Efficacy of Intravitreal Bevacizumab Monotherapy in the Treatment of Retinopathy of Prematurity

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ABSTRACT

Purpose: To evaluate the results of intravitreal bevacizumab (IVB) monotherapy applied for retinopathy of prematurity (ROP) during a 6 year period in a tertiary referral for ROP.

Materials and Methods: The files of patients treated with IVB for ROP between January 2012 and October 2018 were evaluated retrospectively. Gestational age, birth weight, indications and results of IVB monotherapy and complications were recorded.

Results: One hundred twenty three eyes of 69 patients were included in the study. Seventy-six eyes (58.5%) of 40 patients had aggressive posterior retinopathy of prematurity (AP-ROP) and 47 eyes (41.3%) of 29 patients had classic Type 1 ROP. One hundred nine eyes (88.7%) of 62 patients were responsive to initial IVB injection but 14 eyes (11.3) of seven patients were non-responsive. Complete resolution was detected in 76 eyes (69.7%) of 44 patients responsive to initial IVB treatment, whereas in 29 eyes (26.6%) of 16 patients, ROP recurred within a mean period of 8.0 ± 3.0 weeks. In four eyes (3.6%) of two patients, peripheral vascularization was not completed.

Conclusion: Although a significant number of patients were responsive to IVB injection, recurrence was an important disadvantage. Thus, long term and close follow up examinations are crucial after IVB injection.

Key words: Bevacizumab, retinopathy of prematurity, recurrence, laser coagulation, VEGF.

INTRODUCTION

Retinopathy of Prematurity (ROP) is one of the leading causes of childhood blindness worldwide.[1] ROP is a proliferative disorder of the newly developing retinal blood vessels in preterm infants who were born with incomplete retinal vasculature.[2] In 2003, the Early Treatment for Retinopathy of Prematurity (ETROP) Cooperative Group proposed that type 1 prethresold and threshold ROP should be treated.[3] After the cryo era, laser ablation of the peripheral avascular retina has been successfully used in the past few decades.[4,5] The application of laser photocoagulation in Zone I and posterior Zone II ROP and Aggressive Posterior Retinopathy of Prematurity (APROP) remains controversial because of the poor anatomical and functional outcomes.[4,6]

Studies on ROP have shown that Vascular Endothelial Growth Factor (VEGF) has key role in the process of angiogenesis.[7,8] The objective of intravitreal anti-VEGF therapy is to cease VEGF induced pathologic neovascularization, preserve avascular peripheral retina and allow physiologic vascularization thereafter. Anti-VEGF therapy was first started to be used for ROP treatment in 2007.[9] Since then, intravitreal VEGF inhibitors have been used as a first line therapy, a combined therapy with laser or a salvage therapy in Type 1 ROP and AP-ROP.[10-14] The first randomized controlled study on anti-VEGF therapy of ROP, Bevacizumab Eliminates Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP), proposed that VEGF inhibitors had better outcomes than laser photocoagulation in Zone I ROP and similar outcomes in Zone II ROP; although the number of cases in the study was not sufficient to evaluate the treatment reliability.[15]

Bevacizumab (Avastin; Genetech Inc., South San Francisco, California, USA) is a recombinant monoclonal antibody hat binds and inhibits all isoforms of VEGF-A.[16]

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Bevacizumab is effective in the treatment of retinal neovascular diseases like neovascular age related macular degeneration, proliferative diabetic retinopathy, retinal vascular occlusion and ROP.[16-18] There is no consensus on intravitreal bevacizumab (IVB) therapy in the treatment of ROP hence, there are small case series and a few case reports.[10-15,19-21] Knowledge on the long-term ocular and systemic side effects of IVB therapy is inadequate. Thus, there are concerns regarding dosage, timing, and efficacy, duration of follow-up and long-term visual results of the IVB therapy.

The objective of this study is to evaluate the efficacy of IVB monotherapy in the treatment of ROP retrospectively. We aimed to study the success and recurrence rates, rates of patients who require additional treatments and complications.

