Insights on Switching Anti-VEGF Agents for Optimal AMD Treatment

Highlights of a roundtable discussion held during the 2013 meeting of the Association for Research in Vision and Ophthalmology (ARVO)

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Switching Anti-VEGF Therapies

Factors to consider when evaluating your AMD treatment plan

Peter Kaiser, MD: Recent clinical trials have compared outcomes achieved with anti-VEGF agents when treating AMD, and new studies have evaluated when and why to switch agents. Today, we will discuss the diagnosis and management of AMD in light of these new data. Anatomic evaluation is an important aspect of our decision-making process as we determine whether or not to switch therapies, so let’s begin our discussion there.

Imaging for Diagnosis and Management

Dr. Kaiser: Dr. Slakter, what imaging devices do you use to assess a new patient and to monitor treatment of AMD?

Jason Slakter, MD: For most new patients, I use photography, fluorescein angiography (FA) and spectral domain OCT. If I determine that a patient does have AMD and that it’s exudative, I look at the pattern of leakage and decide on initial treatment.

Seenu Hariprasad, MD: I usually perform FA at baseline and use OCT to monitor therapy. I repeat the fluorescein if the patient isn’t responding as I expected.

Dr. Kaiser: Dr. Hariprasad, do you think FA matters at baseline as much as it did in the past?

Dr. Hariprasad: In my opinion, OCT is critical, but FA has a distinct and important role, especially to tease out other conditions. Fluorescein gives us a unique view of a lesion: its geography and perfusion characteristics, and its location relative to the fovea. When a patient isn’t responding well to treatment, fluorescein can help provide answers. I think we can take very good care of the vast majority of patients with OCT, but I would hate to see the day when FA isn’t part of the management of wet AMD.

Dr. Kaiser: On average, how frequently do you perform fluorescein angiography?

Dr. Hariprasad: We typically perform under two fluorescein angiograms per year. Most patients undergo only one per year. The burden is minimal, and I think it makes sense at baseline.

Atul Jain, MD: I perform fluorescein angiograms on about 10% of patients newly diagnosed with wet AMD, usually for an atypical presentation or if I’m providing a second opinion. Otherwise, I rely on OCT and my clinical examination.

Dr. Kaiser: Dr. Jain, what are some of the features you’re looking for on OCT?

Dr. Jain: I typically look for intraretinal or subretinal fluid, pigment epithelial detachment (PED),
hemorrhage and retinal thickening. If a patient has metamorphopsia or other symptoms, I add those findings to the Constellation (Alcon) to make a diagnosis. If I note any inconsistency in signs and symptoms, I use FA to help pinpoint my diagnosis.

**Dr. Kaiser:** Dr. Ehlers, what scan patterns do you use on OCT?

**Justis Ehlers, MD:** We predominantly use the Cirrus system (Carl Zeiss Meditec), so I look at the macular thickness analysis, horizontal and vertical rasters, and change analysis. Line-by-line review of the macular cube can also be critical in some situations.

**Dr. Kaiser:** Dr. Slakter, at your reading center, how often do you find change analysis incorrect, especially in the setting of AMD?

**Dr. Slakter:** Unfortunately, it’s incorrect often enough that it’s suspect. In our office, we almost universally go through line by line. Even if no change is apparent using automated detection, often when we review line by line, we see some tiny intraretinal cysts or subretinal fluid, and these factors may be critical to achieving the best outcomes. I think it’s worth the few extra seconds it takes to scan line by line.

**Dr. Kaiser:** Dr. Ehlers, do you use any other imaging at baseline?

**Dr. Ehlers:** If a patient is seeking a second opinion, particularly when it’s related to resistance to anti-VEGF therapy, I will often get fundus autofluorescence and indocyanine green, because they may be particularly useful for differentiating the two masquerading syndromes: polypoidal choroidal vasculopathy (PCV) and central serous retinopathy (CSR).

**Dr. Kaiser:** What are you looking for with fundus autofluorescence?

**Dr. Ehlers:** I look for patterns of fluid chronicity. For example, you may see troughs that may be indicative of chronic fluid in central serous. I am also starting to look at the ultra-widefield fundus autofluorescence patterns, which may detect anomalies in the periphery that are asymptomatic. Looking at bilateral changes, as well, can help pin down a differential diagnosis for tough-to-treat patients.

**Dr. Kaiser:** Dr. Jain, do you use any other OCT scan patterns?

**Dr. Jain:** I’ve started looking at enhanced depth imaging (EDI) on OCT, because there is a question of whether persistent VEGF suppression causes a thinning of the choriocapillaris and subsequent reduced blood flow to the outer retina.

**Therapeutic Options and Dosing Regimens**

**Dr. Kaiser:** We’re fortunate to have multiple therapies for macular degeneration. Let’s briefly review the anti-VEGF drugs and the various dosing regimens.

**Dr. Jain:** We’ve seen an evolution from a specific type of VEGF blockade with pegaptanib (Macugen, Eyetech) to pan-VEGF blockade with ranibizumab (Lucentis, Genentech) and bevacizumab (Avastin, Genentech) and now pan-VEGF blockade plus placental growth factor (PIGF) inhibition with aflibercept (Eylea, Regeneron).

