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Anti-vascular endothelial growth factor (VEGF) drugs for treatment of retinopathy of prematurity.
*Cochrane Database of Systematic Reviews* 2016, Issue 2. Art. No.: CD009734.
DOI: 10.1002/14651858.CD009734.pub2.

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[Intervention Review]

# Anti-vascular endothelial growth factor (VEGF) drugs for treatment of retinopathy of prematurity

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**Editorial group:** Cochrane Neonatal Group.
**Publication status and date:** Edited (no change to conclusions), published in Issue 5, 2016.

**Citation:** Sankar MJ, Sankar J, Mehta M, Bhat V, Srinivasan R. Anti-vascular endothelial growth factor (VEGF) drugs for treatment of retinopathy of prematurity. *Cochrane Database of Systematic Reviews* 2016, Issue 2. Art. No.: CD009734. DOI: 10.1002/14651858.CD009734.pub2.



## ABSTRACT

### Background

Vascular endothelial growth factor (VEGF) plays a key role in angiogenesis in fetal life. Recently, researchers have attempted to use anti-VEGF agents for the treatment of retinopathy of prematurity (ROP), a vasoproliferative disorder. There is currently uncertainty regarding the safety and efficacy of these agents in preterm infants with ROP.

### Objectives

To evaluate the efficacy and safety of anti-VEGF drugs when used either as monotherapy, i.e. without concomitant cryotherapy or laser therapy or in combination with planned cryo/laser therapy in preterm infants with type 1 ROP (defined as zone I any stage with plus disease, zone I stage 3 with or without plus disease or zone II stage 2 or 3 with plus disease).

### Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL 2016, Issue 1), MEDLINE (1966 to January 1, 2016), EMBASE (1980 to January 1, 2016), CINAHL (1982 to January 1, 2016), conference proceedings, and previous reviews.

### Selection criteria

Randomised or quasi-randomised controlled trials that evaluated the efficacy and safety of administration, or both, of anti-VEGF agents compared with conventional therapy in premature infants with ROP.

### Data collection and analysis

We used standard Cochrane and Cochrane Neonatal methods for data collection and analysis.

### Main results

Three trials, in which 239 infants participated, fulfilled the inclusion criteria. Two trials compared intravitreal bevacizumab with conventional laser therapy (monotherapy) while the third compared intravitreal pegaptanib *plus* laser treatment with laser and cryotherapy (combination therapy) in infants with type 1 ROP.

Of the two studies that evaluated intravitreal bevacizumab, one randomized infants while the other randomized eyes of the infants to the intervention and control groups. The former did not report any difference in the incidence of complete or partial retinal detachment

between the groups (143 infants; RR 1.04, 95% CI 0.21 to 5.13; RD 0.00, 95% CI -0.06 to 0.07; very low quality evidence) but reported a significant reduction in the risk of refractive errors - very high myopia - at 30 months of age (211 eyes; RR 0.06, 95% CI 0.02 to 0.20; RD -0.40, 95% CI -0.50 to -0.30; low quality evidence) and recurrence of ROP by 54 weeks' postmenstrual age (143 infants; RR 0.22, 95% CI 0.08 to 0.62; RD -0.20, 95% CI -0.31 to -0.09; moderate quality evidence) in the bevacizumab group. The study found no difference in the risk of mortality before discharge from the hospital (150 infants; RR 1.50; 95% CI 0.26 to 8.75; RD 0.01; 95% CI -0.04 to 0.07; low quality evidence), mortality at 30 months of age (150 infants; RR 0.86, 95% CI 0.30 to 2.45; RD -0.01; 95% CI -0.10 to 0.08; low quality evidence), corneal opacity requiring corneal transplant (286 eyes; RR 0.34, 95% CI 0.01 to 8.26; RD -0.01; 95% CI -0.03 to 0.02; very low quality evidence), or lens opacity requiring cataract removal (286 eyes; RR 0.15, 95% CI 0.01 to 2.79; RD -0.02; 95% CI -0.05 to 0.01; very low quality evidence). The second trial that randomized eyes of the infants did not find any difference in the risk of complete retinal detachment between the eyes randomized to bevacizumab and those that were randomized to laser therapy (13 eyes; RR 0.33, 95% CI 0.01 to 7.50; RD -0.08, 95% CI -0.27 to 0.11).

When used in combination with laser therapy, intravitreal pegaptanib was found to reduce the risk of retinal detachment when compared to laser/cryotherapy alone (152 eyes; RR 0.26, 95% CI 0.12 to 0.55; RD -0.29, 95% CI -0.42 to -0.16; low quality evidence). The incidence of recurrence of ROP by 55 weeks' postmenstrual age was also lower in the pegaptanib + laser therapy group (76 infants; RR 0.29, 95% CI 0.12 to 0.7; RD -0.35, 95% CI -0.55 to -0.16; low quality evidence). There was no difference in the risk of perioperative retinal haemorrhages between the two groups (152 eyes; RR 0.62, 95% CI 0.24 to 1.56; RD -0.05, 95% CI -0.16 to 0.05; very low quality evidence). The risk of delayed systemic adverse effects with either of the drugs is, however, not known.

### Authors' conclusions

Implications for practice: Intravitreal bevacizumab reduces the risk of refractive errors during childhood when used as monotherapy while intravitreal pegaptanib reduces the risk of retinal detachment when used in conjunction with laser therapy in infants with type 1 ROP. Quality of evidence was, however, low for both the outcomes because of the risk of detection and other biases. Effect on other critical outcomes and, more importantly, the long-term systemic adverse effects of the drugs are not known. The insufficient data precludes strong conclusions favouring routine use of intravitreal anti-VEGF agents in preterm infants with type 1 ROP.

Implications for research: Further studies are needed to evaluate the effect of anti-VEGF agents on structural and functional outcomes in childhood and delayed systemic adverse effects such as myocardial dysfunction and adverse neurodevelopmental outcomes.

## PLAIN LANGUAGE SUMMARY

### Anti-vascular endothelial growth factor (VEGF) drugs for treatment of retinopathy of prematurity

### Background

Retinopathy of prematurity (ROP) is a vascular disorder of the immature retina that can result in impairment of vision and even blindness in premature infants. It is treated primarily by removal of the part of the retina without any blood vessels ('avascular' retina) by cryotherapy or laser therapy. Though these treatments result in a significant improvement in long-term outcomes, the results are far from perfect. In addition, they cause permanent loss of the peripheral visual field. Recently, studies have been done to evaluate the use of anti-VEGF agents to treat ROP. These agents inhibit the action of vascular endothelial growth factor (VEGF), a key regulator of new vessel formation in fetal life. Animal studies had shown significant reduction in the neovascular response following injection of anti-VEGF antibodies into the vitreous cavity of the eyes ('intravitreal' therapy).

### Study characteristics

We searched scientific databases in January 2016 for studies evaluating the efficacy and safety of intravitreal therapy with anti-VEGF agents in preterm infants with ROP. We identified three randomized controlled trials involving 239 infants. Two trials compared intravitreal bevacizumab with conventional laser therapy. The third trial compared intravitreal pegaptanib *plus* laser therapy with laser/cryotherapy alone.

### Key results

The results suggest that intravitreal bevacizumab reduces the risk of refractive errors (high myopia) during childhood while intravitreal pegaptanib used in conjunction with laser therapy reduces the risk of retinal detachment. Effects on other critical outcomes including delayed side effects like stroke are not known. Further studies are needed to assess these outcomes.

### Quality of the evidence

The quality of the evidence was graded as very low or low for most of the key outcomes.