Original Article

Taiwan J Ophthalmol 2018;8:243-248

Access this article online

Quick Response Code:

Website:
www.e-tjo.org

DOI:
10.4103/tjo.tjo_69_18

Bevacizumab or laser for aggressive posterior retinopathy of prematurity

Michael Blair[1,2], Jose Maria Garcia Gonzalez[2], Laura Snyder[1], Sidney Schechet[1], Mark Greenwald[1], Michael Shapiro[2], Sarah Hilkert Rodriguez[1]

Abstract:

PURPOSE: The purpose of this study was to report the rate of reactivation and structural outcome, after the laser or bevacizumab treatment for aggressive posterior retinopathy of prematurity (APROP).

METHODS: Retrospective chart review was conducted on consecutive infants with APROP treated with (1) laser or (2) bevacizumab, followed by fluorescein angiography and prophylactic laser to the persistent avascular retina.

RESULTS: Thirty-six eyes of 19 patients were included in this study. The mean gestational age was 24.5 weeks with a mean birth weight of 632 g in the bevacizumab group and 24.7 weeks and 777 g in the laser group. Unfavorable outcome occurred in 1 of 22 eyes treated with bevacizumab and in 5 of 14 eyes in the laser group ($P = 0.002$). Reactivation requiring treatment was common in both groups, 9/22 after bevacizumab and 6/14 after laser (ns).

CONCLUSION: Regardless of the initial treatment reactivation requiring retreatment is common in eyes with APROP. The unfavorable structural outcome was significantly more common after initial laser treatment than after initial bevacizumab treatment.

Keywords:

Aggressive posterior retinopathy of prematurity, bevacizumab, retinopathy of prematurity, treatment completion laser

Introduction

Aggressive posterior retinopathy of prematurity (APROP) is ill-defined posterior retinopathy with the prominence of plus disease and flat network of neovascularization.[1] Structural outcomes for APROP treated with laser are worse than those for classic ROP, with rates of retinal detachment around 20%.[2-4] Given that bevacizumab eliminates the angiogenic threat-ROP (BEAT-ROP) demonstrated a significant benefit of bevacizumab over the laser regarding recurrence[5] and retinal detachment,[6] bevacizumab may be a better treatment for APROP. Since APROP was not specifically addressed in the initial BEAT-ROP report, and few APROP eyes were presented in the follow-up report,[7] we sought to compare reactivation rates and anatomic outcomes of APROP after laser to that after bevacizumab.

Methods

Patients

Charts of patients with ROP and treated at the University of Chicago Comer Children's Hospital were examined retrospectively. The study was approved by the University of Chicago IRB and was Health Insurance Portability and Accountability Act compliant. Inclusion criteria included being screened and treated for APROP between January 1, 2006, and June 30, 2016. Starting in the spring of 2010, after the publication of BEAT-ROP,[5] all patients with APROP were treated initially with bevacizumab. Exclusion criteria included the eyes with

[1]Department of Ophthalmology and Visual Science, University of Chicago, 5841 S. Maryland Avenue, MC2114, Chicago, IL, [2]Retina Consultants, Ltd., Des Plaines, IL 60016, USA

Address for correspondence:
Dr. Michael Blair, 2454 East Dempster Street, Suite 400, Des Plaines, IL 60016, USA.
E-mail: michaelblairmd@gmail.com

Submission: 21-06-2018
Accepted: 16-09-2018

How to cite this article: Blair M, Gonzalez JM, Snyder L, Schechet S, Greenwald M, Shapiro M, *et al*. Bevacizumab or laser for aggressive posterior retinopathy of prematurity. Taiwan J Ophthalmol 2018;8:243-8.

media opacity, classic ROP (CROP) rather than APROP, and treatment at another hospital before transfer. Patients with follow-up <80 weeks postmenstrual age (PMA) were also excluded from the study.