MATERIALS AND METHODS

This is a retrospective interventional study to evaluate the efficiency of IVB therapy. This study was approved by institutional review board. Medical records of prematurely born infants followed at a tertiary referral clinic specialized in ROP diagnosis and treatment and those referred from other centers were reviewed retrospectively. The study included premature infants born between January 2012 and October 2018, given IVB therapy as a first-line treatment and followed for at least 6 months.

All parents were informed about the possible complications of the injection procedure and systemic concerns of the drug in the future. Parents signed detailed informed consent according to the tenets of Declaration of Helsinki. Gestational age, birth weight, indication for treatment, postmenstrual age at the time of injection, follow up period, timing of reinjection or additional laser ablation if indicated, complications and anatomical results were recorded for each patient. Examinations were made by indirect ophthalmoscopy with scleral depression and documented by video indirect ophthalmoscopy (Omega 2C, Heine, Germany). ROP was categorized according to the revised International Classification of Retinopathy of Prematurity and the treatment protocol followed the guidelines laid out by the Early Treatment of ROP study.[3,22] Treatment was considered in case of the development of type 1 prethresold ROP and APROP. Type 1 ROP was defined as zone I, any stage ROP with plus disease, zone I, stage 3 ROP without plus disease and zone 2, stage 2 or 3 ROP with plus disease. APROP was defined as ROP with posterior location, four quadrant plus disease and ill-defined retinopathy, which may appear as only flat neovascularization at the junction between vascularized and non-vascularized retina

Preterm infants with Type 1 ROP located posterior Zone II and APROP were selected eligible for IVB treatment.

All injections were applied in the neonatal intensive care unit under topical anesthesia. Pupillary dilation was achieved by a drop of tropicamide 0.5% (Tropamid; Bilim, Istanbul, Turkey) followed by a drop of 2.5% phenylephrine (Mydfrin, Alcon Labs, Fort Worth, Texas, USA) five minutes apart. Following cleaning of the conjunctival sac with 5% povidone-iodine, topical anesthetic (0.5% proparacaine hydrochloride: Alcaine; Alcon, Puurs, Belgium) were applied. Sterile lid speculum was inserted and 0.625mg/0.025ml bevacizumab (Altuzan, 100 mg/4 ml flacon, Roche, Mannheim, Germany) was injected 1-1.5mm away from the limbus from inferotemporal quadrant into the vitreous cavity avoiding the crystalline lens. Central retinal artery patency was checked immediately. Topical antibiotics were given for one week. Patients control examinations were made the day after the injection and followed weekly, every two weeks or monthly thereafter until vascularization of the peripheral retina was completed without any active sign of disease such as hemorrhages and fibrovascular tractional tissues.

Treatment efficacy was evaluated time dependently because of the retrospective nature of this study. Prominent decrease in retinal venous dilation, arterial engorgement and extraretinal fibrovascular proliferation and increase in clarity of the vitreous with disappearance of pupillary rigidity were considered as “responsive to IVB therapy”. Absence of any favorable improvement in vascular engorgement and extraretinal fibrovascular proliferation despite the injection were considered as “non-responsive” to IVB therapy. Recurrence was described as relapse of vascular engorgement and extraretinal fibrovascular proliferation together with discontinuance of peripheral vascularization with vascular anomalies like vascular tufts, circumferential shunts and collaterals at least one month after an initial positive response to the first treatment. Complete resolution of ROP was described as regression of vascular engorgement and extraretinal fibrovascular proliferation together with complete vascularization of the peripheral retina. Complete vascularization was described clinically as full retinal vascularization in close proximity to the ora serrata.[23] Incomplete retinal vascularization was described as avascular retina from the ora serrata was more than two disc diameters (DD) at 55 weeks PMA.[24]

Laser photocoagulation was considered as first retreatment option in patients with recurrence. However, in patients whose systemic condition was not eligible for laser photocoagulation, a second dose of IVB was administered. Peripheral laser photocoagulation was applied using an 810-nm diode laser (Iridex, Oculight SL, USA) to the

entire avascular zone under remifentanil sedoanalgesia in the Neonatal Intensive Care Unit.

Unfavorable structural outcome was defined as development of retinal detachment or a retinal fold affecting the macula.

