

Comparison of Clinical Outcomes of Intravitreal Bevacizumab and Aflibercept in Type 1 Prethreshold Retinopathy of Prematurity in Posterior Zone II

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Abstract

Purpose: To evaluate the efficacy and safety of intravitreal injection (IVI) of bevacizumab (IVB) versus aflibercept (IVA) in premature infants with type 1 prethreshold retinopathy of prematurity (ROP) in the posterior Zone II.

Methods: The study was a multicenter, historical cohort of premature newborns diagnosed with type 1 prethreshold ROP in the posterior Zone II, treated with IVB or IVA. Demographic features, complications, and treatment outcomes were then compared between the two groups.

Results: Seventy-six patients received aflibercept (the IVA group), and 210 received bevacizumab (the IVB group). The two groups were not significantly different in terms of postmenstrual age (PMA) at the time of ROP diagnosis and other known risk factors for ROP development and progression. All eyes in both the groups responded to IVI; however, recurrence was observed in four eyes (1.9%) in the IVB group and 12 (15.8%) in the IVA group ($P = 0.001$). Recurrence occurred 9.1 ± 0.83 (5–12) and 15.5 ± 0.98 (12–18) weeks after primary treatment in the IVB and IVA groups, respectively ($P = 0.000$). In the IVA group, retinal vascularization was completed in 38.18 ± 6.5 weeks (21–48) after IVI, and it happened in 23.86 ± 9.3 weeks (13–60) in the IVB group ($P = 0.009$). Furthermore, vascularization reached the peripheral retina in 73.25 ± 6.5 (56–84) and 58.75 ± 8.8 (45–93) weeks, PMA in the IVA and IVB groups, respectively ($P = 0.03$). No acute postoperative complications were observed in the treated eyes in either group.

Conclusion: This study shows that both IVA and IVB are effective and well tolerated for the management of type 1 prethreshold ROP in the posterior Zone II; however, IVA needs a significantly longer time for vascularization completion and has a higher recurrence rate compared with IVB.

Keywords: Aflibercept, Anti-vascular endothelial growth factor, Bevacizumab, Retinopathy of prematurity

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INTRODUCTION

Despite advances in the neonatal intensive care units, retinopathy of prematurity (ROP) has become a common reason for blindness and visual disabilities in premature infants so that it accounts for about 5% and 30% of such complications in developed and developing countries.¹ The pathophysiology

of ROP is multifactorial. Supplemental oxygen demand and lower gestational age (GA) and birth weight (BW) are among the major risk factors for the occurrence and progression of ROP.² In the proliferative phase of ROP, overactivation of the vascular endothelial growth factor (VEGF) and other

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proangiogenic factors induced by the avascular retina causes abnormal neovascularization and subsequent problems, which in turn can lead to vitreous hemorrhage and finally tractional retinal detachment.³ Hence, VEGF, acting as a pivotal mediator for the normal development of retinal vasculature, might be considered the major biomarker for ROP pathophysiology.⁴ Compared to ablative treatment, intravitreal injection (IVI) of anti-VEGF restrains abnormal neovascularization while preserving the development of avascular periphery and subsequent complications.⁴ Many trials demonstrate the safety and effectiveness of intravitreal anti-VEGF, bevacizumab (IVB) and ranibizumab (IVR), especially in Zone I and posterior Zone II. However, none of the anti-VEGF agents are approved thus far by the Food and Drug Administration for the management of ROP.⁵⁻⁷

Aflibercept is a “VEGF Trap,” a recombinant protein that fused to VEGF-A, VEGF-B, and the placental growth factor (PlGF) and inhibits neovascularization.^{8,9} It has a longer action time than IVR¹⁰ and less systemic VEGF suppression compared to IVB.¹¹ However, studies on the safety and efficacy of the intravitreal aflibercept (IVA) for ROP treatment are limited, especially in developing countries like Iran.

The present study aimed to evaluate the efficacy and safety of two intravitreal VEGF inhibitors, bevacizumab and aflibercept, in infants with type 1 prethreshold ROP in the posterior Zone II.

