Anti-VEGF and the Eye Course # 40041

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**COURSE DESCRIPTION:**

Intravitreal Anti–VEGF injections have a wide range of applications for retinal disease, including Age–Related Macular Degeneration, Diabetic Retinopathy, and Retinal Vein Occlusions. This course will teach you how to manage these retinal conditions. You will learn the evidence for when to refer and the effectiveness of Anti–VEGF.

**LEARNING OBJECTIVES:**

- Discuss low vision as additional treatment
- Understand AMD, diabetic retinopathy, and retinal vein occlusions
- Discuss effectiveness of Anti–VEGF
- Develop a referral strategy
- Highlight benefit through case study

The course begins on page 2.
Hello, and welcome to Pacific University Online Continuing Education. My name is Anthony DeWilde, and I am an optometrist at the Kansas City VA Medical Center where I specialize in Low Vision Rehabilitation and Ocular Disease. What I’m going to talk about for the next hour or so is Anti-VEGF and the eye. This is an incredibly important topic now, since the advent of Anti-VEGF treatment for the eye. We’ve had a lot of breakthroughs with this, including how we can utilize it; specifically, now we can utilize it on vein occlusions in addition to macular degeneration. In addition to that, we also are treating diabetic complications with it. What I want to do today is walk you through those three diseases, talk you through specifically how this affects the eye, and how we as optometrists are going to utilize this in our referral strategies and our patient education.

I have three goals for today. The first is to talk about macular degeneration, diabetic retinopathy and vein occlusions. I want you to have a clear understanding of how we are diagnosing these, and what we are going to see in the eye. We are going to develop a referral strategy – how bad does the vision have to be, or what signs are we looking for in order to refer these patients. Finally, let’s talk about evidence regarding how effective Anti-VEGF treatment is. Once we know how effective it is, we can have a very good conversation with our patients about what to expect. What are the side effects, how effective is the medication, how many injections should they expect, etc. Therefore, when they move forward, they can make an informed decision as far as treatment? It’s very common for me to see patients that just flat-out refuse the treatment. They don’t feel that it’s beneficial enough, or they don’t really want to have an injection into the eye. If you can have those good conversations with patients to tell them what to expect, then once you refer to the retinal specialist, the patient will have a much clearer idea.

Anti-VEGF

Let’s start with what is VEGF. VEGF stands for Vascular Endothelial Growth Factor. This is a very important part of development. In fact, in embryological development, it helps us develop our vascular supply. Collateral development is also supplied by this VEGF, specifically collaterals in our carotid artery system, coronary artery system, etc. and it is very important to have this VEGF. If we don’t have it, if for some reason it is suppressed, we may not get full recovery, and in embryonic development we may not get a full-term birth.

We also know that VEGF is important in the growth of new blood vessels, especially in ischemic diseases like diabetic retinopathy and like vein occlusions. It seems to be propagated in AMD as well, though we are not thinking of it as much as we do in an ischemic disease. Thus, we can see where the appeal is in treating people with Anti-VEGF, where we can stop these new blood vessels from growing, because often times these new blood vessels bring about problems.

In 1994, we found that VEGF was increased in patients who have hypoxia. Our patients at the time were likely mice and different lab animals. Then we were seeing that in humans in the 2000’s that Anti-VEGF could be used to treat certain tumors. The type of tumor we were finding benefit in was the kind that
had feeder vessels. Specifically in the colon, it’s common to have feeder vessels for these tumors, and if we could suppress that, then we could suppress the growth of the tumor.

In 2006 it was found that Anti-VEGF was actually beneficial for wet AMD in the form of ranibizumab, or Lucentis. That was some of the original trials that came out for this, showing benefit to the eye. I don’t know how they decided to use something for the colon for tumors in the eye, but whomever did that was genius, and it turns out it has been very advantageous for our patients in certain ocular diseases.

The big way we are getting this into our patient’s eyes is through an intra-vitreal injection. (Fig 1) As painful and horrible as this looks, thankfully, most patients are not complaining of complications from this. We will talk about that more, later on. Trying to sell this to patients can be somewhat of a hard sell – when talking about injections into the eyeball, most patients will cringe at the thought of that. To be quite honest, I cringe at the thought of that, too.

This is, for now, how we get Anti-VEGF into the eye. Hopefully at some point we can get some sort of sustained-release medication into the eye, whether that is through surgery or injection, I don’t know. Maybe some sort of topical medication that can penetrate through to the posterior segment. Those are all being explored, but at the moment, nothing is FDA approved.

We have three complications we are going to talk about today: Macular Degeneration, Diabetic Retinopathy, and Vein Occlusions. Let’s start with Macular Degeneration (AMD).

Macular Degeneration

In any eye disease I think about, I like to think about what I call the ‘Threats to Vision.’ What are the things of AMD that could lead a patient to have long-lasting vision loss? When you think about AMD the two big ones are atrophy of the macula, and neovascularization of the macula. While commonly we will see RPE changes or drusen, those do not always cause vision loss. They are definitely signs we see, but we may not be seeing complications from those. They are just things that we are noticing, and that give us an idea of the risk of future complications.

Figure 2 shows what atrophy looks like in the back of the eye. This specifically is typically what is commonly called Geographic Atrophy. You can see centrally it’s got a lot of thinning. What we are seeing poking through there is the choroid – essentially we have an open window to the choroid underneath. Surrounding that, we will see some small RPE changes and drusen, but if it gets this bad, patients can often have very bad central vision loss and central scotomas.

The main complication we are going to talk about today is neovascularization. What neovascularization does is it can
cause bleeding in the back of the eye, or plasma to leak out into the back of the eye. In Figure 3, you can see centrally that the patient has a pretty dense sub-retinal hemorrhage. This is the only treatable condition with AMD, when the patient has wet, or neovascular, AMD, right? But 90% of our patients don’t have neovascularization, and there is not a whole lot we can offer them at this point. However, if they do have neovascularization like this, we have the ability to offer them Anti-VEGF treatment, which is what we will talk about today.

