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Improving Outcomes in Patients With RVO: Tailoring Treatment

Announcer Open:
Welcome to CME on ReachMD. This activity titled, Improving Outcomes in Patients With RVO: Tailoring Treatment, is provided by Clinical Care options LLC, and is supported by an independent educational grant from Regeneron Pharmaceuticals Incorporated. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Danzig:
Hello, everyone. Welcome to this continuing medical education webinar, Improving Outcomes in Patients With RVO: Tailoring Treatment. My name is Dr. Carl Danzig and I'm here with a good friend of mine, Dr. Arshad Khanani. This webinar is provided by Clinical Care Options. This program is supported by an educational grant from Regeneron Pharmaceuticals. Again, I'm Carl Danzig from the Rand Eye Institute in South Florida, near Fort Lauderdale. I have the pleasure of working with a good friend of mine and my former co-fellow, Dr. Arshad Khanani. Arshad, welcome.

Dr. Khanani:
Thanks, Carl. Looking forward to great discussions tonight about RVO.

Dr. Danzig:
Great. It’s great having you here, Arshad. For everyone, Dr. Khanani is based in Reno, Nevada, at Sierra Eye Associates.

Here are our disclosures.

The learning objectives tonight, we want to compare the current anti-VEGF therapies for RVO to select the most appropriate therapy for an individual patient. We also want to develop treatment protocols in RVO to use current therapies most effectively for a particular patient and then include appropriate follow-ups to improve outcomes in patients with RVO. We also want to modify an individualized treatment protocol for patients with RVO who are nonresponsive to first-line therapies and who require chronic treatment for macular edema.

So, let's start with an overview of retinal vein occlusion, RVO. It’s the second most prevalent retinal vascular disease. It is estimated to affect about 28 million adults worldwide, and is the second most common cause of vision loss due to retinal vascular disease. The most common reason for vision loss in RVO is macular edema. And of note, BRVO is 3 to 10 times more common than CRVO. So, what do you need to know also? Prevalence increases with age. It affects men and women equally. And prevalence may be higher in Asian and Hispanic populations.

In terms of epidemiology, we talked about how it's the second most common type of retinal vascular disease. It can be central retinal vein occlusion, CRVO; hemiretinal vein occlusion, HRVO; branch retinal vein occlusion, BRVO. And BRVOs account for nearly 80% of all RVOs. The average age is 65. Age and visual acuity at presentation are both predictors of outcomes. And risk factors include hypertension, diabetes, atherosclerosis, and open-angle glaucoma.

Now, when you think about evaluation and treatment, now let's talk about – we talked about systemic risk factors just now, diabetes, arthrosclerosis. And the treatment goals are to address macular edema. Now, if we see ischemia, well, we can’t resolve that, and that actually may progress even with the best of treatment. From a systemic evaluation, there's no real definitive guidelines, but we do look at patients with certain risk factors. We looked at patients greater than 50. You know, looking at their high cholesterol, blood pressure, and we may refer them back to their primary care doctor to optimize these conditions. In patients under 50 years old without risk factors, we commonly search for causes of a hypercoagulable state.

Now, how do we diagnose an RVO? It's usually clinically; we see it, we have certain, you know, typical appearance, and we can diagnose it pretty regularly. We look at dilation and tortuosity of the retinal veins and retinal hemorrhages. And this is usually sufficient; however, there are multimodal imaging techniques which may assist. Especially in patients who are young with atypical features, chronic condition, we want to confirm the diagnosis. We want to confirm the presence of macular edema. We want to look at certain characteristics of the retina tissue itself in the macula. We use the OCT for these findings. And we also use OCT for biomarkers and prognosis. We also may want to quantify ischemia, whether in the periphery or in the foveal avascular zone. Furthermore, we use different imaging techniques to evaluate response to therapy and need for further therapy, maybe even direct treat-and-extend protocols, and to also better understand pathogenesis.

There are options for multimodal imaging, our OCT, to confirm macular edema and to tailor our treatment regimen. We may look at certain biomarkers. We may even do an OCT angiography, and this may reduce the need for fluorescein, it's also noninvasive. But fluorescein angiography is important especially in atypical RVOs, and especially important also in young patients. You may be able to look at the ischemic index to prevent – to predict neovascular response. And you may also be able to diagnose artery occlusions. Furthermore, widefield angiography allows us to look at peripheral nonperfusion.

