AN UPDATE ON THE LATEST CLINICAL TRIALS IN DIABETIC MACULAR EDEMA

A review of outcomes from recent studies on DME and how those findings impact clinical treatment patterns.

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INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS
EYLEA® (aflibercept) Injection is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR) in Patients with DME.

CONTRAINDICATIONS
EYLEA® (aflibercept) Injection is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

WARNINGS AND PRECAUTIONS
Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.

Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

ADVERSE REACTIONS
Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.

The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

Please see brief summary of full Prescribing Information on the following page.

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5.3 Thromboembolic Events. There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 3.2% (12 out of 382) in the control group compared with 2.9% (8 out of 287) in the control group. For the first 6 months of the RVO studies, there were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in the full prescribing information section or labeling:

- Endophthalmitis and retinal detachments
- Increased intraocular pressure
- Thromboembolic events

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice. A decision must be made whether to discontinue nursing or to discontinue the drug and take the infant to a hospital. Breastfeeding should not be discontinued if this drug is determined to be essential to the patient's care and no satisfactory alternative has been established.

8.1 Pregnancy.

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For the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment.

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By 2035, it is estimated that close to 600 million people worldwide will be living with diabetes, a marked increase from the 382 million in 2013. Yet, according to the American Academy of Ophthalmology, upwards of 40% of people with diabetes forego annual screenings for diabetic retinopathy. The current gold-standard for the management of diabetic macular edema is anti-VEGF agents. However, treatment frequency, evaluation methods, and identifying treatment failure/nonresponders remain a complex issue for clinicians. Moreover, diabetic patients are already at a heightened risk of infection, so concerns about endophthalmitis are warranted when considering treatment regimens, as are concerns about postoperative worsening of macular edema, and systemic exposure to anti-VEGF agents.

Retina Today gathered a group of leading retina specialists to discuss outcomes from recent clinical studies on diabetic macular edema, and to discuss how those findings impact our treatment patterns.

—Peter K. Kaiser, MD, moderator
Peter K. Kaiser, MD: We all know the Diabetic Retinopathy Clinical Research Network (DRCR.net) has published results from several clinical studies this past year. Two in particular are interesting, Protocol S and Protocol T. Both examined different treatments for patients with DR. Protocol T evaluated the anti-VEGF drugs for center-involved diabetic macular edema (DME), and Protocol S comparing outcomes between intravitreal ranibizumab and panretinal photocoagulation in proliferative disease. Let us explore in more detail how these studies have impacted our clinical care.

When we look at the patients enrolled in Protocol T, are those the same patients who are coming to your clinics? In other words, do your typical patients meet the same inclusion criteria?

Elias Reichel, MD: In Protocol T, subjects had to have center-involved DME. Baseline vision could be anywhere in the range of 20/32 to 20/320. They did not have to be treatment-naive, but could not have received any anti-VEGF treatment within the previous 12 months. Subjects had to have controlled diabetes as well, and the median hemoglobin A1c at baseline was around 7.7.

Nancy M. Holekamp, MD: Also, the DRCR.net study group make a point of stating in the conclusion that because their eligibility criteria were broad, and that enrollment was across 89 community and university-based sites, the results are likely generalizable to patients in our clinics. I disagree, not because our patients are different, but because how the patients enrolled in Protocol T were treated. And that has to do with the algorithm. If we look at the year 2 data, patients were seen in the office on average of 10 times. I do not think that is an accurate assessment of what occurs in the everyday world of our clinics. A protocol-driven treatment algorithm certainly lends itself to more visits and (likely) more treatments.

K. Bailey Freund, MD: In terms of the range of visual acuity, glycemic control, and compliance with follow-up visits, the patients enrolled in Protocol T are fairly similar to those I care for in my private group retina practice in New York City. However, many of the patients I see with residents and fellows in a hospital serving a large urban indigent population would not meet these inclusion criteria.

