RETINA

Anti-VEGF Treatment and Dry AMD: Finding the Balance

BY MIRIAM KARMEL, CONTRIBUTING WRITER
INTERVIEWING MARTIN FRIEDLANDER, MD, PHD, DANIEL F. MARTIN, MD, AND PHILIP J. ROSENFELD, MD, PHD

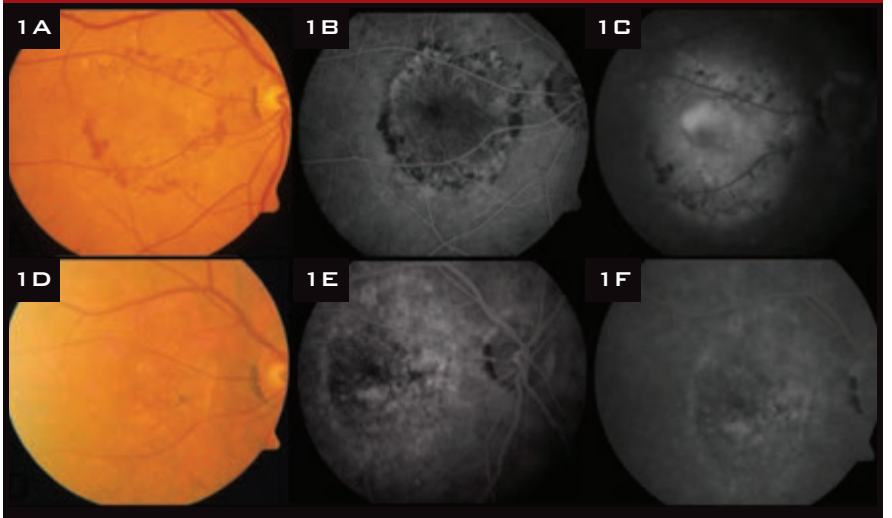
When it comes to VEGF inhibition for retinal disease, can there be too much of a good thing? That was the question asked by Martin Friedlander, MD, PhD, in his recent presentation at the 2013 Angiogenesis, Exudation, and Degeneration meeting in Miami.[1] Dr. Friedlander is professor of cell and molecular biology at Scripps Research Institute and chief of the retina service at Scripps Clinic, La Jolla, Calif.

"The concern is, are we drying the retina too much?" said Daniel F. Martin, MD, chairman of the Cleveland Clinic Cole Eye Institute. In going after neovascular AMD, are we increasing the risk for the development of advanced dry AMD or geographic atrophy (GA) in some patients?

Despite these pressing questions, the experts are not advocating a retreat from anti-VEGF therapy. "The number-one goal is to treat wet AMD," said Philip J. Rosenfeld, MD, PhD, professor of ophthalmology at Bascom Palmer Eye Institute. "If you don't stop the wet macular degeneration, you're not going to prevent this rapid vision loss from wet macular degeneration."

Instead, retina specialists are seeking a better understanding of the mechanisms underlying the possible association of anti-VEGF therapy and dry AMD or GA. Such knowledge may help refine drug and dosing regimens to achieve the optimal balance between adequate treatment of wet AMD and avoidance of side effects.

Increased RPE Abnormalities



Patient in the ANCHOR trial at baseline (1A, B, C) and after 24 months of ranibizumab treatment (1D, E, F). Although leakage (seen in early [B] and late [C] angiography at baseline) from the predominantly classic neovascular lesions had diminished greatly by month 24 (E, F), the color fundus photo (D) shows pigmentary changes, referred to as RPE abnormalities, that were not apparent at baseline (A). VA decreased from Snellen equivalent of 20/125 to 20/320.

Safety Signals Emerge From Studies

Concern has been mounting over several years. Dr. Rosenfeld noted that approximately 8 to 10 percent of patients lose vision over two years with monthly anti-VEGF therapy; this loss most likely results from progression of the underlying dry macular degeneration. "The 8 to 10 percent is fairly consistent among all the studies."

Retrospective review of ANCHOR, MARINA. To better understand the characteristics and possible causes of vision loss in patients receiving anti-VEGF therapy, Dr. Rosenfeld retrospectively reviewed data from the phase 3 ANCHOR and MARINA trials. He first presented his observations in 2007[2]; he updated his findings in a 2011 article showing that 10 percent of patients who received monthly ranibizumab injections in those studies lost 15 or more letters of visual acuity (VA) over the course of 24 months.[3] (By comparison, 38 percent of patients in ANCHOR and 30 percent in MARINA gained at least 15 lines of vision in 24 months.)

