study had limitations. Only 58% of original cohort participated in the 2-year examination. It was necessary to reconsent families for this extension study; that may have been a factor in the relatively low retention rate. Furthermore, Bayley test scores were available for only 51 of 70 children who had a 2-year examination, which reduced the precision in assessing associations between dosage and neurological outcomes at 2 years. Also, Bayley scores and their norms may not be generalizable to populations outside of the United States.[18] An additional limitation was that birth weight and racial distribution differed between those completing and those not completing the 2-year study examination. Finally, grating acuity measured using Teller Acuity Cards was available for only a limited number of participants.

We did not observe a statistically significant association between total dosage of bevacizumab and Bayley scores at 2 years. However, our sample size was small and the retention rate relatively low. Based on confidence intervals, we cannot exclude a weak direct or inverse correlation, or even a moderate inverse correlation that would be consistent with our hypothesis that lower doses are associated with better neurodevelopmental outcomes. Additional studies, including randomized trials, are needed to determine whether IVB has a detrimental effect on neurodevelopment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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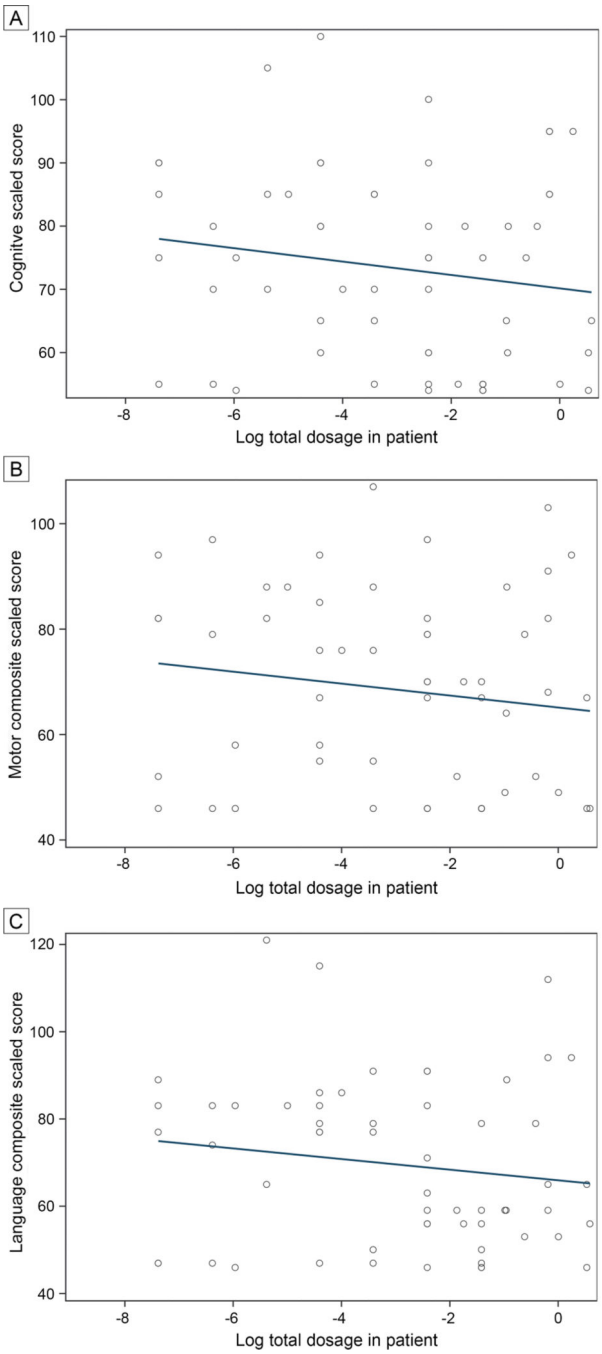

FIG 1.

Bayley score versus logarithm base 2 of total bevacizumab dosage in mg. Each of the three Bayley composite scores is plotted against the $\log_2$ of the total dosage (in the patient): cognitive (A), Spearman's ρ (95% CI) = −0.20 (−0.45, 0.08); motor (B), Spearman's ρ (95% CI) = −0.15 (−0.41, 0.14); language, Spearman's ρ (95% CI) = −0.19 (−0.44, 0.10) Higher composite scores indicate better development in that domain. Total dosage in the patient ranged from 0.002 mg ($\log_2$ 0.002 = −9.0) to 1.5 mg ($\log_2$ 1.5 = 0.6).