Dr. Kaiser: Protocol T did not exclude patients if they had prior treatments for DME, including focal/grid laser, anti-VEGF injections, panretinal photocoagulation (PRP), intravitreal corticosteroid, peribulbar corticosteroid, or vitrectomy, but did mandate treatments could not have been within the previous 12 months. The treatment protocol used is unique, and I would argue there are many of us who do not follow that protocol or even really understand it. For example, the treatment protocol is much more aggressive than the as-needed (prn) treatment protocol many of us use in clinical practice. How would you describe the treatment protocol used?

Szlárd Kiss, MD: The treatment protocol in Protocol T is fairly complex, and sort of mirrored what was done in Protocol L. In Protocol T, essentially laser was withheld until month 6, and starting at the 24-week visit, injections were withheld if there was no improvement or worsening after two consecutive visits, but treatment was re-initiated if the visual acuity letter score of central subfield thickness worsened. During those first 6 months, anti-VEGF therapy was given if there was persistent macular edema and/or some improvement on optical coherence tomography (OCT). Laser photocoagulation was prohibited in those first 6 months, but then could be used if the eye met the definition of “treatment failure.”

At 2 years, about 40% of the aflibercept (Eylea; Regeneron), 65% of the bevacizumab (Avastin; Genentech), and 52% of the ranibizumab (Lucentis; Genentech) groups ended up receiving focal laser. The treatment with the anti-VEGF therapy was somewhat similar to the first 6 months, although the re-injection criteria were a little bit looser to allow for more investigator discretion of focal laser administration. Let us not overlook the fact that these patients were relatively well controlled with hemoglobin A1C levels around 7, and they came in every 4 weeks during that first year. Between 85% and 90% of the original 660 patients completed the study visits to year 2, which, for a diabetic population that now has complications from their diabetes, is somewhat unusual in the real world. At least compared to what I see in my clinic.

Dr. Kaiser: The protocol was interesting to me in that, if the OCT was essentially unchanged between visits, but the patient had improved vision, re-treatment with another injection was warranted, even when the OCT was dry. Is this something that you do in clinical practice? And what do you think about that part of the protocol?

Darius M. Moshfeghi, MD: I am still mystified by the protocol, having read both of the papers multiple times. My treatment regimen varies considerably: If my patient has center-involving foveal thickness, I will offer them four treatments and then re-evaluate after those four treatments. I will not perform an OCT until those initial four treatments are complete.

I cannot fault the DRCR.net for the treatment protocol. Is it any better or worse than what I have done? No, it is just different. We need to evaluate the results. Where I vary considerably from the DRCR.net is that I have not performed focal macular photocoagulation for DME since 2009, with rare exception—patients who have very focal disease or very external disease. But, by and large, my patients are not being treated with laser. And I think that if you look at the anti-VEGF results in these groups, by and large, it was very successful.

Dr. Freund: I typically prioritize structural OCT findings over visual acuity when making re-treatment decisions, but during the initiation of intravitreal anti-VEGF therapy I will put more emphasis on vision (Figure 1).

If visual acuity is still improving, I may give another injection even though the maximal anatomic response appeared to have been reached at the prior visit. I want to be sure I am not depriving my patient of a further visual benefit, and I believe that more aggressive treatment at initiation will result in fewer treatments later on. For me, the ability of anti-VEGF therapy to reduce overall diabetic retinopathy
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severity supports this approach, as resolution of edema is not the sole treatment benefit.

**Dr. Kaiser:** Has anyone else stopped using focal laser in DME? Or are there any laser believers in the group?

**Dr. Kiss:** I have not routinely performed focal laser for my DME patients since 2010—anti-VEGF therapy works extremely well in nearly all patients. Before turning to focal laser, I may switch to another anti-VEGF agent, or give an intravitreal steroid, such as dexamethasone intravitreal implant 0.7 mg (Ozurdex; Allergan). As a result, it is actually becoming more difficult to achieve the required focal laser numbers for our residents.

