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A comparation of three different anti-VEGF drugs in development of persistent avascular retina in premature children

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Our current prospective cross-sectional study aimed to investigate the effect of anti-vascular endothelial growth factor (VEGF) drugs used in the treatment of retinopathy of prematurity on retinal maturation and persistent avascular retina (PAR). Retinal imaging was performed with Optos confocal laser ophthalmoscopy for 100 patients aged 4 to 8 years who were screened and treated for retinopathy of prematurity (ROP) during the neonatal period. The ROP examination findings (stage and zone) and treatment history (age in weeks at time of treatment and anti-VEGF drug used) from the neonatal period were reviewed. Retinal vascularization was assessed in fundus images using the green filter on the Optos device and the presence of PAR was evaluated by two investigators. Relationships between the rate of PAR, age in weeks at time of treatment, and type of anti-VEGF drug used were analyzed statistically. The study included 196 eyes of 100 patients. Sixty-four eyes were analyzed in Group 1 (no ROP), 23 eyes in Group 2 (ROP, no treatment), and 108 eyes in Group 3 (treated group; anti-VEGF treatment of ROP with ranibizumab, bevacizumab, or aflibercept). The number of eyes with PAR in these groups was 2 (3.7%), 4 (17.4%), and 45 (41.7%), respectively. PAR was detected in 30 of 44 eyes treated with aflibercept. The rate of PAR was higher after aflibercept treatment (68.2%) with statistical significance ($p = 0.000$). This study showed that the prevalence of PAR differs between anti-VEGF drugs. Patients treated with aflibercept have a higher risk of late complications and should be followed closely.

Keywords Retinopathy of prematurity, Persistent avascular retina, Anti-VEGF therapy

Retinopathy of prematurity (ROP) is a disease caused by abnormal vascularization of the retina due to preterm birth and low birth weight[1]. Approximately 10% of patients who develop retinopathy require treatment[2]. Treatment options include laser photocoagulation and intravitreal anti-vascular endothelial growth factor (VEGF) injection[3]. The main goal of treatment is to reduce the concentration of VEGF in the avascular areas and restore normal vascularization[4]. Treatment with laser therapy, the gold standard for ROP, permanently halts vascularization, preventing the affected vessels from reaching the periphery and causing visual field loss[5]. In contrast, anti-VEGF therapy stops abnormal vascularization by reducing the amount of VEGF in the retina, and permanent maturation of the retina can occur upon allowing vessels to progress to the periphery of the retina[6]. Anti-VEGF therapy is being used with increasing frequency to avoid permanent laser damage and visual field loss[7].

With the increase in premature births and the widespread use of anti-VEGF treatment, it has been observed that vascularization of the peripheral retina is not completed in some cases and the avascular area becomes permanent. Persistent avascular retina (PAR) was thus defined[8]. In the latest edition of the International Classification of Retinopathy of Prematurity, it was emphasized that PAR may occur as a result of spontaneous regression or after anti-VEGF treatment, and it was reported that the prevalence of PAR after anti-VEGF treatment is higher and wider areas of the eye are affected. PAR has even been accepted as a consequence or complication of anti-VEGF treatment[9]. However, the prevalence of PAR in eyes with retinopathy, whether treated or untreated, remains unclear[10]. Studies have found PAR to occur at different rates depending on age group, ethnicity, and the drug administered[11–13]. We planned the present study to determine the effects of anti-VEGF drugs on retinal maturation and their relationship with the prevalence of PAR in ROP.

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Methods

Approval for this cross-sectional prospective study was obtained from the local ethics committee of the University of Health Sciences Antalya Training and Research Hospital (approval number-date: 139-2024-06.06.2024). The study was conducted in compliance with the ethical standards set out in the Declaration of Helsinki. Written informed consent was obtained from the parents and/or legal guardians of the patients.