METHODS

In this multicenter, historical cohort study, all premature neonates diagnosed with ROP by ophthalmological examinations performed by retina specialists in tertiary ophthalmology hospitals in Northwestern Iran were included. Medical records filed from 2017 to 2018 were evaluated, and the patients were followed up until June 2021. The clinical records of treatment-requiring patients with ROP receiving intravitreal anti-VEGF agents, bevacizumab (Avastin®, Genentech, San Francisco, CA, USA) or aflibercept (Eylea®, Regeneron, Tarrytown, NY, USA), for the last 4 years were reviewed, and infants with type 1 prethreshold ROP in the posterior Zone II, diagnosed based on the International Classification of ROP,¹² were enrolled. The anti-VEGF selection was based on routines available in different centers and parental choice. Cases with a follow-up period of <3 years and aggressive posterior ROP (APROP) were excluded from the study. The current study was approved by the local Ethical Committee of the Tabriz University of Medical Sciences (code IR.TBZMED.REC.1399.723) and complied with the tenets of the Declaration of Helsinki. Informed consent was obtained from the parents of all patients.

All demographic characteristics and clinical information, including gender, GA, BW, and postmenstrual age (PMA), of the treatment-requiring subjects diagnosed with ROP were recorded. Other possible risk factors for ROP development and progression, such as 1 and 5-min Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) scores

and maternal risk factors (diabetes, premature rupture of membranes, chorioamnionitis, hypertension, hypothyroidism, hemolysis, elevated liver enzymes, and low platelets syndrome [HELLP], etc.), were extracted from patients' records. Ophthalmologic variables were collected, including the anti-VEGF (bevacizumab or aflibercept) agents administered, PMA at the completion of retinal vascularization, refractive error (RE) at the last follow-up in 3 years of PMA, and ocular complications (i.e., endophthalmitis, cataract, glaucoma, retinal detachment, etc.). Response to treatment is defined as at least one stage reduction in ROP and elimination of plus diseases, i.e., the loss of arteriolar tortuosity and venous engorgement of posterior retinal vessels. Furthermore, recurrence was defined as the relapse of plus disease along with neovascularization.

Neonates were grouped based on the type of anti-VEGF agent, IVB or IVA, administered and being followed up by a trained retina specialist. All patients received a single dose of the intravitreal anti-VEGF drug, with half of the adult dosage. The injection was performed under local anesthesia (tetracaine hydrochloride ophthalmic solution 0.5%), under the supervision of a neonatologist at the ophthalmology operation room. After the adjustment of the eye speculum and instillation of 5% povidone-iodine, 1 mg/0.025 mL of aflibercept or 0.625 mg/0.025 mL of bevacizumab was injected through the conjunctiva approximately 1.0 mm behind the superotemporal limbus via the pars plicata with a 30 G × 4 mm microneedle. The intraocular pressure and patency of the central retinal artery were immediately checked, following the injections. Systemic conditions of the infants were continuously monitored in the recovery room during the pre and postinjection periods. After the injection, patients received topical ophthalmic drop sulfacetamide 10% every 5 h for 3 days.

Ophthalmoscopy was periodically performed once a day for a week after treatment to evaluate the postsurgery acute complications (i.e., endophthalmitis and iatrogenic cataract) and response to treatment. The follow-up was scheduled based on ROP severity and response to treatment until complete retinal vascularization. Furthermore, all patients were followed up for the late onset of ocular complications (i.e., cataract, glaucoma, retinal detachment, etc.) and RE after 3 years. A primary positive response was considered the reduction of at least one stage of the disease and elimination of the plus disease in the follow-up visit, 1 day after treatment. In cases of no response to anti-VEGF treatment or recurrence of the disease, patients were candidates for repeated intravitreal anti-VEGF injection or laser photocoagulation based on clinical evaluation. The efficacy and safety of IVA monotherapy for the treatment-requiring ROP of were compared with IVB.

Statistical analysis

The data were analyzed using SPSS software version 13 (South Wacker Drive, Chicago, USA). The data were presented using descriptive statistical methods (mean, standard deviation, frequency, and percentage). The normality of data was tested using the Kolmogorov–Smirnov test. The analysis of variance and Chi-square tests were used for ratio and nominal variables,

respectively, to compare the data. $P < 0.05$ was considered statistically significant.

RESULTS

In the current study, 286 clinical records of eyes with type 1 prethreshold ROP in the posterior Zone II, initially treated with intravitreal anti-VEGF monotherapy (bevacizumab or aflibercept), were reviewed. Seventy patients were male (48.3%), and 80 patients were female (51.7%). The male-to-female ratio was 0.93. The mean GA and BW in patients were 28.62 ± 2.1 w (25–35 w) and 1052.58 ± 263.8 g (600–2200 g), respectively.