Now, let's talk about predictors of outcomes. So, there are certain OCT biomarkers. Now, we all use an OCT, and honestly myself, I couldn't live without my OCT. It drives treatment and helps diagnose diseases. And it helps my patients also understand how they're doing. Here, we can see with an OCT, with central subfield thicknesses, we can see intraretinal cysts, subretinal fluid, and hyperreflective foci. Furthermore, we can look at disorganization of the retina interlayers, called DRIL. And patients that have DRIL have a worse prognosis in hemiretinal and central retinal vein occlusion.

So, the factors that affect visual prognosis: baseline best-corrected visual acuity, the poorer the baseline visual acuity and possible greater VA gains, but there's a ceiling effect. And overall visual acuity outcomes are related to initial visual acuity presentation. With BRVO, eyes with initial vision of greater than or equal to 20/60, greater than 75% maintained or improved vision. But in eyes with vision less than 20/60, only over half had improved vision. CRVO also had a schism based on vision here, 20/40 or better, 65% maintained vision in that range. But if you presented with 20/200 or worse, 80% stayed in that range. Furthermore, older patients fare worse than younger patients, and maybe this has to do with the ability of the photoreceptors to recover. We also look at ischemic status in the beginning. And we look at the type of RVO, whether it's CRVO or BRVO, because BRVO has a better prognosis. Now, in a CRVO, if it's nonischemic, about half the patients will return to baseline or near baseline vision. But prompt treatment is important; the shorter duration of macular edema is associated with better visual outcomes.

So, there's a timeline of different interventions for retinal vein occlusion. In the 1980s, vitrectomy for RVO with, you know, vitreous hemorrhage was the only option. And you know, in the 90s, we did vitrectomy, they started doing laser. They tried doing laser anastomosis, and even optic nerve sheath decompression which is not practiced anymore. In the early 2000s, they did intravitreal thrombolysis, radial optic neurotomy, also not used currently. But later on, we started seeing effects for – of laser, anti-VEGF therapy, and steroids.

So, I'm going to hand over to Dr. Khanani to discuss clinical trial results.

Dr. Khanani:
Thank you, Carl, for an excellent overview. I'm super excited to share some of the RVO clinical trials data with you and the audience. And you know, as you said, as clinicians, you know, we see RVO quite a bit. We use OCT to diagnose. You talk about imaging techniques and biomarkers. But what is the evidence we have in terms of drugs that we can use to help our patients? And you know, we are lucky to have excellent agents currently. And the question is how we are going to be able to do better than the current treatment options. So of course, I'll review, you know, the approved agents and then some of the trials that didn't move forward and then later on we'll also discuss, you know, upcoming possible treatment options.

So, the first agent approved for retinal vein occlusion, for branch retinal vein as well as central retinal vein occlusion, was ranibizumab. This was studied in two pivotal trials, BRAVO and CRUISE. And the RVO trials are usually shorter than neovascular AMD and DME studies. They're 6 months endpoint, and usually is the last indication because it's the smallest indication out of the three indications, neovascular AMD being first, DME second, and RVO third. In BRAVO and CRUISE, we were able to use ranibizumab monthly and this was compared to sham, and it showed improvement in visual acuity. The endpoint was mean change in vision compared to baseline versus 2 to 6 months.

Then we had aflibercept trials, GALILEO and COPERNICUS for CRVO, and VIBRANT study for BRVO. You know, aflibercept was the second approved agent in terms of for the treatment of RVO. And in these trials, you know, patients were treated with loading doses and then these were longer trials in terms of doing PRN treatment, and q8-week treatment in the VIBRANT study. Patients did go PRN BRAVO and CRUISE also with ranibizumab, but those were shorter trials, ending at 1 year.

Then the SCORE2 trial, which was an independent trial looking at bevacizumab. Of course, bevacizumab is not approved for RVO, it's an off-label indication. And then the LEAVO study out of the UK also looked at bevacizumab compared to ranibizumab and aflibercept. And then the RAPTOR and RAVEN studies with brolucizumab for CRVO and BRVO were ongoing, and they were discontinued because of the safety signal we saw in the monthly neovascular AMD MERLIN study of increased risk of inflammation.

