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Short-term Outcomes After Very Low-Dose Intravitreal Bevacizumab for Retinopathy of Prematurity

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This study assesses the lowest effective dose of intravitreal bevacizumab for severe retinopathy of prematurity.

Key Points

Question

What is the lowest effective dose of intravitreal bevacizumab for infants with severe retinopathy of prematurity?

Findings

In this masked phase 1 dose de-escalation study, 55 premature infants with type 1 retinopathy of prematurity were treated with intravitreal bevacizumab. Success, defined as improvement by 5 days and no recurrence requiring additional treatment within 4 weeks, was achieved in 13 of 13 eyes (100%) receiving 0.016 mg, and 9 of 9 eyes (100%) receiving 0.008 mg, 9 of 10 eyes (90%) receiving 0.004 mg, but only 17 of 23 eyes (74%) receiving 0.002 mg.

Meaning

These findings suggest that 0.004 mg may be the lowest dose of bevacizumab effective for retinopathy of prematurity.

Abstract

Importance

Intravitreal bevacizumab (0.25 mg to 0.625 mg) is commonly used to treat type 1 retinopathy of prematurity (ROP), but there are concerns about systemic toxicity, particularly the risk of neurodevelopmental delay. A much lower dose may be effective for ROP while reducing systemic risk. Previously, after testing doses of 0.25 mg to 0.031 mg, doses as low as 0.031 mg were found to be effective in small cohorts of infants.

Objective

To find the lowest dose of intravitreal bevacizumab effective for severe ROP.

Design, Setting, and Participants

Between April 2017 and May 2019, 59 premature infants with type 1 ROP in 1 or both eyes were enrolled in a masked, multicenter, dose de-escalation study. In cohorts of 10 to 14 infants, 1 eye per infant received 0.016 mg, 0.008 mg, 0.004 mg, or 0.002 mg of intravitreal bevacizumab. Diluted bevacizumab was prepared by individual research pharmacies and delivered using 300- μ L syringes with 5/16-inch, 30-gauge fixed needles. Analysis began July 2019.

Interventions

Bevacizumab intravitreal injections at 0.016 mg, 0.008 mg, 0.004 mg, or 0.002 mg.

Main Outcomes and Measures

Success was defined as improvement by 4 days postinjection and no recurrence of type 1 ROP or severe neovascularization requiring additional treatment within 4 weeks.

Results

Fifty-five of 59 enrolled infants had 4-week outcomes completed; the mean (SD) birth weight was 664 (258) g, and the mean (SD) gestational age was 24.8 (1.6) weeks. A successful 4-week outcome was achieved for 13 of 13 eyes (100%) receiving 0.016 mg, 9 of 9 eyes (100%) receiving 0.008 mg, 9 of 10 eyes (90%) receiving 0.004 mg, but only 17 of 23 eyes (74%) receiving 0.002 mg.

Conclusions and Relevance

These data suggest that 0.004 mg may be the lowest dose of bevacizumab effective for ROP. Further investigation is warranted to confirm effectiveness of very low-dose intravitreal bevacizumab and its effect on plasma vascular endothelial growth factor levels and peripheral retinal vascularization.

Introduction

Recently, it has become common practice in many neonatal intensive care nurseries to treat severe retinopathy of prematurity (ROP) by intravitreal injection of drugs blocking the bioactivity of vascular endothelial growth factor (VEGF). Bevacizumab is often used for this purpose, typically at doses of 0.25 mg to 0.625 mg,^{1,2} the latter being the dose that demonstrated efficacy in the Bevacizumab Eliminates the Angiogenic Threat of ROP (BEAT-ROP) trial.¹ After intravitreal injection, bevacizumab is found in the systemic circulation and plasma VEGF levels decrease,³ so there are concerns about possible adverse effects. Vascular endothelial growth factor is necessary for normal development of tissues such as the brain, lungs, bones, kidneys, and retina, so blocking its action is potentially harmful to neonates.⁴ There is particular concern that anti-VEGF drugs could increase the risk of neurodevelopmental disability.⁵ To determine the lowest dose of bevacizumab that may be effective in severe ROP that warranted treatment (type 1), we conducted a masked, multicenter, dose de-escalation phase 1 study. Previously, we reported that doses as low as 0.031 mg were associated with improvement in retinopathy in a small cohort of infants.⁶ Herein, we report results of 4 lower doses (0.016 mg-0.002 mg).

