JANUARY/FEBRUARY 2013

Retinal PHYSICIAN

Emerging Concepts in Anti-VEGF Treatment

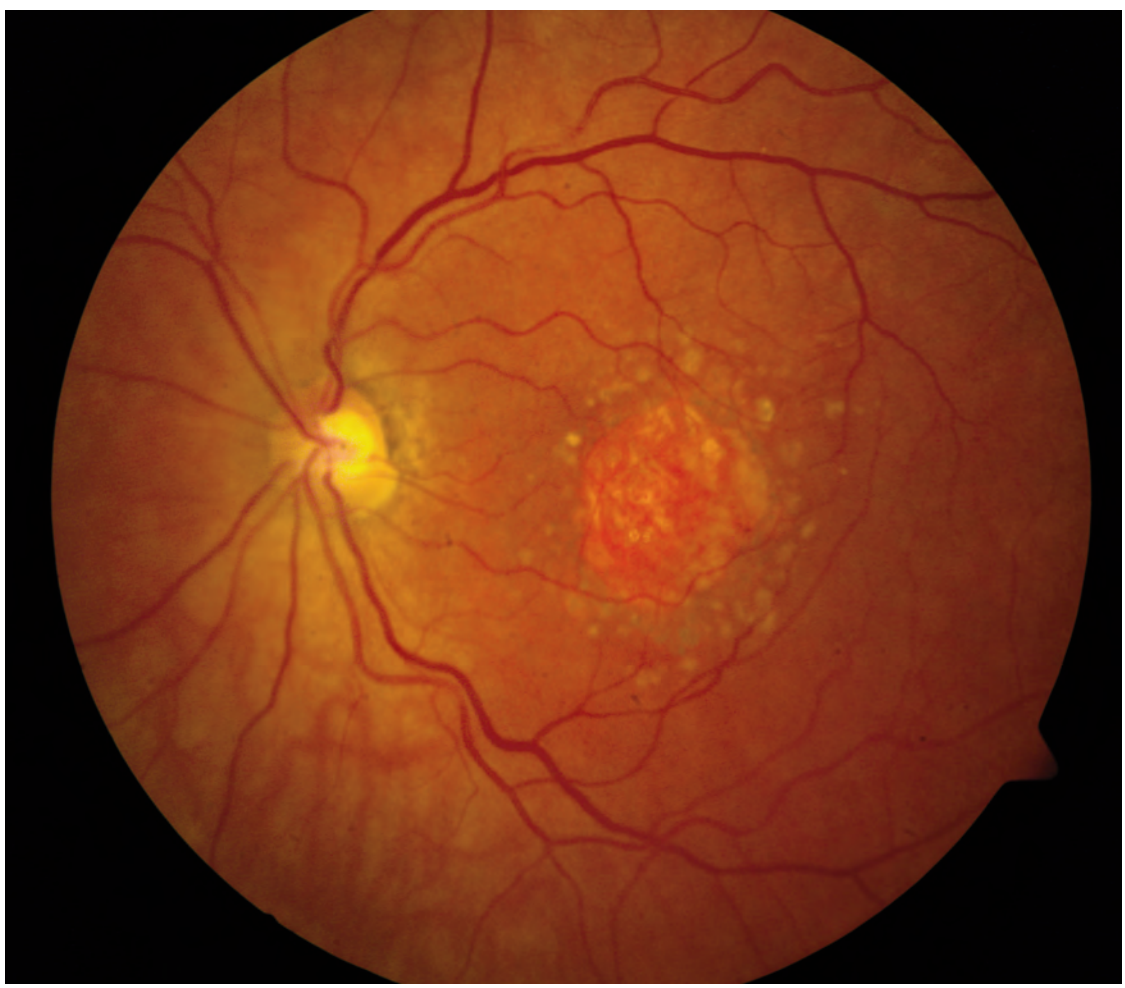

PHOTO COURTESY OF NATIONAL EYE INSTITUTE, NATIONAL INSTITUTES OF HEALTH

Roundtable Faculty:

Peter K. Kaiser, MD (Moderator)
David S. Boyer, MD
David M. Brown, MD
Karl G. Csaky, MD
Jeffrey S. Heier, MD

INSIDE:

■ **Recap of expert roundtable panel** ■ **Highlights from key ASRS presentations** ■ **Case studies**

Sponsored by an unrestricted educational grant from Regeneron Pharmaceuticals.

Treating the Patient

Newer diagnostics are helping tailor more specific treatments for people with retinal disorders.

Peter Kaiser, MD: When a patient initially presents with AMD, what diagnostic tests are performed to verify the diagnosis?

Jeffrey Heier, MD: After obtaining the history and performing the exam, if we have a high suspicion for AMD, we will obtain fluorescein angiography (FA) and spectral domain OCT in the form of volume scans. The scans usually confirm neovascular AMD or bring to light variants such as vitelliform disease or high-risk drusen that are masquerading as AMD. I want a view of the entire macula to fully assess what is going on. It is too easy to miss disease with single-line scans.

David Brown, MD: Particularly in AMD, there is too much risk of selection bias if you only evaluate a few scans. If you do not look at *all* the best high-resolution scans, you are not giving your patient the best care he can receive.

Dr. Kaiser: What role does FA play in the current management of AMD and in determining lesion size and composition?

Karl Csaky, MD: If someone presents with visual complaints and I am not certain there is absence of fluid on the OCT scans, I will order FA. Even with volume scanning on the OCT, there is still a chance you could miss some fluid. The fluorescein can add information. For example, you can then see an area of increased hyperfluorescence with some leakage, which would indicate the presence of a neovascular complex. For me, FA still has an important role in making the diagnosis.

Dr. Heier: For new patients in my clinic, I order both OCT and FA in order to appropriately evaluate disease status. Our established patients already have SD-OCT by the time I see them, and if changes warrant further evaluation, we order the FA at that time.

Management Strategies

Dr. Csaky: I do not think the lesion composition is as important as it was in the past because the anti-VEGF injections seemed to work across all classifications. The only caveat to that is when I am led to believe there is polypoidal activity — where evidence suggests the anti-VEGF treatments are not as effective as photodynamic therapy (PDT). Many patients already know about the anti-VEGF medications and how effective they can be in some cases; I want to ensure that patients also know that we might make a switch to PDT earlier in their treatment regimen.

David Boyer, MD: For patients who have definite polypoidal disease, the EVEREST trial showed anti-VEGF therapy was visually equivalent to PDT but that the polyps seemed to close down better with PDT. In our hands, aflibercept (Eylea, Regeneron) for polypoidal disease may be better, but I am not yet certain why that is.

