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New Anti-VEGF Trial Results at ARVO 2017: SCORE-2 and CLARITY

New feature below: highlighting the "10 Take-away" findings and messages from the **Association for Research in Vision and Ophthalmology** (ARVO)

After participating in this activity, the participant will demonstrate the ability to:

- Evaluate how recent clinical research into anti-VEGF agents can inform treatment for proliferative diabetic retinopathy and for retinal vein occlusion.
- Describe how newly available therapies may alter current treatment options for patients with retinal vein occlusion or proliferative diabetic retinopathy.

Guest Faculty Disclosure
Dr. Scott has disclosed that she has served as a member of the Data and Safety Monitoring Committee for a clinical trial sponsored by Thrombogenics.

Dr. Sivaprasad has disclosed that she has served as a consultant for Bayer Corporation, Novartis AG and Roche.

Unlabeled/Unapproved Uses
Dr. Scott has disclosed that her discussion will reference bevacizumab, which, although commonly used in current practice, is not currently FDA approved for treating ocular conditions.

Dr. Sivaprasad has dislcosed that her discussion will reference the unlabeled/unapproved uses of aflibercept.

MEET THE AUTHORS

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10 Highlights from ARVO - 2017

Jun Kong, MD and Neil Bressler, MD

1. CLARITY: Randomized Clinical Trial – Proliferative Diabetic Retinopathy: Anti-VEGF with Aflibercept vs. PRP
Sobha Sivaprasad, A Toby Prevost, Joana C Vasconcelos, et al, for the CLARITY Study Group.

DRCR.net Symposium: Monday, May 8, 2017; 2:30-3:45pm Ballroom 2

***e*Ophthalmology Summary:** CLARITY, a multicenter, single-masked, non-inferiority trial conducted in the UK, compared 1-year outcomes of intravitreous 2.0-mg aflibercept (n=122) versus panretinal photocoagulation (PRP) (n=109) for proliferative diabetic

retinopathy (PDR). Following an initial three monthly injections, a median of one additional injection was given for reactivation of neovascularization based on monthly assessments or additional PRP as needed from week 12 based on every 8-week assessments. At 1 year, the aflibercept arm was four letters (median) superior (P<10.0001) to the PRP arm, with less visual field loss, fewer eyes developing macular edema and fewer eyes undergoing vitrectomy, without safety differences identified. CLARITY, with similar outcomes to results from the DRCR.net Protocol S, confirms that anti-VEGF is a viable alternative to PRP, although compliance with follow-up, cost, and lack of long-term outcomes should be considered.

2. SCORE2: Aflibercept vs. Bevacizumab for Macular Edema due to Central or Hemi-Retinal Vein Occlusion
Ingrid U. Scott, Paul C. VanVeldhuisen, Michael S. Ip, et al, for the SCORE2 Investigator Group

SCORE2 Symposium: Tuesday, May 9, 2017; 2:30-3:45 pm Ballroom 2

***e*Ophthalmology Summary:** Given the cost differential and lack of comparative vision outcome data of different anti-VEGF agents for macular edema from retinal vein occlusions, SCORE2 compared repackaged (compounded) 1.25-mg bevacizumab to 2.0-mg aflibercept. Eyes with macular edema from central or hemi-retinal vein occlusion were assigned intravitreous bevacizumab or aflibercept every 4 weeks until the primary outcome at 6 months when the mean visual acuity letter score (approximate Snellen equivalent) improved from 50.7 (20/100) to 69.3 (20/40) in the bevacizumab group and from 50.4 (20/100) to 69.3 (20/40) in the aflibercept group. The bevacizumab group had a lower proportion of eyes with resolution of macular edema; whether this difference affects longer term outcomes may be determined from 1-year results. The SCORE2 group has provided valuable comparative data regarding 6-month visual and anatomic outcomes when using considering anti-VEGF treatment options for macular edema from retinal vein occlusions.

3. SCORE2: Baseline Predictors of Visual Acuity and Retinal Thickness Outcomes in Patients with Central Retinal Vein Occlusion or Hemi-retinal Vein Occlusion
SobhIngrid U. Scott, Paul C. VanVeldhuisen, Michael S. Ip, et al, for the SCORE2 Investigator Group

SCORE2 Symposium: Tuesday, May 9, 2017; 2:30-3:45 pm Ballroom 2

***e*Ophthalmology Summary:** Following the primary results of the SCORE2 study, the study group evaluated whether there were baseline factors associated with 6-month visual acuity or retinal thickness outcomes. Younger patient age and worse baseline visual acuity were associated with a greater likelihood of a 6-month visual acuity letter gain of at least 15 (gain of approximately 3 or more lines) among eyes treated with bevacizumab or aflibercept. Aflibercept treatment, higher baseline central retinal thickness, and no prior anti-VEGF therapy were associated with higher odds of macular edema resolution over the 6-month period. These findings may be useful in assessing expected responses following six monthly injections of anti-VEGF agents for treating macular edema due to central or hemi-retinal vein occlusion. However, the analysis did not identify factors that should influence how individual eyes should be treated at this time.

