

The Evaluation of Efficacy of Intravitreal Aflibercept and Bevacizumab in the Treatment of Zone I Retinopathy of Prematurity

Dilbade Yildiz Ekinci¹, Nilufer Okur²

ABSTRACT

Purpose: To evaluate the clinical outcomes of the patients who received intravitreal aflibercept (IVA) or intravitreal bevacizumab (IVB) due to zone I retinopathy of prematurity (ROP).

Materials and Methods: In this study, the data of patients who received IVA or IVB due to aggressive posterior ROP (APROP) or type 1 ROP in zone I were retrospectively reviewed. Patients' birth weights (BW), gestational age (GA), postmenstrual age during treatment (PMA), regression and recurrence rates, and additional treatments were recorded.

Results: The study included 33 patients who were treated due to APROP or type 1 ROP in zone I. The IVA group with 22 eyes of 11 patients (Group 1) and the IVB group with 42 eyes 22 patients (Group 2). The mean BW of the patients were 932.7±330 grams and 1117.0±578 grams (p=0.07) and the mean GA values were 26.6±2.3 weeks and 28±3.5 weeks (p=0.83) in Group 1 and Group 2, respectively. The follow-up duration was 16.5±2.3 months and 8.0±2.6 months in Group 1 and Group 2, respectively (p=0.000). The PMA at treatment was applied was 33.5 weeks in Group 1 and 34.2 weeks in Group 2 (p=0.146). Regression rate after initial treatment was 100% in Group 1 and 88.0% in Group 2 (p=0.046). The rate of additional treatment due to recurrence was 27.2% and 23.8%, respectively (p=0.537).

Conclusion: ROP in zone I can be successfully treated with IVA and IVB. However, requiring additional treatment due to recurrence at high rates is a disadvantage of these therapies.

Keywords: Intravitreal aflibercept; Intravitreal bevacizumab; Zone I; Retinopathy of Prematurity.

INTRODUCTION

Increasing incidence of premature retinopathy (ROP) requiring treatment is observed with the survival of very low birth week and birth weight babies.¹⁻⁴ In the literature, it has been reported that ROP is observed particularly in zone I and more rapidly progress, retinal detachment is more common, and the anatomical success rate may be low despite laser photocoagulation (LPC) therapy among extremely premature infants.⁴⁻⁹ After vascular endothelial growth factor (VEGF) has been revealed to be the main factor in the pathogenesis of the disease, anti-VEGF agents have started to be used in the treatment of the disease.^{7, 9-12}

Rubeosis iridis, plus disease and retinal neovascularization are more rapidly regressed compared to LPC in patients diagnosed with zone I ROP and treated with anti-VEGF agents.^{7,10,11} Furthermore, the anatomical success rate of this therapy is higher in the long-term and it causes less refractive errors and ensures the continuation of the retinal revascularization.¹¹⁻¹⁶ Therefore, in recent years, intravitreal administration of anti-VEGF agents has been widely and increasingly preferred in the treatment of zone I ROP instead of LPC, which destroys the peripheral retina and causes permanent visual field loss.⁶⁻⁹ This study aims to compare the clinical results of patients who received intravitreal aflibercept (IVA) or intravitreal bevacizumab

1- MD, Gazi Yasargil Training and Research Hospital, Ophthalmology, Diyarbakir, Turkey

2- Assoc. Prof., Gazi Yasargil Training and Research Hospital, Ophthalmology, Diyarbakir, Turkey

Received: 08.02.2021

Accepted: 06.07.2021

Ret-Vit 2021; 347-353

DOI: 10.37845/ret.vit.2021.30.60

Correspondence Address:

Dilbade Yıldız Ekinci
Gazi Yasargil Training and Research Hospital., Ophthalmology,
Diyarbakir, Turkey

Phone: +92 505 369 4918

E-mail: dilbadeekinci@gmail.com

(IVB) due to aggressive posterior ROP (APROP) or type 1 ROP in zone I and to determine superior treatment modality.