Dr. Heier: Also, in patients with a suspicion of vitelliform disease, I obtain autofluorescence to help show the lesion. It is a little more difficult to diagnose with fluorescein alone.

Dr. Kaiser: What imaging device(s) do you use for follow-up?

Dr. Boyer: I usually obtain an OCT and compare it to the previous scans. I typically utilize a treat-and-extend protocol, so I treat until dry and then I will extend it by 1 or 2 weeks depending on the status of the other eye. If after several injections the patient is not dry, I double the dose and bring him back in 2 weeks to see if I have missed a masquerade syndrome or if the lesion is non-VEGF responsive. I then run an indocyanine green angiography (ICG), enhanced depth OCT and autofluorescence.

What's Important to Notice?

Dr. Kaiser: How do you define "wet" vs. "dry" and what do you look for on OCT to make that determination?

Dr. Boyer: To me, dry means there is no intraretinal cysts or subretinal fluid left as far as I can tell on OCT. I do not tolerate intraretinal fluid, and I certainly will not

Highlights from a roundtable held during the Retina Society Meeting in Washington, D.C. on October 5, 2012. View video from the roundtable at http://www.retinalphysician.com/regeneron.aspx.

tolerate subretinal fluid. I may over-treat as a result, but if I can eliminate all the fluid, I go to an extend mode.

Dr. Kaiser: Where do you place subretinal pigment epithelial (sub-RPE) fluid within that classification scheme?

Dr. Boyer: I attempt to dry all eyes and in some cases, the sub-RPE fluid does go away. But if it persists after three or four injections, I move to a maintenance phase. Recently, I have been switching some of those non-responders to aflibercept because it seems it may close the detachments a little better.

Dr. Brown: New sub-RPE fluid, defined as darkness below the RP level that was not there on the previous scan, is always disease activity. Some large serous pigment epithelial detachments (PEDs) may or may not be related to wet AMD — they could just be a manifestation of their dry pump.

> **"We are probably underutilizing FA, based on CATT and HARBOR PRN data."**
>
> *— David Brown, MD*

Dr. Csaky: There is no set guideline that is applicable to a majority of patients with wet AMD. When is persistent fluid bad? I may tolerate a little subretinal fluid that remains despite several reinjections more than intraretinal fluid, which has been shown in the CATT study to be associated with more severe vision loss. It is those variations that necessitate individualized decisions. I am finding there is no 'one size fits all' treatment.

Dr. Boyer: The other eye's status and the overall health of a patient need to be considered as well. Some patients just cannot come in every 4 weeks. Either they do not have the caretakers or some other reason prevents them from coming. If the other eye was already lost to hemorrhage, I would continue to treat the patient's other eye monthly.

Dr. Heier: CATT and VIEW tell us these patients are not drying, that the majority will have some degree of fluid that can range from a few intraretinal cysts to much more. For me, if there is a small amount of fluid, volume scans are essentially unchanged over several visits and they have not undergone a drug switching protocol, I may leave them where they are. But, if a patient has a PED and it gets smaller after each subsequent injection, I continue to treat to achieve an effect. However, if I treat and the fluid dissipates but the PED is stable, I will not go after it.

Dr. Kaiser: Does anyone use other imaging besides OCT during routine follow-up visits?

Dr. Heier: You need to compare to the previous scans utilizing volume scans to ensure you are not missing subtle disease.

Dr. Csaky: If patients are not doing as well as I would like, I might run another FA to see what is occuring with the neovascularization on a year-to-year comparison. There was a small subgroup of patients in ANCHOR and HARBOR where the neovascularization grew but visions remained stable or improved, even on monthly ranibizumab (Lucentis, Genentech).

Dr. Brown: We are probably underutilizing FA, based on CATT and HARBOR PRN data. In the latter, the lesions continued to grow, which you would not know without FA. I think of PRN as Progressive Retinal Neglect. It may be that even though we think we are doing the right thing with treat-and-extend, we may be doing 'treat and extinguish.' If we allow lesions to leak at all, they may grow over time. The studies alluded to a dry OCT but leakage still presents on FA. In my opinion, if extending treatment out to 8 or 10 weeks is being considered, an angiogram should be done before going any longer.

Dr. Heier: What if you do not see leakage?

Pharmacy Compounding

Issues surrounding accreditation and methodology remain, as do ideas on how to store the medications.

Dr. Heier: When issues about contamination in bevacizumab became public, the American Academy of Ophthalmology (AAO) and the American Society of Retina Specialists (ASRS) issued recommendations for pharmacy accreditation and methods that should be used, and some pharmacies did not meet those standards.

Dr. Csaky: In the CATT study, we were very involved in testing the quality of bevacizumab. We performed extensive testing on both bioactivity and aggregation. The FDA required a great deal of testing to be done, which some compounding pharmacies do not require.

Dr. Kaiser: Fractionation is the big safety issue with bevaciuzmab in my mind. You have lost control in terms of what you receive and deliver into the eye. Are there steps we can take to ensure the sterility, to ensure the drug did not undergo a freeze/thaw cycle, and to ensure no contaminants are present?

Dr. Heier: We have to ensure our compounding pharmacy follows the recommendations of AAO and ASRS.

Dr. Kaiser: What about storage? Any pearls?

Dr. Csaky: We keep everything from the compounding pharmacy at 4 degrees and store it for a maximum of 3 months. You can start losing some activity in a syringe with bevacizumab, so practices should be careful with how much they purchase.

Dr. Kaiser: At the Cole Eye Institute, our fractionation is done by our own pharmacy under a sterile hood and using all the standard pharmacy procedures. We send out random samples of syringes from every lot for microbiologic testing before we actually use that particular lot. Does anyone test their compounded bevacizumab?

Dr. Brown: Initially, we followed the Bascom Palmer pharmacy guidelines and sent some for culture, some for endotoxins.

Dr. Csaky: We use a pharmacy in San Francisco that follows those guidelines.

Dr. Brown: I find fluorescein very difficult to read after anti-VEGF therapy, whether there is leakage or staining. OCT has become an invaluable tool. However, late leakage on FA in the absence of OCT activity usually means that the lesions are leaking but the RPE pump is doing an acceptable job. If there is no activity visible on OCT and no late leakage on FA, one can consider watching observantly.

Different Dosing Regimens

Dr. Kaiser: What are your dosing regimens?

Dr. Csaky: If I have a one-eyed patient with a hemorrhage in the fellow eye, I tend to be aggressive and treat on-label or go out to 6 weeks at most between injections. For the routine patient, I will try to go beyond monthly injections or try to go beyond every 6 weeks.

Dr. Heier: About a third of my patients have disease in the fellow eye with poor vision, but not necessarily submacular hemorrhage. For those patients, I treat somewhere around a 4-6 week interval. It might occur that each time I extend to 6 weeks, they are brittle and leaking but at 5 weeks they are okay.