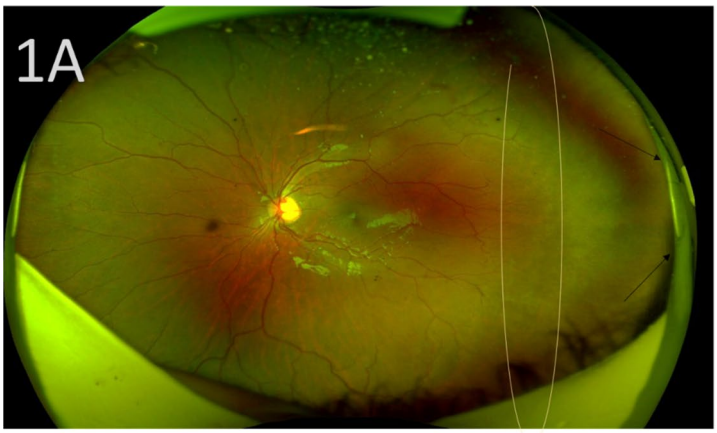
Between January 2016 and December 2020, 100 patients aged 4–8 years who were under follow-up for the diagnosis and treatment of ROP in a tertiary health center were included in the study. Detailed clinical examinations were conducted for all patients, including assessments of visual acuity, intraocular pressure, and slit-lamp examination, followed by undilated ultra-widefield (UWF) fundus imaging using the Optos device (Optos PLC, Dunfermline, UK) with a green filter. All images were thoroughly evaluated by two researchers (A.C.U. and M.A.). Fundus images in the horizontal quadrant were included in the study. Using UWF with the green filter, detailed images of each patient's peripheral retina, ora serrata, vascular–avascular junction area, and any vascular terminations extending toward the junction region were captured (Figs. 1 and 2).

The following exclusion criteria were applied to images and patients: (1) loss of image quality due to artifacts, especially when over 60% of the nasal and temporal peripheral retina could not be evaluated (e.g., insufficient lighting of the fundus due to intraocular medium opacities such as cataracts, corneal lesions, and eyelash interference); (2) images of eyes with prior laser treatment or the presence of other retinal pathologies, such as hemorrhages, exudation, or visible signs of previous retinal surgeries; (3) use of anti-VEGF treatments other than for type 1 ROP and multiple applications of anti-VEGF drugs. Ultimately, 4 eyes were excluded from the study, resulting in a total of 196 eyes being included in the analysis.

The GA, BW, results of ROP examinations during the neonatal period (stage and zone), and treatment history (including age in weeks at the time of treatment and the specific anti-VEGF drug used) were retrieved for all patients from the institution's records and documented.

Group assignments

Group 1 (no ROP) comprised 64 eyes of children born prematurely but without retinopathy, Group 2 (ROP, no treatment) comprised 23 eyes with type 2 disease and spontaneous regression, and Group 3 (ROP, treated group)



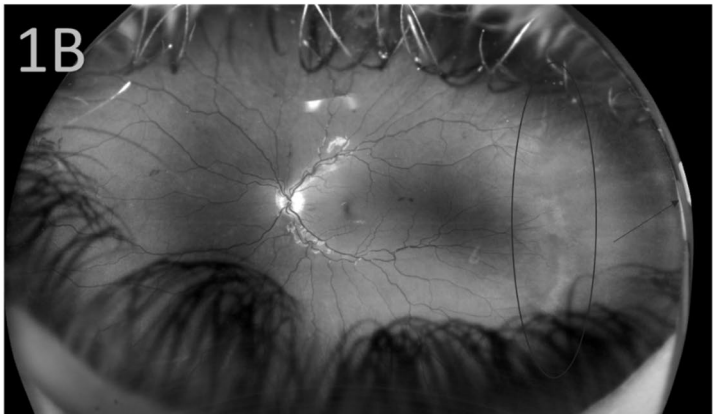
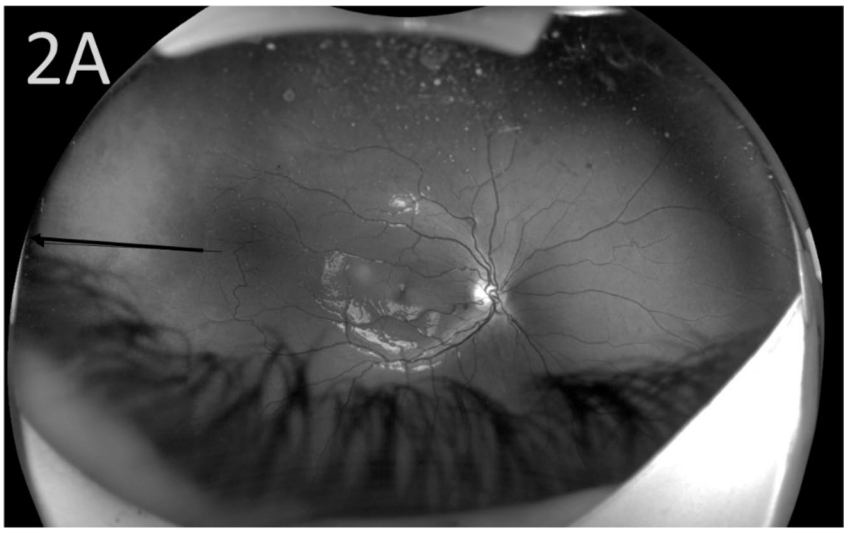


