



## Sequential Short Interval Anti-VEGF for the Treatment of Stage 4 ROP

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### Abstract

**Purpose:** This case describes a unique case of an infant referred with stage 4A retinopathy of prematurity (ROP) and plus disease that was successfully controlled with intravitreal injections of bevacizumab.

**Methods:** Case report.

**Results:** A 23 months-old-age female born at 23 weeks gestational age with a birth weight of 453 grams and retinopathy of prematurity (ROP) Stage 4A in 360 degrees and plus disease in both eyes treated in another institution with laser, complicated with two cardiac arrests during the procedure.

The patient was referred and treated at 31 weeks with repeated intravitreal bevacizumab injection in both eyes secondary to a progressive ROP.

Treatment with multiple anti-VEGF therapy as monotherapy led to resolution of a retinal detachment (RD) and full vascularization of the retina in both eyes

**Conclusion:** To the best of the authors' knowledge, this is the first description of a patient with stage 4A ROP treated solely with anti-VEGF after failed laser treatment that led to complete resolution of an RD without surgical intervention.

**Keywords:** Retinopathy of Prematurity; Stage 4A; Plus Disease; Laser; Cardiac Arrest; Intravitreal Injection; Anti VEGF

### Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative disease affecting premature and low- birthweight infants [1]. Characterized by aberrant angiogenesis, peripheral retinal ischemia and fibrovascular proliferation. ROP remains one of the leading causes of childhood blindness in the world. Recent literature suggests that it accounts for 14% of childhood blindness within the United States and greater than 20% in developing countries [2].

The standard of treatment used to be laser photocoagulation, now it has shifted to anti-VEGF especially for Type 1 ROP. Treatment used to involve peripheral retinal ablation (cryotherapy or laser photocoagulation) destroying the peripheral retina and leading to visual field defects. Anti-VEGF therapy is nondestructive and allows for vascular growth. For advanced stages of retinal detachment scleral buckling and vitrectomy are the standard of care [3,4].

This case describes an infant that presented with bilateral stage 4A ROP and plus disease due to her extreme prematurity of 23 weeks. During laser photocoagulation at the referring facility the baby experienced two cardiac arrests. She was referred for treatment after ROP progression despite laser treatment. She was treated with repeated intravitreal bevacizumab (IVB) injections in both eyes as monotherapy at the bedside with local anesthesia.

Repeated IVB injections were effective in decreasing the neovascular activity and causing spontaneous retinal reattachment. To the best of the authors' knowledge, this is the only reported case of bilateral stage 4A ROP plus disease treated with repeated IVB injections as monotherapy for progressive ROP. This case supports the safety and effectiveness of IVB for stage 4A ROP with plus disease.

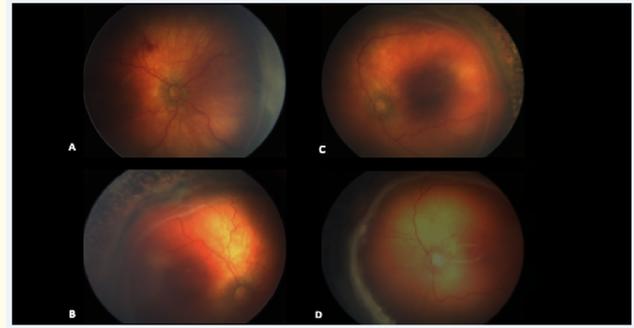
### Case Report

A 23-month-old female, born at 23 weeks gestational age (GA) and 453 grams, was diagnosed with retinopathy of prematurity (ROP) stage 4A with 360 degrees involvement in both eyes (OU). Both her parents and siblings were all noted to have normal visual development without any family history of ocular diseases. As a neonate, she had spent six months in intensive care, where she received supplemental oxygenation for bronchopulmonary dysplasia, patent ductus arteriosus and intraventricular hemorrhage grade 2, in addition to inguinal hernia repair.

The patient received 360° laser ablation therapy OU at 29 weeks GA at another hospital. During her laser treatment, the patient experienced two cardiac arrests. She was successfully resuscitated. However, she developed a permanent cerebral compromise with developmental delay, and her ROP still progressed. She was referred to our clinic for nystagmus and progressive retinal detachment OU at 31 weeks GA.