With wet macular degeneration, there are four potential findings when we are looking for a neovascular net. As I mentioned at the very beginning, I want to teach you about these diseases, what we are looking for, and when to refer.

In wet AMD, we are looking for one of the four findings mentioned in Table 1, and that is when we are going to refer. There can be a sensory detachment, pigment epithelial detachment (PED), a sub-retinal hemorrhage or sub-RPE hemorrhage. There are two potential spaces: sub-retinal, which is between the retina and the RPE, and sub-RPE, which is between the RPE and the choroid. We can either get plasma leaking out, or blood.

A sensory detachment is simply that the retina is being lifted off of the RPE by plasma. That is going to look like a clear fluid lifting a clear retina, which sounds quite complicated to see if you think about it, and it can be challenging. This is something that we have to look for. I don’t remember being taught this in school, to be quite honest, and maybe I missed that day. But now that I’m in practice, especially in a high-level disease practice like the VA, I’m seeing quite a bit of macular degeneration caused by a sensory elevation. Thus, we need to pay very close attention to this. It is something that can be seen on OCT, but if we’re not knowing when to look by doing a great fundus evaluation, we may not know to look for this.

A PED is going to be a serous elevation of the RPE. Fundoscopically, this looks like a very large, soft, confluent drusen, as opposed to multiple soft drusen.

A sub-retinal-hemorrhage looks like the hemorrhage does in Figure 3. A sub-RPE hemorrhage looks gray-green, like we were taught about in school. The RPE masks that blood and makes it look grey-ish or green-ish.

Figure 4 is an example of a patient who has multiple problems. Off to the periphery of the macula, we have a sub-retinal hemorrhage. Centrally, that is actually sub-retinal serous fluid. It’s hard to see in this 2D photo, but when you’re looking at this...
funduscopically, you can see that it is actually elevated. Very centrally, that is a PED, a large elevation of the RPE due to plasma.

Historically, Macular Degeneration was not really treated with anything. We patted patients on the back and basically told them, “Sorry.” As you’ve heard me mention earlier, I do Low Vision Rehabilitation, and hearing me say that there was nothing we could do kind of makes me cringe. That’s not true – there’s always something we can do. Too often our patients are told that there is nothing more their eye doctor can do for them. Even if the treating doctor has nothing more they can do, typically there are things that a Low Vision Rehabilitation specialist can do. At the very least, we can do magnifiers, some sort of adaptations to their home environment, audio products like audio books, or whatever it may be. There are a slew of things, but that is not the topic of today’s lecture. Even today, with our best treatments possible, even with Anti-VEGF, it’s very important to tag along with Low Vision Rehab, because these patients don’t get back to perfect vision. They get better vision often, but not perfect, and they may still have some functional difficulties, so please consider low vision. I think optometrists and ophthalmologists have historically been not very good about referring for that, so I encourage you to work hard and do better if you don’t do low vision yourself.

After that whole ‘nothing’ period, where we weren’t really treating these patients, there was a time where we were treating it with laser. The problem with the laser, however, is that you can get collateral damage, and collateral damage at the macula is a really bad idea. You can get scar tissue and even larger scotomas. That didn’t work out as well as we hoped, unless the net was extra-foveal, or pretty far away from the fovea. To be quite honest, I don’t really see many of those, now days.

Visudyne came along and offered a huge change in the idea of how we could treat this: by injecting a medicine into the eye and using a selective laser to treat the net. The hope was to minimize collateral damage. Unfortunately, Visudyne was not a very good medication.

Along came Anti-VEGF with the MARINA/ANCHOR trial that showed that Lucentis was beneficial. I’m going to talk about that trial and then four other trials: VIEW, CATT, GEFAL, and the newer idea of Treat and Extend.

When we are looking at a study, we have to ask what medicine they are using, did they use a placebo, and what outcomes matter? In all three of these diseases I’m talking about today, vein occlusions, diabetic retinopathy, and AMD, we have to ask what are the outcomes that matter to our patients? Sure, we can measure OCT and the macular thickness, we can measure contrast sensitivity, but does that matter to our patient? The answer is that I don’t know. I think that the visual acuity type things really do matter, specifically in macular degeneration we are thinking about outcomes of reading-type tasks. The #1 thing that my AMD patients complain of in low vision is reading-type tasks. That may not be reading a magazine or a book, but it may be threading a needle or tying a fishing lure. These are common things people complain about. We have to think, “If my patient were reading this study along with me, what would matter to them?”

MARINA/ANCHOR RESULTS

| Lucentis | Gain ≥ 3 lines | 41% |
| Sham    | Gain ≥ 3 lines | 6%  |

**MARINA/ANCHOR Trials**

In the MARINA and the ANCHOR trial, they treated Lucentis compared to a Sham injection. This study came out almost 10 years ago – 2006. They found that patients who were treated with Lucentis gained acuity – they gained about 3 lines, not quite 50% of the time – 40% of the time, compared to the only 6% of patients who gained 3 lines with the sham injection.

There’s a couple of themes I’m going to have throughout this talk, and one of those is: don’t memorize these numbers. Soak them in, take them in, have some talking points for your patients, but don’t feel like you have to memorize these. They are not that important to memorize. The second is: wow – look at that – we went from medication that could barely sustain acuity, to gaining acuity. In fact, pre-Lucentis, we used to tell patients that we hope to keep their vision about where it was. When they reported studies on this, if they reported a loss of less than 3 lines, that was their goal – to keep the patient from losing 3 lines. Now, the goal is to gain 3 lines of acuity. A huge change from Anti-VEGF.

They found that if they did measure stability of acuity, which they defined as losing 3 lines, was that 90% of these patients were able to maintain something similar to what they came in with. If the patient comes in with 20/400 vision, you might not be bragging a whole lot about that. But, if they came in with 20/40 vision, you’re going to be relatively happy that they only lost to 20/70. Keep that in mind when you’re educating your patients on their numbers. The worse their acuity is, typically the worse the outcome is in the end. By that thought, the better their acuity is in the beginning, the better in the end, so that’s a good point for educating patients.

