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Original Article

Intravitreal bevacizumab monotherapy for retinopathy of prematurity

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Abstract ***Background***: The aim of this study was to evaluate the treatment outcomes of intravitreal bevacizumab (IVB) injections, used as a monotherapy in type 1 retinopathy of prematurity (ROP).

Methods: A retrospective chart review was performed for 17 type 1 ROP patients (34 eyes), who had IVB injection between July 2011 and June 2012. Birthweight, gestational age at birth, stage and location of ROP, IVB injection time, time of complete retinal vascularization, and additional treatments if needed, were noted. A total of 0.625 mg (0.025 mL) bevacizumab was injected intravitreally.

Results: Thirty eyes of 17 patients with type 1 ROP enrolled in the study were treated with IVB injection. Of them seven had aggressive posterior-ROP, six had stage 2 ROP, and four had stage 3 ROP. The mean gestational age was 28.44 weeks (range, 26–31 weeks); and the mean birthweight was 1151.88 g (range, 600–1600 g). The mean age for IVB injection was 35.47 weeks. The mean full retinal vascularization time was 136.6 ± 26.6 days. The mean follow-up time was 285.3 ± 70 days. ROP was regressed and retinal vascularization was completed in all cases except one eye, which had threshold disease.

Conclusion: IVB injection, used as a monotherapy, is an effective treatment approach in patients with type 1 ROP. Timely treatment of stage 2 and early stage 3 ROP in which disease progression was observed, prevents vitreoretinal membrane formation in posterior disease. Further studies need to be performed to determine the safety of IVB injection.

Key words bevacizumab, monotherapy, retinopathy of prematurity.

Retinopathy of prematurity (ROP) is a retinal vascular disease that occurs in premature infants with gestational age <32 weeks and birthweight <1250 g. ROP is the leading cause of childhood blindness in developing countries.[1] The worldwide prevalence of blindness due to ROP is approximately 50 000 per year.[1]

In current practice, laser photocoagulation of the avascular retina is the accepted treatment modality. This treatment destroys the avascular retinal cells that express exceedingly large quantities of vascular endothelial growth factor (VEGF) in the retina.

In contrast, especially in posterior disease, laser photocoagulation may cause permanent loss of the peripheral visual field and may induce high myopia. In spite of laser photocoagulation treatment, the disease can progress and may lead to tractional retinal detachment.

Optimal treatment for ROP should allow for the retinal vasculature to reach the edge of the ora serrata. Recently, bevacizumab, an anti-VEGF, has been used in an off-label manner to treat a variety of ocular vascular diseases. As in the other retinal vasculopathies, such as diabetic macular edema, age-related macular degeneration or macular edema due to retinal vein occlusions, anti-VEGFs also have a therapeutic effect on ROP.[2]

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Although it is an off-label agent, bevacizumab is known to be used as an adjuvant therapy or as monotherapy in the treatment of ROP.[3,4] Because adjuvant treatment prevents progression of the disease, it cannot save the peripheral visual field. Thus new treatment approaches are needed to rescue the entire retina, and to let vascularization be completed. In the current practice anti-VEGFs are the candidates for this approach. Intravitreal bevacizumab (IVB) monotherapy has been shown to be beneficial for the treatment of ROP, especially in zone 1 stage 3 disease.[4]

The Early Treatment for Retinopathy of Prematurity (ETROP) study group emphasized the treatment of pre-threshold ROP in 2003.[5] Even though they recommend ablative laser photocoagulation in the treatment of pre-threshold ROP we have preferred IVB monotherapy since 2011. The aim of the present study was to report the treatment outcomes of IVB monotherapy in patients with type 1 ROP.

Methods

Institutional review board approval was obtained through the University of Dicle, and the study was conducted in compliance with the Declaration of Helsinki. The medical records of patients with type 1 ROP who received IVB monotherapy were reviewed in the current study. Patients received other treatments before IVB injection were excluded.

Birthweight, gestational age at birth, stage and location of ROP, IVB injection time, time of complete retinal

vascularization, additional treatments if needed, and any adverse local or systemic side-effects of the procedure were noted.

