Systemic Safety of Ranibizumab for Neovascular Age-Related Macular Degeneration: Do Ophthalmologists Still Have to Sweat the Small Stuff?
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For retina specialists, therapy with anti-vascular endothelial growth factor (VEGF) agents has become the Rosetta Stone for the management of retinal vascular disease, dramatically improving visual outcomes for patients with neovascular age-related macular degeneration (nAMD), diabetic macular edema, and venous occlusive disease. Landmark randomized clinical trials comparing the relative efficacy of the various anti-VEGF agents in these diseases and the alternate dosing regimens of monthly administration versus treat-and-extend have simply added a layer of finesse to how these diseases are managed, elevating the art of ophthalmology. An underlying concern that we physicians continue to face while combating vision loss in our patients is whether the systemic inhibition of VEGF, at even low levels, increases our patients’ risk of arterial thromboembolic events (ATEs).

In this issue of Ophthalmology Retina, Zarbin et al evaluate the cardiovascular and cerebrovascular safety profile of ranibizumab 0.5 mg with sham ± verteporfin, as well as ranibizumab 0.3 mg with sham and ranibizumab 0.5 mg to 0.3 mg, in patients with nAMD. In their pooled analysis, patient-level data from phase II, III, and IV randomized, double-masked clinical trials, sponsored by Genentech, Inc. (South San Francisco, CA), or Novartis Pharma (Basel, Switzerland), in which patients with nAMD received treatment in at least 2 of the 3 previously mentioned study arms, with a completion date before December 31, 2013, were included. These 7 clinical trials—ANCHOR, MARINA, PIER, SAILOR, EVEREST, EXTEND I, and EXCITE—comprise the largest ever patient-level pooled analysis of patients with nAMD treated with ranibizumab and combine regimens of monthly dosing with those allowing quarterly or pro re nata (prn) dosing. Standardized Medical Dictionary for Regulatory Activities queries and extended searches were used to identify safety end points, such as ATE, myocardial infarction (MI), stroke, or transient ischemic attack (TIA), stroke (excluding TIA), vascular deaths, and major vascular events as defined by the Antiplatelet Trialists’ Collaboration. For patients with multiple ATEs, only the first event was included in the analysis of a particular end point, such as MI, ensuring that each patient was only counted once. For composite end points where a patient might have multiple events, such as MI and stroke, only the time to the first event was included in the analysis.

The pooled data set included 4080 patients in total, with subgroup pairwise comparisons of ranibizumab 0.5 mg versus sham in 480 and 462 patients, respectively; ranibizumab 0.3 mg versus sham in 434 and 441 patients, respectively; and ranibizumab 0.5 mg versus 0.3 mg in 1814 and 1764 patients, respectively. Analyses showed rates of overall ATEs, MI, stroke (excluding TIA), stroke or TIA, vascular death, and Antiplatelet Trialists’ Collaboration events were similar in both the comparison of ranibizumab 0.5 mg versus sham and in the comparison of ranibizumab 0.3 mg versus sham. In addition, the 95% confidence intervals all included 1, indicating no clinically meaningful differences.

Although these findings are consistent with reports on safety from other meta-analyses of clinical trials in patients with nAMD receiving intravitreous anti-VEGF therapy, do pooled analyses actually allow better interpretation of safety outcomes compared with what is observed in individual clinical trials, especially for events occurring infrequently? Certainly, one limitation with pooled analyses that has to be considered is the assumption that there is homogeneity across the individual trials that make up the pooled analyses. In the patient-level pooled analysis presented by Zarbin et al, the authors admit that the 7 clinical trials included had differing study designs, patient demographics, treatment durations, dosing regimens, pro re nata re-treatment criteria, and cardiovascular and cerebrovascular inclusion and exclusion criteria. For instance, ANCHOR, MARINA, and PIER had no cardiovascular or cerebrovascular exclusion criteria, whereas EVEREST, EXTEND I, and EXCITE excluded patients with prior stroke. Patients with uncontrolled cardiovascular disease were excluded from SAILOR. Trials that had monthly treatment guidelines, such as MARINA, ANCHOR, and EXTEND I, were combined with trials that had pro re nata treatment regimens (EVEREST and SAILOR), as well as with those that had quarterly treatment regimens (PIER, EXCITE). These 2 study design variables alone (cardiovascular and cerebrovascular exclusion criteria; treatment regimen) limit the degree to which an association between exposure to ranibizumab and increased risk of ATE can be made in a particular cohort and then extrapolated to the general population. For example, does the exclusion of patients with nAMD with a history of stroke or heart attack...
suppress the sensitivity of a study to detect already infrequent systemic adverse events? Finally, when ATEs were detected in the various patient cohorts, those affected, although a small number, were discontinued from the study, precluding collection of data on multiple occurrences of an ATE.

A second limitation with pooled analyses, in general, that must be considered is related to publication bias. Depending on the criteria for selecting studies to be included in the pooled analyses, authors may be compounding the publication bias toward positive rather than negative results. For instance, the pooled analysis presented by Zarbin et al arbitrarily included only those randomized trials sponsored by Genentech, Inc., or Novartis Pharma that had the prescribed ranibizumab, verteporfin, and sham arms and that were also completed by December 31, 2013. Because of these selection criteria, HARBOR, a more recent study that compared ranibizumab 0.5 mg with 2.0 mg ranibizumab was not included. However, it should be noted that HARBOR demonstrated similarly low rates of ATEs associated with either dose of ranibizumab in the management of patients with nAMD.

A third potential limitation with pooled analyses is related to the inability to judge the quality of the individual studies in the pooled analysis, in general, without the application of special metrics. With respect to the Zarbin et al pooled analysis, the individual clinical trials included, fortunately, are held in high regard by the ophthalmology community as well-designed, randomized studies that support evidence-based medicine.

Despite the inherent limitations of pooled analyses, the data presented by Zarbin et al confirm the low rates of cerebrovascular and cardiovascular events observed in patients with nAMD who are managed with intravitreal ranibizumab. That these low rates of ATEs associated with intravitreal ranibizumab do not appear to be clinically or statistically significantly different from sham treatment is also supported by individual clinical trials looking at the frequency of ATEs, in general, in patients receiving intravitreal anti-VEGF therapy for macular edema secondary to diabetic retinopathy and retinal vein occlusion. Thus, a reasonable extrapolation from this and other analyses, both individual and pooled, of the systemic safety of ranibizumab used to treat nAMD to the real-world population can and should be made. Personally, I see enough similar evidence for ranibizumab and the other commonly used anti-VEGF drugs that I no longer sweat the small stuff for aflibercept and bevacizumab across the spectrum of retinal disease that I manage in adults.

References


Footnotes and Financial Disclosures

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