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Favorable outcomes of adequate laser photocoagulation and salvage bevacizumab treatment for aggressive posterior retinopathy of prematurity

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ABSTRACT

Purpose: To evaluate the effect of salvage therapy with bevacizumab after laser photocoagulation for infants with recurrence of zone I aggressive-posterior retinopathy of prematurity (AP-ROP).
Methods: This was a retrospective case series documenting the 2-year outcomes of 8 patients diagnosed with zone I AP-ROP and treated with bevacizumab for recurrence after laser photocoagulation. Prior to intravitreal bevacizumab, additional laser treatment was performed when any skip areas on the avascular retina remained. Anatomical and functional outcomes were evaluated.
Results: The median gestational age at birth was 23.7 weeks and the median birth weight was 541.5 g. The median time of initial laser treatment and intravitreal bevacizumab treatment were 32.1 weeks and 36.7 weeks' postmenstrual age, respectively. All 14 eyes developed a normal macular appearance and all 8 patients had visual responses. Visual acuity was measurable in 13 eyes (92%) between the chronological ages of 12–24 months.
Conclusions: and Importance: Adequate laser treatment and salvage intravitreal bevacizumab achieved favorable anatomical and functional outcomes in AP-ROP patients with recurrence.

1. Introduction

Retinopathy of prematurity (ROP) is a developmental vascular disorder characterized by disoriented growth of retinal blood vessels in the incompletely vascularized retina of premature infants.[1] Though advances in neonatal care and ROP management have led to better visual outcomes compared with earlier studies[2,3], ROP is still a leading cause of blindness in childhood worldwide.[4] The major risk factors for the development of ROP are premature birth and low birth weight.[5] In Japan, advances in neonatal care have reduced the mortality rate in neonates born at < 25 weeks' gestation compared with that of other countries, whereas the mortality rate in infants born at > 28 weeks' gestation was similar to that of other countries. Therefore, the incidence of severe ROP occurs in > 10% of very low birth weight infants in Japan.[6–8]

Aggressive posterior retinopathy of prematurity (AP-ROP) is regarded as a subtype with a poor prognosis in significantly premature infants with low birth weight (< 750 g) and low gestational age (GA) (< 26 weeks).[9] Because AP-ROP may not pass through the typical stage of disease, but rather progresses rapidly to retinal detachment, it should be treated without delay upon diagnosis.[10] Laser treatment for AP-ROP is unsatisfactory to achieve anatomical success in all cases.[9] To overcome the issue that some patients still develop retinal detachment despite laser photocoagulation, the suppression of vascular endothelial growth factor (VEGF) in the eye has been attempted as a new therapeutic approach. Recent studies indicated that anti-VEGF agents not only led to the regression of abnormal retinal vessels, but also facilitated the development of normal retinal blood vessels.[11] Based on these insights, anti-VEGF agents currently tend to be applied as first-line therapy.[12]

The administration of anti-VEGF drugs to infants, however, raises other challenges. Treatment with ROP and anti-VEGF agents can cause delayed retinal vessel extension, persistent ischemia in the peripheral retina and disease recurrence with proliferative responses. Furthermore, based on accumulating knowledge and experience, there are concerns that intravitreal bevacizumab also affects systemic neurological development.[13] This is especially true for infants with AP-ROP, who are at a more immature stage when anti-VEGF agents are applied as first-line therapy because the timing for initial AP-ROP treatment is usually earlier than for other type 1 ROP.[14] Considering the

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unknown systemic side effects of anti-VEGF agents, it might be safer to determine whether a combined therapy of complete laser photocoagulation for first-line therapy and then anti-VEGF agents for salvage therapy is an optimal treatment option equivalent to anti-VEGF monotherapy in extremely low birth weight infants (< 1000 g BW) with AP-ROP.

Adequate laser treatment can suspend the use of anti-VEGF agents until disease recurrence, and infants can grow during that time. The purpose of this study was to evaluate the outcome of adequate laser treatment by one or more sessions and subsequent intravitreal bevacizumab injection as salvage therapy for eyes with recurrence in infants with AR-ROP.

2. Materials and methods

2.1. Study design and subjects

This was a retrospective, institutional case series. Eight consecutive patients diagnosed with AP-ROP disease and treated with bevacizumab for recurrence after laser treatment between January 2013 and June 2015 were included. All patients completed at least 2-year follow-up visits. The patient's caregivers signed a consent form before the injection of intravitreal bevacizumab in an off-label use. A single ophthalmologist (Y.F.) performed all the laser photocoagulation and the intravitreal injections. The study adhered to the tenets of the Declaration of Helsinki (1964). The Ethical Review Board of the Osaka Women's and Children's Hospital approved the study.