There is no defined treatment protocol for IVB in ROP. The ETROP study results recommended treating type 1 ROP with laser photocoagulation. They defined type 1 ROP as follows: zone 1 ROP with plus disease; zone 1, stage 3 ROP without plus disease; or zone 2, stage 2 or 3 ROP with plus disease.[5,6] We used these ETROP criteria for the treatment of type 1 ROP with IVB rather than laser photocoagulation.

Before IVB injection, the parents or legal guardian of the babies were informed about the procedure. After informed consent was obtained for IVB injection, the injections were performed in the operating theater. The pupil was dilated with 2.5% phenylephrine (Mydfrin; Alcon, Fort Worth, TX, USA) and 0.5% tropicamide (Tropamide; Bilim Ilac, Istanbul, Turkey) before intravitreal injection. Vital signs were carefully monitored throughout the entire procedure. Following sedation with sevoflurane via mask, povidone-iodine 10% swab was applied on the eyelids, and eyelashes. After that the patient was completely draped. A sterile eyelid speculum (Katena, Denville, NJ, USA) was inserted. Each eye was meticulously bathed with 5% povidone-iodine solution for 3 min before intravitreal injection. A total of 0.625 mg (0.025 mL) bevacizumab (Altuzan; Roche, Istanbul, Turkey) was injected intravitreally 1 mm posterior to the superior temporal limbus via 30 G injector. All injections were performed by a single surgeon (AŞ). The fellow eyes of the patients were treated 5–7 days after IVB injection of the primary eyes to avoid any ocular complications such as endophthalmitis and intraocular inflammation.

After the intravitreal injection, retinal artery perfusion was checked, and patients received topical lomefloxacin (Okacin; Novartis, Ophthalmics, Hettlingen, Switzerland) for 7 days. All patients were reexamined daily for sign of infection for 3 days after injection. Subsequent examinations were performed weekly until full retinal vascularization was observed. Good response to the IVB injection was defined as follows: disappearance of the tunica vasculosa lentis, recovery of the plus disease, and regression of any stage of ROP.

Results

The background and clinical data, treatment indications, and anatomical results are listed in Table 1. IVB injection led to regression of the active neovascularization in all cases except one eye of patient 1. None of the eyes received multiple injections. No patients had both eyes treated in the same session.

A total of 30 eyes of 17 infants with type 1 ROP were treated with IVB between July 2011 and June 2012. Of them, seven had aggressive posterior ROP, six had stage 2 ROP, and four had stage 3 ROP. The mean gestational age was 28.44 weeks (range, 26–31 weeks), and the mean birthweight was 1151.88 g (range, 600–1600 g). The mean age for IVB injection was 35.47 weeks (range, 32.71–38.14 weeks). The plus sign disappeared 1–3 days after injection. The mean retinal vascularization time was a 136.6 ± 26.6 days (range, 95–210 days) following the injection. The mean follow-up time was 285.3 ± 70 days (range, 210–440 days). Following complete retinal vascularization, neither recurrence of the disease nor vascular abnormality was observed.

In four eyes of two patients with stage 3 ROP, vitreoretinal band formation was observed. One of these eyes progressed to retinal detachment.

In one eye of an infant who had advanced stage 3 ROP, disease reactivation occurred 20 days after the injection. This eye had threshold ROP before IVB injection.

In another patient who received IVB in her right eye, we observed regression of ROP also in the fellow eye also and we did not perform IVB to the left eye. Given that the parents of three infants gave informed consent for IVB injection only for one eye, we treated the fellow eyes of these three infants with laser photocoagulation.

The fundus photographs of a case of aggressive posterior ROP before and after injection are given in Figure 1. The plus sign disappeared 2 days after injection.

We observed retinal hemorrhage in five eyes that spontaneously regressed. There were no other ocular complications such as endophthalmitis, cataract, or ocular inflammation. None of the infants died, and no systemic (neurologic, cardiovascular, respiratory or gastrointestinal disorders) or local adverse effects were observed to the end of the follow-up period.

