LONG-TERM EFFECT OF ANTIANGIOGENIC THERAPY FOR RETINOPATHY OF PREMATURITY Up to 5 Years of Follow-up

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Purpose: To evaluate ocular function and systemic development in premature infants treated with intravitreal bevacizumab injections for retinopathy of prematurity over a period of 5 years.

Methods: A prospective, interventional, noncomparative case study. The primary outcome measure was visual acuity. The secondary outcomes were structural assessment, other ocular functional measurements, and developmental state.

Results: Eighteen eyes of 13 consecutive patients were divided into 3 groups: Group 1, Stage 4 unresponsive to previous conventional treatment (n = 4); Group 2, in which conventional treatment was difficult or impossible because of inadequate visualization of the retina (n = 5); and Group 3, newly diagnosed high-risk prethreshold or threshold retinopathy of prematurity (n = 9). All patients showed initial regression of neovascularization. One patient was diagnosed with recurrence of neovascularization and was treated with intravitreal bevacizumab. Visual acuity was preserved, and median vision was 20/25 (excluding 2 operated eyes). Twelve eyes developed mainly low myopia over the years, with an overall mean value of 3.2 diopters. Electroretinograph was normal in 4 eyes that had no previous detachment. One patient showed delay in growth and neurodevelopment, whereas all the others were within the normal range.

Conclusion: Five years of follow-up in a small series suggest that intravitreal bevacizumab for retinopathy of prematurity results in apparently preserved ocular function and systemic development.

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Retinopathy of prematurity (ROP) is a neovascular disorder of the developing retina that remains one of the most frequent causes of childhood blindness.[1–4] It is the leading cause of blindness in the United States. Lad et al[5] have recently found an incidence of 15.58% among premature infants, emphasizing the role of low birth weight. Retinopathy of prematurity has also become a significant cause of blindness in many middle- and low-income countries in Latin American and Eastern Europe, which have introduced neonatal intensive care services and improved survival of high-risk neonates.[6]

Since the 1980s, ablative therapy of the peripheral retina was recommended as the gold standard for the treatment of ROP.[7,8] Cryotherapy and laser photocoagulation act by destroying the vascular endothelial growth factor–producing retina, thus promoting the regression of neovascularization (NV).

Although prematurity and low birth weight are major risk factors,[9] there are other factors that have been implicated in its pathogenesis.[10,11] It has been

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recently understood that ROP is a biphasic disease consisting of an initial phase of oxygen-induced vascular obliteration followed by a period of hypoxia-induced vessel proliferation.[12] Vascular endothelial growth factor plays an important role in ROP with significantly high levels detected in eyes with ROP.[12–19]

In the last few years, anti–vascular endothelial growth factor intravitreal therapy has emerged as a new treatment modality for ROP. Beginning in 2007, several retrospective reports presented promising experience with off-label use of anti–vascular endothelial growth factor in infants with progressive ROP.[20–24] The results of the recently published Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT ROP) Trial, a prospective, controlled, randomized trial, showed significant benefit of intravitreal bevacizumab (IVB) monotherapy for Stage 3+, Zone I disease.[25]

Concerns and controversies were raised about the drug's long-term effect on ocular health, long-term visual outcome, and systemic safety profile, given so early in life.[26,27] These issues were not addressed in the literature yet.

The aim of our study was to evaluate the long-term effect of IVB on ocular health and systemic development in preterm neonates treated for ROP over a follow-up period of 5 years.

Materials and Methods

We conducted a prospective, interventional, noncomparative case study, approved by the Internal Review Board of the Asociación para Evitar la Ceguera en México Hospital "Luis Sanchez Bulnes" in México City and performed in accordance with the ethical standards of the Declaration of Helsinki. Enrollment occurred between September 2005 and July 2006.

