Good News for Anti-VEGF Therapy

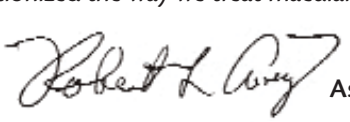
There has been controversy over the systemic safety of anti-vascular endothelial growth factor (VEGF) agents for several years. The 1-year results of ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD) and MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD) trials of ranibizumab (Lucentis, Genentech) showed a slight increase in arterial thromboembolic events (ATEs) with the 0.5-mg dose of ranibizumab over sham or 0.3-mg doses. These numbers were very small and not statistically significant. After 2 years of follow-up, the differences resolved, and concern was greatly reduced. However, in January 2007, we received a "Dear Doctor" letter, which noted a statistically significant increased risk of stroke in the interim analysis of cohort 1 of the SAILOR (Safety Assessment of Intravitreal Lucentis for AMD) study between the 0.3- and 0.5-mg doses of ranibizumab. At 6 months, there was a fourfold increased risk of stroke in the higher dose group. The overall rates of stroke (0.3% and 1.2%) were lower than expected for this age group, and no change in clinical use was recommended.

Fortunately, the final, 1-year results of cohort 1 of the SAILOR study were recently presented by David Boyer, MD, at Bascom Palmer's Angiogenesis and Exudation 2008 meeting, and they demonstrate a significant reduction in the difference between the stroke rates for the two doses (0.7% for 0.3 mg and 1.2% for 0.5 mg). This difference is no longer statistically significant, and thus the safety of ranibizumab seems more secure.

Subgroup analysis of stroke rate by preexisting risk factors revealed trends for higher stroke rates in the higher dose group for patients with a history of prior stroke or those with arrhythmias, but these differences did not reach statistical significance. Nevertheless, some may have been surprised that patients with a previous history of stroke had a 9.6% incidence of stroke during the 1-year SAILOR study if they were receiving 0.5 mg of ranibizumab. Controversy still exists as to whether AMD alone predisposes patients to the development of stroke. Alexander et al[1] recently analyzed a large Medicare database and found no significant increased risk of ATEs between patients newly diagnosed with neovascular AMD and matched controls. The history of recent stroke, however, greatly increased the stroke risk in this study. Conversely, a recent 10-year prospective study by Tan et al[2] found a tenfold increased risk of stroke-related mortality in Australian patients with advanced AMD who were younger than 75 years old at the start of the study.

The lack of any statistically significant increase in stroke risk in the SAILOR cohort 1 data, even within the high-risk groups, is very reassuring. Even so, we must continue to remain vigilant to ensure that we do not miss these infrequent adverse events in our own patients.

Fortunately, another long-anticipated trial has just started. After numerous delays, many of the 47 sites of CATT (Comparisons of Age-related Macular Degeneration Treatments Trials) have now begun to enroll patients in this head-to-head study of ranibizumab and bevacizumab (Avastin, Genentech). Although we will have to wait a few years for results, this study should provide us with a wealth of safety and efficacy data comparing these similar but distinct molecules that have revolutionized the way we treat macular degeneration. ■



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2. Tan JSL, Wang JJ, Liew G, et al. Age-related macular degeneration and mortality from cardiovascular disease or stroke. *Br J Ophthalmol.* 2008; Feb 28 [Epub ahead of print].