MATERIAL AND METHODS

This retrospective comparative study was carried out in accordance with the principles stated in the Declaration of Helsinki and was approved by Diyarbakir Gazi Yasargil Training and Research Hospital Ethics Committee (28.02.2020; 431). Informed consent was obtained from the parents of all treated newborns that they agreed to participate in the study.

The files of patients who treated for zone I ROP were retrospectively analysed. The study included patients who received IVA (Group 1) or IVB (Group 2) due to APROP or type 1 ROP in zone I and were followed for at least six months at Diyarbakir Gazi Yasargil Training and Research Hospital between 2018 and 2020. Patients with irregular follow-up and those with the additional ocular disease and patients who were treated with LPC as the first line treatment were excluded from the study.

The disease in newborns was defined according to The International Classification of Retinopathy of Prematurity (ICROP). Cases in which there were no classic stages of ROP, plus disease was prominent, and there were flat neovascularization or vascular shunts in zone I were diagnosed to be APROP whereas the cases with any stage ROP accompanied by plus disease or stage 3 ROP not accompanied by plus disease in zone I were diagnosed to be type 1 ROP.¹⁷ Treatment was given to newborns diagnosed with type 1 ROP or APROP according to the Early Treatment for Retinopathy of Prematurity (ETROP) criteria.¹⁸

The parents of the infants to be treated with the diagnosis of zone I APROP or type 1 ROP were given information about the prognosis of the disease and the treatment modalities that could be applied. They were explained that there might be severe loss in peripheral vision area, a high degree of myopia and low anatomic success rate with the LPC therapy compared to anti-VEGF agents. It was further emphasized that the success rate with anti-VEGF agents was high, but LPC might be required due to late recurrences and delay of vascularization and that more frequent follow-up intervals were required.^{6,7,11-13} Parents who did not accept LPC was informed that aflibercept and ranibizumab were drugs produced for ophthalmic use and intravitreal ranibizumab (IVR) has a higher recurrence rate compared to IVA.¹² It was also explained that, bevacizumab was a drug used in cancer treatment and used as an off-label

drug in ROP. IVR could not be applied to patients because none of the parents accepted ranibizumab injection. For patients who underwent IVA, off-label use permission was obtained from the Ministry of Health.

Informed consent was obtained according to the parents' decision, and treatment was given a maximum of 72 hours after diagnosis. All injections were performed by same ophthalmologist (DYE) under local anesthesia. After asepsis was achieved, intravitreal 0.625 mg/0.025 mL IVB or 1 mg/0.025 mL IVA was injected. Topical antibiotic drop was initiated four times a day in the postoperative period. The patients were examined on the first postoperative day, first postoperative week, and monthly periods after the disease was completely regressed.

The following data of the patients were recorded: birth weight (BW), gestational age (GA), postmenstrual age (PMA) at treatment, type of anti VEGF agent, regression rates, complications, presence of recurrence, additional treatment due to recurrence, anatomical and functional success rate, and retinal vascular zone in the last examination. The obtained results were compared according to the anti-VEGF agent administered.

Statistical Methods

Statistical analyses were performed using the statistical package SPSS for Windows v. 21.0 (SPSS Inc., Chicago, Illinois). Normally distributed data were given as mean and SD; others presented as median and range. Demographic percentage and mean outcome measures of patients were compared between the two groups with Fisher's exact test, a chisquared test, and a t-test. A p value of < 0.05 was considered statistically significant.

RESULTS

In this study, the data of 33 patients who received anti-VEGF due to the diagnosis of APROP or Type 1 ROP in zone I were analyzed retrospectively. Twenty-two eyes of 11 patients receiving IVA (Group 1) and 42 eyes of 22 patients receiving IVB (Group 2) were included in the study. The mean BW of the patients were 932.7±330 grams and 1117.0±578 grams (p=0.70) and the mean GA values were 26.6±2.3 weeks and 28±3.5 weeks (p=0.83) in Group 1 and Group 2, respectively. Four (36.3%) of the patients were male and seven (63.6%) were female in Group 1 whereas 12 (54.5%) of the patients were male and 10 (45.5%) were female in Group 2 (p=0.21) (Table 1). The follow-up duration was 16.5±2.3 months and 8.0±2.6 months in Group 1 and Group 2, respectively (p=0.00). The clinical characteristics of the patients were given in

Table 1: Demographic characteristics of the patients.