Here is one important point about any study that looks at macular function, such as AMD, diabetic macular edema, macular edema from a vein occlusion, etc.: what is the reading acuity afterwards? A lot of these studies actually don’t measure reading acuity per se, they measure what they call a ‘surrogate endpoint,’ which is ‘reading-like’ acuity.

20/40 on a distance chart doesn’t mean that the patient can sit down and read 20/40. Especially 20/40 in a fluid manner. It doesn’t mean they can sit down and read Time magazine. We know that patients who have 20/40 distance acuity tend to do pretty well up close. They tend to have comparable acuity up close. Thus, when I am looking at a trial like this, I’m asking myself, “What is the reading-like acuity? What is the 20/40 or 20/50 vision?” If they happen to measure reading acuity, great. They didn’t do that in this trial. I’m going to settle as 20/40 as the surrogate for reading acuity. They found that 40% of patients were able to do that with Lucentis, as opposed to only 6% with the sham. That’s pretty impressive results.
VIEW Trial

Let’s move on to a different trial called the VIEW trial. The VIEW trial compared two medications: Eylea (Afibercept) vs Lucentis (Ranibizumab). This was just in 2014, and the question really was: Can Eylea be given less frequently? This is a huge question to be answered. The reason why is sometimes our patients on Lucentis could be getting an injection a month for maybe years, and the trials with MARINA/ANCHOR included 24 injections over 2 years, typically. Can we give less injections? Try to minimize the cost of the injections, and the burden of going to see the doctor – that would be huge if we could do that.

At 96 weeks, they wanted to know how many patients had stability, and in their minds stability equaled less than 3 lines lost per year. Secondarily, they wanted to note any anatomy and VA changes at 52 weeks and beyond.

What they found was that Eylea was non-inferior to Lucentis. That sounds like weird jargon of some sort, right? Basically, non-inferior means that it was the same as. Whenever you have an established medication like Lucentis, and you’re trying to see if a new contender is the same as or better than it, you’re essentially asking if the new medication is about the same. You don’t want it to be worse, and that was what they were looking for. They basically found that it was about the same as Lucentis. 92% of patients maintained their acuity, defined as that less than 3 line loss. 33% of all groups achieved 20/40, so they had pretty comparable numbers to the MARINA/ANCHOR study, were 90% maintained their acuity in that trial. And 33% got 20/40 in this trial, compared to 42% in the MARINA/ANCHOR trial. Eylea is non-inferior to Lucentis, and that is great, because maybe we can give it less.

What they found is that they had two groups of Eylea, an every 4 weeks group, and an every 8 weeks group. The people in the every 8 week group had comparable outcomes, and fewer injections; 5 fewer injections. That is less money spent, less burden on getting in, less complications from the medication, etc. That is great – if we can use this fewer times, and get the same results, that would be fantastic.

They found that the safety of these were very good. There were some non-fatal strokes (0.7%), and non-fatal heart attacks (1.4%), so that is good results there. That is one of the biggest concerns we have about this medication, that it can cause strokes and heart attacks, so thankfully it was very low in this trial.

GEFAL and CATT Trials

The GEFAL trial compared Avastin (Bevacizumab) to Lucentis (Ranibizumab). Now, this was done in 2013, and you may be asking yourself, “Didn’t they have this trial done several years ago back in 2011 with the CATT trial?” The answer is yes, but I’m going to compare the two trials and see if there is any difference between Avastin and Lucentis. What they did here is they did an every 3 month regimen, and then ‘as needed.’ As needed was based on acuity, and OCT.
Primarily they wanted to know how, on average, patients did on best corrected visual acuity (BCVA), and what was their final acuity in number of letters gained and lost. They found that in the Avastin, they got about 5 letters, which is 1 line of acuity. They got about 3 letters, which is about half a line of acuity, with Lucentis.

This is in comparison with the CATT Trial. You will see that they did a lot better on both ends in the CATT trial than they did with the GEFAL Trial.

The final VA in Lucentis and Avastin were both around 20/60 in the GEFAL trial, with around 40% reaching the 20/40 mark in each group.

If you’re like me, you are looking at this number and thinking, “This is incredible! Three different trials reaching about the same number, of 40%.” That is almost eerie. When you’re looking at this and explaining it to patients, you can have some optimism that 40% of patients were able to read after this. Now, that’s not 100%, and patients may balk at this, thinking, “That’s it?” But that is compared to years ago where we had nothing we could do, and their only hope was Low Vision. Now, it’s Low Vision plus 40% better than 20/40. And again, the better the starting acuity, the more likely these patients are to get there. If both groups – Lucentis and Avastin – got around 20/60, that’s pretty good vision all-in-all. It’s not something I would wish for, but if I knew I had a disease that could cause me to be count fingers or worse, I’d take 20/60 any day.

90% of these patients in GEFAL maintained their acuity, so the numbers are looking pretty comparable there, as well. Safety was good also, with no strokes and only one heart attack in each group.

**Treat and Extend**

Let me talk briefly about something called Treat and Extend. The goal of Treat and Extend is to try to get the patient to have fewer injections, fewer visits, and maybe, as I said, fewer complications and less money spent on this treatment.

There are two different competing exit strategies for how to get these patients off of Anti-VEGF. The first one is to do a PRN, or as-needed strategy. The PRN strategy is to basically treat the patient a few times, and then back off and only treat them if they seem to be getting worse. The second strategy is Treat and Extend, which is to treat them for 3 months, and then, if the patient is stable, spread the injections out. Thus, one injection a month for the first 3 months, and then on the 4th month, they will do 5 weeks, instead of 4 weeks. An injection to start, 4 weeks later another injection, then wait 4 weeks and another injection. That is our first three injections. Then they have the patient go 5 weeks, and at that 5 weeks, regardless of how the patient is doing, do an injection. Then if the patient had a net that was treated at the 5 week interval, they could extend the treatment out another 5 weeks and see how they’re doing. As long as the patient is stable, they can push it out 5, 6, 7 or 8 weeks. Every single visit that they are extending, they are doing an injection – it is not on an ‘as needed’ basis. As needed would only be an injection as the patient is having complications. Treat and Extend gives an injection every
time one is scheduled, and only extends the interval out if the patient is stable. If they have a net, then the surgeon may bring the patient back in at a shorter interval and tighten the reins a little bit. The goal is to try to push the patient off of this treatment, or to do it less frequently.

