DIABETIC RETINOPATHY: CHANGING TREATMENT PARADIGMS

The evolving role of anti-VEGF injections in the treatment of diabetic eye disease.

PART ONE OF TWO

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The Goal and Key Questions

Panretinal photocoagulation (PRP) has been the gold standard treatment for diabetic retinopathy (DR) since the results of the Early Treatment Diabetic Retinopathy Study (ETDRS) clinical trial were released in the mid-1980s. Intravitreal anti-VEGF injections may yield regression of DR in select patients, thus offering a new option for treatment. Using this medical approach in DR has been likened to slowing a moving train: similar to how steady pressure on a brake mechanism will slow a train, anti-VEGF injections over time offer to slow the disease process, if not stop it in its tracks. Yet, despite the potential advantages associated with the medical management of DR, there are many unanswered questions surrounding the use of anti-VEGF injections in diabetic eye disease. This roundtable from ASRS 2018 will explore many facets of this new treatment paradigm, including:

- What are the current data, and how do those data translate for use in the clinic?
- How are patients selected for therapy?
- What is the optimal timing of doses?
- What treatment endpoints help with decision-making?
- Is it possible to stop treatment at some point, and if so, when and how should that be determined?
- What is the role of laser as adjunctive therapy?

—Rishi P. Singh, MD, Moderator

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DIABETIC RETINOPATHY: CHANGING TREATMENT PARADIGMS

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REVIEWING THE DATA: PROTOCOL S

Rishi P. Singh, MD: Two-year follow-up data from the Protocol S study are now available. What are the important findings from this data set?

Nancy Holekamp, MD: The most important outcome from the 2-year data from Protocol S was the improvement in VA, even in the absence of diabetic macular edema (DME). We would expect to see VA gains among patients with proliferative DR (PDR) and DME, so this was a somewhat unexpected outcome. The secondary endpoints have not garnered as much attention, but they are equally as important. For example, the rate of vitrectomy was 4% among patients in the anti-VEGF group compared to 15% in the PRP group, and there were fewer cases of retinal detachment, vitreous hemorrhage, iris neovascularization, and neovascular glaucoma. Collectively, these findings seem to suggest that medical therapy arrested the disease process, and as a result, patients experienced fewer complications.

Dr. Singh: Among patients without baseline DME, the anti-VEGF group experienced a +1.3 greater letter gain in VA compared to laser. As expected, patients with DME experienced more profound VA gains after medical therapy. The difference in the absence of DME may appear underwhelming.

Tarek S. Hassan, MD: The differences you are highlighting may not be considered what we term “clinically meaningful,” but there is more to the story here. As Dr. Holekamp referred to, anti-VEGF injections yield regression in DR severity, which is supported by reversal in DR severity score in this and other studies. That regression implies that anti-VEGF injections are impacting the microvasculature of the retina. That is a much different outcome than showing vision gains, and yet it is certainly meaningful to direct therapy to the underlying disease process as well.

Dr. Singh: This trial randomized patients to receive three initial injections and then prn in the anti-VEGF arm. Is that a reasonable way to do this in clinical practice?

Nikolas J.S. London, MD: I start patients on a loading dose, but I prefer to transition to a maintenance injection schedule that is more similar to treat-and-extend than prn. I am interested to see what the outcomes of the Protocol W study (NCT02634333) are to help guide decision-making with respect to timing of doses. For now, I have found that injecting every 3 to 4 months after the loading phase will help prevent recurrent vitreous hemorrhages and other complications.

PROTOCOL S: 5-YEAR RESULTS

- 69% and 65% of patients in the ranibizumab and panretinal photocoagulation (PRP) group completed 5 years of follow-up (excluding deaths)
- Cumulative mean number of injections over 5 years: 19.2 in ranibizumab group versus 5.4 in PRP group
- Mean change in VA letter score at 5 years was not statistically different: +3.1 ranibizumab versus +3.0 PRP
- Mean change in cumulative visual field total point score (-330 vs -537) and rate of developing vision-impairing diabetic macular edema (22% vs 38%) were lower in ranibizumab-treated patients versus PRP-treated patients
- Based on equivalent VA at 5 years of 20/25 in each group, investigators concluded that anti-VEGF and PRP are viable treatment options

*Note: These data were presented at ASRS 2018 after the roundtable discussion occurred. A more robust discussion of these data will be presented in Part Two of this series.

Dr. Singh: Protocol S followed as-needed injections based on whether...
there was regression of neovascularization. How are you determining the need for subsequent therapy in clinical practice, and are you using imaging to gauge treatment decisions?

Arshad M. Khanani, MD, MA: I believe widefield angiography is the most useful tool for monitoring for DR regression. Color fundus photography is helpful, but fluorescein angiography (FA) will sometimes reveal relevant information about the vasculature and whether the neovascularization is stable. For this reason, I have shifted to performing FA more frequently for these patients.

