Systemic Pharmacokinetics of Anti-VEGF Compounds Following Ocular Injections

AN INTERVIEW WITH ROBERT L. AVERY, MD

There have been ongoing questions about the systemic bioavailability of the various anti-VEGF agents following injection into the eye. A recent study by Avery and colleagues demonstrated "notable differences in systemic pharmacokinetics and pharmacodynamics among anti-VEGF treatments after intravitreal administration" among a population of patients treated for neovascular age-related macular degeneration.[1] In the study population, aflibercept (Eylea, Regeneron) and bevacizumab (Avastin, Genentech) caused a rapid suppression of plasma free VEGF soon after a single ocular administration, while unbound VEGF levels remained largely unchanged among patients given ranibizumab (Lucentis, Genentech). Further, bevacizumab and aflibercept accumulated in the blood after the third dose, but ranibizumab did not. Although by no means conclusive, these data have intriguing and potentially important implications. *Retina Today* spoke with the study's lead author, Robert L. Avery, MD, of California Retina Consultants and the Associate Medical Editor of *Retina Today*, to discuss the findings and implications of this study.

Retina Today: What are the main take-home points from this study and what do you hope your peers will take away from it?

Robert Avery, MD: The 3 main intravitreal anti-VEGF inhibitors are all very effective in combatting a variety of retinal diseases; however, this study shows that there are large differences in their systemic pharmacokinetics and pharmacodynamics that may provide biological plausibility for potential differences in their systemic safety. Fortunately, registration and comparative trials have demonstrated good systemic safety profiles for these agents, but, in some studies, imbalances have been observed which could point to a safety concern after more patients are studied with longer follow-up.

Physicians should be cognizant that after the injection of these powerful agents into the eye, the drugs leach into the bloodstream at concentrations high enough to affect plasma free VEGF levels. Further study is required to determine if this reduction in circulating VEGF has clinical relevance, but it is conceivable that it might be important in at-risk patients—for instance, the elderly AMD patient with diabetes and a history of recent stroke, or the premature baby undergoing organogenesis who receives an injection for retinopathy of prematurity.

RT: Are there any aspects of the study methods or important limitations to note?

Dr. Avery: The measurement of free plasma VEGF can be difficult, as platelet rupture can release VEGF and increase the measured levels. We used special collection tubes and handling to minimize this effect. However, other researchers, such as those in the IVAN study, have also noted a similar difference between the drugs when they allowed the platelets to rupture and measured serum free VEGF levels.[2,3]

Hence, both plasma and serum levels of VEGF seem to be reduced by the drugs to different degrees.

RT: The study data indicated differences among ranibizumab, bevacizumab, and aflibercept in terms of systemic exposure. Can you explain briefly how this was determined?

Dr. Avery: By measuring the drug levels in the bloodstream over many time points, we can plot a curve of concentration over time. The area under this curve is the systemic exposure.

RT: Are there differences in these molecules that may help explain these finding or is there a scientific or biologic rationale?

Dr. Avery: The systemic exposure, or area under the curve from the concentration graph, was much lower for ranibizumab than for bevacizumab or aflibercept. The most likely explanation for this that bevacizumab and aflibercept can bind Fc receptors on endothelial cells that have been implicated in recycling antibodies and significantly prolonging their systemic half-life. Ranibizumab lacks the Fc-antibody component and is, therefore, not recycled.

RT: What are the implications of this study for clinical practice? Should these findings at all affect how clinicians use these medications?

Dr. Avery: These 3 agents are all very powerful and effective in combating VEGF-mediated eye disease and have been of tremendous benefit to our patients. They work by the same mechanism and are all extremely potent, but the finding of such different systemic exposures would seem to imply that, if there are systemic side effects of intravitreal anti-VEGF agents, the risks of these side effects could be different among the agents. Fortunately, we have not seen any definitive systemic side effects in the registration trials, but these trials are not powered to detect differences in uncommon events.

RT: Is there a need to identify patients at risk for systemic events due to inhibition of plasma free VEGF?

Dr. Avery: If there were a large risk to the general population from these drugs, I think we would have already seen it in the trials to date. However, there are at-risk populations we have identified from the systemic use of anti-VEGF agents—such as those at increased risk of stroke or those undergoing wound healing—that I believe still warrant increased scrutiny.

RT: Data from CATT show a higher rate of systemic adverse events with bevacizumab compared with ranibizumab. Does the data from this study at all answer why that may be?

Dr. Avery: These data do not answer the question, but rather provide biologic plausibility to the hypothesis that the difference could be due to different systemic levels of the drugs. The group of serious adverse events was heterogeneous and, hence, difficult to study. Although the imbalance seen in the CATT study has been seen in several other studies, it has not been seen in all of them.

RT: What other data are available in the literature on this subject?

Dr. Avery: Further meta-analyses are needed to drill down on the SAEs. At the Association for Research in Vision and Ophthalmology 2014 Annual Meeting, Scott and colleagues presented interesting data on an increased incidence of gastrointestinal-related adverse events in a meta-analysis of 5 trials, in which they found a doubling of the risk with bevacizumab versus ranibizumab.[4]

RT: What other research needs to be done to follow on these data?

Dr. Avery: More studies such as this one are needed to see if there are significant differences in systemic risk profile—especially in any at-risk population—among these drugs, or to determine if we are just seeing noise. Larger numbers and further study is going to help answer this question. ■

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1. Avery RL, Castellarin AA, Steinle NC, et al. Systemic pharmacokinetics following intravitreal injections of ranibizumab, bevacizumab or aflibercept in patients with neovascular AMD [Published online ahead of print July 7, 2014]. *Br J Ophthalmol*. doi:10.1136/bjophthalmol-2014-305252.
2. Chakravarthy U, Harding SP, Rogers CA, et al; IVAN Study Investigators. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. *Ophthalmology*. 2012;119(7):1399-1411.
3. Wang X, Sawada T, Sawada O, et al. Serum and plasma vascular endothelial growth factor concentrations before and after intravitreal injection of aflibercept or ranibizumab for age-related macular degeneration. Am J Ophthalmol. 2014; doi:10.1016/j.ajo.2014.06.009.
4. Scott L, Chakravarthy U, et al. Gastrointestinal serious adverse events in patients treated with intraocular ranibizumab or bevacizumab for age-related choroidal neovascularisation, what do the recent trials tell us? Paper presented at: Association for Research in Vision and Ophthalmology 2014 Annual Meeting; May 3-8, 2014; Orlando, FL.