4. Interim Safety Data Comparing Ranibizumab and Panretinal Photocoagulation in Patients with Proliferative Diabetic Retinopathy
Jeffrey G. Gross, Adam R. Glassman, Margaret J. Klein, et al, for the Diabetic Retinopathy Clinical Research Network
DRCR.net Symposium: Monday, May 8, 2017; 2:30-3:45pm Ballroom 2

***e*Ophthalmology Summary:** Systemic intravenous anti-VEGF therapy increases the risk of vascular events. Data through the 2-year primary outcome of Protocol S of the Diabetic Retinopathy Clinical Research (DRCR) Network, which compared intravitreous ranibizumab vs panretinal photocoagulation (PRP) for managing proliferative diabetic retinopathy, did not identify any differences in systemic safety outcomes between groups. At the ARVO 2017 Annual Meeting, 4-year interim safety data of Protocol S were reported. Among three of the four prespecified systemic safety outcomes, including all-cause death, serious adverse events and hospitalizations, no differences were found across treatment groups. However, the study noted a trend (P = .10) toward increased Antiplatelet Trialists' Collaboration-defined arterial thromboembolic events among the bilateral treatment group (one study eye assigned to ranibizumab and one study eye assigned to PRP: 12%), the ranibizumab group (only one study eye, assigned to ranibizumab: 18%), and the prompt PRP group (only one study eye, assigned to PRP: 8%). The results were not sufficiently indicative of an increased risk to warrant discontinuing the ranibizumab treatment as the statistical analysis plan specified that P values less than .01 would be considered statistically significant (to adjust for multiple comparisons). Of note, 50% of the PRP group received ranibizumab for diabetic macular edema during the study; therefore, the prompt PRP group should not be thought of as a treatment group without any ranibizumab exposure. The DRCR Network plans a full safety report on the completion of the 5-year follow-up in 2018.

5. Change in Diabetic Retinopathy through 2 Years Secondary Analysis of a Randomized Clinical Trial Comparing Aflibercept, Bevacizumab, and Ranibizumab
Susan B. Bressler, Danni Liu, Adam R. Glassman, et al, for the Diabetic Retinopathy Clinical Research Network

DRCR.net Symposium: Monday, May 8, 2017; 2:30-3:45pm Ballroom 2

***e*Ophthalmology Summary:** The Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T compared three commonly used anti-VEGF agents—2.0-mg aflibercept, 1.25-mg repackaged (compounded) bevacizumab, and 0.3-mg ranibizumab—for diabetic macular edema (DME). Percentages with diabetic retinopathy severity level improvement were based on centralized grading of annual fundus photographs. Cumulative probabilities for diabetic retinopathy worsening were based on fundus photograph severity level grading or other worsening events such as vitreous hemorrhage or panretinal photocoagulation, through 2 years, without adjustment for multiple outcomes. At 1 and 2 years, approximately one-fifth to one-third of eyes with non-proliferative diabetic retinopathy receiving any of the anti-VEGF agents for DME had improvement in diabetic retinopathy severity level. Less improvement was demonstrated with bevacizumab at 1 year than with aflibercept or ranibizumab, although no differences among the three anti-VEGF agents were identified at 2 years. Aflibercept was associated with more improvement in the smaller subgroup of participants with PDR at baseline. All three anti-VEGF treatments were associated with low rates of worsening of diabetic retinopathy severity levels. These data provide additional

outcomes that might be considered when choosing an anti-VEGF agent to treat DME.

6. Incremental Cost-Effectiveness of Intravitreous Ranibizumab Compared with Panretinal Photocoagulation for Proliferative Diabetic Retinopathy
David W. Hutton, Joshua D. Stein, MD, Neil M. Bressler, et al, for the Diabetic Retinopathy Clinical Research Network

DRCR.net Symposium: Monday, May 8, 2017; 2:30-3:45pm Ballroom 2

***e*Ophthalmology Summary:** The Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol S randomized clinical trial results suggest that ranibizumab is a reasonable treatment alternative to panretinal photocoagulation (PRP) when managing proliferative diabetic retinopathy (PDR). The relative cost-effectiveness was reported in this talk. Compared with PRP, ranibizumab as given in the clinical trial is within the $50,000/quality-adjusted life-year to $150,000/ quality-adjusted life-year range frequently cited as cost-effective in the United States for eyes presenting with PDR and vision-impairing DME, but not for those with PDR without vision-impairing DME. From a societal perspective, in developed countries such as the United States, ranibizumab through 2 years as an alternative therapy to PRP for PDR *with* vision-impairing DME at baseline provides clinically relevant benefits and is cost-effective. However, for PDR *without* vision-impairing DME, PRP is the more cost-effective treatment option through at least 2 years.

7. Incidence and Risk Factors for Neovascular AMD in the Fellow Eye in The Comparison Of AMD Treatment Trials (CATT) Follow-Up Study
Maureen G. Maguire, W. Pan, J. E. Grunwald, et al.