Dr. Singh: The Protocol S investigators reported that 4% of patients in the anti-VEGF group required a vitrectomy following anti-VEGF injections for fibrosis and tractional detachments. Other studies have noted a similar rate of fibrovascular contraction, although it was lower in Protocol S. What was your impression of that finding?

Dr. Holekamp: The baseline characteristics in those studies may be important to consider. It seems reasonable that older individuals and those with more severe DR manifestations may be at risk of the crunch phenomenon. We should be cautious about making any conclusions based on comparing data from different clinical trials.

Dr. Singh: As patients being treated with anti-VEGF therapy are followed long-term, what, if anything, are you looking for that might change your mindset?

Dr. Hassan: The biggest thing for me will be whether the treatment effect is sustained or whether we see suggestion of anti-VEGF resistance. The outcomes regarding recurrences of neovascularization will be important. The other thing I am interested to see is if there is any impact from long-term anti-VEGF therapy, such as unusual or unexpected damage to the retinal pigment epithelium. Based on our experience treating other eye diseases with anti-VEGF injections, that is unlikely, but confirmatory data are always helpful.

Dr. London: It will be interesting to see whether treating patients with anti-VEGF therapy is sustainable from a practical standpoint. Historically, these are patients who are younger, potentially of working age, who have a high need for health care resources, and we are asking them to visit for injections several times throughout the year. So, the rate of loss to follow-up may be meaningful to consider. Beyond the ramifications for the study outcomes, this raises questions about what happens to these patients when they come back for treatment. Recent data suggest that 20% to 30% of patients on anti-VEGF therapy are lost to follow-up. When those patients return, they tend to have much worse pathology compared to those treated with laser. That is a concern for me, but does that mean we need to rethink how we use laser and how we evaluate the potential for compliance with the treatment protocol? I am not sure we have answers to those questions at the current time.

Dr. Khanani: The paradigm is shifting, but I do not currently treat mild to moderate NPDR with anti-VEGF injections. It will be interesting to see the longer-term data, which might tell us something about the durability and sustainability of this approach. They may also help us identify the best candidates for medical management of DR.

Two points are worth considering in this context:

1. The amount of DR regression largely depends on where you start, and
2. 51% of patients with severe NPDR will progress to PDR in 1 year.

These factors, as well as considerations for the treatment burden, will likely be beneficial for personalizing treatment decisions. There may be a role for treating appropriately selected patients with NPDR to effect a long-term benefit.

Dr. Holekamp: I believe there is or will be a role for treating patients with moderately severe DR manifestations may be at risk of the crunch phenomenon. We should be
CASE 1: MANAGING DIABETIC RETINOPATHY IN WORKING-AGE PATIENTS

By Rishi P. Singh, MD

CASE BACKGROUND
- At the time of the evaluation, his hemoglobin A1C level was 8.9, and historically, it had been around 8 to 9 since diagnosis.
- The IOP was 21 mm Hg in each eye.
- A fundus photograph obtained during a previous visit with an optometrist showed areas of hemorrhage and microaneurysms for 360° (Figure 1A).
- Hemorrhage was evident in four quadrants in each eye.
- Areas of neovascularization were evident on ultrawide-field imaging (Figure 1B).

TREATMENT PLAN
- The optometrist recommended follow-up 6 months later.
- The patient returned in 6 weeks with decreased vision and pain in both eyes.
- At that time, VA was 20/20 OU, and IOP was 43 mm Hg OD and 35 mm Hg OS.
- The patient was referred to me and was seen on the same day.
- A fluorescein angiogram showed nonperfusion temporally and neovascularization of the disc in the left eye (Figure 1B).

CASE DISCUSSION
Rishi P. Singh, MD: How would you treat the neovascular glaucoma in a patient like this? Is there concern that an anti-VEGF agent might raise the pressure, even transiently? Does the fact that he is reporting eye pain and is symptomatic from the neovascular glaucoma sway your decision?

Nikolas J.S. London, MD: I would tend to be pretty aggressive in a case like this. I would start anti-VEGF injections and consider decompressing prior to the injection or doing an anterior chamber tap afterward.

Tarek S. Hassan, MD: I would do the same.

Nancy Holekamp, MD: If I were concerned about the pressure in a patient like this, I would give only half the dose and would follow with laser within a week.

Dr. Singh: To add to this case, the patient is employed by an auto manufacturer, and he is responsible for operating a piece of machinery on an assembly line. He is routinely monitored with dilated fundus examination and visual fields as a requirement for his job, and if he loses any part of his vision, he cannot perform his work duties. However, he relayed that he was told previously that he had no retinopathy, so the value of those exams is suspect. Nevertheless, my preference is not to do panretinal photocoagulation on the same day as the initial visit unless the presentation really demands it. And so, a decision was made to start IOP-lowering medications and perform an anterior chamber tap, followed by anti-VEGF injections in each eye. I scheduled him for possible laser treatment within 6 or 7 days after this and a pressure check.