(n=number of patients)	Intravitreal Aflibercept Group (n=11)	Intravitreal Bevacizumab Group (n=22)	p
Gender (Male/Female)	4(36.3%) /7(63.6%)	12 (54.5%)/10 (45.5%)	0.21 ^{X²}
Birth weight (gram)	932.7±330	1117.0±578	0.70 ^m
Gestational Age (week)	26.6±2.3	28±3.5	0.83 ^m

^{X²} Chi-square test (Fischer test), ^m Mann-whitney u test

Table 2: The type of disease, presence of plus disease, and the regression rate following the first treatment according to groups.

(n=number of eyes)	Intravitreal Aflibercept Group (n=22 eyes)	Intravitreal Bevacizumab Group (n=42 eyes)	p
APROP/Type 1 ROP	10 (45.4%)/12 (54.5%)	28 (66.6%)/14 (33.4%)	0.193 ^{X²}
Treatment week	33.5 (31-40)	34.2(31-40)	0.146 ^m
Plus Disease	22 (100%)	42 (100%)	1.00 ^{X²}
Regression rate, n (%)	22 (100%)	37 (88.0%)	0.046 ^{X²}
APROP/Type 1 ROP regression rate	10 (100%)/12 (100%)	25 (89.2%)/12 (85.7%)	

^{X²} Chi-square test (Fischer test), ^m Mann-whitney u test

APROP: aggressive posterior retinopathy of prematurity, ROP: retinopathy of prematurity

Table 2.

Regression rate after initial treatment was 100% in Group 1 and 88.0% in Group 2 (p=0.046). In group 2, 5 unresponsive eyes were undergone LPC treatment and the disease was completely resolved.

After complete regression was achieved, additional treatment was applied to six eyes (27.2%) in Group 1 and ten eyes (23.8%) in Group 2 due to recurrence as AP-ROP or type 1 ROP (p=0.537). Forms of recurrences are presented in Table 3 and treatment modalities after

Table 3: Recurrence rates and types of recurrence.

Type of Recurrence	Intravitreal Aflibercept Group (n=22 eyes)	Intravitreal Bevacizumab Group (n=42 eyes)	p
APROP	0 (0%)	2 (0.04%)	0.537 ^{X²}
Type 1 ROP	6 (27.2%)	8 (19.0%)	
Type 2 ROP	2 (9%)	2 (0.04%)	
	8 (36.36)%	12 (28.5%)	

^{X²} Chi-square test (Fischer test)

APROP: aggressive posterior retinopathy of prematurity, ROP: retinopathy of prematurity, LPC: laser photocoagulation, Anti VEGF: Anti vascular endothelial growth factor

Table 4: Treatment modalities applied after recurrence.

(n=number of eyes)	Intravitreal Aflibercept Group (n=22 eyes)	Intravitreal Bevacizumab Group (n=42 eyes)	p
No treatment	2 (9%)	2 (0.04%)	0.537 ^{X²}
LPC	6 (27.2%)	8 (19.0%)	
Anti VEGF injection	0 (0%)	2 (0.04%)	
Total	8 (36.36)%	12 (28.5%)	

^{X²} Chi-square test (Fischer test)

LPC: laser photocoagulation, Anti VEGF: Anti vascular endothelial growth factor

recurrence are presented in Table 4. In Group 2, recurrence and vitreous hemorrhage developed in zone I in two eyes of one patient. The second dose of IVB was applied to both eyes, but despite the regression, an increase in vitreous hemorrhage was observed to prevent retinal examination. Pars plana vitrectomy and LPC were performed to two eyes of this patient. In Group 1, there was no vitreous hemorrhage requiring treatment in any eye. There was no difference between the groups in terms of development of vitreous hemorrhage (p=0.234).

