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Perspectives How the Comparison of Age-related Macular Degeneration Treatments Trial Results Will Impact Clinical Care

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Abstract

Purpose—To provide a perspective on the impact of the Comparison of Age-related Macular Degeneration Treatments Trial (CATT) on future clinical practices.

Design—Interpretation of trial outcomes relative to clinical use of neovascular age-related macular degeneration (AMD) treatments, assessment of the influence of study design and execution on results, and review of unanalyzed safety data in the online supplement.

Methods—Expert opinion.

Results—The CATT study supports the selection of either ranibizumab or bevacizumab for treatment of AMD based on factors other than efficacy, such as cost, because monthly administration of bevacizumab was noninferior to the reference treatment of monthly ranibizumab in improving visual acuity at 1 year. Visual acuity results for bevacizumab as needed were inconclusive for noninferiority relative to monthly administration of either drug. The secondary outcome of decrease in thickness at the foveal center as measured by time-domain optical coherence tomography significantly favored the monthly ranibizumab group vs the bevacizumab-as-needed group but is more difficult to interpret as it did not correlate with visual acuity and is less appropriate for a noninferiority design. Bevacizumab groups had a statistically higher observed risk of serious adverse events; however, scrutiny of the online supplements shows similar numbers of cardiac and neurologic events in bevacizumab and ranibizumab users. Information regarding fellow eye treatment with anti-VEGF agents was not given.

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Conclusions—CATT provides the first level I evidence for bevacizumab in a large number of patients with neovascular AMD. The trial supports use of either drug as primary therapy and suggests that modification of monthly dosing regimens is feasible. A difference in cardiovascular safety between the 2 drugs was not apparent on inspection of the supplementary safety data.

The Long-Awaited Primary Outcome of the Comparison of Age-related Macular Degeneration Treatments Trial (CATT) study was that groups receiving either monthly bevacizumab (Avastin; Genentech, South San Francisco, California, USA) or monthly ranibizumab (Lucentis; Genentech) had equivalent visual acuity at 1 year.¹ For the majority of clinicians who already preferentially used bevacizumab for age-related macular degeneration (AMD),² the data validate their choice of this much less expensive drug (\$50) rather than the much more expensive ranibizumab (\$2000). Clinicians who made this choice did so despite quite modest clinical data for the safety and efficacy of bevacizumab compared to the robust level I data for ranibizumab. Economic considerations likely influenced the selection of drug for individual patients. The decision to design, fund, and execute a clinical trial by the CATT leadership, the National Institutes of Health, and the numerous investigators, coordinators, technicians, and patients who chose to participate was also motivated by a need to acquire level I evidence about the safety and efficacy of a drug that blossomed to widespread off-label use without ever having undergone rigorous clinical trials.

The Trial in Context: A Historical Timeline

The Era of Clinical Pharmacotherapy for AMD is only slightly more than 10 years old. The US Food and Drug Administration (FDA) approved intravenous verteporfin (Visudyne; Novartis, East Hanover, New Jersey, USA) as a photosensitizer for photochemical light activation in 2000. Administered intravenously at 3-month intervals, it reduced the risk of significant vision loss compared to thermal laser photocoagulation or observation for predominantly classic AMD.³ Pegaptanib sodium (Macugen; Pfizer, New York, New York, USA), approved in December 2004 and administered intravitreally at 6-week intervals, also prevented severe vision loss and worked irrespective of the pattern of leakage on fluorescein angiography.⁴ Pegaptanib targeted a pathway in the underlying biology of AMD: the molecule is an aptamer that selectively binds the vascular endothelial growth factor (VEGF) 165 isoform. Both agents were better at preserving than improving vision. Only about 6% of patients gained 3 or more lines of vision.

In July 2005, the American Society of Retina Specialists heard presentations of the Systemic Avastin for the Treatment of Neovascular AMD (SANA) trial as well as case reports of intravitreal bevacizumab use supported by optical coherence tomography (OCT) documentation.^{5–7} MARINA, a placebo-controlled trial of ranibizumab, and ANCHOR, a randomized comparison of ranibizumab and photodynamic therapy, were published in 2006.^{8,9} Clinicians could obtain bevacizumab in 2005 and 2006 but were unable to use ranibizumab until weeks after FDA approval in June 2006. With its easy availability, low cost, and suggested efficacy, intravitreal bevacizumab use for AMD expanded and multiple uncontrolled case series appeared in 2006 and 2007^{10–16} with no obvious evidence of side effects or safety issues. After FDA approval of ranibizumab in June 2006, many clinicians

continued to use bevacizumab preferentially. Analysis of fee-for-service Medicare Part B claims data revealed that bevacizumab accounted for 58% and ranibizumab for 41% (with pegaptanib sodium accounting for the other 1%) of intravitreal injections for AMD in 2008; bevacizumab was used in nearly two-thirds of individual AMD patients treated with an anti-VEGF agent.