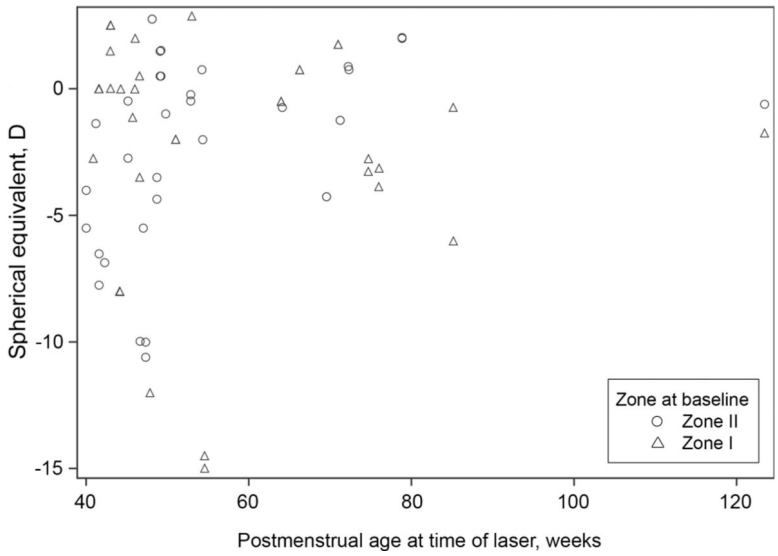

FIG 2.

Refractive error vs postmenstrual age (PMA) at laser. Refractive error at the 24-month examination plotted against PMA at the time of laser if the eye received laser. Circles represent eyes that were in zone I at baseline; triangles, eyes that were in zone II.

Table 1.

Baseline characteristics of participants stratified by completion of the Bayley test

Study parameter	Completing (n = 51)	Not completing (n = 69)[a]
	No. (%)	No. (%)
Sex		
Female	20 (39)	29 (42)
Race/ethnicity[b]		
White	24 (47)	41 (59)
Black / African American	6 (12)	13 (19)
Hispanic or Latino	11 (22)	6 (9)
Asian/American Indian/Alaskan Native/Hawaiian	3 (6)	5 (7)
More than one race	2 (4)	2 (3)
Unknown/not reported	5 (10)	2 (3)
Gestational age, weeks		
Mean ± SD	24.8 ± 1.4	24.9 ± 1.7
Median (quartiles)	24.7 (23.6, 25.6)	24.6 (23.9, 25.6)
Initial IVB dose in study eye, mg		
0.002	7 (14)	17 (25)
0.004	2 (4)	10 (14)
0.008	4 (8)	5 (7)
0.016	10 (20)	4 (6)
0.03125	5 (10)	5 (7)
0.0625	12 (24)	12 (17)
0.125	6 (12)	10 (14)
0.25	5 (10)	6 (9)
Stage of ROP in study eye at baseline		
Stage 2 or 3 in zone II with plus disease	27 (53)	37 (54)
Stage 3 in zone I w/o plus disease	8 (16)	12 (17)
Any stage in zone I with plus disease	16 (31)	20 (29)
Birth weight, g		
Mean ± SD	692.7 ± 235.1	682.7 ± 312.9
Median (quartiles)	650.0 (580.0, 740.0)	630.0 (520.0, 750.0)
Head circumference, cm		
Mean ± SD	25.6 ± 4.1	26.8 ± 4.4
Median (quartiles)	26.0 (22.0, 29.0)	27.0 (23.0, 30.0)
Preexisting medical conditions related to neurodevelopment[c]		
Yes	15 (29)	21 (30)

IVB, intravitreal bevacizumab; *SD*, standard deviation.

[a]The 11 patients who completed the Bayley examination outside analysis window (639–821 days adjusted age) are included as “not completing.”

[b]Ethnicity was self-reported by parent as Hispanic or Latino, Not Hispanic or Latino, or unknown / not reported. Race was self-reported by parent as White, Black-African-American, Asian, Native Hawaiian / other Pacific Islander, American Indian/Alaskan Native, more than one race,

or unknown / not reported. If ethnicity was self-reported as Hispanic or Latino, then race/ethnicity was considered Hispanic or Latino; otherwise, race/ethnicity was considered to be race self-reported by the parent.

[c]Preexisting conditions prior to enrollment that could impact neurodevelopmental milestones, including intraventricular hemorrhage, periventricular leukomalacia, and hydrocephalus.

Table 2.