Poster B0298: Monday, May 8, 2017; 3:45-5:30 pm

***e*Ophthalmology Summary:** The Comparison of AMD Treatments Trials (CATT) investigators, comparing bevacizumab to ranibizumab for neovascular age-related macular degeneration (nAMD), conducted a prospective follow-up study to describe the incidence and risk factors of neovascular age-related macular degeneration (nAMD) through 5 years in the fellow eye of patients with unilateral nAMD. The incidence of nAMD in the fellow eye per year was approximately 10%. The risk increased with the AREDS Risk Score (1 point for larger drusen, 1 point for hyperpigmentation) in the fellow eye or presence of pseudodrusen in the fellow eye. Characteristics of the study eye including hemorrhage associated with the lesion, elevation of the retinal pigment epithelium and an occult pattern of choroidal neovascularization on fluorescein angiography, also were linked with a higher incidence of nAMD in fellow eyes. However, CHF, ARMS2 and C3 SNP risk alleles did not show any correlations with the incidence of nAMD in fellow eyes.

8. Ranibizumab versus verteporfin photodynamic therapy for myopic choroidal neovascularization: Results from RADIANCE Randomized Clinical Trial
Nathan Steinle, A. Ghanekar, C. Quezada-Ruiz.

Poster B0656: Thursday, May 11, 2017; 11:30-1:45 pm

***e*Ophthalmology Summary:** RADIANCE was a phase 3 randomized double-masked clinical trial that compared ranibizumab with verteporfin photodynamic therapy (vPDT) for the treatment of patients with visual impairment caused by myopic choroidal neovascularization (mCNV). Patients were assigned randomly to a visual acuity guided ranibizumab 0.5 mg group (RBZ-VA) or a disease activity guided ranibizumab 0.5 mg group (RBZ-DA) or a vPDT group. Both ranibizumab arms provided superior visual acuity gains compared with vPDT (12.1 letters in RBZ-VA, 12.5 letters in RBZ-DA and 1.4 letters in vPDT) at 3 months and (13.8 letters in RBZ-VA, 14.4 letters in RBZ-DA and 9.3 letters in vPDT) at 12 months after baseline. Best-corrected visual acuity gains were maintained through month 12 in both ranibizumab arms following a median of 2 to 4 injections.

9. PLANET – Randomized Clinical Trial: Aflibercept with and without PDT "Rescue" for Polypoidal Choroidal Vasculopathy
Won Ki Lee, Y. Ogura, T. Iida, et al.

Talk: Monday, May 8, 2017; 9:30-9:45 pm Hall G

***e*Ophthalmology Summary:** PLANET was a randomized, double-masked, sham-controlled clinical trial evaluating the efficacy and safety of intravitreous 2.0-mg aflibercept injection compared with aflibercept plus "rescue" photodynamic therapy with verteporfin (vPDT) as needed in patients with polypoidal choroidal vasculopathy (PCV). Rescue therapy could be given if: (1) visual acuity change from baseline was <5 letter gain or between 5 and <1010 letters but investigator judged that PDT would be of benefit, and (2) evidence of "active polyps" on indocyanine green angiography. Following 3 consecutive monthly aflibercept injections, study participants were assigned randomly to aflibercept without or with rescue vPDT as needed. Among 318 study participants, only 5% and 7% of participants at week 12, and only an additional 12% and 14% of participants by week 52 received "rescue" therapy in the sham and vPDT groups, respectively. For the primary endpoint of mean change in visual acuity from baseline, aflibercept with sham rescue vPDT (+10.7 letters) was non-inferior to aflibercept with rescue vPDT (+10.8 letters) at week 52. Absence of any "active polyps" on indocyanine green angiography at 52 weeks was 38.9% and 44.8% in the sham rescue vPDT and rescue vPDT groups, respectively. The incidence of ocular treatment-emergent adverse events also was similar (31.2% vs 29.2%) in the sham rescue vPDT and rescue vPDT groups at week 52. The PLANET study proved that aflibercept is an effective treatment for patients with PCV, with most participants not needing rescue vPDT as defined in this study.

10. EVEREST2 Results: Randomized Clinical Trial of Ranibizumab vs. Ranibizumab Plus verteporfin Photodynamic Therapy in Polypoidal Choroidal Vasculopathy
Colin S. Tan, C. Feller, P. Margaron, T. H. Lim.

Poster A0274– Sunday, May 7, 2017; 1:30-3:15 pm

Posters A080, A085– Sunday, May 7, 2017; 3:15-5:00 pm

***e*Ophthalmology Summary:** EVEREST2 study was a 24-month phase IV, double-masked, multicenter study that recruited patients with polypoidal choroidal vasculopathy (PCV) across 42 sites in Asia. Among 322 study participants randomly assigned to 0.5-mg ranibizumab without verteporfin photodynamic therapy (vPDT) or ranibizumab with vPDT, the primary outcome was change in visual acuity from baseline to month 12. Secondary outcomes included "complete polyp regression" assessed by indocyanine green angiography at month 12. Results showed ranibizumab with sham vPDT had a 5.1 letter gain in visual acuity at 12 months, versus an 8.3 letter gain when combined with vPDT. The percentage of patients showing complete polyp regression over 12 months was 33.8% in the ranibizumab with sham vPDT group and 69.7% in the ranibizumab with vPDT group. While these results show superior visual acuity gains for the ranibizumab plus vPDT group over the ranibizumab plus sham vPDT group, additional secondary outcomes (such as percentage of eyes gaining at least 10 or at least 15 letters from baseline) can help highlight the clinical relevance of these differences in mean change from baseline.

