Pharmacological Intervention for Preterm Infants With Retinopathy of Prematurity (ROP)

BACKGROUND

Retinopathy of prematurity (ROP) is a potentially blinding eye disease that occurs when the normal development of retinal blood vessels that typically reach completion at full-term pregnancy is interrupted due to birth at a young gestational age or low birth weight.[1] On a global scale, ROP remains one of the leading causes of childhood blindness.[2]

Changes in oxygen levels, which are common during the neonatal incubation period, are thought to activate oxidative and inflammatory processes, resulting in hyperactive activation of retinal vascular endothelial growth factor (VEGF) receptors.[3] This stimulation causes an unbalanced environment, which leads to the irregular angiogenesis of the retina seen in ROP.[3]

Laser photocoagulation is currently the standard of care treatment for ROP.[4] Long-term studies have established that laser treatment effectively stops peripheral angiogenesis with no concern for endophthalmitis or systemic pharmacologic exposure.[5]

Anti-VEGF therapies, on the other hand, are significantly less invasive than laser photocoagulation, and have quicker recovery periods. Intravitreal anti-VEGF injections preserve peripheral retinal tissue and have become the preferred alternative for specific cases of ROP.[6,7]

In February 2023, the Food and Drug Administration approved aflibercept, an injectable intravitreal VEGF-inhibitor, for the treatment of retinopathy of prematurity (ROP).[8] “With no existing FDA-approved guidance for the treatment of retinopathy of prematurity with anti-VEGF therapies, there was a significant need for research to understand how best to treat the disease in a manner that puts patient safety first and preserves vision for a lifetime,” explained Jeff Todd, President and Chief Executive Officer of Prevent Blindness, in a news release by Regeneron.[8]

EDUCATIONAL ANALYSIS

Gap #1: Clinicians may be unaware of the recent FDA approval of aflibercept for the treatment of ROP in preterm infants.

Learning Objective #1: Differentiate the current pharmacological intervention trends for preterm infants with ROP.

Preterm infants born in the United States at 30 weeks or less of gestational age who required treatment for ROP increased from 3.4% to 5.3% between 2009 and 2018[6] . However, use of standard laser photocoagulation fell from 36.8% to 11.9% ($P < 0.001$) in that same time period and intravitreal anti-VEGF administration rose from 2% to 7.6% ($P < 0.001$).[6]

Anti-VEGF therapy has shown greater efficacy particularly in treating zone I ROP compared to laser therapy. The BEAT-ROP study revealed that infants with zone I disease experienced greater benefits from bevacizumab (91%) and ranibizumab (78%) treatments compared to laser therapy (66%).[10,11,12] Conversely, infants with zone II disease experienced reduced benefits, with laser-based therapy resulting in the highest success rate at 89%, followed closely by bevacizumab (87%), aflibercept, and ranibizumab (81% and 74%, respectively).[10]

Dr. Darius Moshfeghi, chief of the Retina Division at Stanford University School of Medicine, said, "Anything in zone I [ROP] is a poor laser candidate. Historically, as retinal specialists over the last decade, and pediatric retinal specialists in particular, we've been gravitating towards anti-VEGF therapy for those groups."[9]

Ranibizumab, an anti-VEGF agent with a relatively shorter systemic half-life than other VEGF inhibitors, is the focus of the ongoing European-based RAINBOW study.[7] When compared to laser therapy, infants treated with ranibizumab had fewer undesirable structural ophthalmological outcomes and fewer undesirable manifestations of refractive errors like myopia.[7] Ranibizumab achieved superior treatment success in 80% of infants included in the trial at the 24-week post-therapy mark, compared to 75% treatment success with the lower dose of 0.1 mg of ranibizumab and 66.2% treatment success with conventional laser photocoagulation.[7] No new structural abnormalities were identified in the ranibizumab group at the 2-year post-treatment mark, either, and treatment remained superior to laser treatments while also demonstrating decreased rates of myopia.[13]