Results

We evaluated 123 eyes of 69 infants of whom 36 (52.2%) were male and 33 (47.8%) were female. Forty-one patients (59.4%) were referred from other centers, whereas 28 patients (40.6%) were born in our hospital and followed in our ROP clinic.

The mean gestational age of patients was 26.4 ± 1.9 weeks (23-32 weeks) and the mean birth weight of patients was 923 ± 255 g (400-1720 g). APROP was the diagnosis in 76 eyes (61.8 %) of 40 patients (58%) and Type 1 ROP was the diagnosis in 47 eyes (38.2 %) of 29 patients (42%).

Sixty-two patients (88.9%) (109 of 123 eyes) were responsive, 7 patients (10.1%) (14 of 123 eyes) were non-responsive to initial IVB injection. Recurrence was observed in 29 eyes (26.6%) of 16 patients (25.8%) who were responsive to initial injection; the mean postmenstrual age for recurrence was 43.25 ± 3.80 weeks (40-54 weeks) and the mean time interval for recurrence after injection was 8.0 ± 3.0 weeks (4-15 weeks). Complete resolution was observed in 76 eyes (69.7%) of 44 patients (63.8%) who were responsive to initial injection. In four eyes of two patients, peripheral vascularization was not completed and laser photocoagulation was applied on avascular retina. Fundus photographs of one of the patients with peripheral avascularity after intravitreal IVB were given in Figure 1.

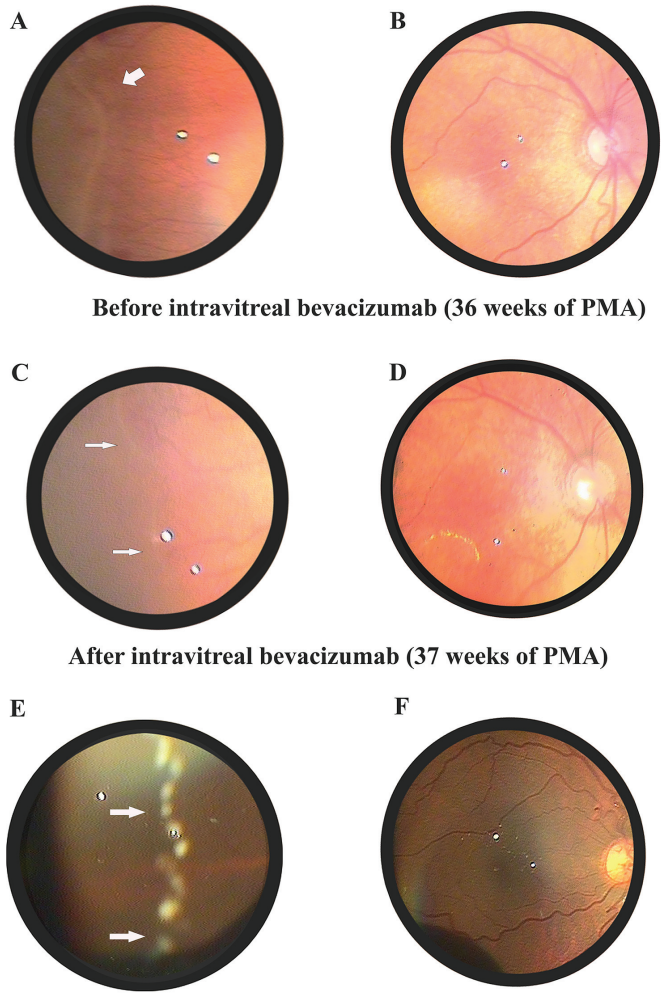

Figure 1. *Fundus images of a patient with peripheral avascularity after intravitreal bevacizumab (IVB) injection. Stage 2 ROP with popcorn lesions (white arrow) in Zone 2 and mild plus disease on posterior pole were shown on (A) and (B) before IVB injection at 36 weeks of postmenstrual age (PMA). Regression of ridge (white arrows) and plus disease one weeks after IVB treatment were shown on (C) and (D).Incomplete retinal vascularization at 67 weeks of postmenstrual age after IVB treatment was shown on (E) and (F). Border of vascular and avascular retina was marked with laser spots (white arrows) during laser photocoagulation.*

Forty-seven eyes (38.2%) of 25 patients (36.2%) were re-treated. Twenty-nine eyes of 16 patients had recurrence, 14 eyes of seven patients were non-responsive to initial IVB injection, and four eyes of two patients had peripheral avascularity.