Fig. 1. (**A**) Color fundus image showing persistent avascular retina (arrow indicates area 1: ora serrata; circle marks the vascular–avascular junction). (**B**) Green filter fundus image showing persistent avascular retina (arrow indicates area 1: ora serrata; circle marks the vascular–avascular junction).



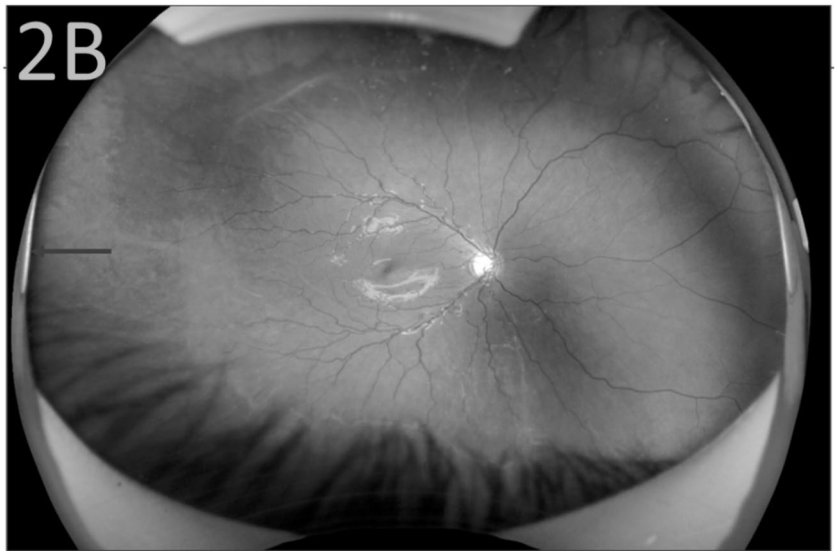


Fig. 2. (**A**) Zone 2 PAR (beginning of arrow: vascular–avascular junction; end of arrow: ora serrata). (**B**) Zone 3 PAR (beginning of arrow: vascular–avascular junction; end of arrow: ora serrata).

comprised 108 eyes treated with an intravitreal anti-VEGF (bevacizumab, 0.025 mL; ranibizumab, 0.025 mL; or aflibercept, 0.025 mL) for type 1 disease.

Differences in the rate of PAR were compared statistically according to groups, the week of treatment for eyes with persistent avascular retina (PAR) in Group 3, and the type of anti-VEGF drug used for treatment.

Optos UWF imaging

Images were obtained using the Optos cSLO wide-angle confocal laser ophthalmoscope without the use of a blepharostat and without pupil dilation or sedation.