Aflibercept, another anti-VEGF agent, is to date the only medical pharmacologic treatment approved for preterm infants with severe ROP.[8] As part of the FIREFLEYE study, an international randomized Phase 3 trial, aflibercept intravitreal injections were compared to laser photocoagulation treatment in infants with ROP at 52 weeks of age.[14] Both therapies demonstrated comparable efficacy in vascular regression, with less unfavorable structural alterations than would have been expected in the absence of treatment.[14] Aflibercept was found to be effective at a rate of 85%, similar to the success rate of laser treatment at 82% (though success rates did not meet the inferiority criteria).[14]

Intravitreal VEGF-inhibitors have been shown to be an effective treatment option for zone I ROP, allowing for better preservation of the peripheral retina and better refractive outcomes than with laser ablation.[7] Raising clinician awareness of the clinical risks and benefits reported in recent studies can aid in determining acceptable use cases for pharmacological therapies in neonatal ophthalmological settings.

Gap #2: Clinicians may be unaware of unique regression and reactivation patterns associated with anti-VEGF treatments for preterm infants with ROP.
Learning Objective #2: Distinguish the unique regression and reactivation patterns associated with preterm infants receiving anti-VEGF therapy.

The introduction of anti-VEGF agents has led to new patterns of disease progression in retinopathy of prematurity (ROP), as noted by David K. Wallace, MD, MPH, chair for the Indiana University School of Medicine Department of Ophthalmology.[15]

The terminology used in these conditions was recently modified inside the Third Edition of the International Classification of Retinopathy of Prematurity (ICROP3).[16] Two terms, “regression” and “reactivation”, were defined in an effort to distinguish the unique patterns observed following pharmacologic treatments from those seen after traditional ablative therapies.[16]

“Regression simply means the disease is going away, spontaneously or in response to treatment,” explained Gil Binenbaum, MD, at the Children’s Hospital of Philadelphia.[15] Regression happens considerably sooner with anti-VEGF therapy, most commonly within 1-3 days[16,17] whereas any regression following ablative therapy normally occurs in a window of 7-14 days.[17,18,19]

In the initial stages of regression, the vasculature within the posterior pole improves rapidly.[16] Successful regression comes after the involution of the tunica vasculosa lentis, improved clarity of the ocular media, better pupil dilation, and absorption of intraretinal hemorrhages.[16]

“Reactivation after anti-VEGF treatment includes vascular dilation, tortuosity, and extraretinal

neovascularization," notes Mary Elizabeth Hartnett, MD, adjunct professor at the University of Utah. "We want to allow physiologic vascularization after anti-VEGF treatment but not to allow pathologic extraretinal neovascularization."[15] The ICROP3 Committee defines the term "reactivation" as the recurrence of acute phase characteristics.[16]

Reactivation is more commonly experienced with anti-VEGF treatment than when associated with spontaneous regression.[16] The ICROP3 committee warns that ROP reactivation often does not occur in the usual sequence that is expected in the acute phases of disease.[16] When compared to pharmacologic treatment, laser photocoagulation less commonly results in reactivation[20] and tends to occur earlier than with anti-VEGF treatment (before 55 weeks postmenstrual age).[21]

The BEAT-ROP study showed that the mean time of reactivation with bevacizumab was 16 weeks post-treatment.[10] Late reactivation has been described up until 60 weeks post menstrual age.[7] Reactivation with poor outcomes and retinal detachment have been reported months and even years after treatment.[22]

The unique regression and reactivation patterns observed with pharmacological therapies for ROP require tight partnerships between neonatologists, pediatric ophthalmologists, and pediatricians to care for long-term consequences.[6]

Gap #3: Clinicians administering anti-VEGF pharmacologic agents to preterm infants for the first time may lack familiarity with guidelines to minimize the risk of complications from intravitreal injections.

Learning Objective #3: Implement intravitreal injection with effective and safe delivery to avoid complications in preterm infants.

