

Examining the Systemic Safety of Anti-VEGF Agents

Although use of anti-VEGF agents seems safe in the general population, systemic safety concerns remain in at-risk patients.

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At the recent annual Vit-Buckle Society meeting in Miami, Robert L. Avery, MD, presented a contrarian view of the systemic safety of anti-VEGF agents. He noted that most retina specialists who treat patients with age-related macular degeneration (AMD), diabetic macular edema (DME), and other posterior segment diseases are well aware of the excellent systemic safety data on the use of anti-VEGF drugs from registration trials. However, he pointed to several lines of evidence that suggest that there may be systemic effects of the small doses of these medicines used to treat retinal diseases. The much larger systemic doses used to treat cancer are known to increase the risk of arteriothrombotic events, and, even though the small intravitreal doses seem safe in the general population, there may be subsets of high-risk patients who could be at increased risk of similar systemic side effects.

CASE STUDY AND LITERATURE REPORTS

Almost a decade ago, Dr. Avery and colleagues reported fellow eye effects and noted concern about potential systemic effects of these agents.¹ A patient with active bilateral proliferative diabetic retinopathy (PDR) received intravitreal bevacizumab (Avastin, Genentech) in one eye, and, 1 week later, the fellow eye demonstrated reduced leakage on fluorescein angiography (FA). Two weeks after the patient's initial presentation, repeat FA demonstrated a return of leakage to baseline, suggesting a transient but demonstrable contralateral effect following intravitreal bevacizumab injection.¹

Subsequently, several other investigators have described apparent bilateral effects of unilateral anti-VEGF injections in DME, uveitic cystoid macular

edema, and retinopathy of prematurity (ROP).²⁻⁴ Others have reported this phenomenon with bevacizumab but not ranibizumab (Lucentis, Genentech) for DME at 2 and 4 weeks following injection.⁵

Dr. Avery presented a series of 25 patients with DME who received unilateral aflibercept (Eylea, Regeneron), and in whom there was an average 43- μ m reduction in retinal thickness in the contralateral eye.⁶ There is inherent fluctuation in DME between visits, but some of these patients demonstrated a greater reduction in retinal thickening in the contralateral eye within 1 week than would be likely to be attributable to chance alone.

SYSTEMIC PHARMACOKINETICS AND PHARMACODYNAMICS

A second line of evidence for systemic effects comes from pharmacokinetic studies. Dr. Avery discussed his group's work, which measured systemic levels of the three common anti-VEGF drugs, as well as plasma free VEGF levels, at 12 time points throughout a period of 3 monthly

At a Glance

- Anti-VEGF agents can enter the circulation and reduce systemic VEGF levels.
- Fellow-eye effects suggest evidence of systemic effects caused by these agents.
- Systemic safety remains unclear in at-risk patients (eg, those with recent stroke or retinopathy of prematurity).

injections in patients with wet AMD.⁷ Bevacizumab and aflibercept were found to linger in the bloodstream much longer than ranibizumab. These systemic drug levels correlated with markedly suppressed plasma free VEGF levels in patients receiving bevacizumab and aflibercept within the first week after administration. In addition, the much lower concentration of systemic ranibizumab correlated with a minimal reduction in systemic free VEGF levels at the same time points.

All three agents quickly moved into the bloodstream, and ranibizumab is rapidly cleared from it. Hence, bevacizumab and aflibercept demonstrated greater systemic exposure, and the marked reduction in free VEGF in plasma correlates with this higher exposure.⁷ Intravitreal aflibercept showed the greatest suppression of free plasma VEGF, with the vast majority of samples below the lower limit of quantification (LLOQ) after the first and third doses. Mean free VEGF levels dropped below LLOQ as early as 3 hours after dose and remained below LLOQ until more than 7 days after dose. In comparison, mean free VEGF levels following ranibizumab injections were largely unchanged, with only a minimal drop compared with the baseline level. This reduction in VEGF has been observed by others looking at free VEGF in the plasma or in the serum.^{8,9}

What is the reason for the increased reduction of systemic VEGF following bevacizumab and aflibercept, compared with ranibizumab, injections? Dr. Avery said that it most likely has to do with the differences in structures of the three molecules. The Fc fragment, or antibody backbone, of the bevacizumab and aflibercept molecule is believed to prolong the drug's half-life in the bloodstream by engaging with the Fc receptor on endothelial cells. This interaction enables translocation across the blood-retina barrier and is believed to rescue the immunoglobulin from catabolic elimination after entering the systemic circulation. Because ranibizumab lacks the Fc region, it persists for only a few hours in systemic circulation before undergoing breakdown.

CLINICAL TRIAL COMPARISONS

Having seen systemic effects of intravitreal anti-VEGF agents in the form of fellow eye effects and in the reduction of circulating VEGF levels, is there any evidence that these drugs have adverse effects on patients? No registration trials have shown any significant systemic safety signal, but none of these studies were powered to detect a difference in uncommon events, such as stroke, heart attack, or death.