**Even if no change is apparent using automated detection, often when we review line by line, we see some tiny intraretinal cysts or subretinal fluid, and these factors may be critical to achieving the best outcomes. I think it’s worth the few extra seconds it takes to scan line by line.**

— Jason Slakter, MD
Dr. Hariprasad: Aflibercept is the only molecule that inhibits PI GF, which may be beneficial in cases that are recalcitrant to older-generation anti-VEGF agents. Also, unlike other monoclonal antibodies, aflibercept has 1:1 stoichiometric binding to VEGF. We don’t, however, know the clinical significance of these differences.

Dr. Kaiser: Dr. Slakter, from a 30,000-foot view, what are the dosing regimens for these drugs?

Dr. Slakter: Basically, there are three established dosing regimens: the on-label, study-related approach, p.r.n. and treat-and-extend. For ranibizumab and bevacizumab, on-label dosing is monthly. For aflibercept, the on-label regimen is three monthly loading doses, followed by treatment every 2 months.

With p.r.n. dosing, we treat patients monthly until the macula is dry, and we monitor at monthly or bimonthly intervals. When leakage recurs, treatment resumes. Some doctors administer a single injection when leakage recurs, while others deliver three loading doses.

Treat-and-extend therapy is based on the idea that in any one eye of any one patient, the macula will stay dry for a specific interval before leakage recurs. The goal is to identify the interval and then treat just before recurrence is expected. Essentially, we administer the loading dose and treat until the macula is dry, then extend a week or two longer. This differs from p.r.n. dosing. With p.r.n., we see patients regularly, but we don’t necessarily treat them. With treat and extend, if the macula is dry for 4 weeks, we see the patient at 6 weeks. If the macula is still dry, we treat the patient and see him in 8 weeks. If at 8 weeks, we detect some fluid, we know that 6 to 7 weeks is the interval for that eye.

Comparison Studies

Dr. Kaiser: Let’s briefly review what we’ve learned from some of the studies comparing ranibizumab with bevacizumab.

Dr. Hariprasad: Many of the comparison studies help tease out differences between the various dosing regimens. The CATT, for instance, provided a wealth of information about monthly versus as-needed dosing with ranibizumab and bevacizumab. At the 2-year mark, it’s clear that as-needed dosing regimens do not seem to do well.

In the first year of VIEW 1 and VIEW 2, with a proactive fixed-dosing regimen, patients did very well with either aflibercept or ranibizumab in terms of visual acuity. In year 2, when all groups were converted from a proactive fixed dosing regimen to a reactive p.r.n. dosing regimen, patients had a slight decrease in vision compared to year 1. From an efficacy standpoint, both CATT and the VIEW trials support proactive rather than reactive dosing regimens.

Dr. Ehlers: Some of the most interesting data from the CATT came at 2 years when the researchers divided the groups. Patients who had been treated monthly during the first year were switched to a p.r.n. regimen, and they quickly began to mirror the original p.r.n. group. Again, it’s not a huge difference between the two groups, but it does beg the question: In a chronic disease, how long can we maintain monthly treatment on-label? How long will our patients adhere to the numerous treatments and visits? I think that’s why we try to individualize treatment, because this is a 4-, 5-, 20-year disease, but we have predominantly short-term data. If we continue with p.r.n. dosing for 5 years, will the outcomes be worse? The CATT study was one of the first studies to show that p.r.n. treatment at 1 year, with essentially zero tolerance to fluid and very close follow-up, does well. As needed dosing doesn’t produce the same success at 2 years, especially compared with monthly treatment.

Dr. Hariprasad: We should remember that p.r.n. dosing in CATT was different from p.r.n.
dosing in previous studies. The criteria to treat were much more stringent, and patients had to come in every month for an examination. CATT is probably one of the only studies that showed, in the first year, that as-needed ranibizumab was noninferior to monthly ranibizumab.

I’d also point out that patients who were treated monthly did better in terms of drier retinas on OCT, especially the ranibizumab group. But to reinforce Dr. Ehlers’ comments, the arms started to separate by year 2; and at the end of year 2, my understanding of the data is that ranibizumab monthly produced somewhat better outcomes than the other groups, especially the p.r.n. arm, from an anatomic standpoint.

Dr. Kaiser: From an anatomic standpoint, the average retinal thickness of eyes receiving ranibizumab monthly in CATT was thinner than normal. What do you make of that, Dr. Slakter?

Dr. Slakter: Researchers were using time-domain OCT in the CATT, and I raise a big red flag about that. I don’t know how much we can rely on the thickness measurements from that system. That said, however, the thinning is an issue and raises several questions. Was there too much VEGF suppression? Can we have too much of a good thing and cause choroidal vascular changes or induce atrophy? The data from CATT are, at best, inconclusive. I think analyses of some studies that have used spectral domain OCT will tell us whether or not there is an issue with atrophy in these eyes.

Dr. Kaiser: Do you think the type of OCT system used could have influenced other findings in the CATT?