Discussion

In the current study IVB injection monotherapy effectively reduced neovascularization and resulted in full retinal vascularization in the majority of patients with type 1 ROP. Only in one eye of one patient with advanced stage 3 ROP, did the disease reactivate 20 days after injection.

Retinopathy of prematurity is an important cause of ocular morbidity and blindness in preterm infants. Timely treatment of ROP is very important to prevent progression and complications.[5] The survival rate of extremely premature infants has been increased with improvement in neonatal intensive care technology and increased availability of health-care services in recent years.[1] As a consequence, the incidence of ROP is increasing with time due to the extremely low-birthweight and birth age of these infants.

Retinopathy of prematurity is biphasic in development: in phase 1 (22–30 weeks of postmenstrual age), there is relative retinal hyperoxia and decreased VEGF, and in phase 2 (31–44 weeks), there is relative retinal hypoxia and increased VEGF.[7] Retinal hypoxia is a driving force for ROP in phase 2.

Anti-VEGF agents could be given via intravitreal injection. The timing of anti-VEGF treatment is very important. In phase 1, blockage of VEGF may be too early and therefore ineffective, whereas delayed injections may cause contraction of vitreoretinal membranes, resulting in retinal detachment.[8] Because VEGF expression is very high in phase 2 (which starts at approx. 32–34 weeks), optimal treatment should be performed within this stage. In the literature, treatment times vary between 32 and 36 weeks.[4,9]

Currently peripheral laser retinal ablation is the standard of care for advanced ROP. Laser photocoagulation is generally successful but it destroys avascular retina that expresses a high amount of VEGF.[4] It cannot, however, prevent the devastating

Table 1 Patient data and bevacizumab injection results

Patient no.	Sex	Gestational age (weeks)	Birthweight (g)	Laterality	Stage of ROP	Location of ROP	Age at treatment (days)	Systemic disease	Vascularization time (days)	Follow-up time (days)
1	F	27	870	OD	3	2-P	59		Recurrence at 20th day	220
				OS	3	2-P	63		100	
2	M	27	1040	OD	AP	1	52		135	255
				OS	AP	1	59		128	
3	F	28	1160	OD	2	2-P	55		120	210
				OS	2	2-P	48		120	
4	M	31	1400	OD	2	2-P	28		155	320
				OS	2	2-P	32		150	
5	M	28	1400	OD	3	2-P	54		150	270
				OS	3	2-P	LPC only		Stage 5	
6	M	30	1600	OD	2	2-P	31	RDS	165	285
				OS	2	2-P	45		135	
7	F	26	880	OD	2	2-P	64		130	240
				OS	2	2-P	68		130	
8	M	30	1150	OD	AP	2-P	46	VPS	115	235
				OS	AP	2-P	67		95	
9	M	30	1350	OD	AP	2-P	42	0	100	235
				OS	AP	2-P	67		95	
10	M	31	990	OD	AP	1	31	0	210	420
				OS	AP	1	LPC only			
11	M	29	1190	OD	AP	2-P	46	RDS	120	300
				OS	AP	2-P	52		115	
12	M	28	1400	OD	AP	2-P	62		150	390
				OS	AP	2-P	70		140	
13	F	26	820	OD	3	2-P	76		160	300
				OS	3	2-P	80		155	
14	M	26	600	OD	2	2-P	LPC only	RDS		440
				OS	2	2-P	85		200	
15	F	28	1000	OD	3	2-P	52	HIE	150	260
				OS	3	2-P	No treatment		150	
16	M	28	1400	OD	AP	2-P	33	0	125	240
				OS	AP	2-P	41		130	
17	M	28	1000	OD	2	2-P	48		140	230
				OS	2	2-P	41		130	

2-P, zone 2 posterior; AP, aggressive posterior; HIE, hypoxic–ischemic encephalopathy; IVB, intravitreal bevacizumab; LPC, laser photocoagulation; OD, right; OS, left; RDS, respiratory distress syndrome; VPS, ventriculo-peritoneal shunt.