Now, you know the bottom line is that, in the past, you know, when this started, agents were used against sham, so the design were superiority studies. So, if you look at BRAVO and CRUISE, GALILEO, COPERNICUS, and VIBRANT, they were superiority studies. And then, now that we have established agents that work really, really well, now we're designing trials that are noninferiority studies because if you have a treatment approved, you don't want to not give that treatment to the patient. So, this is the evolution that actually happened for neovascular AMD and DME. So, for any drug going forward, it will be compared to an approved agent and likely would be showing or designed to show durability.

In terms of laser treatment for macular edema from RVO became standard of care for the treatment of BRVO back in the day, based on the branch vein occlusion study. What we saw was in the central vein occlusion study, CRVO study, the laser was not helpful. Now, of course, we are moving away from lasers. This is before the advent of anti-VEGF. Sometimes we combine laser with anti-VEGF if the patient is getting maximum dosing and they're still not improving.

So, let's look at some of the details of the trials that we have. The phase 3 BRAVO study, as I said, looked at ranibizumab for macular edema following BRVO, hence BRAVO, where patients were randomized 1:1:1 to sham, ranibizumab 0.3 mg which is approved dose for DME, and ranibizumab 0.5 mg which is approved dose for neovascular AMD, monthly injections versus sham injections, and then PRN treatment after that. Again, 1-year study looking at patients with vision loss from RVO with macular thickening.

If you look at the results, not surprising, but at that time the results were revolutionary because we didn't have treatments to improve visual acuity in these patients. We were stabilizing and slowly improving with laser. So, here we are able to see almost 18-letter gains compared to sham which was at 7 letters, really showing that we are able to improve vision. And if you notice, the visual acuity continues to improve over time, but most of the vision gains happen in the first three or so injections.

In terms of anatomy, you see that there's a robust decrease in anatomy after the first injection and then the anatomy slowly improves a little bit more and gets stabilized. Now of course, you know after the six monthly injections, patients went to PRN injection and you can see the anatomy actually start to get a little bit worse. So, we know that as practitioners, RVO can be very time sensitive and patients may need more treatment and they need treatment on time. If they go too long, the fluid can come back. So, that's the danger of PRN treatment. And Carl and I will discuss our treatment paradigm later. But, you know, I don't do PRN treatment in retinal vein occlusion.

In terms of the CRUISE study, it looked at central retinal vein occlusion. Again, 1:1:1 randomization. Again, monthly injections and then PRN after that. And you can see that there is improvement in visual acuity. And there is improvement in CST. So again, you can see the decrease in macular edema is much better with CRVO. And that's not because the drugs work better; it's because CRVO usually has more thickening. And here you can see the visual acuity improvements again. One thing that was surprising is that the sham gained more vision in BRVO compared to CRVO. And that's why I think we know the CRVOs are much more advanced, much more limitation in visual acuity, and that's why treatment is super, super important. When you look at the PRN part of the CRUISE study, you can again see that the anatomy starts to get a little bit worse. And again, showing that the PRN treatment may not be beneficial in some patients.

Now, let's look at aflibercept. So, that was ranibizumab, then aflibercept for macular edema from BRVO based on the VIBRANT study. And here you can see that patients either had BRVO or HRVO, and they received 2 mg of aflibercept. So, one thing with aflibercept is that it's a VEGF trap, while ranibizumab is a Fab, but here we are able to give 2 mg. And we know as clinicians that the levels of VEGF are very high in patients with RVO compared to, let's say, neovascular AMD or DME. And there may be more differences that we see between aflibercept and ranibizumab in patients with RVO. And we will of course discuss those. So, in this, patients were treated monthly. Again, the endpoint was at 6 months.

So, here what you can see is patients who were treated with aflibercept or with laser, and you can see that the visual acuity and CST improvements here in this graph. And I think laser patients went to aflibercept, you know, at 12 months, but the vision outcomes were lagging. So, it really shows us that we need to treat patients with RVO acutely and quickly. We can't sit on these patients.

