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Anti-VEGF treatment for ROP: which drug and what dose?

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Intravitreal injection of anti-VEGF drugs has increasingly been used for treatment of severe (type 1) retinopathy of prematurity (ROP). These drugs inhibit the action of vascular endothelial growth factor (VEGF), an important signaling agent for new blood vessel development but one that is present in excess in eyes of infants with severe ROP. Initial results with anti-VEGF treatment are promising, but we have much to learn about these drugs and their effects on rapidly developing premature infants.

First, which of the anti-VEGF drugs is the best one for ROP? Choices include bevacizumab (Avastin), ranibizumab (Lucentis), pegaptanib (Macugen), and aflibercept (Eylea), each of which have different molecular structures and actions. Bevacizumab is a monoclonal antibody, whereas ranibizumab is an antibody fragment, and both bind to all VEGF-A isoforms. Pegaptanib is a single strand nucleotide that binds specifically to one VEGF-A isoform. Aflibercept is a "VEGF trap"—a fusion protein that binds VEGF-A with high affinity.

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Several authors have reported very high rates of disease regression after treatment with bevacizumab.[1,2] The BEAT-ROP (Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity) study randomized infants with zone I or posterior zone II, stage 3 ROP with plus disease to laser verses 0.625mg of intravitreal bevacizumab.[2] Recurrence of neovascularization in one or two eyes requiring retreatment by 54 weeks' postmenstrual age occurred in 4 of 70 infants (6%) in the bevacizumab group verses 19 of 73 infants (26%) in the laser group ($P = 0.002$ for zone I, $P = 0.27$ for zone II). Two years after treatment, the mean refractive error after bevacizumab versus laser, respectively, was −1.9 versus −11.2 D for zone I eyes and −0.6 D versus −5.6 D for zone II eyes.

There are a few reports of outcomes after other anti-VEGF drugs for ROP. Arambulo and colleagues[3] found that 14 of 16 eyes did not progress to stage 4 or 5 after treatment with ranibizumab. Yi and colleagues[4] found that 58 of 66 eyes regressed after one ranibizumab injection, and 8 eyes required a second injection. Castellanous and colleagues[5] found that 6 of 6 eyes treated with ranibizumab had complete resolution without recurrence. Wong and colleagues[6] found less favorable results; of 6 eyes treated with ranibizumab, 5 had reactivation of ROP and required additional treatment, at an average time of 6 weeks later. Autrata and colleagues[7] randomly assigned 76 infants to pegaptanib plus laser or to laser alone, and they found that the pegaptanib-augmented group had a success rate of 90% versus 61% for laser alone. Salman and Said[8] treated 26 infant eyes with aflibercept, and 25 of those had a favorable structural outcome; remarkably, the median refractive error after 1 year was +0.75 D.

There are several advantages to anti-VEGF injections compared with laser, including less stress to the infant with treatment, more rapid improvement, less myopia, and possibly better peripheral vision. It has been hypothesized that the progressive growth of blood vessels into the retinal periphery after anti-VEGF treatment will translate into better visual fields than after laser; however, this has yet to be confirmed by visual field data. Despite these advantages, there are significant concerns about the potential for ocular and systemic side effects. The effect of anti-VEGF treatment on retinal function is unknown, and a study by LePore and colleagues[9] raised significant concerns about retinal vascular development after bevacizumab. They treated 13 infants with 0.5 mg bevacizumab in one eye and laser for the other eye. All of the eyes treated with bevacizumab developed vascular abnormalities that were not observed in the majority of eyes treated with laser, including large avascular areas, abnormal branching and shunts in the retinal periphery, hyperfluorescent lesions in the posterior pole, and absence of the foveal avascular zone. The long term visual implications of these changes are unknown.

After intravitreal injection, anti-VEGF drugs reach the systemic circulation. In one study, bevacizumab blood levels after intravitreal injection peaked 2 weeks after injection, and it was detectible for up to 60 days. Large reductions in serum VEGF levels have been observed up to 6-8 weeks after injection. This likely occurs because vascular endothelial cells endocytose the bevacizumab full-length antibody and then release it later, a natural mechanism that prolongs the half-life of antibodies in the circulation. Ranibizumab also gets in the bloodstream, but it has a shorter half-life than bevacizumab. Zhou and colleagues[10] observed that after 0.5 mg of ranibizumab, VEGF levels decreased from 46 pg/ml at baseline to 11 pg/ml one day after injection, but then they returned to normal by 1 week.