Dr. Slakter: I think p.r.n. dosing might have fared better if spectral domain OCT had been used, because we don’t know what we were missing.

Dr. Kaiser: Dr. Slakter, your reading center read the HARBOR dataset, which, in a way, mirrored part of the CATT, in that patients were treated with ranibizumab monthly and p.r.n., but investigators used spectral domain OCT in HARBOR.3 Can you enlighten us with any findings from that study?

Dr. Slakter: I can tell you the ability to identify very tiny bits of fluid, the subtle findings that time-domain OCT would easily have missed, may be important. The HARBOR study will look at that detail, as well as other factors that we can identify with spectral domain OCT that couldn’t be done before.

Dr. Jain: In clinical trials and studies, researchers are bound by the entry criteria and treatment guidelines. In CATT for example, only time-domain OCT was utilized. While in other clinical trials, a fixed amount of OCT change was required to warrant re-treatment. In clinic, I only use SD-OCT and will treat a patient as soon as I see changes that demonstrate worsening. Thus, in my opinion, a treat-and-extend protocol is a hybrid between p.r.n. dosing and on-label dosing regimen, possibly giving us the best of both paradigms.

Dr. Kaiser: Two other studies — IVAN and MANTA — also compared ranibizumab and bevacizumab.4,5 Did they show anything different from the CATT, Dr. Ehlers?

One other factor to consider is that the number of serious adverse events tends to be higher in the p.r.n. arms and not in the monthly arms. What that means, again, we just don’t know.

— Justis Ehlers, MD

Dr. Ehlers: Findings from IVAN and MANTA were similar to those from the CATT from a trend standpoint, in that the two agents produced similar visual acuity results.

Dr. Kaiser: Dr. Slakter, how would you summarize the findings of studies comparing the efficacy of ranibizumab to bevacizumab to date?

Dr. Slakter: If you use the drugs monthly, outcomes are similar. When you use an alternate treatment regimen, such as p.r.n., there may be differences that are important to the patient, with ranibizumab having better anatomic and visual outcomes than bevacizumab on a p.r.n. basis.
Overall, as we’ve seen repeatedly, regular monthly treatment produces the best visual result of anything we’ve done to date in clinical trials, and that’s why the results of the treat-and-extend studies will be important.

**Safety Signals**

**Dr. Kaiser:** Dr. Ehlers, what’s your opinion of the safety of ranibizumab and bevacizumab?

**Dr. Ehlers:** We’re gaining information, but we don’t have definitive answers yet. The IVAN study was designed to be folded into CATT to enable meta-analysis. At 1 year, researchers looked at the safety differences and determined there was no difference between the drugs in the proportion of patients experiencing serious systemic adverse events. Ironically, the IVAN study showed a statistically significantly higher risk of heart failure and myocardial infarction with ranibizumab compared with bevacizumab. The 2-year data from CATT, however, showed the proportion of patients with one or more systemic serious adverse events was higher with bevacizumab than with ranibizumab. What that means we just don’t know, because some of those events have not been associated with anti-VEGF use.

The IVAN data showed that bevacizumab reduces serum VEGF levels more than ranibizumab, and monthly treatment reduced serum VEGF levels more than p.r.n. treatment. From that data, there’s no correlation between serum VEGF reduction and adverse events. We’re still evaluating whether or not that’s involved in systemic safety, but it’s something to watch.

One other factor to consider is that the number of serious adverse events tends to be higher in the p.r.n. arms and not in the monthly arms. What that means, again, we just don’t know.

**Dr. Hariprasad:** At 2 years, CATT showed about a 25% higher incidence of serious adverse events in the bevacizumab arm compared with the ranibizumab arm, which was significant \((P = 0.009)\). We don’t know why. I think we have to advise our patients that there may be safety differences between the two agents.

In addition, the IVAN data are showing significantly greater systemic VEGF suppression with bevacizumab compared to ranibizumab. To add to the safety concerns, we have to consider the recent drug compounding issues with bevacizumab — only adding another layer of complexity to how we advise our patients.

**Dr. Kaiser:** Are there any safety signals between ranibizumab and aflibercept?

**Dr. Jain:** They are essentially equal. Based on unpublished data, there are no statistical differences nor are there trends with one versus the other up to 2 years out.

**Patient-specific Treatment Regimens**

**Dr. Kaiser:** What treatment regimen do you follow for a treatment-naïve patient?

**Dr. Slakter:** I administer aflibercept on a treat-and-extend basis.

**Dr. Hariprasad:** When using aflibercept, I use a fixed-dosing regimen in the majority of patients. I start out with 3 consecutive monthly injections in essentially all patients. If dry at month 4, I start an every 8 week fixed dosing regimen for year 1. If the patient has a thickened OCT at month 4, I continue monthly aflibercept until the retina is dry. In year 2, I switch to a treat and extend paradigm. When using bevacizumab or ranibizumab, I routinely use a treat-and-extend regimen.

**Dr. Jain:** I treat-and-extend with aflibercept, but if the macula is dry after the first injection, I start
extending. I’ll go to 6 weeks, 8 weeks and up to 10 weeks and maintain at 10 weeks with aflibercept.