Neonates were divided into the IVB and IVA groups based on medical histories. Seventy-six (40 patients) out of 286 eyes were treated with IVA, and the remaining 210 eyes (110 patients) received IVB. In the IVB group, 98 out of 210 patients were male (46.7%) and 112 female (53.3%). In the IVA group, the combination was 52.6% male, 40 eyes out of 76, and 47.3% female, 36 eyes ($P = 0.37$). The mean GA and BW were 28.52 ± 2.1 (25–35) weeks and 1060.38 ± 280.8 (600–2200) g in the IVB group and 28.89 ± 2.0 (25–32) weeks and 1031.05 ± 211.5 (700–1600) g in the IVA group, respectively ($P = 0.68, 0.08$). Furthermore, the two groups were not significantly different in terms of PMA at the time of the ROP diagnosis or treatment ($P = 0.84$ and 0.96 , respectively), 1 and 5-min APGAR scores ($P = 0.35$ and 0.55 , respectively), and known maternal risk factors for ROP development and progression (diabetes, premature rupture of membranes, chorioamnionitis, hypertension, hypothyroidism, HELLP, etc.). The characteristics of the patients in both the groups are described in Table 1. As shown in Table 1, there was no significant difference between the two groups in terms of the ROP development and progression risk factors.

All eyes in both the groups responded to primary treatment with intravitreal anti-VEGF monotherapy and peripheral retinal vascularization continued. However, recurrence after the IVI was observed in four eyes (1.9%) from the IVB group and in 12 eyes (15.8%) from the IVA group. The recurrence rate was significantly higher in the IVA group compared to the IVB group ($P = 0.001$). Following the primary treatment, the recurrence occurred after 9.1 ± 0.83 w (5–12 w) in the IVB group and 15.5 ± 0.98 w (12–18 w) in the IVA group ($P = 0.000$), and photocoagulation laser therapy was applied to the patients as an additional treatment. The age of patients who underwent treatment for recurrence was PMA of 44.01 ± 3.34 w for the IVB group and 52.67 ± 4.12 w for the IVA group ($P = 0.000$).

In the IVA group, retinal vascularization was completed in 38.18 ± 6.5 w (21–48 w) after IVI which was significantly longer than that of the other group, 23.86 ± 9.3 w (13–60 w) ($P = 0.009$). Vascularization reached the ora-serrata at 73.25 ± 6.5 w (56–84 w) and 58.75 ± 8.8 w (45–93 w) PMA in the IVA and IVB groups, respectively ($P = 0.03$).

The absolute value for spherical equivalent RE (SERE) was 1.78 ± 0.9 D (0–4.0 D) in the IVB group and 1.58 ± 1.3 D (0–5.5 D) in the IVA group. While it was not remarkable clinically, this difference between the two groups was statistically significant ($P = 0.01$). On the other hand, GA and BW were not significantly associated with the absolute value of SERE (Pearson correlation = -0.046 and 0.124 , $P = 0.451$ and 0.51 , for IVA and IVB groups, respectively), while they had a significant inverse relationship with the completion of vascularization (Pearson correlation = -0.24 and 0.284 , $P = 0.000$ and 0.000 , for the IVA and IVB groups, respectively). Anatomical, functional, and refractive outcomes in the two study groups are summarized in Table 2.

No acute severe complications such as postoperative endophthalmitis or iatrogenic cataracts were observed in the patients of the two groups. However, 40 weeks after IVI, unilateral peripheral posterior subcapsular lens opacity developed in one eye from the IVA group. Due to the long-time interval between IVI and cataract progression, it was unlikely attributed to the direct needle-related damages; hence, it was considered a sporadic complication. In this patient, a lensectomy was not performed due to the unaffected visual axis.

DISCUSSION

Conventionally, the standard procedure for the treatment-requiring ROP was destructing the avascular immature retinas with laser photocoagulation. However, in posterior zone-affected severe ROP patients, this treatment results in low efficacy and high ocular complications.^{9,13-15} In recent years, anti-VEGF agents are considered an attractive therapeutic strategy because of their key role in the pathophysiology of disease and advantages over ablative therapy, especially in Zone 1.¹⁶

PIGF, a cofactor during retinal neovascularization by increasing the activity and expression of VEGF, has a crucial role in developing pathological neovascularization and endothelial cell proliferation and migration in adults.^{17,18} However, the action of PIGF and VEGF-B in neonatal retinal vascular development is still unclear, and some studies indicate that they are not essential for normal maturation.¹⁷

A comprehensive randomized controlled clinical trial entitled “Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity” (BEAT-ROP) showed the safety and effectiveness of anti-VEGF IVI in the management of prethreshold type 1 ROP, especially in Zone 1 with positive anatomical results.¹⁶ According to the study on BEAT-ROP, bevacizumab 0.625 mg was more effective than photocoagulation laser therapy for the most severe type of ROP (Zone I).¹⁶ However, there were several hypotheses concerning intravitreal anti-VEGF injection in neonates, such as systemic suppression of VEGF followed by cessation of organ development. Therefore, the long-term side effects of this treatment are still being considered.