2.2. Screening and classification

Patients were screened for ROP using monocular indirect ophthalmoscopy if they were born at a gestational age (GA) < 33 weeks or with a birth weight (BW) ≤ 1800 g or if they were determined to be at high risk by a neonatologist. The first fundus examination was performed at 29 or 30 weeks of postmenstrual age (PMA) or at 3 weeks of chronologic age, whichever was later. Follow-up examinations were scheduled more than once a week if vascular extension was present within zone I or posterior zone II. We diagnosed AP-ROP according to the International Classification of Retinopathy of Prematurity revisited.[10] AP-ROP disease was distinguished from other type 1 ROP by its posterior location, prominent plus disease, flat neovascularization, and arteriovenous shunt vessels.

2.3. Treatment

Based on the Early Treatment of Retinopathy of Prematurity guidelines[3] we treated patients immediately when the disease reached AP-ROP. Laser photocoagulation therapy with a 532 nm green-light Diode Pumped Solid State laser (Novus Spectra®, Lumenis, Tokyo, Japan) delivered through an indirect ophthalmoscopic system) was performed for the initial treatment. The laser was applied to the avascular retina and 2–3 rows posterior to the vascular extending edge in a nearly confluent pattern. All patients received laser treatment in an operating room under general anesthesia. Patients were re-examined the next day and then twice a week for a month followed by every week for a month to monitor their ROP status until additional treatment was given. ROP recurrence was determined as disease reactivation with plus disease and extraretinal fibrovascular proliferation toward retinal detachment. When disease recurred, a second course of laser treatment was added if any skip areas on the avascular retina were present. Intravitreal bevacizumab injection was subsequently administered as salvage therapy.

A 0.5 mg dose of bevacizumab in 0.02 ml was administered for cases where only one required treatment, and 0.25 mg in 0.01 ml for cases where both eyes required treatment.[15] Intravitreous injection techniques were as follows: topical anesthesia, sterile gloves, sterilization with povidone-iodine, insertion of a lid speculum, instillation of topical povidone-iodine, injection of bevacizumab with a sterile 30-gauge needle at 1.0 mm posterior to the limbus, and instillation of topical levofloxacin. If the other eye was to be treated, all new equipment was used. The bevacizumab injection procedure without laser treatment was performed in the NICU. Topical levofloxacin was administered for 5 consecutive days. Initial assessment was the day after the injection and then twice a week to every week for 2 months, at which point the acute-phase weekly follow-up for ROP was terminated.[16] Fundus photography before laser treatment and before and after IBV were taken with a RetCam (Clarity Medical Systems, Pleasanton, California, USA).

2.4. Data collection and analysis

The following data were recorded: gender, GA, BW, Apgar score at 1 and 5 min, general health conditions, type of ROP, PMA at treatment, and local or systemic adverse effects. The patients were evaluated for clinical course, treatment interventions, anatomical outcomes, visual response outcomes and visual acuity by Teller acuity cards. Given the small sample size and data that were normally distributed, continuous variables were expressed as the median with range.

3. Results

Fourteen eyes of 8 patients were included in this study. Table 1 summarizes the demographic and clinical characteristics of the patients, and Table 2 summarizes the treatment data for this study. The medians of GA and BW were 23.7 weeks (range, 22.5–24.5 weeks) and 541 g (range, 498–740), respectively. Three patients (37.5%) were male. All patients were initially treated with laser treatment for bilateral zone I AP-ROP. The median PMA of the initial treatment, when the patients were diagnosed and treated as zone I AP-ROP, was 32.1 weeks (range, 30.0–32.5 weeks). Six patients had recurrence in both eyes, and two had with recurrence in one left eye. The median PMA of recurrence was 36.3 weeks (range, 33.3–38.6 weeks). Proliferative tissue at initial treatment was located at the nasal retina in 11 eyes, whereas at recurrence it was present at the temporal retina in 13 eyes. Although discontinuous flat neovascularization completely regressed after initial laser treatment, continuous neovascularized membrane was newly formed at recurrence in all eyes. All 14 eyes received intravitreal bevacizumab injection once as salvage therapy. Of 14 eyes, 7 eyes required additional laser photocoagulation on the skip areas. The median PMA of bevacizumab injection was 36.7 weeks (range, 33.3–41.1 weeks). In all 14 eyes, a regression of ROP recurrence was observed after intravitreal bevacizumab. Although only one eye progressed slowly to stage 4A ROP despite ROP regression, localized fibrotic tissue

Table 1
Patient demographics and characteristics.