Laser photocoagulation was applied to all nonresponsive eyes (14 eyes of 7 patients) and 4 eyes of 2 patients with incomplete retinal vascularization and 24 eyes of 13 patients with recurrence. Five eyes of 3 patients with recurrence were given second IVB injection and complete involution was observed in these eyes. In four eyes (3.6%) of two patients (2.8%), ROP progressed to Stage 4A despite IVB and laser treatment and vitreoretinal surgery was applied in another center. In 119 eyes (96.8%) of 67 patients (97.1%), anatomic success was achieved. Only in one eye cataract developed as a complication of injection and surgical intervention was applied in another center. Fundus photographs of one patient with recurrence and one patient to unresponsive to the initial treatment were given in Figure 2 and 3, respectively.

The mean PMA for IVB injection was 34.68 ± 2.34 weeks (31-40 weeks). The mean PMA for retreatment of nonresponsive patients was 36.00 ± 2.24 weeks (33-40 weeks) and the mean PMA for retreatment of patients with recurrence was 43.25 ± 3.80 weeks (40-54 weeks). Demographic and clinical characteristics of patients were summarized in Table 1.

Recurrence rate was statistically higher in APROP group compared to the Type 1 ROP patients ($p<0.01$) and all of

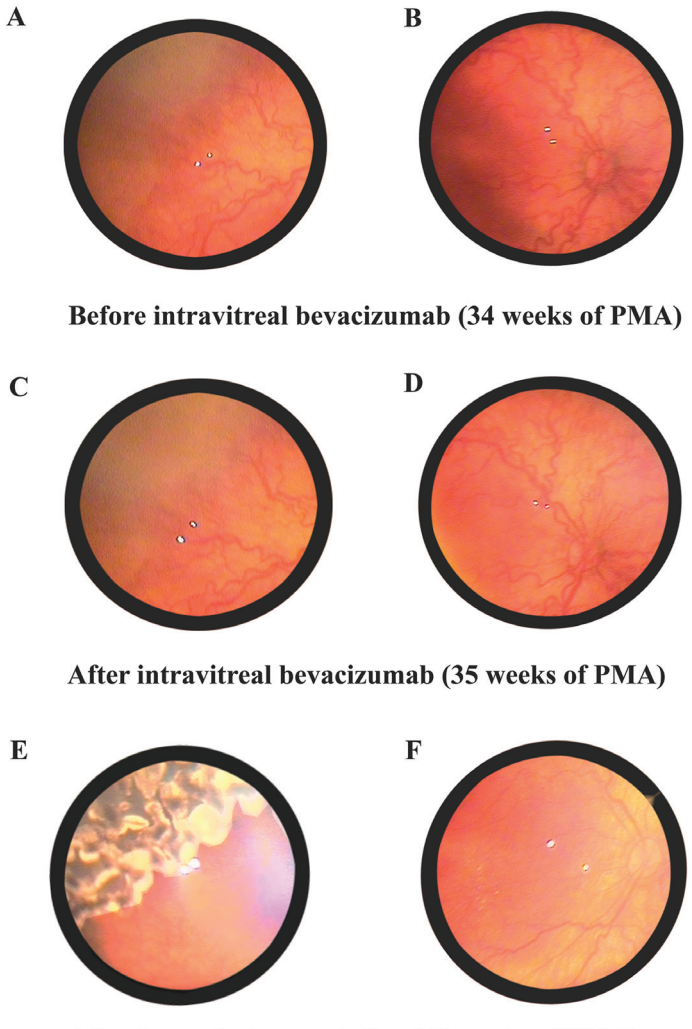

Figure 2. *Fundus images of a patient non-responsive to initial intravitreal bevacizumab injection (IVB). The patient was treated with intravitreal bevacizumab injection for aggressive posterior retinopathy of prematurity (APROP) at 34 weeks of postmenstrual age. Flat neovascularization located Zone 2 posterior and marked plus disease on posterior pole was shown on (A) and (B). Insufficient regression of plus disease and retinal neovascularization one weeks after treatment was shown on (C) and (D) Regression of the disease4 weeks after laser photocoagulation due to insufficient response were shown on (E) and (F).*

