Preventing Complications of DR, Part 1: The PANORAMA Study

Anti-VEGF pharmacotherapy has become a first-line or alternative treatment for center-involved diabetic macular edema (DME) and proliferative diabetic retinopathy (DR). But can anti-VEGF medication be used proactively to prevent these vision-threatening complications of DR?

"Given the excellent efficacy of anti-VEGF agents, the obvious follow-up hypothesis was, can you treat earlier to prevent complications?" said Rajendra Apte, MD, PhD, at the Washington University School of Medicine in St. Louis. "And can you actually reverse the diabetic retinopathy process?"

Two leading studies—PANORAMA and DRCR.net Protocol W—sought to shed light on the ability of aflibercept (Regeneron) to prevent complications in patients with DR. Results of both studies have spurred debate about managing moderate to severe nonproliferative DR.[1] The key question: is it better to use aflibercept prophylactically to try to stave off complications—or should clinicians monitor patients and use aflibercept once disease progresses?

Part 1 of this story focuses on the Regeneron-sponsored PANORAMA trial; part 2 will cover Protocol W.

PANORAMA At a Glance

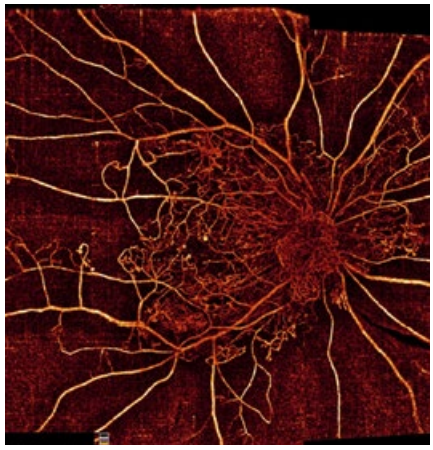
In PANORAMA, aflibercept was found to be superior to sham treatment at preventing center-involved DME and proliferative DR (PDR), but it didn't improve visual acuity (VA).

Why PANORAMA matters. "The PANORAMA study is important because it was the first prospective study to show that anti-VEGF agents decrease the rate of progression," as measured by the Diabetic Retinopathy Severity Scale (DRSS), said Jennifer I. Lim, MD, at the University of Illinois in Chicago. "Aflibercept also showed an impressive 70% to 80% reduction in the rates of vision-threatening complications, though it didn't affect mean VA at two years."

"The major take-home point from PANORAMA is that you can meaningfully decrease the rate of development of clinically relevant endpoints—PDR or center-involved DME—with consistent dosing, [given] as infrequently as every 16 weeks," said Charles C. Wykoff, MD, PhD, at Retina Consultants of Texas in Houston. "The clinical challenge is that these injections have some degree of risk and cost, so it's a risk/benefit question for each patient depending on their clinical situation and goals."

Study specifics. The international prospective randomized controlled trial lasted 100 weeks, with data collected on 402 eyes.[2] Participants had moderately severe to severe non-PDR and 20/40 or better best-corrected VA. Patients were randomized as follows:

- In aflibercept group 2q16, patients (n = 135) received three initial monthly doses of 2 mg, followed by injection every 16 weeks with one eight-week interval.
- In aflibercept group 2q8/PRN (pro re nata), patients (n = 134) received five initial monthly doses of 2 mg, followed by injection every eight weeks, with injections as necessary starting at week 56.
- In the control group, patients (n = 133) received sham injections.



ISCHEMIC DAMAGE. *OCT angiograms from a 32-year-old female patient with type 1 diabetes who had experienced repeated and extended bouts of hypoglycemia.*

Study results. Through the 100-week mark, 16.3% of those in the 2q16 cohort experienced vision-threatening complications, versus 18.7% of those in the 2q8/PRN cohort. In contrast, 50.4% of controls experienced such complications.

At 52 weeks, 65.2% of those in the 2q16 cohort experienced DRSS level of two-step improvement or more, versus 79.9% of those in the 2q8/PRN cohort

BY REBECCA TAYLOR, CONTRIBUTING WRITER, INTERVIEWING **RAJENDRA APTE, MD, PHD, JENNIFER I. LIM, MD,** AND **CHARLES C. WYKOFF, MD, PHD.**

and 15% of controls. Moreover, no new safety signals were detected.

