

# AWARE Study to Clarify Safety of Anti-VEGF Agents

The AWARE group hopes this study will serve as a model for safety analyses for drugs developed in the retina arena and beyond.

BY CONNI BERGMANN KOURY, EDITOR-IN-CHIEF

**T**he Analysis of Safety Outcomes with Anti-VEGF Treatment (AWARE) is a landmark longitudinal study exploring the safety of anti-vascular endothelial growth factor (VEGF) therapies for the treatment of neovascular age-related macular degeneration (AMD) (Figure 1) and diabetic retinopathy (DR).

According to Scott W. Cousins, MD, Director, Center for Macular Diseases at Duke University Eye Center, this is the first study to access the full repository of Medicare data to document treatment patterns and explore the association between the use of anti-VEGF therapies and potential adverse effects both locally and systemically. Dr. Cousins spoke at a media briefing held in conjunction with the Association for Research in Vision and Ophthalmology 2007 Annual Meeting in Fort Lauderdale, Fla.<sup>1</sup>

## STUDY RATIONALE

Neovascular AMD, as well as DR and vein occlusion, are driven predominantly by VEGF, Dr. Cousins said (Figure 1). “What this means is that these diseases are going to be more and more commonly treated—especially vein occlusion and diabetes—with intraocular anti-VEGF therapies. We also know that VEGF does both good and bad things in the body, with the good things sometimes being forgotten.”

VEGF mediates blood flow, including blood flow to the kidneys and systemic blood pressure. VEGF is also a neuroprotectant, a survival factor, and a fenestration factor (Figure 2).

When anti-VEGF agents are injected intraocularly they do show up systemically in physiologically significant concentrations. “My colleague at Duke, Carl Csaky, MD, along with Robert Avery, MD, from Santa Barbara, Calif, are completing a study<sup>2</sup> in which they found that >10% of patients who received bevacizumab (Avastin; Genentech, San Francisco)

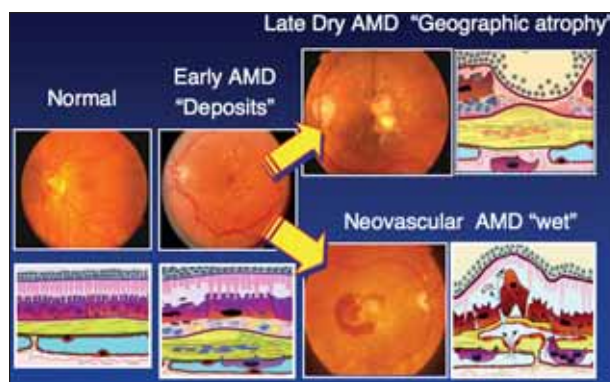


Figure 1. The progression of AMD: Geographic atrophy and neovascular conditions.

had measurable levels in the blood for a month after the injection,” Dr Cousins said.

This means—theoretically—that bevacizumab is free to block VEGF somewhere in the body. “It’s clear that in some patients who are in a VEGF-depleted state—they have just enough VEGF for their systemic needs—that bevacizumab could soak up that systemic VEGF and potentially put those patients at a specific risk.”

The potential systemic side effects of VEGF blockade include stroke, myocardial infarction (MI), and gastrointestinal perforation, according to Dr. Cousins. These are side effects that need to be monitored systemically to identify potential adverse effects of VEGF blocking.

Food and Drug Administration approval (FDA) of pegaptanib (Macugen; OSI/Eyetech and Pfizer, both in New York, NY) was based on the VEGF Inhibition Study In Ocular Neovascularization (VISION) trial, in which there were no safety signals.<sup>3</sup> In the pivotal Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascular-

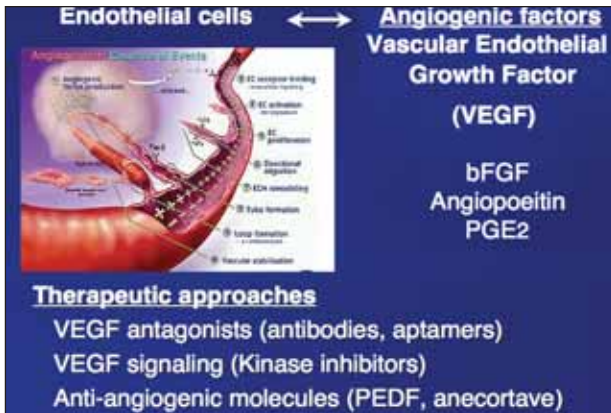


Figure 2. Angiogenesis paradigm for neovascularization.