In Group 1, six eyes (27.2%) of three patients who were 1 year old were treated with LPC due to vascular arrest in zone II after a joint decision with the parents. Prophylactic LPC was not applied in Group 2 due to short term follow-up period. Retinal vascularization status in the last examination is given in Table 5.

During the follow-ups, no retinal pathology at the level that could cause complete loss of vision was observed in either group. Light perception and following of objects was poor in one patient from each group due to severe cerebral ischemia (p=0.965). Other patients had normal visual development.

DISCUSSION

The prognosis of the disease is poor in cases with ROP in zone I and if it is not treated urgently, it can progress to advanced stages in a very short time.⁵⁻⁷ The disease has been found to progress in less than a week following the identification of disease in zone I in 50% of the cases.¹⁹ Furthermore, stage 1 disease in zone I has been shown to progress to stage 3 in an average of 1.3 weeks and treatment has been reported to be applied 10 days after stage 1 ROP is detected in the majority of cases.⁵ The success rate of treatment performed with cryotherapy and LPC is known to be low in eyes developing ROP in zone I.^{18,20} With the introduction of anti-VEGF agents in the treatment of ROP, anatomical success rates increased in this group compared to cryotherapy and LPC.^{7,10-16,21}

In the present study, the mean GA and BW values were found to be less than 28 weeks and 1250 grams in both

groups, respectively. All infants in the IVA group were born under 32nd gestational week and under 1,250 grams whereas 5 infants in the IVB group were born after 32nd gestational week and 6 infants's birth weights were over 1250 grams. In a study conducted in Turkey in which zone I cases were evaluated, the mean GA and BW were reported to be above 28 weeks and 1,200 grams.²² In a study, involving patients with zone I ROP in Romania, the mean BW and GA values were found to be similar to that of the present study.²³ However, in two studies conducted in the USA, the mean GA and BW of infants with a disease of similar severity were found to be 26 weeks and below 1,000 grams.^{7,24} This finding has shown that infants with larger BW and higher GA are being affected by a severe disease in developing countries. In addition, based on the ROP screening criteria applied in the USA, it suggests that in some babies in our country, the disease will be skipped in line with these criteria and it may be more appropriate to screen any premature baby with an intensive care history. Moreover, different results obtained in the present study compared with other study conducted in the same country have revealed that neonatal intensive care conditions are not standardized in Turkey and existing conditions should be improved.

Studies in zone I ROP reported a success rate of 82.5% -100% with a single dose of IVB injection.^{22,23,25-27} In a study, the success rates achieved were reported to be 100% in type 1 ROP and 78% in APROP.²³ In the present study, the success rate achieved with a single dose injection was 100% in the IVA-treated group and 88.0% in the IVB-treated group. In the IVB group, the regression rates of the APROP and type 1 ROP subgroups have been found to be 89.2%. and 85.7%, respectively. Although these data showed a higher rate of regression in zone I ROP with IVA compared to IVB, both agents provided high anatomical success rate unlike low success rates reported with cryotherapy and LPC.^{18,20}

In patients treated with anti-VEGF, PMA at treatment and the presence of membrane formation are known to affect prognosis. In particular, the contraction of membranes

Table 5: Retinal vascular zone detected at the last visit.

(n=number of eyes)	Intravitreal Aflibercept Group (n=22)	Intravitreal Bevacizumab Group (n=42)	p
Zone I	0 (0%)	5 (11.9%)	0.137 ^{x2}
Zone II	16 (72.7%)	27 (64.2%)	
Zone III	6 (27.3%)	10 (23.8%)	

^{x2} Chi-square test (Fischer test)

and retinal detachment due to the late administration of anti-VEGF agents make disease management difficult and may require vitrectomy.²⁸ It is a known fact that ROP developing in zone I is more severe compared to ROP in zone II and that treatment should be initiated in an earlier PMA.^{29,30} In the Bevacizumab Eliminates the Angiogenic Threat for Retinopathy of Prematurity (BEAT-ROP) study, the patients with zone I ROP in the IVB-treated group were treated at PMA of 34.5 weeks.²⁴ In the present study, IVA and IVB were administered at an earlier PMA, similar to the literature.^{24,29,30} In Diyarbakir, in which the present study was conducted, there is no pediatric vitreoretinal surgeon who is able to treat retinal detachment due to late administration of treatment. In addition, the fact that babies who develop diseases in very small PMA and are hospitalized in intensive care unit during their treatment period, are difficult to refer to the surgical centers, which may adversely affect the prognosis. Therefore, we think that it is a better approach to treat the patients who are predicted to progress rapidly, not to wait too long, and to treat them in the early weeks.