Bayley neurodevelopmental examination findings at 24 months[a]

Study parameter	Overall	Total dosage of bevacizumab injected into both eyes prior to 24-months			
		0.002 to 0.024 mg	≥0.024 to <0.1875 mg	≥0.1875 to 0.375 mg	≥0.375 to 1.5 mg
	(N = 51)	(n = 8)	(n = 15)	(n = 9)	(n = 19)
	no. (%)	no. (%)	no. (%)	no. (%)	no. (%)
Cognitive[b,c]					
Severely impaired (<70)	20 (39)	2 (25)	3 (20)	4 (44)	11 (58)
Slightly impaired (71–84)	14 (27)	3 (38)	5 (33)	3 (33)	3 (16)
Normal (≥85)	17 (33)	3 (38)	7 (47)	2 (22)	5 (26)
Mean (95% CI)	73.7 (69.4–78.1)	74.3 (62.4–86.1)	80.3 (72.0–88.7)	71.6 (59.2–84.0)	69.3 (61.8–76.8)
Median (IQR); range	75.0 (60.0–85.0); 54.0 to 110.0	75.0 (62.5–87.5); 54.0 to 90.0	80.0 (70.0–90.0); 55.0 to 110.0	70.0 (60.0–80.0); 54.0 to 100.0	65.0 (55.0–85.0) 54.0 to 95.0
Language[b,c]					
Severely impaired (<70)	26 (51)	3 (38)	3 (20)	5 (56)	15 (79)
Slightly impaired (71–84)	12 (24)	4 (50)	6 (40)	2 (22)	0 (0)
Normal (≥85)	12 (24)	1 (13)	5 (33)	2 (22)	4 (21)
Mean (95% CI)	70.2 (64.6–75.9)	69.4 (53.4–85.3)	81.4 (69.7–93.0)	67.7 (54.7–80.7)	63.6 (54.3–72.9)
Median (IQR); range	65.0 (53.0–83.0); 46.0 to 121.0	80.0 (47.0–83.0); 46.0 to 89.0	81.0 (77.0–86.0); 47.0 to 121.0	59.0 (56.0–83.0); 46.0 to 91.0	59.0 (50.0–65.0) 46.0 to 112.0
Motor Skills[b,c]					
Severely impaired (<70)	26 (51)	4 (50)	4 (27)	4 (44)	13 (68)
Slightly impaired (71–84)	13 (25)	3 (38)	4 (27)	4 (44)	2 (11)
Normal (≥85)	11 (22)	1 (13)	5 (33)	1 (11)	4 (21)
Mean (95% CI)	68.6 (63.2–74.0)	67.4 (51.5–83.2)	76.5 (66.2–86.9)	67.0 (53.1–80.9)	64.4 (54.9–73.9)
Median (IQR); range	68.0 (46.0–82.0); 46.0 to 107.0	68.5 (49.0–82.0); 46.0 to 94.0	76.0 (67.0–88.0); 46.0 to 107.0	70.0 (46.0–79.0); 46.0 to 97.0	64.0 (46.0–82.0) 46.0 to 103.0

CI, confidence interval; *IQR* = interquartile range; *SD*, standard deviation.

[a] Excludes 9 patients who completed the Bayley test outside the Bayley analysis window (639 to 821 days adjusted age).

[b] Four out of 8 patients with cerebral palsy could not do Bayley (were untestable) and were therefore assigned scores as follows: cognitive = 54, motor = 46, language = 46.

[c] One patient had a cognitive score but was missing the language and motor skills scores; another was missing just the motor skills score. Therefore N = 50 for language and N = 49 for motor skills.

[d] *P* value for the relationship between Bayley scores and $\log_2$ total dose as a continuous variable from a linear regression model. Spearman correlation coefficients shown are the relationship between $\log_2$ total dose of bevacizumab and Bayley subscales.

Table 3.

Linear regression analysis of Bayley neurodevelopmental examination findings at 24 months as a function of bevacizumab dosage

Study parameter	*P* value[a]	Spearman correlation coefficient (95% CI)[b]
Cognitive	0.14	−0.20 (−0.45, 0.08)
Language	0.13	−0.19 (−0.44 0.10)
Motor skills	0.36	−0.15 (−0.41, 0.14)

[a] *P* value from a linear regression model for the relationship between Bayley scores and log base 2 total dosage as a continuous variable.

[b] Spearman correlation coefficients shown are the relationship between log base 2 total dosage of bevacizumab and Bayley subscales.

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Table 4.