**Dr. Freund:** We should keep in mind that about half of all patients in Protocol T received thermal laser with the highest percent (61%) in the bevacizumab group and the lowest percent (41%) in the aflibercept group. As laser was part of the study protocol, it is impossible to know how the results would have changed if laser had not been given. Personally, I believe there is still a limited role for focal thermal laser, but I will admit this assertion is based more on clinical experience than clinical trial data. Targeting a few discrete extrafoveal microaneurysms in an attempt to avoid continuous monthly injections seems reasonable to me.

**Dr. Kaiser:** In Protocol T, there was actually a very high rate of laser use especially in the bevacizumab-treated patients. Does anyone think that laser may have affected outcomes?

**Dr. Kiss:** That was the real question after year 1, whether the laser itself was doing harm. I think the best analysis was before week 24. The results start diverging, especially in the 20/50 group, even before focal laser was used. The differences start to emerge after one injection, but definitely after four or five. So to answer your question, it is not clear. I think about the results of Protocol I, where there was some indication that, at least at year 1, we were leaving vision on the table when evaluating prompt versus deferred laser versus only ranibizumab injections. But that was a different population with a different treatment protocol. In Protocol T, the visual acuity outcomes among the three anti-VEGF agents start to diverge even prior to the first use of focal laser. Whether not allowing focal laser and just continuing with the anti-VEGF injections alone would have resulted in even better vision outcomes remains to be debated—Protocol T did not give us an answer to that question.

**Dr. Holekamp:** I am glad Dr. Kiss mentioned Protocol I. The prompt and deferred laser groups with the ranibizumab-treated arms was really the first time we questioned whether or not laser could be harmful to our patients. If clinicians are using laser as an adjunctive treatment, I think we need to use a gentler, kinder type of focal laser treatment and bear in mind using a laser may not always be necessary and, in some cases, could limit visual acuity benefits.

**Dr. Moshfeghi:** When laser is used these days, it is very rare for it to be used on center-involving DME, for extrafoveal lesions, or for those with circinate exudates. But there is still a role for focal laser. Just not for the center-involving macular edema. We need to reiterate that is a different definition than the ETDRS and what was used to enroll the Protocol T participants, where it appears using anti-VEGF is more beneficial.

**Dr. Kaiser:** That brings up another point. The laser protocol used in Protocol T is different from what I do. What was the re-treatment protocol for laser, once laser was started?

**Dr. Reichel:** Most of the patients enrolled had undergone previous laser. So it was at the investigators’ discretion to give more laser after the first 6 months. The investigators were using conventional laser, not necessarily lasers that use subthreshold protocols that we may be comfortable using. Personally, I am somewhere in the middle and use laser about 20% to 30% of the time at 6 months. I would say about 15% to 20% of patients who have center-involving DME are not served by anti-VEGF alone and require alternative therapies that include laser and corticosteroids.

**Dr. Kaiser:** In year 1, the result of the DRCR.net Protocol T showed a pretty striking difference between drugs overall and especially in certain subgroups. What are your thoughts on that?
Dr. Holekamp: In year 1, the results essentially showed that baseline visual acuity was a major determinant of outcome.\textsuperscript{17} If the patient’s baseline visual acuity is 20/32 or 20/40, all of the anti-VEGF agents were essentially equivalent. Now, I want to emphasize that we saw good visual acuity improvement when patients had nine or 10 injections that first year.

But in patients with a baseline visual acuity of 20/50 or worse, we really saw the results start to separate, as it appeared aflibercept was better in this group to both ranibizumab and bevacizumab.\textsuperscript{17} When we looked at the number of patients who gained at least 15 letters, the differences were quite striking: 67% of the aflibercept group, 41% of the bevacizumab group, and 50% of the ranibizumab group.\textsuperscript{17} I think that matters very much for these patients who may still be working and driving and need good vision.