Dr. Kaiser: Dr. Jain, you’re doing treat-and-extend from baseline with aflibercept. I assume you evaluate the patient 1 month after the first injection, and if the macula is dry, you extend to 6 weeks. Do you think a loading dose matters?

Dr. Jain: Researchers in the MANTA study achieved the best visual outcomes when they gave three loading doses. When they switched to p.r.n. dosing, patients lost 1.5 to 2 letters. I think the loading dose matters to the extent that we can measure it with OCT. If OCT shows no fluid after one injection, however, what are you really loading?

Dr. Kaiser: Do you think there are loading dose issues?

Dr. Ehlers: Most of the studies have shown the main increase in visual acuity over the first three injections. However, CATT showed a similar curve and did not use a mandatory loading dose. I think it’s still unclear whether a loading dose is helpful.

In your treatment-naïve patient, is the other eye healthy?

Dr. Kaiser: Yes.

Dr. Ehlers: I often use a modified p.r.n. regimen. I would start with p.r.n. dosing, but if significant edema and vision loss were to occur, I would shift to treat-and-extend. If a minimal amount of edema is shown on OCT but vision isn’t significantly affected during a recurrence, I would continue with p.r.n. and monitor the patient monthly.

Dr. Kaiser: I treat-and-extend with aflibercept from baseline. I don’t necessarily start with a loading dose from baseline. I bring the patient back in 1 month for an injection, and then the next treatment is 1 month or 6 weeks after that.

Suppose a patient’s second eye becomes affected. Let’s say the first eye has geographic atrophy or disciform scars. What do you do?

Dr. Slakter: Whether it’s the first eye or the second eye, my goal is to keep the macula dry. I’m very attentive to the first eye, because you don’t know when that eye will become the better eye.

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In my opinion, only a small number of patients are true nonresponders — people whose retinas don’t change after treatment with an anti-VEGF agent. I think most patients, with any of the drugs, show some response, and then the question becomes, which drug will work best for that particular disease pattern.

— Jason Slakter, MD

Dr. Hariprasad: As a side note, before aflibercept became available, my patients with bilateral disease would have to come in every 2 weeks to have one eye and then the other eye treated. The fixed-dosing regimen of aflibercept every other month is a godsend to these patients because they don’t need to see me as frequently.

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Re-treatment Signs

Dr. Kaiser: If you are using a p.r.n. regimen, how do you decide whether or not to treat?

Dr. Jain: My main criteria are visual acuity and intraretinal or subretinal fluid or cystoid macular edema. If I see a fibrovascular pigment epithelium detachment (PED) with some irregularities and fluid at the tails but not in the center, I might extend treatment a week or a few days at a time. I consider a serous PED as dry.

Dr. Kaiser: In terms of OCT data, the CATT investigators concluded the intraretinal fluid at the fovea correlated best with vision. So, do we really need to chase some cystic changes 3 mm or 4 mm away, or can we just use the foveal scan? What do you think, Dr. Slakter?

Dr. Slakter: The fact that fluid exists somewhere in the macula indicates that VEGF is being produced. Today, it may be cysts 1,000 microns from the fovea. A week from now, there may be cystic changes over the fovea. To me, any kind of
fluid in the macular area is an indicator of biologic activity, and I want to suppress that.

**Dr. Ehlers:** In addition to OCT-based criteria, I’m also concerned about hemorrhage.

One of the challenges for p.r.n. and treat-and-extend regimens is that we may see patients with a little bit of fluid that never changes. It might be extrafoveal, either subretinal or intraretinal, perhaps over an atrophic scar. Dealing with that can be a real challenge in terms of follow-up and treatment.

**Dr. Slakter:** It’s difficult to know what to do with fluid over a scar or atrophy. I’ll see the patient in a week or two to determine if it’s a durability effect or a therapeutic effect. If there’s no change and it’s over an area that’s clearly atrophic on spectral domain OCT or clearly over an area of fibrosis that’s essentially nonfunctional retina, to me, that is a stable situation. I’ll decide to pretend it’s not there and look at everything else, but I do want to confirm that it’s not changing at that early stage.

**Dr. Hariprasad:** Being a retina specialist today is difficult, because we have such a wealth of data from so many clinical trials. We have a great deal to learn about OCT and how we should use it to guide our treatment regimens. We’ve heard many times in this discussion that we want a dry macula on OCT, and CATT showed the more stringent the protocol, and the drier the macula, the more effective the vision gains are. But there’s an interesting finding in VIEW 1 and VIEW 2 — a “sawtooth” pattern on OCT — where the every-other-month dosing of aflibercept produced a fluctuation in OCT between 25 microns early on to about 12 microns by the end of the year. By the end of year 2, however, the every-other-month aflibercept group had the driest maculas on OCT. This shows us that despite minor fluctuations in OCT from less frequent dosing in year one, patients still did well visually and anatomically at the end of year 2.

**Dr. Slakter:** I would add a note of caution. When we divide these populations for subanalysis, we find some patients with fluid may not do as well visually. It may be that fluid present at certain time points isn’t a good thing.