They've studied this in 2015, and they found that 90% of patients had stability at 2 years. (Source: Ophthalmology 2015; 122:1212-1219) 45% had 20/40 acuity. This is very similar numbers-wise to every single trial we've talked about today. The benefit, though, is that patients were able to receive fewer injections and were able to spread those out further over time. In this trial, they found patients had 13 injections with Treat and Extend, compared to 17 on patients who were not on Treat and Extend. They also had fewer visits. If we can get comparable numbers, and comparable outcomes, but fewer injections and fewer visits, I think that is a win.

In my mind, I'm wondering if we could do Eylea and Treat and Extend, and see if we can stretch that out even more? We haven't had that trial yet.

Figure 5: 2007 undus photo of a patient with AMD and a PED OD. [Center] Early fluorescein angiography of that same patient showing hyperfluorescence. [Right] Late fluorescein angiography showing hyperfluorescence but no leaking.

Patient Case

Let me go over a patient really quickly. This is an 80 YO White male with Macular Degeneration OU. I saw him first in 2007 with 20/50 OD, and 20/20 OS. Looking in Figure 5 [Left] centrally, that is a PED. It's a little bit harder to see without stereopsis, but there is a PED there, which is not too bad. We did a fluorescein angiography to see if it was leaking anything, and if there was any neovascularization. Figure 5 [Center] is a very early stage FA. It's a little bit hyperfluoresced temporally. We'll see on the late-stage fluorescein angiography (Fig 5 [Right]) that it is still hyperfluoresced, but it is not spreading out. That’s what a PED does – it increases in volume, but it doesn’t increase in size.

Figure 6 is the left eye, and we have a small PED there. The FA was fine on that one.

In 2009, the patient had VA’s of 20/50 OD and 20/40 OS. Figure 7 shows the PED again, and that's larger, so we were pretty concerned. However, the acuity in that eye was the same. In Figure 7 [Center], you'll see the black lines that radiate out like bicycle spokes. Those are sometimes called Hot Cross Buns – kind of a fun FA sign for PED’s.
Again, it changes in intensity between early and late presentations, but doesn’t change in size over time. Another PED that is not a net. We did not treat this.

Figure 8 is the OCT, showing you what the PED looked like on OCT. There was quite a lot of elevation underneath the RPE, but no net.

You will see that there has been a change in the patient’s left eye – it went from 20/20 to 20/40, and now we have a sub-retinal hemorrhage. (Fig 9 [Left]) This is when we need to refer the patient, right? We did a referral, we did the FA (Fig 9 [Center] and [Right]), and we saw a net on the FA.

Figure 10 shows the OCT of the PED we saw, but we are also noticing some hemorrhaging nasally. That’s where the net is.

The patient was started on Lucentis OS. They have a stable PED but no net in the right eye. Our patient was referred out for 5 years to a retinal specialist, and ended up getting a lot of injections between 2009 and 2014 (Lucentis OD x16, OS x22 and Eylea OS x3) to no avail in the right eye with a final VA of 20/400 OD, and a final VA of 20/25 OS. Quite a success in the left eye, however.
Figure 11 shows the patient’s right eye after all of the treatment. That large PED that is there has involuted in on itself and now he has a lot of atrophy and scar tissue. We also see what his retina looks like on OCT. It looks pretty scarred up, atrophic, and not healthy.

Figure 12 shows the patient’s left eye. You can compare it with Figure 9 [Left] to see where he was. If you compare that to how he was in 2009 with the pre-retinal hemorrhage and neo net, that is a pretty good outcome there. There are some RPE changes and atrophy there, but with a final VA of 20/25, that is not too bad.

**AMD Summary**

To summarize, Lucentis and Eyelea are similar. You may be able to give Eyelea less frequently. Lucentis and Avastin are similar, though we give them at the same rate.

We are still developing an exit strategy for these patients. Do we do as-needed, or Treat and Extend? Or is it maybe Treat and Extend, or as-needed, combined with something like Eyelea, which we can give less frequently? We don’t know when to stop for these patients, and some patients may need to be on Anti-VEGF for a long period of time.

For education purposes, we can tell patients that about 90% of patients treated with Anti-VEGF had stable vision. Around 25-40% had a 20/40 acuity with Anti-VEGF. It also has a good safety profile.

When do we refer? If there is wet AMD, and any of those four signs mentioned in Table 1. It probably does not matter what their acuity is – most retinal specialists are going to be treating this regardless of acuity. The concern is that if you don’t catch it early, it may get to a point where it can get worse.

On the flipside, what if the patient has really bad vision? We had these trials that typically had patients with 20/30 to 20/320 acuity. What if the patient’s acuity is really bad – hand motion or count fingers? That is going to have to be a clinical judgement on your part, as to if you think the patient would benefit from this or not.
Vein Occlusions

Let’s move on to vein occlusions. Table 2 lists the threats to vision, especially in BRVO’s. You can get different things with proliferative disease, but they mostly get vitreous hemorrhages in BRVO’s.

Table 2

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<th>Threats to vision in BRVO</th>
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<td>Macular Edema</td>
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<td>Macular Ischemia</td>
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<td>Proliferative (mostly V-Heme)</td>
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Figure 13 is a good example of a BRVO – you have flame hemorrhages in one segment of the posterior pole. If you’re thinking more like two to four segments, then we are thinking more of a CRVO. This picture highlights those flame-shaped hemorrhages that go along the arcades. In this patient, we have edema extending down into the superior macula with exudates.

Table 3

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<th>Threats to vision in CRVO</th>
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<tr>
<td>Macular Edema</td>
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<td>Macular Ischemia</td>
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<td>Proliferative (mostly NVG)</td>
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Threats to vision in CRVO’s are listed in Table 3. They are very similar to a BRVO, but the proliferative disease is much more likely to be neovascular glaucoma than a vitreous hemorrhage. Both BRVO’s and CRVO’s can lead to tractional retinal detachments, but they don’t happen quite as frequently as the others.

