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ORIGINAL PAPER

Efficacy of intravitreal aflibercept monotherapy in retinopathy of prematurity evaluated by periodic fluorescence angiography and optical coherence tomography

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Abstract

Purpose To evaluate the efficacy of intravitreal aflibercept (IVA) in vascular and macular maturation in neonates with type 1 retinopathy of prematurity (ROP) and aggressive posterior retinopathy of prematurity (APROP).

Materials and methods Thirty-six eyes of 18 patients with type 1 ROP or APROP in zone I or posterior zone II were enrolled in our study. At baseline, only fluorescein angiography (FA) was performed. After IVA injection, both FA and optical coherence tomography (OCT) were performed after 6.8 ± 0.8 (range 6–8) and 19 ± 0.9 (range 18–20) weeks to follow vascular and macular changes.

Results Both diffuse flat neovascularization with leakage and abnormal vascular branching at the small arteriolar level were detected in all eyes (100%) at baseline FA. Regression of the disease was observed in 34 eyes (94.4%) in the first week with binocular indirect ophthalmoscopy. Early unresponsiveness in remaining two eyes of an infant required an IVA re-treatment. Late reactivation was detected only in 19.4% of eyes, none of which required treatment during 12 months of follow-up. The most common feature after IVA injection was abnormal branching at capillary level, which was noted in 100% in the first post-injection FA and 50.0% of all eyes in the second FA. Meanwhile, the end limit of vascularization was observed in zone III in 83.3% of eyes. No vascular abnormality was also detected in 27.3% of eyes. The OCT examination at a mean postmenstrual age of 43.4 weeks revealed cystoid macular changes in four eyes of two infants (11.1%), normal foveal contour in 30 eyes of 15 infants (83.3%) and matured ellipsoid zone at the foveal center in 28 eyes of 14 infants (77.8%). Macular maturation was complete in all eyes in the last OCT analyses.

Conclusion Intravitreal aflibercept monotherapy has been an effective treatment in type I ROP and APROP with much lower early and late re-treatment rates because of early unresponsiveness and late reactivation, respectively. In most of the eyes, rapid vascular outgrowth beyond zone III together with normal

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macular maturation was observed more precisely by periodic FA and OCT.

Keywords Aflibercept · Fluorescein angiography · Optical coherence tomography · Retinopathy of prematurity

Introduction

Retinopathy of prematurity (ROP) is a neovascular retinal disorder of prematurely born children, which is a leading cause for childhood blindness both in developed and developing countries [1]. The production of vascular endothelial growth factor (VEGF) plays an important role in the development of the disease [2, 3]. The production of VEGF is mainly triggered by avascular parts of the retina. Several studies have favorable outcomes with anti-VEGF monotherapy in patients with zone I and posterior zone II ROP [4–9]. Other anti-VEGF therapies such as bevacizumab [10, 11], ranibizumab [12] or pegaptanib [13] were also reported as alternative treatment options. Unlike laser therapy, anti-VEGF agents eliminate VEGF-induced neovascularization as well as preserve the avascular periphery and allow normal vascularization. Aflibercept (Eylea, Regeneron Pharmaceuticals Inc., Tarrytown, New York, USA) is the most recent anti-VEGF agent. It is a "VEGF trap," which is a recombinant fusion protein that binds VEGF-A with high affinity [14]. There are limited studies presenting results of aflibercept therapy (IVA) for the treatment of ROP [15, 16].

In the present study, we evaluated vascular and macular maturation after IVA monotherapy with fluorescein angiography (FA) and optical coherence tomography (OCT), respectively. As far as we know, it is the first study that investigates effectiveness of IVA monotherapy (re-treatment of IVA in case of early unresponsiveness) in infants with type 1 ROP or aggressive posterior retinopathy of prematurity (APROP) evaluated by periodical follow-up of both FA and OCT.