OTHER RESOURCES

Download the podcast transcript

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Podcast Transcript

BOB BUSKER:

Welcome to this *e*Ophthalmology Review podcast. I'm Bob Busker, managing editor of the program. Today's discussion comes from the recently concluded ARVO — Association for Research in Vision and Ophthalmology — 2017 Annual Meeting in Baltimore, where findings from the CLARITY and SCORE-2 studies were presented.

***e*Ophthalmology Review is presented by the Johns Hopkins University School of Medicine and is supported by educational grants from Genentech Inc, Regeneron Pharmaceuticals Inc, and Carl Zeiss Meditec. This activity has been developed for ophthalmologists and retina specialists. There are no fees or prerequisites to participate.**

Learning objectives for this activity include:

- **Evaluate how recent clinical research into anti-VEGF agents can inform treatment for proliferative diabetic retinopathy and for retinal vein occlusion**
- **Describe how newly available therapies may alter current treatment options for patients with retinal vein occlusion or proliferative diabetic retinopathy**

Our host is eOphthalmology Review course director, Dr. Neil Bressler, James P. Gills Professor of Ophthalmology, and Chief of the Retina Division at the Wilmer Eye Institute at Johns Hopkins in Baltimore. Dr. Bressler has disclosed that he has served as a principal investigator for grants to Johns Hopkins University School of Medicine from Bayer Corporation, Novartis AG, Regeneron, Roche, and Samsung.

Dr. Bressler's first guest today is Dr. Sobha Sivaprasad, Professor of Retinal Clinical Studies in the Institute of Ophthalmology, University College London, to discuss the recently presented results of the CLARITY study on proliferative diabetic retinopathy.

Dr. Sivaprasad has disclosed that she has served as a consultant for Bayer Corporation, Novartis AG, and Roche.

Her discussion with Dr. Bressler today will reference the unlabeled/unapproved uses of aflibercept.

And now, from ARVO 2017, Dr. Neil Bressler and Dr. Sobha Sivaprasad.

DR. BRESSLER: Thank you, Bob, and thank you Dr. Sobha Sivaprasad for taking the time to be with us today. We are going to discuss one of the most important presentations that occurred at the ARVO annual meeting this year in Baltimore,

Maryland: the results of the CLARITY study that was done in the United Kingdom under the direction of Dr. Sivaprasad as the study chair. So Sobha, maybe you could walk me through: why did you even design or plan this study in the first place?

DR. SIVAPRASAD: Dr. Bressler, we have been doing laser treatment for the last 40 years for this condition of proliferative diabetic retinopathy. We are all aware of the multiple side effects that laser treatment has. At that time there were several more studies that suggest that anti-VEGF agents do work well in the short term, so we decided that we should try a long-term study for this condition. It's about the same time that we saw that the Protocol S had released their protocol, and we thought we should go for another agent or the latest anti-VEGF agent, and that was aflibercept. That's how we designed the study so that we could find the effects of aflibercept in proliferative diabetic retinopathy.

DR. BRESSLER: Now certainly in Protocol S it was a similarly designed study, as I understood, where they compared an anti-VEGF agent to laser or pan retinal photocoagulation for people who walked in with proliferative diabetic retinopathy. Was that the same in your study; were you also looking at an anti-VEGF agent? Was it the same agent?

DR. SIVAPRASAD: Protocol S used ranibizumab for the intervention, while the CLARITY study used aflibercept as the intervention. Both are anti-VEGF agents, but aflibercept has more targets that it acts on such as VEGF-A, VEGF-B, PlGF, and galectin. So we thought, it's a more broad-spectrum anti-VEGF agent.

DR. BRESSLER: Very good. And as I understand it, the results were published just recently in *The Lancet* journal, so maybe you could tell me how you compared these two agents, how is it designed, how often did somebody receive laser, how often did somebody receive this anti-VEGF agent aflibercept?

DR. SIVAPRASAD: The study was designed as a noninferiority study, and we had 232 patients assigned 50% to ranibizumab and 50% to aflibercept randomly. The aflibercept arm received three mandated injections: at baseline, four weeks, and eight weeks; and then from 12 weeks they were seen monthly but dosed on a PRN basis if there was reactivation of the new vessels.

DR. BRESSLER: And what did the laser people receive; what's the typical PRP that might be given in the UK?

DR. SIVAPRASAD: In the UK about 60% of the sites use PASCAL or multispot laser. We allowed both types of lasers, single spot or multispot, to be used for the study to mirror how clinical practices are doing in general practice. We allowed the patients to have their initial pan retinal photocoagulation completed within the first eight weeks, which is routine practice in the UK, and were reviewed eight weeks following that for supplemental PRP if required.

DR. BRESSLER: Patients that have proliferative retinopathy often can have a lot of medical problems, and one thing that always concerns us is whether people come back for their final outcome at one year to analyze whether they got laser or the aflibercept agent. What did you find in this, — did people come back, did you have a lot of loss to follow-up? Was it the same in both groups?