Treatment Decision-making

Dr. Kaiser: How do you decide what treatment to use in a treatment-naïve patient who has confirmed wet AMD?

Dr. Brown: I show the patient a healthy eye on OCT and then I show him his scan, explaining that the fluid and thickness is why he cannot see. I explain that he is

going to need shots in his eye, and that we tend to use ranibizumab or aflibercept (I prefer FDA labeled treatment for patients, if possible), but insurance issues may necessitate using bevacizumab instead. We tell patients they will need at least three shots, and that 70-80% of patients will need injections for the rest of their lives.

Dr. Kaiser: Do you start your patients with FDA approved drugs? What about bevacizumab?

Dr. Heier: I start the majority of my patients on bevacizumab. I explain it is solely a cost issue, that it is an off-label use, but that the CATT study has shown both drugs do a good job. However, we have a very low threshold for switching them. If cost was not an issue, I would rarely use bevacizumab. In Massachusetts, we have received letters from insurers telling us that they have reviewed the results of CATT, that their experts have determined that the drugs are equivalent and they are asking us to use bevacizumab at least as first-line therapy.

> **"We tell patients they will need at least three shots, and that 70-80% of patients will need injections for the rest of their lives."**
>
> *— David Brown, MD*

Dr. Csaky: I believe a dry retina is a happy retina and if I can get that more effectively with aflibercept or ranibizumab — which the data support — I will use one of those first. If there is a co-pay insurance issue, then I will use bevacizumab.

Dr. Heier: The reality is that bevacizumab is effective for many patients. If a patient has the typical strong anti-VEGF response, then I have a very low threshold for moving them off. I probably start 80% of patients on bevacizumab, but my overall numbers are probably 50% because I move them off so quickly.

Dr. Brown: If it was not for the compounding pharmacy issues, I would agree. But you have to explain to patients that we have two approved drugs and one that is not approved, but is much cheaper. If insurance will pay for the approved drug, I feel more comfortable with that from a safety standpoint. From an efficacy standpoint, I absolutely agree with you — 50-70% of patients do great with monthly bevacizumab. But until we can have it in a form that is safe from endophthalmitis, I think you are exposing patients to an unecessary risk if they have good insurance.

Dr. Boyer: I tend to start with bevacizumab, but again have a very low threshold because I utilize treat-and-extend and I want the drug that dries the eye most effectively, most quickly and for the longest duration of time. I have had patients extended out to 2-2.5 months with good vision and I have never moved them to another treatment. But if patients do not dry up after a couple of treatments and I do not see a positive response, then I immediately switch them.

Dr. Csaky: Overall, most of the neovascular AMD clinical trial data supports the notion that aflibercept and ranibizumab produce better anatomic results than bevacizumab, so I am a little less likely to use bevacizumab. My approach is to start out being as aggressive with getting whatever regression of the CNV and removal of fluid I can, so down the road they may need fewer injections. I am willing to try anything to get them on a schedule that will result in fewer injections later on.

Dr. Heier: The VIEW data suggests that aflibercept may actually dry the retina more thoroughly than ranibizumab. We have all had a large batch of suboptimal responders over the past 6 or 7 years. We had roughly 150 patients we switched to aflibercept and after a single injection, 75% had a significant anatomic

response, but the visual response was small. Now, in a year we may have suboptimal aflibercept responders we will switch to ranibizumab, but the VIEW data suggests aflibercept may provide an advantage.

Dr. Kaiser: I currently use aflibercept in most of my treatment-naïve patients because I think it is identical to ranibizumab in terms of efficacy, and better in terms of cost and duration of action. In patients without insurance coverage or with financial/insurance issues, I start with bevacizumab.

Dr. Csaky: At least having aflibercept in the background allows you to offer something to the patient down the road. Dr. Heier's approach of having bevacizumab as a first-line, then ranibizumab, and then aflibercept as a step-wise approach needs to be considered. There is no data to suggest that any one approach is better than another.

Dr. Boyer: A study by Saada and colleagues showed bevacizumab failures who were switched to ranibizumab had an improvement,[1] but the reverse was also true. We are going to have patients who are non-responders to aflibercept and may have to go back to ranibizumab, which may work.

Dr. Heier: We may all have patients who do better with bevacizumab than ranibizumab, but more often, it is the other way around, and there may be the same gradient with aflibercept and ranibizumab. The one thing we have overlooked is we have labeled usage saying we can treat every other month with aflibercept and have good outcomes.

Dr. Csaky: That is what has surprised me the most — the number of patients who need injections every 6 weeks, or even every 5 weeks instead of every 2 months. We have seen very inconsistent results with that 2-month window in our practice.

Dr. Brown: There may have been some selection bias because they were typically monthly ranibizumab patients we switched over. But even in the treatment-naïve patient, I think it is 20-30% who have to be treated more frequently.

Dr. Boyer: I find that many patients cannot extend to 2 months before experiencing leakage.

Dr. Heier: In suboptimal responders, I may treat with a double dose monthly of ranibizumab, but it is reasonable to expect they would require more therapy. We know from the VIEW results that only about 50% were dry. At 1 year, it stands to reason patients were fluctuating throughout even with monthly therapy. About 73% were dry at 1 year versus 60% on ranibizumab, so there is still a large number of patients who have fluid even with monthly therapy.

Dr. Brown: Ranibizumab has the most years of patient use. It has the shortest systemic half-life and the least anti-VEGF suppression. In diabetic patients (with DME or AMD), decreased VEGF receptors in the myocardium leads to silent ischemia and any little bit of VEGF suppression may potentially block the development of collaterals. If you worry about any of that, then you should start with ranibizumab.

> **"I currently use aflibercept in most of my treatment-naïve patients because I think it is identical to ranibizumab in terms of efficacy, and better in terms of cost and duration of action."**
>
> *— Peter Kaiser, MD*

Dr. Csaky: For patients who have been on ranibizumab for 5 to 6 years or longer, there has been no long-term retinal degeneration or long-term ill effects. At this time, we do not have that information with aflibercept and it has a much higher affinity for VEGF. It gives me a little room for pause, especially if someone has an existing geographic atrophy (GA) and presents with choroidal neovascularization. I try to avoid aflibercept in those patients. Again, we do not have the data, but it does give me pause.

Non-responders and Suboptimal Responders

Dr. Kaiser: How do you define a suboptimal responder?

Dr. Heier: Someone who has intraretinal or subretinal fluid, and that fluid has persisted following at least three monthly injections. That does not mean that they do not have good vision. There may be patients with 20/30 vision but persistent fluid. If I can get rid of the fluid, maybe there is a line or two of vision still to gain.

