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Assessment of Lower Doses of Intravitreous Bevacizumab for Retinopathy of Prematurity
A Phase 1 Dosing Study

David K. Wallace, MD, MPH; Raymond T. Kraker, MSPH; Sharon F. Freedman, MD; Eric R. Crouch, MD; Amy K. Hutchinson, MD; Amit R. Bhatt, MD; David L. Rogers, MD; Michael B. Yang, MD; Kathryn M. Haider, MD; Deborah K. VanderVeen, MD; R. Michael Siatkowski, MD; Trevano W. Dean, MPH; Roy W. Beck, MD, PhD; Michael X. Repka, MD, MBA; Lois E. Smith, MD, PhD; William V. Good, MD; Mary Elizabeth Hartnett, MD; Lingkun Kong, MD; Jonathan M. Holmes, BM, BCh; for the Pediatric Eye Disease Investigator Group (PEDIG)

IMPORTANCE Intravitreous bevacizumab (0.25 to 0.625 mg) is increasingly used to treat type 1 retinopathy of prematurity (ROP), but there remain concerns about systemic toxicity. A much lower dose may be effective while reducing systemic risk.

OBJECTIVE To find a dose of intravitreous bevacizumab that was lower than previously used for severe ROP, was effective in this study, and could be tested in future larger studies.

DESIGN, SETTING, AND PARTICIPANTS Between May 2015 and September 2016, 61 premature infants with type 1 ROP in 1 or both eyes were enrolled in a masked, multicenter, phase 1 dose de-escalation study. One eye of 10 to 14 infants received 0.25 mg of intravitreous bevacizumab. If successful, the dose was reduced for the next group of infants (to 0.125 mg, then 0.063 mg, and finally 0.031 mg). Diluted bevacizumab was delivered using 300 µL syringes with 5/16-inch, 30-gauge fixed needles.

INTERVENTIONS Bevacizumab injections at 0.25 mg, 0.125 mg, 0.063 mg, and 0.031 mg.

MAIN OUTCOMES AND MEASURES Success was defined as improvement in preinjection plus disease or zone I stage 3 ROP by 5 days after injection or sooner, and no recurrence of type 1 ROP or severe neovascularization requiring additional treatment within 4 weeks.

RESULTS Fifty-eight of 61 enrolled infants had 4-week outcomes completed; mean birth weight was 709 g and mean gestational age was 24.9 weeks. Success was achieved in 11 of 11 eyes at 0.25 mg, 14 of 14 eyes at 0.125 mg, 21 of 24 eyes at 0.063 mg, and 9 of 9 eyes at 0.031 mg.

CONCLUSIONS AND RELEVANCE A dose of bevacizumab as low as 0.031 mg was effective in 9 of 9 eyes in this phase 1 study and warrants further investigation. Identifying a lower effective dose of bevacizumab may reduce the risk for neurodevelopmental disability or detrimental effects on other organs.

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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The Pediatric Eye Disease Investigator Group members participating in this study are listed at the end of this article.

Corresponding Author: David K. Wallace, MD, MPH, c/o Jaeb Center for Health Research, 15310 Amberly Dr, Ste 350, Tampa, FL 33647 (pedig@jaeb.org).

Retinopathy of prematurity (ROP) is a leading cause of childhood blindness worldwide.[1] Treatment for severe ROP by ablative therapy (usually laser) can significantly reduce the incidence of retinal detachment and blindness.[2] Increasingly, drugs that block the bioactivity of vascular endothelial growth factor (VEGF) are administered by intravitreous injection to treat severe ROP, typically at about one-half the adult dose for macular degeneration. In the BEAT-ROP randomized trial, bevacizumab, 0.625 mg, was more effective than laser for the most severe type of ROP (zone I).[3] However, intravitreous bevacizumab reaches the systemic circulation, with large persistent reductions in serum VEGF levels,[4] raising concerns about potential systemic toxicity. Because VEGF is necessary for normal development of many tissues, including brain, lungs, bones, kidneys, and retina, blocking VEGF action could be detrimental to premature infants. In particular, there is concern that anti-VEGF drugs increase the risk for neurodevelopmental disability[5] and delayed retinal vascularization necessitating longer outpatient follow-up. We conducted a masked, multicenter, dose de-escalation phase 1 study to determine whether a much lower dose of bevacizumab than previously used may be effective in treating severe ROP with the aim of reducing systemic risk without compromising benefit.