DR. SIVAPRASAD: The loss to follow-up was surprisingly very low. We had 10% dropout rate over the period of a year. Our perception is that this group are usually difficult to follow up in clinics, but that wasn't the case, and there were equal number of withdrawals in both.

DR. BRESSLER: So even though people had to come in monthly to determine if they might need more anti-VEGF agent, you found that over 90% came in for their follow-up, is that right?

DR. SIVAPRASAD: Yes. Especially for the aflibercept arm, the patients were very satisfied with the treatment, that we later realized when we did the satisfaction score they really wanted to come in and have their treatment.

DR. BRESSLER: Now before we get to the results, let's talk about how many treatments were actually done. In the aflibercept arm you said they had to get at least three and then I think you said they were evaluated on a monthly basis to see if there was some sort of worsening of the proliferative retinopathy. So how many injections on average did they actually get over the year?

DR. SIVAPRASAD: Over the year they received 4.4 injections, which included the first three injections. So from week 12 to the end of the year they only received 1.4 injections.

DR. BRESSLER: Now typically we give these anti-VEGF agents to treat diabetic macular edema, so did they not need injections for diabetic macular edema. Did these people have diabetic macular edema when they entered the trial?

DR. SIVAPRASAD: Diabetic macular edema was an exclusion criterion, so they were not included at entry and they did developed macular edema over the study period and the frequency of macular edema was significantly higher in the arm that had laser. And they were not treated with anti-VEGF agents in either arm for macular edema.

DR. BRESSLER: Okay. So it seems that there aren't a lot of injections that were needed for worsening of retinopathy. In other words, you gave almost five over the year, but three of those five were in the first three months, so that's an average of almost two injections from months 3 to the end, is that right?

DR. SIVAPRASAD: So for aflibercept I would say it's a median of one after the mandated doses. For 40 weeks they had a median of one injection.

DR. BRESSLER: And how about the laser arm? So I know you say they had to complete the PRP in a reasonable time. After it was completed, did they need any more laser through the year? What percentage of people might have needed additional pan retinal photocoagulation?

DR. SIVAPRASAD: So 65% of the patients underwent supplemental pan retinal photocoagulation following the initial completion of the laser treatment.

DR. BRESSLER: So it's not necessarily one and done for a majority of the people?

DR. SIVAPRASAD: No. That also averaged a mean of 1.17 sessions, so very similar to aflibercept.

DR. BRESSLER: So, many of them needed at least one additional session of some additional laser for worsening of their retinopathy.

DR. SIVAPRASAD: Correct.

DR. BRESSLER: So let's get to the results now. What was the main outcome that you were looking at? What was the primary outcome in the study at one year?

DR. SIVAPRASAD: The primary outcome was just the difference in mean change in visual acuity between arms. We found that aflibercept had superior outcome to laser treatment.

DR. BRESSLER: Superior by how much? Was it just one letter but you were confident it was one letter difference between the means, or was it more than that?

DR. SIVAPRASAD: It was +4 on an average.

DR. BRESSLER: And do we know that that's clinically relevant? Do you have information yet to know what percentage of the people maybe gained 10 or more letters or some magnitude like that in the two groups with aflibercept vs PRP? Or not yet?

DR. SIVAPRASAD: The baseline visual acuity of these patients are very good because macular edema was an exclusion, so the mean was above 80 letters. It is difficult to get an improvement above that due to the ceiling effect, and yet we had a 2% increase in the PRP arm and a 5% increase in the aflibercept arm, and, of course, that is then clinically statistically significant.

DR. BRESSLER: And how about the risk of worsening vision?

DR. SIVAPRASAD: Fifteen percent of the patients in the laser arm lost 10 or more letters, compared to 5% in the aflibercept arm, so three times as many patients lost vision with PRP.

DR. BRESSLER: That may indeed be very relevant for some of these patients. Let's talk about secondary outcomes. Did you look at anything other than showing that the visual acuity not only was as good as, let's say PRP, but was actually superior? That was your primary, visual acuity; were there secondary outcomes you looked at, and what were the main ones and what were the results?

DR. SIVAPRASAD: So we did do some visual function secondary outcomes, and that including visual field test, low luminance test and binocular visual field. And of the visual function the significant findings we noted were that the aflibercept arm had superior outcomes in terms of binocular visual acuity and binocular visual field. So the visual field defects were favoring the aflibercept arm.

DR. BRESSLER: So these secondary outcomes supported your primary visual acuity outcome, as well.

DR. SIVAPRASAD: Correct.

DR. BRESSLER: And what are some of the limitations to this study? I mean it seems that you had this random assignment to try to minimize any bias between the groups. You show that the aflibercept arm on average is superior for visual acuity than the PRP arm, you show secondary outcomes that seem to favor some clinically relevant benefits for the aflibercept group — any limitations to this study?

DR. SIVAPRASAD: The major limitation to the study is that it was only a one year study, and as we all know, proliferative diabetic retinopathy is the longstanding disease, and they should have had at least a five-year follow-up. But this is a phase 2B study, a proof-of-concept study, and we should try and plan a phase 3 study if at all possible.

