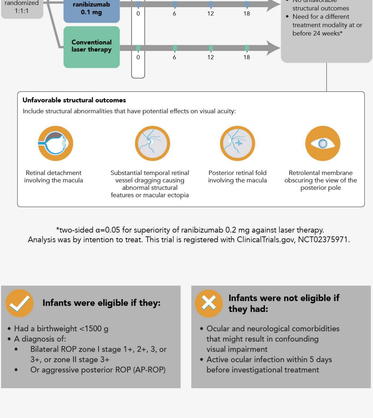
Ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW): an open-label randomized controlled trial

Stahl A, Lepore D, Fielder A, et al. *The Lancet*. 2019;394:1551-1559.
doi:10.1016/S0140-6736(19)31344-3

Despite increasing worldwide use of anti-vascular endothelial growth factor agents for treatment of retinopathy of prematurity (ROP), there are few data on their ocular efficacy, the appropriate drug and dose, the need for retreatment, and the possibility of long term systemic effects. This study evaluated the efficacy and safety of intravitreal ranibizumab compared with laser therapy in treatment of ROP.

This randomized, open-label, superiority multicenter, three-arm, parallel group trial was conducted in 87 neonatal and ophthalmic centers in 26 countries.

Infants were screened with birthweight <1500 g who met criteria for treatment for retinopathy. Individuals were stratified by disease zone and geographical region using computer interactive response technology.



*two-sided α=0.05 for superiority of ranibizumab 0.2 mg against laser therapy.
Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, NCT02375971.

Infants were eligible if they:

- Had a birthweight <1500 g
- A diagnosis of:
  - Bilateral ROP zone I stage 1+, 2+, 3, or 3+, or zone II stage 3+
  - Or aggressive posterior ROP (AP-ROP)

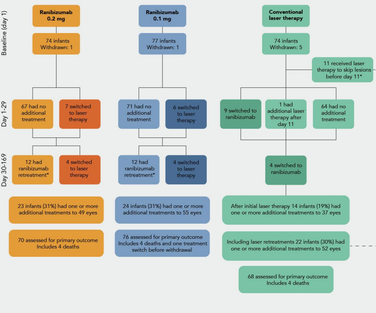
Infants were not eligible if they had:

- Ocular and neurological comorbidities that might result in confounding visual impairment
- Active ocular infection within 5 days before investigational treatment

Number of infants receiving additional treatment

Between Dec 31, 2015, and June 29, 2017, 225 participants were randomly assigned.

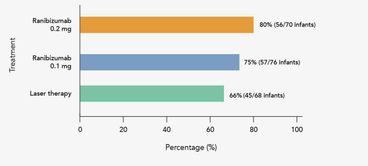
Progress of infants with retinopathy of prematurity through additional post-baseline study treatments.



Seven infants were withdrawn before treatment and 17 did not complete follow-up to 24 weeks; 214 infants were assessed for the primary outcome. Number of infants receiving at least one additional treatment (ranibizumab or laser therapy), either allowed in the protocol (up to 29 days when ranibizumab retreatment was first allowed) or up to 169 days, and treatment switches, which contributed to the primary outcome (darker shades of each color in the figure). Infants might have received one or more additional treatments in one or both eyes. Laser treatments to skip lesions were allowed as part of the baseline treatment but are included because they represent extra treatment episodes. *Allowed in protocol.

Ranibizumab 0.2 mg resulted in fewer eyes with unfavorable structural outcomes versus ranibizumab 0.1 mg or laser therapy. A ranibizumab dose of 0.1 mg offered no advantage over the 0.2 mg dose.

Treatment Success



Odds Ratio (OR) of Treatment Success

This was performed using a hierarchical testing strategy.

* (P= .051)

One infant had an unfavorable structural outcome following ranibizumab 0.2 mg, compared with five following ranibizumab 0.1 mg and seven after laser therapy. Death, serious and non-serious systemic adverse events, and ocular adverse events were evenly distributed between the three groups.

This trial had several limitations

Care was provided by clinicians from a wide range of settings and experience to mimic routine clinical practice.

Instructions for the administration of ranibizumab were provided but not training in the use of fundoscopy to determine the primary outcome, and not all centers had access to retinal photography.

The trial was open label, not masked, and used no placebo.

Decisions on retreatment were made on an individual basis and retreatment with ranibizumab restricted to intervals of 28 days.

Clinician preference for one treatment could lead to biased decisions to re-treat.

The study was limited by slow enrollment, which led to a modified recruitment target and reduced power.

It is unclear why the significance of the primary comparison was marginal. Retrospectively, it is difficult to ascribe this result either to treatment effects being similar or to an inadequate sample size.

Conclusions

In summary, ranibizumab 0.2 mg was as effective and safe in the treatment of active ROP as laser therapy, might be superior, was associated with better short-term ocular outcomes, and had an acceptable 24-week safety profile. Compared with laser treatment, the potential for procedural complications and the need for regular clinical follow-up after ranibizumab treatment must be balanced against fewer adverse structural outcomes.