Dr. Holekamp: I would want to see a visual field test performed as soon as he was stabilized to establish a baseline.

Dr. London: I would be concerned about the level of compliance in a patient with neovascular glaucoma.

CONCLUSION
After a series of three anti-VEGF injections over a 3-month period, the hemorrhage
severe to severe NPDR. The rate of two-step improvement from this study is encouraging, and longer-term data will be interesting. Beyond that, it could also be interesting to quantify the failure to progress.

Dr. Hassan: Failure to progress is a win. That sounds like stalling on train tracks, but it really is not, because we are actually preventing the patient from riding backwards on this disease train. And this may be an apt analogy for another reason in the context of anti-VEGF therapy, because there is potential to help the patient ride towards the goal of disease regression. Treating patients with NPDR with anti-VEGF injections is not simply trying to forestall the inevitable disease progression or maintain the status quo, but rather there is potential to actually improve their underlying retinopathy.

Dr. Singh: What is your current approach to treating patients with PDR, and has your thinking evolved in light of recent data?

Dr. Holekamp: I prefer to start with anti-VEGF injections followed by laser, if needed. My approach has changed in these patients in light of Protocol S and PANORAMA because of the ability to potentially yield regression but also because we can delay the need for laser, which is another way we are helping patients maintain vision with anti-VEGF injections.

Dr. Hassan: Two factors become important to consider for the patient with severe PDR:
1. the severity of the disease and
2. the willingness of the patient to comply with follow-up, which can be difficult to judge.

Often, patients progress to severe PDR because they are not diligent in managing their underlying disease. They may have had diabetes for years, and both of those things are of concern in light of the need for routine monitoring and repeated injections over time. The point was made earlier about patients returning after missing a few appointments with much worse disease, and that is something we will need to consider going forward in terms of whether we use laser alone or in addition to anti-VEGF treatments. We can offer laser or anti-VEGF injections, and how we educate our patients on the importance of compliance will be important.

Dr. London: I have considered creating a contract with the patient, letting them know that, if we start with anti-VEGF injections, here are the potential outcomes, but also that there is some work the patient needs to do. That would put some of the decision on the patient, which I think is appropriate, because, in my experience, outcomes are better when patients are engaged in their own care, especially in diabetes. For us, as retina specialists, the severity of the disease is really the tipping point. In the case of severe PDR, anti-VEGF monotherapy is unlikely to be successful, and either laser or surgery is a possibility. Moderate or earlier NPDR really does not warrant the application of laser; it is really in the early to moderate PDR patient where you have to make a decision. However, for the treatment to be successful, we need the patient to comply with the treatment protocol.

Dr. Khanani: Education starts during the first visit. I like to start the patient with PDR on anti-VEGF injections with instructions to return in 4 to 6 weeks. I explain all the risks and benefits associated with laser and anti-VEGF during the

**Figure 3.** Right eye after three monthly anti-VEGF injections (presentation on the left side and posttreatment on the right side).

**Figure 4.** Left eye of the same patient after three monthly anti-VEGF injections (presentation on the left side and posttreatment on the right side).

We are now performing bilateral injections every 3 months in this patient, and the eye is now stable, albeit with a slightly compromised visual field. For me, this case demonstrates some of the realities of treating diabetic retinopathy in working patients and the urgent need to help preserve vision.
encounter and then give the patient time to absorb that and consider what he or she wants to do going forward.

THE EVOLVING ROLE OF LASER

Dr. Singh: The role of laser in treating DR is evolving. As a result of incorporating anti-VEGF injections for DR and DME, has your use of laser changed?

Dr. Holekamp: The ability to yield regression with anti-VEGF injections has enabled me to perform less destructive laser even in those cases where the drug alone is not enough to get the result. Laser will likely continue to have a role going forward. For me, even though Protocol S and PANORAMA, together, show that anti-VEGF injections are effective treatments for DR, we still need longer-term data. On the other hand, by definition, if these people have advanced retinopathy, they likely got that way by being noncompliant. Laser is the current antidote for those two things. As we work through those two issues, we may find ourselves using even less laser.

Dr. Singh: Does anyone incorporate anti-VEGF injections before, during, or after surgery?

Dr. Hassan: I use anti-VEGF agents prior to surgery in only a limited number of cases, but I do think it can be helpful in those select instances. And it can continue to be useful after surgery. The notion that having vitreous surgically removed reduces the efficacy or durability of anti-VEGF injections does not ring true to me. But what we are really discussing here is that anti-VEGF therapy prevents patients from getting to the point where surgery is even indicated.

Dr. Singh: Does anyone use anti-VEGF intraoperatively?

Dr. London: That is not something I do currently, but that is related to the fact that it is difficult to get anti-VEGF injections in the hospital setting I am in.

Dr. Singh: Does anyone use anti-VEGF after surgery?

Dr. Khanani: I use imaging to show patients why I think it is necessary to start anti-VEGF therapy with regard to outcomes and follow-up.