Definition of aggressive posterior retinopathy of prematurity and classic retinopathy of prematurity

APROP was defined according to the revised international classification of ROP (ICROP).[1] APROP was defined as ROP with posterior location and prominence of plus disease out of proportion to the peripheral retinopathy, which may appear as a flat network of neovascularization at the deceptively featureless junction between vascularized and nonvascularized retina, and which usually does not progress through the classic Stages 1–3 [Figure 1]. Eyes with CROP had ROP that progressed through the usual stages of demarcation with typical extraretinal fibrovascular proliferation (EFP), if Stage 3 was reached.

Injection

Intravitreal injections were performed at the bedside with topical anesthetic and povidone-iodine with sterile lid speculum. The needle was introduced 0.5 mm from the limbus and was directed posteriorly to avoid the lens. 0.5–0.625 mg of bevacizumab was injected in a volume of 0.02–0.025 cc.

Laser

In the laser group, the laser photocoagulation was performed using a diode green or infrared delivered by indirect ophthalmoscopy under general anesthesia in an operating suite. The treatment targeted the complete avascular zone in a near confluent pattern with approximately ¼ spot area untreated space between spots. Complete treatment was confirmed with a second observer and/or RetCam photography [Figure 2].

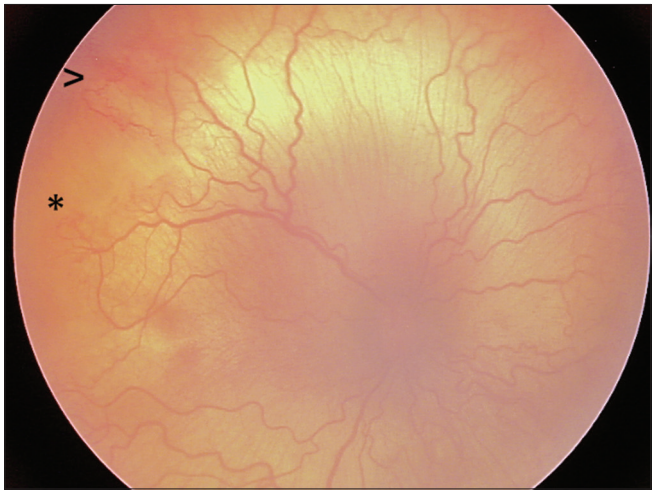

Figure 1: Fundus photograph of the right eye showing plus disease out of proportion to perceived retinopathy. Note blush of fine vessels (*) and shunt (>) at the border of perfused and nonperfused retina consistent with aggressive posterior retinopathy of prematurity. This eye received bevacizumab. Care was transferred, and no prophylactic treatment completion laser was performed. This eye ultimately progressed to retinal detachment at age 2

Follow-up and acute retreatment

The follow-up examinations after bevacizumab injection were performed weekly for 1 month, biweekly for 2 months, and then every 3–4 weeks until planned prophylactic laser (see below), guided by fluorescein angiography (FA), was performed to prevent late reactivation of ROP.

Eyes that had reactivation of ROP were treated with bevacizumab or laser at the discretion of the treating physician after discussion with family. Reactivation was defined as the redevelopment of EFP after initial regression. EFP redevelopment was usually at a more anterior location than the original ridge but could also occur again at the original more posterior location. A "poor structural" outcome was considered to be when retinal detachment or macular dragging occurred.

Late prophylactic treatment completion laser

Due to known late recurrence of ROP after bevacizumab injection,[8-13] our standard protocol was to perform FA after 60 weeks PMA to treat any persistent avascular retina with laser. Normal pediatric avascular retina has been defined as up to 1.5 disc-diameters from the ora serrata temporally;[14] hence, in this study, the laser was performed to the retina that was avascular beyond the aforementioned definition, or to the avascular retina less than defined but with leakage on FA. We term this "treatment completion" to emphasize the primary treatment with bevacizumab may be a temporary treatment. One can consider that if these eyes had been treated initially with laser and areas of avascular retina remained untreated then the treatment would be considered incomplete, and these "skip areas" would generally be treated to prevent the reactivation of disease. Delaying the timing of laser treatment to after 60 weeks is for reasons including (1) reduction of anesthesia risk and postanesthesia apnea[15,16] such that the infant does not need to have an overnight admission at our institution, and (2) allowing more anterior growth of the retinal