Premature infants in the neonatal intensive care unit, with a birth weight of 1,600 g or less and gestational age of 32 weeks or less, were examined for ROP. The examination was performed beginning at 4 weeks of chronologic age or 31 weeks of postmenstrual age, whichever was later, as per the guidelines published by the American Academy of Ophthalmology.[28] Retinopathy of prematurity was classified according to the Revised International Classification for Retinopathy of Prematurity.[29]

Infants with ROP having at least high-risk prethreshold (Type 1) disease requiring treatment were included in the study. Exclusion criteria were leukocoria, absence of neovascular activity, and any other congenital eye anomalies. Parents provided written informed consents for all enrolled participants in concordant with the guidelines of the Mexican Official Standard 168.

The various clinical outcome measures included visual acuity as a primary outcome. Structural assessment including recurrence of retinopathy, other ocular functional measurements (refraction, biometry, and electrophysiology), and developmental testing were considered secondary outcomes.

Injection Protocol

All eligible infants received IVB (Avastin; Genentech, Inc, South San Francisco, CA) injections. Treatment was performed under general anesthesia in the operating room. Topical 5% povidone–iodine was applied to the periocular skin and the conjunctiva. A lid speculum was placed, and 0.05 mL (1.25 mg) of bevacizumab were injected 1 mm posterior to the corneoscleral limbus, in the inferotemporal quadrant, using a 27-gauge needle. An anterior chamber paracentesis was performed at the end to normalize intraocular pressure. Topical ofloxacin (Ocuflox; Allergan S.A. de C.V., Mexico City, Mexico) was prescribed 4 per day for 5 days after the procedure.

Ocular Assessment

Monocular visual acuity. Assessment of visual acuity was accomplished using the Teller Acuity Cards II (Stereo Optical Company, Inc., Chicago, IL), a preferential looking testing method, for patients aged 3 months to 36 months. Starting cards were used according to age: <6 months/any child with visual impairment, 0.64 cycles per centimeter; 6 months to 18 months, 1.3 cycles per centimeter; and >18 months, 2.4 cycles per centimeter. Low vision (LV) cards (0.23 cycles per centimeter) and, if necessary, a penlight were used if no response was measured. The following test distances were applied for the different age ranges: infants between birth and 6 months of age, 38 cm (15 in) and between age 7 months and 3 years, 55 cm (21.7 in). Patients who demonstrated poor acuity required an unusually close test distance: 19 cm and 9.5 cm (7.5 in and 3.7 in). The grating visual acuity outcomes were divided, as in the Early Treatment for Retinopathy of Prematurity (ETROP) trial (using conversion from cycles/degree to cycles/cm according to test distance), into 4 categories of functional response: normal, defined as ≥5.35 cycles per centimeter; below normal, defined as 2.67 to <5.35 cycles per centimeter; poor, if <2.67 cycles per centimeter but measurable with one of the standard acuity cards (not the LV card); and blind/

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LV (no light perception, light perception only, or LV only). These results were further grouped into "favorable" and "unfavorable" designations. The favorable group included eyes in the normal and below normal categories. The unfavorable group included eyes in the poor and blind/LV categories. Allen cards, a recognition acuity test, were used for older patients, 48 months to 60 months of age. All tests were performed by the same observer.

Refraction. Cycloplegic retinoscopy with handheld lenses was performed every year beginning at 12 months. Refractive errors were determined after instilling 1% cyclopentolate hydrochloride. Results were recorded in the form of spherical equivalent = sphere/cyl/2.

Biometry. Measurements of the axial length (AL), anterior chamber depth (ACD), and lens thickness (LT) were obtained with the Alcon Ultra Scan (Alcon, Fort Worth, TX) at 36 months. The biometry was performed at the time of cycloplegic refraction to eliminate any variation in biometric parameters that may have occurred because of accommodation.

Electrophysiology. A standard full-field electroretinography (ERG) was performed at 24 months to evaluate the electrical responses of the various cell types in the retina. The ERG was done using oral sedation with midazolam, under the supervision of an anesthesiologist. A contact lens was placed on the eye, and the photopic, scotopic, mesopic, and flicker responses were recorded.

Fundus examination. Infants were evaluated for anatomical success and recurrence of ROP requiring retreatment. Examinations were performed by the same retina specialist every week for the first 4 months, every month until the first year, and every 6 months later on.