One of the most serious problems that can be encountered after applying anti VEGF agents in ROP treatment is recurrence and ocular morbidity that may develop accordingly.^{7,10,12,22,24,31,32} In a study comparing the efficacy of IVR and IVB, the recurrence rate was found to be higher in eyes that had ROP in zone I, required treatment in early PMA and treatment with IVR.³² In a study conducted in India, the recurrence of the disease was reported in 31 of 46 eyes treated with aflibercept. In the same study, recurrence was observed in about 80% of the eyes treated for ROP in zone I.³³ In a study, recurrence was observed in 7.7% of the eyes treated with IVA and the authors emphasized that these two eyes were treated due to stage 2 ROP in zone I.³⁴ In the study of Mintz-Hittner, the recurrence rate was reported to be 18% in cases with a disease in zone I who were treated with IVB.³¹ Additional treatment was applied to 27.2% of the eyes in the IVA group and to 23.8% of the IVB group due to recurrence. High recurrence rates which seen with IVA and IVB have demonstrated that eyes developing ROP in zone I should be followed closely and for a long time following the anti-VEGF treatment.

It is known that retinal vascular development delays in the eyes which treated with anti VEGF agents, and avascular retina remains in the periphery in the majority of the eyes.^{10,12-14} Although the reason for the presence of retinal avascular areas is not known exactly, but genetic predisposition, the presence of disease in zone I, and APROP-type disease have been reported to be possible risk factors.^{12,34,35,36} A study evaluating the effect of IVA

and IVB on vascular growth showed that vascular growth rate was higher in the IVA-treated group whereas the final vascularization was at a more advanced level in the IVB-treated group.³⁷ During follow-ups, vascularization reached zone III in only 6 (27.2%) eyes in the IVA group and 10 eyes (23.8%) in the IVB group. In both groups, retinal vascularization was not completed in any eyes and no difference was observed between the groups in terms of the final state of vascularization. However, the high rate of vascularization reaching zone III in the IVA group may be due to the longer follow-up time in this patient group.

The limitations of our study were the small number and heterogeneity of patients in both groups and the different follow-up times between the groups. After changing the rules for using anti-VEGF agents in retinal diseases in 2019, we started using bevasizumab instead of aflibersept. We have also started to treat patients who have been referred from different cities in the last 2 years. Therefore, follow-up times and patients characteristics between the two groups differed. However, high treatment success rates can be achieved with both anti-VEGF agents in both type 1 ROP and APROP in contrast to the low success rates reported with LPC. Although the success rates are high, retinal avascular areas remaining and recurrences during the follow-ups suggest that patients should be followed more closely and carefully. There is a requirement for multicenter trials with a larger population, in which the efficacy of IVA and IVB in zone I ROP are evaluated, to reveal which agent is superior.

Acknowledgments

Informed consent: “Informed consent was obtained from all individual participants included in the study.”

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest: The authors declare that they have no conflict of interest. Manuscript have not been published previously.

REFERENCES

1. Pedersen P, Bilsteen JF. Outcomes and follow-up programmes in extreme preterm children in Denmark in the EPICE/SHIPS cohort. *Dan Med J* 2020; 67: A08190472.
2. Rysavy MA, Horbar JD, Bell EF, et al. Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network and Vermont Oxford Network. Assessment of an Updated Neonatal Research Network Extremely Preterm Birth Outcome Model