Bevacizumab is not a generic form of ranibizumab; ranibizumab and bevacizumab are different molecules produced in different cell culture systems. Although both are murine-derived humanized monoclonal antibodies (-zumabs), the active binding site of ranibizumab has been affinity matured to produce stronger binding.¹⁷ Bevacizumab (149 kDa) is larger than ranibizumab (48 kDa) and may not penetrate the retina as well. Because bevacizumab includes the Fc (constant region) of the immunoglobulin chain, it may be a more potent antigenic stimulus as well as persisting longer in blood if the molecule escapes the eye.¹⁸ All of these differences have potential implications for therapeutic action, pharmacokinetics, and possibly systemic safety and may also have implications for dosing interval.

Genentech developed both bevacizumab and ranibizumab. Monkey experiments conducted at Genentech and published in 1999 showed that 25 micrograms of full-length HER2 antibody in 50 microliters, similar in chemical structure but one-fifth the usual human dose of bevacizumab, did not penetrate the internal limiting membrane (ILM) of the retina, whereas 25 micrograms of a FAB fragment of anti-VEGF antibody in 50 micro-liters, similar to ranibizumab but one-half the usual human dose, penetrated the ILM. There also was greater systemic exposure from injection of the full-length antibody.¹⁹ These observations may explain why Genentech chose to pursue clinical testing only on ranibizumab for intravitreal use. In addition, bevacizumab as an intravenous treatment for AMD certainly would not have been viewed favorably for development, because of potential systemic side effects. In patients with colorectal cancer receiving systemic chemotherapy that included bevacizumab, notable adverse events were gastrointestinal perforations (1.9%), arterial thromboembolic events (2%), grade 3–4 bleeding (2.2%), and de novo hypertension requiring medication (22%).²⁰

While clinicians were using ranibizumab and bevacizumab to treat AMD for the past 6 years, researchers have continued to develop new anti-VEGF drugs. The next available drug will likely be aflibercept (VEGF Trap-eye; Regeneron Pharmaceuticals, Tarrytown, New York, USA), a fusion protein with the second binding domain from VEGFR-1 and third binding domain from VEGFR-2 fused to the constant (Fc) region of human IgG1.²¹ The VEGF Trap-eye's (VTE's) high VEGF binding affinity (dissociation constant [Kd] < 1 pM), compared to bevacizumab (Kd between 0.1 and 10 nM) and ranibizumab (Kd < 192 pM), and intermediate molecular size (110 kDa) between bevacizumab (149 kDa) and ranibizumab (48 kDa), should result in a time-dependent VEGF binding activity that exceeds both drugs.^{2,22,23} The recently presented 1-year primary outcome data from VIEW 1 (Heier J, Miami, FL, February 12, 2011; unpublished data) and VIEW 2 (Schmidt-Erfurth U, Miami, FL, February 12, 2011; unpublished data) AMD clinical trials showed that 2 mg VEGF trap-eye injected either monthly or every other month was comparable to monthly dosing of ranibizumab in visual acuity gain and safety. The second year of the study will explore the feasibility of as-needed dosing, with treatment intervals not to exceed 3 months.

The FDA's Ophthalmic Drug Advisory Committee recommended the VTE (expected trade name of Eylea) for bimonthly dosing, with a final approval decision expected by August 20, 2011.

Ranibizumab Vs Bevacizumab and Fixed vs Variable Dosing

Importantly, CATT was a noninferiority trial. Primary outcome results were stated as showing that “there were equivalent mean changes in visual acuity averaged over the 1-year period”¹ in all pairwise comparisons. The 2-sided 95% confidence interval to establish non-inferiority at 1 year was the loss or gain of 5 ETDRS letters. The bevacizumab-as-needed group lost more than the prespecified 5-letter difference, when compared to either bevacizumab-monthly (– 5.7 letters) or ranibizumab-monthly (– 5.9) groups. Since noninferiority trials increase the possibility of finding an inferior treatment to be noninferior (type 1 error), this is potentially a concern.