No. of patients	8
No. of eyes	14
Birth weight, median (range)	541.5 (498–740)
Gestational age, median (range)	23.7 (22.7–24.7)
Male gender, no. (%)	3 (37.5)
Apgar score, median (range)	
1 Minute	3.5 (1–6)
5 Minute	6 (1–8)
Intraventricular hemorrhage, no. (%)	
0	3 (37.5)
1-2	3 (37.5)
3-4	2 (25)
Periventricular leukomalacia, no. (%)	0 (0)
Respiratory distress syndrome, no. (%)	6 (75)
Chronic lung disease, no. (%)	8 (100)
Patent ductus arteriosus (%)	0 (0)
Sepsis, no. (%)	2 (25)
Necrotizing enterocolitis, no. (%)	0 (0)
Focal intestinal perforation, no. (%)	3 (37.5)

Table 2
Timing of treatments and anatomical outcome.

PMA at initial treatment, median (range)	32.1 (30–32.5)
PMA at IVB, median (range)	36.7 (33.3–41.1)
Interval from initial treatment to recurrence (wks)	4.25 (1–7)
Number of laser treatment, no. (%)	
1	7 (50)
2	7 (50)
PMA of last treatment, median (range)	37.1 (33.3–43.6)
Anatomical outcome, no. (%)	
Normal macula	14 (100)
Retinal fold	0 (0)
Disc dragging	0 (0)
Retinal detachment	0 (0)
Visual response	
Positive	100 (100)
Negative	0 (0)

PMA, postmenstrual age; IVB, intravitreal bevacizumab injection; wks, weeks.

at the temporal initial ridge was removed by lens-sparing vitrectomy and consequently the retina was reattached. The eye finally developed a normal macula appearance. The median PMA of the last treatment including vitrectomy was 37.1 weeks (range, 33.3–43.6 weeks). The clinical characteristics of individuals are summarized in Table 3. Details of ocular findings and laser treatment at initial treatment and recurrence are shown in Table 4.

All 14 eyes reached a favorable outcome without macular dragging, retinal fold, or retinal detachment during the 2-year follow-up period. A visual response was obtained in 14 eyes. Monocular visual acuity was measurable for 13 of 14 eyes (92.8%) at the chronological age of 12–24 months and was at least better than 20/1400 in eyes with measurable visual acuity (Table 3).

No serious ocular complications or systemic adverse events associated with intravitreal bevacizumab or systemic adverse events subsequent to intravitreal bevacizumab were observed in this case series.

4. Case report (Case 4)

A female infant was 23 weeks of age and weighed 500 g at birth. She had bilateral zone I AP-ROP with plus disease in all 4 quadrants and flat neovascularization at 32 weeks' PMA, and was treated immediately with laser photocoagulation (Fig. 1A and B). One week later, ROP had regressed gradually in both eyes. Four weeks after the initial treatment, the disease recurred with increasing vessel dilation and tortuosity, and extending extraretinal fibrovascular proliferation was observed in her right eye, which was treated with intravitreal bevacizumab injection (Fig. 1C). Five days later, when ROP recurrence had manifested in the

Table 3
Summary of patient characteristics.

	Case/Eyes/Gender/Eye	GA (wks)	BW (g)	PMA at Laser	PMA at IVB	Additional Laser	RD	Surgery	Final Retinal Attachment	Visual response	Visual acuity
1	1/1/M/R	23	588	32	37	–	–	NA	Yes	Positive	20/670
2	1/1/M/L	23	588	32	38	–	–	NA	Yes	Positive	20/1400
3	2/1/F/R	23	544	31	40	+	+	LSV	Yes	Positive	unmeasurable
4	2/2/F/L	23	544	31	41	+	–	NA	Yes	Positive	20/1000
5	3/1/M/R	23	740	32	36	+	–	NA	Yes	Positive	20/1000
6	3/2/M/L	23	740	32	36	+	–	NA	Yes	Positive	20/1400
7	4/1/F/R	23	500	32	36	+	–	NA	Yes	Positive	20/380
8	4/2/F/L	23	500	32	37	+	–	NA	Yes	Positive	20/380
9	5/1/F/R	24	539	32	37	+	–	NA	Yes	Positive	20/380
10	6/1/F/L	24	652	32	33	–	–	NA	Yes	Positive	20/260
11	7/1/F/R	22	518	30	35	–	–	NA	Yes	Positive	20/710
12	7/2/F/L	22	518	30	34	–	–	NA	Yes	Positive	20/710
13	8/1/M/R	23	498	30	36	–	–	NA	Yes	Positive	20/470
14	8/1//F/L	23	498	30	37	–	–	NA	Yes	Positive	20/380