Interpreting the Data

Preventing complications. DR progresses from severe non-PDR to PDR, with center-involved DME occurring at any stage, Dr. Apte noted. "PDR has enough ischemic damage to the retina for new blood vessels to form, and these abnormal vessels bleed, lead to hemorrhage and retinal detachment, and cause vision loss."

The low rate of complications in the study's treatment arms may be PANORAMA's most straightforward result, although the question of how to apply that data is under debate. "In PANORAMA, 16% to 18% of eyes developed PDR or DME in the aflibercept-treated patients; that's an underappreciated point," said Dr. Wykoff. "We've seen this in prior DME studies, where some patients receiving anti-VEGF therapy nonetheless experience disease progression—so whether patients start treatment or wait, they need to be followed closely since more frequent anti-VEGF therapy or laser treatments may be indicated."

Among patients eventually treated for macular edema or PDR, Dr. Lim said, "15% to 25% won't regain the VA they had prior to diabetic complications; that's why there's so much debate." There are good reasons both for starting and postponing prophylaxis, she said.

Tracking DRSS levels. As noted above, participants in PANORAMA's treatment arms experienced a two-step improvement in DRSS levels.[2] But it is unclear whether prophylactic aflibercept leads to durable DRSS regression, said Dr. Lim. However, as she pointed out, "PANORAMA starts to answer that, with 80% of the 2q8 group keeping their two-level DRSS regression at year 2 despite less frequent dosing."

Improvements in DRSS levels are relevant for regulatory approvals, but they have less utility in the clinic, said Dr. Wykoff. Although patients "don't really care about how many hemorrhages they have, they do care strongly about preserving vision and decreasing the risk of disease progression," he said. He added, "In PANORAMA, the large majority of patients maintained clinical stability with every-16-week dosing."

Assessing visual acuity. Because PANORAMA reported no improvement in VA, Dr. Apte posed a question for clinicians: "Could we not follow these patients carefully and have them control hemoglobin A1c, blood pressure, and lipids—and treat the macular edema or neovascularization when it develops?" Doing so would reduce the treatment burden, costs, and potential risk of injections, he said, and "you'd only want to start treatment early if you have evidence that you can change the course of disease."

Prophylaxis Quandaries

Drs. Apte and Lim cited additional quandaries to consider before employing anti-VEGF prophylaxis:

Endophthalmitis risk. "Endophthalmitis is a known complication of intraocular injections, and with 500 million diabetics around the world, if you're treating everybody with moderate or higher [e.g., more severe] non-PDR, you're treating millions of patients," said Dr. Apte. "You have to weigh the rare but real risk of infection."

Dr. Lim agreed. "You have to weigh the risk of endophthalmitis," she said, particularly because a subset of anti-VEGF–treated patients will go on to develop vision-threatening complications. (For more on postinjection endophthalmitis, see "Managing Endophthalmitis After Intravitreal Injections" in the December 2021 *EyeNet* at aao.org/eyenet/archive.)

Costs and the treatment burden. "Depending on insurers, aflibercept is about $2,000 per injection, so it's a substantial health care cost when you're making recommendations for an entire population," said Dr. Apte. His analysis of the DRCR.net Protocol S study of ranibizumab for macular edema calculated a $662,978 cost per quality-adjusted life-year for patients, concluding that treatment was not cost-effective.[3] Furthermore, "the PANORAMA authors rightly said that to maintain the two-step [DRSS] improvement required treatment in the second year," he said, "so you might have to treat people continuously, and that's a heavy treatment burden without a clear visual acuity benefit."

On the other hand, said Dr. Lim, "If you factor in the number of untreated patients who would develop permanent visual loss, that's also significant." As she noted, it's difficult to put a price on preventing blindness.

Critical Messages

"My recommendation is that people who have non-PDR prior to macular edema or proliferative disease need to be counseled rigorously to control their diabetes," said Dr. Apte. "Then titrate how aggressively you follow them with multimodal testing, imaging, and angiography, rather than just treating everybody with injections."

"My take-home message is to watch these people carefully and keep them in the [health care] system," said Dr. Wykoff, "whether you're treating them or not."

1 Nanegrungsung O, Bressler NM. *Curr Opin Ophthalmol.* 2021;32:590-598.
2 Brown DM et al. *JAMA Ophthalmol.* 2021; 139(9):946-955.
3 Apte RS, Hwang CK. *JAMA Ophthalmol.* 2021; 139(7):713-714.

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