**Dr. Ehlers:** Also, in the second year of the VIEW studies, when patients were switched to the capped p.r.n. regimen, they were still seen monthly. In the every-other-month arm, if fluid was present, patients could have been treated on a more frequent basis than they were in the first year, which may have contributed to the drying.

**Dr. Kaiser:** I think the sawtooth pattern also indicates that individualized treatment is important. HARBOR showed it very nicely. If you look at the number of treatments in the p.r.n. arm, there was no bell curve to show that patients did well with a certain number of treatments. Some patients needed two or three injections; some needed 24, and there’s no way to know at baseline who needs two and who needs 24.

**Defining Nonresponse**

**Dr. Kaiser:** How do you define nonresponse, Dr. Slakter?

**Dr. Slakter:** Defining nonresponse elicits probably the single biggest diversity of opinion in our field right now. I’ve identified three different levels of response. First, there’s what I call lack of durability; then there’s partial response and true anti-VEGF nonresponse.

When a macula is dry 2 weeks after treatment with ranibizumab, for example, but leaking again at week 4, I consider that lack of durability. That’s someone who is responding, but fluid is recurring...
sooner than expected. A partial responder is someone whose macula has less fluid but is never completely dry, even at 1 or 2 weeks. Fluid decreases and then increases again.

In my opinion, only a small number of patients are true nonresponders — people whose retinas don’t change after treatment with an anti-VEGF agent. I think most patients, with any of the drugs, show some response, and then the question becomes, which drug will work best for that particular disease pattern.

**Dr. Ehlers:** When we talk about what defines response, we don’t discuss vision, because it isn’t really part of it, but in the end, what really matters to patients is vision. Anatomically, some patients may respond brilliantly to the drug, but their vision doesn’t improve. When I think about switching drugs, the effect on vision is most difficult to predict.

**Dr. Jain:** We may have patients whose OCT scans show subretinal fluid, but their vision is 20/25. Is that a failure to respond to treatment? Our goal is to maintain vision, so I would say to that patient, “Let’s not rock the boat. Let’s keep you where you’re at.”

**Dr. Kaiser:** Dr. Ehlers, you start many of your patients with bevacizumab. At what point do you decide someone is not responding?

**Dr. Ehlers:** Owing to the heterogeneity of our patient populations, there is no clear-cut definition. In the end, it becomes more of a comfort and judgment call. At 1 month, I’d like to see significant response, not necessarily a dry macula, but some improvement. If I see zero response, I start to think about my diagnosis. That’s something else we must consider when a patient doesn’t respond to therapy. Is the diagnosis correct? Generally, if the diagnosis is correct and the response is suboptimal both visually and anatomically after 3 months, I start thinking about changing therapies.

**Dr. Kaiser:** Let’s discuss that aspect of managing AMD: when and how you switch therapy.

### Deciding When to Switch

**Dr. Kaiser:** Dr. Ehlers, if a patient isn’t responding to bevacizumab, what do you try next?

**Dr. Ehlers:** I usually switch to aflibercept, but I always discuss a change in therapy with patients. I’ve had some patients tell me they’d rather try the drug with the longer track record, so we switch to ranibizumab.

**Dr. Slakter:** Some individuals will not respond, for whatever idiosyncratic reason, to one drug or another. A couple of my patients started with aflibercept but seem to be doing better on ranibizumab. I’ve converted many more patients from ranibizumab or bevacizumab to aflibercept, and I’ve seen a fairly dramatic response. That is why I start with aflibercept. I weigh all three options and start with the one that I think may be best for each patient. I’m not married to one drug, however, and if a patient is having a suboptimal response to one, I will try a different one. We are fortunate that we have three medications from which to choose.

**Dr. Jain:** I recently completed a 6-month study* of patients who had incomplete responses with either bevacizumab or ranibizumab. After I converted them to aflibercept, I found their vision remained stable or improved slightly, but, more importantly, these patients got an extra 2-week break between treatments. That’s a huge benefit for patients.

**Dr. Hariprasad:** There’s much discussion about defining a suboptimal response, but when we see it, we know it. It’s based on either visual acuity, poor anatomy or the need for too frequent dosing. We also have to consider the patient’s perspective and communicate with our patients about their goals in terms of therapy.

Our options are limited: number one, we can increase the dosing frequency with bevacizumab or ranibizumab, although that creates a significant treatment burden and number two, we can increase the dose. The Super-dose Anti-VEGF (SAVE) trial showed some potential benefit with a higher dose,6 but the HARBOR study showed no effect with a quadruple dose of ranibizumab.3 Our third option is to switch to aflibercept.

If I start a patient with aflibercept, but he doesn’t respond as well as I expected, I increase the dosing frequency from every other month to monthly, because VIEW 1 showed a statistically significant benefit for monthly aflibercept compared with monthly ranibizumab. ■

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* Study not yet published.
New Insights from ARVO

Exploring patient outcomes when switching anti-VEGF therapies.