Developmental Assessment

Neurodevelopment. Developmental skills were evaluated every year by the pediatricians using the standardized Denver Developmental Screening Test II.[30,31] This is the most often used and accessible screening test in Mexico for children from birth to 6 years. The scale reflects what percentage of a certain age group is able to perform a certain task. Tasks were grouped into four general function categories: receptive and expressive language, gross motor, fine motor adaptive, and personal social skills. Each patient's performance was recorded for every item and then compared with age-based norms corresponding to 25%, 50%, 75%, and 90% passing score for each item. Social class, ethnicity, gender, and place of residence of children are all related to differences in development. Developmental delay in the present study was defined as a score of $<75\%$ as adapted and standardized for children up to 5 years of age in Mexico.

Growth. Height, weight, and cephalic perimeter were routinely recorded for all patients every year. All results were compared with the anthropometric scales matched for age and sex according to the Mexican Official Standard (NOM-007-SSA2-1993).

Results

Patient Characteristics

Eighteen eyes of 13 consecutive patients (6 men and 7 women) were included in the study as summarized in Table 1. The mean gestational age was 29.3 ± 1.8 weeks (range, 27–32 weeks) with a mean birth weight of 1233.3 ± 238.3 g (range, 900–1,600 g). Mean corrected gestational age at the time of injection was 38.2 ± 4.6 weeks (range, 33–50 weeks).

Eyes were divided into 3 groups: Group 1: 4 eyes with ROP Stage 4a or 4b, unresponsive to previous conventional treatment with laser or cryotherapy; Group 2: 5 eyes presenting with poor visualization of the retina because of inadequate pupillary dilation, vitreous hemorrhage, or persistence of the *tunica vasculosa lentis* with signs of NV (rubeosis iridis). All were unable to receive conventional treatment with laser or cryotherapy. An ultrasound was performed to rule out retinal detachment; Group 3: 9 eyes with a new diagnosis of high-risk prethreshold (Type 1) or threshold ROP with plus disease requiring treatment. All eyes were assigned for IVB injections. No patient dropped out, underwent laser, or died during the study.

Structural Outcome

Regression of NV was observed in all eyes in the first 48 hours. Sixteen eyes (88.8%) required only 1 IVB injection with complete resolution including adequate visualization of the retina. Only 1 patient with bilateral ROP (Eyes 5 and 8) was diagnosed with recurrence of disease after 2 months of follow-up and required additional treatment. He was injected again, this time with complete resolution.

Two patients with ROP Stage 4b (Eyes 3 and 4) presented with detachment progression. A pars plana vitrectomy with lensectomy and silicone oil injection was performed 1 week after the injection. The patients remained attached over the whole follow-up period.

Two patients with ROP Stage 4a and 4b (Eyes 1 and 2) had spontaneous reattachment of the retina after 5 weeks to 8 weeks of follow-up.

Intravitreal bevacizumab allowed for continued vessel growth into the peripheral retina in 11 patients

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Table 1. Patient Characteristics

Patient	Eye	Sex	Birth Weight, g	Gestational Age, Weeks	Age at Injection, Weeks	ROP Classification*	Previous Treatment	Systemic State†
1	Bilateral	F	1,450	29	38	OD: Stage 4b OS: inadequate visualization	CRYO NA	Cardiac, IVH, PHT
2	Bilateral	M	900	27	44	OD: Stage 4a OS: Stage 4b	Laser Laser	Sepsis, pneumonia, IVH, multiple blood transfusions
3	Unilateral	F	1,550	30	50	Stage 4b	Laser	Pulmonary dysplasia
4	Bilateral	M	1,110	30	36	OU: inadequate visualization	NA	Cardiac, PHT, prolonged o_2 treatment, IVH Grade 3
5	Unilateral	M	1,550	32	39	Inadequate visualization	NA	Sepsis, hyperbilirubinemia
6	Unilateral	F	1,100	31	37	Inadequate visualization	NA	Pneumonia, IVH
7	Unilateral	F	1,040	27	33	High-risk prethreshold	NA	Cardiac, sepsis
8	Bilateral	F	850	28	36	OU: high-risk prethreshold	NA	Bowel disease
9	Bilateral	M	1,233	28	34	OU: threshold	NA	Sepsis, pneumonia, multiple blood transfusions
10	Unilateral	M	900	29	38	Threshold	NA	Sepsis, pneumonia
11	Unilateral	M	1,600	31	40	High-risk prethreshold	NA	Cardiac, pulmonary
12	Unilateral	F	1,150	27	33	Threshold	NA	Pulmonary, sepsis
13	Unilateral	F	1,600	32	39	Threshold	NA	Bowel disease, IVH

