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Serious Adverse Events with Bevacizumab or Ranibizumab for Age-Related Macular Degeneration: Meta-analysis of Individual Patient Data

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Topic: A comparison between ranibizumab and bevacizumab of the incidence of systemic serious adverse events (SAEs) among patients with neovascular age-related macular degeneration (nAMD) who participated in a large-scale randomized trial. Use of individual patient data, rather than aggregate data, allowed adjustment for strong predictors of SAEs.

Clinical relevance: Relative safety of ranibizumab and bevacizumab is important in choosing an anti−vascular endothelial growth factor (anti-VEGF) drug for the hundreds of thousands of patients with nAMD treated each year worldwide.

Methods: Results of a Cochrane aggregate meta-analysis of the relative efficacy and safety of bevacizumab and ranibizumab that used searches of bibliographic databases and clinical trial registries as of March 14, 2014, and hand searching were reviewed to identify 6 large-scale, multicenter clinical trials. Individual patient data on SAEs, assigned drug and dosing regimen, and baseline prognostic factors were requested from the leaders of the 6 trials. A 2-stage approach was used to estimate relative risks and 95% confidence intervals (CIs) from Cox proportional hazards models adjusting for baseline prognostic factors. The primary outcome measure was development of $\geq$1 SAE; secondary outcome measures were death, arteriothrombotic events, events associated with systemic anti-VEGF therapy, and events not associated with systemic anti-VEGF therapy.

Results: Individual patient data were received from 5 trials to provide information on 3052 patients. There were no large imbalances between drug groups on baseline factors. The adjusted relative risks and 95% CIs for bevacizumab relative to ranibizumab were 1.06 (95% CI 0.84−1.35; $P = 0.61$) for $\geq$1 SAE. For secondary outcomes, adjusted relative risks were 0.99 (95% CI 0.69−1.43; $P = 0.97$) for death, 0.89 (95% CI 0.62−1.28; $P = 0.53$) for arteriothrombotic events, 1.10 (95% CI 0.81−1.50; $P = 0.54$) for events related to anti-VEGF treatment, and 1.11 (95% CI 0.87−1.40; $P = 0.40$) for events not related to anti-VEGF treatment.

Conclusion: Our findings support the absence of large differences in risk of systemic SAEs between these 2 anti-VEGF drugs (i.e., relative risks of $\geq$1.5 are unlikely). Because additional head-to-head trials are unlikely, any further investigation of differential risk between anti-VEGF agents will be achieved only through postmarketing surveillance or through the interrogation of health-care databases. *Ophthalmology Retina 2017;■:1−7 © 2017 by the American Academy of Ophthalmology*

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The management and prognosis of patients with neovascular age-related macular degeneration (nAMD) changed dramatically in 2005 with the release of results from phase III clinical trials of intravitreally administered ranibizumab (Lucentis; Genentech, South San Francisco, CA), an inhibitor of all active forms of vascular endothelial growth factor (VEGF).[1,2] On average, eyes treated with ranibizumab gained visual acuity whereas untreated eyes or eyes treated with photodynamic laser therapy lost substantial visual acuity. While waiting for approval from regulatory agencies in the United States and Europe, ophthalmologists began using intravitreal bevacizumab (Avastin; Genentech, South San Francisco, CA) off label to treat nAMD because it was structurally similar to ranibizumab, was available for use because it had been approved for treatment of cancer, and was inexpensive. Short-term outcomes related to vision and retinal morphology after treatment with bevacizumab seemed similar to those of ranibizumab, leading to rapid

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adoption of bevacizumab as first-line therapy. The fact that after ranibizumab was approved by the Food and Drug Administration, ranibizumab was sold for approximately $2000 per dose in the United States, compared with $50 for bevacizumab, amplified the need for comparison of longer term efficacy and safety between the 2 drugs.[3]

Planning for large-scale, multicenter clinical trials of the 2 drugs was started in 6 different countries. These multicenter clinical trials were the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) in the United States, the Alternative Treatments to Inhibit VEGF in Age-Related Choroidal Neovascularization (IVAN) in the United Kingdom, the Groupe d'Etude Français Avastin versus Lucentis dans la DMLA néovasculaire (GEFAL) in France, the Multicenter Anti-VEGF Trial in Austria (MANTA), Lucentis Compared with Avastin Study (LUCAS) in Norway, and Bevacizumab and Ranibizumab in Age-Related Macular Degeneration (BRAMD) in the Netherlands.[4–12] In 2011, CATT was the first of the trials to provide 1-year results.[4] The mean change in visual acuity under treatment with bevacizumab was noninferior to the mean change in visual acuity under treatment with ranibizumab. The results on efficacy from the other multicenter clinical trials have been consistent with no difference or only a small difference in change in visual acuity between drugs after the initiation of treatment; a recent meta-analysis yielded a mean difference of −0.5 letters (95% confidence interval [CI] −1.6 to +0.6), with a negative difference indicating less improvement in eyes treated with bevacizumab.[13]