Phase 3 COPERNICUS and GALILEO studies enrolled patients with CRVO, and again, vision loss from macular edema, aflibercept 2 mg monthly compared to sham here. And then both studies were designed the same way. And what happened here was, you know, the endpoint is at 24 weeks in COPERNICUS study, patients who are eligible to receive aflibercept for PRN basis, and then they were extended in an extension study with PRN extension, while in the GALILEO study, continued treatment for week 52, and again, this was PRN for aflibercept and monthly for sham injection.

So, here are the results. When you look at the visual acuities, I want you to pay attention to the center graph, you can see again, robust improvement in visual acuity that happens very fast, you know, 17 or so letters in these patients. And then what we saw was in the sham group, the visual acuity actually got worse. One thing we did notice, as you can see here in terms of CST, is that there was some decrease in CST in patients who were treated with sham, but again, there was significant improvement in anatomy with aflibercept treatment. And what we see is that it happens after the first injection where most of the edema is gone, and then we stabilize. And then, you know, when these patients received aflibercept after the primary endpoint in the sham group, you can see that anatomy does improve but the visual acuity lag again, showing that we need to treat these patients sooner than later. So, and this is 12-month results.

Again, consistently what we have seen is that patients with RVO do really well with anti-VEGF and they're getting maximum doses. I think as a field we need to know which anti-VEGF can work better than the other in terms of durability, hence, the design of new studies will be based on durability and noninferiority.

Now, in terms of SCORE study, it evaluated triamcinolone, which is a steroid for macular edema due to retinal vein occlusion. And the SCORE studies were two phase 3 trials comparing 1 or 4 mg of triamcinolone versus standard of care for BRVO and CRVO. And for CRVO, triamcinolone was superior to observation. And for BRVO, triamcinolone did not show a difference in primary endpoint or laser photocoagulation. Again, older studies happening before the advent of anti-VEGF for these conditions. And you know, one thing, as I mentioned, the delay in treatment in COPERNICUS, patients with CRVO are treated with monthly aflibercept or sham. And as I showed you that both arms crossing over to aflibercept as needed at week 24, we did not see that the sham group catching up in visual acuity, even though that the anatomy got better. And in a subgroup analysis, a higher proportion of eyes gained 15 letters at 52 weeks in patients who receive aflibercept, less than 2 months after the diagnosis, and those who receive aflibercept greater than 2 months after the diagnosis, again, showing that we need to treat this disease acutely. And the sooner we treat it, the better outcomes we have.

So, in terms of steroid, you know, of course SCORE looked at triamcinolone here. Here is GENEVA study looking at dexamethasone for macular edema from RVO. And the GENEVA studies were two 6-months randomized controlled trials, including 1,267 patients with BRVO and CRVO. And patients were randomized to receive two different doses of dexamethasone 0.7 mg or 0.35 mg compared to sham. And again, primary outcome here was time to achieve a 15-letter BCVA improvement. It's a little bit different than that mean change in BCVA at week 24 from baseline.

And what did we see? In terms of mean change in vision, you can see that both 0.35-mg and 0.75-mg patients did well in terms of improving visual acuity in terms of decreasing CST compared to sham. RVO also has inflammation. Steroids target inflammation, including VEGF; they don't lower the levels of VEGF, like we do with anti-VEGF injections, but they clearly address that. So, you can see that there is a peak of visual acuity gains about day 60, which we expect with dexamethasone, knowing that the maximum activity is 6 to 8 weeks, and then over time it starts to go down, again, showing the benefit of dexamethasone.

Now, obviously, steroids like dexamethasone have side effects, that's when they're not first line agents. We have cataracts as well as IOP. And when we look at GENEVA, though there was no significant difference in cataract rate between groups over 180 days, what we know with dexamethasone that usually one injection doesn't cause increase in cataracts, it is the cataract over time. And that's why in the MEAD study, cataract grade was about 65% for over 3 years for patients treated with dexamethasone. That was a study for DME. So, the one injection didn't show it, but we know that continuous treatment will show it. But we do get IOP increases, you know, with steroids, so that's something to keep in mind. And of course, it's transient, it usually happens 6 to 8 weeks after the steroid injection and in most cases just be managed with topical drops.

