A lower dose of intravitreal bevacizumab effectively treats retinopathy of prematurity

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PURPOSE To determine whether a low dose (0.25 mg/0.01 mL) of intravitreal bevacizumab is effective in the treatment of type 1 retinopathy of prematurity (ROP).

METHODS This prospective, noncomparative, interventional case series included all consecutive infants who received 0.25 mg/0.01 mL of intravitreal bevacizumab for type 1 ROP. Infants were followed for ROP persistence/recurrence until 90 weeks' postmenstrual age.

RESULTS A total of 49 eyes of 25 infants (24 bilateral and 1 unilateral) underwent intravitreal injection of a reduced dose (0.25 mg/0.01 mL) of intravitreal bevacizumab. ROP regressed in all eyes. Follow-up continued until 90 weeks' postmenstrual age and showed no recurrences of plus disease or neovascularization.

CONCLUSIONS All eyes treated with 0.25mg/0.01ml intravitreal bevacizumab showed complete regression, with no recurrence of plus disease or neovascularization. No safety issues were attributable to bevacizumab during the study period. (J AAPOS 2016;20:490-492)

The pathophysiology of ROP is incomplete peripheral retinal vascularization, leading to peripheral mesenchymal shunt formation, retinal neovascularization, and retinal detachment in advanced cases.[1,2] Vascular endothelial growth factor (VEGF) is increased in the vitreous of infants with ROP, and anti-VEGF therapy is a newly emerging therapy.[3-5] Several studies have reported successful use of intravitreal bevacizumab in the treatment of ROP.[1,6-8] However, bevacizumab can escape the eye and circulate systemically, reducing the serum level of VEGF in treated infants.[9] The systemic half-life of the drug in adults after an intravitreal injection of 1.25 mg/0.05 mL of bevacizumab is about 3 weeks[10]; the half-life of bevacizumab after an intravitreal injection in premature infants can even last for about 8 weeks in infants with ROP.[10,11] It has been shown that normal concentrations of VEGF are necessary for the development of the kidney,[12] lung,[13] and brain.[14] Accordingly, it is important to use the lowest possible effective dosage of intravitreal bevacizumab. Studies published to date have used a dose of 0.625 mg/0.025 mL to treat ROP.[1,6] The purpose of the present study was to assess whether type 1 ROP will regress with a smaller bevacizumab dose of 0.25 mg/0.01 mL.

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Subjects and Methods

Preterm infants with a gestational age of <32 weeks or birth weight of <2000 g were examined at 4 weeks' chronological age or 31 weeks' postmenstrual age (whichever was later) by indirect ophthalmoscopy at the Farabi Eye Hospital, Tehran, Iran, between September 2014 and January 2015. The Farabi Eye Hospital Ethics Committee approved this study, and informed consent was obtained from parents, who were apprised that intravitreal bevacizumab injection is an off-label therapy for ROP and its long-term systemic adverse effects are not known. Also, we stressed that a smaller-than-usual dosage of bevacizumab would be used.

The study included preterm infants with type 1 ROP, defined according to ET-ROP guidelines[15]: zone 1, any stage, with plus disease; zone 1, stage 3, without plus disease; or zone 2, stage 2 or 3, with plus disease. Infants with any eye disease other than ROP, such as glaucoma and congenital cataract, and infants with a history of prior treatment for ROP were excluded.

All infants were treated with intravitreal injection of 0.25 mg/0.01 mL of bevacizumab. All injections were performed in the operating room under topical anesthesia (tetracaine 0.5%). After inserting the eye speculum, the fornices were soaked with betadine 5% solution, and the eye was fixed by a cotton applicator. Injections were performed using a 29-gauge needle in the inferotemporal or superotemporal quadrants 1.5–2 mm from the limbus. In bilateral cases, both eyes were injected on the same day. Infants received sulfacetamide 10% eyedrops every 6 hours for 3 days after the injection.

Infants were reexamined at day 1 after treatment. The next follow-up visits were weekly for 4 weeks, biweekly for the next 8 weeks, and then monthly until 90 weeks' postmenstrual age. RetCam photos were taken before treatment, 1 week after treatment, and at 90 weeks' postmenstrual age.

The primary outcome was the rate of treatment failure, which was defined as ROP persistence or recurrence. Persistence of ROP was defined as the absence of regression of neovascularization and plus disease 1 week after treatment.

Table 1. Patient demographics

Patient	Birth weight, g	Sex	PMA, weeks	Treatment age, weeks	ROP stage and zone
1	980	F	28	35	Zone II/stage 3 (both eyes)
2	1450	M	30	38	Zone II/stage 3 (both eyes)
3	950	M	27	35	Zone I/stage 2 (both eyes)
4	950	M	29	34	Zone I/stage 3 (both eyes)
5	830	F	29	40	Zone II/stage 3 (both eyes)
6	1220	M	29	34	Zone II/stage 3 (both eyes)
7	870	M	25	34	Zone I/stage 3 (both eyes)
8	1850	M	30	37	Zone II/stage 3 (left eye only)
9	1300	F	28	35	Zone II/stage 2 (both eyes)
10	1200	M	28	35	Zone I/stage 3 (both eyes)
11	1375	M	30	39	Zone II/stage 3 (both eyes)
12	680	M	27	37	Zone II/stage 2 (both eyes)
13	1400	M	30	34	Zone II/stage 2 (both eyes)
14	850	F	30	34	Zone II/stage 3 (both eyes)
15	900	F	27	36	Zone II/stage 3 (both eyes)
16	850	M	30	35	Zone II/stage 3 (both eyes)
17	920	M	28	39	Zone II/stage 3 (both eyes)
18	1300	M	30	37	Zone II/stage 2 (both eyes)
19	950	F	26	39	Zone I/stage 2 (both eyes)
20	950	F	28	35	Zone II/stage 2 (both eyes)
21	975	F	26	37	Zone II/stage 3 (both eyes)
22	980	F	26	39	Zone I/stage 3 (both eyes)
23	1055	F	28	37	Zone II/stage 2 (both eyes)
24	1100	F	30	34	Zone I/stage 3 (both eyes)
25	1250	F	32	37	Zone II/stage 3 (both eyes)

