

CATT Shows Equivalency of Anti-VEGF Molecules

Retina Today Editorial Board members provide their impressions of the data from the trial, as well as thoughts on the Genentech-sponsored Medicare patient claims data study.



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On May 1 at the Association for Research in Vision and Ophthalmology (ARVO) meeting, Daniel Martin, MD, presented the results of the Comparison of AMD Treatments Trial (CATT), an

important, well-run study that showed comparable efficacy for two anti-vascular endothelial growth factor (VEGF) molecules injected intravitreally on a monthly basis.¹ When we review the totality of the data, however, there are some secondary efficacy measures that suggest a slight change in the story as we look into the second year. For example, on optical coherence tomography (OCT), monthly ranibizumab (Lucentis, Genentech) at every time point had a numerically greater reduction in OCT thickness than bevacizumab (Avastin, Genentech), which may have an effect on visual acuity over time.

The finding that was most surprising to me was that as-needed (PRN) dosing of ranibizumab was noninferior to the monthly treatment arms of both ranibizumab and bevacizumab, which was not the case with PRN bevacizumab. When we look at the PRN dosing arms in CATT, however, it is important to consider that these patients were followed every month to ascertain whether they met the liberal criteria for retreatment—certainly not a treat-and-extend regimen.

CATT showed us nothing new in terms of safety, but the study was not powered to determine differences in adverse events.

I continue to use both ranibizumab and bevacizumab in my practice, and my sense is that, to date, practice patterns have not changed significantly.

As we look to the future, it remains to be seen when payers will begin to develop overt clinical practice guidelines based on comparative research studies; in some areas of the United States, this is happening in an indirect fashion as

payers demand higher copays for high-priced therapies. As retina specialists we must continue to advocate for doctor and patient choice in determining best treatments.

In regard to safety, also during the ARVO meeting, Emily Gower, PhD,² presented the abstract from a Genentech-sponsored study that analyzed Medicare claims data to compare systemic and ocular adverse events for more than 77,000 patients who received intravitreal ranibizumab or bevacizumab injections. In my opinion, this study has several limitations. Most important, as Dr. Gower stated, this was an uncontrolled study, and causality cannot be established, as the patients who received bevacizumab might have been a less healthy patient population with reduced access to health care. Overall, the findings of this study did not alarm me, but we must remain vigilant for our patients with respect to systemic safety issues and their potential relationship to intraocular therapies.



ROBERT L. AVERY, MD

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The primary outcome of CATT¹ was the mean change in visual acuity at 1 year, and there is no question that ranibizumab and bevacizumab were equivalent in this respect. The level

of visual improvement was in line with what one would expect given the mix of classic and occult cases in the study, although one might have expected even more improvement given the number of patients enrolled without subfoveal choroidal neovascularization. Overall, these are excellent results.

Regarding the secondary outcomes, I was a little surprised at how well the PRN arms did when compared with the monthly arms. I had feared that a small percentage of patients who were responding well at 11 months, and who did not receive an injection, would recur at

month 12 and lower the results at the primary endpoint. This may have occurred, but it obviously was not common enough to cause a major problem given the excellent visual results in the PRN arms. Nevertheless, I am concerned that the visual acuity curves appear to start to diverge slightly after 36 weeks, and it will be interesting to see if this continues into the second year.

The OCT data showed that ranibizumab was more effective than bevacizumab in drying the retina at month 1 and throughout the first year (20 μ m at month 1 and 32 μ m at month 12). What surprised me was the finding that even monthly ranibizumab for 1 year did not completely dry the retina in the majority of cases, although it was more successful in doing so than bevacizumab. I expect that when spectral domain (SD) OCT is used, even more fluid will be detected. It is unclear what the persistence of small amounts of fluid means, as it did not seem to have a major adverse effect on the visual acuity at 1 year. It will be interesting to reevaluate this at 2 years. Similarly, the PRN arms had significant growth in lesion size relative to the monthly arms, and if this continues into the second year it could have a significant effect on visual acuity.

I continue to use both agents in my practice, and the major change that I am experiencing as a result of CATT is that I am spending more time explaining the trial results to my patients. The case for bevacizumab is strengthened, as the visual results are equivalent at 1 year and come at a fraction of the cost of ranibizumab. However, there are still arguments for ranibizumab, most notably that it was anatomically superior in drying the retina and, hence, required slightly fewer injections in the PRN arm.

The increased risk of serious adverse events seen with bevacizumab is difficult to interpret. Most of these events required hospitalization but were distributed across a wide range of organ systems not felt to be affected by systemic bevacizumab administration for cancer treatment. There are several reports of prolonged reduction of systemic VEGF levels after intravitreal bevacizumab injections, so it is difficult to completely exclude the possibility that some of these adverse events could have been related. Theoretically, the significantly shorter systemic half-life of ranibizumab vs bevacizumab would be a benefit, but at present the data are inconclusive.

Dr. Gower's ARVO presentation on the Medicare patient claims database analysis² was interesting, but, as is the case with any abstract, the full details of the methodology still require peer review. An underlying bias in any Medicare database study is that patients with poor or nonexistent secondary insurance are more likely to receive bevacizumab due to cost, and these are the same patients who may be less likely to receive good care for their systemic diseases or be compliant with comorbid health regi-

mens (eg, antihypertensive medications). An attempt was made to correct for this bias, but I would like to see the full paper to assess the investigators' success in mitigating this issue. However, despite its weaknesses, when taken with other database studies and the systemic VEGF level studies, the totality of data reminds us that we should remain vigilant in evaluating the potential side effects of these agents.



DAVID S. BOYER, MD
Section Editor

I commend Dr. Martin and all the individuals involved in CATT.¹ I was certainly impressed by the equality of efficacy between ranibizumab and bevacizumab and by the data showing that careful

monthly follow-up and PRN treatment with ranibizumab provide good results at 1 year. That ranibizumab dosed monthly provided better anatomic results on OCT causes me to wonder whether the 2-year data will show a visual acuity difference between the monthly groups, but of course this remains to be seen. I also think that the use of SD-OCT in the second year will result in increased detection of fluid, improving the results in the PRN arms but increasing the number of injections.

Although many clinicians inject intravitreal anti-VEGF agents at 5- to 6-week intervals, CATT implies the need for more frequent injections when bevacizumab is being used. Even in MARINA and ANCHOR, there was a slight drop-off in visual acuity in the second year, so we must determine whether the visual acuity differences between monthly bevacizumab or ranibizumab and the PRN treatment arms widen.

In regard to safety and the Gower study,² more data are needed. Curtis et al³ also found a systemic safety difference between bevacizumab and ranibizumab that favored ranibizumab, but this was also a Medicare analysis, which has limitations. However, these findings should be considered. I would recommend that the Retina Society, the Macula Society, and the American Society of Retina Specialists form a task force to look at this issue to see if it is a clinically significant problem. ■

1. The CATT Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration [published online ahead of print April 28, 2011]. *New Engl J Med*. doi:10.1056/NEJMOa1102673.

2. Gower EW, Cassard S, Chu L, et al. Adverse event rates following intravitreal injection of Avastin or Lucentis for treating age-related macular degeneration. Abstract presented at: the Association of Research in Vision and Ophthalmology Annual Meeting; May 1-5, 2011; Fort Lauderdale, FL. Abstract 6644.

3. Curtis LH, Hammill BG, Schulman KA, Cousins SW. Risks of mortality, myocardial infarction, bleeding, and stroke associated with therapies for age-related macular degeneration. *Arch Ophthalmol*. 2010;128(10):1273-1279.

Editor's note: See page 12 for full news coverage from ARVO.