Key Points

Question Could a lower dose of intravitreous bevacizumab effectively treat severe retinopathy of prematurity?

Findings In this masked phase 1 dose de-escalation study, premature infants with type 1 retinopathy of prematurity were treated with bevacizumab. Success, defined as improvement by 5 days and no recurrence requiring additional treatment within 4 weeks, was achieved in 11 of 11 eyes at 0.25 mg, 14 of 14 eyes at 0.125 mg, 21 of 24 eyes at 0.063 mg, and 9 of 9 eyes at 0.031 mg of bevacizumab.

Meaning A dose of bevacizumab as low as 0.031 mg was effective in this study, and further investigation is needed to determine the optimal dose and assess effectiveness and systemic safety.

Methods

After obtaining institutional review board approval from all participating institutions and written informed consent from parent(s), infants with severe ROP (type 1) in 1 or both eyes and no previous treatment were enrolled. For infants with bilateral type 1, the study eye was randomly selected. An intravitreous injection of bevacizumab, 0.25 mg, in 10 µL was given to the study eye using a 300-µL syringe with a 5/16-inch, 30-gauge fixed needle. Follow-up examinations were performed after injection at 1 day, 3 to 5 days (if not improved at day 1), and weekly for 4 weeks. Success was defined as improvement by 4 days or sooner and no recurrence of type 1 ROP or severe neovascularization requiring additional treatment within 4 weeks. Up to 14 infants were treated to ensure there were at least 10 infants with 4-week outcomes. An independent data safety and monitoring committee reviewed the outcomes and determined the next bevacizumab dose to test in 10 to 14 infants based on the success proportion: dose reduced for 80% or greater success, dose repeated for 70% to less than 80% success, and dose increased or the study ended for less than 70% success. Three dose reductions were evaluated, with each one-half the previous dose concentration (0.125 mg, 0.063 mg, and 0.031 mg each in 10 µL, diluted with normal saline). If the nonstudy eye also required treatment, then the last dose found to be effective in the study was used (ie, 1 dose higher than the study eye dose).

Results

Fifty-eight of 61 enrolled infants had 4-week outcomes completed; mean birth weight was 709 g and mean gestational age was 24.9 weeks. Results are shown stratified by ROP subtype and dose for study eyes (**Table 1**) and fellow eyes (**Table 2**). Success was achieved in 11 of 11 eyes at 0.25 mg, 14 of 14 eyes at 0.125 mg, and 21 of 24 eyes at 0.063 mg. Even at the lowest dose of 0.031 mg, success was achieved in 9 of 9 eyes.

Discussion

Advantages of anti-VEGF therapy over laser include relative ease of administration, more rapid improvement of ROP, less

Table 1. Success of Intravitreous Bevacizumab at the 4-Week Primary Outcome Examination for Study Eyes[a]

	No./Total No.				
ROP Subtype	0.625 mg	0.250 mg	0.125 mg	0.063 mg	0.031 mg
Zone I ROP with plus disease	NA	3/3	4/4	10/10	2/2
Zone I, stage 3 without plus disease	NA	1/1	3/3	1/2	1/1
Zone II, stage 2 or 3 with plus disease	NA	7/7	7/7	10/12	6/6
All type 1 ROP study eyes	NA	11/11	14/14	21/24	9/9

Abbreviations: NA, not applicable; ROP, retinopathy of prematurity.

[a] Three infants who died prior to the 4-week outcome examination were excluded.

Table 2. Success of Intravitreous Bevacizumab at the 4-Week Primary Outcome Examination for Fellow Eyes[a]

	No./Total No.				
ROP Subtype	0.625 mg	0.250 mg	0.125 mg	0.063 mg	0.031 mg
Zone I ROP with plus disease	2/2	5/5	7/7	1/1	NA
Zone I, stage 3 without plus disease	1/1	3/3	1/2	0/0	NA
Zone II, stage 2 or 3 with plus disease	6/6	6/6	10/12	5/5	NA
All type 1 ROP fellow eyes	9/9	14/14	18/21	6/6	NA

Abbreviations: NA, not applicable; ROP, retinopathy of prematurity.