For each eye, several images were recorded using the Optos device and the image of the best quality for each analyzed eye was selected for the evaluations. The duration needed to record each image was approximately 0.25 s and motion artifacts were minimized. One of the researchers or an experienced technician carried out all steps of the scanning process, which required approximately 3–5 min, including the positioning of the patient.

The minimal optical path required by the utilized Optos device is 2 mm. Furthermore, the device's mirror-based set-up allows for a wide field of imaging (180–200°) and pupil dilation is not required. The device used in the present study had optical resolution of 3900 × 3072 pixels, equating to approximately 17–20 pixels/degree[14].

The Optos device utilizes blue (488 nm), green (532 nm), and red (635 nm) laser wavelengths, allowing for three-channel color imaging[15]. Using the Optos software, images were recorded as original images (composite filter), red-filtered images, and green-filtered images. With its wide imaging capability and use of various color filters, the Optos device has been widely applied in the diagnosis and monitoring of the vitreoretinal interface and retinal and choroidal diseases[15]. The green filter is particularly effective for visualizing superficial retinal

	Group 1 ($n=63$)	Group 2 ($n=23$)	Group 3 ($n=108$)	P
Sex, M/F	31/32	12/11	57/51	0.902[1]
Gestational age, weeks	31 ± 1.8	28.6 ± 2.90	27.70 ± 2.49	0.000[2]
Birth weight, grams	1726.5 ± 386.0	1424.5 ± 513.3	1019.2 ± 328.9	0.000[2]
Age at time of examination, years	6.66 ± 1.81	6.08 ± 2.06	5.42 ± 1.30	0.000[2]

Table 1. Demographic data. [1]Chi-square test. [2]Kruskal–Wallis test.

		Group 1 ($n=63$)	Group 2 ($n=23$)	Group 3 ($n=108$)	p
Number of PAR– eyes		61 (96.8%)	19 (82.6%)	63 (58.3%)	0.000[1]
Number of PAR + eyes		2 (3.2%)	4 (17.4%)	45 (41.7%)	
PAR+ ($n=51$)	Zone 2 PAR	1	3	31	0.000[1]
	Zone 3 PAR	1	1	14	

Table 2. PAR (persistant avascular retina) detection rates. [1]Chi-square test.

	IVB ($n=41$)	IVR ($n=23$)	IVA ($n=44$)	p
GA, weeks	27.6 ± 2.38	28.1 ± 2.30	27.4 ± 2.69	0.370[1]
BW, grams	1055.7 ± 338.1	1022.7 ± 363.6	983.4 ± 304.4	0.585[1]
Time of treatment, age in weeks	35.8 ± 2.21	37.4 ± 2.60	36.4 ± 2.65	0.090[1]
PAR– ($n=63$)	38 (92.7%)	11 (47.8%)	14 (31.8%)	0.000[2]
PAR+ ($n=45$)	3 (7.3%)	12 (52.2%)	30 (68.2%)	

Table 3. Anti-VEGF drugs and their associations with PAR. *GA* Gestasyonal age, *BW* Birth weight, *PAR* Persistant avascular retina. [1]Kruskal-Wallis test. [2]Chi-square test.

layers and retinal blood vessels[16,17]. In our study, to optimize the assessment of the peripheral retina with the green filter, the green filter setting in the software was maintained between 55% and 60%[18].

Using the Optos cSLO, images with high contrast and sharpness were obtained with reduced sensitivity to media opacities, and PAR areas were identified with the green filter without the use of fluorescein. Fundus angiography is the gold standard method for the identification and treatment of peripheral retinal changes and persistent avascular retina. However, fundus angiography was not used in our study due to the invasive of fundus angiography, allergic reactions due to flourescein, difficulty in performing especially in children and the need for anesthesia. In this study, we planned to investigate the presence of PAR after anti VEGF treatment using the green filter in wide angle imaging.

Determination of PAR

Relevant studies in the literature were reviewed for the definition of PAR. Many studies have defined PAR as the presence of avascular areas of more than 2 optic disc diameters temporally and more than 1 optic disc diameter nasally that persist beyond 60 weeks of postmenstrual age or at least 6 months after treatment[12].