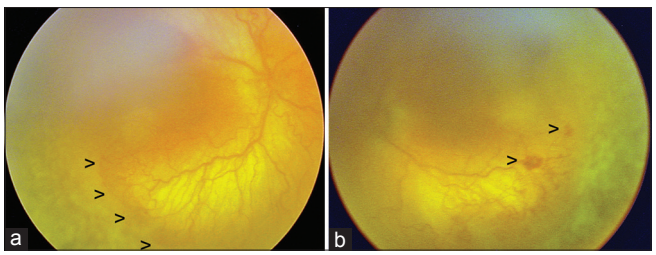

Figure 2: (a) Right (a) and left (b) eyes demonstrating aggressive posterior retinopathy of prematurity at the time of laser. The focal plane is above the retina. Note elevated vessels without fibrosis (>) in the right (a) and elevated ring hemorrhages (>) in the left (b). Both of these eyes progressed to detachment despite laser ablation

vasculature which decreases area of laser ablation, and thus should also decrease visual field loss and myopia progression.

Results

Patient characteristics

Fourteen eyes of seven patients were treated with laser as the initial treatment. The mean gestational age was 24.7 weeks, and the mean birth weight was 777 g. Twenty-two eyes of 12 patients were initially treated with bevacizumab. The mean gestational age was 24.5 weeks, and the mean birth weight was 632 g. Two fellow eyes were excluded for inability to examine the retina ophthalmoscopically, one with persistent fetal vessels and another with vitreous hemorrhage. The mean age of the first treatment was 34.7 weeks (standard deviation [SD] 1.5, range 32–38) in the bevacizumab group and 34.6 weeks (SD 1.6, range 32–37) in the laser group (ns). The mean age of the treatment requiring recurrence was 44.4 weeks (SD 5.1, range 37–51) in the bevacizumab group and 40 weeks (SD 3.3, range 34–43) in the laser group (P = 0.08). The mean follow-up was 114 weeks in the bevacizumab group and 243 weeks in the laser group.

Retina outcomes

Outcomes for APROP are summarized in Table 1. Nine eyes had acute reactivation in the bevacizumab group, while six eyes had reactivation in the laser group (ns). Twenty-two eyes received initial bevacizumab, eight of which did not reactivate but received treatment completion with laser, three received a second bevacizumab injection without subsequent laser [Figure 3], three received a second bevacizumab injection before prophylactic treatment completion with laser, two received salvage laser for acute reactivation, and one underwent vitrectomy. The remaining five eyes received a single injection and were fully vascularized and did not receive additional treatment. In the initial laser group comprising 14 eyes, one received salvage bevacizumab, and three received bevacizumab and surgery, while two received surgery. Only one eye in the initial bevacizumab group had a poor structural outcome, while five had poor structural outcome in the laser group (P = 0.002).

Discussion

The data demonstrate a significant benefit of bevacizumab over laser photocoagulation in the treatment of APROP regarding poor structural outcomes. Of note, recurrence was frequent in both groups. Although the study was retrospective, there was no imbalance in birth weight or gestational age; there was a trend to lower birth weight in the bevacizumab group. The difference in follow-up reflects the change from laser treatment to bevacizumab over time. As this is a retrospective, nonrandomized study, it cannot be excluded that an unrelated change in the neonatal intensive care unit care could explain the difference in the outcome. However, this seems unlikely given the biologic plausibility due to the slower decline in vascular endothelial growth factor (VEGF) concentration after laser ablation of the tissue producing it rather than the more rapid onset of action due to the binding of VEGF with bevacizumab.