Dr. Brown: A non-responder is often a misdiagnosed central serous retinopathy, but maybe because the patient has drusen, we call it AMD. But a half-dose of PDT later and the retinal fluid is gone, and the patient does not need the injections.

Dr. Kaiser: How do you differentiate a non-responder from a suboptimal responder from a responder?

Dr. Boyer: After three injections without a response, I may double the dose (depending on what I am using) and have the patient return in 2 weeks. If there is absolutely no response, then I probably have the wrong diagnosis. If I do not see any VEGF response, I might switch to aflibercept or ranibizumab. If there is still no response, I start enhanced depth imaging. I will start autofluorescence, but I am looking for another diagnosis at that point.

Dr. Csaky: Some patients have extensive polypoidal disease, which is extremely recalcitrant to the anti-VEGF drugs. That is not necessarily a misdiagnosis, but it may require redirecting your therapy toward something else.

Dr. Heier: I learned years ago that ICG is clearly still useful, and some of the newer imaging devices can aid us in appreciating more of these masquerade syndromes like polypoidal or retinal angiomatous proliferation. Now I look at ICG very early on.

When Nothing Else Can Be Done

Dr. Kaiser: Is there ever a point where you will not treat because the eye is too far gone?

Dr. Csaky: In a disciform scar, I look for any degree of subretinal fluid or intraretinal fluid. You might not get them back to 20/40, but you can increase some of their ambulatory vision and may get to 20/80 even if they have significant fluid. If there is a dry disciform scar, I may try a single injection but I am much less optimistic. If there is fluid over a scar, some patients may benefit from the anti-VEGF medications.

Dr. Brown: I always try that, and it almost never works and patients cannot tell a difference between the two eyes.

Dr. Csaky: But patients always want to feel like everything was done.

Dr. Heier: I will give an injection and ask them for feedback. If patients cannot recognize a change, I see little point in continuing. There are some who notice or report a benefit, albeit a small benefit. Whether it is real or not is difficult to accurately ascertain, but even if it is subjective, I believe the emotional benefit can be helpful for patients who are already prone to depression.

Dr. Boyer: I think it is very hard to stop treatment knowing that if the patient comes back with a hemorrhage, he usually cannot regain his vision. A major hemorrhage is the kiss of death with this disease, so I tend to follow these patients forever. But we have to look at the whole patient and how they are functioning and try to avoid that major hemorrhage if their get-around eye is 20/400.

Dr. Csaky: You have to consider the visual response as well. If the retina is dry but they are at 20/200 you are going to be in a holding pattern to keep things stable. There will be a good number of patients who have an anatomic response but no visual improvement. ✦

Reference

1. Gasperini JL, Fawzi AA, Khondkaryan A, Lam L, Chong LP, Eliott D, Walsh AC, Hwang J, Sadda SR. Bevacizumab and ranibizumab tachyphylaxis in the treatment of choroidal neovascularisation.Br J Ophthalmol. 2012 Jan;96:14-20. Epub 2011 Jul 26.

Summarizing the Key Anti-VEGF Study Results

Several comparison studies should help guide clinicians through the decision-making process.

Dr. Kaiser: The results of several studies — CATT, IVAN, MANTA, HARBOR and VIEW — comparing different anti-VEGF treatments (and their dosing regimens) have recently been reported. What are your thoughts on these trial results?

CATT, IVAN and MANTA Trials

Dr. Boyer: CATT essentially showed that monthly injections of ranibizumab or bevacizumab resulted in approximately the same visual outcomes at the end of 1 and 2 years. In the PRN group, with as-needed treatment beginning after the first injection, the bevacizumab group did not show non-inferiority. It actually was inferior to the monthly injection groups, where ranibizumab given on a PRN basis provided a better result. Total drying on OCT was seen more in the ranibizumab-treated arm that was receiving monthly treatment than in the monthly bevacizumab-treated arm. A discrepancy in systemic safety was found in the first year. There were more serious adverse events (SAEs) in the first year in the patients receiving bevacizumab. The events did not seem to be related to any known anti-VEGF side effects and the discrepancy was dismissed. But in the second year, a higher SAE rate was again reported in the bevacizumab group. Safety of all the anti-VEGF agents is really a question, although I cannot find a biological reason for some of the events, and that is a problem. We do not know why it is biologically occurring, but safety issues with bevacizumab occurred at a higher rate in both years of CATT.

Dr. Brown: The CATT also showed that bevacizumab does not dry out the retina as well as ranibizumab. The treatment burden is increased with bevacizumab. I have a hard time extrapolating the bevacizumab CATT data to my clinic because the study used an FDA-monitored fill and finish formulary where there is almost no chance of infection, or a very limited chance, anyway. There is a much higher chance of infection when using a compounding pharmacy.

> **“We do not know why it is biologically occurring, but safety issues with bevacizumab occurred at a higher rate in both years of CATT .”**
>
> *— David Boyer, MD*

Dr. Kaiser: We recently heard the interim results of the IVAN study. What are some of the design differences between CATT and IVAN that clinicians should understand?

Dr. Brown: In IVAN, there was a three-letter margin of inferiority; CATT had five letters. The PRN treatment

group in IVAN received three injections before moving to as-needed treatments, but if there was any leakage, the patient received another three monthly doses. So, a patient with two recurrences could have had nine or 10 injections, making the overall number of injections higher in IVAN than in CATT. IVAN aggregated data between the monthly doses, and the PRN data were also aggregated. So, we do not have data on monthly ranibizumab; without the four individual groups it is difficult to interpret the data. In the primary outcome, ranibizumab did not meet the non-inferiority margin, but by a very small amount. The *P* value is 0.056, so literally two patients may have skewed the results. Had five patients gone the other way, bevacizumab would have been shown to be inferior to ranibizumab. Not "non-inferior," inferior period. Unlike CATT, IVAN showed systemic anti-VEGF suppression with a serum sample, not a plasma sample. In CATT, the monthly curves are almost on top of each other and look truly equivalent, but in IVAN, it is clear that bevacizumab was not equal.

Dr. Kaiser: I agree. If you look at the confidence intervals around the mean difference between the drugs, the interim outcome was almost inferior. We will see what happens in the second year when the primary outcome is reported.

Dr. Csaky: Whenever fluid was detected, the protocol necessitated three injections. We typically do not mandate three injections in day to day clinical practice. The PRN regimen was much more aggressive in the trials and that is one reason why there were more injections and better visual outcomes in IVAN. That is why, I think, there was no change between the discontinuous and continuous dosing.