Materials and methods

This study is a retrospective study, which has been approved by the local ethical committee and attended to the tenets of the *Declaration of Helsinki*. Routine screening for the diagnosis of ROP was performed according to the guidelines reported in the literature [17] in all infants by indirect ophthalmoscopy with scleral indentation with the help of a 28 D condensing lens. Infants who were referred by neonatologists were also examined despite they are over 32 weeks of gestational age (GA), or birth weight (BW) of 1500 g. Infants who had laser treatment or any surgical procedure were excluded from the study. Moreover, infants with any ocular and/or systemic disorders that might confound the interpretation of the study results were also excluded from the study.

Intravitreal aflibercept injection

Decisions to treat infants were made according to the indications established by the Early Treatment for ROP (ETROP) Study [18]. An informed consent with regard to the off-label use of the drug, its unknown safety and efficacy for this indication was obtained from all the parents. Between June 2016 and December 2017, 36 eyes of 18 infants who had been treated with IVA were included into the study. All patients had been followed at least 12 months. Follow-up examination was performed on first day, first week and weekly thereafter until the vascular development reached zone III.

In order to increase success rate and decrease recurrence rate, IVA is preferred in our study, because it has longest half-life and most potent affinity to VEGF. All patients received half of the adult dosage of IVA, which is 1 mg/0.025 ml. The injection procedure was performed under topical anesthesia with the supervision of a neonatologist at the Neonatal Intensive Care Unit (NICU). After the adjustment of the eye speculum and the instillation of 5% povidone iodine, aflibercept was injected through the conjunctiva approximately 1.0 mm behind the superotemporal limbus by using a 30-gauge micro-needle with a 4 mm length. The intraocular pressure and central artery patency were immediately checked following the injections. Systemic conditions of the infants were continuously monitored in the NICU during pre- and post-injection periods. After the injection, the patients

received topical moxifloxacin, five times a day for 5 days. The criteria for early unresponsiveness were persistent or progressive activity of vascular changes (progressive plus disease, fibrovascular proliferation and vascular changes at the junction or posterior to the junction). Reactivation of ROP (late recurrence) was diagnosed when there are fibrovascular proliferation and/or dye leakage on FA with plus disease appeared 10–12 weeks after a post-injection period of no or low-grade vascular activity signs.

Fluorescein angiography and optical coherence tomography

Fluorescein angiography (FA) (with the RetCam III Imaging System Clarity Medical Systems, Pleasanton, CA, USA) was performed under sedation analgesia by intravenous midazolam in a dosage of 0.01 mg/kg. Optical coherence tomography was performed simultaneously by using two handheld probe spectral domain optical coherence tomography (SD OCT) systems (Envisu C2300 and R2310; Bioptigen, Inc., Durham, NC).

Fluorescein angiography and SD OCT imaging were undertaken after 6.8 ± 0.8 weeks (range 6–8; first post-injection) and 19 ± 0.9 weeks (range 18–20; second post-injection). Vascular findings of FA, summarized in Table 1, were classified according to the descriptions suggested by Lepore et al. [19]. The vascular outgrowth was determined by the ratio between DB (the distance from the center of the disk to the border of the vascularized zone) and DF (the distance from center of the disk to the fovea) [20]. The ratio of full vascularization up to the ora serrata is 4 for the nasal part and 5 for the temporal part. The ratio of DB/DF more than four temporally and more than three nasally denotes that vascularization has reached zone III.

Presence or absence of ellipsoid zone (EZ) in the foveal center, cystoid macular changes (CMCs) and epiretinal membrane was noted on the OCT examination. The SD OCT imaging parameters described in another study [21] were used to optimize image quality.

Results

The mean BW was 1297 ± 540 g (range 640–2290 g) and the mean GA at birth was 28.6 ± 3.9 weeks (range 23–35 weeks). Seven of the infants were female and 11 were male. At baseline, the diagnoses