Data are presented for 18 eyes of 13 patients.
*ROP classification according to the Revised International Classification for Retinopathy of Prematurity.[28]
†IVH, intraventricular hemorrhage; PHT, pulmonary hypertension; NA, not applicable.

during a follow-up period of 5 years. All demonstrated attached retina without any signs of adverse outcome, except 1 patient (with ROP 4b) who developed macular dragging and folds. Two of our patients developed a peripheral avascular fibrotic membrane. We did not find any ocular side effects that could be attributed to the injection itself such as cataract.

Functional Outcome

Visual acuity. Table 2 summarizes monocular visual acuity measurements at 3, 6, 12, 24, 36, 48, and 60 months. Sixteen eyes exhibited a gradual and consistent increase in their grating acuity as measured with the Teller Acuity Cards II from 3 months to 36 months (mean of 0.69 and 13.32 cycles per centimeter, respectively). Table 3 shows an overall significant benefit of treatment with a substantial reduction in unfavorable visual acuity outcome for a follow-up period of 3 years.

At 5 years of age, the median visual acuity, measured with the Allen chart, was 2.0 logarithm of the minimum angle of resolution (counting fingers) in Group 1, 0.4 logarithm of the minimum angle of resolution (20/50) in Group 2, and 0.03 logarithm of the minimum angle of resolution (20/20) in Group 3. Fourteen eyes had an effective visual acuity of ≥20/80 (median 20/20–20/25) 5 years after treatment. Four eyes were considered legally blind (≤20/200); 3 of them were initially diagnosed with ROP Stage 4.

Refractive errors. The distribution of refractive errors at 12, 24, 36, 48, and 60 months is shown in Table 4. The average refractive errors (excluding 2 operated eyes with aphakia) at 5 years of age were −2.75 diopters (D) (range, −2 to −3.5 D), −3.15 D (range, −0.25 to −7.0 D), and −1.75 D (range, +2.5 to −6.75 D) for each group, respectively.

Eleven eyes (61%) were myopic (≥0.5 D) at 12 months. Myopia gradually increased during the follow-up period. The average myopic change for a period of 4 years was 0.92 D (range, 0.37–2.25 D).

Twelve eyes were myopic (≥0.5 D) at 60 months. Two thirds of them demonstrated low myopia (≤3 D) with a mean value of 2.06 D. Only 2 eyes were considered highly myopic (≥6 D) at 5 years of age.

One patient developed esotropia and underwent strabismus operation at age 3, and another patient developed hyperopia with accommodative esotropia that were corrected with glasses.

Biometry. Table 5 illustrates AL, ACD, and LT measured with an A-scan biometry at 36 months. The average measurements for AL, ACD, and LT were 22.49 ± 0.47 mm (range, 21.54–23.1 mm), 2.79 ± 0.24 mm (range, 2.4–3.2 mm), and 3.9 ± 0.21 mm (range, 3.6–4.2 mm), respectively.