Fundus images were examined and the ora serrata was identified. The vascular–avascular junction was marked using the green filter on the Optos device. If the distance between the ora serrata and the vascular–avascular junction was equivalent to 2 disc diameters, it was classified as zone 2 PAR, while an avascular area of 1 optic disc diameter was classified as zone 3 PAR (Fig. 2).

Results

The demographic data of the patients are presented in Table 1. Lower mean gestational age (GA) and birth weight (BW) were found in the group receiving anti-VEGF treatment (Group 3) and the differences were statistically significant ($p=0.000$). The mean age at the time of examination with Optos wide-angle imaging was 6.66 ± 1.81 years in Group 1, 6.08 ± 2.06 years in Group 2, and 5.42 ± 1.30 years in Group 3 (range: 4–8 years) (Table 1). PAR was detected in 2 of 64 eyes in Group 1, 4 of 23 eyes in Group 2, and 45 of 108 eyes in Group 3. Thus, PAR detection rates were 3.2%, 17.4%, and 41.7%, respectively, constituting a statistically significant difference ($p=0.000$) (Table 2).

Among the 108 eyes included in Group 3, 41 had been treated intravitreally with bevacizumab (IVB), 23 with ranibizumab (IVR), and 44 with aflibercept (IVA). When the differences between these anti-VEGF drugs were analyzed, no significant differences were found between the three drug groups in terms of BW ($p=0.370$) or GA ($p=0.585$). PAR was detected in 3 of the 41 eyes treated with IVB, 12 of the 23 eyes treated with IVR, and 30 of the 44 eyes treated with IVA. The rate of PAR after IVA treatment was 68.2% and the difference was statistically significant ($p=0.000$) (Table 3). No significant difference was found for the occurrence of PAR according to week of treatment ($p=0.090$) (Table 3).

Statistical analysis

Descriptive statistics are presented as number and percentage, mean ± standard deviation (SD), and minimum–maximum values. The Pearson chi-square test was used to analyze the relationships between categorical variables. The Kolmogorov–Smirnov test was used for the normality test. The Kruskal–Wallis test was used to analyze differences between measurement values across groups because the data did not comply with normal distribution. Values of $p < 0.05$ were considered statistically significant.

Discussion

In this study, patients who were screened and treated for ROP were compared in terms of retinal maturation and the presence of PAR in childhood. The rate of PAR was statistically significantly higher in patients treated with an anti-VEGF (Group 3), particularly in eyes treated with aflibercept compared to those treated with bevacizumab or ranibizumab. To the best of our knowledge, the comparison of different anti-VEGF therapies for type 1 ROP in terms of advanced PAR has been evaluated using the Optos confocal laser ophthalmoscope, which provides wide-angle imaging with a green filter, for the first time in this study.

Researchers have suggested that the prevalence of PAR will continue to increase due to the survival of very low-birth-weight babies, most of whom do not require treatment for retinopathy[19]. In our study, PAR was detected in 3.2% of Group 1, constituting the premature group without ROP; in 17.4% of Group 2, where ROP followed by regression was observed; and in 41.7% of Group 3, which included patients treated with anti-VEGF therapy. In a previous study investigating the prevalence of PAR in 703 eyes, Ho et al. detected PAR in 6 eyes without retinopathy and in 18 eyes after retinopathy[20]. Hanif et al. detected PAR in 36 of 43 untreated eyes from images taken at an average age of 4–8 years, finding a high rate of 91%[11]. In a study conducted by Warren et al., the rate of PAR detection in untreated eyes was 1.8%, while PAR was detected in 44% of eyes treated with IVB[21]. Cheng et al. similarly found avascular areas of 2 optic disc diameters in 34 of 154 eyes treated with IVR[22]. Alyamaç et al. found that avascular areas remained at 1 year of age in 18% of infants treated with IVB and 26% of infants treated with IVR[13]. Tahija et al. reported that approximately 55% of eyes treated with IVB failed to achieve normal retinal vascularization[23]. Roohipoor et al. found zone 3 PAR in 82.8% of eyes in the IVB (0.625 mg) treatment group at 1 year and 53.4% at 2 years after treatment[24]. Chen et al. reported that of 92 eyes treated with IVB, only 3 eyes (3.3%) reached full vascular maturity, while 39 eyes (43.8%) had PAR and 34 eyes (38.2%) had PAR plus persistent tortuosity[25]. In a study by Arámbulo et al., 12 of 85 eyes (11.6%) treated with IVR had PAR in zone 2[12]. Ling et al. found PAR rates of 0%, 33.33%, and 31.65% in the non-ROP, regressed ROP, and treated groups, respectively. There was no statistically significant difference between the regressed ROP group (33.33%) and the treated group (31.65%)[26]. According to these studies, the prevalence of PAR varies according to the drug administered, the time of the examination, and the patient's ethnicity. In our study, 3 anti-VEGF drugs were compared and the occurrence of PAR at later ages was analyzed. The rate of PAR after IVB treatment was found to be 7.3%, while it was 52.2% after IVR and 68.2% after IVA. Thus, PAR was found to be more common after treatment with aflibercept.