Table 1 Classification of FA findings to describe vascular abnormalities

Location	Classification number	Definition
At the junction vascular–avascular retina	1	Dye leakage at the site of active ROP
	2	Abnormal vascular branching
	2a	At the large arteriolar level
	2b	Small arteriolar level
	2c	Precapillary level
	3	Circumferential vessel (“naked” arteriovenous shunt)
	4	Hyperfluorescent lesion (cotton wool like, vascular tuft = popcorn posterior to the ridge)
	5	Capillary tuft formation, focal dilatation of capillaries, rosary bead-like lesions inside the vessels
Inside vascularized zone	6	Areas of hypofluorescence
	7	Periarteriolar loss of capillary bed
Macula	8	Absence of FAZ
	9	Hypoperfusion
	10	Hyperfluorescence due to leakage

FA fluorescein angiography, *FAZ* foveal avascular zone

were APROP in zone I in eight eyes of four infants (22.2%), stage III+ ROP in zone I in ten eyes of five infants (27.8%), stage II+ ROP in zone I in four eyes of two infants (11.1%) and stage III+ ROP in zone II in 14 eyes of seven infants (38.9%).

Regression of the disease has occurred in 34 eyes (94.4%) in the first week of IVA injection. Other two eyes with no improvement needed an IVA re-treatment. We detected late recurrences totally in seven eyes (19.4%) as stage I ROP in three eyes, stage III ROP without plus disease in two eyes and only fluorescein leakage in two eyes (between 10 and 15 post-injection weeks); all of which regressed without treatment.

At baseline, FA showed increased vascular tortuosity and significant delay of choroidal filling in all eyes (100%). Vascular findings before and after IVA injection are summarized in Table 2. Some characteristic vascular changes are demonstrated in Figs. 1, 2, 3 and 4.

At the first OCT examination after IVA injection, CMC (Fig. 5) was detected in four eyes of two infants in whom EZ was also absent at the subfoveal area. Ellipsoid zone was absent in foveal center in other four eyes of two infants without CMCs (Fig. 6). Among these infants, foveal pit was also completely absent in two eyes of an infant and maturely formed in the other eyes. All of the eight eyes lacking EZ in the foveal center (GA of infants ranging between 23 and 28 weeks) were treated with diagnosis of zone I stage 3 ROP. Foveal center and EZ were completely formed in 28 eyes of 14 infants (77.8%) at a mean PMA of 43.4 weeks. On last OCT, normal foveal center and fully developed EZ were detected in all eyes. No CMC and ERM were detected.

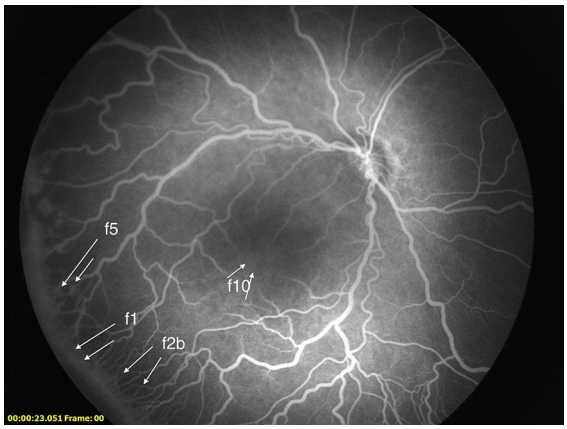

Fig. 1 Leakage of fluorescein from neovascularization at the vascular–avascular junction (f1) in an infant with a GA of 28 weeks, BW of 900 gr and diagnosis of zone I stage 3+ ROP. Abnormal vascular branching at the small arteriolar level (f2b), rosary bead-like lesions inside the vessels (f5), hyperfluorescence due to leakage in the macula (f10) before treatment

First FA examination after IVA injection showed stabilized retinal vessels and vascular growth to the periphery of the retina. The far peripheral retina did

Table 2 Percentages of FA findings at baseline and after injection according to the classification described in Table 1

Classification no.	Baseline FA		FA1		FA2	
	Number of eyes	Percentage	Number of eyes	Percentage	Number of eyes	Percentage
1	36	100.0	0	0.0	0	0.0
2a	16	44.4	0	0.0	0	0.0
2b	36	100.0	14	38.9	0	0.0
2c	2	5.6	36	100.0	18	50.0
3	0	0.0	4	11.1	14	38.9
4	20	55.6	0	0.0	0	0.0
5	28	77.8	0	0.0	0	0.0
6	22	61.1	0	0.0	0	0.0
7	20	55.6	30	83.3	6	16.7
8	12	33.3	0	0.0	0	0.0
9	2	5.6	0	0.0	0	0.0
10	10	27.8	0	0.0	0	0.0