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Table 2. Monocular Visual Acuity Measurements at Key Time Points up to 60 Months

Eyes	3 Months*	6 Months*	12 Months*	24 Months*	36 Months*	48 Months†	60 Months†
Group 1							
1	0.64	0.86	3.2	6.5	9.8	20/200	20/200
2	0.86	4.8	6.5	9.8	13	20/60	20/60
3	LV 19 cm	LV 9 cm	LV 9 cm	LV 9 cm	LV 9 cm	LV 9 cm	HM
4	LV 9 cm	LV 9 cm	LP	LP	LP	LP	LP
Group 2							
5	0.43	0.64	0.8	1.6	6.5	20/200	20/200
6	0.86	1.3	1.3	6.5	9.8	20/80	20/80
7	0.64	0.86	1.3	6.5	13	20/30	20/25
8	0.64	0.64	1.6	4.8	9.8	20/60	20/40
9	0.64	1.3	1.6	6.5	13	20/40	20/20
Group 3							
10	0.64	1.6	1.6	4.8	13	20/40	20/25
11	0.64	1.3	1.6	4.8	13	20/30	20/20
12	0.86	1.3	2.4	6.5	13	20/30	20/20
13	0.64	1.6	1.6	9.8	9.8	20/30	20/20
14	0.86	1.6	1.6	6.5	13	20/30	20/20
15	0.86	0.86	2.4	4.8	19	20/40	20/25
16	0.43	1.6	1.6	9.8	19	20/30	20/20
17	0.64	1.6	3.4	6.5	19	20/40	20/25
18	0.86	2.4	2.4	9.8	13	20/30	20/20

Data are presented for 18 eyes of 13 patients.
*Teller Acuity Cards II (cycles per centimeter).
†Allen cards.
HM, hand motion; LP, light perception.

Electroretinography. Electroretinography was performed at 24 months in 8 eyes of 4 patients chosen from all 3 groups. We could not obtain ERGs in other patients because of technical problems, poor cooperation, and the need for sedation. Four eyes with ROP Stage 3+ (Group 3) had a normal retinal electric response. Decreased ERG was recorded in 2 eyes (Patient 1). No response could be elicited in 2 eyes (Patient 2) with ROP Stage 4 (retina attached at that time).

Developmental Outcome

Neurodevelopment. Results of the Denver Developmental Screening Test II are shown in Table 6 for all patients at 60 months. We found only 1 patient with developmental delay in personal social skills, language skills, and fine motor adaptive, matching the 25 and 50 percentiles for his age, respectively.

Growth. Twelve patients showed normal growth with height, weight, and cephalic perimeter in the 50 to 90 percentiles according to the Mexican Official Standards through the follow-up. At the age of 5, the average weight was 18.9 ± 3.5 kg and 18.2 ± 1.3 kg for men and women, respectively. The average height at that time was 103.2 ± 5.3 cm and 103.7 ± 1.7 cm for men and women, respectively. The average cephalic perimeter at the last routine checkup, held at 2 years of age, was 48.1 ± 1.9 cm and 49 ± 1.6 cm for men and

Table 3. Grating Acuity Outcomes* in the First 3 Years

Outcome†	3 Months			36 Months		
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
Favorable						
Normal (≥5.35 cycles/cm)	—	—	—	2	5	9
Below normal (5.35 to <2.67 cycles/cm)	—	—	—	—	—	—
Unfavorable						
Poor (measurable but <2.67 cycles/cm)	2	5	9	—	—	—
Blind/LV (NLP, LP only, LV card only)	2	—	—	2	—	—

Data are presented as number of patients (total = 13).
*Measured with Teller Acuity Cards II (cycles per centimeter).
†The grating visual acuity outcomes were divided, as in the ETROP trial, using conversion from cycles per degree to cycles per centimeter according to test distance, into four categories of functional response.[8]
LP, light perception; NLP, no light perception.