The low rate of progression to retinal detachment after bevacizumab found in the present study compares favorably to prior reports of the response of APROP to laser, and our rate of progression to detachment despite laser is similar to prior studies. Drenser *et al*.[3] reported progression to retinal detachment in 8 of 44 eyes with APROP and Pandya *et al*.[4] described 3 of 6 eyes with APROP progressing to detachment despite laser. Sanghi *et al*. reported 17% of APROP eyes progressed to detachment after laser.[2] Gunn *et al*. reported 2 of 11 APROP eyes progressing to detachment.[17]

With regard to the comparison of the efficacy of bevacizumab to laser for APROP, most studies are from outside the United States, and results from may be

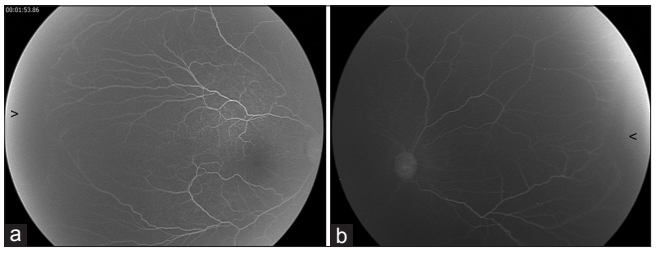

Figure 3: (a) This eye received bevacizumab at 33 and 40 weeks postmenstrual age. Fluorescein angiography with RetCam at 1.5 years of age demonstrates vascular termination 2 DD from the ora serrata (>, <) temporally (a) and 0.5 DD nasally (b)

Table 1: Aggressive posterior retinopathy of prematurity reactivation

	Bevacizumab	Laser	*P*
Initial treatment			
Total APROP eyes	22	14	
Mean birth weight (g)	632	777	0.06
Mean gestational age (weeks)	34.7 (SD 1.5, range 32-38)	34.6 (SD 1.6, range 32-37)	0.85
Reactivation by initial treatment			
APROP that needed retreatment (%)	9	6	1.0
APROP with unfavorable structural outcome*	1	5	0.002

*Includes eyes which underwent surgery for detachment or were deemed inoperable. APROP=Aggressive posterior retinopathy of prematurity, SD=Standard deviation

different when infants are larger. In a study from Turkey, Gunay *et al*. reported 0 of 25 APROP eyes progressing to detachment after bevacizumab, while 2 of 15 APROP eyes detached after laser.[18] The mean birth weight of infants in the bevacizumab group was 900 g. Nicoară *et al*., similarly, found improved regression of APROP after bevacizumab (94%) versus laser (83%) in a Romanian population with a mean birth weight of over 1 kg.[19] Outcomes for the smaller infants treated for APROP in the present study, with a mean birth weight of 632 g in the bevacizumab group, might have been expected to be worse. However, the single detachment out of 22 eyes that received initial bevacizumab compares favorably.

One reason for the difficulty treating APROP is that the levels of VEGF in APROP eyes are likely higher than CROP as evidenced by the decreased efficacy of a reduced dose of bevacizumab. Lorenz *et al*. showed that 0.312 mg bevacizumab-induced regression in 100% of Zone II CROP eyes, 80% of Zone I eyes, but only 25% of APROP eyes.[20] It is likely that larger areas of persistent avascular retina found in APROP than CROP after bevacizumab contribute to the likely higher VEGF load.[8,21,22] This may explain why APROP is more likely to reactivate than CROP. In a recent study, Mintz-Hittner *et al*. found 6/6 eyes with APROP reactivated.[7] The present study found a lower, but still high, 41% reactivation rate for eyes with APROP. The difference in morphology of APROP may point to a meaningful difference in molecular environment that is related to the increase in reactivation rate. Therefore, APROP may behave differently than CROP in the same zone regarding the response to initial treatment and rate of reactivation.

