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Reply to comment on: "Advantages of bevacizumab for aggressive posterior retinopathy of prematurity"

We would like to thank Dr. Samanta for interest in our recent manuscript regarding aggressive posterior retinopathy of prematurity (APROP).[1]

The first question was with regard to zone of the disease, since zone I disease would be expected to be worse. In the bevacizumab treatment group, 20 eyes were in zone I and only two were in zone II. However, in the laser treatment group, six eyes were in zone I but eight were in zone II. Thus, given the higher proportion of zone I eyes in the bevacizumab group, one would have expected these outcomes to be worse; however, in fact, we found the opposite that the laser treated eyes did worse. In eyes that progressed to detachment in the laser group, treatment was limited by hemorrhage in one eye and pupil/tunica remnants in three eyes. Treatment uptake was partially limited by broad flat neovascularization in three eyes as well. Skip areas likely contributed to progression and detachment in these eyes. There was not an opportunity for supplemental laser as most media issues remained, and these eyes progressed rapidly to retinal detachment. This points to one a major advantage of bevacizumab treatment: It is not dependent on clear media.

With respect to the assertion that the better outcomes in the injection-treated group were related to combination treatment rather than injection alone, we agree in principle that eyes that receive initial Anti-vascular endothelial growth factor (anti-VEGF) treatment will need laser treatment, some for acute reactivation and the rest to prevent late reactivation. However, we believe that there is significant advantage to performing the laser at a later procedure rather than a combination treatment in a single setting. Delaying laser allows the anti-VEGF to induce regression of tunica vasculosa lentis and improve media, allows the retinal vessels to continue anterior growth which decreases amount of ablated retina, likely improves visual field, reduces myopia,[2] and decreases the risk of anesthesia by allowing infants time to grow and mature. Treatment for acute reactivation was relatively common in the bevacizumab-treated eyes; however, on average, this was needed 10 weeks later. Since most of the patients were significantly unwell at injection, the delay of 10 weeks allows for improved health of the infant and reduces the extent and stress of the laser treatment. As long as the retinopathy is not active, this late laser can be done electively either after 60 weeks postmenstrual age when the risk of apnea from anesthesia is lower,[3] or before discharge from hospital if follow-up may be difficult.

With regard to the "crunch" phenomenon (rapid contracture of massive fibrovascular proliferation and detachment) after anti-VEGF, this can be avoided by treating at an appropriately early time point, i.e., before development of fibrotic elements of late APROP. This requires timely detection of "naked," likely flat, neovascular tangles that make up APROP. Examiners must have a high suspicion of APROP, particularly in infants with poorly dilating pupils, poor progression of anterior growth of retinal vasculature, early tortuosity and dilation of vessels, and annular or C-shaped hemorrhages. No eyes in our study experienced this crunch phenomenon. It is not known whether eyes that experience "crunch" would actually have better outcomes with laser or other treatment. This ROP "crunch" is similar to diabetic retinopathy, where studies have shown benefit of anti-VEGF over laser photocoagulation for proliferative disease, but where surgeons are concerned about "crunch" if significant fibrotic tractional elements have developed already. The idea is to treat before fibrosis occurs. We cannot comment about this phenomenon in the APROP subtype caused by oxygen-induced retinopathy

With regard to systemic safety concerns, we discussed this extensively in our paper but essentially studies that claimed to show worse neurodevelopmental outcomes in anti-VEGF treated eyes suffer from significant treatment bias. For example, sicker infants and infants with worse ROP were more likely to have been treated with anti-VEGF.[4] Sicker infants and worse ROP are correlated with worse neurodevelopmental outcomes.[5,6] Conclusive data regarding neurodevelopmental effects of anti-VEGF are lacking. However, given the number of infants treated with anti-VEGF and lack of conclusive data, the effect, if it exists, is likely to be small. Some eyes with APROP may do well with laser; however, in our study, the proportion of eyes progressing to retinal detachment was significantly lower in bevacizumab-treated eyes. Moreover, the impact of blindness on neurodevelopment should not be overlooked; in the CRYO-ROP cohort, favorable visual acuity predicted

a lower chance of special education placement.[7] Treatment must be individualized for each patient, and optimal treatment in different countries may be different due to differences in birth weights and ages, comorbid conditions, and other factors. One must remember that denial of an effective tool to prevent blindness should be based on solid evidence. Finally, the effort to prevent neurodevelopmental problems may fail by increasing blindness, which is in itself a poor neurodevelopmental outcome.[8]

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Conflicts of interest

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

Sidney A. Schechet[1], Sarah Hilkert Rodriguez[1], Michael J. Shapiro[2], Michael P. Blair[1,2]

[1]Department of Ophthalmology and Visual Science, University of Chicago, 5841 S. Maryland Avenue, MC2114, Chicago, [2]Retina Consultants, Ltd, 2454 E Dempster St, Suite 400, Des Plaines, IL, USA

Address for correspondence:
Dr. Michael P. Blair,
Retina Consultants, Ltd, 2454 E Dempster St, Suite 400,
Des Plaines, IL, 60016, USA.
E-mail: michaelblairmd@gmail.com

References

1. 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.
2. Anand N, Blair MP, Greenwald MJ, Hilkert Rodriguez S. Refractive outcomes comparing primary laser to primary bevacizumab with delayed laser for type 1 ROP. J Am Assoc Pediatr Ophthalmol. [In press].
3. 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.
4. 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.
5. 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.
6. Bolisetty S, Dhawan A, Abdel-Latif M, Bajuk B, Stack J, Lui K, *et al.* Intraventricular hemorrhage and neurodevelopmental outcomes in extreme preterm infants. Pediatrics 2014;133:55-62.
7. 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.
8. Msall ME. The panorama of cerebral palsy after very and extremely preterm birth: Evidence and challenges. Clin Perinatol 2006;33:269-84.

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