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Table 4. Distribution of Refractive Error Measurements (SE*) by Cycloplegic Retinoscopy Every Year up to 60 Months

Eyes	12 Months	24 Months	36 Months	48 Months	60 Months
Group 1					
1	–3	–3	–3	–3.75	–3.5
2	–1.5	–1.75	–1.75	–1.75	–2
3 Aphakia	+5.5	+5	+5.5	+6.5	+7
4 Aphakia	+10.5	+10.5	+10.5	+12.5	+11
Group 2					
5	–3.5	–4	–4	–4.75	–5
6	–5	–4.75	–6	–6.75	–7
7	+0.12	+0.12	+0.12	+0.12	–0.25
8	–2	–2.5	–2.5	–2.75	–3
9	–0.5	–0.5	–0.5	–0.5	–0.5
Group 3					
10	–1.25	–1.5	–1.5	–1.5	–1.5
11	–0.75	–1.25	–2	–2.5	–3
12	–0.12	0.0	0.0	0.0	–0.25
13	–5	–5	–5.5	–6	–6.75
14	+0.5	+3.5	+3	+2.75	+2.5
15	–2	–2.75	–2.75	–3	–3
16	+0.75	+0.5	0.0	0.0	–0.25
17	–2.5	–2.5	–2.5	–2.75	–3
18	+0.5	0.0	0.0	0.0	–0.5

Data are presented for 18 eyes of 13 patients in diopters.
*SE (spherical equivalent) = sphere/cycle/2(D)
0.0, emmetropia.

women, respectively. One patient had growth retardation with parameters in the third percentile.

Discussion

Retinopathy of prematurity is a disease that continues to be a major cause of visual impairment in children. Retinal ablation with laser photocoagulation or cryotherapy is the current standard of care. The CRYO-ROP study showed a clear benefit of retinal ablative therapy, but the results in zone 1 eyes were not impressive.[7] The ETROP trial found that early treatment of high-risk prethreshold ROP (Type 1) significantly reduced unfavorable visual acuity and structural outcomes.[8] Despite properly scheduled treatment, the ETROP trial suggested that the recurrence rates with conventional laser therapy can go up to 50% for zone I disease and up to 20% for zone II posterior disease.[32] Long-term follow-up of treated infants with regressed disease also showed gradual increase in unfavorable structural outcomes such as late-onset vitreoretinal complications.[33–35] Moreover, these treatment modalities have major side effects such as clinically significant visual field loss, myopia, and cataract.[36,37]

Intravitreal bevacizumab has recently emerged as an important and promising yet controversial treatment option in ROP.[25,38] It is an easier treatment to administer than ablative therapy. The procedure is shorter, does not require special equipment, and can be carried out with short-acting topical anesthesia and so avoiding general anesthesia or sedation. It is of special interest in premature infants in the intensive care units with other comorbidities. Intravitreal bevacizumab has other potential advantages in the treatment of ROP.

Table 5. Measurements of Ocular Biometric Parameters at 36 Months

Eyes	AL, mm	ACD, mm	LT, mm
Group 1			
1	22.93	2.7	3.7
2	22.42	2.6	3.8
3 Aphakia	21.78	3.8	NA
4 Aphakia	21.00	3.7	NA
Group 2			
5	22.96	2.6	3.7
6	23.10	2.8	3.9
7	22.02	2.5	3.8
8	22.80	3.1	4.2
9	22.04	2.6	4.1
Group 3			
10	22.24	2.9	3.7
11	22.80	2.4	3.8
12	22.04	2.7	4.1
13	21.54	2.9	4.1
14	21.97	3.2	3.7
15	22.96	2.8	3.8
16	22.25	3.1	3.6
17	22.76	2.7	4.2
18	22.93	3.1	4.2

Data are presented for 18 eyes of 13 patients. NA, not applicable.

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Table 6. Results of the DDST II at 60 Months

Patients	Gross Motor, %	Fine Motor Adaptive, %	Language, %	Personal–Social Skills, %
1	75	75	75	75
2	75	75	75	75
3	75	75	75	75
4	75	50	25	25
5	75	75	75	75
6	75	75	75	75
7	75	75	75	75
8	75	75	75	75
9	75	75	75	75
10	75	75	75	75
11	75	75	75	75
12	75	75	75	75
13	75	75	90	75

Data are presented for 13 patients in percentiles. Accentuated numbers represent developmental delay (defined as a score of <75% as adapted and standardized for children up to 5 years of age in Mexico).

DDST, Denver Developmental Screening Test.