FA fluorescein angiography, *FA1* first post-injection fluorescein angiography, FA2 second post-injection fluorescein angiography

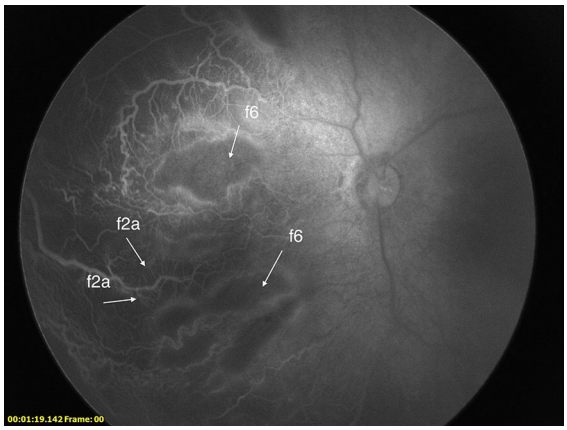

Fig. 2 In an infant with GA of 25 weeks, BW of 640 gr and diagnosis of zone 1 APROP; abnormal vascular branching at the large arteriolar level (f2a). Areas of hypofluorescence due to retinal of choroidal filling errors (f6) before treatment

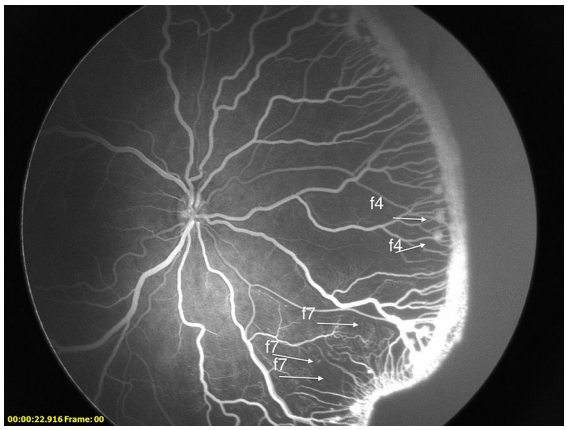

Fig. 3 In an infant with GA of 25 weeks, BW of 830 gr and diagnosis of zone I stage 3+; hyperfluorescent lesions in the form of cotton wool-like structures (f4). Periarteriolar loss of capillary bed (f7) before treatment

not fully vascularize, and a few terminal point leakages could be shown in only two eyes (5.5%). We noted abnormal vascular branching at precapillary level (class 2c, Table 1) in all eyes (100%) at the vascular–avascular junction (Fig. 4). We detected periarteriolar loss of capillary bed (class 7, Table 1) inside the vascularized zone in 83.3% of all eyes (Fig. 3). At the last FA (long term), the most common feature was abnormal branching at the capillary level (class 2c, Table 1) that was noted in 50.0% of all eyes. Also we detected circumferential vessels ("naked" arteriovenous shunt) (class 3, Table 1) (Fig. 7) by 38.9% of all eyes. By 27.3% of the eyes, there was no

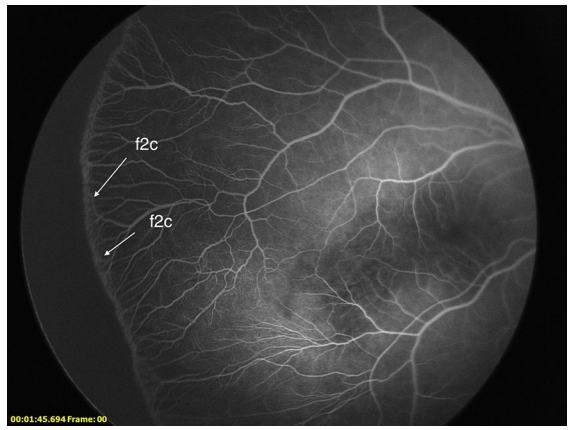

Fig. 4 Abnormal vascular branching at the precapillary level (f2c) in an infant with a GA of 23 weeks, BW of 665 gr and diagnosis of zone I stage 3+ ROP on FA 6 weeks after IVA injection