DR. BRESSLER: Very good. What's the relevance of this now for the ophthalmologist? What should they be considering now that they've heard the results of your study comparing aflibercept to pan retinal photocoagulation? Should they do this in everyone? Should they wait until more studies are out? What's the relevance for the next patient that walks in with proliferative diabetic retinopathy and no macular edema?

DR. SIVAPRASAD: So, so far we have never had superiority on an anti-VEGF agent for proliferative diabetic retinopathy. Since this study has declared that aflibercept is superior, I'm obliged to tell all my patients who come in through the door

with this condition that there is a superior option available compared to the standard we used to do, and that standard is photocoagulation. But I would also have to explain that what we know of is only one-year data and that we would require more. And I will have to explain all the other positive and negative findings we received so that patients can make an informed decision about the choice of agent. I would have to explain to them about the compliance required with these conditions.

DR. BRESSLER: Now I think the DRCR Network had a two-year outcome and, in fact, showed better outcomes on average at one year than they did at two years, although two years was their primary outcome. At least it seems to confirm what you found as well, very good superior outcomes at one year. Do you think your outcomes will diminish by two, years or we just won't know, we won't have an opportunity to get that information?

DR. SIVAPRASAD: I presently don't have the information and we really need to plan the study to give you the results. But I would be comfortable to inform a patient that you could start off with aflibercept for a year because that's the data we have and then inform them that they can continue on aflibercept, but it will not be backed up with evidence at the end.

DR. BRESSLER: Well that's a fascinating study. It's a well-designed study, and it's very relevant to treating the tens of thousands of people in the US and more throughout the world that have proliferative diabetic retinopathy. I thank you so much not only for sharing it with us today, but for doing the study and then coming right away to our Johns Hopkins CME approach here and sharing it so that we can share it on this podcast with the world. Thank you very much.

DR. SIVAPRASAD: Thank you very much, Dr. Bressler.

DR. BRESSLER: Thank you, Dr. Sobha Sivaprasad for being with us today. We want to tell you about a new feature of our *e*Ophthalmology Review Podcast, and then I'll be back to talk with Dr. Ingrid Scott about another fascinating report at the ARVO annual meeting, looking at aflibercept compared with bevacizumab for people that have macular edema due to a central or hemiretinal vein occlusion.

BOB:

Hello, I'm Bob Busker, managing editor of *e*Ophthalmology Review. I'd like to take a moment to tell you about a new feature we've added to this program.

The amount of important new information about advances in retinal care that's presented at every major ophthalmology meeting is more than we're able to discuss through these podcasts. So to help keep you more fully informed, we now offer "*e*Ophthalmology Review Conference Highlights" — a quick overview of 10 other important developments in retinal science featured at each of our attended conferences.

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Once again, to access our website, please go to www.*e*ophthalmologyreview.org. Thank you.

BOB:

Welcome back to this *e*Ophthalmology Review podcast, reporting from ARVO 2017. Dr. Bressler's next guest is Dr. Ingrid Scott — Jack and Nancy Turner Professor, Professor of Ophthalmology and Public Health Sciences, at Penn State College of Medicine in Pennsylvania — to discuss how the SCORE-2 trial might impact the treatment of patients with macular edema caused by a retinal vein occlusion.

Dr. Scott has disclosed that she has served as a member of the Data and Safety Monitoring Committee for a clinical trial sponsored by Thrombogenics.

Their discussion will discuss bevacizumab, which, although commonly used in current practice, is not currently FDA-approved for treating ocular conditions.

And now Dr. Neil Bressler — with Dr. Ingrid Scott.

DR. BRESSLER: Thank you, Bob, and thank you, Dr. Scott, for joining me today for a discussion on the SCORE-2 results.

This was just presented at the ARVO annual meeting, and one of the most important discussions I think that affect our clinical practice. So Dr. Scott, maybe you could tell me why you wanted to do this study.

DR. SCOTT: There are two FDA approved anti-VEGF therapies for macular edema associated with central retinal vein occlusion: aflibercept and ranibizumab. There is also an off-label anti-VEGF agent used for this indication, bevacizumab which has the same target action as ranibizumab, but is much less expensive. At the time SCORE-2 was designed, each of the on-label therapies had been compared to sham to demonstrate their effectiveness, but there had not been a head -to - head comparison among the various anti-VEGF therapies.

DR. BRESSLER: Now what would make you want to do a head -to- head comparison?

DR. SCOTT: Ideally, we would have compared all three of the anti-VEGF agents, but because of limited resources, we were able to compare two of the agents. At the time SCORE-2 was designed, the CATT trial had already demonstrated similar efficacy and safety profiles between bevacizumab and ranibizumab for patients with neovascular age-related macular degeneration (nAMD) . The Diabetic Clinical Research Network showed, in Protocol T, similar efficacy and safety profiles between bevacizumab and ranibizumab for patients with diabetic macular edema. Bevacizumab and ranibizumab have a similar target biologic action; that is, they both inhibit VEGF-A. Aflibercept, in contrast, has a broader mechanism of action. It inhibits not only VEGF-A, but also VEGF-B and placental growth factor, and it has been shown in the Diabetic Retinopathy Clinical Research Network Protocol T to be associated with better visual acuity outcomes in a subset of eyes with diabetic macular edema. Finally, bevacizumab is much less expensive than ranibizumab and aflibercept. Thus, given all these factors, we felt that the most important comparison at this time is bevacizumab and aflibercept.