Dr. Kaiser: Did the year-1 results change your treatment preferences?

Dr. Kiss: Absolutely it did. What often gets missed when we are discussing these results is just how effective anti-VEGF therapy is in an independently run study (independent from pharma industry input). The DRCR.net Protocol T\textsuperscript{17} validates the pivotal drug company-run studies used to secure Food and Drug Administration approval for ranibizumab and aflibercept. When we analyze the overall cohort in year 1, it really was in those patients with a baseline of 20/50 on an ETDRS chart where the differences were most dramatic. There was almost a 19-letter gain in the aflibercept arm compared to a 14-letter gain with ranibizumab and about a 12-letter gain for bevacizumab.\textsuperscript{17} In my practice, the shift towards using aflibercept was significant. I was already skeptical and hesitant about using bevacizumab, especially due to issues surrounding compounding pharmacies and the compounding process. With the 1- and 2-year results of Protocol T, I would be hard pressed to use compounded bevacizumab when I can give ranibizumab or aflibercept.

Dr. Moshfeghi: The year-1 results did not really change my treatment protocols. I was using aflibercept and bevacizumab and had eliminated ranibizumab mostly because of the confusion surrounding ranibizumab for DME. I do not have access to a lot of technicians—and sometimes they would give me the wrong dose of ranibizumab. It is easy to use either bevacizumab for patients who cannot afford on-label, or when we do not know what the insurance status is, or aflibercept for those other patients.

Dr. Kaiser: In my mind, one outcome that is not often discussed with Protocol T year 1 is that the visual acuity results at month 12 were also based on baseline retinal thickness. What are your thoughts on that?

Dr. Reichel: So when central retinal thickness (CRT) was greater than 400 μm, there was definitely a benefit in the same order as expected with visual acuity favoring aflibercept over the other anti-VEGFs, and when CRT was less than 400 μm, there was not a clear benefit.\textsuperscript{17}

Dr. Kaiser: I think that is a key point because that subgroup analysis was irrespective of baseline visual acuity based solely on OCT thickness. What do you think about the OCT results from year 1?

Dr. Reichel: The question is, how dry does the retina need to get, and are we overdoing it? Are we underdoing with certain drugs? I do not know if we have the answers to that.

The correlation with visual acuity is important—historically the correlation coefficient is weak between visual acuity and OCT. But in the Protocol T studies,\textsuperscript{21} it is actually rather good.

Our instinctual idea is that the drier the retina, the better. And maybe in DME that is correct to a certain degree. In neovascular age-related macular degeneration (AMD), leaving a bit of subretinal fluid on the table a year or 18 months later is not as detrimental. But the 2-year DRCR.net Protocol T results show a drier retina is somewhat correlated with better vision.\textsuperscript{18}

Dr. Kaiser: For patients with vision worse than 20/50, about 70% of patients with aflibercept had a central retinal thickness less than 250 μm at month 12, compared to about 55% in the ranibizumab group, and about 40% in the bevacizumab group.\textsuperscript{17} That tells us that the patients in the aflibercept group could not improve all that much more since their retinal thickness was essentially normal.

That leaves about 30% who could still improve after year 1. So, in my opinion, the OCT results were predicting what was going to happen in the second year. Because those patients, theoretically, were not going to suddenly improve visual outcomes, and the other groups, theoretically, could catch up as they dried the retina to the same extent as aflibercept.

Dr. Holekamp: Are you referring to a “ceiling effect” for aflibercept when analyzing the outcomes?

Dr. Kaiser: Yes, I think there is a ceiling effect where retinal thickness cannot improve to beyond normal. And where the vision is, at that point, is what you are going to get, because that is not going to improve either.

