

CATT 5-YEAR DATA RELEASED

The 5-year results of the CATT, a clinical trial assessing the role of anti-VEGF therapy in neovascular age-related macular degeneration (AMD) management, found that, although the vision gains made during the first 2 years of the study were not maintained at 5 years, half of the study eyes assessed had at least 20/40 vision.¹ The study was published online ahead of print in *Ophthalmology*.

The 5-year results confirm that anti-VEGF therapy is “a major long-term therapeutic advance for neovascular AMD,” the study authors concluded.

In the CATT, researchers randomly assigned patients to bevacizumab (Avastin, Genentech) or ranibizumab (Lucentis, Genentech) treatment and to one of three dosing regimens. At the 2-year study endpoint, patients were released from the clinical trial protocol. At 5 years, patients were recalled, and 647 of 914 living patients were assessed. With an average of 5.5 years follow-up, 60% of patients assessed had been treated at least once with a drug other than their assigned drug.

At the 5-year time point, 50% of eyes had visual acuity of 20/40 or better, and 20% had visual acuity of 20/200 or worse. On average, eyes lost 3 letters from baseline and 11 letters from the 2-year study endpoint. Between years 2 and 5, the group originally assigned to ranibizumab for 2 years lost 4 more letters than the bevacizumab group ($P = .008$); otherwise, no significant differences in visual acuity among study groups were observed.

Of 515 eyes available for grading, geographic atrophy (GA) was present in 41%. Among 467 eyes with fluorescein angiography, mean total lesion area was 12.9 mm², a mean of 4.8 mm² larger than at 2 years. Mean foveal thickness was 278 μ m, a decrease of 182 μ m from baseline and 20 μ m from the 2-year mean.

Among patients originally assigned to ranibizumab, 7.6% experienced an arteriothrombotic event (ATE), compared with 4.5% originally assigned to bevacizumab ($P = 0.04$). Otherwise, there were no differences in serious safety events among the drug and dosing regimen groups.

INDUSTRY RESPONSE

In a statement reacting to the release of the CATT 5-year outcomes, Genentech pointed out that this assessment comes 3 years after patients were released from the study protocol. The company highlighted several of the study authors' comments in the paper, wherein the authors suggest that the study results speak more to the effect on neovascular AMD of anti-VEGF therapy in general rather than to any specific drug or dosing patterns.

The study authors wrote, for example, that “Because very few patients continued to receive the originally assigned



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drug or dosing schedule between the end of year 2 and follow-up at approximately 5 years, the CATT Follow-up Study results provide information primarily on overall treatment outcomes with anti-VEGF drugs and limited information on effects of different drugs and dosing regimens.”

The Genentech statement also notes that study authors cautioned that safety conclusions about the drugs should be considered with the study design in mind. The authors wrote, “With most patients changing drugs over time, the ability to identify differential safety effects of the two drugs is compromised. Because of the absence of any difference [in ATEs] when the history of drug exposure was certain, we do not believe that the difference in events observed when a large portion of patients were not receiving ranibizumab are meaningful.”

PHYSICIANS' RESPONSES

Retina Today and EyewireTV spoke to retina specialists to gather comments on the study.

Rahul Khurana, MD, said he sees many positives from the study. Speaking with EyewireTV, Dr. Khurana said, “In our previous treatment, even with photodynamic therapy, only about 15% [of patients] were 20/40 or better, so going up to 50% is a truly large advance and is very exciting.”

Dr. Khurana noted that, even with a high number of patients with 20/200 or worse vision at 5 years, anti-VEGF therapy is an improvement. “Compared to the natural history,” he said, “that’s much better.”

In a conversation with *Retina Today*, John A. Wells, MD, said that he felt that expanded lesion size was the primary cause of vision loss for many patients at 5 years, with GA development being the second most common cause. The expansion of lesion size, he said, could be addressed by

increased treatment; on average, patients received 15.4 treatments in the 3 years between the 2-year time point and the 5-year follow-up.