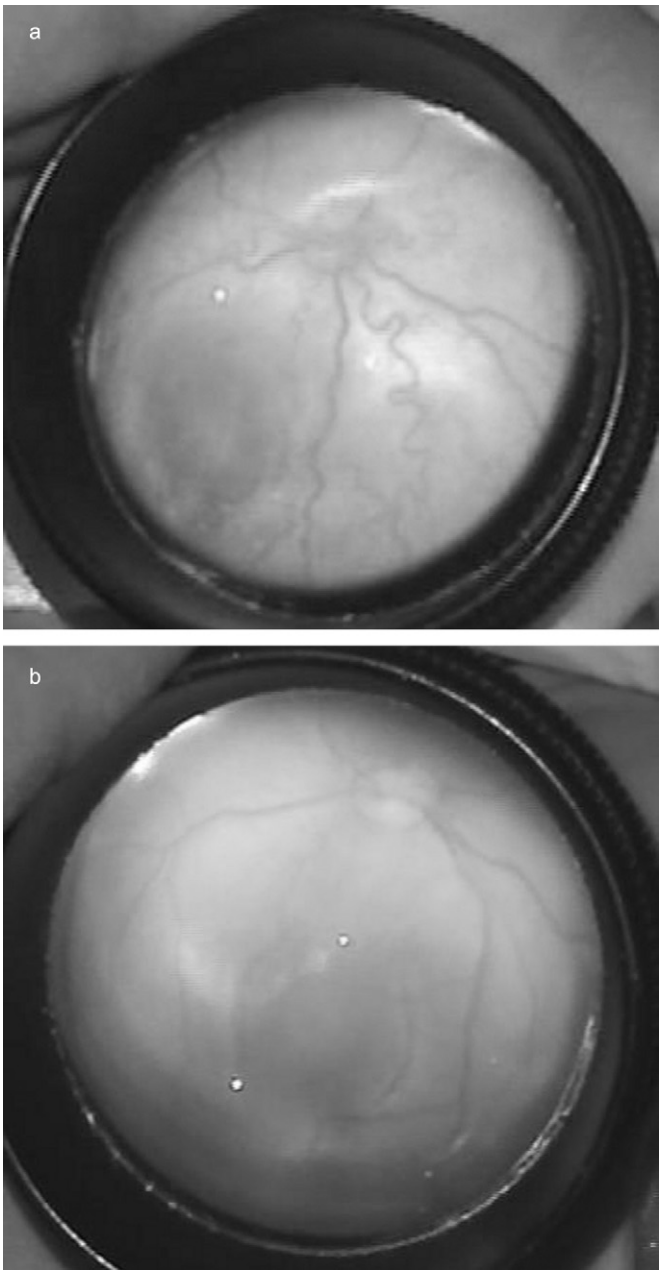

Fig. 1 Posterior segment photographs showing (a) plus disease that (b) disappeared 2 days after injection of bevacizumab.

effects of previously expressed VEGF in the vitreous cavity. In clinical practice plus disease disappearance takes approximately 10–14 days following laser treatment. In this period, VEGF in the vitreous cavity may cause progression of the disease.

Anti-VEGF agents have been widely used in the treatment of several vascular diseases of the retina during the last decade. There is excess VEGF expression in the avascular retina in patients with ROP.[10] IVB injection blocks all isoforms of VEGF located in the retina and also in the vitreous. Physiological change due to laser photocoagulation, however, is unclear. Plus disease, a clinical sign of the severity of ROP, usually disappears 1–3 days after IVB injection.

Laser photocoagulation treatment prevents only the progression of ROP, but causes destruction of the peripheral retina. IVB injection, however, both prevents progression of the disease and supports normal retinal vascularization. In this way, it prevents the loss of peripheral vision, especially in patients with posterior ROP. Its application takes a short time compared to laser photocoagulation.