Dr. Khanani: I use imaging to show patients why I think it is necessary to start anti-VEGF therapy with regard to outcomes and follow-up.

But it is also my impression that there is not much benefit from intraoperative use of anti-VEGF agents. I do perform an injection within the first week postoperatively to reduce the risk of a rebleed.

Dr. Singh: A paper was published a few years ago examining risk factors for postoperative vitreous hemorrhages in patients with PDR. The analysis found that the only correlating factor was time since surgery, which probably indicates the number of tractional components dealt with during the surgery.

PRACTICAL CONSIDERATIONS

Dr. Singh: How do you counsel your patients when they are started on anti-VEGF therapy with regard to outcomes and follow-up?

Dr. Khanani: I use imaging to show patients why I think it is necessary to start anti-VEGF therapy. I explain that they have a systemic disease that can manifest in the eye. But this is a good opportunity to talk about the importance of systemic control for reducing the risk of losing vision. We also discuss that this approach requires treatment every 4 to 6 weeks initially, with the possibility to extend the interval later but with an indefinite endpoint. It is important to relay the relevant safety information, including the potential for manageable irritation with the actual injection and a very low risk of endophthalmitis. Counseling is also important for managing expectations. I have found that most patients think their vision will improve significantly after the first injection, and they need to be notified in advance about their expectations. Patients with DME and vitreous hemorrhage usually gain vision; others may not notice any improvement, as we are just regressing the PDR to lower the risk of losing vision over time. Over the course of treatment, imaging again becomes useful for educating and showing the patients the impact of treatment on the retina. Overall, I use this opportunity to instill in the patient that this is a team effort, that I can inject a drug that will help treat their DR or DME, but that they need to gain control of their hemoglobin A1C and comply with the treatment schedule.

Dr. Singh: Do you find that patients are aware of the treatment options?

Dr. London: I do not believe patients come in with awareness about what the options are. We have to remember these are typically younger patients, and they have families and busy lives. That may be part of the reason they do not do so well.

FAILURE TO PROGRESS IS A WIN. THAT SOUNDS LIKE STALLING ON TRAIN TRACKS, BUT IT REALLY IS NOT, BECAUSE WE ARE ACTUALLY PREVENTING THE PATIENT FROM RIDING BACKWARDS ON THIS DISEASE TRAIN. AND THIS MAY BE AN APT ANALOGY FOR ANOTHER REASON IN THE CONTEXT OF ANTI-VEGF THERAPY, BECAUSE THERE IS POTENTIAL TO HELP THE PATIENT RIDE TOWARDS THE GOAL OF DISEASE REGRESSION. —TAREK S. HASSAN, MD
with managing their systemic disease. For that reason, the retina specialist has an opportunity to play an important role in education, not just about the eye disease, but also about the systemic diabetes.

**Dr. Khanani:** Patients are usually not aware of their treatment options. When we mention that we want to do an injection in the eye, many patients get nervous. I use this opportunity to educate them about the disease, the need for good blood sugar control, and the need for strict follow-up. Compliance is always a challenge with this population, but that partially depends on how involved they are in their own treatment. When patients are more aware of their disease, they are more likely to be engaged.

**Dr. London:** In the population of patients in my practice in San Diego, patients do not come in with a great deal of knowledge about treatment options, but they do want to learn about their disease and how we can help them.

**Dr. Holekamp:** There is a growing concept in medicine called “shared decision-making.” I think that is likely to impact very prominently in our management of diabetic patients, precisely because they have a thirst for knowledge. Generally, patients with diabetes want to be a part of the decision-making process.

**Dr. Hassan:** They need to be involved, because they may have more going on in their lives than the typical age-related macular degeneration (AMD) patients and others in our care. They are more likely to have jobs, families, and younger children, and they may be taking care of their parents who have AMD, for example. They have to be involved in the decision-making process because this is a different population than your 80-year-old AMD patient, and only they can fully understand the life pressures with which they grapple.

**Dr. Khanani:** How do you see compliance going forward in terms of treating PDR or severe NPDR with anti-VEGF alone?

**Dr. Holekamp:** By definition, all of these diabetic patients who are in our office with PDR or DME are noncompliant. How do we change behavior? Is it enough to lose your vision to change behavior? Sometimes. Is it enough to tell a patient that getting frequent injections will make an improvement even if they do not get vision improvement? Will that change behavior? That is going to be a challenge.

**Dr. Singh:** In terms of monitoring patients, is anyone using serial angiography, either FA or OCT angiography? If so, what do you look for on those studies?

**Dr. Holekamp:** For DR without DME, fundus photographs provide the most compelling information. Showing a patient blood on the retina has an immediate impact, and that degree of alarm is what will drive compliance. Later on, repeat imaging may show improvement, which will encourage continued compliance. For DME, OCT is the most useful imaging we have for patients’ education and for making treatment decisions.