- in the Vermont Oxford Network. *JAMA Pediatr* 2020; 174: e196294.
3. Taner A, Tekle S, Hothorn T, et al. Higher incidence of retinopathy of prematurity in extremely preterm infants associated with improved survival rates. *Acta Paediatr* 2020 Jan 28. doi: 10.1111/apa.15197.
 4. Tavassoli S, Wach R, Haynes R, et al. Estimate of incidence of ROP requiring treatment in extreme preterms and impact on service-7 year review in tertiary unit. *Eye (Lond)* 2019; 33: 845-849.
 5. Soh Y, Fujino T, Hatsukawa Y. Progression and timing of treatment of zone I retinopathy of prematurity. *Am J Ophthalmol* 2008; 146: 369-374
 6. Sen P, Abraham S, Jain S, et al. Treatment outcomes of zone I retinopathy of prematurity: A study from a tertiary eye care center in South India. *Taiwan J Ophthalmol* 2019; 9: 255-261.
 7. Mintz-Hittner HA, Kuffel RR. Intravitreal Injection Of Bevacizumab (Avastin) For Treatment Of Stage 3 Retinopathy Of Prematurity In Zone I or Posterior Zone II. *Retina* 2008; 28: 831-838.
 8. Fukushimaa Y, Fujinob T, Kusakac S, et al. Favorable outcomes of adequate laser photocoagulation and salvage bevacizumab treatment for aggressive posterior retinopathy of prematurity. *American Journal of Ophthalmology Case Reports* 2018; 11: 66-71.
 9. Kychenthal A, Dorta P, Katz X. Zone I Retinopathy Of Prematurity. *Clinical Characteristics and Treatment Outcomes. Retina* 2006; 7: 11-5.
 10. Patel SN, Klufas MA. Evidence to date: ranibizumab and its potential in the treatment of retinopathy of prematurity. *Eye Brain* 2019; 11: 25-35.
 11. Ekinci DY, Çelik K. Comparison of the Efficacy Between Intravitreal Aflibercept and Laser Photocoagulation in the Treatment of Retinopathy of Prematurity. *J Pediatr Ophthalmol Strabismus* 2020; 57: 54-60.
 12. Sukgen EA, Koçluk Y. Comparison of clinical outcomes of intravitreal ranibizumab and aflibercept treatment for retinopathy of prematurity. *Graefes Arch Clin Exp Ophthalmol* 2019; 257: 49-55.
 13. Vural A, Perente İ, Onur İU, et al. Efficacy of intravitreal aflibercept monotherapy in retinopathy of prematurity evaluated by periodic fluorescence angiography and optical coherence tomography. *Int Ophthalmol* 2019; 39: 2161-9.
 14. Ekinci DY, Vural AD, Bayramoglu SE, et al. Assessment of vascular leakage and its development with FFA among patients treated with intravitreal anti-VEGF due to aggressive posterior ROP. *Int Ophthalmol* 2019; 39: 2697-705.
 15. Lepore D, Ji MH, Quinn GE, et al. Functional and Morphologic Findings at Four Years After Intravitreal Bevacizumab or Laser for Type I ROP. *Ophthalmic Surg Lasers Imaging Retina* 2020; 51: 180-6.
 16. Lin CJ, Tsai YY. Axial length, refraction, and retinal vascularization 1 year after ranibizumab or bevacizumab treatment for retinopathy of prematurity. *Clin Ophthalmol* 2016; 10: 1323-1327.
 17. International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. *Arch Ophthalmol* 2005; 123: 991-9.
 18. Early Treatment For Retinopathy Of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: Results Of The Early Treatment For Retinopathy Of Prematurity Randomized Trial. *Arch Ophthalmol* 2003; 12: 1684-94.
 19. Isaza G, Modabber M, Arora S, et al. Zone I and Posterior Zone II Retinopathy of Prematurity. *Journal of Clinical Neonatology* 2015; 4: 237-43.
 20. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity. Three-month outcome. *Arch Ophthalmol* 1990; 108: 195-204.
 21. Wang SD, Zhang GM; Shenzhen Screening for Retinopathy of Prematurity Cooperative Group. Laser therapy versus intravitreal injection of anti-VEGF agents in monotherapy of ROP: a Meta-analysis. *Int J Ophthalmol.* 2020 May 18;13(5):806-815. doi: 10.18240/ijo.2020.05.17.
 22. Kimyon S, Mete A. Comparison of Bevacizumab and Ranibizumab in the Treatment of Type I Retinopathy of Prematurity Affecting Zone I. *Ophthalmologica* 2018; 240: 99-105.
 23. Nicoară SD, Nascutzy C, Cristian C, et al. Outcomes and prognostic factors of intravitreal bevacizumab monotherapy in zone I stage 3+ and aggressive posterior retinopathy of prematurity. *J Ophthalmol* 2015; 2015:102582.
 24. Mintz-Hittner HA, Kennedy KA, Chuang AZ, BEAT-ROP Cooperative Group. Efficacy of Intravitreal Bevacizumab for Stage 3+ Retinopathy of Prematurity. *N Engl J Med* 2011; 364: 603-15.
 25. Karkhaneh R, Torabi H, Khodabande A, et al. Efficacy of Intravitreal Bevacizumab for the Treatment of Zone I Type I Retinopathy of Prematurity. *J Ophthalmic Vis Res* 2018; 13: 29-33.
 26. Özmen MC, Karaatli S, Köklü E. İntravitreal Bevacizumab ile Prematüre Retinopatisinde Maküla Koruyucu Tedavi. *Ret-Vit* 2013;21:205-208
 27. Beyazyildiz E, Şimşek M, Beyazyildiz Ö. Agresif Posterior Prematüre Retinopatisinde İntravitreal Bevacizumab Monoterapisinin Uzun Dönem Etkinliğinin Değerlendirilmesi. *Ret Vit* 2019; 28: 44-50
 28. Faia LJ, Trese MT, "Retinopathy of prematurity," S.Ryan, A. Schachat, C.Wilkinson, D. Hinton, and P.Wiedemann, Eds., vol. 2, pp. 1920-1932, Elsevier, New York, NY, USA, 5th edition, 2013.
 29. Mueller B, Salchow DJ, Waffenschmidt E, et al. Treatment of type I ROP with intravitreal bevacizumab or laser