apparent vascular abnormality and the vascular end limit of 30 eyes (83.3%) was at zone III. The vascular abnormalities detected on pre-injection FA and two post-injection FAs are summarized in Table 2. Post-injection DB/DF ratios are summarized in Table 3. In the last FA, the mean DB/DF ratio was 3.5 ± 0.4 at nasal side for both right and left eyes. The mean DB/DF ratios were 4.0 ± 0.4 4.2 ± 0.4 at temporal side of right and left eyes, respectively.

Discussion

We demonstrated that regression of the disease occurred in most of the eyes after a single aflibercept injection at the end of a week in infants with type 1 ROP and APROP. Although a similar response was also reported after a single injection of IVA, therapy was shifted to laser photocoagulation in early unresponsive eyes in another study [15]. On the other hand, we treated early unresponsiveness with the same dose of IVA re-injection and finally reached 100% success rate with IVA monotherapy. Our study is the first report to use IVA re-injection, instead of laser photocoagulation, in rare early unresponsiveness of IVA injection.

We also detected adequate vascular outgrowth in 83.3% of the eyes at 19 ± 0.9 weeks after IVA. Vascular outgrowth into the periphery is an important feature, and the presence of a peripheral avascular zone of less than 2 disk diameters may be considered

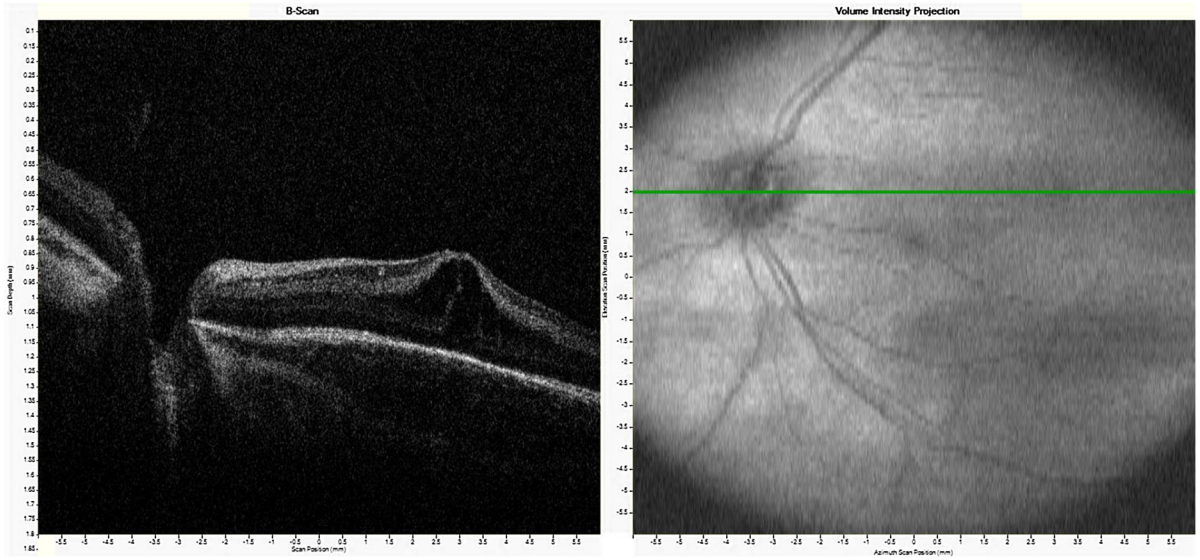

Fig. 5 Cystoid macular changes (CMCs) on OCT image of an infant with a GA of 25 weeks, BW of 845 gr and diagnosis of zone I stage 3+ ROP 7 weeks after IVA injection