Part of the poor outcomes with APROP, in general, may be related to the difficulty in detection and thus late treatment. The International Classification defined it as an "ill-defined" retinopathy with prominent plus disease out of proportion to the peripheral disease.[1] This reliance on plus disease in ICROP[1] and early treatment for ROP[23] has certainly aided in its detection as it is easily recognizable. Other features described by ICROP include difficulty distinguishing arteries from veins, anastomoses, fine vessels, and hemorrhages [Figures 1 and 2]. ICROP describes APROP as progressing rapidly and not through the usual progression of demarcation lines and ridges. Improving outcomes may be related to not only treatment method but also to the timing of treatment. Indeed, a "crunch" phenomenon in ROP after anti-VEGF[24] has only been seen by the present authors in a few cases that were sent late for examination and treatment. Treating when the amount of extraretinal neovascularization is less extensive may be important in avoiding this "crunch." Detection of APROP at an early stage may be aided by using a 20 D lens rather than the usual 28 D lens used in ROP examination. The presence of annular or C-shaped hemorrhages and extraretinal fine vascular tangles without fibrosis are key findings that point to APROP [Figures 1 and 2], and thus either early treatment or increased vigilance is suggested.[25] Other related features of APROP that allow for early detection are prominent demarcation vessels, transparent pink overlay "blush," and persistent tunica vasculosa lentis.

With respect to the selection of anti-VEGF medication, bevacizumab has the most experience worldwide and appears to work well for Type 1 ROP in general and APROP in particular. Ranibizumab use is increasing due to systemic safety concerns (discussed below), but appears to have a higher rate of reactivation, ranging from 26% to 64% for ROP in general, not APROP.[26-33] Moreover, Chuluunbat found an 18% rate of nonresponsiveness.[32] The lack of efficacy may be related to shorter half-life and therefore early reactivation. Treatment failure for APROP is likely higher. Given the lack of concrete data on adverse systemic safety issues, the possibility of blindness due to suboptimal anti-VEGF must be considered.

With regard to the systemic safety concerns regarding anti-VEGF, the concern stems from the known appearance of medication in systemic circulation and suppression of systemic VEGF which are longer for bevacizumab than ranibizumab.[34] The implications of this VEGF suppression and even optimal levels in preterm neonates[35] are not known; however, there is concern regarding neurodevelopment particularly after work by Morin.[36] That data were gathered retrospectively and were unfortunately fraught with bias.[37] The first bias was for the treatment of sicker infants with anti-VEGF, which is demonstrated by the score for neonatal acute physiology II scores that measure the severity of systemic illness. The second was for the treatment of worse ROP with anti-VEGF in that study since 11 patients in the laser arm had mild enough disease to not even meet usual criteria for treatment. Importantly, both sicker systemic disease and worse ROP are known risk factors for poorer neurodevelopment.[38-41] The study also suffers from significant loss to follow-up of 28% of patients. Moreover, nine patients in the laser arm were excluded for inability to perform testing for reasons such as poor cooperation, development delay, blindness, and deafness whereas only one such patient was excluded from the bevacizumab arm. These patients really should have been included as having poor neurodevelopment. Recalculating their outcomes with the above patients included changes the difference in severe developmental delay to be nonsignificant. Indeed, other studies have failed to find a difference in neurodevelopment between children whose ROP was treated with laser or bevacizumab.[42-45]

To date, there exists no good evidence that anti-VEGF causes harmful systemic effects. Given the favorable effect of bevacizumab over laser, and likely ranibizumab, for APROP, the real risk of blindness from retinal detachment must be weighed against the theoretical risk of neurodevelopmental harm in neonates.

The choice of the term ROP "reactivation" over "recurrence" takes into account several observations. First, bevacizumab binds VEGF to suppress neovascularization but does not prevent its continued production. Second, the pathologic avascular retina is the most essential part of ROP as this retina produces VEGF that drives ROP. Indeed, ICROP Stages 1, 2, 3, 4, and 5 can be thought of as secondary complications of ischemia. Third, treatment that maintains a pathologic ischemic zone of the retina has not cured the ROP and is incomplete. Fourth, pathologic neovascularization after the period of VEGF suppression in the face of ischemia is expected rather than a surprise. Finally, as long as there is pathologic avascular retina, the disease is manifestly persistent, and the progression is, therefore, not a recurrence. The idea of reactivation is that ROP persisted (in a dormant state) and then became active again progressing to neovascularization or worse, to tractional retinal detachment.