Table 1: Demographic findings and frequency of risk factors hypothesized for retinopathy of prematurity development and progression in two study's group patients

	IVB group (n=210)	IVA group (n=76)	Overall	P
Number of patients/eyes	110/210	40/76	150/286	
Male/female	98/112	40/36	138/148	0.37
BW _(gr) , mean±SD (range)	1060.38±280.8 (600-2200)	1031.05±211.5 (700-1600)	1052.58±263.8 (600-2200)	0.08
GA _(w) , mean±SD (range)	28.52±2.1 (25-35)	28.89±2.0 (25-32)	28.62±2.1 (25-35)	0.68
APGAR score	5.61±1.96	5.14±2.03		0.35
APGAR score 5 min later	7.57±2.01	7.25±1.67		0.55
Maternal risk factors, n (%)				
No risk factor	119 (56.6)	53 (69.7)		0.09
DM	8 (3.8)	3 (3.9)		0.98
PROM	21 (10.0)	3 (3.9)		0.21
Chorioamnionitis	1 (0.5)	0		-
HTN	23 (11.4)	11 (14.4)		0.10
Hypothyroidism	15 (7.1)	8 (10.5)		0.10
HELLP	2 (0.9)	0		0.78
PMA _(w) at ROP diagnosis, mean±SD (range)	32.80±1.0 (30-39)	33.3±1.7 (30-36)	32.93±1.9 (30-39)	0.84
Neonatal weight _(gr) at ROP diagnosis, mean±SD (range)	1539.01±288.1 (1250-1750)	1594.97±264.2 (1300-1800)	1553.06±281.7 (1250-1800)	0.83
PMA _(w) at IVI, mean±SD (range)	34.87±2.2 (31-42)	34.97±2.1 (31-39)	34.89±2.2 (31-42)	0.96
Neonatal weight _(gr) at IVI, mean±SD (range)	1741.92±167.3 (1550-2500)	1787.91±188.1 (1500-2250)	1753.90±172.8 (1500-2500)	0.94

IVB: Intravitreal bevacizumab, IVA: Intravitreal aflibercept, BW: Birth weight, GA: Gestational age, DM: Diabetes mellitus, PROM: Premature rupture of membrane, HTN: Hypertension, HELLP: Hemolysis, elevated liver enzymes, and low platelets syndrome, PMA: Postmenstrual age, IVI: Intravitreal injection, ROP: Retinopathy of prematurity, SD: Standard deviation, APGAR: Appearance, pulse, grimace, activity, and respiration

Table 2: Results of anatomical, functional, and refractive treatment response in two study's group patients

	IVB group (n=210)	IVA group (n=76)	Overall	P
Response to treatment, n (%)	210 (100)	76 (100)	286 (100)	1
Recurrence, n (%)	4 (1.90)	12 (15.78)	16 (5.6)	0.000
Completion of vascularization _(w) ±SD (range)	23.86±9.3 (13-60)	38.18±6.5 (21-48)	27.26±10.6 (13-60)	0.009
PMA _(w) at completion of vascularization, mean±SD (range)	58.75±8.8 (45-93)	73.25±6.5 (56-84)	62.18±10.4 (45-93)	0.03
[SERE]	1.78±0.9 (0-4.0)	1.58±1.3 (0-5.5)	1.73±1.0 (0-5.5)	0.01
SERE (minimum-maximum)	-1.50, +4.00	-5.5, +3.50	-5.50, +4.00	

IVB: Intravitreal bevacizumab, IVA: Intravitreal aflibercept, PMA: Postmenstrual age, [SERE]: Absolute value of spherical equivalent refractive error, SERE: Spherical equivalent refractive error

Several intravitreal anti-VEGF drugs are applied in treatment-requiring patients with ROP. IVB and IVR are the most common treatments worldwide due to their low cost and wide availability. It is hypothesized that IVB results in greater suppression of the systemic VEGF level than IVR due to its long presence in the systemic circulation. On the other hand, some trials reported that the recurrence rate was higher with IVR than with IVB.^{19,20} Therefore, the efforts to find a superior treatment are ongoing.

Unlike the other retinal vascular diseases, the clinical applications of IVA in ROP remained limited.