Dr. Heier: The one consistent finding between CATT and IVAN is the ability to dry out the retina; both studies found ranibizumab was better than bevacizumab in that respect. We do not have hard data yet to confirm if it makes a visual difference, but I believe that visual outcomes will be affected by persistent fluid.

Dr. Kaiser: The MANTA study also compared ranibizumab and bevacizumab using a PRN dosing regimen after three monthly loading doses with the primary outcome at 1 year in 317 patients at 10 study centers in Austria. Like the bevacizumab used in CATT, the bevacizumab was compounded at central pharmacies. MANTA had a non-inferiority margin of seven letters, so once again it is different from CATT and IVAN. At 1 year, there was no difference in the mean change in vision from baseline, or in the five or 15 letter gainers, but more patients numerically lost 15 letters in the ranibizumab group, although this was not statistically significant. The reasons are not completely clear as to why this occurred and further analysis is being done. The systemic safety was the same between the two groups.

VIEW I and VIEW II

Dr. Heier: VIEW I and VIEW II included more than 2,400 patients, so there were 600 patients in each arm: 2.0 mg aflibercept monthly and 0.5 mg aflibercept monthly; 2.0 mg aflibercept with a loading phase and then every 8 weeks; and the control arm, ranibizumab, 0.5 mg monthly. The data showed that essentially all four of these groups were comparable. In particular, the finding from VIEW Year 1 that was most interesting to us was not simply that the 2.0 mg aflibercept and the 0.5 mg ranibizumab were comparable, but that the 2.0 mg dosed every 8 weeks after the loading phase was comparable. In VIEW Year 2, patients were treated in a capped PRN and followed monthly, but there was a mandatory quarterly dosing so patients would not go more than 3 months without a treatment. Again, the four arms largely maintained the gains they had, but there was some falloff ranging from 0.8 to 1.7 letters. What was interesting is that the number of injections was essentially the same, except in patients who received the most injections. Patients in the ranibizumab group were more likely than those

in the aflibercept group to need more than six injections.

Dr. Kaiser: Some would argue that the number of injections of ranibizumab and aflibercept were essentially the same in the second year of VIEW and that aflibercept did not appear to maintain biologic activity longer than other drugs, though this has been postulated.

Dr. Brown: In VIEW Year 2, we did not want a true PRN where we knew vision would be lost. The capped PRN gave everyone a floor they could not fall below. The average number of injections in the second year was 4.1 in the aflibercept arm and 4.2 in the ranibizumab arm. If you look at those numbers, they do not seem to be much different. However, when you compare patients who actually required 9, 10 or 11 injections in the second year, there were more of those patients in the ranibizumab arms than in the aflibecept arms, which implies more of a difference in patients who require more anti-VEGF therapy. The anatomic OCT data at 1 year also suggest aflibercept dries out more retinas. The odds ratio of being dry was much better for patients who were randomized to the every 2 months (q8w) aflibercept arm than the monthly ranibizumab arm based on OCTs at 1 year. I think that is the strongest data of all that aflibercept q8w is keeping patients seemingly drier than ranibizumab monthly.

> **Patients who have been treated with anti-VEGF agents are slowly losing vision in the 5- to 7-year framework.**
>
> *— Peter Kaiser, MD*

HARBOR and SAVE

Dr. Kaiser: Another study was the HARBOR trial, which compared 0.5 mg vs. 2.0 mg ranibizumab monthly as well as PRN after a three monthly loading dose. What were some highlights of this comparison study?

Dr. Boyer: HARBOR compared 0.5 mg and 2.0 mg ranibizumab monthly and PRN after three initial injections. At 1 year, no increased incidence of systemic adverse events was found and the visual outcomes were approximately the same between the 0.5 mg and the 2.0 mg dose in the two different dosing regimens. There was no significant difference found between the doses.

Dr. Kaiser: One concern raised about increased dosing of anti-VEGF agents was an increase in SAEs, and in particular systemic SAEs, and that did not appear to be the case in HARBOR. How was HARBOR different from the SAVE study?

Dr. Brown: The PRN was not shown to be non-inferior. That is only at 1 year. I think the 2-year data will be very interesting. The SAVE study showed that in recalcitrant patients, the higher dose did dry out more patients and achieved a statistically significant improvement in visual acuity. HARBOR found that in a treatment-naïve patient, dose levels do not make a difference. Maybe these patients over time develop resistance, or tachyphylaxis, or some other mechanism wherein they need a higher dose to be effective. But in my mind, tachyphylaxis has never really been demonstrated in anti-VEGF treatments. It would, however, be one explanation as to why these recalcitrant, hard-to-treat patients might need more drugs.

Dr. Csaky: We did not see significant differences in the CNV change with 2.0 mg or 0.5 mg, so this suggests that we are at the top end of the curve in the majority of naïve patients in the amount of anti-VEGF treatments needed. Even with 0.5 mg ranibizumab, we are starting at the top dose and I do not think, in the majority of patients, we can achieve a better response in naïve patients with 2.0 mg.

Dr. Heier: We had a series of patients we considered sub-optimal and we doubled the dose to 1.0 mg. A significant number did have an anatomic response, but a minimal visual response. It's clear some patients will benefit from the higher doses, but the number is rela-

tively small when you look at the clinical trials. Yet it is relatively high when you look at patients who occupy our exam rooms.

Dr. Csaky: This gets back to the issue of patient variability. Each patient demonstrates to some degree a unique mode of presentation. That is why we can to some degree generalize about clinical trial results but at the same time for an individual patient, I do not think we can generalize and say that 2.0 mg does not work or that 0.5 mg is always the best for every patient.

> **"The anatomic OCT data at 1 year also suggest aflibercept dries out more retinas. The odds ratio of being dry was much better for patients who were randomized to the every 2 months aflibercept arm than the monthly ranibizumab arm based on OCTs at 1 year."**
>
> *— David Brown, MD*

Are We Undertreating?

Dr. Kaiser: The second year of the CATT study clearly showed that monthly dosing was better than PRN dosing. So are we undertreating our patients, or are we discounting the study conclusions?

Dr. Brown: We are slowly realizing we are undertreating. After MARINA and ANCHOR, we thought 24 shots would be enough, and people would not need more. But there are people who need monthly shots at year 7, 8 and 9. Every time we try to extend, I think we run the risk of losing some of those vision gains we saw in the curve. The risk of endophthalmitis is about 1 in 3,000, but PRN dosing eliminates the gains you have achieved. We hope we are somewhere in the middle with treat-and-extend.