Clinical examination showed a normal anterior segment in both eyes. The fundoscopic examination of the posterior pole revealed attached macula, arterial tortuosity and venous dilation of the posterior vessels. In the retinal periphery, there was a ridge with subretinal fluid 360 degrees (Figure 1A-1D). The patient had a bilateral Stage 4A ROP and plus disease with asymmetric involvement, more prominent in the right eye (OD) than in the left eye (OS). The patient then received an intravitreal bevacizumab injection (Avastin®, Genentech, California, USA) 1.25 mg/0.05 ml OU. One week

after the first injection, the height of the RD decreased, but there was no improvement in the vessels' tortuosity OU. Subsequently, the patient received one week later a second intravitreal bevacizumab 1.25 mg /0.05 ml OU.

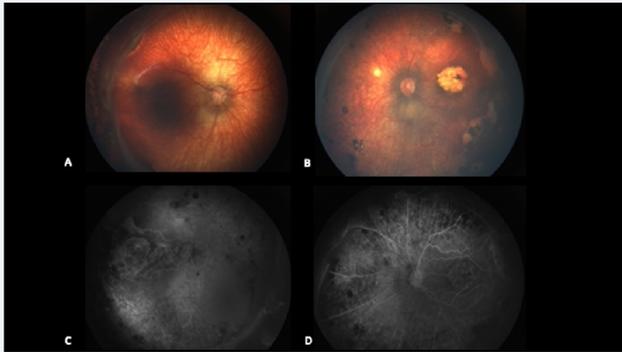


**Figure 1:** Color fundus photographs before treatment with intravitreal injections. A Fundus photographs of the right eye before treatment showed arterial tortuosity and venous dilation of the posterior vessels with a hemorrhage in the superior temporal retina, there was a ridge with subretinal fluid 360 degrees in the peripheral retina. B ridge with subretinal fluid and retinal detachment with an attached macula, 360° degrees laser in the peripheral retina of the right eye. C&D Fundus photographs of the left eye before treatment with arterial and venous tortuosity less prominent than in the right eye with ridge and subretinal fluid 360° degrees more prominent in the nasal area, 360° degrees laser in the peripheral retina.

The patient underwent regular clinical evaluations, where there was improvement of the retinal detachment. During the clinical evaluations there was recurrence of plus disease during injections. These were treated with anti-VEGF. Over the course of treatment, the patient received 5 intravitreal bevacizumab treatments in both eyes. The fibrotic traction of the vitreous resolved, the retinal detachment regressed OU and the patient did not require any further intervention. During this time, there was not any adverse events during her NICU stay.

Fifteen months after the last injection, the retina remained attached and fully vascularized OU (Figure 2A-2D). The patient did

not need any additional surgical intervention. The patient remains stable, with developmental delay and a refractive error of  $-3.00 = +3.00 \times 90^\circ$  OD,  $-2.50$  OS.



**Figure 2:** Color fundus photographs after treatment with intravitreal injections. A Fundus photographs of the right eye after treatment revealed a fully attached retina, without plus disease, with a fibrotic ridge without traction in the peripheral retina and laser. B macular atrophy with an attached retina and fully vascularized with a fibrotic ridge without traction with  $360^\circ$  laser. C Late-phase fluorescein angiography after treatment showed staining in the macula without leakage or active disease with  $360^\circ$  hypofluorescence secondary to laser. D Late-phase fluorescein angiography after treatment of the left eye revealed staining in the macula with a fully vascularized retina and hypofluorescence in the periphery secondary to laser treatment.

## Discussion and Conclusion

Retinopathy of prematurity (ROP) is a vasoproliferative illness in which there is abnormal vessel growth, which can lead to blindness. The pathogenesis of retinopathy of prematurity involves two phases: phase 1 occurs from 22 to 30 weeks postmenstrual age and involves relative hyperoxia and decreased VEGF levels, whereas phase 2 occurs from 31 to 44 weeks postmenstrual age and involves relative hypoxia and increased VEGF levels [4].