Although IVB injection adjuvant to laser photocoagulation has previously been found to be an effective treatment for ROP, the side-effects related to retinal photocoagulation remain as a significant problem of the treatment.[3,11]

The results of the BEAT-ROP Cooperative Group study demonstrated that IVB monotherapy, as compared with conventional laser therapy, in infants with stage 3+ ROP, showed a significant benefit for zone 1.[4] In contrast, the rate of recurrence in zone 2 posterior disease alone did not differ significantly between the laser therapy group and the bevacizumab group. Distinctively, the development of peripheral retinal vessels proceeds following treatment with IVB monotherapy. In contrast to the BEAT-ROP study we also performed IVB injection in stage 2 ROP in which disease progression was observed. We propose that the timely treatment of stage 2 and early stage 3 ROP prevents vitreoretinal membrane formation in posterior disease.

The ETROP study recommended that premature infants with type 1 ROP should be treated promptly with the use of peripheral retinal ablation.[5] In the treatment of patients with type 1 ROP we used the ETROP classification. But IVB injection is our preference because it allows for the vascularization of the retina. Nevertheless we gave the parents of the patients a choice of treatment modality (IVB or laser photocoagulation). All of the parents accepted IVB injection. Only three of the parents chose to have one eye treated with IVB and the fellow eye with laser photocoagulation.

In advanced stage 3 ROP, tractional retinal detachment can occur following IVB injection because of preformed fibrous vitreoretinal membrane.[9] In the current study vitreoretinal membrane formation occurred in four eyes of two stage 3 patients after IVB injection, and only one eye progressed to stage 4 ROP despite IVB injection, in which 5 clock hours of stage 3 ROP was noted. In this case the eye initially responded well to the IVB injection, whereas 20 days after injection the disease reactivated. Laser photocoagulation and pars plana vitrectomy were needed for this infant.

Patients treated with IVB should undergo regular examination until full retinal vascularization is observed. According to the BEAT-ROP study, the mean recurrence time for IVB injection versus laser photocoagulation is 19.2 $\pm$ 8.0 weeks and 6.4 $\pm$ 6.7 weeks, respectively.[4] In the present study the mean time of complete retinal vascularization was 19.5 weeks. Therefore, ROP patients who received IVB injection should be closely followed for more than 5 months after treatment, even if the disease seems to have regressed.

Bevacizumab given to extremely premature infants by intravitreal injection as a single, low dose has not shown systemic or local toxicity.[4] Experimental studies indicated that IVB injection is not toxic to the retinal cells, even after repeated injections.[12,13]

Although bevacizumab is not toxic to the retina, there is some speculation about possible systemic side-effects. Sato *et al*. reported that bevacizumab can escape from the eye into the systemic circulation and reduce the serum level of VEGF in infants.[14] In the present series, one infant who had received IVB in her left eye, had regression also in the fellow eye without treatment. This may support the possibility of escape of bevacizumab from the eye into the systemic circulation. The VEGF levels in the eyes of that patient would be lower because of the response to the possibly low systemic concentration of bevacizumab.

Vascular endothelial growth factor is critical to the development of brain,[15] lungs,[16] and kidneys.[17] Bevacizumab blocks all isoforms of VEGF. Because bevacizumab can escape from the eye into the systemic circulation and reduce the serum level of VEGF in infants, it may cause functional and structural changes in these organs. In adults treated with IVB there is an increased risk of hemorrhagic stroke.[18,19] Although there is no report on any systemic complications in premature infants treated with IVB, clinicians should be aware of potential harmful effects of bevacizumab.

The limitations of the present study were the retrospective nature of the study, lack of control group treated with laser photocoagulation, and the low number of patients enrolled in the study. Nevertheless we successfully treated 11 eyes of six patients with stage 2 disease with IVB injection without any ocular or systemic side-effects. We used ETROP criteria in the treatment decision-making. In contrast with ETROP study recommendations, we performed IVB monotherapy instead of laser photocoagulation.

In the current approach, treatment options targeting complete retinal vascularization seem to be more physiologic and may prevent ocular complications. According to the present results, IVB injection is very effective in treatment of type 1 ROP, including stage 2 disease. We suggest that patients should be treated before disease severity reaches the stage 3, in case of progression. In stage 3, IVB injection may lead to such consequences as vitreoretinal membrane formation, resulting in retinal detachment because of preformed fibrovascular tissue.

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