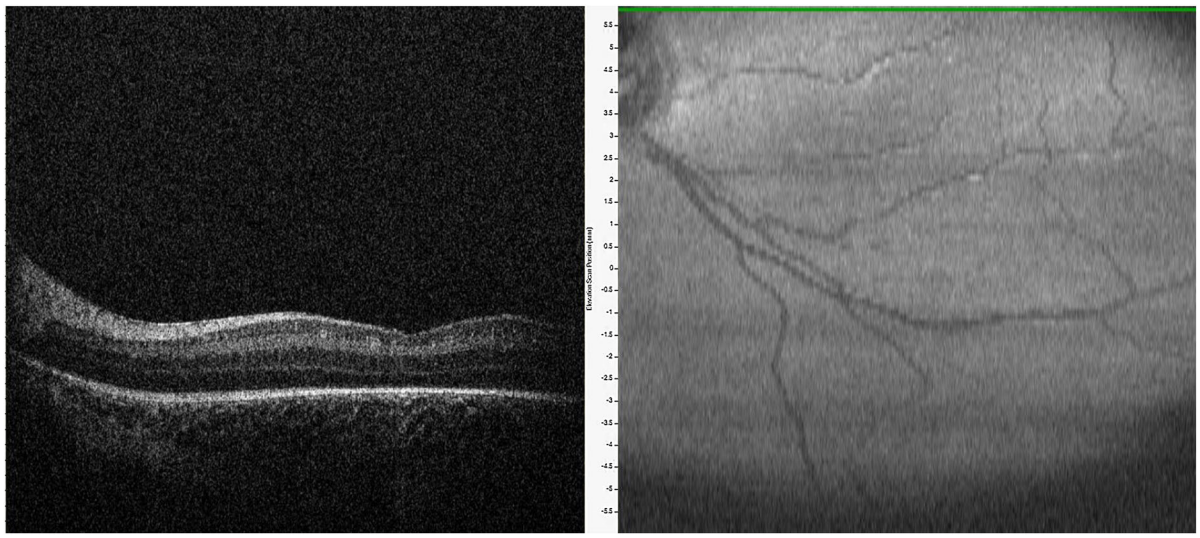

Fig. 6 Absence of Ellipsoid zone in an infant with GA of 23 weeks, BW of 663 gr and diagnosis of posterior zone II stage 3+ ROP on FA 6 weeks after IVA injection

normal in healthy infants [22]. On the other hand, Lorenz et al. [20] indicated that vascularization reached zone III after IVB (87.5% of eyes in 9–187 weeks of follow-up) is an adequate response. We periodically followed our patients with a narrow range (up to 49–60 weeks) and only kept long-term follow-up with additional FAs in six eyes of three infants with vascular ratio lower than 4 in temporal and 3 in nasal region. In contrary, we did not apply re-administration of IVA or other therapies in late reactivation unless plus disease was detected. Our finding indicates that prophylactic laser therapy for avascular area after anti-VEGF injection as reported in previous studies [23–25] could be unnecessary in most of the patients.

Early positive response of IVA in our study was similar to that of intravitreal ranibizumab [26] in another study (94.4% vs. 96.2%, respectively).

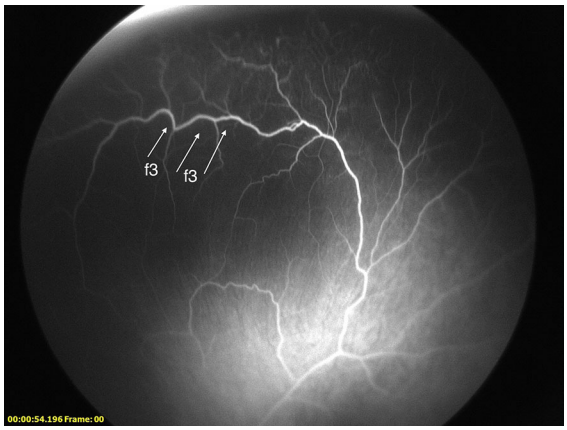

Fig. 7 Circumferential vessel (naked arteriovenous shunt) (f3) on the FA of an infant with BW of 930 gr, GA of 28 weeks and diagnosis of stage 3 ROP in zone II, 18 weeks after IVA injection

the long-term examination although it was retarded in those with increased prematurity and severity of ROP. The development of the EZ is a marker of photoreceptor development. Cystoid macular changes were associated with lower gestational age and ROP severity in previous studies [19].