In the wake of the FDA's approval of this anti-VEGF pharmacologic agent for preterm infants, clinicians may need to become more familiar with strategies for lowering the risk of complications through intravitreal injections in this population. Administering these injections improperly can increase risk of cataract formation, endophthalmitis, and vitreous hemorrhage in preterm infants with ROP.[23]

The acronym SAFER was designed to bring attention to five important aspects of intravitreal injection administration: (S) the use of a shorter 4-mm needle to account for preterm infant size, (A) application of antiseptic or antibiotic (5% to 10% topical betadine), (F) follow-up at 48 to 72 hours post-injection to check for endophthalmitis, (E) ensure a clean working area and precise injection site location, which is 0.75 mm to 1.0 mm posterior to the limbus, and (R) recheck the retina closely every 1 to 2 weeks post-injection until mature vascularization is reached, or until laser photocoagulation is deemed necessary.[23]

Rather than focusing solely on needle size, the SAFER-ROP protocol guidelines provide a comprehensive framework for intravitreal injection delivery techniques needed for treatment of ROP in preterm populations.[23]

SUGGESTED FACULTY LIST

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5. Gil Binenbaum, MD, Chief of the Division of Ophthalmology, Children's Hospital of Philadelphia, Philadelphia, PA

CONCLUSION

Retinopathy of prematurity (ROP) continues to be one of the major causes of childhood blindness worldwide. Recent FDA approval of the first intravitreal anti-VEGF treatment marks a significant step towards ROP management and outcomes. Anti-VEGF therapy has shown efficacy and is emerging as a potential laser therapy alternative. However, clinicians administering pharmacological treatments must identify the appropriate use cases, recognize unique clinical presentations associated with pharmacological treatments compared to traditional laser ablation treatments, and must adhere to proper safety protocols. Knowing when and how to apply pharmacological interventions to these vulnerable patients can help everyone achieve the best outcome possible.

REFERENCES

1. Higgins RD. Oxygen Saturation and Retinopathy of Prematurity. *Clin Perinatol.* 2019;46(3):593-599. doi:10.1016/j.clp.2019.05.008

2. Darlow BA, Gilbert C. Retinopathy of prematurity - A world update. *Semin Perinatol.* 2019;43(6):315-316. doi:10.1053/j.semperi.2019.05.001

3. Ramshekar A, Hartnett ME. Vascular Endothelial Growth Factor Signaling in Models of Oxygen-Induced Retinopathy: Insights Into Mechanisms of Pathology in Retinopathy of Prematurity. *Front Pediatr*. 2021;9:796143. Published 2021 Dec 9. doi:10.3389/fped.2021.796143

4. Good WV; Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial. *Trans Am Ophthalmol Soc*. 2004;102:233-250.

5. White JE, Repka MX. Randomized comparison of diode laser photocoagulation versus cryotherapy for threshold retinopathy of prematurity: 3-year outcome. *J Pediatr Ophthalmol Strabismus*. 1997;34(2):83-122. doi:10.3928/0191-3913-19970301-06

6. Cudjoe GA, Ameley A, Ohemeng-Dapaah J, Bhatt P, Donda K, Dapaah-Siakwan F. National trends in the incidence and management of retinopathy of prematurity in the United States, 2009 -2018. *J Neonatal Perinatal Med*. 2022;15(3):553-557. doi:10.3233/NPM-210826

7. Tsiropoulos GN, Seliniotaki AK, Haidich AB, Ziakas N, Mataftsi A. Comparison of adverse events between intravitreal anti-VEGF and laser photocoagulation for treatment-requiring retinopathy of prematurity: a systematic review. *Int Ophthalmol*. 2023;43(3):1027-1062. doi:10.1007/s10792-022-02480-6

8. Eyelea© (aflibercept) injection approved as the first pharmacologic treatment for preterm infants with retinopathy of prematurity (ROP) by the FDA. News release. Regeneron: Investors and media. February

28, 2023. Accessed May 11, 2023. https://investor.regeneron.com/news-releases/news-release-details/eylear-aflibercept-injection-approved-first-pharmacologic/

9. Joszt L. Anti-VEGF Therapy vs Gold Standard in Preterm Babies With ROP: Dr Darius Moshfeghi. *Am J Manag Care*. February, 2023. Accessed May 11, 2023. https://www.ajmc.com/view/anti-vegf-therapy-vs-gold-standard-in-preterm-babies-with-rop-dr-darius-moshfeghi/