ization in AMD (ANCHOR) study of ranibizumab (Lucentis; Genentech), at the FDA-approved dose, there was a trend that was not statistically significant toward increased cardiovascular events.<sup>4</sup>

“The problem with pivotal trials is that they are not powered to pick up safety signals. Therefore, we do not know if that was a statistical glitch or a safety signal for the study,” Dr. Cousins said. “Then Genentech sent out a ‘Dear Doctor’ letter that suggested a higher incidence of stroke—1.2%—among treated patients in the [Safety Assessment of Intravitreal Lucentis for AMD] SAILOR trial interim results.”<sup>5</sup>

It is unclear whether this number is large enough to be of concern in relation to the event rate in the normal population. It is certainly not high enough that any one retina specialist will see the risk in practice, Dr. Cousins said. “In fact, the sham group in the [Minimally Classic Occult Trial of the Anti-VEGF Antibody Ranibizumab] MARINA trial had a 1.7% rate of MI over 2 years.<sup>6</sup> Compare this with the Medicare database that shows AMD patients have a 4.3% MI rate over 2 years.<sup>7</sup> We put healthier patients in clinical trials than what we take care of in our practices, so the safety issues that we saw in the trials may not bear out when we actually look at what is going in real-world patients.”

The current system for adverse event reporting is doctor self-report through FDA Medwatch. “The problem with this is that when you are the doctor whose treatment causes a side effect, but you are not the one who manages that side effect, it is going to fall through the cracks,” Dr. Cousins said.

In the AWARE Study, Dr. Cousin’s group at Duke will have access to Medicare claims data and assessments from a new program called the Chronic Condition Warehouse database, which is managed by the Iowa Foundation for Medical Care (IFMC), a Medicare contractor.

“We are going to take claims for every patient who has neovascular AMD, diabetic macular edema, or proliferative DR (Figure 3), and who also receives treatment, and compare them to patients with the same diagnoses but who are not

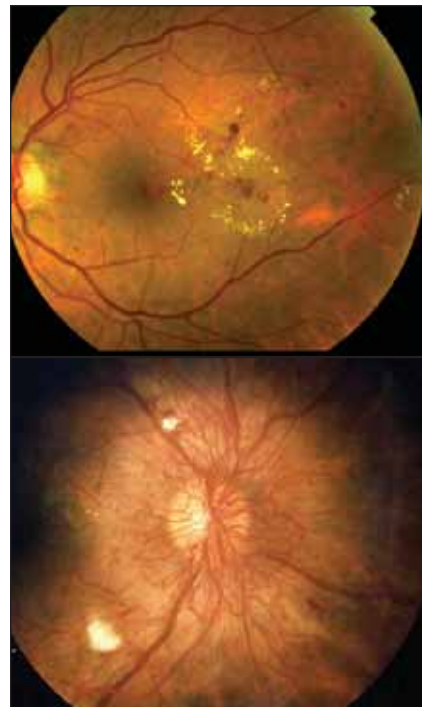


Figure 3. Nonproliferative DR with microaneurysms (top), and proliferative DR.

treated,” Dr. Cousins said. The group will analyze the rate of hospitalizations and new diagnoses of stroke, MI, bowel operations, as well as doctor visits.

“If we find something, we can actually do a chart audit and try to confirm that the safety event was indeed something that was rational and would be expected as a side effect the drug,” Dr.

Cousins said. “This is exciting because it is the first time that this approach has been taken to explicitly look at safety.”

The intent of Dr. Cousin’s group is to set this up as a model for safety analyses for every drug that is developed in the retina arena. This would potentially be part of the FDA’s response to how a company has to do postmarketing surveillance. Dr. Cousins said that the first pass of the 2006 data is expected by late summer. The Duke Clinical Research Institute is conducting the study in collaboration with the Duke Eye Center. Support is provided by OSI/Eyetech. ■

*Scott W. Cousins, MD, is Director, Center for Macular Diseases, Duke University Eye Center. Dr. Cousins disclosed that he is a paid consultant for Alcon, Allergan, OSI/Eyetech, and Genentech. He receives research support from Carl Zeiss Meditec and Novartis. He may be reached at scott.cousins@duke.edu; phone: 919-684-3090; or fax: 919-681-6474.*

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