Dr. Kaiser: At the 2013 ARVO meeting, researchers presented numerous papers, describing outcomes after patients were switched from other anti-VEGF agents to aflibercept (Eylea, Regeneron). Dr. Hariprasad, what are your impressions of the data presented?

Dr. Hariprasad: Some 15 presentations dealt with switching anti-VEGF agents (one of which was from our group at the University of Chicago). I found wide variability in these studies — their definitions of suboptimal responders, inclusion/exclusion criteria, types of imaging used — but all of them studied suboptimal responders to ranibizumab (Lucentis, Genentech) or bevacizumab (Avastin, Genentech). This is what I took away from those studies:

- 1 study showed that vision and OCT didn’t change.
- 3 studies showed that vision didn’t change, but OCT improved.
- 1 study showed that vision improved, but OCT stayed the same.
- 10 of 15 studies showed that vision and OCT improved.

The key message is that no patient lost vision or showed anatomic worsening on OCT. This leads me to believe we can safely switch to aflibercept from older-generation anti-VEGF agents, and a distinct population of patients will respond and may even benefit in terms of dosing regimen.

Dr. Ehlers: Most of these studies were retrospective, and interpreting findings and drawing significant conclusions from them is difficult. I did note, however, that anatomic improvement seemed to be fairly universal, while vision was somewhat variable. For example, Barbazetto and colleagues looked at 80 eyes and then a subset of 12 eyes that lost vision when they were switched to aflibercept. Of those 12 eyes, seven returned to baseline vision with continued therapy, while all 12 improved from an anatomic standpoint.

Dr. Kaiser: In a study led by Rishi Singh at the Cleveland Clinic, we are prospectively following about 26 patients, who had three injections of aflibercept after switching and then an injection every 8 weeks. At 6 months, these patients had gained about seven letters of vision. I didn’t expect to see such a large improvement in such a short period. (There is preliminary, unpublished data addressing this in the ASSESS study.)

Dr. Hariprasad: Especially in the hardest-to-treat patients.

Dr. Slakter: And in chronically treated patients.

Dr. Kaiser: Why do you think this is, Dr. Slakter?

Dr. Slakter: In considering possible reasons for aflibercept showing a better treatment response, we might consider tachyphylaxis for patients who have been receiving chronic therapy. However, I have seen patients who received only one or two doses of ranibizumab or bevacizumab respond dramatically after being switched to aflibercept, so I can’t consider that a tachyphylaxis issue.

The ability of aflibercept to bind placental growth factor (PIGF) is something to consider. In my practice, we found that a majority of chronically treated patients with sub-optimal response have features of either a thick choroid that might...
suggest underlying central serous chorioretinopathy (CSC) or have patterns on indocyanine green angiography suggesting PCV. Many of the patients whom we are considering poor responders have these other features. Some researchers have studied some of the growth factors or angiogenic factors in AMD, and PlGF never seems to be on the list, but that’s in “typical” AMD. The question is: what about cases with central serous or polypoidal components? Maybe PlGF does play a role.

The tight binding affinity of aflibercept may be part of the answer. If the binding affinity is tighter and longer, it will hold the VEGF and prevent it from hitting its receptor. Most poor responders have RPE elevations. Most of them have occult-type CNV on fluorescein. Most of them have at least some degree of sub-RPE fluid. From the moment we inject any of the anti-VEGF drugs, regardless of the size of the molecule, the lowest concentration of drug from day 1 is under the RPE, so that would be the area where binding affinity might play the biggest role. The driving factor may be as simple as the affinity of the aflibercept for VEGF.

Evidence on Switching

Dr. Kaiser: As we’ve seen at ARVO 2013, research into the efficacy of switching anti-VEGF agents to treat AMD continues to mount. Two recently published papers are representative of the data being reported. Let’s discuss our own clinical experiences in comparison with the findings of these researchers.

In a retrospective study, Ho and colleagues looked at 96 eyes of 85 patients who had been treated with bevacizumab, ranibizumab or both and then were switched to aflibercept. After 4 months, the researchers found most eyes demonstrated stable visual acuity and anatomic improvements.

What clinical features would lead you to switch anti-VEGF therapies?

Dr. Hariprasad: Suboptimal resolution of macular fluid and inability to stabilize or improve vision leads me to try a different drug. I also consider switching to aflibercept if the patient has a too-frequent treat-and-extend schedule on an older generation therapy.

Dr. Ehlers: Switching may be warranted if fluid persists, or if fluid recurs rapidly on a p.r.n. or a treat-and-extend regimen.

Dr. Jain: The main reasons I switch drugs are the following: 1) incomplete response to therapy; 2) inability to extend to greater than 6 to 8 weeks on current therapy; 3) a patient’s desire to use an FDA-approved medication.

Does Lesion Type Still Matter?

Dr. Kaiser: With older treatments for AMD, lesion composition was important. Is that still the case in this era of anti-VEGF therapy?

Dr. Slakter: When we began using anti-VEGF therapy, we thought lesion type was no longer as important. As we’ve gained experience with these agents, however, we’re starting to see subgroups of patients who may do better or worse with treatment.