**Dr. Khanani:** Using anti-VEGF therapy is most successful in the context of personalized medicine. Every patient is different, and many factors, including systemic control, renal status, and health of the cardiovascular system, influence the impact of diabetes on the microvasculature in the eye. For this reason, I repeat an angiogram about every 6 to 12 months to guide treatment, especially if the disease is stable. That usually provides information about the status of proliferative disease and ischemia and helps me understand whether the treatment interval can be extended.

**Dr. London:** I use OCT angiography and widefield FA. I have found that, in some cases, showing patients macular and peripheral nonperfusion can be motivating. I explain that it is an area where they have lost vessels, and we cannot get them back, and that going forward, we can stabilize or improve what is left if they keep returning for their follow-ups.

**Dr. Singh:** On the other side of things, is there an endpoint to therapy where injections can be stopped?

**Dr. Hassan:** We do not know the answer to that question. In my own experience, I have yet to see a patient where all the signs of DR have gone away, but even if they did go away, I would be concerned about it coming back without therapy at some interval, even if it is after quite some time. We need new parameters to understand how we can assess the continued need for treatment.

**Dr. London:** That really gets to the point of how we are making treatment adjustments and extending the interval.

**Dr. Hassan:** Unfortunately, we do not have metrics for that, either. I have not gone beyond 3 to 4 months, which possibly raises a question about whether they will actually come back to the office. But when patients ask me what I would do if I were in their position, I tell them I would gladly come into the office every 3 to 4 months to receive an injection if it would help improve the long-term health of my retina and potentially preserve vision indefinitely.

**POTENTIAL NOVEL TREATMENT APPROACHES**

**Dr. Singh:** There are some new developments lately that may impact treatment of DR in the future. The TIME-2 study investigated a subcutaneous injection of AKB 9778 (Aerpio Pharmaceuticals) alone and in combination with ranibizumab (Lucentis, Genentech).
CASE 2: HOW AND WHY ANTI-VEGF THERAPY FITS INTO A DIABETIC RETINOPATHY TREATMENT PARADIGM

By Tarek S. Hassan, MD

CASE BACKGROUND
- A case of 67-year-old woman with a 15-year history of diabetes who was referred by her ophthalmologist for evaluation of bilateral proliferative diabetic retinopathy.
- The eye was largely asymptomatic, and the patient stated that she was unsure of why she was sent to my clinic.
- VA was 20/40 OD and 20/30 OS at the time of examination, and her hemoglobin A1C level was 6.8.
- On examination, some areas of neovascularization were evident, more pronounced in the right eye, and there was mild diabetic macular edema (DME) in each eye (Figure 1).
- There were areas of nonperfusion in each eye, more so in the right eye.

TREATMENT PLAN
- In the past, this is a patient we likely would have observed off therapy based on the presentation of mild DME.
- Other treatment options might have included panretinal photocoagulation or focal laser for the right eye.
- After discussing the options with the patient, a decision was made to start anti-VEGF injections in each eye.

CASE DISCUSSION
Nancy Holekamp, MD: It is evident that treatment options have expanded. Even with respect to anti-VEGF injections, it would have been reasonable to inject just in the left eye and observe the right eye. More options for treatment might mean that our conversations with patients are longer and more involved, but the expanded options really make that a worthwhile discussion.

Tarek S. Hassan, MD: After three ranibizumab (Lucentis, Genentech) injections, the neovascularization regressed in both eyes, and the mild DME resolved in each eye (Figure 2). VA improved to 20/25 in each eye, which represented a 2-line gain in Snellen acuity. The effect of anti-VEGF injections on the status of the retina is easily apparent on color fundus photographs and fluorescein angiography (FA) after only three monthly ranibizumab injections (Figure 3).

Arshad M. Khanani, MD, MA: What did you do long-term with this patient?

Dr. Hassan: Anti-VEGF injections have been continued, and I more than likely will start a treat-and-extend protocol, hopefully extending to every 3 to 4 months.

Nikolas J.S. London, MD: Will you repeat FA each time, looking for redevelopment of neovascularization to determine the interval?

Dr. Hassan: I will monitor for that. In general, I increase the interval by 1 to 2 weeks at a time, hopefully extending to several months. I do not repeat FA to look for neovascularization. That is something I look for clinically and then follow up with OCT to monitor for DME. I may occasionally obtain FA to assess my progress in controlling the neovascularization, but certainly this is not something that is needed frequently.

CONCLUSION
Overall, this patient is very happy with the way treatment is unfolding. This case demonstrated that we can introduce anti-VEGF therapy, even for patients in whom we typically might not think about using it, because of our ability to prevent progression of the overall disease. Observation would have been a reasonable approach, and in fairness, there might not have been any progression in the short term. But here, we are being proactive rather than reactive in managing this patient’s disease, which is an important shift in how we treat diabetic retinopathy.
What are the most important findings from this clinical study?