PAR can be observed in spontaneously regressing ROP and after anti-VEGF therapy, but it can also occur in premature children without ROP or any other pathological outcomes. In the present study, for example, PAR was found in 3.2% of Group 1, which included premature children without ROP. Based on such findings, researchers have argued that peripheral avascular retina is not always pathological and may even be a metabolically well-tolerated vascular anomaly[27]. Conversely, some studies have suggested that avascular retinas are thinner than normal retinas and this thinning may increase with axial elongation, potentially leading to atrophic retinal holes after hyaloid separation[28]. Hamad et al. found that atrophic retinal holes and retinal breaks were common in avascular peripheral retinal areas along or just anterior to the ROP line, suggesting that untreated PAR may be associated with late-onset tractional and/or exudative detachments[19]. There are conflicting opinions regarding the decision to treat PAR. Some clinicians emphasize that although vascularization may be incomplete after anti-VEGF injections, there may be no observed pathological neovascularization or complications, and such cases should be monitored[29]. Some studies suggest prophylactic treatment of PAR with peripheral photocoagulation to reduce the risk of complications such as retinal tears and tractional or exudative detachments[30,31]. Laser ablation of the avascular retina in eyes with zone 2 PAR has also been recommended, while zone 3 cases can be monitored. Treatment is especially recommended for eyes with increased peripheral vascular tortuosity, abnormal branching, and peripheral vessels at the border of the vascular and avascular areas[32]. Many studies have emphasized that fundus fluorescein angiography (FFA) should be performed when deciding on treatment and prophylactic laser photocoagulation should be considered in cases of leakage at vascular terminals[30,33]. Al-Taie et al. found leakage on FFA in 3 out of 72 eyes with PAR, and laser treatment was applied for those eyes[32]. Tahija et al. reported that vascular leakage was present in approximately half of the eyes with IVB treatment[23]. Cheng et al. found vascular leakage on FFA in 8 out of 34 eyes with PAR[22]. It is also thought that continuous low levels of VEGF production in the avascular retina with leakage may lead to reactivation and nocturnal complications[34]. Reviewing these publications, it is evident that leakage is not detected in most cases of avascular retina. Accordingly, researchers agree that leakage seen on FFA should be considered when choosing a treatment for PAR. However, the studies described here also emphasize that FFA is not available in all centers, requires anesthesia (especially in preschool children), and can cause allergic reactions to fluorescein. In our study, we used Optos wide-angle imaging because it is less invasive, can visualize 200° of the retinal area with a single acquisition, and provides a wide-angle view of the temporal quadrant. Our study has demonstrated that the avascular–vascular junction can be identified with the help of filters integrated into the Optos device. For patients with a history of prematurity, fundus imaging of the peripheral retina at later ages can be performed more practically, quickly, and without anesthesia using the Optos device. Although individualized treatment decisions can be challenging, we believe that wide-angle fundus imaging performed with an Optos filter will facilitate PAR

screening and follow-up and will likely become more widely used in the future due to its compatibility with telemedicine.