However, the results from 1 of the clinical trials raised concerns on the safety of bevacizumab relative to that of ranibizumab. In CATT, the proportion of patients with 1 or more systemic serious adverse events (SAEs) at 1 year was higher with bevacizumab than ranibizumab (24.1% vs. 19.0%; adjusted relative risk, 1.29; 95% CI 1.01−1.66), and the elevated risk persisted at 2 years (39.9% vs. 31.7%; adjusted relative risk, 1.30; 95% CI 1.07−1.57; $P = 0.009$).[4,5] Rates of death and arteriothrombotic events were similar for the 2 drugs. As the results from other clinical trials became available, several groups of investigators performed meta-analyses of overall SAEs and specific adverse events based on the aggregate data.[13–19] The most comprehensive analysis of SAEs was a Cochrane review led by Moja consisting of 3665 patients, with 3356 from the 6 multicenter clinical trials noted above and 309 patients from 3 smaller-scale studies.[15] The combined risk ratio for 1 or more systemic adverse events was 1.08 (95% CI 0.90−1.31). Similar to the researchers conducting previous meta-analyses, Moja et al concluded that there was no strong evidence of a difference in risk but that the data available were not sufficient to rule out clinically important differential risks, particularly for specific adverse events.

The purpose of the present investigation was to use individual patient data, rather than aggregate data, from the large-scale multicenter clinical trials evaluating bevacizumab and ranibizumab for treatment of nAMD to estimate the relative risk of serious systemic adverse events and selected specific SAEs adjusted for prognostic baseline variables. Although randomization is expected to provide treatment groups that are balanced on predisposing conditions, small imbalances on strong prognostic factors such as age, smoking, hypertension, and use of anticoagulant medications can artificially inflate or deflate the difference in risk between the 2 drugs. Accounting for covariates also may increase the precision of the estimates of the relative risk.

Methods

Clinical Trials Included

Investigators for a recent Cochrane aggregate meta-analysis of the relative efficacy and safety of intravitreal bevacizumab and ranibizumab searched electronic bibliographic databases and clinical trial registries as of March 14, 2014, and used hand searching to identify 5249 records that might address the topic.[13] Nine trials were identified by the Cochrane investigators. We targeted for this review the 6 multicenter, randomized clinical trials that compared bevacizumab with ranibizumab, reported counts for patients with 1 or more SAEs, had at least 1 patient reported to have an SAE, and had results published or presented at a national meeting by December 2015. Eligibility criteria for all the trials specified enrollment of eyes with active neovascularization.

Specification of Outcomes and Effect Measures

The primary outcome for the review was the percentage of patients experiencing 1 or more SAEs as defined by the Food and Drug Administration of the United States and the European Medicines Agency.[20,21] This definition includes all deaths, life-threatening events, hospitalizations, events resulting in persistent or significant disability, important medical events, and congenital anomalies. Secondary outcomes were the specific SAEs of death, arteriothrombotic events as defined by the Antiplatelet Trialists' Collaboration, events previously associated with systemic anti-VEGF treatment (arteriothrombotic events [including but not limited to myocardial, cerebellar, and cerebral ischemia and infarction, coronary artery occlusion, transient ischemic attack, cerebrovascular accidents, and embolism], systemic hemorrhage [including duodenal, gastric, gastrointestinal, rectal, respiratory tract, urogenital, cerebral, and intracranial hemorrhage and hematoma], cardiac failure [including congestive heart failure], venous thrombotic events [including pulmonary embolism, deep vein thrombosis, and thrombosis], hypertension [including hypertensive heart disease and accelerated hypertension], vascular death), and events not previously associated with systemic anti-VEGF treatment.[22–24] Because of an imbalance reported from CATT, gastrointestinal hemorrhages were also summarized. The difference in risk was summarized by the relative risk (hazard ratio) and the associated 95% CI.

Data Collection and Statistical Analysis

The Coordinating Center for CATT managed the data and performed the statistical analyses for the review. The lead author or primary contact person as listed in a registry of clinical trials was invited to provide individual patient data. Data were to be provided in 2 electronic data files containing only deidentified data. The first file contained age at enrollment, gender, drug (bevacizumab or ranibizumab), dosing regimen (pro re nata, monthly, or treat-and-extend), study eye (right or left), smoking status at baseline (current, past, or never), diabetes at baseline (yes or no), use of medications for hypertension at baseline (yes or no), treatment of the fellow eye with anti-VEGF drugs during the study period (drug