So, what happens in real world? So, patients, you know, in studies, have, you know, different inclusion and exclusion criteria. And they cannot have certain risk factors, their blood pressure has to be, you know, a certain range. So, real-world patient population is much different than clinical trials. Carl and I do a lot of clinical trials, our coordinators are really strict at getting these patients in on time, they get all the services, the VIP care. In real world, that's very difficult to do. So, that's why we need to look at the data in the real world to see how these patients are doing. These patients are very heterogeneous, they have less rigorous follow-up and treatment compared to randomized controlled trials. And the question is: What are the outcomes for these patients?

So, one way to look at it is to look at the big data analysis. Of course, the pros are that it's a massive patient population, and it can tell us the signals, but of course cons are it's incomplete dataset, individual data, sometimes anatomy data and other things are missing. And of course, there's privacy concerns, so you can only look at certain characteristics. So, we have, you know, the IRIS registry which is an amazing registry by AAO. And it is the largest dataset. And what this shows is just the demographics here in terms of RVO. And this paper by Li and colleagues, she looked at age, gender, and laterality of retinal vein occlusion in a retrospective fashion. And what we saw was from 2013 to 2017, there were 1,251,476 RVO cases in the database. And it was more like retinal vascular cases they looked at, and a quarter of them was retinal artery occlusion, which is not the focus of this webinar, but 76% were RVOs. Not surprisingly, majority of them were BRVO. So, you can see almost two times more common, BRVO. And the risk of these conditions increased with

age, not surprisingly. And then CRVO are more frequent in men and BRVO were more frequent in women, based on this analysis.

Other analysis from the IRIS registry, which is also interesting, is cataract surgery is not associated with decreased risk of retinal vein occlusion. This is Bagdasarova and colleagues, looking at the data in patients with CRVO and BRVO developing in patients who underwent cataract surgery compared to a matched control. And they had multiple different parameters: age, race, insurance, etcetera, to look at to try to see if there are differences. And what they concluded was that cataract surgery is associated with small but likely not clinically significant increase in RVO. So, when patients come in and say, 'Well, am I going to be at more risk?' And the answer from this database looks like it's no.

So, Carl, I'll pass it back to you now for the next portion of this webinar.

Dr. Danzig:
A really great overview, Arshad, discussing the clinical trial results. And also, that last point regarding cataract surgery is a really important point to drive home for a group of ophthalmologists, not necessarily everyone's a retina specialist. So, great job. Thank you.

You know, RVO is a difficult disease for many patients. Some patients do great, but many don't. And part of the problem is, is that these patients need such regular appointments, and 53% of working patients have to take greater than one day off of work per appointment. And 71% of these patients require caregiver assistance for these appointments. And patients that have RVO incur greater healthcare expenditures over the course of 1 and 3 years compared with patients with hypertension or glaucoma.

And let's be honest, frequent injections does not – that does not make patients happy. It's intensive, it's frequent, and 75% of patients experience injection anxiety. Personally, I think that sounds low, 75%, so 1 out of 4 were just not anxious at all? But, 54% report anxiety for at least 2 days before the injection. And I see this in my clinical practice all the time. So, it's a priority. It's just irrefutable. People desire fewer injections and fewer appointments in hopes of achieving the same visual results.

So, in the real world, just like Dr. Khanani, you know, talked about, patients with RVO continue to require frequent anti-VEGF injections, and that imposes a significant burden. And a personalized treatment approach may help reduce this. Because what we see is in the real world, as opposed to in the clinical trials, you know, patients are not able to maintain the same vision that we see in the trials.

And we saw in observational studies, they found worse vision gains in maintenance and visual gains with anti-VEGF therapies in the real world compared to the trials. Because in the trials, there's a higher rate of treatment adherence.

So, what we see is that vision gains in clinical trials are unsustained over the long term. We see that even in the long-term extension trials. Okay, patients with CRVO experienced significant vision loss in the open-label extension study, that's what the OLE stands for. And patients with CRVO who completed the CRUISE trial, which was the 12-month phase 3 trial to assess efficacy and safety of ranibizumab, they were enrolled in this extension study, but what we see is that those visual gains were not maintained.