Retinal angiomatous proliferation lesions, which were the most difficult to treat with the older therapies, have become some of the most responsive to anti-VEGF therapy, although they may need more treatment. On the other hand, if I see a patient with an occult lesion with features that suggest a polypoidal component even on fluorescein, I start to worry that this patient may not be as responsive. It doesn’t necessarily change what I do from day one, but it certainly changes what I might say to the patient and what my expectations are going forward it also alerts me to pay more attention to that. So, I think that lesion type and classification — even with anti-VEGF therapy — may be important. Certainly, as we move into a new era of adjuvant therapies, lesion type and classification may become critical for custom-tailoring therapy.
**Dr. Slakter:** I switch from other anti-VEGF agents to aflibercept in several situations. One is when an ongoing monthly regimen of the original agent fails to dry the macula in spite of at least four injections. In some cases, I have patients who have received injections as close as every 2 weeks without resolution of exudation. Another indication for switching therapy is when I’m unable to extend the treatment interval beyond 4 to 5 weeks without recurrent exudation. If this happens, I try aflibercept to get a longer treatment interval.

**Dr. Kaiser:** What treatment regimen do you follow when you switch to aflibercept?

**Dr. Hariprasad:** I treat monthly, and then, depending on the clinical response, I conservatively treat and extend.

**Dr. Ehlers:** My regimen varies based on the clinical scenario or the patient’s desires and priorities. Typically, I treat monthly until the macula is dry or a plateau is reached, and then I switch to treat-and-extend or p.r.n.

**Dr. Slakter:** I initiate treatment with the standard three loading doses used with treatment-naive patients, followed by a slow treat-and-extend strategy. Given that many switched patients have chronic exudation, I plan for several monthly treatments before extending.

**Dr. Jain:** For a patient who has had an incomplete response, I load with three aflibercept injections. For transition patients who have had a complete response to previous anti-VEGF therapy, I give a single injection of aflibercept, have them return in 6 weeks, re-treat and extend to 8 weeks if the macula is dry.

**Dr. Kaiser:** How many cases do not respond to switching to aflibercept?

**Dr. Ehlers:** A significant proportion of patients respond from an anatomic standpoint with less predictable functional improvement.

**Dr. Slakter:** About 80% to 90% of my patients show some or major reduction in leakage or extension of treatment interval. About 10% show no significant difference using aflibercept.

**Dr. Jain:** It depends on how you define “respond.” I tend to base my decision less on OCT findings and more on visual acuity and subjective changes that patients report to me.

The bottom line in my experience of switching patients to aflibercept is that we can increase the interval of treatment by 2 weeks compared with other anti-VEGF agents and maintain or slightly gain some visual acuity.

**Dr. Kaiser:** Does your experience mirror the Ho article?

**Dr. Hariprasad:** Yes. In fact, my resident Dr. Khushboo Agrawal and I presented our research at this ARVO meeting. We looked at 35 patients whom we were unable to treat and extend beyond 6 weeks with ranibizumab or bevacizumab, and we switched them to aflibercept. They showed an improvement in vision and drying on OCT. We also administered the Visual Function Questionnaire (VFQ-25) and found an improvement in the patients’ perceptions of their disease, mainly driven by fewer visits.9

**Dr. Ehlers:** I believe my experience mirrors the findings of Ho and colleagues fairly closely, but I do think I have seen a higher percentage of anatomic and vision improvement.

**Dr. Slakter:** I see similar anatomic benefits, but in many patients, I see a significant visual benefit, as well, beyond what Ho reported. I believe the major limitation in vision gain is related to the extent of chronic damage already present when we change treatment. If therapy is switched sooner, there’s more potential for improvement.

**Dr. Jain:** I have found a slight improvement in visual acuity at the 6-month mark, otherwise my outcomes are similar to those reported by Ho.

**Dr. Kaiser:** Are patients generally accepting of a switch to a different anti-VEGF agent?

**Dr. Hariprasad:** Patients definitely have questions about my decision-making process and the reasoning behind my recommendation to switch therapies. Billing issues sometimes arise; however, acceptance is high.

**Dr. Kaiser:** What OCT features do you monitor to see if switching was beneficial?

**Dr. Slakter:** Initially, I was observing only for reduced subretinal fluid and retinal cystic changes. Over time, however, I have found many instances when a chronic PED that was not changing or was even worsening when treated with other anti-VEGF agents now shows reduced height or total resolution with aflibercept.
Therefore, I’ve now added RPE elevation to the parameters I monitor to determine the effect of the change in medication.  
**Dr. Jain:** I also look for PED height and volume, as well as cystoid macular edema volume and subretinal fluid volume.  
**Dr. Ehlers:** I look for evidence of exudation or disease activity, including intraretinal fluid, subretinal fluid, sub-RPE fluid and extent of pigment epithelial elevation.  
**Dr. Kaiser:** Why do you think patients who are switched to aflibercept have anatomic improvement?  
**Dr. Hariprasad:** I can only theorize that the anatomic improvement is related to aflibercept’s higher affinity to VEGF and its inhibition of PlGF, or the patient may have experienced tachyphylaxis to the previous anti-VEGF agent.  
**Dr. Ehlers:** At this point, we don’t know why one patient may respond to one anti-VEGF agent versus another. Responses may be patient-specific or related to the various VEGF inhibitors. There’s likely a difference between true nonresponders and those with incomplete response or early recurrence with other anti-VEGF agents. I agree that tachyphylaxis may play a role in some patients. The additional blocking of PlGF may be important, as well as differences in drug potency or binding affinity.  