For OCT, pairwise comparisons between ranibizumab monthly and bevacizumab as needed at 1 year demonstrated that the ranibizumab showed a significantly greater decrease in thickness at the foveal center and the proportion of patients with no fluid on OCT. In the ANCHOR and MARINA trials,^{8,9} OCT data were not used, although a later publication showed superiority of ranibizumab to photodynamic therapy in decreasing central point thickness at 7 days in a subset of 61 ANCHOR patients.²⁴ A stronger effect on leakage by ranibizumab might eventually lead to actual differences in visual acuity outcomes; thus, the secondary outcomes of the 2-year data are important. However, at 1 year, there did not appear to be a significant correlation between amount of fluid, or the presence of fluid, and visual acuity outcomes. OCT changes have not correlated with visual acuity in other studies.²⁵

Randomization in the CATT trial was not only to drug, but also to dosing schedule. Roughly half of the patients randomized to each drug did not receive injections on a fixed monthly schedule but rather *pro re nata* (PRN; as needed) from month 2 onward based on clinical assessment, OCT findings, and fluorescein angiography if desired. Ranibizumab and bevacizumab yielded statistically similar visual acuity results when administered on the PRN dosing schedule as they did with the monthly schedule. With ranibizumab, the PRN-treated eyes had 1.7 fewer letters of mean visual acuity score than eyes treated monthly at 1 year, but this difference was not statistically significant. With bevacizumab, there was also no statistical difference between visual acuity outcomes in monthly vs PRN dosing, but there were 2.6 fewer letters of mean visual acuity score with PRN bevacizumab than with monthly ranibizumab at 52 weeks. Although this was not statistically significant, the comparison was felt to be “inconclusive”¹ and a potential concern.

The figure charting the mean change in visual acuity score for monthly and PRN treatments shows the 4 groups fairly close together from baseline to 36 weeks. By 52 weeks, there appears to be a divergence between the 2 monthly groups and the 2 PRN groups, favoring the monthly treatment. One of the jobs of the Data Safety and Monitoring Board during the second year of the study will be to monitor this divergence for statistical significance that would likely lead to a change in treatment assignments for the participants. Previous studies

using various PRN regimens have suggested some flattening in the benefit of treatment over time.^{26,27} For now, PRN dosing seems feasible and worthy of further study.

The PRN dosing schedule resulted in 4 to 5 fewer injections over 1 year, a potentially huge economic benefit no matter which drug is used. The bevacizumab-as-needed group required a statistically greater number of injections than the ranibizumab-as-needed group (7.7 ± 3.5 vs 6.9 ± 3.0) with an average per-patient cost of the study drug in the first year in the as-needed groups of \$385 for bevacizumab vs \$13 800 for ranibizumab, with not all costs related to the drug. It is critical to note, however, that the CATT protocol required investigators to bring patients back to the office for examination at monthly intervals, regardless of whether they were assigned to the monthly or PRN arms of the study. This is different than the typical “treat and extend” regimen now in common use, in which both the evaluations and the treatments become less frequent if fluid is not present on the OCT. It is difficult to extrapolate outcomes comparable to the CATT study if eyes are not assessed every 4 weeks. Previous attempts to increase the intervals between ranibizumab injections and physician visits to 3 months (PIER²⁸ and EXCITE²⁹) resulted in the forfeiture of previous visual gains. Also, PRN treatment was given by the CATT investigators in slightly less than 75% of visits in which subsequent reading center assessment of the OCT indicated that an injection should have been given according to study protocol.¹ Strict adherence to protocol might have led to different results.

Safety Concerns

Two Secondary Outcomes in the Catt Trial were designated as safety issues: complications of treatment such as incidence of endophthalmitis, retinal detachment, cataract, or uveitis at 12 and 24 months; and the incidence of adverse events at 12 and 24 months. The 12-month safety data were reported with the 1-year primary outcome data.¹

Ocular adverse events were rare, occurring in less than 1% of patients. There were 2 cases of endophthalmitis among monthly ranibizumab users and 4 cases of endophthalmitis among monthly bevacizumab users ($P = .45$), as well as 1 case of pseudoendophthalmitis in the monthly ranibizumab group. Ophthalmologists used 1 of 3 povidone-iodine-based preinjection regimens, or a short course of topical antibiotics if allergic. Both drugs were supplied in glass vials wiped with alcohol prior to withdrawing medication according to a specific protocol. Half of the investigators used postinjection antibiotics. One in a hundred patients in the monthly injection groups were reported to have endophthalmitis. Because ranibizumab is supplied in unit-dose packaging and the “off-label” use of bevacizumab requires aliquoting and storing in syringes, concerns have been raised about additional risk of infection. However, this additional risk seems small and is not really predictable or ascertainable from this study.

Assessment of the overall risk ratio for serious adverse events in both bevacizumab groups, after adjustment for demographic and baseline characteristics, was reported as 1.29 (95% confidence interval 1.01 to 1.66). This result was mainly attributable to hospitalizations for infections and to gastrointestinal disorders such as hemorrhaging, nausea, and vomiting.