Dr. Kaiser: In the SEVEN-UP study (7-year follow-up of patients in ANCHOR and MARINA) when patients were converted to PRN after 24 monthly injections and followed over a long period of time, one-third of the patients were 20/200 or worse at 7 years, whereas in the first 2 years of monthly dosing, fewer than 10% were 20/200 or worse. I think we are running into that challenge with the anti-VEGF agents. How do we maintain good vision at years 6, 7, or longer after initiating therapy? Patients who have been treated with anti-VEGF agents are slowly losing vision in the 5- to 7-year framework. We have to be careful with some of our early decisions because we do not know the repercussions of these decisions down the road.

Dr. Boyer: The other surprising finding in the SEVEN-UP study was that 50% of the patients still had active neovascularization 7 years after beginning anti-VEGF therapy. So, we are not really curing anything, we are just controlling the leakage for an unspecified amount of time while we continue to treat. I think we may need to use auto-fluorescence or fluorescein angiography periodically to check for disease progression.

Dr. Heier: We have a few patients who had been enrolled in the original multi-injection ranibizumab study (circa 2001) and one patient in particular developed AMD in the second eye during the study, so we could not treat the fellow eye. That second eye is 20/400 but the one enrolled in the study is still 20/30, and the patient is treated regularly. I think a more pressing issue is non-exudative disease that is also ongoing; it can be difficult to differentiate between the two.

Dr. Kaiser: The CATT 2-year data found patients

receiving monthly ranibizumab had larger amounts of geographic atrophy (GA) and a greater enlargement of GA area than the other groups. What are your thoughts on this finding — is this real?

Dr. Brown: I do not think it is likely to be real. We have not seen it in the diabetic macular edema (DME) trials, we have not seen it in the retinal vein occlusion (RVO) studies, and we do not think we have seen it much in patients we have been treating for 10 years. I would like to see that replicated in other studies — HARBOR, VIEW I and II — before I put a lot of credence in it.

> **"We have to be careful with some of our early decisions because we do not know the repercussions of these decisions down the road."**
>
> *— Peter Kaiser, MD*

Dr. Csaky: One hypothesis that has been proposed is that patients who have a thin choroid with CNV may be more susceptible to the development of some GA with anti-VEGFs. Do you think measuring choroidal thickness at baseline has a role in this development of GA? Do you think this is a place where we should concentrate more efforts?

Dr. Brown: There are patients with GA with really robust, healthy choroids and patients with almost no choroid where their retinal pigment looks solid, so there is certainly not a linear correlation. If we kill off a patient's choroid and get secondary RPE atrophy, it is usually from PDT rather than anti-VEGF. I have not seen any data to demonstrate that we are killing off choroid with anti-VEGF therapy.

Dr. Heier: Looking at the anatomic effects of the treatments leads me to believe the persistence of fluid is more likely to have a long-term effect than the development of GA. In most of the studies and in our own experience, under-treatment seems to cost more vision than over-treatment.

Dr. Brown: We all have patients 10 years out seeing well. If we're hurting the RPE, we need to figure out does one agent do it more than others. Until we have other evidence, it does not concern me that there were small amounts of non-foveal GA seemingly increased in one cohort of the CATT trial.

Dr. Kaiser: I am not certain that the GA seen in CATT was truly due to monthly ranibizumab versus a spurious statistical finding. Were there baseline differences in GA, for instance? For example, it is difficult to see GA in wet maculas, and the monthly ranibizumab subjects had the driest maculas so the GA was easy to see. Maybe the other groups had similar levels of GA, but their wet retinas prevented the GA from being seen. We have to look at other studies where monthly ranibizumab was delivered to see if they also showed similar GA events. Did we see increased GA in HARBOR or VIEW? In HARBOR where they quadrupled the dose of ranibizumab, I would expect to see more atrophy in those patients if the CATT findings are real.

Dr. Brown: We do not have the 2-year long-term data of GA sizes yet. There was autofluorescence, but it was not uniformly used.

Dr. Heier: It is similar with VIEW. It is very hard to assess when you were not looking for it at baseline.

Dr. Brown: It is hard to assess on OCT, too. We looked at it in the SAVE trial where we had a population where all these patients had monthly OCTs. We were disappointed with it because it was so hard to get reproducible signals to grade if there was overlying choroidal neovascular membrane or fibrosis.

Dr. Csaky: The caveat to that is the main reason people go to 20/200 or worse in both ANCHOR and MARINA was the development of GA. So, is it just the natural history of AMD progression, or is it an anti-VEGF issue? I think it needs more study.

Dr. Kaiser: I agree. The GA issue is one we need to watch closely, and in future clinical trials we have to prospectively follow it. I am not convinced yet that the anti-VEGF drugs produce GA. ✦

Anti-VEGF Therapies Continue to Impress

At the 2012 ASRS conference, several presentations illustrated how effective aflibercept can be in patients with recalcitrant disease.

By Michelle Dalton, ELS

Anti-VEGF drugs have rapidly become the first-line treatment for patients with wet AMD, yet some patients remain non-responders while others have improved vision even though retinal fluid remains.

During the 2012 American Society of Retinal Specialists' meeting in Las Vegas, several presentations highlighted findings on aflibercept (Eylea, Regeneron), the newest of the anti-VEGF treatments for the treatment of AMD. The study results presented at the meeting suggested that aflibercept could improve outcomes in patients who are recalcitrant to ranibizumab (Lucentis, Genentech) or bevacizumab (Avastin, Genentech) and may improve anatomic outcomes after a single injection based on OCT, regardless of previous treatment regimens.

Presenters said the move to aflibercept was an attempt to dry the retina in the hopes of improving visual acuity down the road. Since long-term damage occurs with persistent retinal fluid, aflibercept may surpass ranibizumab as a first-line treatment of choice, especially if the ability to dry the retina can be maintained over the long term, some of the clinicians suggested.

Recalcitrant Patients

Vincent S. Hau, MD, PhD, of the Retina Institute of California, dose-loaded 41 eyes (35 patients) that had previously undergone a mean of 17.2 anti-VEGF injections (7.1 injections of ranibizumab and 10.1 injections of bevacizumab), with three monthly injections of 2.0 mg aflibercept, then moved patients to as-needed therapy, which averaged 4.5 injections over 6 months. Central foveal thickness went from 350 µm before the aflibercept treatment to 275-280 µm at month 6, which was statistically significant. Visual acuity improved as well, but didn't reach statistical significance, he said.

"Some of these patients saw immediate improvement with just one injection," said Dr. Hau.

In one of the larger retrospective chart reviews, **Chirag P. Shah, MD, MPH**, and colleagues at Ophthalmic Consultants of Boston analyzed the effects of one intravitreal aflibercept injection in 155 patients who had been classified as suboptimal responders to other anti-VEGF regimens; 123 patients (79%) showed an anatomic response after one aflibercept injection. Central subfoveal thickness went from 311 µm to 284 µm ($P<0.001$). Of the 123 patients who responded anatomically, 67% had improved subretinal fluid, 40% had improved intraretinal fluid, 12% had improved pigment epithelial detachment (PED), and 23% were dry.