M, male; F, female; R, right eye; L, left eye; GA, gestational age; wks, weeks; BW, birth weight; PMA, postmenstrual age; IVB, intravitreal bevacizumab injection; RD, retinal detachment; NA, not applicable; LSV, lens-sparing vitrectomy.

Table 4
Details of individual ocular findings and laser treatment.

	Case/Eyes/Gender/Eye	Initial FP	Initial Laser (shots)	Recurrence FP	Add Laser (shots)	Total Laser (shots)
		Location, Char of NV, Clock hours		Location/Char of NV/ Clock hours		
1	1/1/M/R	Nasal, D, < 3	1695	Temporal, C, < 3	–	1685
2	1/1/M/L	Nasal, D, < 3	1728	Temporal, C, < 3	–	1728
3	2/1/F/R	Temporal, D, < 3	1456	Temporal, C, < 3	682	2138
4	2/2/F/L	Temporal, D, < 3	1456	Temporal, D, < 3	547	2003
5	3/1/M/R	Nasal, D, < 3	1626	Temporal, C, > 3	796	2422
6	3/2/M/L	Nasal, D, < 3	1238	Temporal, C, < 3	414	1652
7	4/1/F/R	Nasal, D, < 3	1664	Whole circumference, D, > 6	809	2473
8	4/2/F/L	Nasal, D, < 3	1198	Upper Temporal, C, > 3	578	1776
9	5/1/F/R	Upper Nasal, D, < 3	1582	Temporal, C, < 3	1417	2999
10	6/1/F/L	Whole circumference, D, < 6	1814	Temporal, C, < 3	–	1814
11	7/1/F/R	Nasal, D, < 3	1947	Temporal, C, < 3	–	1947
12	7/2/F/L	Nasal, D, < 3	1654	Temporal, C, < 3	–	1654
13	8/1/M/R	Nasal, D, < 3	1084	Temporal, C, < 3	–	1084
14	8/1//F/L	Nasal, D, < 3	1181	Temporal, C, < 3	–	1181

M, male; F, female; R, right eye; L, left eye; Initial FP, fibrovascular membrane at initial treatment; Char of NV, characteristics of neovascularization; D, discontinuous flat neovascularized membrane; C, Continuous neovascularized membrane; Recurrence FP, fibrovascular membrane at recurrence treatment; Add laser, additional laser.