[a] When both eyes were treated, the fellow eye received 1 dose level higher than the study eye. More study eyes than fellow eyes were treated because some infants had type 1 ROP in 1 eye only.

myopia,[6] and vascular growth toward the retinal periphery that might lead to better peripheral vision.[3] A lower dose may reduce the risk for neurodevelopmental disability or detrimental effects on other organs. A limitation of this study was that the sample size was small; therefore, the true success rate may be much lower. We are following up study participants beyond 4 weeks and will report recurrence rates and long-term outcomes.

Conclusions

We found that a dose of bevacizumab as low as 0.031 mg, or 5% of the dose used in the BEAT-ROP trial,[3] was effective in 9 of 9 eyes. Further investigation is warranted to determine the optimal dose for these fragile premature infants and to assess effectiveness and systemic safety in a larger, long-term trial.

ARTICLE INFORMATION

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Author Affiliations: Duke Eye Center, Durham, North Carolina (Wallace, Freedman); Jaeb Center for Health Research, Tampa, Florida (Kraker, Dean, Beck); Eastern Virginia Medical School, Norfolk (Crouch); Emory University School of Medicine, Atlanta, Georgia (Hutchinson); Texas Children's Hospital, Houston (Bhatt); Pediatric Ophthalmology Associates Inc, Columbus, Ohio (Rogers); Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio (Yang); Riley Hospital for Children, Indianapolis, Indiana (Haider); Boston Children's Hospital, Boston, Massachusetts (VanderVeen, Smith); Dean McGee Eye Institute, University of Oklahoma, Oklahoma City (Siatkowski); Wilmer Eye Institute, Baltimore, Maryland (Repka); Smith-Kettlewell Eye Research Institute, San Francisco, California (Good); John A. Moran Eye Center, Salt Lake City, Utah (Hartnett); Baylor College of Medicine, Houston, Texas (Kong); Mayo Clinic, Rochester, Minnesota (Holmes).

Author Contributions: Mr Kraker and Mr Dean had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Wallace, Kraker, Crouch, Hutchinson, Rogers, VanderVeen, Siatkowski, Beck, Repka, Smith, Good, Kong, Holmes.
Acquisition, analysis, or interpretation of data: Wallace, Kraker, Freedman, Crouch, Hutchinson, Bhatt, Rogers, Yang, Haider, VanderVeen, Siatkowski, Dean, Repka, Hartnett, Kong, Holmes.
Drafting of the manuscript: Wallace, Kraker, Crouch, Rogers, VanderVeen, Siatkowski.
Critical revision of the manuscript for important intellectual content: Wallace, Kraker, Freedman, Crouch, Hutchinson, Bhatt, Rogers, Yang, Haider, VanderVeen, Siatkowski, Dean, Beck, Repka, Smith, Good, Hartnett, Kong, Holmes.
Statistical analysis: Kraker, Dean, Kong.
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Administrative, technical, or material support: Kraker, Crouch, Bhatt, Rogers, Yang, VanderVeen, Beck, Repka, Good, Holmes, Kong.
Study supervision: Kraker, Crouch, Hutchinson, Rogers, Yang, VanderVeen, Siatkowski, Repka.