Several additional presentations highlighted improved anatomic responses after a single injection.

In eyes receiving multiple previous anti-VEGF injections with no response, PED height was reduced by about 17% in 79 eyes, with a majority showing improvement in as little as 1 week after the aflibercept injection in one such study. "The number of anti-VEGF injections before switching to aflibercept was significantly but weakly correlated to the response," said **James C. Major Jr., MD, PhD, FACS**, Retina Consultants of Houston.

In 54 eyes, the mean foveal thickness (FT) decreased from 351 µm to 300 µm. Of the 44 patients with macular volume data, the mean improvement was from 7.72 mm^3 to 7.25 mm^3, both of which were statistically significant changes, said **Patrick Dewey Williams, MD**, Texas Retina Associates.

"One injection of aflibercept may reduce persistent fluid on OCT," he said. "Whether or not improved OCT data reduces the risk of future vision loss in these patients is still unclear."

Another study showed that by 1 month after an initial aflibercept injection in eyes with chronic neovascular AMD that had previously been treated with either ranibizumab or bevacizumab, 38/93 eyes (41%) showed resolution of subretinal fluid, 12/93 (13%) had partial resolution, 29/93 (31%) had improvement, and 14/93 (15%) had no change, said **Ashish G. Sharma, MD, FACS**, Retina Consultants of Southwest Florida.

"In our patients, there was some improvement in visual acuity as well, with 7% gaining three or more lines in that first month," he said. Central foveal thickness decreased from 368 µm to 275 µm at month 1, but slowly increased to 294 µm in an extended follow-up subgroup.

"All of these patients had previously undergone anti-VEGF therapy, with a range of 6-34 injections per eye before we switched

them to aflibercept," Dr. Sharma said.

Irene Barbazetto, MD, with Vitreous Retina Macular Consultants in New York, reported on 61 eyes of 50 patients who had received an average of 18 prior injections (ranging from 1-56 previous treatments); treatment failure was the primary reason for switching to aflibercept. In a short-term evaluation (4 months), visual acuity (VA) improved, but did not reach statistical significance. Central retinal thickness, however, improved from 279.2 µm to 252.9 µm (P<0.01). On OCT, the number of patients with subretinal fluid dropped by more than half, and cystic changes improved similarly.

"Further studies are needed to determine if patients stabilized with other anti-VEGF agents require three monthly loading doses for optimal response," she said. In a subgroup analysis of 45 eyes that underwent three monthly doses, central thickness decreased from 298.8 µm to 254.6 µm (P<0.001); VA improved but was not statistically significant.

Early Experiences

"Having some fluid on OCT while on anti-VEGF therapy is fairly common," said **Kirk H. Packo, MD**, professor and chairman, Rush University Medical Center, Chicago, noting that well over half his patients have persistent fluid after 2 years, regardless of monthly or PRN dosing with ranibizumab or bevacizumab (although PRN dosing resulted in a higher percentage of patients with persistent fluid). In a retrospective review of all patients who were being treated "on demand" with ranibizumab therapy, Dr. Packo identified 20 with chronic recalcitrant fluid, defined here as "persistent intraretinal fluid, subretinal fluid, and/or subretinal pigment epithelium (RPE) fluid in at least six consecutive visits," he said. Any patient who had skipped visits or had at least one fluid-free visit in the same time period was excluded. The mean total ranibizumab injections was 25, with a range of 6 to 45 injections, and the mean consecutive injections was 18, with a range of 6 to 43 injections. Mean central macular thickness on OCT was 257 µm (ranging from 151 µm to 357 µm).

Each of the 20 patients was given a single injection of aflibercept, with additional injections given if fluid remained after one month. If the retina was dry, some patients received additional injections and others were observed. After one injection, 65% of patients (13/20) were completely dry; 3/20 (15%) were significantly better, but not dry — although for two patients a second injection rendered complete dryness; 2/20 (10%) had no change in fluid — one went totally dry with a second aflibercept injection and one did not; and 2/20 (10%) had slightly worse fluid and a second injection "didn't help," Dr. Packo said. The mean central macular thickness decreased to 228 µm (P=0.05).

Five of the 13 patients who were completely dry were observed and 80% (4/5) had recurrent fluid on the subsequent visit. Of the remaining eight patients who were also dry and re-injected, three developed recurrent fluid.

"In our patients, aflibercept may have a rapid drying effect (within a week) that needs to be considered when looking at overall response," Dr. Packo said. "Aflibercept showed a release of effect, and some patients subsequently showed fluid, but less than seen with ranibizumab." He added that subretinal fluid and intraretinal fluid seemed to respond better to aflibercept than sub-RPE fluid, although the reasons remain unclear.

Philip Ferrone, MD, and colleagues from Long Island Retina retrospectively analyzed 250 patients' response to aflibercept, (29 were treatment naive; 145 had been on ranibizumab; 76 had been on bevacizumab). The previously treated group averaged injections every 6 weeks. The treatment-naive group was injected with aflibercept on a 4 week/4 week/7 week induction schedule, while the previously treated group immediately went to an every-7-week aflibercept injection regimen.

Visual acuity improved substantially for the treatment-naïve with baseline vision of 20/200 or worse (P=0.0023). Although vision improved in the previously treated (regardless of baseline VA) and treatment-naïve groups with baseline vision better than 20/200, none of those groups reached a statistically significant improvement.

"There was some decrease in VA on average in the treatment-naïve group when the treatment interval increased from 4 to 8 weeks," Dr. Ferrone said.

OCT improved also over time, reaching statistical significance in the treatment-naïve group, regardless of baseline vision.

"There was a small improvement overall with respect to PED, subretinal fluid and macular edema findings on OCT after switching from bevacizumab or ranibizumab to aflibercept in most patients," he said.

Aflibercept Use in the Presence of Active Disease

In eyes that are being actively treated with anti-VEGF therapy, but have active choroidal neovascularization (CNV) secondary to AMD, can a single injection of aflibercept be useful? **H. Matthew Wheatley, MD**, and colleagues at the Retina Vitreous Center, PA, and Robert Wood Johnson University Hospital, New Brunswick, NJ, addressed this question by analyzing chart data from 43 eyes of 43 patients who had persistent CNV despite being actively managed with anti-VEGF injections. The eyes had received 22 injections on average.

"On average, these patients were last injected between 5 and 6 weeks before the aflibercept injection," Dr. Wheatley said.