This treatment modality does not destroy the peripheral retina, thus avoiding some of the late complications of ablative treatment. It can also be applied when there is inadequate visualization of the retina that prevents the use of laser. Moreover, IVB should be considered in advanced disease such as the newly recognized aggressive posterior retinopathy of prematurity, where there is limited evidence on the effectiveness of laser in these cases.

In the present study, IVB effectively inhibited NV in patients with high-risk prethreshold and threshold ROP, with prompt regression after one injection only. Patients with inadequate visualization of the retina showed impressive regression of rubeosis iridis and persistent tunica vasculosa lentis, resulting in good visualization of the retina. Fifteen eyes (83%) had favorable anatomical outcome without any signs of retinal detachment, macular dragging, or folds after 60 months of follow-up. Although 2 of our patients with ROP Stage 4 showed disease regression and flattening of the retina after 1 injection, we suggest using IVB with caution in this stage. We found 1 patient (Patient 4) with bilateral recurrent disease after 52 weeks postmenstrual who promptly responded to another IVB with complete resolution. This recurrence can be attributed to prolonged oxygen therapy because of pulmonary hypertension, from which the patient suffered.

The ETROP trial results showed a reduction in unfavorable grating visual acuity outcomes at 9 months from 19.8% to 14.3% ($P < 0.005$) with early treatment of high-risk prethreshold ROP.[8] Our findings showed a favorable grating visual acuity outcome of 100% at 36 months with IVB treatment in patients with high-risk prethreshold, threshold ROP, and inadequate visualization with clear signs of NV (rubeosis iridis). Final results from the multicenter trial of cryotherapy for ROP (CRYO-ROP) for ROP showed unfavorable visual acuity (20/200 or worse) outcomes in 44% of treated eyes at 10 years to 15 years after treatment.[33,34] Shalev et al[39] reported the visual outcome of 18 eyes of 10 patients, 7 years after cryo or laser treatment for threshold ROP. The geometric mean visual acuity of the paired eyes after laser photocoagulation and cryo was 20/33 and 20/133, respectively ($P < 0.03$).

Visual acuity was preserved in our patients. Fourteen eyes had an effective visual acuity of ≥20/80 (mean, 20/20–20/25) 5 years after treatment. Even though 4 eyes were considered blind, 3 of them were initially diagnosed with ROP Stage 4.

Although current literature supports the effectiveness of IVB in ROP, concerns are raised regarding the use of antiangiogenic treatment in young children. Vascular endothelial growth factor is involved in a wide variety of physiologic processes throughout the body including organogenesis.[40] Intravitreal bevacizumab leaks into the systemic circulation in animals and humans including neonates with ROP.[41,42] Because preterm infants are still undergoing organogenesis at the time of ROP treatment late in the third trimester, there are real concerns of potential harm. Glade-Bender et al[43] published a series of 21 patients treated with IVB for refractory solid tumors. Therapy was well tolerated with no adverse effects on growth or development. In the eye, vascular endothelial growth factor is required not only for angiogenesis but also for normal neural retinal development.[44]

Ocular growth and refractive errors in infants treated with IVB for ROP were not addressed in the literature yet. A comparison can be made only with results published for full term, preterm, and ROP infants treated with ablation therapy.

Prematurity and ROP, especially if treated with ablative therapy, have long been known to be implicated in the development of myopia.[45–50] This abnormal refractive state appears in infancy and persists into middle childhood in 20% to 70%. Cook et al[45] studied the refractive error development in premature infants with ROP from 32 weeks to 52 weeks. Eyes that were treated for ROP showed significantly less hypermetropia at 3 months. Choi et al[46] explored changes in refraction from 6 months to 6 years in 65 premature infants with and without ROP. Myopia occurred at 6 months and increased in severity until the age of 3. No further progression was noticed at 6 years of age. Overall mean spherical equivalents were −2.58, −3.3, and −3.0 D at 6 months, 3 years,

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and 6 years, respectively. Quinn et al[47] examined the prevalence of myopia in 401 premature infants who participated in the ETROP study, between age 6 months and 3 years. They found that approximately 58% developed myopia at 6 months that gradually increased to 70% at 3 years of age. The timing of laser treatment, the ROP stage, zone, and plus disease had an insignificant impact on the prevalence of myopia.