Methods

After obtaining institutional review board approval from the Jaeb Center for Health Research Institutional Review Board and other participating institutions' institutional review boards and written informed consent from parents, infants with type 1 ROP in 1 or both eyes without previous treatment were enrolled between April 2017 and May 2019. If type 1 ROP was bilateral, then the study eye was randomly selected. Four doses were evaluated, with each one-half the previous dose concentration (0.016 mg, 0.008 mg, 0.004 mg, and 0.002 mg), each in 10 µL after dilution with normal saline by individual research pharmacies. Investigators were masked to dose throughout the study. Each dose was planned to be used in up to 14 infants to ensure at least 10 infants with 4-week outcomes. Bevacizumab was given by intravitreal injection to the study eye using a 300-µL syringe with a 5/16-inch, 30-gauge fixed needle. Postinjection follow-up eye examinations were performed at day 1, days 3 to 5 (if not improved at day 1), and weekly for 4 weeks.

Success was defined as improvement by 4 days, and no recurrence of type 1 ROP or no severe neovascularization requiring additional treatment within 4 weeks. An independent data safety and monitoring committee reviewed the outcomes for each cohort and determined the next bevacizumab dose to test based on planning committee consensus guidelines: dose reduced for 80% or more 4-week successful outcome, dose repeated for 70% to less than 80% success, and dose increased or study ended for less than 70% success. If the nonstudy eye also required treatment, then the last dose found to be effective in the study was used (ie, twice the concentration of the study eye dose). Analysis began July 2019. This trial is registered with ClinicalTrials.gov ([NCT02390531](https://clinicaltrials.gov/ct2/show/study/NCT02390531)), and the statistical analysis plan can be found in the [Supplement](#).

Results

Fifty-five of 59 enrolled infants (93%) had 4-week outcomes; the mean (SD) birth weight was 664 (258) g, and the mean (SD) gestational age was 24.8 (1.6) weeks. Results stratified by ROP subtype and dose for study and fellow eyes are shown in the [Table](#). At the lowest dose of 0.002 mg, a 4-week successful outcome was achieved in 17 of 23 eyes (74%; 95% CI, 52%-90%; [Figure](#)).

Discussion

Future studies with masked outcome assessment are needed to determine if low-dose bevacizumab is associated with long-term improvement, to assess its effect on plasma VEGF levels and peripheral retinal vascularization compared with higher doses, and to compare the effect of a low dose on retinal and neurodevelopment outcomes vs treatment with laser photocoagulation.

Limitations

This study was limited by a small sample size, so the true success rate may be lower. Also, we report outcomes to only 4 weeks, but we will follow up these infants and report recurrence rates and 2-year outcomes.

Conclusions

We found that a dose as low as 0.004 mg (0.6% of the BEAT-ROP¹ dose) met criteria for successful outcome at 4 weeks in 9 of 10 study eyes (1 per infant). However, at the lower dose of 0.002 mg, a short-term successful outcome was achieved in only 74% of 23 eyes, suggesting that 0.004 mg may be the lower limit of bevacizumab dose effectiveness for ROP.

Notes

Supplement.

Statistical analysis plan

Notes

Journal Club Slides

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Figures and Tables

Table.