In both trials, the loss was associated with RPE abnormalities and growth

ROSENFELD PJ ET AL. OPHTHALMOLOGY. 2011;118(3):523-530

of total lesion area. But these lesions didn't look like typical advanced wet AMD; rather, they looked more like lesions that he speculated might evolve into GA.

CATT data. The 2012 publication of two-year results of the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) raised more red flags. The trial was designed to compare the effects of ranibizumab and bevacizumab administered monthly or as needed (PRN). Both drugs substantially and immediately reduced fluid in or under the retina, and both achieved a similar mean gain in VA.[4] But there was an unexpected finding, said Dr. Martin, the CATT study chairman. At two years, the prevalence of GA was higher in the monthly treatment groups for both ranibizumab and bevacizumab compared with the PRN treatment groups, with the highest rate occurring in the monthly ranibizumab group—which also had the lowest proportion of patients with fluid visible on optical coherence tomography. Although 80 percent of the GA did not involve the foveal center, when central involvement was present, visual acuity was affected.

These new CATT findings on GA have generated a debate, with some arguing that the atrophic lesions might have already been present but were masked by the small amount of fluid that persisted during therapy in a larger proportion of eyes treated PRN or with bevacizumab. Dr. Martin said that the likelihood of this phenomenon accounting for the differences in rates of observed GA is "vanishingly small." The mean difference in retinal thickness between drugs or treatment regimens was 30 µm at most, and the mean amount of fluid was on the order of 10 µm, he said. Moreover, he doubted that it could substantially affect assessment of atrophy by the expert graders who pore over photographs and fluorescein angiograms at the trial's fundus photograph reading center.

Mouse study suggests mechanism. Dr. Friedlander and colleagues developed a mouse model to explain why inhibiting VEGF to dry the macula might induce GA or something that looks very much like it. They deleted the *Vegfa* gene—responsible for VEGF-A production—from adult mouse RPE cells. Deletion of *Vegfa* resulted in dramatic and rapid loss of endothelial cells of the choriocapillaris and severe vision loss due to cone cell death.[5] Dr. Friedlander said this suggests that RPE-derived VEGF plays an essential functional role in supporting the adult subretinal vasculature, including the choriocapillaris, which nurtures the cone photoreceptors and maintains central vision.

Dr. Rosenfeld agreed. "VEGF is an important neuroprotective protein, and the maintenance of the choriocapillaris is dependent on VEGF."

Anti-VEGF affects kidneys, too. Some years earlier, Susan E. Quaggin, MD, a nephrologist at the University of Toronto, had coauthored a study reporting an analogous phenomenon. She found that in the kidney, VEGF production by glomerular podocytes is required for maintenance of the glomerular microvasculature and kidney function.[6] A small subset of patients receiving bevacizumab therapy for cancer developed thrombotic microangiopathy, a disease characterized by dramatic glomerular endothelial injury. In "Turning a blind eye to anti-VEGF toxicities," a companion article to Dr. Friedlander's mouse study report, Dr. Quaggin noted that RPE cells share a number of characteristics with podocytes.[7]

Dr. Friedlander's study "should send a note of caution to clinicians who are treating patients with anti-VEGF agents for retinal disease," she wrote. "It will be important to carefully screen treated patients for detrimental long-term effects of VEGF knockdown on their vision."

Dr. Quaggin acknowledged that lab studies aren't foolproof predictors of what happens in patients. Because therapy is administered intermittently in the real world, damaged endothelium may be able to recover during drug-free periods, she said. In addition, the degree of VEGF knockdown that occurs at therapeutic doses of anti-VEGF is different from the "sledgehammer" effect of complete deletion of genes in mouse models.

Despite these limitations, Dr. Friedlander believes that "you can have too much of a good thing, too much VEGF antagonism. Dr. Quaggin's kidney study made that very clear."

Areas for Future Study

Confirm the associations. Findings from these studies raise further questions. "First, we have to confirm that anti-VEGF therapy has any effect on the progression of the underlying dry macular degeneration," said Dr. Rosenfeld. "We have a lot of circumstantial evidence, but I'm not convinced that we have that smoking-gun data yet. The more data we have about monthly versus PRN dosing, the more convincing the argument may or may not be."