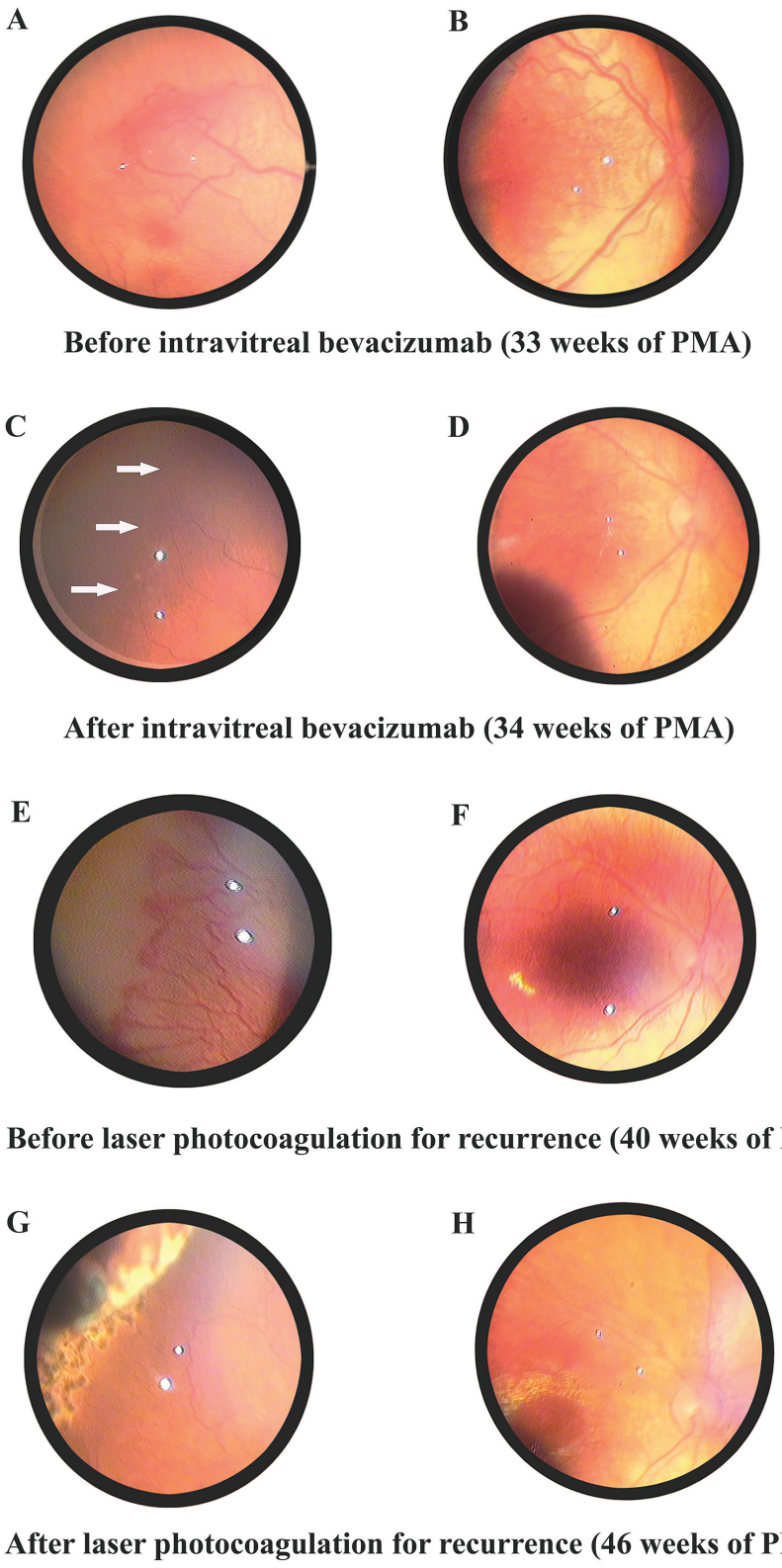

Figure 3. *Fundus images of a patient with recurrence after intravitreal bevacizumab injection (IVB) for aggressive posterior retinopathy of prematurity (APROP). Flat neovascularization located on Zone 2 posterior and plus disease at 33 weeks postmenstrual age were shown on (A) and (B), respectively. Regression of plus disease and neovascularization (white arrows) after IVB treatment at 34 weeks were shown on (C) and (D). At 40 weeks postmenstrual age,* ***disease recurred.*** *Return of vascular dilation and tortuosity with new peripheral neovascularization located on Zone 2 anterior was shown on (E) and (F). Regression of the disease 6 weeks after laser photocoagulation were shown on (E) and (F).*

Table 1. *Demographic and clinical features of all patients.*		
Gender (n, %)	Female (n, %)	33 (47.8%)
	Male (n, %)	36 (52.2%)
Gestational age at birth (weeks)	Mean ± SD	26.4 ± 1.9
	(Range)	(23-32)
Birth weight(gr)	Mean ± SD	923 ± 255
	(Range)	(400-1720.0)
Referral status (n, %)	In-patient	28 (40.6%)
	Out-patient	41 (59.4%)
Indication for treatment (n, %)	APROP	40 (42%)
	Type 1 ROP	29 (58%)
PMA at initial treatment (weeks)	Mean ± SD	34.68 ± 2.34
	(Range)	(31.00-40.00)
Response to the initial treatment (n, %)	Absent	7 (10.1%)
	Present	62 (89.9%)
Recurrence after initial treatment (n, %)	Absent	46 (74.2%)
	Present	16 (25.8%)
Interval from treatment to recurrence (weeks)	Mean ± SD	8.0 ± 3.0
	(Range)	(4-13)
Retreatment type for recurrence (n, %)	LPC	13 (81.3%)
	IVB	3 (18.8%)
PMA at retreatment for recurrence (weeks)	Mean ± SD	43.25 ± 3.80
	(Range)	(40-54)
Incomplete retinal vascularization (n, %)	Absent	60 (96.8%)
	Present	2 (3.2%)
PMA at retreatment for incomplete retinal vascularization (weeks)	Mean ± SD (Range)	75.50 ±12.02 (67.00-84.00)