It must be remembered that late retinal detachment can occur up to (and likely past) 3 years of age.[8-10] Most eyes that received bevacizumab in this study as an initial treatment for APROP underwent treatment completion FA and laser to the persistent avascular retina to prevent late retinal detachment. Indeed, the only eye that progressed to detachment in this group did not receive prophylactic late laser and has been described elsewhere.[8] Although we believe bevacizumab to be superior to laser in the treatment of APROP, the late prophylactic laser is recommended.

Conclusion

Regardless of the initial treatment, reactivation requiring retreatment is common in eyes with APROP. The unfavorable structural outcome was significantly more common after initial laser treatment than after initial bevacizumab treatment. Initial antiVEGF therapy followed by planned treatment completion laser is recommended for APROP.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

References

1. International Committee for the Classification of Retinopathy of Prematurity. The international classification of retinopathy of prematurity revisited. Arch Ophthalmol 2005;123:991-9.
2. Sanghi G, Dogra MR, Katoch D, Gupta A. Aggressive posterior retinopathy of prematurity: Risk factors for retinal detachment despite confluent laser photocoagulation. Am J Ophthalmol 2013;155:159-64.e2.
3. Drenser KA, Trese MT, Capone A Jr. Aggressive posterior retinopathy of prematurity. Retina 2010;30:S37-40.
4. Pandya HK, Faia LJ, Robinson J, Drenser KA. Macular development in aggressive posterior retinopathy of prematurity. Biomed Res Int 2015;2015:808639.
5. 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.
6. Geloneck MM, Chuang AZ, Clark WL, Hunt MG, Norman AA, Packwood EA, *et al.* Refractive outcomes following bevacizumab monotherapy compared with conventional laser treatment: A randomized clinical trial. JAMA Ophthalmol 2014;132:1327-33.
7. Mintz-Hittner HA, Geloneck MM, Chuang AZ. Clinical management of recurrent retinopathy of prematurity after intravitreal bevacizumab monotherapy. Ophthalmology 2016;123:1845-55.
8. Snyder LL, Garcia-Gonzalez JM, Shapiro MJ, Blair MP. Very late reactivation of retinopathy of prematurity after monotherapy with intravitreal bevacizumab. Ophthalmic Surg Lasers Imaging Retina 2016;47:280-3.
9. Hajrasouliha AR, Garcia-Gonzales JM, Shapiro MJ, Yoon H, Blair MP. Reactivation of retinopathy of prematurity three years after treatment with bevacizumab. Ophthalmic Surg Lasers Imaging Retina 2017;48:255-9.
10. Hu J, Blair MP, Shapiro MJ, Lichtenstein SJ, Galasso JM, Kapur R, *et al.* Reactivation of retinopathy of prematurity after bevacizumab injection. Arch Ophthalmol 2012;130:1000-6.
11. Hoang QV, Kiernan DF, Chau FY, Shapiro MJ, Blair MP. Fluorescein angiography of recurrent retinopathy of prematurity after initial intravitreous bevacizumab treatment. Arch Ophthalmol 2010;128:1080-1.
12. Ittiara S, Blair MP, Shapiro MJ, Lichtenstein SJ. Exudative retinopathy and detachment: A late reactivation of retinopathy of prematurity after intravitreal bevacizumab. J AAPOS 2013;17:323-5.
13. Patel RD, Blair MP, Shapiro MJ, Lichtenstein SJ. Significant treatment failure with intravitreous bevacizumab for retinopathy of prematurity. Arch Ophthalmol 2012;130:801-2.
14. Blair MP, Shapiro MJ, Hartnett ME. Fluorescein angiography to estimate normal peripheral retinal nonperfusion in children. J AAPOS 2012;16:234-7.
15. Walther-Larsen S, Rasmussen LS. The former preterm infant and risk of post-operative apnoea: Recommendations for management. Acta Anaesthesiol Scand 2006;50:888-93.
16. Coté CJ, Zaslavsky A, Downes JJ, Kurth CD, Welborn LG,