Figure 14 is a CRVO. This is classic – it has flame hemorrhages in all four quadrants, we have macular edema centrally, as well as optic nerve edema. These are harder to miss, I think.

Historically with a BRVO, we treated these patients with a sector PRP if they had neovascularization. If there was edema, and especially if there was a hemorrhage at the macula, we waited three months. We waited for two reasons: first, we wanted the hemorrhage to clear, and secondly, we wanted to see if this resolved a little bit on its own, and a lot of times they did. If it didn’t resolve after three months, then we would treat them with laser.

Historically, if a CRVO had neovascular glaucoma, it was treated with PRP. However, if there was edema, there was no treatment available. In fact, in the Central Vein Occlusion Study (CVOS), they found that treating these patients with macular edema with a laser actually led to worse outcomes.

Then they found, through different trials, that intravitreal steroids could actually improve vision. You will probably remember something called the SCORE trial, and they found that this improved vision. However, there were a lot of complications. Many patients had cataracts, and many had IOP increases, sometimes IOP increases that were very difficult to manage. In fact, in some trials, up to 10% of patients needed a filter after having these injections of steroids. Clinically, in my own practice, I have seen patients in the same boat, whether it’s intravitreal steroids or even sub-Tenon’s steroids – years later they still have pressures that are difficult to manage.
BRAVO/CRUISE/RETAIN

There are a couple of different studies I want to talk about. BRAVO and CRUISE were kind of the mainstays of telling us how effective this is. RETAIN was an extension study of those. We will also cover GALILEO and COPERNICUS... by the way, who comes up with these names? They’re pretty interesting, aren’t they?

The BRAVO trial in 2010 looked at Lucentis versus a sham injection for BRVO. By the way, I should back up and say that we cannot treat the macular ischemia from a BRVO or a CRVO. These are for edema, not ischemia.

The 6 month results found that with Lucentis, these patients gained acuity about 61% of the time, while only about 30% did with the sham injection. Looking at those numbers, that’s pretty impressive, right? That even 30% of the patients in the sham group had some improvement. This echoes very similarly to what we found years ago, when we studied this in the BVOS, or Branch Retinal Vein Occlusion Study, which found that a lot of patients were actually improving without treatment. However, in this trial, even more patients improved with Lucentis.

The 20/40 acuity, which is again what we are hoping to get, we are almost getting 70% of patients with that at 6 months with Lucentis. When they extended this study out to 1 year, they found that patients were maintaining those gains.

The CRUISE trail is similar to BRAVO except that now we’re looking at CRVO’s. What they found at 6 months was that half of the patients treated with Lucentis gained 3 lines of acuity. Let me say that again: half of the patients treated with Lucentis gained 3 lines of acuity! If you would have told me at the very start of my practice years ago that we would be able to treat CRVO’s, I would have been astounded. If you had told me that I’d be able to send a patient to a retinal specialist, and have their CRVO improved, I would have just been blown away. I don’t think I would have believed it. Now, here we are in the era of Anti-VEGF, and we don’t only treat CRVO’s, but we can gain 3 lines of acuity in half of the patients. That’s just incredibly impressive. As I’ve mentioned earlier, that is one theme through this lecture – amazement. Amazement that we can treat these patients, and get these sort of acuity gains, rather than just keeping it from getting worse.
This is another amazing thing: almost half of patients reach that 20/40 acuity once treated with Lucentis, and only 20% without. That’s pretty impressive that 20% of patients with a CRVO got to that acuity level without treatment – it kind of makes you wonder if they had milder CRVO’s in this trial. These results were maintained at 1 year.

Then they did an extension trial on this, and that study is called RETAIN. They did a 2 year extension of the BRAVO/CRUISE, still treating with Lucentis for these CRVO’s and BRVO’s. They had about 34 BRVO patients who were continuing on with treatment, and 80% had 20/40 or better acuity. The problem, however, was that half of them still needed an occasional injection, even after 4 years! It’s like, “man, when can we stop this medication for some of these patients?” A lot of BRVO patients are treated, the BRVO goes away, the body helps collateralize the remaining blood that’s in there, the blood drains, and we don’t have to worry about them as much. However, it looks like some of these patients, even years after, still have edema that needs to be treated.

Clinically, I’ve seen this in many patients, pre-Anti-VEGF. They would undergo the laser treatment, and then years later, still have this persistent edema that doesn’t want to go away. We treat those patients with Anti-VEGF, and it still doesn’t go away very well. It may be that with some patients, it will just never react well to the medication or treatment as well as we’d hope.

With the CRVO patients, what RETAIN found is two things: they had people who had resolution of edema, and those who did not. The 44% who had resolution had very good gains – 78% gained 3 lines of acuity, and 64% had 20/40 or better; really good outcomes. For those who had no resolution of edema, only 1/3 of them gained 3 lines, and only about 1/3 of them gained 20/40 or better.

I’m a little disappointed in those who did not have resolution of the edema – I wish that was better. However, to be quite honest, to be quite honest, if you look at that, 33% gained 3 lines with a CRVO. Again, that is still incredibly impressive compared to nothing, in the past, when we really couldn’t treat these patients, and our few treatments in fact made them worse. To get that 28% at 20/40 or better, and 1/3 gaining 3 lines, it’s still quite impressive.

RETAIN also found that Ischemic CRVO’s fared worse than non-ischemic, and I think that’s something that we knew from years ago when we looked at the CVOS. They had 13 deaths during this study. None of the deaths were attributed to the medications, and all were attributed to pre-existing conditions.
GALILEO
The GALILEO trial was using Eylea versus sham for CRVO. As you will remember with Eylea with AMD, the hope is that we can give that less frequently. In this trial, they did an injection every 4 weeks for 20 weeks, and then after that they did an as-needed dosing. Thus, they are already thinking ahead as to how we can wean patients off of this medication.