DR. BRESSLER: Now let's look at the design of your study. I understand that people had to have macular edema due to this retinal vein occlusion, but you specifically said it was due to a central retinal vein occlusion. Okay, I understand what that is — we see hemorrhages in all four quadrants and dilated retinal veins. But you also allowed people that had macular edema due to a hemiretinal vein occlusion. What's a hemiretinal vein occlusion?

DR. SCOTT: A hemiretinal vein occlusion is one in which there are retinal findings consistent with a retinal vein occlusion in 5 or more clock hours of the retina but in fewer than all four quadrants of the retina. This definition was used by our reading center at the University of Wisconsin Madison. So if you have retinal findings of a retinal vein occlusion in all four quadrants, we consider that a central retinal vein occlusion. If we see retinal findings consistent with a retinal vein occlusion in fewer than 5 clock hours of the fundus, we consider that a branch retinal vein occlusion. A hemiretinal vein occlusion is between the two.

DR. BRESSLER: And as I understand it, people could walk in with a wide range of visions as they might with these retinal vein occlusions from their macular edema — what's the average vision that someone may walk in with a retinal vein occlusion in your study. And what's the average thickness in the central subfield that they might have on OCT?

DR. SCOTT: So the average vision is around 20/100, and the average central subfield thickness is well over 600, around 650 microns.

DR. BRESSLER: And let's talk about the treatment. So how often would they get one of these intravitreous injections with either aflibercept or bevacizumab?

DR. SCOTT: So in SCORE-2, patients were randomized in a 1:1 allocation ratio to intravitreal aflibercept every four weeks for six months, or intravitreal bevacizumab every four weeks for six months.

DR. BRESSLER: What was your success in getting people to come in to do their six-month follow-up? Was it the same with aflibercept or bevacizumab, and how many actually did come back for the six-month follow-up?

DR. SCOTT: Participant retention was outstanding in SCORE-2 with approximately 96% of participants completing a month 6 visit, and there was no significant difference between the two treatment arms with respect to participant retention.

DR. BRESSLER: Would they be willing to take all those injections? How successful were you in having people comply with getting either aflibercept or bevacizumab through these six months?

DR. SCOTT: The mean number of injections in both of the treatment groups was 5.8, and over 90% of participants did receive all six injections.

DR. BRESSLER: So very successful. Did you find a difference between aflibercept and bevacizumab?

DR. SCOTT: In a nutshell, the primary outcome result is that intravitreal bevacizumab was noninferior to intravitreal aflibercept in mean visual acuity letter score at six months, with a noninferiority margin of five letters. So the difference at six months was negative 0.14 letters with a one-tailed 95% confidence interval ranging from -3.1 to infinity, and this is well within the five- letter noninferiority margin.

DR. BRESSLER: So as I understand it, the percentage results or the mean change in vision results were almost on top of each other, and at most one could be maybe on average three letters less than the other. And we don't typically think of a three letter change between groups as being clinically relevant, and that's the most it could have been, is that correct?

DR. SCOTT: Correct. The five letter noninferiority margin has been used previously in clinical trials — it was used in CAT, it's been used by the Diabetic Retinopathy Clinical Research Network, and it has been published in the literature that in clinical trials of patients with retinal disease, a difference between groups of five letters or more is considered clinically important.

DR. BRESSLER: You showed no clinically relevant difference in visual acuity between the groups through six months. Did you look at any secondary outcomes that were not related to vision anatomic outcome?

DR. SCOTT: We looked at number of spectral domain optical coherence tomography outcomes. There was a statistically significant difference between the groups in some of those outcomes. Perhaps most interestingly, the proportion of eyes that achieved complete resolution of macular edema, and as defined by essential subfield thickness less than 300 microns, no intraretinal or subretinal fluid, and no cystoid spaces on OCT, was about 54% in the aflibercept group compared to about 28% in the bevacizumab group.

DR. BRESSLER: So we have a disconnect: despite the 30% or so difference in that outcome, it didn't translate to a vision outcome difference that was readily apparent. Is that right?

DR. SCOTT: That's correct. What we can say is, that at least at six months, the difference in the proportion of eyes that achieved that complete resolution of macular edema did not translate into a significant difference in visual acuity outcomes. Again, that's only at six months, and we do look forward in SCORE-2 to continuing to follow these patients and investigate this further.

DR. BRESSLER: Well we'll come back to that follow-up, let's talk about safety issues. So when we are doing a head-to-head trial comparing two anti-VEGF agents, we want to often know there are differences in any ocular or eye safety or differences systemically. Did you find any with respect to ocular adverse events or systemic events?