Our FA findings before and after IVA treatment were similar to those of previous studies [20, 21]. On the other hand, we detected perivascular leakage only in 18.2% of all eyes (decreased to 0% in the second FA), which is much lower than a previous report of 83% [23]. This may be related to molecular characteristics of aflibercept, as previously discussed. In our analyses, communicating shunt vessels or abnormal branching at precapillary level detected between the main branching retinal vessels at the vascular–avas-

Table 3 DB/DF ratios measured in two post-injection FAs

Location of measurement	Values		
	Min.–Max.	Median	Mean ± SD
Measurement 1			
Right DB/DF temporal	2.5–4.3	3.2	3.2 ± 0.5
Right DB/DF nasal	1.7–3.7	2.6	2.7 ± 0.5
Left DB/DF temporal	2.3–4.5	3.4	3.4 ± 0.6
Left DB/DF nasal	2.1–3.5	2.9	2.8 ± 0.5
Measurement 2			
Right DB/DF temporal	2.8–4.7	4.1	4 ± 0.4
Right DB/DF nasal	2.5–3.8	3.5	3.4 ± 0.4
Left DB/DF temporal	3.4–4.8	4.2	4.2 ± 0.4
Left DB/DF nasal	2.4–4.2	3.5	3.5 ± 0.4

DB/DF distance between optic disk and border of the vascularized zone/distance between optic disk and fovea, *FA* fluorescein angiography

However, a late reactivation rate is much higher (19.4% vs. 44.9%) in the latter study [26] compared to our findings. Actually, late reactivation rate was very low in IVA monotherapy and none of them have required additional treatment during 12 months of follow-up in our patients. The reason would be longer half-life of aflibercept (7.13 days) compared to bevacizumab and ranibizumab (4.32 and 4.75 days, respectively) in the eye [27]. In addition to that, the binding affinity of aflibercept for VEGF was also greater than that of either anti-VEGF agent. As a result, we believe that better results of IVA monotherapy should probably be related to both longer duration and more potent action of aflibercept.

On OCT, we detected normal foveal contour without CMC and fully developed EZ in all eyes at

cular junction was the most common vascular feature. Baseline abnormal vascular branching at the level of large and small arterioles was improved and only seen in precapillary level in a descending order both in first and second post-injection FAs. Abnormal vascular branching at the precapillary level is also defined as the tungsten filament sign [28] or saw-toothed shunts [29] in other studies. We believe that vascular developmental changes might be misdiagnosed and unnecessarily treated as a reactivation, but indeed it is probably a course of normal vascular remodeling process of avascular retina.

In our study, periarteriolar loss of capillary bed is the feature that peaked in the first post-injection FA with 72.7% incidence and then decreased to 18.2% in the second post-injection FA. During the vascular

development, large arterials proceed toward the periphery which increases the oxygen concentration and results in capillary obliteration so periarterial extend of capillary free zone increases, which disappears after vascular remodeling completed [30]. Moreover, we detected circumferential vessels ("naked" arteriovenous shunt) in 38.9% of all eyes in the second post-injection FA and regarded them as a normal vascular structure because circumferential vessels have already been detected over half of normal infants in another study [22].

Conclusion

Intravitreal aflibercept injection allows safe and effective treatment of ROP with appropriate vascular development, higher early response and lower late reactivation rates. Adequate vascular outgrowth that means reaching zone III could be achieved in most of the infants after IVA injection. The process of macular maturation was not significantly delayed because of IVA and/or disease itself as it had been confirmed with a periodical OCT analyses. Even if late reactivation develops very rarely, we think that its re-treatment is not necessary as long as plus disease develops, which could easily be diagnosed with binocular indirect ophthalmoscopy.

Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest.

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