

# Anti-Vascular Endothelial Growth Factor Medications in Retinopathy of Prematurity

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## Keywords

- Retinopathy of prematurity (ROP) • Vascular endothelial growth factor (VEGF)
- Bevacizumab • Prematurity • Aggressive posterior retinopathy of prematurity

## Key points

- The use of anti-vascular endothelial growth factor (VEGF) medications is increasing in the treatment of retinopathy of prematurity (ROP).
- Although there may be advantages to anti-VEGF therapy, such as rapid effect, ease of use, and reduction of the risk of refractive errors during childhood, treatment with these medications changes the course of disease with aberrant retinal vasculature, and later recurrences of treatment warranting disease. Therefore, the use of anti-VEGF medications as first-line treatment in ROP is reserved to a small subset of clinical scenarios.
- Systemic absorption of anti-VEGF agents after intravitreal injection has been demonstrated, and the effect on developing vascular beds, organogenesis, and neurodevelopment is unknown.
- Prospective, randomized, multicenter studies are needed to define the optimal therapeutic approach to the different ROP clinical phenotypes.

## INTRODUCTION

Retinopathy of prematurity (ROP) is a vasoproliferative retinal disorder that affects preterm infants. Thanks to improvements in the neonatal care, younger and younger premature infants with lower birth weights are surviving. Interestingly, the prevalence of ROP over the past 30 years appears to be stable in the

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United States [1]. Increased prevalence of ROP is seen in developing countries [2], with more severe phenotypes of the disease possibly due to uncontrolled oxygen delivery or perhaps to a different genetic basis of the disease [3–6]. Despite increasing understanding of pathophysiology, optimization of screening guidelines, and improved treatment approaches, ROP remains the leading cause of blindness in premature infants around the world. Vision loss occurs secondary to retinal detachment, macular dragging, and vitreous hemorrhage.

Retinal vascularization is incomplete in the preterm infant, and the peripheral avascular retina becomes hypoxic as an infant is moved from supplemental oxygen to room air, causing the release of angiogenic factors that induce vasoproliferation into the vitreous. These angiogenic factors include vascular endothelial growth factor (VEGF), insulin-like growth factor-1, erythropoietin, and placental growth factor [7]. VEGF inhibition, which has revolutionized the treatment of several adult diseases, such as neovascular age-related macular degeneration and diabetic macular edema, seems to be an ideal treatment of a vasoproliferative disease such as ROP. However, there are numerous systemic and ocular concerns regarding anti-VEGF drugs in preterm infants. VEGF is important in physiologic development of the retina as well as organogenesis (including the kidneys, brain, and lungs) [7].

The gold standard of treatment of type 1 ROP is laser to the avascular retina to prevent progression of disease and cause regression of the extraretinal vascularization [8]. VEGF plays a key role in angiogenesis, organogenesis, as well as the pathophysiology of ROP. Despite the systemic concerns, the first report of intravitreal anti-VEGF use in infants with severe ROP was published in 2007 [9], and since, many studies have reported high rates of disease regression after treatment, mainly with bevacizumab.

The reported advantages to anti-VEGF medications in ROP compared with laser include a faster decrease of VEGF levels, a less stressful procedure to the infants due to a shorter procedure, and better refractive and structural outcomes. However, recurrences of ROP necessitating re-treatment have been described at up to 2.5 years after the initial treatment with intravitreal anti-VEGF agents [10]. Moreover, there are many unanswered questions about which anti-VEGF drug to use, dosage, injection technique, timing of treatment, and follow-up, as well as monotherapy versus combined therapy.

This article aims to review the current trends and future directions of anti-VEGF therapy in the treatment of ROP.

## **SIGNIFICANCE/IN-DEPTH ANALYSIS OF THE TOPIC**

The current understanding of the natural history of the disease, treatment paradigms, and screening guidelines is based on 2 seminal studies: The Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) and The Early Treatment of Retinopathy of Prematurity (ETROP) [8,11].

An international classification system of ROP divided infants with ROP into prognostic subgroups of higher risk of unfavorable outcomes and facilitated the

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