DR. SCOTT: We did not find any significant differences between the two groups in terms of ocular or systemic events. Of course, SCORE-2 is not powered to detect the significant differences in rare outcomes, but the adverse event profile, fortunately the ocular adverse events of interest and systemic adverse events of interest were rare in both of the groups. And SCORE-2 did not identify any new safety concerns with regard to ocular or systemic adverse events associated with anti-VEGF therapy.

DR. BRESSLER: So let's compare this to what we have in the world's literature. As I understand it, there is no other head-to-head trial comparing other anti-VEGF agents for macular edema due to retinal vein occlusion, is that correct?

DR. SCOTT: Correct.

DR. BRESSLER: And how about other macular edema, like diabetic macular edema; is this similar to what was seen by the DRCR Network when they looked at different agents for diabetic macular edema?

DR. SCOTT: It is similar in the respect that anti-VEGF therapy has been shown to be an effective treatment for both diabetic macular edema and macular edema associated with central retinal vein occlusion.

There is also a similarity in that in both of those patient groups aflibercept was associated with more favorable OCT outcomes. That is it was more effective in drying out the retinas in both of those conditions. In Protocol T, which evaluated all three of the anti-VEGF agents in patients with diabetic macular edema, aflibercept was associated with significantly better visual acuity outcomes compared to bevacizumab in the subgroup of eyes with a baseline of visual acuity of ETDRS equivalent approximately 20/50 or worse. We did not find that in the SCORE-2 study.

DR. BRESSLER: So there are some similarities and some differences when looking at macular edema due to these different retinal vascular diseases.

Well let's get back to the final thing that you mentioned: and that is these are the results through the primary outcomes at six months. What's beyond that; how are you treating these patients and what's next, what else might we learn from SCORE-2 in the future?

DR. SCOTT: SCORE-2 was designed with an adaptive treatment strategy so that at six months, patients were classified as either good responders or poor responders, and that was based on composite visual acuity and OCT outcomes. The good responders in each group were randomized to either continued monthly treatment with the originally assigned treatment, vs a treat-and-extend dosing regimen. The poor responders in the aflibercept group were provided with rescue therapy with the dexamethasone delivery system, and the poor responders in the bevacizumab group were offered rescue therapy with aflibercept.

DR. BRESSLER: I want to thank you so much for pulling this information together for us on the very day that you published these results in the *Journal of the American Medical Association* and presented to a wide audience at the annual meeting at ARVO here in Baltimore this year. So thank you very much, Dr. Scott.

DR. SCOTT: Thank you, Dr. BRESSLER.

DR. BRESSLER: Now let's quickly summarize our discussion today in light of our learning objectives. The first learning

objective was to explain how recent therapeutic advances have altered the treatment landscape in proliferative diabetic retinopathy and in retinal vein occlusion.

We learned from Dr. Sobha Sivaprasad from the CLARITY study that in proliferative diabetic retinopathy, aflibercept was actually superior with respect to visual acuity outcomes at one year, compared with using pan retinal photocoagulation. It did not have as much field loss, it had some better functional outcomes, and there was excellent follow-up through one year with patients complying with monthly follow-up.

In addition, we learned that very few injections were actually needed when starting with three required monthly injections and also requiring additional treatment if there was worsening of proliferative retinopathy thereafter, And so maybe this doesn't require monthly treatments beyond three months except in some people.

We also learned that pan retinal photocoagulation, while a very effective treatment, may result in the need for additional laser treatment at some point between three months and one year, when about two-thirds of the patients actually needed some additional laser treatment.

With respect to retinal vein occlusions, we learned that, in fact, aflibercept and bevacizumab seemed to work in a very similar manner; there is very little likelihood through six months that using six monthly doses of aflibercept and six monthly doses of bevacizumab will give any different visual acuity outcomes. We also see that there is no difference in systemic or ocular safety.

Interestingly, you do get less thickening by six months with aflibercept than with bevacizumab, but obviously, based on the primary outcome, this did not result in any differences in the visual acuity outcomes between the two groups.

Now our second learning objective was to review these newly available therapies and figure out how this works with our armamentarium in treating people. And we learned with retinal vein occlusion that we cannot necessarily extrapolate the results of diabetic macular edema treatments from the DRCR Network to the results of the SCORE-2 study because in the DRCR Network it was reported when visual acuities on average are worse than 20/50, we may get on average better outcomes with aflibercept than with ranibizumab or bevacizumab at one year. That was not seen at six months when comparing aflibercept to bevacizumab.

We learned, finally, from the CLARITY study, that we may have an alternative to pan retinal photocoagulation, not only if these anti-VEGF agents like aflibercept are accessible, but if patients are willing to return for monthly follow-up.

I really want to thank both of my guests, Dr. Sobha Sivaprasad from the Moorfields Eye Hospital and Kings College Hospital in London, and Dr. Ingrid Scott from the Penn State Hershey Eye Center, for sharing their groundbreaking results that came at the ARVO annual meeting in Baltimore this year in 2017.

DR. BRESSLER: I'm Neil Dr. Bressler from the Johns Hopkins University School of Medicine and we'll be returning soon with our next *e*Ophthalmology Podcast from the Macular Society Annual Meeting in June to be held in Singapore this year. Thank you.

BOB:

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