Dr. Holekamp: My perspective is a bit different: patients may have good vision and relatively thin retinas, but they still have center-involving DME or they would not be in Protocol T. But these same patients also likely have a predominantly VEGF-mediated type of DME and they did well in year 1.\textsuperscript{17} What is really separating the agents is, what we used to call “diffuse DME,” those patients with extremely poor vision and extremely thick retina. And that is where the year-1 data separated the anti-VEGF agents, and aflibercept came out on top (Figures 2 and 3).\textsuperscript{17}

Dr. Kaiser: Do you think that there is a difference in the molecules? Or a difference in their mechanism of action? How can we explain the differences we saw between the drugs in year 1?

Dr. Kiss: Sometimes we forget that not all anti-VEGF agents are the same. The obvious example here is pegaptanib (Macugen; Eye Tech)—the first of the anti-VEGF molecules—how many of us still use it? So when we are looking at the pharmacokinetics and the binding...
kinetics of aflibercept, there may be some differences compared to ranibizumab or bevacizumab.

In AMD, we saw a difference in the drying effect, although visual acuity outcomes were closer between bevacizumab and ranibizumab in CATT.\textsuperscript{22,23}

With Protocol T, there is a distinct difference in drying after week 12, both in the overall cohort and in the 20/50 or worse group.\textsuperscript{17}

Just a comment here on OCT: Ultimately, my patients care about vision and we have an agent that dries the retina and improves vision at 1 and 2 years significantly better than a third agent (bevacizumab). As Dr. Reichel pointed out, it is nice to see the correlation but ultimately it is the visual acuity I go by after seeing the results from year 1.

**PROTOCOL CHANGES**

**Dr. Kaiser:** Before discussing year 2 in detail, it is important to understand how the protocol changed.

**Dr. Moshfeghi:** Year 2 suffers from a lot of the same problems as other trials: Follow-up was less frequent. And it was not uniform in this study. Dr. Holekamp alluded to this earlier when she originally addressed the issue. In year 2, follow-up could range anywhere from 4 to 16 weeks\textsuperscript{18} and that is not how I manage my patients. Sixteen weeks is a long time for patients that you are actively treating for DME. For me, that makes year 2 very difficult to interpret. It does reinforce that anti-VEGF treatment is a powerful strategy to treat DME. But I do not know how much we can interpret if a 4- to 16-week follow-up is supposed to be the best way to manage our patients.

**Dr. Kiss:** With a median number of follow-ups of around 10,\textsuperscript{18} I would argue these patients are coming back more frequently than most of my real-world patients. After five injections or so, most of my patients no longer want to return to the office. We are still trying to determine why. I was impressed by how many times the study patients came in for re-evaluation.

**Dr. Moshfeghi:** I disagree. I will inject four times, re-evaluate, do another four injections and then every once in a while I give patients a 3-month reprieve, no matter how they are doing. And then I bring them back. That break serves to let them catch their wind, so to speak, before we get back into the battle.
These are chronic patients. Even if they get their diabetes under control, I believe they are going to continue to have relapsing DME because the damage has already been done. So we are going to be fighting this war for the rest of their lives.

Some of my patients I have been treating for more than 7 years, and it was different when we were using laser. We were not really expecting any visual acuity benefits. Anti-VEGFs give patients the visual acuity benefit that makes us want to bring these patients back aggressively. But at some point you have to back off; I do not feel comfortable sending them out 4 months. With Protocol T, the median may have been 10 visits, but there were patients who were seen monthly and those who were out to 4 months. That throws up a red flag for me. I like a very standard follow-up and evaluation. If you look at the break points in year 2, something happened between weeks 68 and 84. We do not know what that is yet.

Dr. Kiss: But that is what we are trying to get at in terms of OCT, right? That aflibercept is such a good drying agent that we saw results much earlier. By year 2, ranibizumab caught up to aflibercept, and I think there is more to go.

Dr. Kaiser: To be fair to the protocol, in year 2, the follow-up interval was based on whether patients had reached a point where they no longer needed injections because the retina was dry and they were maintaining vision. There was a whole set of criteria to determine when people needed to return.

