

# Bevacizumab (Avastin) for retinopathy of prematurity: Wrong dose, wrong drug, or both?

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Interest in and controversy over the use of bevacizumab (Avastin; Genentech/Roche, South San Francisco, CA) for the treatment of retinopathy of prematurity (ROP) have increased dramatically after the Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) study.<sup>1-3</sup> Off-label bevacizumab has been used extensively for age-related macular degeneration (AMD) for more than 6 years, and recently the Comparison of AMD Treatments Trials showed it to have similar safety and efficacy to ranibizumab (Lucentis; Genentech/Roche, South San Francisco, CA) in this population.<sup>4</sup> There was, however, an increased incidence of systemic adverse events scattered across many organ systems in the bevacizumab arm of this study, the significance of which remains unclear.<sup>4</sup>

There are pharmacokinetic differences between these two vascular endothelial growth factor (VEGF) inhibitors that may be important in at-risk populations such as infants with ROP undergoing organogenesis.<sup>5,6</sup> In adults the intrinsic serum elimination half-life of ranibizumab is approximately 2 hours, whereas that of bevacizumab is approximately 20 days because it is a full-length antibody with an Fc domain that binds Fc receptors on endothelial cells and reduces systemic clearance.<sup>5</sup> The systemic pharmacokinetics of both ranibizumab and bevacizumab in children is unknown but could be longer.

Early in the use of bevacizumab for proliferative diabetic retinopathy (DR), we noted a reduction in leakage of neovascularization in the contralateral, uninjected fellow eye, a finding that raised concern about systemic levels capable of therapeutic effects.<sup>7</sup> This observation prompted us to evaluate lower doses of intravitreal bevacizumab, and we showed reduction in neovascularization even when injecting a dose 200-fold below the typical dose (6.25  $\mu$ g instead of 1.25 mg).<sup>7</sup> There was initial skepticism as to the causality of fellow eye effects, but these effects have now been observed after bevacizumab injection in DR, vein occlusion, and uveitic cystoid macular edema (CME).<sup>5,8</sup> One recent report even demonstrated the resolution of CME and retinal neovascularization in the

fellow eye of a patient treated with ranibizumab in a prospective trial for uveitic CME.<sup>9</sup>

In several studies authors have not demonstrated fellow eye effects in the setting of AMD, but systemic effects may be most notable when there is significant breakdown of the blood-retina barrier, as in uveitis or rubeosis; furthermore, preretinal neovascularization seems to be much more sensitive to anti-VEGF agents than the more commonly treated choroidal neovascularization.<sup>7,10</sup> Other evidence for systemic effects comes from pharmacology studies in rabbits and monkeys that have demonstrated detectable levels of bevacizumab in fellow eyes after intravitreal injection.<sup>11,12</sup>

After observing fellow eye effects and the sensitivity of preretinal neovascularization to anti-VEGF agents, I proposed the use of lower doses of bevacizumab or changing to ranibizumab when treating ROP to lower the systemic risk in this susceptible population.<sup>13</sup> Subsequently, several investigators<sup>14,15</sup> have confirmed the presence of bevacizumab in the serum after intravitreal injection; however, the assays for bevacizumab in human serum are technically challenging because of the presence of other human IgG. Decreased VEGF levels in human plasma or serum have also been reported after the injection of intravitreal bevacizumab. Ziemssen and colleagues<sup>14</sup> showed a reduction in serum VEGF 1 day and 1 week after treatment of AMD in several patients. This finding was consistent with the increased serum bevacizumab levels they detected at these times.

Matsuyama and colleagues<sup>16</sup> noted a dramatic reduction in plasma VEGF levels 1 day, 1 week, and 1 month after a single injection of intravitreal bevacizumab in 11 patients with proliferative DR. Qian and colleagues<sup>17</sup> showed a significant reduction in plasma VEGF after preoperative bevacizumab injections in patients with diabetes. Ma and colleagues<sup>18</sup> have recently confirmed this finding in patients with diabetes injected more than 1 month before the plasma VEGF level was measured. The authors of a large, prospective, randomized, controlled clinical trial in the United Kingdom, the Inhibit VEGF in Age-related choroidal Neovascularization (IVAN) trial, are comparing bevacizumab to ranibizumab for the treatment of AMD. Although this trial is ongoing and individual patients remain masked for treatment received, the authors recently reported a reduction in serum VEGF levels of the pooled samples from both treatment arms (Glenn JV et al. Fluctuating levels of circulating VEGF in a subset of patients as part of the multicentre IVAN study. IOVS 2011;52: ARVO E-abstract 5930). There was a statistically significant reduction in serum VEGF at 1 and 11 months into the trial, but the difference did not reach statistical significance at 12 months.

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Submitted November 11, 2011.

Revision accepted November 15, 2011.

Published online January 12, 2012.

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J AAPOS 2012;16:2-4.