**Refractory and Recurrent AMD**  
**Dr. Kaiser:** Yonekawa and colleagues recently published a retrospective chart review of 102 eyes of 94 patients with chronic refractory or recurrent neovascular AMD. They found converting these patients to aflibercept resulted in stabilized vision and improved anatomic outcomes, while allowing injection intervals to be extended. Are the clinical features that Yonekawa and colleagues used to decide to switch agents similar to those used by Ho and colleagues? Are they similar to what you use in your practice?  
**Dr. Ehlers:** As with any retrospective study, assessing what factors prompted a change in therapy is difficult. In general, patients who are refractory or rapidly recurrent are those whom I most frequently consider switching.  
**Dr. Slakter:** In the Yonekawa paper, there are no clearly defined criteria for switching. Patients were switched for a variety of reasons and with various prior treatment histories. In Ho’s paper, there seems to be a somewhat better definition of the switch criteria but again this was retrospective in nature. The descriptions generally apply to what I do in practice.  
**Dr. Kaiser:** Do you switch patients who are recurrent or only those who are refractory?  
**Dr. Hariprasad:** Both.  
**Dr. Ehlers:** I consider possible alternative therapies for either of these types of patients.  
**Dr. Slakter:** I switch when a patient is not showing an adequate response to treatment, or when a regular schedule of frequent injections is required to control the exudation, or if it becomes necessary to shorten the interval to control the exudative process. For example, if a patient has been stable on every-6-week treatment and suddenly develops new exudative activity requiring more frequent injections, I consider switching drugs.  
**Dr. Jain:** I switch all types of patients — recurrent, refractory and complete responders who cannot be extended.  
**Dr. Kaiser:** How many injections do you consider adequate to determine if a switch is required?  
**Dr. Hariprasad:** This is a difficult question to answer. Suboptimal responders can occur in year 1 or even year 2 of therapy. In most cases, we can identify suboptimal responders before the end of 1 year.  
**Dr. Ehlers:** It’s impossible to know what’s “adequate.” Generally, if I detect no anatomic response after three injections, I start to discuss the possibility of switching drugs.  
**Dr. Jain:** Typically, I consider switching after three injections.  
**Dr. Slakter:** I prefer to give a minimum of four injections to see if an anti-VEGF treatment is working. This is one injection beyond the usual loading dose and will typically be sufficient to determine if there is a beneficial response. If I observe slow but gradual improvement on each examination, I continue the same medication until no further improvement is noted. Therefore, in some cases, more than four injections may be required to determine if a change in medication is needed.  
**Dr. Kaiser:** Why do you think there’s a disconnect...
between the visual and anatomic results in the Yonekawa study?

Dr. Ehlers: Determining the specific etiology of the vision/anatomy disconnect is difficult. The chronicity of lesions may influence the visual outcomes in these cases. In addition, the short follow-up may also influence the overall functional outcome.

Dr. Slakter: As in the Ho study, many anatomic reasons relate to damage of the retina or RPE that will limit visual outcome in spite of a positive anatomic response. Also, there was a mean of just over three injections in this study, suggesting limited follow-up. Perhaps the vision would have improved with ongoing therapy and time.

Dr. Jain: There has always been a disconnect between OCT findings and visual acuity outcomes. This shows us that we cannot use a single method to determine how best to treat our patients. All aspects are important: visual acuity, anatomy, clinical examination and the patient’s subjective experience.

Dr. Kaiser: Is the treatment regimen after the switch to aflibercept, as described in the Yonekawa paper, similar to what you follow in your practices?

Dr. Ehlers: The treatment regimen is not particularly clear in the manuscript. The multi-clinician and retrospective nature of the study make identifying specific regimens difficult. Generally, my approach is to switch to a fairly consistent dosing regimen (e.g., monthly) until the macula is dry or a plateau is reached. Once that is achieved, I try a treat-and-extend or p.r.n. regimen, based on the patient’s preference and the clinical features.

Dr. Kaiser: Do you have any concerns about switching anti-VEGF agents?

Dr. Slakter: No.

Dr. Jain: None to date.

Dr. Hariprasad: Further research is necessary, but evidence showing benefit is mounting in the literature. I have no concerns, except that we need to give patients realistic expectations when switching. We should explain that there may be no benefit or only anatomical benefit and no vision gain. Hopefully, both vision and OCT will improve, but this isn’t always the case.

Dr. Kaiser: We’ve talked at length about the diagnosis and treatment of macular degeneration, particularly in light of multiple anti-VEGF agents from which to choose. We look forward to receiving new data from continuing research on these and other therapies to guide our clinical decisions.

References