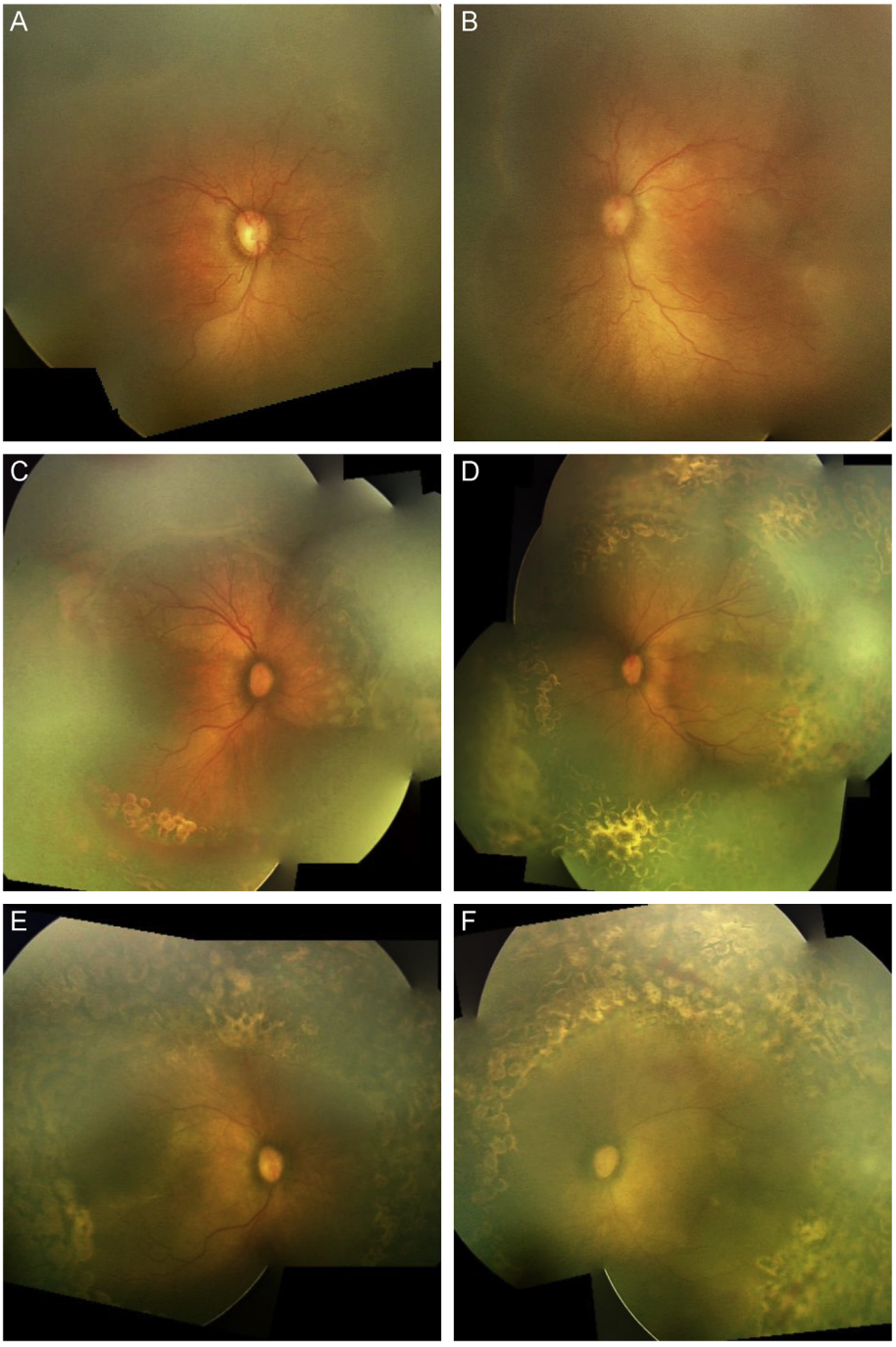

Fig. 1. Fundus images of the right (A, C, and D) and left (B, D, and E) eyes in patient 4. **A** and **B,** Images obtained just before initial laser treatment at 32 weeks' CGA. Plus disease and nasal flat neovascularization are shown. **C** and **D**, Montage images showing disease recurrence at 36 weeks' CGA (C) and 37 weeks' CGA (D). Small isolated tufts in the vascularized area and extraretinal proliferation in a circumferential manner are shown. Laser scarring on the peripheral retina is not shown because of poor mydriasis in the right eye (C). Sporadic skip area in the left eye (D). **E** and **F**, Complete regression of extraretinal proliferation at 2 weeks after additional laser and intravitreal bevacizumab.

left eye, additional laser treatment was performed on the skip area in both eyes and intravitreal bevacizumab injection was administered to the left eye (Fig. 1D). Both eyes were successfully treated and reached complete regression (Fig. 1E and F).

5. Discussion

AP-ROP is ROP subtype characterized by rapid progression rather than by a sequence of disease stages.[10] AP-ROP had a poor prognosis with retinal detachment compared with classic ROP despite early laser photocoagulation therapy.[9,10,14,17] Based on previous reports with good anatomical results by multiple sessions of laser photocoagulation for zone I type 1 ROP including AP-ROP[18] we selected an salvage bevacizumab injection after adequate laser photocoagulation at disease recurrence of AP-ROP, which led to favorable outcomes in all eyes. In this report, the disease recurrence might have been related to whether laser ablation of the technically challenging temporal wedge was confluent, because for most cases the fibrovascular membrane was recognized in the temporal retina at recurrence. Even in cases where the skip area was left, we successfully managed to induce the recurrence of AP-ROP using this strategy.

To date, there has been no case series limited to patients with the recurrence of AP-ROP by salvage therapy. Previous case reports including salvage therapy for AP-ROP patients showed anatomical outcomes with unfavorable results ranging from 16% to 83%, such as macula dragging and retinal detachment,[19–21] while few reports have demonstrated visual acuity as a functional outcome. Our study has an advantage over previous studies as it demonstrated both anatomical and functional outcomes.