Approximately 60% of the study eyes were already myopic (≥0.5 D) at 12 months. Although myopia progressed, the average myopic change in 4 years was <1 D. The average myopia found at 5 years of age was less than in previously reported studies at 3 years to 6 years of age. Two thirds of the patients had only low myopia (≤3 D). Infants with high-risk prethreshold and threshold ROP (Group 3) had the most favorable results with an average myopia of 1.75 D.

Myopia in premature infants, especially with ROP, is not necessarily related to increased AL but is mainly influenced by anterior segment components. The biometric components that have been shown to contribute to this refractive error include shallower anterior chambers, increased lens power, and highly curved corneas. The present results are consistent with previously published data of ACD, LT, and AL measurements in premature infants with and without ROP. Choi et al[46] studied ocular growth from 6 months to 6 years of 125 eyes of premature infants, with ROP in 83.2% of them. They found the total AL, ACD, and LT to be 22.56, 3.15, and 3.91 mm, respectively, at the age of 6 years. Severity of ROP disease and ablative treatment was statistically significant. Chen et al[50] reported the optical component status of children aged 7 to 9 years born prematurely; 44% of them had ROP. They concluded that the presence of ROP itself, especially if advanced and requires treatment, may be associated with significantly shorter ACD, thicker lens, and higher myopia. Our results suggest that the alterations we found in anterior segment growth are not related to IVB injections but rather to prematurity and disease process.

As for the ERG results, normal electrical responses of the retina at 24 months were found in 4 eyes treated for high-risk prethreshold and threshold disease. These findings imply the absence of retinal toxicity of IVB. Fulton et al[51] demonstrated only minimal dysfunction of the cones in children with previous mild and untreated ROP and somewhat greater dysfunction in those who had more severe ROP that required treatment. Cones are less vulnerable than rods to ROP, suggesting better resistance and earlier maturation that protects against changes in retinal oxygenation. We hypothesize that the narrow time window of the disease and the prompt regression of NV after IVB with almost complete vascularization of the retina later account for the normal ERGs and good visual outcome.

The reduced and flat response in the other four eyes is probably related to their advanced disease, complicated with retinal detachment, before treatment with IVB or surgery.[52] The abnormal ERGs may account for their poor visual outcomes.

Preterm infants especially with comorbidities are more exposed to varying degrees of long-term neurodevelopment and growth impairment in early childhood.[53] The information we obtained through the Denver Developmental Screening Test II shows that IVB therapy had no apparent effect on neurodevelopment at the age of 5. Twelve patients achieved satisfactory results in the different developmental skills. Moreover, all patients except one showed normal growth compared with the anthropometric scales matched for age, sex, and ethnicity through the years. The only patient found with combined neurodevelopment and growth delay was a critically ill premature infant with pulmonary dysplasia and intraventricular hemorrhage Grade III, resulting in neurologic deficits later on in life. Published data support the association of growth parameters (especially weight) with neurodevelopment in preterm infants.[54]

In light of the BEAT-ROP study and the prevalent use of IVB in ROP, the present study provides important information regarding the long-term safety of bevacizumab in the neonate. Our series has obvious limitations as the small number of patients and the lack of a control group. Yet, it is the first one to address the potential effect of intravitreal antiangiogenic therapy on ocular growth and systemic development. Five years of follow-up in this small series suggest that IVB for ROP results in apparently preserved ocular function and systemic development.

In conclusion, the promising results found in this study further support the use of IVB in ROP. However, there is not enough evidence to ascertain without doubt that intravitreal antiangiogenic therapy is devoid of systemic complications. Further large, prospective, controlled, randomized trials are needed to establish its long-term safety and efficacy.

Key words: antiangiogenic, bevacizumab, anti–vascular endothelial growth factor (VEGF), retinopathy of prematurity (ROP).

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