Warner LO, *et al.* Postoperative apnea in former preterm infants after inguinal herniorrhaphy. A combined analysis. Anesthesiology 1995;82:809-22.
17. Gunn DJ, Cartwright DW, Gole GA. Prevalence and outcomes of laser treatment of aggressive posterior retinopathy of prematurity. Clin Exp Ophthalmol 2014;42:459-65.
18. Gunay M, Celik G, Gunay BO, Aktas A, Karatekin G, Ovali F, *et al.* Evaluation of 2-year outcomes following intravitreal bevacizumab (IVB) for aggressive posterior retinopathy of prematurity. Arq Bras Oftalmol 2015;78:300-4.
19. Nicoară SD, Ştefănuţ AC, Nascutzy C, Zaharie GC, Toader LE, Drugan TC, *et al.* Regression rates following the treatment of aggressive posterior retinopathy of prematurity with bevacizumab versus laser: 8-year retrospective analysis. Med Sci Monit 2016;22:1192-209.
20. Lorenz B, Stieger K, Jäger M, Mais C, Stieger S, Andrassi-Darida M, *et al.* Retinal vascular development with 0.312 mg intravitreal bevacizumab to treat severe posterior retinopathy of prematurity: A longitudinal fluorescein angiographic study. Retina 2017;37:97-111.
21. Garcia Gonzalez JM, Snyder L, Blair M, Rohr A, Shapiro M, Greenwald M, *et al.* Prophylactic peripheral laser and fluorescein angiography after bevacizumab for retinopathy of prematurity. Retina 2018;38:764-72.
22. Toy BC, Schachar IH, Tan GS, Moshfeghi DM. Chronic vascular arrest as a predictor of bevacizumab treatment failure in retinopathy of prematurity. Ophthalmology 2016;123:2166-75.
23. 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;121:1684-94.
24. Yonekawa Y, Wu WC, Nitulescu CE, Chan RV, Thanos A, Thomas BJ, *et al.* Progressive retinal detachment in infants with retinopathy of prematurity treated with intravitreal bevacizumab or ranibizumab. Retina 2018;38:1079-83.
25. Shapiro MJ, Blair MP, Gonzalez JM. Aggressive posterior retinopathy of prematurity (APROP). In retinopathy of prematurity (1st ed., pp. 49-70). Cham, Switzerland: Springer International Publishing 2017. doi:10.1007/978-3-319-52190-9.
26. Ells AL, Wesolosky JD, Ingram AD, Mitchell PC, Platt AS. Low-dose ranibizumab as primary treatment of posterior type I retinopathy of prematurity. Can J Ophthalmol 2017;52:468-74.
27. Huang Q, Zhang Q, Xu Y, Ji X, Fei P, Peng J, *et al.* Asymmetric outcomes of type 1 retinopathy of prematurity after bilateral intravitreal ranibizumab treatment. J Ophthalmol 2017;2017:1741386.
28. Hu Q, Bai Y, Chen X, Huang L, Chen Y, Li X. Recurrence of retinopathy of prematurity in zone II stage 3+ after ranibizumab treatment: A retrospective study. J Ophthalmol 2017;2017:5078565.
29. Huang Q, Zhang Q, Fei P, Xu Y, Lyu J, Ji X, *et al.* Ranibizumab injection as primary treatment in patients with retinopathy of prematurity: Anatomic outcomes and influencing factors. Ophthalmology 2017;124:1156-64.
30. Sukgen EA, Koçluk Y. The vascularization process after intravitreal ranibizumab injections for aggressive posterior retinopathy of prematurity. Arq Bras Oftalmol 2017;80:30-4.
31. Lyu J, Zhang Q, Chen CL, Xu Y, Ji XD, Li JK, *et al.* Recurrence of retinopathy of prematurity after intravitreal ranibizumab monotherapy: Timing and risk factors. Invest Ophthalmol Vis Sci 2017;58:1719-25.