Dr. Holekamp: I treat my patients the same way as Dr. Moshfeghi: an initial series of four injections, re-evaluation, four additional injections if needed. And I give people short breaks from time to time because the treatment schedule can be intense. But what is critical about the year-2 study findings is that patients could be extended up to 4 months. That translates to three visits in the second year, but essentially no one received extended treatment (one patient in the aflibercept arm, four in the bevacizumab arm, and two in the ranibizumab arm). To me, that shows that these diabetic patients need continued follow-up.

We also need to remember these are study patients who tend to be more compliant with follow-up compared with our clinic patients in the real world.

What I thought was most impressive is that in the first year of anti-VEGF therapy, the lines go straight up in the first 3 to 4 months, and then there is still some gradual improvement. In year 2, the follow-up was relaxed, but the visual acuity results across the board were maintained. And they were maintained because people had an average of 10 follow-up visits. I want people to read Protocol T and think these patients were followed closely in the second year and that is how we maintained the visual acuity benefits we achieved in year 1. And that visual acuity at baseline did not matter.

Dr. Kaiser: Dr. Reichel pointed out we are seeing a stronger correlation with loss of fluid and improved visual acuity. What Dr. Holekamp is alluding to is that stronger follow-up results in better visual acuity outcomes. But, what we do not know is whether the patients who are receiving continued injections despite having fluid is what is keeping them in the game and helping maintain their vision. When you look at the whole protocol, for me it is difficult to apply it to my patient population. Protocol T has a regimen that I do not follow.

Dr. Holekamp: That is a very fair statement. If patients do not see the doctor on a regular basis, they are not going to receive timely or appropriate anti-VEGF treatment if needed. During the second year, patients were seen on average 10 times, but only received five or six injections. So even when they were not treated, they were being monitored.

Dr. Kaiser: It is unfair to the protocol to say that the patients were not being seen frequently enough. They were actually seen more frequently than many of us see our own patients. But there were some pretty big differences in the way patients were monitored, versus the way a lot of clinicians follow patients.

YEAR 2 RESULTS

Dr. Kaiser: What were the top-line results in year 2 of DRCR.net Protocol T?

Dr. Reichel: The main top-line result is things evened out at the 2-year point. Statistically, there was no difference among the drugs. The reality is that it is an oversimplification, and everyone has sort of alluded to that here. The primary endpoint showed a difference between aflibercept and bevacizumab.

For 18 months, there was a difference between the three drugs. Only at the very end did things narrow, which leaves us asking ourselves if we want immediate gratification or delayed gratification. I think we all want to give the best visual acuity as soon as possible to our patients. It seems somewhat counterintuitive to me to note that after 2 years it is all balanced and equal. I want to know about the first 6 months of the first year.

Draw a line at the 12-letter improvement to see when each drug reached that benefit: for aflibercept, it was 3 months, for ranibizumab it took about 7 or 8 months, and bevacizumab took a bit longer than that. That is the way I am evaluating this study.

Probably the most important finding, as Dr. Holekamp pointed out, is that while patients averaged 10 injections the first year, they averaged five in year 2. That gives us a guideline of sorts of how to treat these patients. They need aggressive therapy in the first 6 months, maybe not as aggressive in the second 6 months, and then relaxed a bit in the next year. I may still see those patients monthly in the second year, or I may see them every other month to maintain their visual acuity. Either regimen is fine.