Other than bleeding, these are not expected systemic complications of VEGF inhibition. No significant changes in systemic diastolic or systolic blood pressure were reported.¹

Careful scrutiny of the data in the Supplementary Appendix³⁰ for raw percentages of probable cardiac or neurologic events does not show a difference between groups that appears clinically important. Fifteen of 599 people (2.5%) in the ranibizumab groups and 15 of 586 (2.6%) in the bevacizumab groups were noted to have had cardiac arrest, cardiorespiratory arrest, coronary artery occlusion, myocardial infarction, cerebellar infarction, cerebral hemorrhage, or cerebrovascular accident by week 52. This is somewhat higher than the 2.1% rate of thromboembolic events (17 of 874 patients) reported in the ranibizumab package insert³¹ for the 1-year pooled data from the PIER,^{28,32} MARINA,⁸ and ANCHOR⁹ studies. Statistical analysis would require uniform definitions and adjustment for baseline characteristics and length of follow-up, which exceed what a cursory look can reveal. However, it appears that the most feared risks, and those most often discussed with patients, are not different between the 2 drugs. Further statistical analysis at 1 and 2 years by the study group might yield a different result. Other caveats regarding safety are that the age and particular comorbidities of patients with age-related macular degeneration may not extrapolate to other diseases such as diabetic macular edema or myopic degeneration.³³ If fellow eyes of CATT participants were also treated with anti-VEGF agents, then the systemic toxicity information comparing drugs is difficult to interpret. Information is not given regarding the doses, drugs, or frequency of anti-VEGF agents used to treat fellow eyes.

The FDA approved ranibizumab as safe for use in the treatment of age-related macular degeneration on the basis of multiple level I randomized controlled clinical trials. A systematic review in 2010 included 13 prospective randomized controlled trials of bevacizumab with a total of 591 patients (range 13–102) and short follow-up that were not felt to meet quality standards for phase III trials.³⁴ Subsequently the randomized ABC trial compared 65 bevacizumab patients to 66 standard-of-care patients; the numbers were deemed too small to reliably assess safety data.³⁵ The CATT trial reports the largest number of bevacizumab recipients to date in a level I study of sufficient quality to provide evidence for the safety of intravitreal bevacizumab in the treatment of wet age-related macular degeneration and corroborates the safety outcomes of ranibuzimab in prior studies.

The Future

A Clinician Treating a Patient with Exudative AMD after release of the CATT results should feel equally justified using either ranibizumab or bevacizumab. The physician may be slightly less comfortable choosing between either fixed or variable dosing, because of the tiny red flag with visual acuity in the PRN bevacizumab group and the lack of adherence of investigators to a strict protocol of PRN treatment that further differs from the commonly used “treat and extend.” It remains unknown whether the statistically significant greater decrease in central retinal thickness seen in the ranibizumab groups will be maintained and whether that will translate into a meaningful effect on visual acuity at 2 years. Similarly, it remains unknown whether the systemic side effects in the bevacizumab groups will coalesce

into a meaningful pattern that indicates this larger and slower-moving molecule, delivered in relatively small ophthalmic doses, is less safe than the FDA-approved ranibizumab.

Importantly, it may be even more dramatic to watch what happens to clinical patterns of use if the VEGF Trap-eye is approved and how it will be priced relative to ranibizumab. Cost has clearly driven the use of bevacizumab over ranibizumab in clinical practice as well as a general familiarity with bevacizumab by the time ranibizumab became commercially available. Reducing the frequency of examinations and injections may well prove to be a cost advantage over ranibizumab, but bevacizumab treatment will likely still cost less than the VEGF Trap-eye, a molecule that will initially be unfamiliar to most clinicians. Now that level I evidence exists regarding safety and efficacy for bevacizumab, it is intriguing to imagine how clinical usage might shift if there were 3 highly effective drugs: 1 that required half the number of injections, 1 that was significantly less expensive, and 1 that was the familiar reference drug, ranibizumab.

The CATT leadership, clinical centers, and the patients who participated are to be congratulated for capturing objective data clinicians can use to guide the selection of pharmacotherapy for exudative AMD. Importantly, we await the 2-year data, especially with regard to mean visual acuity outcomes in relation to retinal thickness, comparisons of monthly vs PRN treatment regimens, and safety outcomes. Even if advantages of ranibizumab over bevacizumab are eventually confirmed, the 40-fold price differential of ranibizumab over bevacizumab will likely remain. We are hopeful that the results of the CATT trial, coupled with competition from newer agents, will provide physicians with more cost-effective means for treating AMD patients.

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