32. Chuluunbat T, Chan RV, Wang NK, Lien R, Chen YP, Chao AN, *et al.* Nonresponse and recurrence of retinopathy of prematurity after intravitreal ranibizumab treatment. Ophthalmic Surg Lasers Imaging Retina 2016;47:1095-105.
33. Zhang G, Yang M, Zeng J, Vakros G, Su K, Chen M, *et al.* Comparison of intravitreal injection of ranibizumab versus laser therapy for zone II treatment-requiring retinopathy of prematurity. Retina 2017;37:710-7.
34. Wu WC, Shih CP, Lien R, Wang NK, Chen YP, Chao AN, *et al.* Serum vascular endothelial growth factor after bevacizumab or ranibizumab treatment for retinopathy of prematurity. Retina 2017;37:694-701.
35. Kandasamy Y, Hartley L, Rudd D, Smith R. The association between systemic vascular endothelial growth factor and retinopathy of prematurity in premature infants: A systematic review. Br J Ophthalmol 2017;101:21-4.
36. Morin J, Luu TM, Superstein R, Ospina LH, Lefebvre F, Simard MN, *et al.* Neurodevelopmental outcomes following bevacizumab injections for retinopathy of prematurity. Pediatrics 2016;137. pii: e20153218.
37. Blair MP, Shapiro MJ; Ad Hoc Group Concerning Neurodevelopment and antiVEGF. Re: Good: Bevacizumab for retinopathy of prematurity: Treatment when pathology is embedded in a normally developing vascular system (Ophthalmology 2016;123:1843-1844). Ophthalmology 2017;124:e74-5.
38. Msall ME, Phelps DL, DiGaudio KM, Dobson V, Tung B, McClead RE, *et al.* Severity of neonatal retinopathy of prematurity is predictive of neurodevelopmental functional outcome at age 5.5 years. Behalf of the Cryotherapy for Retinopathy of Prematurity Cooperative Group. Pediatrics 2000;106:998-1005.
39. Molloy CS, Anderson PJ, Anderson VA, Doyle LW. The long-term outcome of extremely preterm (<28 weeks' gestational age) infants with and without severe retinopathy of prematurity. J Neuropsychol 2016;10:276-94.
40. Cooke RW, Foulder-Hughes L, Newsham D, Clarke D. Ophthalmic impairment at 7 years of age in children born very preterm. Arch Dis Child Fetal Neonatal Ed 2004;89:F249-53.
41. Beligere N, Perumalswamy V, Tandon M, Mittal A, Floora J, Vijayakumar B, *et al.* Retinopathy of prematurity and neurodevelopmental disabilities in premature infants. Semin Fetal Neonatal Med 2015;20:346-53.
42. Lien R, Yu MH, Hsu KH, Liao PJ, Chen YP, Lai CC, *et al.* Neurodevelopmental outcomes in infants with retinopathy of prematurity and bevacizumab treatment. PLoS One 2016;11:e0148019.
43. Kennedy KA, Mintz-Hittner HA; BEAT-ROP Cooperative Group. Medical and developmental outcomes of bevacizumab versus laser for retinopathy of prematurity. J AAPOS 2018;22:61-50.
44. Araz-Ersan B, Kir N, Tuncer S, Aydinoglu-Candan O, Yildiz-Inec D, Akdogan B, *et al.* Preliminary anatomical and neurodevelopmental outcomes of intravitreal bevacizumab as adjunctive treatment for retinopathy of prematurity. Curr Eye Res 2015;40:585-91.
45. Kong L, Dinh KL, Schechet S, Coats DK, Voigt RG, Steinkuller PG. Comparison of ocular and developmental outcomes in laser-and bevacizumab-treated infants with retinopathy of prematurity. Ophthalmol Res Int J 2015;3:13-22.