The CATT study reported a higher cumulative proportion of systemic serious adverse events (SAEs)—a broad category of events including anything requiring hospitalization—in the bevacizumab arms relative to

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the ranibizumab arms at 1 and 2 years.^{10,11} A Cochrane meta-analysis from last year of six published comparative AMD trials similar to and including the CATT trial showed this same increased risk of systemic SAEs with bevacizumab (relative risk [RR] 1.27; 95% CI, 1.06-1.52)¹²; however, a second, larger Cochrane meta-analysis from 2014 included three additional unpublished comparative studies and found no statistically significant difference in the rate of systemic SAEs between bevacizumab and ranibizumab (RR 1.08; 95% CI, 0.90-1.31; $P = .42$).¹³

However, Dr. Avery noted that the jury might still be out in this analysis because, without inclusion of the SAE data from the LUCAS trial, the difference remains significant (RR 1.19; 95% CI, 1.06-1.34, $P = .0038$) with the remaining eight trials, according to this same report.¹³ Furthermore, the LUCAS authors noted that there was a statistically significant imbalance at baseline with respect to more than twice as many patients with a previous myocardial infarction (MI) enrolled in the ranibizumab arm than in the bevacizumab arm ($P = .02$).¹⁴ Of interest, during the trial, a large imbalance developed, with more cardiac SAEs in the ranibizumab arm, almost triple those in the bevacizumab arm, and this imbalance was responsible for the majority of the difference in systemic SAEs in the trial.¹⁴ To complicate the issue further, the large Cochrane analysis used estimates of the total SAEs in the LUCAS trial, which do not correlate with the recently published number of SAEs in the LUCAS trial, in part due to the method of estimation, and in part due to LUCAS including ocular SAEs in what was published as systemic SAEs.^{13,14} Further patient-specific evaluation of the those enrolled into LUCAS with a history of MI will help determine if the baseline imbalance in these patients contributed to the increased incidence of SAEs in the ranibizumab arm of the LUCAS trial.

Risk of Stroke

Stroke is an area of concern, as systemic administration of anti-VEGF agents is associated with an increased risk in cancer patients.¹⁵ Before most trials excluded

patients with recent strokes, an interim analysis of the SAILOR trial raised concern that the higher dose of ranibizumab (0.5 mg) might be associated with increased risk of stroke; however, upon completion of the trial and final analysis, the imbalance was no longer statistically significant. Bressler and coworkers analyzed the risk of stroke in five randomized controlled ranibizumab AMD clinical trials (FOCUS, MARINA, ANCHOR, PIER, and SAILOR), and found no overall increased risk of cerebrovascular accident (CVA); however, when patients were stratified by their baseline risk of stroke, the subgroup with a high baseline risk of stroke had a sevenfold increase in risk of stroke during the trials with use of 0.5-mg ranibizumab compared with control.¹⁶ This was only seen in the subgroup analysis, but it lends support for the theory that there could be increased risk in predisposed patients.

Finally, within the European Public Assessment Report of the safety profile of aflibercept for AMD in the VIEW studies, there is a suggestion of an increased risk of cerebrovascular events with aflibercept relative to ranibizumab.^{17,18} This effect was particularly apparent in patients older than 85 years.

AT-RISK DISEASE STATES

In addition to patients with a history of cardiovascular events, patients with diabetes also have a much greater risk for having a stroke or MI. The RISE and RIDE studies evaluated two doses of ranibizumab and sham injection (0.3 vs. 0.5 mg vs. sham), and demonstrated a slightly numerically higher rate of stroke in the 0.5-mg arm.¹⁹ Boyer has presented Kaplan-Meier curves of the development of CVA and death during RISE/RIDE that show the separation of the 0.5 mg arm from the 0.3 mg arm and sham arm mostly in the second year of the trials.²⁰

A recent large Cochrane meta-analysis of anti-VEGF treatment of DME did not show any safety signal across the entire population of treated patients.²¹ This study lumped patients receiving different doses of the agents and undergoing different treatment protocols—monthly, bimonthly, and as-needed—into the analysis. Dr. Avery postulated that it might be useful to assess systemic safety in this at-risk population of patients with diabetes by looking at the subgroup of these patients with maximum exposure to the anti-VEGF agents. He predefined maximum exposure as monthly injections for 2 years, and then performed a meta-analysis of randomized trials of anti-VEGF therapy for DME. Only four trials met this criteria: RISE, RIDE, VIVID, and VISTA.^{19,22} The analysis did not demonstrate any significant increased risk of treat-

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ment over sham for MI or arterial thromboembolism; however, analysis of the highest dose group, monthly 0.5 mg ranibizumab or 2.0 mg aflibercept, showed a threefold increased risk of death over sham ($P = .003$). The risk of stroke and vascular death was also elevated in this group, but only to a borderline significant level. Again, the results were from a subgroup analysis of an at-risk group (eg, patients with DME), so caution must be exercised when interpreting these results. The population studied (monthly dosing for 2 consecutive years) is clearly representative of only a small portion of patients in clinical practice, where much less frequent dosing is usually administered. In fact, many trials, such as the DRCR.net Protocol I, have shown a dramatic reduction in the number of injections required in year 2 and beyond, still maintaining excellent visual results.^{23,24} Also, numerous studies, such as all registration trials and meta-analyses, have shown excellent safety of anti-VEGF agents in the treatment of DME in the entire population of patients treated, not just a very high-risk subgroup.

CONCLUSION

There is no question that the use of anti-VEGF agents, which has saved the vision of countless patients, seems safe in the vast majority of patients. However, the available studies are not large enough to be powered to prove safety in uncommon events, and there are certain at-risk populations of patients, such as patients with DME and recent stroke, who have been excluded from trials. The observation of fellow eye effects, along with the pharmacokinetic studies showing concentrations of the agents in the bloodstream correlating with reduction in circulating free VEGF levels, provide biologic plausibility for potential systemic effects of these agents. Fortunately, all the registration trials and meta-analyses have shown good safety in the general population; however, it is difficult to exclude the possibility of potential adverse events in high-risk populations. Dr. Avery stated that he hoped this situation would not be analogous to

the early use of timolol (Timoptic, Merck), which was approved by the US Food and Drug Administration without any warnings of cardiovascular or bronchopulmonary side effects. It is clear that anti-VEGF agents have tremendous benefits for a huge population of patients, but Dr. Avery recommended further evaluation of the safety of these injections in at-risk patients. ■

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