Structural outcome (n, %)	Unfavorable	67 (97.1%)
	Favorable	2 (2.9%)
PMA: Postmenstrual age, IVB: Intravitreal bevacizumab; LPC: Laser photocoagulation		

the nonresponsive patients were in the APROP group (p: 0.01). Complete involution rate was statistically lower in the APROP group (47.5% vs. 86.2%, p: 0.01). The mean PMA of IVB injection for APROP group was 33.58±1.95 weeks and statistically shorter than the mean PMA of IVB injection for Type 1 ROP group (35.9±2.21 weeks) (p<0.01). In terms of recurrence, there was no difference for zone 1 and zone 2 cases in the APROP group (p: 0.43). Demographic and clinical features for APROP and Type 1 ROP groups were summarized in Table 2.

DISCUSSION

In this study, anatomical success rate was found as 97.1% overall and as 63.8% after IVB monotherapy. Recurrence developed in 26.6% of eyes (25.8% of patients) in a mean period of 8 weeks after injection.

The recurrence rate was higher and the time of recurrence was earlier compared to BEAT-ROP study.[15] (25.8% vs. 4% recurrence rates and 8 weeks vs. 16 weeks after the injection respectively). Hwang et al.[25] showed 3% recurrence after laser treatment (2.6 weeks after treatment at 35.3 weeks PMA) and 14% recurrence after IVB injection (9 weeks after treatment at 45 weeks PMA) in 54 eyes with Type 1 ROP. Mueller et al.[6] showed no recurrence in the laser cohort compared with 12% recurrence after IVB injection (12.7 weeks after treatment) in 54 infants with Type 1 ROP. Karkhaneh et al.[21] found the recurrence rates after IVB and laser treatments 10.5% and 1.4% respectively in Type1 ROP patients. Lepore et al.[26], in a randomized clinical study, found recurrence rate 18.2% in laser treated group (2 out of 11 eyes) whereas they did not observe recurrence in anyone of the IVB treated eyes (12