Dr. Martin, also, cautions against reading too much into the data. "The findings in CATT raise the question of whether or not the drug and treatment frequency could be associated with development of geographic atrophy," he said. "Before definitively concluding that the two are indeed related, this should be replicated in additional studies. In my mind, it's not conclusive yet. However, the findings so far are provocative."

Different ways to assess disease activity. To help determine whether findings from the mouse study are applicable to humans, Dr. Friedlander suggested electrophysiology studies to assess cone function and indocyanine green imaging to assess the choriocapillaris. Also, he said, we should monitor for loss of photoreceptors (for example, using adaptive optics to image cones) in patients on chronic anti-VEGF therapy. However, this type of imaging may be beyond the capabilities of individual physicians' offices. "This calls for clinical study to carefully control and observe for signs of adverse events involving the choriocapillaris and photoreceptors."

New possibilities for therapy. We need to think of other ways to target VEGF, Dr. Friedlander said. His study

suggests newer targets upstream of VEGF, particularly hypoxia-inducible factors (HIFs), which regulate VEGF-A production.[5] Like VEGF-A, their expression is upregulated in retinal diseases. He observed that loss of HIFs did not cause vision loss or endothelial damage in mice. If HIFs can shut down pathologic angiogenesis without damaging healthy vessels, they could be a more desirable target in eye disease.

Dr. Friedlander added that future therapies might include drugs that don't bind as tightly to VEGF receptors as some of the current VEGF antagonists. Binding too tightly may stimulate an unwanted trophic effect.

Finding the Therapeutic Balance

Although the experts agreed that further study is needed, what is the best practical approach now? "You've got to adequately treat the neovascularization and keep the macula dry, or patients will lose vision from wet macular degeneration," said Dr. Rosenfeld. But don't overtreat, he warned. "Automatically treating every month is expensive and potentially dangerous, if in fact treatment causes rapid progression of the underlying dry macular degeneration." He proposes "the Goldilocks approach: not too much anti-VEGF, not too little anti-VEGF, but just the right amount of anti-VEGF therapy."

The problem is determining the amount that is "just right." For guidance, Dr. Rosenfeld refers to ANCHOR, MARINA, VIEW, IVAN, HARBOR, and CATT; but so far, only CATT has raised concerns over monthly dosing. "The data are provocative, but we need to confirm the outcome with additional studies." Until then, he said the data appear to suggest that the appropriate dosing strategy is probably either "treat as needed" or "treat and extend."

Dr. Martin said he typically treats monthly until the retina is dry. Then he follows the patient and treats as needed or he treats and extends. "I still think treating to a dry retina is a good goal," he said. "The question is, once you've achieved a dry retina, should you continue to treat beyond that? And if you achieve an almost dry retina, and vision is very good, is that enough? I don't have the answer to that. But the CATT data make me a little more tolerant of a small amount of nonprogressive fluid."

Don't let fear interfere! Recently Dr. Rosenfeld treated a new patient, a "snowbird" who was overdue for an anti-VEGF injection. The patient, who wintered in Florida, explained that his regular doctor was afraid that too much treatment would accelerate the dry AMD. But Dr. Rosenfeld is more concerned that doctors will undertreat the wet AMD before anyone can confirm that VEGF inhibitors are causing an unwanted effect.

"You don't have a choice," he said. "Withholding anti-VEGF therapy because of a fear of accelerating the dry macular degeneration is like withholding chemo because of the potential side effects. Our number-one goal is to save the vision as much as possible. And without anti-VEGF therapy, patients will lose vision."

1 Friedlander MF. VEGF antagonism—can you have too much of a good thing? Presented at: Angiogenesis, Exudation, and Degeneration 2013; Feb. 9, 2013; Miami.

2 Rosenfeld PJ et al. Baseline and treatment characteristics of patients losing vision at year 1 of the MARINA and ANCHOR trials. Poster presented at: ARVO; May 3, 2007; Fort Lauderdale, Fla. E-4576.

3 Rosenfeld PJ et al. *Ophthalmology.* 2011; 118(3):523-530.

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5 Kurihara T et al. *J Clin Invest.* 2012; 122(11):4213-4217.

6 Eremina V et al. *N Engl J Med.* 2008; 358(11):1129-1136.

7 Quaggin SE. *J Clin Invest.* 2012;122(11): 3849-3851.

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