"Patients most likely lost vision after they left the CATT because they were undertreated and this allowed lesion size to increase," Dr. Wells said. "To me, the message is that patients need more treatment."

"The low injection frequency reported in the trial jells with claims data that have been reported elsewhere," Dr. Wells continued. "Some patients lost vision due to GA, but it seems obvious that too many patients are being undertreated for AMD."

Dr. Wells noted that the study's limitations were important to understand.

"I want to emphasize that the 5-year results do not give us any information about the relative effectiveness and safety of ranibizumab and bevacizumab, due to the fact that, after the CATT ended, only 20% of the original ranibizumab group and only 31% of the original bevacizumab group continued to receive their CATT-assigned drug," he said. "Most eyes received various treatment combinations, so you really cannot draw conclusions from the 5-year endpoint about changes in vision or systemic adverse events in one group versus the other."

Ehsan Rahimy, MD, coauthor and cofounder of the blog MakingARetinaSurgeon.com, said that, although the data are positive in many respects, the percentage of eyes with 20/200 vision at 5 years is a signal that the retina profession and pharmaceutical industry still have a long way to go before all physicians can effectively treat all patients with AMD.

"We must do better," Dr. Rahimy wrote on his blog. "To date, our treatment paradigm for macular degeneration has been so VEGF-centered because, let's face it, that's the best we have. With new agents on the horizon that target different pathways in the disease cascade, combination therapy will be the next frontier, and may help prevent the progression of geographic atrophy or the size of the lesion complex."

Dr. Rahimy said he interprets the study results as simultaneously a tribute to the success of anti-VEGF therapy and a demand for further pharmacologic advancement. "We are sitting on the brink of a second revolution in retina," he wrote. "The 5-year CATT Follow-up Study was an ode to the first one, but I certainly cannot wait to see what the next 5 years has in store."

1. Maguire MG, Martin DF, Ying G, et al; Comparison of Age-related macular Degeneration Treatments Trials (CATT) Research Group Writing Committee. Five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration [published online ahead of print May 2, 2016]. *Ophthalmology*.

Neurotech Halted Phase 2 Wet AMD Study, Will Refocus on MacTel

Neurotech has halted a phase 2 study evaluating a possible wet AMD therapy and announced a renewed focus on a phase 2 study evaluating therapy for macular telangiectasia (MacTel), according to a press release.

The halted study was evaluating a soluble anti-VEGF receptor protein delivered via encapsulated cell technology (ECT) in wet AMD patients. The study was stopped due to a larger-than-anticipated number of patients requiring rescue injection in the treatment arm. ECT was well tolerated for the duration of the trial, and no observed safety signals contributed to the decision to discontinue to trial.

The company's phase 2 study evaluating ECT-delivered ciliary neurotrophic factor (CNTF) in patients with MacTel will continue. CNTF is a growth factor that stimulates and protects photoreceptor cells, Müller cells, and retinal ganglion cells, and has been shown to slow vision loss due to photoreceptor death in animal models. Data from year 2 of the study are expected in the second quarter of 2017.

Phase 2 Trial: Combination Therapy for RVO Resulted in Fewer Anti-VEGF Injections

The phase 2 Tanzanite trial evaluating concomitant administration of aflibercept and a proprietary form of suprachoroidal triamcinolone acetate (TA; Zuprata, Clearside Biomedical) for macular edema secondary to retinal vein occlusion reached its primary endpoint, according to a press release.

The trial compared the number of aflibercept injections needed during the 3 months following treatment with combination therapy (aflibercept and suprachoroidal TA) or aflibercept monotherapy. The study found that patients in the combination therapy arm qualified for approximately 60% fewer aflibercept injections compared with patients in the monotherapy arm ($P = .013$). At the end of the 3-month observation period, patients in the combination therapy arm had an average BCVA improvement from baseline of approximately 19 letters; patients in the monotherapy arm improved by approximately 11 letters.

No serious adverse events were reported in the trial. ■