Table 2. *Demographic and clinical features of the patients with aggressive posterior retinopathy of prematurity (APROP) and Type 1 retinopathy of prematurity.*

		APROP	Type 1 ROP	p value
Gender (n, %)	Female (n, %)	19 (47.5%)	14 (48.3%)	0.94*
	Male	21 (52.5%)	15 (51.7%)	
Gestational age at birth (weeks)	Mean ± SD	26 ± 2	27 ± 2	0.32†
	Range	23-31	23-32	
Birth weight (gr)	Mean ± SD	907 ± 253	944 ± 260	0.45†
	Range	400-1720	525-1470	
Zone	Zone 1	18 (45.0%)	0 (0.0%)	<0.001‡
	Zone 2	22 (55.0%)	29 (100%)	
Stage	Stage 2	-	16 (55.2%)	
	Stage 3	-	13 (44.8%)	
Response to initial treatment	Absent (n, %)	7 (17.5%)	0 (0.0%)	0.01 ‡
	Present (n, %)	33 (82.5%)	29 (100%)	
Recurrence after initial treatment	Absent (n, %)	20 (60.6%)	26 (89.7%)	<0.01*
	Present (n, %)	13 (39.4%)	3 (10.3%)	
Incomplete retinal vascularization after initial treatment	Absent (n, %)	31 (97.0%)	28 (96.6%)	1.0 ‡
	Present (n, %)	1 (3.0%)	1 (3.4%)	
PMA at initial treatment (weeks)	Mean ± SD (Range)	33.58 ± 1.95 (31.00-39.00)	35.97 ± 2.21 (33.00-40.00)	<0.001†
PMA at time of recurrence (weeks)	Mean ± SD (Range)	43.31 ± 4,01 (40.00-54.00)	43.00 ± 3.61 (40.00-47.00)	1.00†
PMA at retreatment for incomplete retinal vascularization (week)	Mean ± SD (Range)	84.00 -	67.00 -	n/a
Structural outcome	Unfavorable (n, %)	2 (5%)	0 (0.0%)	0.50 ‡
	Favorable (n, %)	38 (95%)	29 (100%)	

SD: Standard deviation; n: number; PMA: Postmenstrual age; *: Chi-square test; †:Mann-Whitney U test; ‡:Fisher's exact test

eyes). However, in angiographic evaluation, they detected vascular anomalies like persistent arteriovenous shunts, absence of foveal avascular zone and hyperfluorescent lesions in 75% of IVB treated group and 36.4% of the laser treated group. In a retrospective study from Romania, the rates of nonresponsive cases were statistically higher in the laser treated group (25%) than the IVB treated group (14.7%).[27] Moran et al.[28] treated one eye of each patient with IVB and the other eye with laser photoablation and found higher recurrence rates in IVB treated eyes. (21.42% versus 7.14 %) Hu et al.[29] detected recurrence in an average period of 14.4 weeks in 17 eyes treated with IVB and in 5 eyes retinal detachment developed.In studies from our country, Beyazyıldız et al.[30] evaluated the efficacy of IVB monotherapy in APROP cases and reported 100% regression following the initial injection; although 19% of the cases required retreatment for recurrence.Hondur et al.[31] evaluated IVB therapy in thirty-nine eyes of 20 infants with high-risk pretreshold ROP who were ineligible for laser therapy and reported all eyes responded to the initial therapy, eight eyes with Zone I disease (36%) and two eyes with Zone II disease (11%) developed recurrence which was consistent with this study.Özmen et al.[32], in twenty-five eyes of 14 patients with a specific subgroup of ROP with the immature macula, studied the efficacy of IVB injection and reported that ROP regressed in 17 eyes with normal retinal vascularization, although two eyes required additional laser therapy.