Since VEGF plays an important role in the pathogenesis of ROP, anti-VEGF therapy has recently become a common treatment[5]. Bevacizumab, the first anti-VEGF drug proposed for the treatment of ROP, is a humanized monoclonal antibody that binds VEGF isoforms[35]. Ranibizumab, a humanized recombinant monoclonal antibody with a shorter half-life and less systemic toxicity than bevacizumab, was subsequently introduced for the treatment of ROP[36]. The most recently introduced anti-VEGF drug, aflibercept, is a 115-kDa fusion protein that combines binding sites from VEGF-1, VEGF-2, and the Fc region of human immunoglobulin G1. Aflibercept binds to multiple isoforms of VEGF-A, VEGF-B, and placental growth factor (PlGF), allowing it to also capture circulating VEGFs[37]. It binds more rapidly to the VEGF receptor and remains in the eye longer, leading to faster regression of ROP and better maintenance of treatment effects[38]. Aflibercept has the potential to be the treatment of choice for patients with ROP due to longer duration of action compared to ranibizumab and less systemic VEGF suppression compared to bevacizumab[39]. With the introduction of various anti-VEGF agents, the efficacy of these drugs in the treatment of ROP, recurrence intervals, early and late complications, and refraction outcomes have been compared in many studies[40]. The effects of anti-VEGFs on the retinal vascularization process are also being investigated in light of the identification of PAR. In a study comparing ranibizumab and aflibercept, it was observed that vascularization was completed in 59.68 ± 9.91 weeks in the ranibizumab group and in 68.36 ± 7.02 weeks in the aflibercept group. The later completion of vascularization with aflibercept was attributed to the fact that aflibercept binds more VEGF and remains in the eye for a longer period of time[41]. In our study, the presence of PAR was found at a higher rate in eyes treated with aflibercept. We concur that aflibercept inhibits vascularization because it remains in the eye longer and binds to two VEGF receptors and PlGF receptors. PlGF is known to play an important role in ocular neovascularization and has been implicated in retinal fibrosis. Unlike other members of the VEGF family, PlGF release is reduced during hypoxia and shows anti-apoptotic effects during hyperoxia. PlGF deficiency was shown to reduce neovascularization, venous dilation, and arterial tortuosity in an oxygen-induced mouse model of ROP[42]. We believe that the effect of PlGF on vascularization may be responsible for the higher rate of PAR observed with aflibercept.

Among the limitations of this study, the progression of PAR could not be followed. In our study, fundus fluorescein angiography was not performed and images with artifacts in the vertical quadrant were not included. Fundus images could not be acquired with fluorescein for comparison. To obtain clearer results, studies with larger sample sizes and longer follow-up periods are needed. Additionally, research on peripheral retinal findings at advanced ages and the molecular effects of anti-VEGF drugs is necessary.

Conclusion

In conclusion, with the widespread use of anti-VEGF drugs, their long-term effects are becoming more apparent. PAR is increasingly associated with late complications. To prevent those complications, high-risk cases should be identified and monitored closely. This study has revealed differences in retinal maturation among the anti-VEGF drugs used for ROP. PAR was observed less frequently after IVB treatment and retinal maturation was completed with vascularization reaching the ora serrata in most cases. In contrast, IVA treatment was associated with a higher frequency of PAR in the avascular areas of the retina, necessitating more frequent and extended follow-up for potential late complications.

Data availability

The raw data will be provided by the corresponding author upon reasonable request.

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A.C.U. Conceptualization, A.C.U. methodology and M.A. investigation, A.C.U., M.A., and M.K.E. resources, A.C.U. and M.A. data curation, A.C.U., M.A., and M.K.E. writing—original draft preparation, A.C.U., and M.K.E. writing—review and editing, A.C.U. and M.A. supervision, M.A., and M.K.E., project administration, A.C.U. and M.A. All authors have read and agreed to the published version of the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

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