Mean VA improved from 20/71.5 to 20/62.6 (P=0.043); mean spectral domain-OCT measurements improved from 278.3 µm to 252.8 µm (P=0.032); and macular volume decreased from 9.58 mm^3 to 9.27 mm^3 (P=0.0003).

"There was significant qualitative improvement," Dr. Wheatley said. "Fifty-four percent had significantly improved or normalized anatomy after one injection."

Conclusions

Aflibercept is capable of drying the retina in as little as one dose in some patients, but it is not yet known whether drying will translate into improved vision. That said, the presentations at ASRS demonstrated that aflibercept is equally effective in its ability to dry the retina in treatment-naïve patients and in patients previously treated with ranibizumab or bevacizumab. ✦

Suboptimal Responder Treated with Aflibercept

By Jeffrey S. Heier, MD, Ophthalmic Consultants of Boston

In this case study, a 77-year-old man was diagnosed with AMD in his right eye and had an initial VA of 20/100. As the disease progressed, his VA decreased to 20/400 after 11 anti-VEGF injections, and he had chronic, persistent subretinal fluid on OCT. We began triple therapy consisting of photodynamic therapy, intravitreal bevacizumab (Avastin, Genentech), and intravitreal triamcinolone (Kenalog).

Over the course of the next 2 years, he underwent three courses of the triple therapy and his vision improved to 20/200, but he still had persistent subretinal fluid. We also tried double-dose intravitreal ranibizumab (Lucentis, Genentech) and yet he still had worsening disease, with fluctuation in vision from 20/100 to 20/200. At this point, he had undergone 25 anti-VEGF injections, including 14 double-dosed Lucentis.

After multiple double-dose ranibizumab, the patient's vision was 20/100, but subretinal fluid remained. We initiated intravitreal aflibercept (Eylea, Regeneron), and after the first injection of aflibercept, the VA was 20/200, but on OCT there was anatomic improvement. At 6 weeks, we injected aflibercept for the second time (vision had improved to 20/100, but fluid still remained). We followed up 7 weeks later, injecting with a third aflibercept treatment; his VA had declined to 20/200 and some of the anatomic improvement was regressing.

At the fourth intravitreal injection 4 weeks later, the VA had improved to 20/80, and there was noticeable improvement of subretinal fluid on OCT. A final intravitreal aflibercept injection was given 5 weeks after that, and the anatomic changes have been maintained along with improved vision. We continue to monitor this patient every 4-5 weeks. ✦

Chronic, Persistent Fluid Treated with Aflibercept

By Karl G.Csaky, MD, Dallas, Texas

A 65-year-old male presented with a 6-year history of choroidal neovascularization in the right eye. Initially, he was treated with monthly doses of ranibizumab and had complete resolution of all intra- and subretinal fluid. Once the eye was dry, a treat-and-extend (TAE) approach was used to increase the intervals between injections to every 8-10 weeks. Unfortunately, during the TAE dosing regimen the patient developed chronic persistent fluid and was switched to bevacizumab, with an every-2-weeks alternate dosing strategy. In this subsequent strategy, we alternated between bevacizumab and ranibizumab. and added triamcinolone to both anti-VEGF injections. The patient's vision remained at 20/80. In February 2012, we switched the patient again, to receive one injection of aflibercept. One month later the patient returned with improvement in visual acuity to the 20/40 level and resolution of both intra- and subretinal fluid. ✦

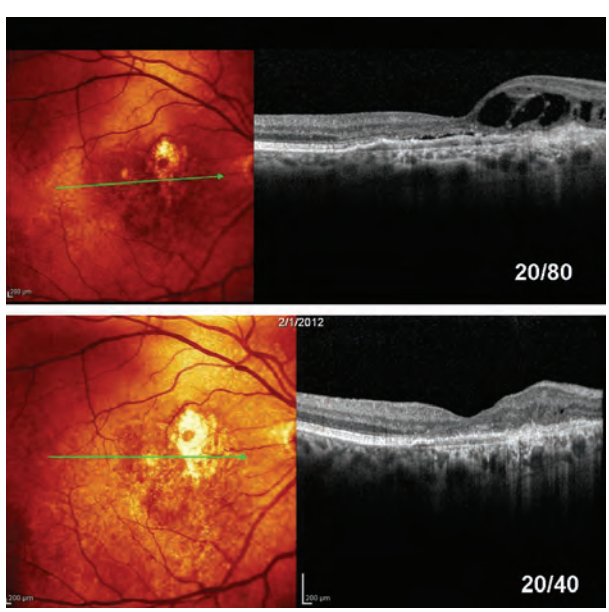

Photo courtesy K. Csaky, MD.

Figure 1. In the top portion, chronic fluid remains, even after adding a triamcinolone injection. In the bottom portion, however, there is no persistence of fluid in the post-aflibercept eye.

David S. Boyer, MD, is in private practice at Retina-Vitreous Associates Medical Group in Los Angeles. He is also a clinical professor of ophthalmology at the University of Southern California Keck School of Medicine, Department of Ophthalmology, in Los Angeles.

David M. Brown, MD, FACS, is the director of the Greater Houston Retina Research Center and practices at Retina Consultants of Houston and the Methodist Hospital in Houston.

Karl G. Csaky, MD, PhD, is associate professor of ophthalmology and director of the Ophthalmic Clinical Trials Unit at the Duke Clinical Research Institute.

Jeffrey S. Heier, MD, is a vitreoretinal specialist at Ophthalmic Consultants of Boston, co-director of the Vitreoretinal Fellowship at OCB/Tufts Medical School, and president of the Center for Eye Research and Education in Boston, Mass.

Peter K. Kaiser, MD, (moderator) is a professor of ophthalmology at the Cleveland Clinic Lerner College of Medicine and a staff surgeon in the Vitreoretinal Department at the Cole Eye Institute, Cleveland Clinic.

Retinal PHYSICIAN®

Editorial Staff
EDITOR-IN-CHIEF, *Retinal Physician*: Peter K. Kaiser, MD
EDITORIAL MANAGER, SPECIAL PROJECTS: Angela Jackson
EDITOR, SPECIAL PROJECTS: Leslie Goldberg
CONTRIBUTING EDITORS: Michelle Dalton, Desiree Ifft

Design and Production
PRODUCTION DIRECTOR: Sandra Kaden
ART DIRECTOR: Claudette McClellan

Business Staff
GROUP PUBLISHER: Douglas A. Parry
ASSOCIATE PUBLISHER: Dan Marsh
MARKETING MANAGER: Marsha Levell
PROMOTIONAL EVENTS MANAGER: Michelle Kieffer

Editorial and Production Offices
323 Norristown Road, Suite 200, Ambler, PA 19002
Phone: (215) 646-8700