As a novel VEGF inhibitor, aflibercept has the strongest binding affinity compared to other agents²¹ (about 100 times greater than bevacizumab or ranibizumab), which brings up IVA as the potential method to achieve faster regression and longer maintenance in ROP treatment.²² IVA remains off-label for treating ROP in the US and the other developed countries thus far.^{5,23}

In this multicenter survey in clinical outcomes of IVB versus IVA treatments for type 1 prethreshold ROP in the posterior Zone II, a complete response was found with no significant ocular or systemic adverse effects in the short and long-term follow-up periods in both the IVA and IVB groups. However, the recurrence rate was significantly higher in the IVA group at longer intervals from the treatment onset. Furthermore, completion of vascularization was significantly longer in the IVA group.

Vural *et al.* reported IVA monotherapy as an effective treatment for the type 1 ROP and APROP with a low recurrence rate in short and long-term follow-ups.⁸ Furthermore, Ekinçi and Çelik introduced IVA as an effective treatment for ROP. However, it required more additional treatments (i.e., secondary photocoagulation) than primary laser photocoagulation during the follow-up visits.⁹

Chen *et al.*,²² in a prospective cohort study, reported that IVA is effective and well tolerable for the management of type 1

ROP, with satisfying anatomical, functional, and refractive outcomes.

Vedantham, in a retrospective case series, reported that IVA was effective in inducing complete regression of high-risk prethreshold ROP, threshold ROP, and APROP.²⁴ In the study by Sukgen and Koçluk,⁵ clinical completion of peripheral retinal vascularization was longer in the IVA group than in the IVR group. Furthermore, in the present study, completion of vascularization lasted longer in the IVA group than the IVB group. These differences may be explained by their different pharmacokinetics in human eyes, especially the longer half-life of aflibercept in the vitreous cavity.

The BEAT-ROP cooperative group reported that the disease recurred in 6 out of 140 eyes (4%) of infants with Stage 3 and plus disease who received bevacizumab monotherapy.¹⁶ In the current study, there was a 1.9% recurrence rate in the IVB group, which was significantly less than that of the previous study report, which may be due to the exclusion of APROP patients from the study that had a less therapeutic response. In another study, Vural *et al.*⁸ reported a treatment failure rate of about 4% in neonates with type 1 ROP and APROP who were on IVA monotherapy, which was clearly less than the recurrence rate in the current study.

The Committee for Medicinal Products for Human Use warned about the increase in a cerebrovascular accident (CVA) as an adverse event with aflibercept use; however, other studies reported no increase in CVA following the intravitreal use of this agent in adults with retinal vascular diseases.²⁵ Furthermore, no major ocular complications or systemic adverse effects occurred in the present study patients in the short and long-term follow-ups. Bazvand *et al.*²⁶ reported a case of CVA and systemic hypertension crisis after the prescription of IVA and complete retinal vascular arrest until 7 months after injection for APROP.

No neurodevelopmental defects were observed in the present study subjects in the 4-year follow-up periods. Nevertheless, the authors believe that further evidence is needed regarding the long-term effects of anti-VEGF drugs on growth and neurodevelopmental maturation.

The main strength of the current study was its multicenter nature with large sample size and control of known risk factors in the development and progression of the ROP. Its most important limitation was the difference in the sample size of the two groups. The reasons were the high price of the aflibercept and its low availability and retrospective manner of methods. Therefore, the authors recommended prospective, randomized, controlled, clinical trials by matching the two groups in the future.

Further studies are needed to obtain the ideal selection and dosing of the anti-VEGF agents for the treatment of ROP with the long-term follow-up periods to evaluate the probable effects on the neurodevelopmental maturation. Furthermore, determination of the ROP zone is prone to intra-observer

variability on the one hand, and the difference in response to treatment tremendously depends on the severity of the disease on the other hand. In order to maximize the matching of the two groups, it was decided to compare only patients with equal disease severity. Therefore, all patients diagnosed with type 1 prethreshold ROP in the posterior Zone II by a retina specialist were included. Further studies are recommended to compare the therapeutic effects of the agents in other disease severity, especially on patients with APROP.

In conclusion, this study shows that IVA and IVB are both safe and effective for the treatment of type 1 prethreshold ROP in the posterior Zone II, as effective and well-tolerable agents, with good anatomical, visual, and refractive outcomes. However, there were significant differences between the IVB and IVA groups in the time and rate of recurrence. Although these two drugs acted based on a similar mechanism in the short-term, they may lead to different outcomes in the development of infants' eyes due to different pharmacokinetics.

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Conflicts of interest

There are no conflicts of interest.

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