Dr. Kaiser: There is a very dramatic difference in the area under the curve between the three drugs, even at 2 years. I agree that we are leaving vision on the table if we wait to catch up at year 2. A lot of these patients are busy working patients who do not necessarily want to come in as many times as a patient in a clinical trial is willing to come in. Did your treatment paradigm change in how you treat your patients in your own practice after the year-2 results were published?
**Dr. Kiss:** I interpreted the top-line results of the 2-year data a little bit differently than Dr. Reichel. It is hard to argue when you look at the overall patient population that bevacizumab is as good as the other two drugs, especially when you add on the area under the curve. Year 2 changed my thinking in that ranibizumab is back in play. Let us say we take the cost off the table, and the visits off the table. I approach my patients by telling them what is best when those other factors are not considered. So if my patient is 20/50, do they want to gain 18 letters at 2 years with aflibercept or 16 letters with ranibizumab and 13 with bevacizumab? We have an agent that dries quickly in aflibercept but ranibizumab is a slower agent that catches up over 2 years. It is a viable option. I do wonder if ranibizumab 0.5 mg would have made a difference. In Europe, they do not use the 0.3-mg version. So the question becomes “are we giving enough ranibizumab early on?” It is a somewhat moot point in the United States, but my interpretation is that the results are not all equal. Regardless, bevacizumab was third.

**Dr. Kaiser:** That is a very important point, that outside the United States, there are many countries where the argument is about whether US retina specialists should be using ranibizumab 0.5 mg for DME. Dr. Kiss, do you think there is a difference in outcomes between the 0.3-mg and 0.5-mg dose?

**Dr. Kiss:** There may be. RISE and RIDE did not show that difference and the curve overlapped between 0.3 mg and 0.5 mg. The 0.5-mg dose is almost doubled so there may be some greater drying effect in patients outside of RISE and RIDE. It is not beyond the realm of possibility.

**Dr. Moshfeghi:** I would like to reiterate what Dr. Reichel originally said—a drier retina results in better vision. But that effect occurred a little late, somewhere between 68 and 84 weeks, when ranibizumab started to really catch up to aflibercept. When we evaluate the OCT effect, aflibercept dipped down at that time, whereas ranibizumab held steady on OCT. It makes me wonder if this was not just a random effect.

**Dr. Holekamp:** Were patients and doctors unmasked after the first year?

**Dr. Reichel:** Investigators and study coordinators were not masked. Participants were masked until the primary results were published and then they were unmasked.

**Dr. Kaiser:** It was not masked in year 2 but if you look at the treatment assignment, remarkably, patients stayed within their treatment groups for the most part. Few of the bevacizumab patients wanted to switch, which, if you read the year-1 results you might think they would. Yet that just did not seem to come to fruition.

**Dr. Moshfeghi:** I think that actually highlights a major point of the study, which is that all anti-VEGF agents resulted in improvement in visual acuity outcomes. And, when patients are demonstrating an improvement, they are likely to stick with what got them there. They do not realize how much better it might have been. They just recognize that their vision improved. It is hard to move away from a winner.

**SAFETY DIFFERENCES**

**Dr. Kaiser:** In both years, there were differences between the drugs in terms of safety. Were these relevant?

**Dr. Reichel:** Five years ago, I stopped wanting to talk about safety. The studies are too small, we are not going to find anything, there is no uniform agreement among the studies, and we cannot draw any conclusions. My conclusion is that the anti-VEGFs are very safe and I am not concerned about Anti-Platelet Trialists Collaboration (APTC) signals, given the number of treatments thousands of retina specialists have done around the world on millions of patients. If we were really seeing a significant safety issue, we would know about it based upon our clinical experience.

**Dr. Kiss:** I second that. You make a great point.

**Dr. Holekamp:** If the question is whether there was a calculated safety difference when you looked at the APTC signals in ranibizumab compared to the other two groups, year 2 results indicated a slightly higher risk, a slightly higher rate of events. There were substantially more nonfatal strokes in the ranibizumab arm than in the aflibercept arm, but during the post-hoc analysis the authors noted that history of stroke was also substantially higher in the ranibizumab arm. So even with randomization, some imbalances can occur. I credit the authors who correctly concluded that we have so much safety data on ranibizumab and the signal is not really seen elsewhere. Clinically we should not place too much emphasis on the findings.

