Preventing Complications of DR, Part 2: DRCR.net Protocol W

Do the benefits of anti-VEGF injections for the prevention of the vision-threatening complications of diabetic retinopathy also translate into vision gains?

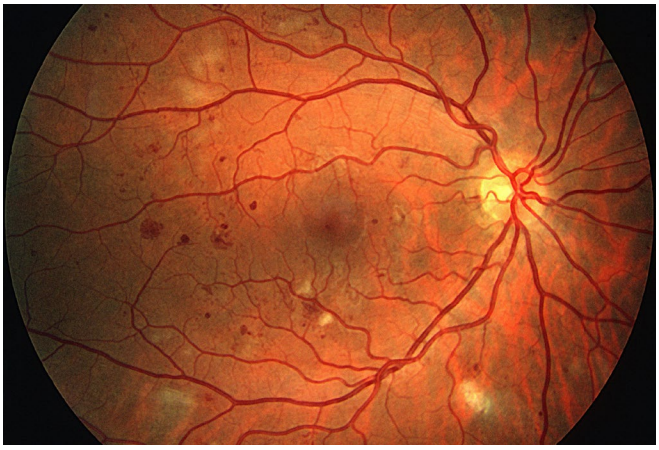
That's the question posed by Protocol W, a four-year clinical trial conducted by the DRCR.net. The study evaluated the prophylactic efficacy of intravitreal injections of aflibercept (Eylea, Regeneron), and the study's two-year results are consistent with those from a similar study known as PANORAMA: aflibercept injections prevent diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR).[1] (For part 1 of this story, which covered the PANORAMA results, see the June issue at aao.org/eyenet.) And like PANORAMA, Protocol W found a roughly threefold-lower chance of vision-threatening complications in those who received aflibercept than in controls.[2]

Nonetheless, now that two-year anatomic benefits have been realized in Protocol W, the question remains: do prophylactic aflibercept injections lead to functional improvements in vision?

Protocol W at a Glance

"The biggest thing about Protocol W is that it's a four-year study with an anatomic endpoint at two years and visual endpoint at year 4," said Raj K. Maturi, MD, at Indiana University in Indianapolis.

Study specifics. The randomized clinical trial was conducted at 64 sites in the United States and Canada. The initial two-year data were collected from Jan. 15, 2016, to May 28, 2020, on 328 participants (399 eyes). Final four-year data are being collected this year, with results expected by early 2023.



QUESTIONS REMAIN. *The two-year results of Protocol W indicate that prophylactic injections of aflibercept have functional benefits for non-PDR. The full picture on VA benefits won't be available until the four-year results are in.*

Participants had moderate to severe non-PDR without center-involved DME and were level 43 to 53, as measured by the Diabetic Retinopathy Severity Scale (DRSS). They were randomized as follows:

- In the aflibercept cohort, 200 eyes received intravitreal injections of 2 mg aflibercept at baseline and at months 1, 2, and 4. This was followed by injections every four months through two years.
- In the control group, 199 eyes received sham injections at all time points.

Of note, treatment was initiated in either group if a participant presented with high risk of PDR or vision loss of 10 or more letters at one visit or 5 to 9 letters at two consecutive visits. (In addition, between years 2 to 4 in the aflibercept cohort, treatment was deferred if disease regressed to "mild" or better non-PDR.)

Study results. At two years, the probability of developing center-involved DME with vision loss was 4.1% in the aflibercept group and 14.8% in controls. The probability of developing PDR at two years was 13.5% in those who received aflibercept and 33.2% in those who received sham injections.

With regard to visual acuity (VA), the mean change from baseline was –.9 letters in the aflibercept group and –2 letters in controls.

Interpreting the Data

Anatomic outcomes—evaluating subgroups. "What's very useful in the two-

BY REBECCA TAYLOR, CONTRIBUTING WRITER, INTERVIEWING **RAJENDRA APTE, MD, PHD, JENNIFER I. LIM, MD, RAJ K. MATURI, MD,** AND **JENNIFER K. SUN, MD, MPH.**

year data is looking at the subgroups to see who ended up developing PDR or DME," said Dr. Maturi. "Of those with level 43 disease [moderate non-PDR], only 3% who were prophylactically treated developed DME or PDR; while in the sham group, 24% did." Similarly, he said, "of the level 53 patients [severe non-PDR] who were prophylactically treated, 36% developed significant disease, while 68% of the sham group did. Prophylactic treatment decreased the risk by half in the severe non-PDR group."

Functional outcomes—evaluating VA. "If we treat those eyes as soon as they develop edema or PDR, then their vision improves. One of the beautiful things about the eye is its resilience," Dr. Maturi said.

"Clearly, from an anatomic perspective [the Protocol W results indicate that] there's a benefit from early treatment," said Jennifer K. Sun, MD, MPH, at the Joslin Diabetes Center and Harvard in Boston. However, she noted, "we did not see a corresponding, significant benefit in the two-year mean vision change."