All these studies show controversial results that may be explained by the diversity in disease forms included or definitions of "recurrence" in the studies or in the severity of the disease forms in study populations. The clinical definition of recurrence remains a challenging point. There is not commonly accepted distinction between the definition of "recurrence" and the different regression forms in literature. The recurrence of plus disease was accepted essential for the definition of "recurrence" by some authors,

whereas some authors found this unnecessary. For example, Hu et al.[29] did not include the recurrence of plus disease in the definition of recurrence. There are well-defined and accepted regression forms following laser photoablation, but they are not clearly defined for IVB treatment. Such as vascular tufts that develops after IVB were accepted as one of the regression forms by some authors and as "recurrence" by some others.[33,34] In addition, it is not clear whether indirect ophthalmoscopic examination is efficacious or angiographic evaluation is necessary. Is "discontinuation of peripheral vascularization" a recurrence criteria? It was further observed that vascularization rate following IVB injection is slower in recurrences (shorter distance at a slower pace) compared to non-recurrences.[35]

In our cohort, we found much higher recurrence rates compared to the studies in literature. It might be related that our study population belongs to a developing country and ROP severity and progression rates might be worse. In addition, our study population included both type 1 ROP and APROP cases and our recurrence criteria were no rigid.

The recurrence rates were much higher in the APROP group compared to type 1 ROP cases in this study. APROP is the most aggressive form of the disease and laser treatment has the lowest success rate in APROP.[36,37] Is it also acceptable for anti-VEGF treatment? High recurrence rates in APROP cases as in our study have been shown in different studies. Blair et al.[38] studied efficacies of IVB and laser treatments in APROP cases and found nine recurrences in 22 patients. In addition, they showed that unfavorable anatomical outcomes were higher in laser treated group. Nicoara et al.[27] found that 14.71% of eyes failed to regress in a study to evaluate the efficacies of IVB and laser treatments, although they did not detect any late recurrence. Gonzalez et al.[39] showed that reactivation requiring retreatment after initial IVB injection was more common in APROP compared to classic ROP. In addition eyes with APROP had larger avascular retina (mean 4.4 DD) and higher percentage of leakage on fluorescein angiography (11/11 eyes) compared to classic ROP (mean 2.6 DD and 22/28 eyes).Minz-Hitner et al.[35] found a 5-fold increased risk of recurrence in APROP compared to stage3+ ROP.

It was found that 10.1% of our patients not responded to initial IVB treatment. In most studies, 90-100% initial response rate was reported.[34,40] In our study group, the lack of initial response may be caused by insufficient dosage of bevacizumab due to inefficient injection or disease severity so that all of the nonresponsive patients having APROP group may support this.

We detected incomplete peripheral vascularization in two patients. Henaine-Berra et al.[41] compatible to our study, demonstrated that vascularization did not reach the ora serrata at a mean period of 6 months in some patients after IVB injection. Tahija et al.[42] showed that peripheral avascular area of more than 2 disc diameters persisted in more than 50% of the eyes up to 4 years of treatment, although the outcome of the IVB therapy considered satisfactory. In this study, peripheral incomplete retinal vascularization rate was found to be much lower than aforementioned studies. This situation may be caused by evaluation of retinal vascularization clinically. It would be possible to observe more incomplete retinal vascularization or peripheral vascular abnormalities if these patients were evaluated angiographically.

Although, in this study, laser photocoagulation was considered as a secondary treatment for recurrences because of concerns about systemic side effects of bevacizumab and retinal vascularization, second IVB injection was administered to four eyes of three patient whose systemic condition was not eligible for laser photocoagulation and complete involution was achieved in these patients. Repeated IVB injections for recurrences were reported in some studies.[43,44] Additionally, in a large study from Turkey, the authors reported repeated injections, of which 11 were second and four were third injection.[34] However, we believe that it should be better and more accurate approach to use repeated IVB injections for recurrences after concerns about systemic side effects and retinal vascularization have been fully clarified.

Retrospective nature of the study, clinical diagnosis of recurrences and vascularization with indirect ophthalmoscopy instead of angiography are limitations of this study. On the other hand inclusion of both subgroups, type 1 ROP and APROP, enables us more objective evaluation that is the strength of our study.

We believe that intravitreal bevacizumab is effective in the treatment of Zone 1 and posterior Zone 2 ROP. It is less invasive, easily administered and has a rapid effect. On the other hand, IVB therapy delays retinal vascularization and requires prolonged monitoring. Long-term visual outcomes and systemic concerns require longer follow-ups. In conclusion, controversies about the efficiency of IVB in ROP treatment need to be clarified by large prospective studies.

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