Cycloplegic refraction and ocular outcomes at the 24-month examination

Study parameter	Overall (N = 140)	Total dosage of bevacizumab, mg, injected into eye prior to 24 months										P value[b,c,d]
		0 (n = 6)	>0 to 0.002 (n = 8)	>0.002 to 0.004 (n = 12)	>0.004 to 0.008 (n = 10)	>0.008 to 0.016 (n = 14)	>0.016 to 0.031 (n = 15)	>0.031 to 0.063 (n = 17)	>0.063 to 0.125 (n = 18)	>0.125 to 0.25 n = 16)	>0.25 (n = 24)	
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	
Cycloplegic refraction (SE)[a]												
Not done	4 (3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7)	1 (7)	0 (0)	0 (0)	1 (6)	1 (4)	
<−5.00 D	21 (15)	0 (0)	0 (0)	2 (17)	1 (10)	2 (14)	2 (13)	3 (18)	1 (6)	1 (6)	9 (38)	
−5.00D to ≤ −1.00 D	36 (26)	1 (17)	5 (63)	3 (25)	4 (40)	2 (14)	5 (33)	3 (18)	4 (22)	3 (19)	6 (25)	
> −1.00D to < +1.00 D	47 (34)	5 (83)	2 (25)	4 (33)	2 (20)	5 (36)	6 (40)	8 (47)	7 (39)	5 (31)	3 (13)	
≥ +1.00D to ≤ = +5.00 D	30 (21)	0 (0)	1 (13)	3 (25)	3 (30)	4 (29)	1 (7)	3 (18)	5 (28)	5 (31)	5 (21)	0.31
>+5.00 D	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Mean ± SD	−1.75 ± 3.99	−0.42 ± 1.66	−1.11 ± 2.13	−0.90 ± 2.81	−1.65 ± 2.89	−1.54 ± 3.75	−2.50 ± 4.68	−1.99 ± 4.10	−0.57 ± 2.95	−0.21 ± 2.44	−4.08 ± 5.88	
Median (quartiles); range	−0.50 (−3.13, 0.75); −16.50 to 3.50	0.13 (−0.75, 0.75); −3.50 to 0.75	−1.38 (−2.00, 0.44); −5.00 to 2.00	−0.13 (−1.63, 0.94); −6.50 to 2.00	−0.75 (−4.25, 1.00); −6.88 to 1.50	−0.50 (−2.75, 1.00); −10.00 to 2.50	−0.81 (−3.88, 0.25) −16.50 to 2.50	−0.50 (−3.13, 0.25); −12.25 to 2.75	−0.50 (−1.00, 1.13); −10.00 to 3.50	0.25 (−1.00, 1.75); −5.50 to 2.75	−1.75 (−8.00, 0.50); −15.00 to 2.88	
Ocular clinical exam findings												
Abnormal anterior segment	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (6)	0 (0)	0.27[e]
Abnormal cornea	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (6)	0 (0)	0.27[e]
Abnormal lens	4 (3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7)	0 (0)	0 (0)	1 (6)	1 (6)	1 (4)	0.05[e]
Abnormal vitreous	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (6)	0 (0)	0.27[e]
ON atrophy	8 (6)	0 (0)	0 (0)	1 (8)	1 (10)	0 (0)	1 (7)	2 (12)	2 (11)	1 (6)	0 (0)	0.50[f]
Macular ectopia	4 (3)	1 (17)	0 (0)	0 (0)	0 (0)	2 (14)	1 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0.01[e]

Study parameter	Overall (N = 140)	Total dosage of bevacizumab, mg, injected into eye prior to 24 months										P value[b,c,d]
		0 (n = 6)	>0 to 0.002 (n = 8)	>0.002 to 0.004 (n = 12)	>0.004 to 0.008 (n = 10)	>0.008 to 0.016 (n = 14)	>0.016 to 0.031 (n = 15)	>0.031 to 0.063 (n = 17)	>0.063 to 0.125 (n = 18)	>0.125 to 0.25 n = 16)	>0.25 (n = 24)	
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	
Retinal detachment	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (6)	0 (0)	0.27[e]
Retinal fold	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	n/a
ON cupping	10 (7)	1 (17)	0 (0)	2 (17)	1 (10)	1 (7)	0 (0)	1 (6)	2 (11)	1 (6)	1 (4)	0.59[f]
Any abnormality present	22 (16)	2 (33)	0 (0)	2 (17)	1 (10)	3 (21)	2 (13)	3 (18)	4 (22)	3 (19)	2 (8)	0.79[f]

ON, optic nerve; *SD*, standard deviation; *SE*, spherical equivalent.

[a] Cycloplegic refraction analysis and tabulation excludes 2 aphakic eyes. Percentages are unadjusted for any correlation between eyes.

[b] *P* value from linear mixed model accounting for any correlation between eyes for an association between the continuous outcome and total dose as categorical factor.

[c] A separate analysis evaluated the relationship between refractive error and laser in the eye (yes vs no) using a linear mixed model accounting for any correlation between the eyes. The difference (laser yes – laser no), 95% CI, and *P* value for this analysis were: −1.70, (95% CI, −5.00 to 1.62), $P = 0.16$.

[d] A separate analysis evaluated the relationship between refractive error and zone at baseline (I vs II) using a linear mixed model accounting for any correlation between the eyes. The difference (zone I – zone II), 95% CI, and *P* value for this analysis were: 0.06, (95% CI, −3.30 to 3.41), $P = 0.95$.

[e] *P* value from the Fisher exact test without accounting for correlation between eyes for an association between the binary outcome and total dose as a categorical factor.

[f] *P* value from logistic regression accounting for correlation between eyes for an association between the binary outcome and total dose as a categorical factor.