10. 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(7):603-615. doi:10.1056/NEJMoa1007374

11. Hård AL, Hellström A. On safety, pharmacokinetics and dosage of bevacizumab in ROP treatment - a review. *Acta Paediatr*. 2011;100(12):1523-1527. doi:10.1111/j.1651-2227.2011.02445.x

12. VanderVeen DK, Melia M, Yang MB, Hutchinson AK, Wilson LB, Lambert SR. Anti-Vascular Endothelial Growth Factor Therapy for Primary Treatment of Type 1 Retinopathy of Prematurity: A Report by the American Academy of Ophthalmology. *Ophthalmology*. 2017;124(5):619-633. doi:10.1016/j.ophtha.2016.12.025

13. Marlow N, Stahl A, Lepore D, et al. 2-year outcomes of ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW extension study): prospective follow-up of an open label, randomised controlled trial. *Lancet Child Adolesc Health*. 2021;5(10):698-707. doi:10.1016/S2352-4642(21)00195-4

14. Stahl A, Sukgen EA, Wu WC, et al. Effect of Intravitreal Aflibercept vs Laser Photocoagulation on Treatment Success of Retinopathy of Prematurity: The FIREFLEYE Randomized Clinical Trial. *JAMA*. 2022;328(4):348-359. doi:10.1001/jama.2022.10564

15. Taylor R. A New Field Guide to ROP: ICROP-3. *EyeNet Magazine*. October, 2022; 28-30. Accessed May 11, 2023. https://www.aao.org/eyenet/article/a-new-field-guide-to-rop-icrop-3/

16. Chiang MF, Quinn GE, Fielder AR, et al. International Classification of Retinopathy of Prematurity, Third Edition. *Ophthalmology*. 2021;128(10):e51-e68. doi:10.1016/j.ophtha.2021.05.031

17. Stahl A, Lepore D, Fielder A, et al. Ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW): an open-label randomised controlled trial. *Lancet*. 2019;394(10208):1551-1559. doi:10.1016/S0140-6736(19)31344-3

18. Coats DK, Miller AM, Hussein MA, McCreery KM, Holz E, Paysse EA. Involution of retinopathy of prematurity after laser treatment: factors associated with development of retinal detachment. Am J *Ophthalmol.* 2005;140(2):214-222. doi:10.1016/j.ajo.2004.12.106

19. Kwon JY, Ghodasra DH, Karp KA, et al. Retinal vessel changes after laser treatment for retinopathy of prematurity. *J AAPOS*. 2012;16(4):350-353. doi:10.1016/j.jaapos.2012.04.002

20. 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(3):255-259. doi:10.3928/23258160-20170301-10

21. Banach MJ, Ferrone PJ, Trese MT. A comparison of dense versus less dense diode laser

photocoagulation patterns for threshold retinopathy of prematurity. *Ophthalmology*. 2000;107(2):324-328. doi:10.1016/s0161-6420(99)00042-1

22. Jang JH, Kang YK, Park HS, et al. Primary and additional treatment preference in aggressive retinopathy of prematurity and type 1 retinopathy of prematurity. *BMJ Open Ophthalmology* 2023;8:e001166. doi:10.1136/bmjophth-2022-001166

23. Beck KD, Rahman EZ, Ells A, Mireskandari K, Berrocal AM, Harper CA 3rd. SAFER-ROP: Updated Protocol for Anti-VEGF Injections for Retinopathy of Prematurity. *Ophthalmic Surg Lasers Imaging Retina*. 2020;51(7):402-406. doi:10.3928/23258160-20200702-05

24. Cernichiaro-Espinosa LA, Harper CA 3rd, Read SP, et al. Report of safety of the use of a short 32G needle for intravitreal anti-vascular endothelial growth factor injections for retinopathy of prematurity: a multicenter study. *Retina*. 2018;38(6):1251-1255. doi:10.1097/IAE.0000000000002172