"After two years, VA was no different whether patients were treated prophylactically—five times in the first year and three times a year for the next three years—or if they developed complications such as macular thickening with vision loss," said Dr. Maturi. However, it's important to note that controls were treated if they developed vision-threatening complications during the study. "That's part of the reason we didn't see a VA difference between the treated and sham groups," Dr. Maturi said.

Given the VA results, Dr. Maturi said, the key question is, if somebody has diabetic retinopathy but not high-risk PDR, is early treatment of benefit?

"What you ultimately want to find with any preventive treatment is long-term benefit for quality of life," said Dr. Sun, who also serves as chair for diabetes studies for the DRCR.net. "Our [previous] Protocol V [study] showed that eyes with good vision despite center-involved DME on average did equally well if we waited and watched very carefully and treated if there was vision loss down the road, compared to starting anti-VEGF injections right away," she said.[3]

Is it unexpected that with such clear anatomic gains after prophylaxis, functional gains may not follow? "If you look at what we're testing—visual acuity—it's only the central 1 degree of your retinal function," said Rajendra Apte, MD, PhD, at the Washington University School of Medicine in St. Louis. "I'm pretty sure if you did multimodal functional testing—contrast sensitivity, dark adaptation, reading speed, perimetry—you might find that you actually are getting some improvement in function."

Assessing quality of life. Another nuance to consider when interpreting the VA data is how frequently patients were followed in Protocol W, said Jennifer I. Lim, MD, at the University of Illinois in Chicago.

"In real life, patients may notice blurred vision but not come in until months later, and by then it may not be possible to regain all of the vision lost," said Dr. Lim. In addition, she noted, it's possible that two years wasn't long enough a period of time for differences in VA outcomes to emerge.

Dr. Lim considers independence, mobility, and quality of life when considering preventive anti-VEGF injections.[4] "It makes sense to drive back the level of retinopathy because it impacts quality of life," she said. And like Dr. Apte, she noted that the impact of anti-VEGF treatment is complex: "There are things happening on a subclinical level [while] we're only looking at VA, so there's a lot more than meets the eye."

Treat Now—or Wait and Watch?

The natural history of progression to PDR and DME needs to be weighed against the risk of prophylactic treatment, said Dr. Lim. "For severe NPDR, PDR develops in 14.6% of eyes at one year and 39.5% at three years." These rates increase to 45% of eyes at one year and 64.9% by three years for very severe NPDR, she said.

"The problem is, we don't know which eyes are going to develop PDR, so it's not unreasonable to consider prophylactic treatment," Dr. Lim said—and she reemphasized that anti-VEGF treatment cannot always return a patient's VA to precomplication levels.[4]

Need for close monitoring. "Anti-VEGF agents have revolutionized our ability to treat diabetic retinopathy complications really well and prevent people from going blind," said Dr. Apte. "But for diabetics with non-PDR, my recommendation would still be to follow them closely at the appropriate interval for their severity of disease and comorbidities and treat them when they develop complications—with the caveat that physicians can change this general recommendation based on individual patients' situations."

Need to consider comorbidities. When making anti-VEGF treatment decisions, Dr. Sun also considers patients' systemic health, such as their glycemic control, lipid levels, and blood pressure, as well as the status of their fellow eye.

"For me, since we haven't shown yet that there's a visual acuity benefit to treating early versus waiting and watching and treating when complications develop, I don't tend to treat patients who have nonproliferative disease alone without other extenuating circumstances like macular edema," she said.

Need to consider burden of treatment. "If you can save a patient five injections in the first year and three every [following] year and monitor and only treat if they develop a complication, then it's a huge savings for the system," Dr. Maturi noted.

Moreover, as Dr. Sun said, "If I can't say to my patient that there's a visual benefit, then the risk of each injection, cost, and additional visits may not balance out." Some patients with severe non-PDR may not ever need treatment, she added.

Looking Ahead

Eager for four-year data. "The four-year results are going to be critical for understanding the study as a whole, and we're waiting with bated breath to see if there will be a visual acuity benefit," said Dr. Sun. Overall, she said, "we'll have an incredible amount of information about how diabetic eye disease progresses, the

role of nonperfusion, and how it relates to outcomes over time."

"The year 4 data are going to be helpful to show whether three to four injections yearly are enough to prevent complications and whether a VA difference will be found with longer follow-up," said Dr. Lim. "These severe non-PDR patients are [already] typically seen at three- to four-month intervals because of their high risk for developing complications such as neovascularization, vitreous hemorrhage, or detachment, which require treatment."

Will Protocol W change the average clinician's use of prophylactic aflibercept in the future? "It might," said Dr. Apte. "If at four years the control group really does poorly in terms of VA outcomes, then we have good reason to pause and ask, 'Should we be reassessing our public health guidelines?'" In any event, clinicians won't have long to wait, he noted. "Those data are coming."

1 Maturi RK et al., for the DRCR.net. *JAMA Ophthalmol.* 2021;139(7):701-712.
2 Nanegrungsunk O, Bressler NM. *Curr Opin Ophthalmol.* 2021;32:590-598.
3 Baker CW et al., for the DRCR.net. *JAMA.* 2019; 321(19):1880-1899.
4 Lim JI. *JAMA Ophthalmol.* 2021;139(7):714-716.

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