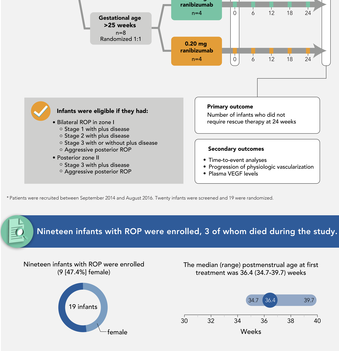
Comparing Alternative Ranibizumab Dosages for Safety and Efficacy in Retinopathy of Prematurity: A Randomized Clinical Trial

Stahl A, Krohne TU, Eter N, et al. JAMA Pediatr. 2018;172:278-286.
doi:10.1001/jamapediatrics.2017.4838

The core of retinopathy of prematurity (ROP) pathophysiology is disturbed blood vessel growth, which can lead to bilateral blindness in early infancy. Because vascular endothelial growth factor (VEGF) is the main angiogenic growth factor driving blood vessel growth in the retina, pharmacologic treatment approaches that target VEGF are being evaluated. Of concern, intravitreally injected drugs leak into the systemic circulation, and it is unknown what adverse effects systemic VEGF suppression has on organ development. A single dose of intravitreally injected bevacizumab, for example, suppresses VEGF plasma levels below the limit of detection for weeks. On the other hand, the anti-VEGF antibody fragment ranibizumab has a systemic half-life of hours rather than days.

The Comparing Alternative Ranibizumab Dosages for Safety and Efficacy in Retinopathy of Prematurity (CARE-ROP) study is a prospective, randomized trial that evaluates the efficacy and safety of 2 different doses of ranibizumab that are lower than 50% of the standard adult dose.

The CARE-ROP study is a randomized, multicenter, prospective, double-blind, 2-arm, parallel-group, phase 2, investigator-initiated trial held at 9 academic medical centers in Germany.



Infants were eligible if they had:

- Bilateral ROP in zone I
  - Stage 1 with plus disease
  - Stage 2 with plus disease
  - Stage 3 with or without plus disease
  - Aggressive posterior ROP
- Posterior zone II
  - Stage 3 with plus disease
  - Aggressive posterior ROP

Primary outcome

Number of infants who did not require rescue therapy at 24 weeks

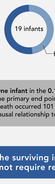
Secondary outcomes

- Time-to-event analyses
- Progression of physiologic vascularization
- Plasma VEGF levels

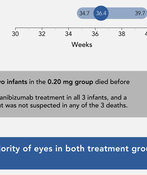
* Patients were recruited between September 2014 and August 2016. Twenty infants were screened and 19 were randomized.

Nineteen infants with ROP were enrolled, 3 of whom died during the study.

Nineteen infants with ROP were enrolled (9 (47.4%) female)



The median (range) postmenstrual age at first treatment was 36.4 (34.7-39.7) weeks



- **One infant** in the **0.12 mg group** and **two infants** in the **0.20 mg group** died before the primary end point.
- Death occurred 101 days or more after ranibizumab treatment in all 3 infants, and a causal relationship to the study treatment was not suspected in any of the 3 deaths.

Of the surviving infants, the majority of eyes in both treatment groups did not require rescue therapy.

Proportion of eyes in the **0.12 mg dose** ranibizumab group not requiring rescue therapy:

Proportion of eyes in the **0.20 mg dose** ranibizumab group not requiring rescue therapy:

Both ranibizumab doses were equally successful in controlling acute ROP.

Cochran-Mantel-Haenszel analysis comparing success in controlling acute ROP in the two ranibizumab doses

- VEGF plasma levels were not systematically altered in either group.

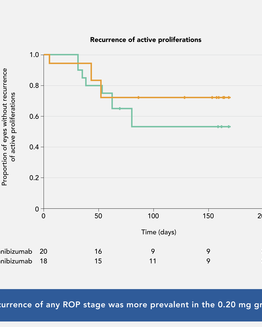
Physiologic intraretinal vascularization was superior in the 0.12-mg group.

Proportion of eyes in the **0.12 mg dose** ranibizumab group with full vascularization:

Proportion of eyes in the **0.20 mg dose** ranibizumab group with full vascularization:

Resolution of the ridge and complete resolution of any ROP were slower to appear, and not all eyes achieved full resolution of ROP.

Time to resolution of any ROP



No. at risk					
0.12 mg of ranibizumab	20	15	8	2	0
0.20 mg of ranibizumab	18	11	7	0	0

Recurrence of more severe signs of ROP (plus disease and active proliferations) were observed, however, these were found to be less frequent than reappearance of a preretinal ridge.

Recurrence of plus disease

No. at risk					
0.12 mg of ranibizumab	20	20	13	12	0
0.20 mg of ranibizumab	18	14	9	8	0

Recurrence of active proliferations

No. at risk					
0.12 mg of ranibizumab	20	16	9	9	0
0.20 mg of ranibizumab	18	15	11	9	0

Recurrence of any ROP stage was more prevalent in the 0.20 mg group.

Recurrence of any ROP

No. at risk					
0.12 mg of ranibizumab	14	6	2	0	0
0.20 mg of ranibizumab	10	0	0	0	0

Conclusions

Ranibizumab was effective in controlling acute ROP, and 24% of the standard adult dose (0.12 mg) appears equally effective as 40% (0.20 mg). Superior vascularization of the peripheral retina with 0.12 mg of ranibizumab indicates that the lower dose may be favorable. Unchanged plasma VEGF levels point toward a limited systemic drug exposure after ranibizumab.