In patients with BRVO, in long-term extension studies and real-world studies received fewer mean injections over 12 months than those in clinical trials. So, in the clinical trials, we can see the mean injection number during year 1, 9, 8.5. And then in real-world studies, almost 5, just under 4. And then in the long-term extension studies, only 2.1. So, these patients are not getting treated as regularly as in the clinical trials. No surprise, these patients don't have the same visual gains over the long term.

Patients with BRVO in real-world studies achieved smaller gains than in clinical trials, while patients maintained initial visual gains achieved in clinical trials during long-term extension studies. So, in the long-term extension studies, they were able to maintain those visual gains, but in the real-world it didn't work out quite the same, they dropped. Because again, even the long-term extension studies have more visits than the real world.

So, patients with CRVO in long-term extension studies and real-world studies, they received fewer mean injections. Well, this correlates to their worse vision. Clinical trial patients received regular injections, commonly q4 weeks for at least six in a row, if not more. And patients with CRVO in real-world studies achieved smaller gains than in clinical trials. And patients did not maintain the initial visual gains achieved in clinical trials when they completed a long-term extension study. So, let me explain that. Patients completed a clinical trial, their vision went up, they entered a long-term extension study with fewer visits, fewer injections, and they weren't able to maintain the vision they gained during the regimented clinical trial.

So, when we look at real-world versus clinical trials in retinal vein occlusion, patients in the real-world studies received fewer mean injections than those in clinical trials or long-term extension studies. And patients in long-term extension studies did not maintain the visual gains achieved in core clinical trials. And patients in real-world studies did not achieve clinical significant visual gains.

So, in conclusion, in randomized controlled trials, patients with macular edema due to BRVO and CRVO experienced significant BCVA gains over the first year of treatment. However, in real-world studies with less frequent monitoring, these patients with macular edema

received fewer injections and did not achieve similar BCVA gains seen in randomized controlled trials. In the long-term extension studies, which also had less frequent monitoring and fewer injections, patients' macular edema due to BRVO, on average, maintained vision gains achieved in randomized controlled trials, whereas patients with macular edema due to CRVO, on average did not maintain their initial gains. And this data highlights a need for new, more durable therapies to reduce treatment burden and alleviate the need for frequent monitoring.

Now, we're going to discuss a couple of studies, a couple of case studies. This is my patient, a CRVO case study from May 2012. It's a 59-year-old woman. She was a dental hygienist. She was very active. She goes to the theater. She goes down to the Florida Keys. She works regularly. And she came into me with vision decreased the 20/400 in the right eye, in the left eye she was 20/25. She had no past medical history. There was no APD. Pressure was good, no NVI, minimal cataract, and otherwise normal slit-lamp examination. But what you see here on fundus examination of this patient, you see that blood and thunder appearance that we learn in training with, you know, hyperemic disc and congested disc, with vascular tortuosity, dot and blot hemorrhages in four quadrants, flame hemorrhages. And in OCT, we can see diffuse macular edema. And on this date, ranibizumab was injected. We sent this patient for laboratory workup. She was 59. You know, sometimes my cut-off is a little bit younger, but this is a patient that had no real risk factors, so I felt that in this otherwise healthy female, that we should do a laboratory workup. And we did find elevated homocysteine and antithrombin III levels. She was referred to cardiology, and she was initiated on baby aspirin.

By November 2012, she had had five ranibizumab injections and her vision was 20/200. The edema is worse. And at this point, we switched to aflibercept. One injection of aflibercept, her vision improved to 20/50. The edema melted away. There's a tiny bit of subfoveal fluid present, but this is a pristine response after one injection. And after four injections – or after three injections, her vision improved to 20/30. And she was injected for the fourth time in an extended 6-week interval. Again, fourth injection of aflibercept.

When you look at how it was earlier to now, this patient is so happy. But unfortunately, you know, we tried to extend her out. Patient works, she goes away she's very active, her vision decreased with recurrent edema 6 weeks later, so we shortened it up back to 4 weeks, but it just couldn't be maintained. This patient was unable to be extended past 5 weeks. She had been coming – tried to come monthly, sometimes it was 6 weeks, sometimes it was a bit more. Her vision dropped from 20/40 to 20/80. Aflibercept was injected multiple times, followed by a dexamethasone implant 2 weeks later.