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Group Information: The Pediatric Eye Disease Investigator Group include the following members. *Durham, North Carolina–Duke University Eye Center:* David K. Wallace (investigator [I]); Sharon F. Freedman (I); Sasapin G. Prakalapakorn (I); Sarah K. Jones (coordinator [C]); David A. Nasrazadani (C); Ann Martin Cranford (pharmacist [P]); Beth McLendon Arvik (P); Mary Miller-Bell (P); Catherine S. Sampey (P); and Barbara Krystyna Wiernek (P). *Norfolk–Virginia Pediatric Eye Center:* Earl R. Crouch III (I); Earl R. Crouch Jr (I); Gaylord G. Ventura (C); and James E. Dice (P). *Atlanta, Georgia–The Emory Eye Center:* Amy K. Hutchinson (I); G. Baker Hubbard, III (I); Joshua E. Robinson (I); Judy L. Brower (C); Xi-Juan Chen (P); and James E. Rhodes (P). *Columbus, Ohio–Pediatric Ophthalmology Associates Inc:* David L. Rogers (I); Don L. Bremer (I); Richard P. Golden (I); Catherine O. Jordan (I); Mary Lou McGregor (I); Rachel E. Reem (I); Sara Ann Maletic (C); Meghan C. McMillin (C); Rachel Tobe Miller (C); Jill E. Blind (P); Julie A. Leary (P); Regina M. Mhaskar (P); and Teresa L. Stiltner (P). *Cincinnati, Ohio–Cincinnati Children's Hospital:* Michael B. Yang (I); Eniolami O. Dosunmu (I); Michael E. Gray (I); William W. Motley III (I); Terry L. Schwartz (I); Patricia Cobb (C); Patricia Hirsch (C); Melissa Reed (C); Denise Lagory (P); and Steven Topmiller (P). *Houston–Texas Children's Hospital Department of Ophthalmology:* David K. Coats (I); Amit R. Bhatt (I); Ann B. Demny (C); Lingkun Kong (C); Vanessa K. Bui (P); Jennifer L. Lynds (P); and Tara P. McCartney (P). *Boston, Massachusetts–Boston Children's Hospital:* Deborah K. VanderVeen (I); Jason S. Mantagos (I); Carolyn Wu (I); Grace Yoon (C); Samantha Goldstein (C); Tamar Winter (C); and Rocco Anzaldi (P). *Indianapolis, Indiana–Riley Hospital for Children:* Kathryn M. Haider (I); Charline S. Boente (I); Heather A. Smith (I); Elizabeth A. Hynes (C); Melissa Allard (P); Annette Head (P); and David Morse (P). *Oklahoma City–Dean A. McGee Eye Institute, University of Oklahoma:* Michael Siatkowski (I); Janine E. Collinge (I); Kelli J. Satnes (C); Michelle H. Blunt (C); and Kaci D. Taylor (P). *Salt Lake City–University of Utah/Moran Eye Center:* Mary E. Hartnett (I); David C. Dries (I); Robert O. Hoffman (I); Katie J. Farnsworth (C); and Susan Sorenson (P). *PEDIG Coordinating Center: Tampa, Florida (as of March 2017):* Raymond T. Kraker, Roy W. Beck, Darrell S. Austin, Nicole M. Boyle, Courtney L. Conner, Danielle L. Chandler, Trevano W. Dean, Quayleen Donahue, Brooke P. Fimbel, Graham M. Hardt, James E. Hoepner, Joseph D. Kaplon, Elizabeth L. Lazar, B. Michele Melia, Gillaine Ortiz, Diana E. Rojas, Jennifer A. Shah, and Rui Wu. *National Eye Institute–Bethesda, Maryland:* Donald F. Everett. *PEDIG Executive Committee:* David K. Wallace (chair), William F. Astle (2013-2015), Roy W. Beck, Eileen E. Birch, Angela M. Chen (2017-present), Susan A. Cotter (2015-present), Eric R. Crouch (2014-2015), Laura B. Enyedi (2014-2016), Ayse Erzurum (2016-present), Donald F. Everett, Sharon F. Freedman (2016-present), Jonathan M. Holmes, Raymond T. Kraker, Scott R. Lambert (2013-2015), Katherine A. Lee (2014-2016), Vivian M. Manh (2016-present), Ruth E. Manny (2013-2016), Michael X. Repka, Jayne L. Silver (2014-2016), Katherine K. Weise (2014-2016), and Lisa C. Verderber (2015-present). *Data and Safety Monitoring Committee:* Marie Diener-West (chair), John D. Baker, Barry Davis, Dale L. Phelps, Stephen W. Poff, Richard A. Saunders, and Lawrence Tychsen.

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