ROP blindness is preventable with early screening and early detection of progression to threshold. The American Academy of Pediatrics recommends that all infants with a birth weight of  $\leq 1500$ g

or a gestational age of 30 weeks or less should be screened for ROP. Risk factors of ROP include extended oxygen therapy and high oxygen concentrations used for infants with respiratory difficulties, low gestational age and birthweight, and associated medical conditions/treatments [5].

The National Eye Institute funded a cooperative agreement to study early treatment for ROP (ETROP). In the study, prethreshold ROP was defined as any ROP in zone I that was less than threshold; or in zone II stage 2 with plus disease (dilation and tortuosity of posterior pole retinal vessels in at least two quadrants); or zone II, stage 3 disease without plus disease; or zone II, stage 3 with plus disease but fewer than five contiguous or eight cumulative clock hours [3,5].

The conventional treatment for threshold/high-risk pre-threshold ROP is laser photocoagulation which eliminates peripheral retinal cells producing vascular endothelial growth factor (VEGF). Cardiorespiratory arrest can occur in up to 5% of infants treated with laser [7]. Anti-VEGFs have recently been used as another first-line treatment for ROP without causing cardiac arrest [6].

The main goal when treating stage 4A ROP is to prevent further progression into stage 4B or stage 5 through timely treatment. Intervention should begin when retinal detachment has just developed and vascular activity has decreased, most often between 30- and 58-weeks PMA. The main treatment of stage 4A ROP involves lens-sparing vitrectomy (LSV) with a success rate of about 90%. However, there are many associated complications with LSV, such as pre-retinal hemorrhage, glaucoma, cataract, and vitreous hemorrhage [6-8].

The use of anti-VEGFs as monotherapy for stage 4A ROP has not been common. This form of treatment is mainly used in combination with surgical management to treat stage 4A ROP [6,7]. One study showed that surgical management was needed in 4 out of 6 eyes with stage 4A ROP treated with bevacizumab as monotherapy [8]. Another study showed that surgical intervention was necessary in 8 out of 18 eyes with stage 4A ROP treated with laser therapy [9].

This case is unique because to our knowledge this is the first time that sequential treatment with anti-VEGF leads to complete

resolution of stage 4A ROP. In the literature we can find surgical intervention for stage 4 ROP such as scleral buckling, vitrectomy, or anti-VEGF treatment combined with vitrectomy have been used as treatments [8,10-12]. Ells, *et al.* reported a case series of additional laser treatment posterior to the neovascular ridge with rapid regression of the ridge in stage 4A with this technique [8].

Different to this case report, where the used of bevacizumab as monotherapy without sequential injections [13], the associated complications [4,14,15], or the lack of plus disease [4,16]. The recurrence of plus disease during injections, may explain why only one injection of anti-VEGF or more laser treatment are not sufficient for the management of progressed ROP. Further studies with a larger cohort are needed to validate IVB treatment as monotherapy for the severe form of ROP particularly in instances where surgical management cannot be used as first-line therapy.

This case is also unique because of the effectiveness of bevacizumab for stage 4A ROP with involvement of 360 degrees. Sukgen, *et al.* suggested that for ROP of stage 4A wider than 6 clock hours, non-surgery regression of the disease is difficult. However, for our case, the patient had stage 4A ROP with involvement of 360 degrees, wider than 6 hours. Therefore, our case supports the non-surgical treatment of stage 4A ROP with involvement wider than 6 hours [9].

Finally, this case also demonstrates the merits of bevacizumab versus laser photocoagulation for stage 4A ROP. The authors decided to treat with sequential anti-VEGF intravitreal injections as monotherapy instead of a combined treatment since after treatment with laser photocoagulation, the patient complicated with cardiac arrest and had permanent cerebral damage. Additionally, laser did not control the disease. On the other hand, bevacizumab stabilized the vasculature without progression of the retinal detachment, rendering surgical management unnecessary. This leads us to believe that we need to consider a future where constant delivery of anti-VEGF may be needed for progression of ROP. That said, we need to remember that timely screening and treatment prevents retinal detachment and blindness for ROP.

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