Out of the 172 patients, they were looking for two outcomes: how many of these patients had a 3 line improvement, and how many of them had neovascularization. As you remember earlier with CRVO, we are really concerned with neovascular glaucoma.

They found that a 3 line improvement was achieved in 60% of patients with Eylea, compared to only 1/3 of patients with the sham. Their average entrance acuity was 20/100, so a 3 line improvement is 20/50, which is still that reading level of acuity.

An interesting aside, they found no difference in this trial between perfused and non-perfused retinas in the Eylea-treated patients. This flies in the face of conventional wisdom, here. Conventional wisdom says that those with ischemic disease fare worse, and in fact, I just said it one page earlier.

Do we still need fluorescein angiography, then, if there is no difference between perfused and non-perfused? The answer is that we probably still do need it. We are probably going to titrate our treatment and follow it differently, but thankfully, I am not the one who has to make that decision. That will be on the shoulders of the retinal specialist.

For development of neovascularization, only 6% of the patients with Eylea, compared to 9% of the patients with the sham, developed it. Years ago, when they did the CVOS, it was 35% of the control group. Keep in mind that they didn’t have a mix of ischemic and non-ischemic – the CVOS was all ischemic. When they were treated with PRP, that number reduced down to 22%.

Safety wise, it was pretty safe. One of the things to point out is the pain. Even 4% of patients with a sham treatment experienced pain, so that may just be someone expecting the injection to hurt. When we are telling patients about this, I think that we should bring up pain. Looking at this, we found that 90% of patients did not experience pain, even with the real treatment. This is something that we should probably discuss with the patient, and discuss with them, because a lot

GALILEO

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<th>Development of Neovascularization</th>
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<th>Sham 9%</th>
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GALILEO Safety (Tx vs Sham)

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<th>Eye Pain</th>
<th>11% vs 4%</th>
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<tr>
<td>Increased IOP</td>
<td>9% vs 6%</td>
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<tr>
<td>Conj Hemorrhage</td>
<td>9% vs 4%</td>
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No deaths, CVA, or MI
of patients fear pain, but a lot don’t actually describe pain when they are finished with the procedure.

**COPERNICUS**

The COPERNICUS study was the same idea as GALILEO, but in a different region. They did a sham group that received Eylea after 24 weeks, also. They had 189 patients, a similar amount to GALILEO, and had a similar asking of what the outcomes would be regarding the 3 line improvement, and the development of neovascularization.

At 2 years, they found that 49% of the Eylea group had a 3 line improvement, while only a 23% did in the sham group.

Development of neovascularization at one year was zero percent in the Eylea group, compared to 7% in the sham. At year 2, the development of neovascularization was higher in the Eylea group, because they quit giving it as frequently would be my guess.

Here has been a question of mine for quite some time: Does using Anti-VEGF in something like a CRVO temporize the ischemia, or does it get rid of the ischemia enough that the eye can collateralize, and get back to a better baseline level? The reason I ask that is, when we’re using Anti-VEGF, are we just holding off the eye from getting neovascularization? Thus, it’s like they eye wants to develop neovascularization, and we are just holding it off, and when we stop the Anti-VEGF, the neovascularization can just rear its ugly head? Or, are we treating it long enough that the body can collateralize and when we stop the medication, the body won’t develop neovascularization because it already has collaterals intact which leads to less ischemia? I don’t know what the answer is. It seems to be that there isn’t as much neovascularization after the fact. It’s like the body takes care of it somewhat. This trial seems to indicate that we are maybe just temporizing it, and it’s still going to rear its ugly head at a later time, just not in the amount that we saw in the CVOS years ago.

Safety-wise, this was also very safe. There were few ocular complications reported. We also had one stroke and one heart attack in the Eylea group, but thankfully both were non-fatal.

**Cases**

Let’s go through a couple of cases of vein occlusions. This is a 46 YO WM who was new to us. He had uncontrolled high blood pressure and was a borderline diabetic. He had a history of a stroke and a heart attack. If you’re like me, you’re looking at this thinking, “46 years old?! My goodness – you’ve already had a stroke and a heart attack?” Something is definitely going on here. He came in saying that, “It seems like letters are there and then missing, in and out of vision.” He’s got these scotoma-like symptoms.
His BCVA is 20/25 OD, 20/40 OS. The anterior segment was unremarkable. The nerve was healthy, and he had very (2+) tortuous vessels. We noticed a paramacular hemorrhage in his right eye from a superior BRVO. He had an old BRVO in the left eye, with collaterals.

Figure 15 [Top] is his right eye’s visual field. You will see that inferior nasal defect much like we will sometimes see in glaucoma, but it can also be from artery occlusions, or as in this case, a vein occlusion. Figure 15 [Middle] shows the superior temporal quadrant of the right eye has edema, extending out right where the macula is. Figure 15 [Bottom] shows that edema further highlighted on the OCT, where the cystic-appearing edema shows up temporally.
Figure 16 [Top]: 30-2 Visual field of the patient’s left eye, again showing a defect inferior nasal. [Middle] OCT showing thinning and atrophy over the area of the old BRVO. [Bottom] OCT showing atrophy of the retina where the old BRVO was.

Figure 16 [Top] is his left eye’s visual field, with an inferior nasal defect, as well. Figure 16 [Middle] shows his old BRVO. You will notice that there is no edema here, but a lot of atrophy – that is what that purple looks like in the left-hand spot. It’s all thinned out and atrophy. On the middle spot, that red indicates the same thing – thinning, in this case due to atrophy. You’ll see that atrophy bare out on the right-hand side of Fig 16 [Bottom], where the retina is thinner and more atrophic than the right hand side.
What about that bi-nasal defect? Many times we are taught that a bi-nasal defect could mean something, either from the carotid arteries or the chiasm. In this case, the bi-nasal defect could be from glaucoma, although he’s got a 0.1 cup OU, so probably not that. It could have been bilateral BRAO’s, but in this case, that is probably not the case. We are seeing bilateral BRAO’s. I just wanted to throw that in there – often times the bi-nasal defect can trip us up a little bit and make us think that it’s neurologic, but in this case it’s clearly retinal.