By October 2013, she still had edema but was tired of the continuous injections and refused treatment on this occasion. Two weeks later, there was new nerve swelling with increased vascular tortuosity and more dot hemorrhages. With presumed ischemic CRVO at this point, aflibercept was reinjected. She returned 2 weeks later for repeat FA and followed by PRP. But with ongoing treatment, her visual acuity could never be improved, and the edema could not be controlled. She had multiple dexamethasone implants, more aflibercept injections, PRP, cataract surgery, and she had burnout of her appointments coming in every 4 to 6 weeks for years in a row. And her vision ended up being counting fingers, whether or not she had edema, or whether it was flat or not. So, it really – this case really highlights the importance of more durable therapies to better, you know, maintain those visual improvements that we see early on.

I'm going to let Arshad take over and discuss his case now.

Dr. Khanani:
Thank you, Carl. Great presentation. And of course, the case really highlights the challenges and need for treatment options that can actually help all of our patients have better durability. So, I'll present his case followed by some of the upcoming clinical trials as well as recent data, and then I'll hand back to you.

So, this is one of my patients, again another young patient, 44-year-old male with no past medical history, showing up in December of 2017 with changes in his vision. And when you look at this OCT image, in infrared, you see tortuosity of the vessels. We did see hemorrhages, but there was not much macular edema. And the question at this point many of patients like this presented to us for Carl and I, and we know what this disease is going to do, especially with this much tortuosity. Of course, a young patient, we did the workup, like Carl did for his patient here, everything was negative. So, I told the patient that you have a lot of tortuosity, you have a lot of hemorrhages, 360. I don't have the fluorescein to share with you, but it was done. But it was in our old system because – and we can retrieve it. But we decided to treat this patient. So, patient was actually treated with ranibizumab. Would observation have been okay with this patient if they're fearful for injection? I think it's okay, but we know what this will do. So, this is the thickness map, you can see all the red obviously highlighting that there is thickening, just not in the center.

So, this patient actually comes back 4 weeks or a month after the ranibizumab injection, and you actually see that there is more edema than it was before the ranibizumab. And the question was that the VEGF load of this patient was so high with this CRVO, that ranibizumab was unable to control. So, we had aflibercept sample available at that time, and we gave this patient aflibercept. Now, you can see visual acuity is down and the CST is quite thick. This is a month after aflibercept. And patient did very well in terms of resolution of edema, as well as improvement in visual acuity. And he was treated with aflibercept again. And then, so this is kind of the

summary, the patient did have much edema, got ranibizumab, got aflibercept. And then what happened was, his insurance won't cover aflibercept. This is 7 weeks after the last aflibercept. So, remember with ranibizumab, patient was worse at 1 month, obviously he just got one injection. But aflibercept, patient got controlled and then received another one, and then 7 weeks after, looks pretty good. We could not get him aflibercept because of insurance coverage. And sometimes that's a real-world problem that Carl and I both have in our clinical practice, so receives ranibizumab.

And this is 5 weeks after ranibizumab number 2. So, and now you can see visual acuity is down again, CST is also quite thick, really showing that this patient is high need. And that's where I was mentioning earlier that there could be differences in controlling disease between ranibizumab 0.5 and aflibercept 2 mg in certain patients. And this is a patient obviously that highlights that. So, patient was put back on aflibercept. We have a bunch of these images showing the historical. And this is patient got treated and then patient was getting better over time. And here, you can see that patient is, again, back to normal anatomy with good visual acuity. And again, baseline ranibizumab, aflibercept, aflibercept, ranibizumab, and then, you know, improvement with aflibercept, controlled with aflibercept.

And this patient has done well. He currently is on aflibercept every 8 weeks, he cannot go longer, but he's very well controlled and is still being treated. You know that's another thing, RVO is a disease that doesn't go away in most patients. I think there's some perception that it will just go away. And this patient is quite young and still needs treatment. So, this case highlights that patient had worsening of disease with ranibizumab, decreased vision. And with aflibercept, he was able to be controlled but also extended to 8 weeks. So, this is just some recent pictures. You can see that this patient is doing well with 20/20 vision and getting aflibercept every 6 to 8 weeks.

