CHEST

Intravitreal Bevacizumab for Retinopathy of Prematurity

Another Hit to the Immature Lung?

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Retinopathy of prematurity (ROP) results from arrest of normal retinal and vascular development with compensatory mechanisms that cause aberrant vascularization of the retina. Deficit of growth factors normally provided in utero prevent normal vascularization of the retina in very preterm infants. Postnatal supplemental oxygen and its effect on angiogenesis also plays a key role in the pathogenesis of ROP, but with different effects depending on the stage of the disease. Hyperoxia drives suppression of angiogenic factors, especially erythropoietin and vascular endothelial growth factor (VEGF) that cause cessation of vascularization and loss of normal vessels during phase 1 of ROP (from preterm birth to approximately 30 to 32 weeks of postmenstrual age). On the contrary, retinal hypoxia drives an increase of vascular growth factors, which leads to formation of abnormal vessels in phase 2 of ROP (from 30 to 32 weeks postmenstrual age until term).[1] Therefore, finding the optimal oxygenation target, in regards to ROP prevention, remains elusive. In the light of large multicenter trials of respiratory support in preterm infants, low oxygen saturation targets (85% to 89%) have been abandoned because of evidence of increased overall mortality rates at the cost of a higher risk of severe ROP,[2] which together with increased survival of extremely preterm infant may explain the increase in ROP incidence observed in recent studies. ROP continues to be a leading cause of childhood blindness and a public health problem around the world.

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Laser photocoagulation has been the standard of treatment of ROP for many years. However, since its introduction in 2007, the use of intravitreal injection of anti-VEGF agents has been incorporated to ROP management. Several trials have shown that anti-VEGF drugs (bevacizumab, ranibizumab) may be superior to laser photocoagulation for type I ROP (zone I [any stage with plus disease] or zone I-stage 3 without plus disease); this treatment is used commonly by pediatric ophthalmologists.[3] However, only recently have trials evaluated data on long-term drug safety,[4] and there is a concern about adverse effects on neurodevelopment and the systemic effects in other organs.[5] In particular, VEGF signaling is essential for lung development (both alveolarization and vascularization) and has been involved in bronchopulmonary dysplasia (BPD) pathogenesis.[6] It has been shown that VEGF is reduced soon after birth in tracheal aspirates of premature infants who later experienced BPD compared with those who did not (most receiving high concentrations of inspired oxygen during treatment of respiratory disease syndrome).[6] Also, increased production of sFlT-1 (an endogenous antagonist of the VEGF) in the amniotic fluid occurs during chorioamnionitis (a known risk factor for BPD and ROP) and has been associated to BPD-like changes and pulmonary hypertension in a rat model.[7] In addition, animal studies have shown impaired alveologenesis and angiogenesis in animal models after intravitreal injection of bevacizumab[8,9]; however, until now, there was no study that showed evidence of adverse effects of anti-VEGF agents in the human neonatal lung.

In this issue of *CHEST*, Huang et al[10] explored the hypothesis that intravitreal bevacizumab may affect respiratory evolution in preterm infants with BPD. They conducted a retrospective review of patients with BPD, depending on whether they received treatment with

bevacizumab for type I ROP or had a different degree of ROP and did not require any treatment. The two groups had different severity of the respiratory disease at the beginning of treatment and different gestational ages, both variables were related to longer duration of respiratory support. Despite this, Huang et al[10] have demonstrated the effect that the treatment itself has on the duration of the ventilatory support, using multivariate analysis through Cox regression. Thus, the intravitreal injection of bevacizumab increases the risk of not being able to withdraw ventilatory support by 2.3 times, regardless of gestational age, patient weight, or the type of respiratory support received when diagnosed with ROP. Unfortunately, the authors did not obtain serum levels of bevacizumab in this cohort, which might have reinforced the causal relationship between bevacizumab and prolonged respiratory support.

Nevertheless, the study by Huang et al[10] is important for several reasons. First, it provides direct clinical evidence that intravitreal anti-VEGF may have systemic adverse effects, which is something that has been questioned in the literature.[11] Second, this is the first study that shows that bevacizumab may cause a detrimental effect on the developing lung, which supports data from animal studies. The findings of the authors suggest that anti-VEGF agents should be used with caution and at the lowest effective dose[12] and that a closer respiratory surveillance of infants who are treated with anti-VEGF agents may be warranted. Finally, this study reminds us that ROP and BPD are both diseases of altered vascular development that may share pathologic pathways. BPD and ROP present frequently in the same infants, and both diseases have many common epidemiologic and physiologic risk factors. The balance between proangiogenic and antiangiogenic signaling seems to be a link between both diseases. Further research should determine the long-term effects of anti-VEGF agents on the lung and deepen the understanding of the interactions between ROP and BPD pathogenesis to improve preventive and therapeutic strategies for both diseases.

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