Vascular Endothelial Growth Factor Antagonist Therapy for Retinopathy of Prematurity

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KEYWORDS

- Vascular endothelial growth factor • Physiologic retinal vascular development (PRVD)
- Intravitreal neovascularization (IVNV) • Bevacizumab • Angiogenesis
- Oxygen-induced retinopathy (OIR)

KEY POINTS

- Before considering anti-vascular endothelial growth factor (VEGF) agents in preterm infants, more studies are needed to determine long-term effects on safety, proper doses, or even the type of anti-VEGF agent or other drug.
- Retinopathy of prematurity phenotypes may vary throughout the world based on environmental factors and potential differences in genetic variants. These considerations are important when comparing outcomes from clinical reports after anti-VEGF therapy.
- Although there is promise with anti-VEGF treatment, there is clinical risk of poor outcome and safety concerns potentially from systemic reduction of VEGF. Other treatments are needed.

INTRODUCTION

Over the past several decades, vascular endothelial growth factor (VEGF) has become recognized as an important pathologic angiogenic factor in several eye diseases, including age-related macular degeneration (AMD),[1–3] diabetic retinopathy,[4,5] retinal vein occlusion,[4] and retinopathy of prematurity (ROP). Before US Food and Drug Administration (FDA) approval of anti-VEGF agents for AMD, a disease affecting elderly adults, preclinical studies tested VEGF inhibitors in animal models of angiogenesis, including models of oxygen-induced retinopathy (OIR) in which blood vessels grow into the vitreous cavity similar to what occurs in diabetic retinopathy and ROP.[6,7] After proven efficacy that anti-VEGF agents reduced intravitreal angiogenesis

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in preclinical testing in models of OIR and aberrant angiogenesis in clinical trials for neovascular AMD and adult eye diseases, a clinical trial was performed to test the effect of inhibiting the bioactivity of VEGF using the monoclonal antibody, bevacizumab, in severe ROP.[8] Success was reported in a subgroup of preterm infants with zone I, stage 3 ROP with plus disease. However, concerns remain.

No dosing studies were performed to determine an effective and safe dose or optimal agent for ROP. VEGF is an important angiogenic factor in development, a survival factor of newly formed capillaries, and also plays a role in the homeostasis of already developed vasculature.[9,10] In adults, repeated treatment with anti-VEGF agents, the standard of care for AMD, has been associated with geographic atrophy, another cause of vision loss in AMD.[11] VEGF is also a neuroprotective agent for retinal neurons.[12] Therefore, concerns of damaging effects from anti-VEGF were raised, particularly in the developing infant retina. In addition, anti-VEGF agents injected into the vitreous cavity reduced serum VEGF for several weeks,[13,14] raising additional concern of the effects of removing systemic VEGF on the development of organs, particularly kidney, brain, and lung in the preterm infant. Following the publication of the clinical trial, complications were reported after a single intravitreal injection of bevacizumab. These complications included persistent avascular retina, recurrent intravitreal angiogenesis, and stage 5 retinal detachment.[15,16] Therefore, before considering anti-VEGF agents in preterm infants, more studies are needed to determine long-term effects on safety, proper doses, or even the type of anti-VEGF agent or other drug.

In this article, the growing problem of ROP worldwide, the standard of care laser treatment in severe ROP, and the need for new treatments are discussed. Also discussed are the reasons to consider inhibiting the VEGF signaling pathway in ROP and the concerns about broad inhibition. Finally, the potential role of VEGF in ROP based on studies in OIR models, the effects of anti-VEGF based on basic research data, and the clinical relevance of these data are covered.

THE PROBLEM: RETINOPATHY OF PREMATURITY IS INCREASING WORLDWIDE AND HAS DIFFERENT PHENOTYPES

With increases in preterm births, ROP has become one of the leading causes of childhood blindness worldwide.[17] In the United States, ~14% of childhood blindness is attributed to ROP and in some developing nations estimates are greater than 20%.[18] In addition, some countries have developed the ability to save preterm infants but lack resources to regulate oxygen and are experiencing not only cases of ROP from extreme prematurity but also additional cases of ROP in larger and older infants from high oxygen-induced damage to newly formed retinal capillaries similar to what occurred in the 1940s and 1950s in the United States, United Kingdom, and Canada.[15,19,20] Compounding these increases in ROP cases throughout the world, the number of adequately trained ophthalmologists to diagnose and treat ROP is not increasing to meet the need.[19] There also appears to be a heritable component to ROP,[20] and genetic pools differ throughout the world. Thus, ROP phenotypes may vary throughout the world based on environmental factors and, potentially, differences in genetic variants. These considerations are important when comparing outcomes from clinical reports after anti-VEGF therapy.

CURRENT TREATMENT FOR RETINOPATHY OF PREMATURITY AND REASONS FOR BETTER THERAPIES

When ROP was first diagnosed as retrolental fibroplasia in the 1940s in the United States, studies in animal models were performed that revealed that high oxygen at