So, now let's talk, Carl, a little bit about recent and ongoing clinical trials. You know, we had a trial in RVO called the BEACON study with KSI-301, that looked at patient with BRVO and CRVO, compared to aflibercept. Patients were treated less often with KSI-301, which is antibody biopolymer conjugate. We did – the study didn't meet the primary endpoint, but tarcocimab development has been stopped based on trials not meeting primary endpoint in diabetic macular edema, and initially in neovascular AMD. Faricimab is a bispecific antibody that's approved for DME and neovascular AMD. We saw the data from COMINO and BALATON study which I'll share, and aflibercept high-dose which is 8 mg, recently approved for DME, neovascular AMD, as well as DR, has ongoing QUASAR study looking at patients with RVO. And I think Carl was the first patient – first physician to enroll the first patient in that study.

Looking at BALATON and COMINO, these were designed in noninferiority studies, as I said, monthly faricimab 60 mg compared to aflibercept 2 mg. What we saw was the studies met the noninferiority with comparable visual acuity gains in both groups, faricimab versus aflibercept in both diseases, BALATON and COMINO. And then, if you're looking at proportion of patients gaining or avoiding loss of vision, this was also comparable between studies and between drugs. And in terms of CST, you see significant reduction in CST in both BRVO and HRVO, CRVO patients, again, more anatomic improvement in HRVO, CRVO because more edema is usually present at baseline, again aflibercept and faricimab doing really well. In terms of macular leakage, there were some differences where more patients achieved absence of macular leakage with faricimab versus aflibercept at week 24. This is a signal we have seen in the DME trials with faricimab also. This could be a biomarker for Ang2 inhibition on top of VEGFA inhibition with faricimab. But more to be learned about that. In terms of safety, faricimab was well tolerated with a safety profile similar to aflibercept.

So, the bottom line is BALATON and COMINO met the primary endpoint. This data will be submitted to the agency and hopefully we have approval of faricimab for RVO in the near future.

Now of course, the second or 12 months past the 6 months of this trial is everybody receiving faricimab in a treat-and-extend kind of fashion, and we are awaiting that data that will be available early next year in terms of how those outcomes are for those patients. And the QUASAR study with high-dose aflibercept 8 mg is an ongoing study. It's a randomized, double-masked, active-controlled phase 3 study looking at safety and efficacy of aflibercept 8 mg in patients with RVO. This is treatment-naïve patients with BRVO, HRVO, or CRVO that were recently diagnosed within the last 16 weeks BCVA 20/40 to 20/320, and CST greater than 300 or 320 based on the machine. And this study has a high-dose regimen 1, regimen 2, and the standard-of-care comparator which is aflibercept 2 mg. So, this is an ongoing study, we'll hopefully have the enrollment and then data from this study in the near future. And the primary outcome is change in BCVA from baseline measured by ETDRS score at week 36. And the secondary outcomes are of course looking at anatomy, number of injections, three-line gainers 47:32, and extension of this.

So, in summary, anti-VEGF agents have become first-line therapy for macular edema from retinal vein occlusion. You know, there appears to be some differences that can be found between drugs. I look at RVO as a high VEGF load and we need more potent drugs to control the disease. We know that treatment initiation may negatively impact vision prognosis. Monthly dosing regimen has been extensively studied; however, data suggests that individualized treatment regimen may lead to comparable outcomes, not PRN, but more like a treat-and-extend fashion. Steroids tend to be efficacious in terms of controlling disease. But, of course, the safety profile is different in terms of cataract, as well as IOP elevation. And then the peripheral laser photocoagulation doesn't seem to improve vision outcomes or decrease anti-VEGF burden in patients with macular edema from RVO.

So, Carl, I'll hand back to you to close this program.

Dr. Danzig:
Great summary there, Arshad. And I'm very excited about the QUASAR study which is ongoing with high-dose aflibercept. And my patients in my clinic I know are excited to participate. I'm sure yours are the same. Thank you very much for attending. And please go on to this website to access the online evaluation form and to print your certificate. Thank you again.

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