- photocoagulation according to retinal zon. *Br J Ophthalmol* 2017; 101: 365–70.
30. Shin DH, Kong M, Kim SJ, et al. Risk factors and rate of progression for zone I versus zone II type 1 retinopathy of prematurity. *J AAPOS*. 2014;18:124-8.
31. Mintz-Hittner HA, Geloneck MM, Chuang AZ. Clinical Management of Recurrent Retinopathy of Prematurity after Intravitreal Bevacizumab Monotherapy. *Ophthalmology* 2016; 123: 1845-55.
32. Ling KP, Liao PJ, Wang NK, et al. Rates and risk factors for recurrence of retinopathy of prematurity after laser or intravitreal anti-vascular endothelial growth factor monotherapy. *Retina* 2020; 40: 1793-803.
33. Vedantham V. Intravitreal aflibercept injection in Indian eyes with retinopathy of prematurity. *Indian J Ophthalmol* 2019; 67: 884-8.
34. Salman AG, Said AM. Structural, visual and refractive outcomes of intravitreal aflibercept injection in high-risk prethreshold Type 1 retinopathy of prematurity. *Ophthalmic Res* 2015; 53: 15-20.
35. Garcia Gonzalez JM, Snyder L, Blair M, et al. Prophylactic peripheral laser and fluorescein angiography after bevacizumab for retinopathy of prematurity. *Retina* 2018; 38: 764-72.
36. Çömez A, Karaküçük Y, Özmen MC, Çelemler P, Saygılı O. The results of intravitreal bevacizumab monotherapy for treating aggressive posterior retinopathy of prematurity and Type 1 retinopathy of prematurity. *Eye (Lond)*. 2021 Jan 29. Online ahead of print
37. Vural A, Ekinci DY. Comparison of Vascular Outgrowth Rate and Retinal Vascular Development Border After Intravitreal Injection of Aflibercept or Bevacizumab to Treat Retinopathy of Prematurity. *Ophthalmologica* 2020; 243: 86-93.