PMA, postmenstrual age.

Recurrence of ROP was defined as new extraretinal fibrovascular proliferation with the arrest of the anterior progression of the retinal vasculature during the follow-up period.

Results

A total of 49 eyes of 25 consecutive infants (24 bilateral and 1 unilateral) with type 1 ROP were included. Median birth weight was 980 g (range, 680–1850 g). Median gestational age was 28 weeks (range, 25-32 weeks). The median postmenstrual age at the time of treatment was 36 weeks (range, 34-40 weeks). Table 1 provides demographic data of the enrolled infants.

Vascular/avascular borders were in zone 1 in 12 eyes (24.5%) and in zone 2 in 37 eyes (75.5%). In all eyes, plus disease had regressed at 1 week's follow-up. Extraretinal neovascularization regressed in about 2-3 weeks. There were no treatment failures during the follow-up period.

At 90 weeks' postmenstrual age, 19 eyes (38%) had a small avascular area in zone 3. The retina was fully vascularized in the remaining eyes.

No ocular or systemic complications or side effects were observed during the follow-up period.

Discussion

After intravitreal injection, bevacizumab enters the systemic circulation, lowering the serum level of VEGF.[9] Serum bevacizumab levels 8 weeks after an intravitreal injection could still prevent VEGF from acting in preterm infants at a stage when VEGF is needed for the development of kidneys, lungs, brain, and other organs.[11-14]

Median plasma concentrations of VEGF in premature babies have been reported to vary widely,[16] although no significant difference was noted between infants with and without ROP at 32 weeks' and at 36 weeks' postmenstrual age. As a result of lower body weight, lower vitreous volume, incomplete retinal blood barrier formation, and incomplete renal development, bevacizumab may lead to substantial VEGF suppression in premature infants compared to adults.[16]

Systemic levels of bevacizumab correlate directly with the dose of intravitreal bevacizumab. Sato and colleauges[9] analyzed the serum level of bevacizumab and VEGF after an intravitreal injection of 0.25 and 0.5 mg of bevacizumab in 11 infants with ROP. The authors concluded that there was a significant negative correlation between the serum concentration of bevacizumab and VEGF.

Because of the possible systemic effects of VEGF suppression in infants, we tested lower-than-usual doses of intravitreal bevacizumab in the treatment of ROP. In our series of 49 eyes with type 1 ROP treated with 0.25 mg/0.01 mL of intravitreal bevacizumab, there was regression of plus disease/extraretinal neovascularization in all eyes during the first weeks after treatment and no recurrence of ROP in any eyes by 90 weeks' gestation.

Harder and colleauges[7] reported regression of ROP in all 57 eyes of 29 patients treated with an intravitreal injection of 0.375 mg/0.03 cc of bevacizumab; only 1 infant with a severely unstable general condition required a second injection. Kuniyoshi and colleauges[17] treated 8 eyes of 4 infants with ROP with 0.25 mg of intravitreal bevacizumab. At follow-up, patients with zone 2 disease did not need any further intervention, but 2 eyes with zone 1 disease needed reinjection and surgery. The authors concluded that intravitreal bevacizumab (0.25 mg per eye) was a good

treatment modality in zone 2 disease. In our study 12 eyes of 49 eyes were in zone 1, but none required a second injection.

In our study 19 eyes (38%) at 90 weeks' postmenstrual age had small avascular area in zone 3. The clinical importance of this long-lasting peripheral retinal avascularity after intravitreal anti-VEGF injection is unknown, and infants treated with intravitreal bevacizumab should be followed until the retina becomes fully vascularized (sometimes up to 2 years). Decreasing the dosage of bevacizumab theoretically may lower the chance of such an avascular area occurring.

It has been hypothesized that high myopia after laser therapy is the result of the maldevelopment of the anterior segment due to laser destructive effects.[15,18,19] Myopia is also common after intravitreal injection of anti-VEGFs in infants with ROP. There is higher refractive error after bevacizumab in comparison to ranibizumab, with longer half-life and longer suppression of VEGF.[20] Similarly, lowering the dose of intravitreal bevacizumab theoretically may reduce the myopic shift commonly seen in infants treated for ROP.

This case series is limited by the small sample size, lack of controls, lack of cohorts receiving other doses of bevacizumab, and uncertainty as to whether some infants might have been selected out for laser treatment; nevertheless, it supports the effectiveness of a lower dose of intravitreal bevacizumab for ROP in some infants.

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