**Dr. Khanani:** Tie-2 is a transmembrane receptor expressed principally in vascular endothelial cells that promotes stability of the vasculature, but in patients with vascular diseases, including diabetes, Tie-2 is deactivated by increased levels of vascular endothelial protein tyrosine phosphatase or angiopoietin-2 (Ang-2), leading to leakage and pathologic angiogenesis. AKB-9778 is a small molecule that inhibits the intracellular catalytic domain of vascular endothelial protein tyrosine phosphatase. The TIME-2 study enrolled patients with DME to study subcutaneous AKB-9778, 15 mg given twice a day, with a sham intravitreal injection versus subcutaneous AKB-9778 plus a ranibizumab 0.3-mg injection versus a ranibizumab 0.3-mg injection plus subcutaneous placebo. The primary endpoint was change in OCT. In the study, there were no serious adverse events attributable to AKB-9778. As for the results, for the patients in the combination group, there was a statistically significant decrease in central subfoveal thickness, suggesting that restoring Tie-2 activity provided additional benefit compared to ranibizumab 0.3 mg alone (Figure 1).14 Interestingly, in the prespecified DR analysis, the rate of a ≥2-step improvement in DR severity scale was about the same among patients who received subcutaneous AKB-9778 alone in the TIME-2 study compared with ranibizumab alone, but importantly without the need for repeated intravitreal injections. Meanwhile, there was a greater rate of fellow eye improvement among those treated with AKB-9778 versus placebo (Tables 1 and 2).14 This is the other benefit of systemic treatment, that you can potentially benefit both eyes. Therefore, AKB-9778 is now being developed as a treatment for DR. The Time-2b study is ongoing and is evaluating the efficacy and safety of subcutaneous AKB-9778 treatment for 48 weeks in patients with moderate to severe NPDR.

**Dr. London:** Does using this molecule have potential to reduce anti-VEGF injection burden?

**Dr. Khanani:** That is unknown as of yet, but as we have discussed here, yielding regression of DR, or at least gaining stability, has every potential to result in an ability to extend the treatment interval.

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**Figure 1.** Combination treatment with AKB-9778 and ranibizumab resulted in a greater reduction in central subfoveal thickness (CST) compared to ranibizumab alone, with a continuing separation of the OCT curves at 3 months. Adapted from Campochiaro et al.

**Table 1.** Rate of ≥ 2-step improvement in DR severity scale after 3 months. Adapted from Campochiaro et al.14

<table>
<thead>
<tr>
<th>Study Eye</th>
<th>Fellow Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranibizumab (n = 34)</td>
<td>8.8%</td>
</tr>
<tr>
<td>AKB-9778 (n = 40)</td>
<td>10.0%</td>
</tr>
<tr>
<td>AKB-9778 + ranibizumab (n = 44)</td>
<td>11.4%</td>
</tr>
</tbody>
</table>

**Table 2.** Rate of ≥ 2-step improvement in DR severity scale in the fellow eye after 3 months. Adapted from Campochiaro et al.14

<table>
<thead>
<tr>
<th>Study Eye</th>
<th>Fellow Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo arm (n = 24)</td>
<td>4.2%</td>
</tr>
<tr>
<td>AKB-9778 (n = 78)</td>
<td>11.4%</td>
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**Dr. Singh:** There was no improvement in VA by month 3, but results for OCT outcomes were positive. What is your first impression of these short-term data?

**Dr. Holekamp:** It is short-term data, and the numbers are small. But it also suggests there is a window of opportunity for combination therapy. The subcutaneous delivery is interesting. Patients with diabetes are used to delivering medications and checking blood subcutaneously, so there is suggestion for good compliance. It is also something they do at home, so that reduces the need to be seen in our clinics. And so, we may reduce the injection burden, but there is still a treatment burden because of the need to monitor patients in the office.

**Dr. Singh:** Data from the BOULEVARD trial looking at faricimab (formerly RG7716, Genentech) may be worth considering.15 This is a bispecific antibody designed with both an anti-Ang-2 Fab fragment and an anti-VEGF-A fragment attached to an optimized Fc portion. At 24 weeks of follow-up among treatment-naïve patients, there was a +3.6 letter greater improvement among patients in the faricimab plus ranibizumab group compared to the ranibizumab alone group. Treatment was stopped at this point, followed by an observation period to assess for time to regression, which was defined as a 5-letter loss of VA or a 50-µm increase in central serous thickness. At the
end of 14 weeks, a higher proportion of treatment-naïve patients maintained vision after the last dose compared to those not treated with faricimab. A similar but less profound effect was noted among individuals who had been previously treated with anti-VEGF injections (Figures 2 and 3).

Dr. Holekamp: The difference between the treatment-naïve and the treated patients is interesting. It would seem logical that treatment-naïve patients might be earlier in the disease and, therefore, more responsive to both the anti-VEGF and the anti-Ang-2 factors. The durability is notable as well. In the past, we have been treating with anti-VEGF injections without really knowing what the rate of regression would be off therapy, so those data are important.