Success of Intravitreal Bevacizumab at the 4-Week Primary Outcome Examination, Stratified by Category of Type 1 ROP

ROP subtype	Bevacizumab dose, mg								
	0.625	0.250	0.125	0.063	0.031	0.016	0.008	0.004	0.002
All type 1 ROP study eyes, No./total No. ^a	NA ^b	11/11 ^b	14/14 ^b	21/24 ^b	9/9 ^b	13/13	9/9	9/10	17/23
Zone I ROP with plus disease	NA ^b	3/3 ^b	4/4 ^b	10/10 ^b	2/2 ^b	4/4	2/2	1/2	5/6
Zone I, stage 3 without plus disease	NA ^b	1/1 ^b	3/3 ^b	1/2 ^b	1/1 ^b	3/3	3/3	4/4	2/2
Zone II, stage 2 or 3 with plus disease	NA ^b	7/7 ^b	7/7 ^b	10/12 ^b	6/6 ^b	6/6	4/4	4/4	10/15
All type 1 ROP fellow eyes, No./total No. ^c	10/10 ^b	14/14 ^b	18/21 ^b	6/6 ^b	10/10	7/8	8/11	16/18	NA
Zone I ROP with plus disease	2/2 ^b	5/5 ^b	7/7 ^b	1/1 ^b	5/5	2/2	1/3	6/6	NA
Zone I, stage 3 without plus disease	1/1 ^b	3/3 ^b	1/2 ^b	0 ^b	2/2	3/3	3/4	2/2	NA
Zone II, stage 2 or 3 with plus disease	7/7 ^b	6/6 ^b	10/12 ^b	5/5 ^b	3/3	2/3	4/4	8/10	NA

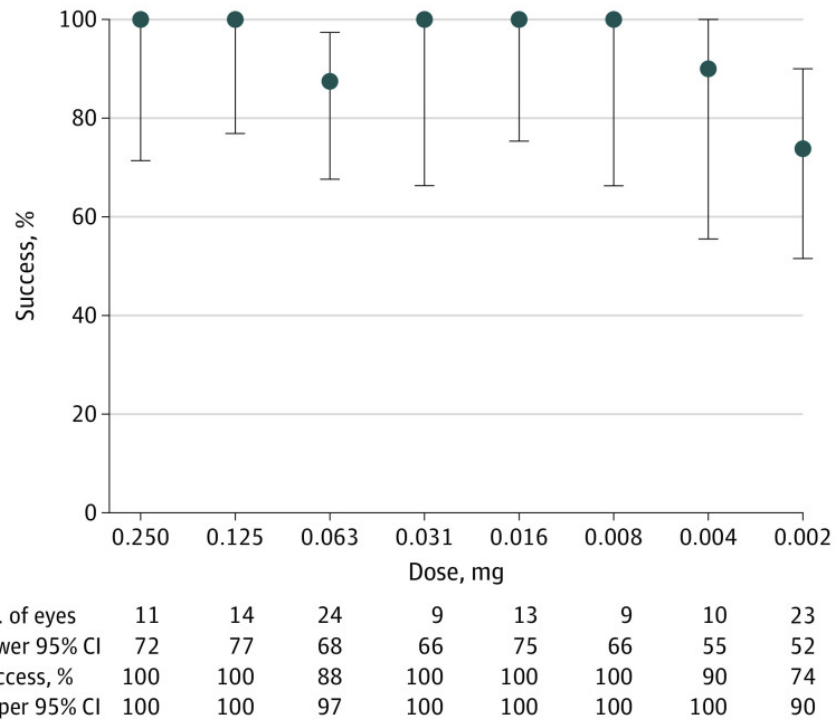
Abbreviations: NA, not applicable; ROP, retinopathy of prematurity.

^aSeven infants were excluded (4 infants died prior to 4-week outcome examination; 1 failed, but it was not confirmed by second examiner; 1 was injected with the wrong dose in the study eye; and 1 had the fellow eye treated in the absence of type 1 ROP within one week of the study eye).

^bData from higher doses were reported previously.⁶

^cWhen both eyes were treated, the fellow eye received the next higher dose than received by the study eye. More study eyes than fellow eyes were treated because some infants had type 1 ROP in one eye only.

Figure.



Success of Intravitreal Bevacizumab in the Study Eye at the 4-Week Primary Outcome Examination