For the last decade, the use of anti-VEGF agents has significantly

increased because of their dramatic regressive effects on vascular proliferative responses in ROP.[11,12] Treatment options for ROP consist of laser photocoagulation, anti-VEGF agents, or a combination of both. Currently, the optimal treatment strategy is still controversial. However, the emphasis on initial therapy has shifted from laser photocoagulation to anti-VEGF agents such as bevacizumab and ranibizumab.

Anti-VEGF agent monotherapy, unlike laser treatment, causes the regression of extra-retinal proliferation and induction of intra-retinal angiogenesis without retinal tissue scarring.[11,12] In contrast to the increased efficacy of anti-VEGF agents against disease activity, late recurrence and vascular extension delay, termed 'chronic vascular arrest' after anti-VEGF agent administration has become a newly emerging issue.[22] The incidence and timing of late recurrence was recently reported to be 8.3% and 49.3 weeks' PMA, respectively, in infants who received intravitreal bevacizumab monotherapy.[23] Of note, infants with AP-ROP are at high risk of recurrent disease and it is necessary to examine them every 1–3 weeks from at least 65 weeks' PMA.[23] Surprisingly, the persistence of vascular arrest was observed up to 108 weeks' PMA in one case.[22]

From recent studies of recurrence and delayed angiogenesis, infants treated with anti-VEGF agents for first line therapy require frequent follow-up examinations for a longer period than those treated with laser treatment. Therefore, there are concerns about the burden on caregivers because of repeated visits over a long period.[24] A 100% follow-up rate is desirable but has rarely been achieved in real clinical settings.[25] Follow-up studies reported a dropout rate of 0–30% at 18-to-24 months of age.[26] In this report, no further treatment was required over 43 weeks' PMA, which substantially coincides with the timing of hospital discharge.[27] Thus, laser photocoagulation is of benefit for infants who are at high risk of being lost to follow-up.

Another concern is neurological development in very immature infants treated initially with anti-VEGF agents. In the immature human brain, periventricular leukomalacia (PVL) is the predominant white matter injury underlying the development of cerebral palsy and it is associated with a poor neurological outcome.[28] PVL frequency and severity are associated with the degree of prematurity. PVL has its peak incidence during a well-defined period of human brain development (23–32 weeks' PMA).[28] In our study, 8 patients received intravitreal bevacizumab at PMA ranging from 33 to 41 weeks and no patients had PVL. However, it should be noted that 8 patients were treated initially at PMA ranging from 30 to 32 weeks in this report. Other studies have also reported infants with ROP treated by 32 weeks' PMA.[9,23,29] In a patient with ROP who received 0.625 mg of bevacizumab by intravitreal injection, bevacizumab appeared transiently in the systemic circulation from the day after its administration and remained detectable at least for 8 weeks.[30] If the amount of ocular bevacizumab absorbed systemically is fixed when the drug is administrated in an equivalent amount, then the theoretical systemic bevacizumab concentration will be higher in a smaller weight infant. To avoid the potential risk of VEGF suppression at early developmental stages, we believe that clinicians should consider the treatment option of initial laser photocoagulation rather than monotherapy or combined therapy.

The ultimate purpose of ROP treatment is to restore visual function in infants with ROP as well as those without ROP. Preterm birth was reported to affect visual development in infants even without ROP, which is associated with ocular and neurological problems.[31] Although the cause of reduced visual acuity in preterm infants does not distinguish between delay in neurological development and ocular condition, our results demonstrated that all infants acquired at least cognitive ability and monocular measurable acuity by the age of 2 years.

Limitations in this case series included its retrospective nature, small sample size, and the lack of a control group that did not receive intravitreal bevacizumab treatment at recurrence. Intravitreal bevacizumab monotherapy is a very effective treatment for ROP; however, our study provided satisfactory treatment results even when laser photocoagulation was initially performed in very immature infants with severe ROP.

6. Conclusion

In conclusion, adequate laser treatment and salvage IVB achieved anatomical success in all cases with zone I AP-ROP. This treatment strategy may be a reasonable option in infants to whom anti-VEGF drug cannot be administered in terms of their systemic condition including growth, health and development, or social factors.

Patient consent

Patient consent was not obtained as all identifying patient information has been removed.

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Conflicts of interest

None. The authors have no financial disclosures.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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