Dr. Hassan: Treating additional pathways appears to be synergistic with anti-VEGF agents. The pathophysiology of DR and DME is multifactorial, so addressing it in a multipronged approach is rational and likely to be more efficacious, whether that is with this molecule or another way.

Dr. London: Something that is interesting to me is to realize how high the bar has been set for anti-VEGF injections. A +3.6 letter difference with combination...
versus ranibizumab alone is not a large difference in clinical trials, but that kind of incremental improvement has meaning for patients in the real world.

**Dr. Singh:** Some additional data from this study were also presented showing a correlation between loss of VA and changes on OCT during the washout period in the treatment-naive group, but there was almost no connection in the previously treated patients.

**Dr. Khanani:** That sounds similar to what we saw in the crossover arm in RISE/RIDE.\(^4\) Delayed treatment means delayed control of disease, which leads to worse outcomes. Permanent photoreceptor damage is not uncommon among patients who have chronic DME where treatment with anti-VEGF agents was delayed. So, it’s not surprising that, even if the edema improves, VA may not necessarily improve. This is supported by data from DRCR.net Protocol U showing almost no VA benefit with steroids among patients treated long-term with anti-VEGF injections.\(^16\) For this molecule, the efficacy in the treatment-naive patients is impressive, whereas the data for the treatment-experienced population show us the need for early treatment to get the disease under control. If you look at the data for the treatment-naive patients in the BOULEVARD study, compared to ranibizumab 0.3 mg monthly, patients treated with faricimab 6 mg monthly had better VA, greater reduction in central subfield thickness, higher rates of DR regression, and longer durability during the off-treatment observation period. This clearly shows the benefit of Ang-2 inhibition and stabilizing the Tie-2 pathway in addition to blocking VEGF.

**CONCLUSION**

**Dr. Singh:** Our far-ranging discussion touched on many facets of using anti-VEGF injections for treating DR and DME. There is already one anti-VEGF agent approved for use in patients with DR with or without DME, ranibizumab, while a second, aflibercept, is currently being reviewed by the US FDA for this same indication—with an expected action date by May 2019.\(^17\) The data we have so far show us the potential to yield regression with disease severity. Using anti-VEGF therapy in this manner has been described like slowing a moving train. We cannot stop the disease with a single injection, but continued therapy over time slows or stops progression.\(^2,3\) This is, indeed, a whole new paradigm for treatment of DR with potential to intervene earlier. While we are at a stage when we do not have precise parameters for selecting appropriate patients and for making decisions about when to treat and when to adjust therapy, this is also not new territory for retina specialists: it was not that long ago that anti-VEGF agents were introduced into DME, and that rapidly became the standard of care for center-involving DME after we found answers to similar questions. What are some early-term impressions with this new treatment approach?

**Dr. Khanani:** PRP was the only treatment for decades, but we now have anti-VEGF agents as an option for our patients with DR. The efficacy of anti-VEGF agents in DR has been supported by several clinical trials. As far as
anti-VEGF therapy is concerned, there is strong rationale for use in patients with PDR, with a role for adjunctive laser. In terms of severe NPDR and earlier, there are very good data to support treatment, but in the real world, anti-VEGF use is still discretionary, and the decision needs to be individualized. As we gather more data, that may well change—and I would include in this the new studies on novel molecules addressing additional pathways in DR and DME pathogenesis.

Dr. Holekamp: The indication for using anti-VEGF agents in DR is an evolution rather than a revolution but nonetheless important. We do not want to be treating patients with DR in 5 or 10 years the same way we are now. Adding new approaches offers to improve outcomes, both anatomically and with regard to visual outcomes. There is some complexity, but as retina specialists, we should stay dynamic as the treatment approach evolves.

Dr. Hassan: The retina community now has experience from clinical trials and personal use with anti-VEGF agents in DR and DME, and this allows us to help our patients make truly informed choices about their treatment. Laser has proven highly successful, and some patients may opt for this approach. But in the interest of full disclosure, we should be educating patients about this alternative option. The data give us the confidence to educate patients about the potential for improved vision and stability of disease with repeat injections, and losing peripheral vision after laser is not something they have to risk. From a practical standpoint, it will be a matter of how it is integrated into one’s practice, although there is likely relevant experience in delivering these agents in patients with AMD and retinal vein occlusions from which to draw upon.

Dr. London: As retina specialists, we are not necessarily used to treating prophylactically, and we are much more attuned to addressing a problem after it occurs. Starting treatment after conversion to wet AMD is one example. With DR, we are talking about initiating treatment to prevent worsening of disease. That is going to take a slightly different mindset to be successful, especially for patients with NPDR who may not be symptomatic. Returning to the Protocol S data, about 25% of patients in the PRP group developed a vitreous hemorrhage. Essentially, if you are waiting for PDR to occur, you are willing to accept the risk of vitreous hemorrhage, whereas we saw in RISE/RIDE that the rate of vitreous hemorrhage is lower after anti-VEGF treatment. We should be cautious about comparing across studies, but I think this highlights that we owe it to patients to explain the differences between the treatment options. When I have done so in a very honest manner with my patients, I have found the vast majority would prefer to reverse their disease and would prefer to preserve their peripheral retina, their night vision, and their visual field.