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1091-8531/\$36.00

doi:10.1016/j.jaapos.2011.11.002

Further results from IVAN are expected in 2012, but there is already published evidence that systemic effects may differ between bevacizumab and ranibizumab.<sup>19</sup> Carneiro and colleagues<sup>19</sup> have recently reported the plasma VEGF levels in a prospective study of patients receiving these drugs for AMD. One month after 3 monthly intravitreal injections, there was no statistically significant reduction in the plasma VEGF levels in ranibizumab-injected eyes, but the bevacizumab-injected eyes had a reduction from 190 pg/ml to 110 pg/ml ( $P = 0.0002$ ).<sup>19</sup>

There is additional evidence of the difference in systemic effects of bevacizumab and ranibizumab from two transgenic mice models of over expression of VEGF.<sup>20</sup> In both models, there was a marked systemic effect with bevacizumab, but not with ranibizumab. In fact, in one model, the uninjected, fellow eyes of mice treated with bevacizumab demonstrated the same treatment effect as eyes that were directly treated with ranibizumab, and in the more severe model, the treatment effect in the bevacizumab fellow eyes was significantly greater than that of the eyes directly treated with ranibizumab.<sup>20</sup> There is evidence that Fc receptors facilitate the movement of intravitreal IgG such as bevacizumab across the blood-ocular barrier into the bloodstream.<sup>21</sup> One potential explanation of these systemic effects is that a prolonged, elevated serum bevacizumab level developed due to its half-life and diffused into the fellow eye.

In infants with ROP, two groups have reported dramatic reductions in the systemic VEGF levels following intravitreal bevacizumab.<sup>15</sup> Sato and colleagues<sup>15</sup> measured not only VEGF levels but also serum bevacizumab levels, which continued to increase from 1 day to 1 week to 2 weeks after injection. The serum VEGF levels dropped from 1628 pg/ml to 269 pg/ml 2 weeks after injection of a total of 0.5 mg of bevacizumab.<sup>15</sup> Lee and colleagues reported the reduction of plasma VEGF levels from 2050 pg/ml pre-injection to 170 pg/ml at 1 week after injection, and a continued weekly decrease to 50 pg/ml at 7 weeks, the last time tested (Lee S-J et al. Plasma level of vascular endothelial growth factor in retinopathy of prematurity after intravitreal injection of bevacizumab. IOVS 2011;52:ARVO E-abstract 3165). These VEGF levels are well below reported plasma levels measured in premature infants with and without ROP.<sup>22</sup> The bevacizumab dose used in this study was 0.625 mg/eye, one half of the normal adult dose, and most of the babies received bilateral injections.

In a canine model that closely resembles ROP in eyes of approximately the same size, 3 doses of VEGF trap (Regeneron Pharmaceuticals, Tarrytown, NY), 5  $\mu$ g, 25  $\mu$ g, and 250  $\mu$ g, were evaluated.<sup>23</sup> All doses markedly inhibited intravitreal neovascularization, but the two higher doses also inhibited retinal revascularization as well as normal retinal vasculogenesis. These higher doses reduced the total retinal vascular area and the capillary density, whereas, the lowest dose inhibited the abnormal neovascularization, but not retinal revascularization or vasculogenesis.<sup>23</sup> Lower doses of VEGF trap were not tested,

and could have shown a beneficial effect, but the 5  $\mu$ g dose is in the range of the 6.25  $\mu$ g dose of bevacizumab, which was shown to reduce diabetic neovascularization in larger, adult eyes.<sup>7</sup> Injection of these doses should produce initial intravitreal concentrations greater than those which have been shown to inhibit VEGF in vitro.<sup>24</sup> However, VEGF trap has a greater affinity for VEGF than does bevacizumab and has been recently reported to have potency similar to ranibizumab.<sup>24</sup> Nevertheless, these observations imply that the dose of bevacizumab (625  $\mu$ g) commonly used for ROP may be an order of magnitude or two greater than what is required to have a beneficial effect. Furthermore, these high doses could potentially interfere with normal retinal vasculogenesis and revascularization.<sup>23</sup>

More importantly, unlike patients with AMD, infants with ROP are still in the processes of organogenesis, and VEGF plays a role in the development of most organs.<sup>5</sup> For example, VEGF has been implicated in alveolar development and lung maturation.<sup>25,26</sup> In the BEAT-ROP trial, there was 1 death caused by lung disease in the laser arm and 4 in the bevacizumab arm, 2 of whom died after they were discharged to home and were off oxygen monitoring at about 49-50 weeks postmenstrual age.<sup>1</sup> This difference was not statistically significant, but the study was not powered to evaluate safety.<sup>1</sup> We know that lung disease is a common comorbidity in infants with ROP and may have nothing to do with the use of bevacizumab, yet there is now evidence that systemic VEGF levels can be depressed for many weeks, if not months, after an injection of intravitreal bevacizumab. Consideration should be given to decreasing the systemic exposure by injecting a lower effective dose and/or changing to a drug such as ranibizumab, which has much more rapid systemic clearance. Further studies evaluating lower doses of these drugs are indicated to achieve the full potential of anti-VEGF therapy for ROP with minimal risk of side effects in this susceptible population.

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