We referred this patient to the University of Kansas. They are not going to do anything about his atrophy in the left eye. Remember, we cannot treat atrophy or ischemia from BRVO. There is mild edema in the right eye, and they decided to treat it with Anti-VEGF.

What is his prognosis like? He started off with 20/25 acuity, with a BRVO that wasn’t quite completely encompassing the macula. I think in this case, the prognosis is very good. If you look at the evidence, we are seeing a lot of patients maintaining acuity, and getting very good acuity on down the line.

Let’s go on to Case 2. This is an 81 YO WM who just came in for a routine exam, with no complications to his knowledge. BCVA was 20/25 in each eye, and the anterior segment was unremarkable. IOP’s were 18 OD and 17 OS.

![Figure 17](image)

Figure 17 [Top Left] OD fundus photo of the patient in Case 2. [Top Right] OCT showing cystic edema almost all the way to the fovea. [Bottom] OCT showing local edema in the area of the BRVO.

We look in the back of the eye, and we see Figure 17 [Top Left]. This is a classic BRVO, and the edema extends all the way down to the macula. You’ll see in Fig 17 [Bottom] that the OCT highlights that, as well. Look how focal that edema is from the hemorrhage. It’s not quite all the way down to the fovea, but it is right about there. Figure 17 [Top Right] shows the OCT highlighting, again, the cystic nature of the edema that we will see sometimes from BRVO macular edema.
He’s got a BRVO on the right eye, with 20/25 acuity. Do we refer this patient? The answer is yes, we refer them. What we are expecting is a very good outcome for this patient, as well. What if the vision was 20/60 or 20/100? The answer is yes, we still refer them. We expect maybe a more guarded prognosis for them – they may get some gain in acuity, but their final VA will likely not be as good as this patient’s.

To summarize BRVO and CRVO, they improve on Eylea, they improve on Lucentis, and the long term outcomes of a CRVO show somewhat of a guarded prognosis. As you’ll remember, 44% of those who had resolution of their edema did really well. Those who didn’t have resolution of their edema didn’t do quite as well.

The most benefit was shown in the first year or two, and it seems to lessen over time, but we don’t have long-term data on this quite yet.

There is very little neovascularization with Anti-VEGF treatment, but as I theorized earlier, does this effect last? We are going to find out more as we go down the line.

How do we refer? If there is central edema and a reduced acuity in a BRVO, we refer. If there is no referral, we monitor very closely. There are several patients whom I’ve seen in the clinic lately who look kind of like the two cases I had, where their acuity is reasonable, and their edema was off to the side, and we monitored them closely. As soon as their acuity dropped, or there was central edema, then we referred.

With a CRVO, the same thing applies. If there is central edema or reduced visual acuity, then you are referring. If there is no referral, then you have to monitor these patients monthly with gonioscopy. Historically, back pre-Anti-VEGF, these patients who had CRVO’s who were not treated for any neovascularization day 1, we monitored monthly doing gonioscopy. With diabetes you can get neovascularization of the anterior segment, right? But it tends to go iris first, then angle. Not so with a CRVO – it can end up in the angle first! You have to do gonioscopy to look for that and make sure it’s not there. This is typically only for patients who have reasonable acuity and no macular edema that you’re following clinically. They are not very common, but we will see some of them from time to time.

**Diabetic Macular Edema**

This is our last topic – hang in there! You’re doing great!

The threats to vision with diabetic macular edema are the same as those with a CRVO and a BRVO: Macular edema, macular ischemia, and proliferative, except that proliferative disease is an equal-opportunity damager here. Neovascular glaucoma, vitreal hemorrhage, and tractional retinal detachments can all be caused by diabetic macular edema. However, in my experience, it tends to be more from a vitreal hemorrhage than anything else.

Of course, we’ve all seen this classic picture in Figure 18 of a diabetic, with the traction down below and a pre-retinal hemorrhage.

**Figure 18: Proliferative diabetic retinopathy.**
hemorrhage. Figure 19 [Left] is a pre-retinal hemorrhage, as well, with probably some central microaneurysms leading to macular edema. Figure 19 [Right] shows very bad traction at the nerve – we don’t know if this patient has had PRP. This may be after the PRP.

We can also get really bad neovascularization of the anterior segment (Fig 20). This is really rare that we see this – the photo is a textbook example, but thankfully we do not see this too often clinically. I’ve only seen one like this a couple of times, thankfully. You’re usually looking for much more subtle neovascularization in a diabetic.

Really, however, what I want to talk about today is the macular edema. The proliferative disease is treatable, but it’s often harder to treat after the fact. If we can prevent that from happening, that’s even better.

To date, there is no evidence that Anti-VEGF actually helps proliferative disease, or that it’s a good, sustainable long-term treatment strategy. Remember, VEGF needs to be given monthly for a proliferative patient, and you don’t know when you need to stop that treatment, either. It seems to me that PRP is probably a little better – it can be done in one, two or maybe even three sessions, and then treatment is finished. You don’t have to keep doing it over & over again.

There is one trial that came out recently asking if Anti-VEGF would help clear a vitreal hemorrhage, possibly to prevent the patient from needing a vitrectomy. Unfortunately, the answer was no, it didn’t do any better than just letting it go.

We are now going to talk about macular edema. We cannot treat the macular ischemia, so we will talk about the edema. Historically, these patients were treated with laser; focal laser for microaneurysms, and grid laser for more diffuse edema. Then, along came intravitreal steroids, and much like CRVO’s and BRVO’s, we found that it was beneficial for these patients although it went along with a high rate of
glaucoma and a high rate of cataracts. We really want to avoid those side effects. Then, Anti-VEGF came along, and it was much better. We will talk about that in just a moment.