Dr. Singh: Thank you, everyone, for your participation.

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Dr. Singh: Thank you, everyone, for your participation.
INDICATIONS AND USAGE

Macular Edema Following Vitreous Vortex Oclusion (RVO)

Macular Edema Following Vitreous Vortex Oclusion (RVO)

1. Neovascular (Wet)-Age-Related Macular Degeneration (AMD)

2. Macular Edema Following Vitreous Vortex Oclusion (RVO)

3. Macular Edema Following Vitreous Vortex Oclusion (RVO)

4. CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

4.2 Hypersensitivity

5. WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

5.2 Increases in Intraocular Pressure

5.3 Thromboembolic Events

5.4 Non-ocular adverse reactions with an incidence of ≥ 5% in patients receiving LUCENTIS are:

6.2 Clinical Studies Experience

6.3 Immunogenicity

6.4 Postmarketing Experience

7. DRUG INTERACTIONS

8.1 Pregnancy

8.2 Lactation

8.3 Females and Males of Reproductive Potential

8.4 Pediatric Use

8.5 Geriatric Use

9. PATIENT COUNSELING INFORMATION

10. ADVERSE REACTIONS

10.1 Injection Procedure

10.2 Serious adverse reactions related to the injection procedure have occurred in ≥ 0.1% of intraocular injections, including endophthalmitis and immunogenicity (see Indications and Usage).
INDICATIONS
LUCENTIS® (ranibizumab injection) is indicated for the treatment of patients with:
• Diabetic retinopathy (DR)
• Diabetic macular edema (DME)

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
• LUCENTIS is contraindicated in patients with ocular or pericocular infections or known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation

WARNINGS AND PRECAUTIONS
• Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis, retinal detachment, and iatrogenic traumatic cataract. Proper aseptic injection technique should always be utilized when administering LUCENTIS. Patients should be monitored following the injection to permit early treatment, should an infection occur
• Increases in intraocular pressure (IOP) have been noted both pre-injection and post-injection (at 60 minutes) with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately
• Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as fatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause)
• In a pooled analysis of Studies DME-1 and DME-2, the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg LUCENTIS, 5.6% (14 of 250) with 0.3 mg LUCENTIS, and 5.2% (13 of 250) with control. The stroke rate at 2 years was 3.2% (8 of 250) with 0.5 mg LUCENTIS, 1.2% (3 of 250) with 0.3 mg LUCENTIS, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg LUCENTIS and 10.8% (27 of 250) with 0.3 mg LUCENTIS; the stroke rate was 4.8% (12 of 249) with 0.5 mg LUCENTIS and 2.0% (5 of 250) with 0.3 mg LUCENTIS
• Fatal events occurred more frequently in patients with DME and DR at baseline treated monthly with LUCENTIS compared with control. A pooled analysis of Studies D-1 and D-2, showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg LUCENTIS, in 2.8% (7 of 250) of patients treated with 0.3 mg LUCENTIS, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg LUCENTIS and in 4.4% (11 of 250) of patients treated with 0.3 mg LUCENTIS. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded

ADVERSE EVENTS
• Serious adverse events related to the injection procedure that occurred in <0.1% of intravitreal injections included endophthalmitis, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract
• In the LUCENTIS Phase III clinical trials, the most common ocular side effects included conjunctival hemorrhage, eye pain, vitreous floats, and increased intraocular pressure. The most common non-ocular side effects included nasopharyngitis, anemia, nausea, and cough
• As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The clinical significance of immunoreactivity to LUCENTIS is unclear at this time

Please see Brief Summary of LUCENTIS full Prescribing Information on following page.

*The following clinical trials were conducted for the DR & DME indications: RISE & RIDE—Two methodologically identical, randomized, double-masked, sham injection–controlled, Phase III pivotal trials (N=759) that studied the efficacy and safety of LUCENTIS 0.3 mg and 0.5 mg administered monthly to patients with DR and DME at baseline. The primary outcome was the proportion of patients gaining ≥15 letters at 2 years. Protocol S—A randomized, active-controlled study that evaluated LUCENTIS 0.5 mg vs panretinal photocoagulation in DR patients with and without DME. All eyes in the LUCENTIS group (n=191) received a baseline 0.5 mg intravitreal injection followed by 3 monthly injections. Further treatments were guided by prespecified retreatment criteria. FDA approval was based on an analysis of the LUCENTIS arm of Protocol S. The primary outcome was mean change in visual acuity from baseline to 2 years.**

LUCENTIS 0.3 mg is recommended to be administered by intravitreal injection once a month (approximately 28 days).1

DME, diabetic macular edema.