Theoretically, these drugs could be harmful by inhibiting VEGF's role in normal vascular development throughout the body, including the brain, lungs and kidneys. Whether or not this occurs is difficult to sort out from observational data, because any cohort of premature infants followed forward will have many comorbidities, such as cerebral palsy and developmental delay. One observational study based on Canadian registry data found that infants receiving bevacizumab had greater odds of motor delay compared with those who had laser.[11] However, the authors acknowledge that the comparison may be confounded by important differences between the groups; for example, those receiving bevacizumab had more severe ROP, which is also associated with adverse neurodevelopmental outcome. We can probably only know if anti-VEGF treatment for ROP causes or contributes to systemic problems by doing adequately powered (typically large) randomized trials comparing different treatments. If it is found that bevacizumab at its optimal dose has negative systemic effects, the shorter half-life of ranibizumab might make it a safer alternative.

It is not known what dose of any of the anti-VEGF medications is optimal for ROP, but it is likely that the doses that are typically used now are much higher than is necessary to neutralize VEGF in the eye and reverse the course of disease. The BEAT-ROP study used 0.625 mg, which is half of the adult dose. Lorenz and colleauges treated 27 eyes with 0.312 mg of bevacizumab, and regression was observed in 19 eyes (70%), including 100% of zone II eyes, 80% of zone I eyes, and only 25% of aggressive posterior ROP eyes.[12]

The Pediatric Eye Disease Investigator Group is conducting a phase 1 dosing study of bevacizumab treatment for severe ROP. The objective of the study is to find a dose of intravitreal bevacizumab that is lower than currently used, is effective in a small study, and can be tested in future larger studies. It is designed as a dose de-escalation study, initially treating one eye of 10 infants with 0.25 mg of bevacizumab. If effective in this group, then additional doses are tested: 0.125 mg, 0.063 mg, and 0.031 mg (5% of the BEAT-ROP dosage). The injection volume is 10 microliters, prepared by institutional research pharmacies by diluting bevacizumab for all doses lower than 0.25 mg. Study investigators are using a syringe with a fixed 30-gauge, 5/16-inch needle, with a total syringe volume of 0.3 cc, which probably allows more

accurate delivery of 10 microliters than with a standard 1 cc syringe. Short-term success is defined as improvement by no later than 5 days after treatment, and no recurrence of type 1 ROP or severe neovascularization requiring additional treatment within 4 weeks. Late recurrences are recorded, and any additional treatment is at investigator discretion. A study examination at 12 months of age will assess visual attentiveness, ocular alignment, retinal structure and cycloplegic refraction. Plasma levels of bevacizumab and VEGF are collected pre-injection and at 2 and 4 weeks after treatment. Results should be available in early 2017, and will hopefully provide guidance for dose selection of future larger studies.

In summary, we have a long way to go to have an evidence-based paradigm for anti-VEGF treatment. There are many unanswered questions about which drug, what dose, relative benefits and possible side effects. Consequently, there are many opportunities for high-quality comparative studies that will shape our future treatment of premature infants and aid in reducing the burden of blindness from ROP.

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Intravitreal injections of bevacizumab: timing, technique, and outcomes

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In March 2008 a prospective, randomized, controlled (intravitreal bevacizumab monotherapy vs laser therapy), multicentered clinical trial for retinopathy of prematurity (ROP) began—Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity, or BEAT-ROP. This clinical trial was based on animal models of ROP, and on bevacizumab clinical trials in human adults with other neovascular retinal disorders.

The BEAT-ROP clinical trial was a prospective, randomized, controlled, multicenter clinical trial comparing intravitreal bevacizumab versus conventional laser therapy. It reported improved efficacy in the bevacizumab group for zone I ROP in 2011[1] and decreased high myopia in the bevacizumab group for zone I and posterior zone II ROP in 2014.[2] However, unanticipated and troublesome delayed recurrences had become a serious problem in follow-up of infants treated by intravitreal bevacizumab monotherapy due to lack of any guidelines. Thus, delayed recurrences