Part of the treatment criteria for treating diabetic macular edema was this CSME, or Clinically Significant Macular Edema. (Table 4) When they did the Early Treatment of Diabetic Retinopathy Study, or ETDRS, they formulated these. They found that patients who did not meet this criteria were no better off with treatment than if they were untreated and just monitored. If a patient has macular edema that does not fit into one of these three criteria, they did not recommend treating that. This seems a little old-fashioned now that we have Anti-VEGF, but I think that it still applies for our patients. There are still some patients that need to have laser treatment, either in addition to Anti-VEGF, or by itself, so it’s really important to know these criteria & have them down cold.

Figure 21 is a good example of a patient who would meet the criterion of having exudates within 500 microns of the center of the fovea with adjacent retinal thickening. On a two-dimensional photo it is hard to see the retinal thickening, but it is there. Nowhere in that criteria does it say anything about visual acuity, and even in the ETDRS they said 20/20 patients would benefit. Most retinal specialists are not treating 20/20 acuity, but that is not part of the original criteria.

One other thing to note when you are looking at the criteria is 500 microns is very difficult to measure. Basically, when you look at the optic nerve, that is split up into 1500 microns typically, so we are looking at 1/3 of a disc diameter away from the center of the fovea.

Now, there is a little bit of a difference between the CSME criteria and the treatment criteria for Anti-VEGF. They want to have central retinal thickening with 20/30 or worse acuity. Keep in mind that central retinal thickening is a funduscopic observation. You can use OCT in addition to it, but you have to be able to find this with your fundus lens – it is very important to take a good look at your patients with diabetes.

There are a few different studies that came out looking at this (BOLT, RESTORE, RISE/RIDE, and DRCR), so let’s talk about each of those.

BOLT was looking at Avastin vs laser for diabetic macular edema. The mean acuity on these patients was 20/50 with Avastin and 20/80 with laser at the end of the trial. 100% of patients lost less than 15 letters, or 3 lines of acuity, compared to 86% of patients on the laser. Thus, both treatment groups maintained acuity pretty well, and both

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<th><strong>Table 4</strong> Treatment criteria for CSME</th>
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<td>Retinal thickening within 500 microns of the fovea</td>
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<tr>
<td>Exudate within 500 microns of the fovea with adjacent thickening</td>
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<td>Greater than one disc area of thickening within 1 disc diameter of the fovea</td>
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<th><strong>BOLT</strong> MEAN ACUITIES</th>
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<th><strong>Lost ≤ 15 Letters</strong></th>
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<th><strong>NUMBER OF TREATMENTS</strong></th>
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ended up with pretty good acuity, though Avastin was better. The mean number of treatments for the patients with Avastin was 13, while with laser they had 4 applications.

The RESTORE trial was a 2 year result of using Lucentis for diabetic macular edema. The first year, they looked at Lucentis, compared to Lucentis plus laser, compared to laser alone. After 1 year, the laser alone group was offered Lucentis. They found that there was some acuity improvement in Lucentis, and Lucentis plus laser, but no improvement with laser alone.

In the 2nd year, 40% of patients treated with Lucentis had 20/50 acuity or better, whereas only 22% who were treated with Lucentis plus laser, and 19% with laser alone. It’s funny, it almost looks like laser made things a little bit worse.

There is a similar safety profile on these patients to vein occlusions and AMD.

There is a brand-new extension for three years in 2014 (Ophthalmology, 2014 May;121(5):1045-53), and basically they said they had the same acuity results with fewer injections needed in the long term.

The RISE and RIDE trials were three-year results for diabetic macular edema. They compared Lucentis to a sham injection. They could have rescue laser if needed, but if they did not need it, then the patients just received Lucentis alone, or sham alone. After two years, the sham patients could have Lucentis, if needed. They found a three-line improvement in about 40% of both Lucentis groups, compared to just 20% for the sham group. A three line improvement from an average acuity of 20/80 gets us to around 20/50.

For VA’s of 20/40 or better, we are looking at 60% of patients on Lucentis 0.5 mg compared to only 42% of those with the sham.

There was a good safety profile. 5% of the Lucentis 0.5 mg experienced CVA, while 3.5% of Lucentis 0.5 mg experienced heart attacks, while 7% with 0.3 mg Lucentis did – interesting that they did find that the 0.3 mg was a little worse off for heart attacks than the 0.5 mg dosage of Lucentis.

The DRCR just came out recently with five year results of focal laser plus Lucentis. They did focal laser plus Lucentis – they could either do focal today, more of a prompt laser, or they could defer the laser and do it later. 20/40 or better VA’s was the same, though they found that deferring the laser was actually better. This is good to know – these patients are often going to have Lucentis first, and maybe laser later.
Thankfully, they found a very low rate of endophthalmitis in this study. They found that there was only a 1% rate, calculated out to 0.06% rate per injection out of 3176 injections given.

A brand new, hot off the press is the VISTA/VIVID trial. These are two-year results of Afiblercept. They did this either monthly or bi-monthly compared to laser. The mean gain in acuity was around 2 lines (10 letters), and laser didn’t really have much of a benefit, at all. A gain of three lines in acuity in the monthly and bi-monthly injections was comparable – 38% in the monthly, 33% in the bi-monthly, but only 13% with the laser.

The average injections were way lower for the bi-monthly (14) than the monthly (22), so again, echoing what we found with vein occlusions and AMD, Eylea often has similar outcomes between 1 and 2-month injections, and the two month dosage seems to have similar outcomes but fewer injections.

The safety profile was similar across all treatments.

**Diabetic Macular Edema Summary**

To summarize diabetic macular edema, these patients were shown to benefit from Lucentis, up to 75% had reading acuity at 5 years. They found that Lucentis 0.3 mg is maybe not quite as safe as Lucentis 0.5 mg. Afiblercept may be given less often, but we have the same question as we have with the other treatments: When can we stop? Especially with a disease like diabetes, which is a chronic ischemic disease, as opposed to Anti-VEGF for AMD or vein occlusions, where it may be a ‘once and done’ sort of thing. In this case, we may have to give the medication chronically for a chronic disease.

I did have a case, but I’m running a little behind on time, so why don’t we end it here? Feel free to email me any questions or concerns you may have at anthony.dewilde@va.gov. I want to thank you so much for your time. I hope it was informative, and if you do have any questions, please let me know.

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