**Dr. Kaiser:** Exactly. We can take these points from the data and agree that there is a threefold higher risk of an APTC event with a previous myocardial infarction, but I also agree that this was just a statistical anomaly. We have had plenty of comparative studies as well as individual studies to suggest that there really is not any safety difference when it comes to APTC events between any of these drugs.

**Dr. Reichel:** What really convinced me was the Protocol I control group data. That group had no anti-VEGF and the APTC events were numerically higher (13%) than they were for ranibizumab in Protocol T (12%).

**Dr. Holekamp:** We cannot forget that these are diabetic patients. They have DME, which makes them sicker diabetic patients than those without DME. They are “vasculopaths,” which makes them prone to these types of issues.

**Dr. Moshfeghi:** We need to be careful because we are disputing data that comes back simply because we cannot explain it. Ranibizumab is noninferior to aflibercept at the 24-month interval, but there is a trend where aflibercept is continuing to improve and...
dehydrate the retina.18 Yet we are blithely accepting that, despite anatomic data that seems to disagree.

What we really need to do is take a step back and realize there are interactions occurring that we just do not understand yet. It is entirely possible that the upswing in the ranibizumab arm toward the end was entirely due to chance.

**Dr. Holekamp:** Excellent point and one of the limitations of having a single study. That may be one of the greatest rationales for why the Food and Drug Administration always requires two parallel, concurrent registration trials for drugs. In the end, you would like to see these things be reproduced in two studies. Protocol T is just a single study.

**Dr. Moshfeghi:** For the record, I also believe that all the drugs so far, based on all the data, are essentially, equally safe.

**FINAL THOUGHTS**

**Dr. Holekamp:** The really big message from the Protocol T study findings, both year 1 and year 2, is that these patients required a lot of injections.17,18 Anti-VEGF agents are not magic, they are pharmacology. In year 1, patients needed nine or 10 injections to achieve good visual acuity improvement. In year 2, they required five or six injections. We know our real-world clinics do not echo those numbers. It is a wake-up call to all of us to follow diabetic patients closely, and lean more toward treating than not treating if we want to get maximal visual acuity benefit for our patients.

**Dr. Reichel:** It is very exciting data for patients who have 20/40 or better. I think it is reasonable to be agnostic as to which drug you use. I think for patients with poorer vision, it is reasonable to consider aflibercept, especially given the robust visual acuity results that you see ongoing for more than a year. These patients need to be aggressively followed and they need to be aggressively treated early on in their disease, and there is some relaxation that can occur in year 2.

**Dr. Kiss:** I think this is the nail in the coffin for laser as first-line therapy for center-involving DME. Anti-VEGF therapy is first-line treatment, and it appears to be safe, and it gives you visual acuity improvement if we are vigilant in follow-up and vigilant in injections, especially in the first year after initiation of treatment.

**Dr. Moshfeghi:** Early and often. You have got to have the long conversation at the beginning of treatment with these patients. Tell them you are looking at a 12- to 24-month time period during which the treatment will be very intensive. Fluid does not equate with good visual acuity, and in the first year we should not expect a completely dry retina. But we have to be aggressive in treating it, and continue being aggressive in year 2. If you can only use bevacizumab, you are going to get decent results. But the results will be much better with aflibercept or ranibizumab. Safety does not appear to be a concern, and this study definitely hints that anti-VEGF is a good monotherapy treatment.

**Dr. Freund:** I agree that early treatment of center-involving DME with frequent anti-VEGF injections appears to be a winning strategy for obtaining optimal visual outcomes. Fortunately, all three agents appear capable of improving visual acuity in these patients, but there were important visual and anatomic differences observed between agents. Also, we should keep in mind that the inclusion of thermal laser in the Protocol T treatment regimens confounds a direct comparison of how the three anti-VEGF agents would have performed as monotherapy. While many retina specialists, including myself, feel that the addition of thermal laser may be of questionable benefit for eyes like those enrolled in this study, its inclusion in the protocol prevents one from being able to make this conclusion based upon these results.

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**References:**

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