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Photodynamic Therapy: Evolving Treatment Strategies and Keys to Effective Delivery


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Content Source

This continuing medical education (CME) activity captures content from a virtual roundtable discussion.

Activity Description

This supplement highlights a panel discussion on how photodynamic therapy (PDT) has evolved over the years. The faculty review disease states best served by PDT, using PDT in anti-VEGF nonresponders, and keys to effective delivery. Cases are presented in which the use of PDT alone or in combination with anti-VEGF were a more efficacious treatment option than using anti-VEGF alone.

Target Audience

This certified CME activity is designed for retina specialists and comprehensive ophthalmologists.

Learning Objectives

Upon completion of this activity, the participant should be able to:

- **Summarize** the mechanism of action and the clinical benefits of PDT in patients with retinal disorders
- **Design** a treatment regimen based on a personalized medicine approach for patients who do not respond adequately to anti-VEGF injections
- **Critique** methods for effective PDTdelivery in clinic settings, including dosing, using and administering reduced fluence protocols, infusion periods, determination of treatment size, and post-treatment care
- **Describe** the benefits of half-fluence PDT or full-fluence PDT on a real-world population

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PRETEST QUESTIONS

Please complete prior to accessing the material and submit with Posttest/Activity Evaluation/Satisfaction Measures for credit.

1. Please rate your confidence in your understanding of photodynamic therapy (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

a. 1
b. 2
c. 3
d. 4
e. 5

2. Please rate your confidence in your ability to apply key concepts of photodynamic therapy (PDT) in the clinic (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

a. 1
b. 2
c. 3
d. 4
e. 5

3. What were the key findings of EVEREST II?

a. PDT monotherapy is more effective than anti-VEGF monotherapy in the complete regression of polypoidal choroidal vasculopathy (PCV) at 6 months
b. Combination PDT and ranibizumab can decrease the need for anti-VEGF injections and improve vision in patients with PCV
c. Patients with PCV can have some amount of subretinal fluid with good long-term visual outcomes
d. Ranibizumab monotherapy is only slightly more effective at improving vision than PDT, therefore PDT is preferred due to the reduced treatment burden

4. PDT can be used to successfully treat the following retinal diseases EXCEPT:

a. Chronic central serous retinopathy
b. Retinal angiomatous proliferation lesions
c. Retinitis pigmentosa
d. Juxtafoveal or extrafoveal choroidal neovascularization

5. Which statement provides the most accurate description of an anti-VEGF nonresponder?

a. Nonresponder is a misnomer; they are really short-term responders
b. Nonresponders are patients who don't respond after 3 loading doses of anti-VEGF
c. Nonresponders are patients who don't respond after 5 to 6 monthly injections of anti-VEGF
d. Nonresponders are patients who have persistent fluid after 4 monthly injections of anti-VEGF

6. Identify the correct settings for half-fluence PDT.

a. 50 J/cm^2 of light at 600 mW/cm^2 for 83 seconds
b. 50 J/cm^2 of light at 300 mW/cm^2 for 83 seconds
c. 25 J/cm^2 of light at 300 mW/cm^2 for 41 seconds
d. 25 J/cm^2 of light at 300 mW/cm^2 for 83 seconds

7. A 75-year-old patient presents with predominately occult subfoveal lesions and a VA of 20/100 OU. _____ would be an appropriate first-line treatment.

a. Half-fluence PDT
b. Full-fluence PDT
c. Monthly aflibercept injections
d. Three loading doses of ranibizumab followed by PRN

8. The same patient from Question 7 has not responded to anti-VEGF after 6 rounds of monthly treatment. What is your next step?

a. Continue with monthly aflibercept injections
b. Classify the patient as an anti-VEGF nonresponder and proceed with half-fluence PDT
c. Switch the patient to another anti-VEGF agent to initiate a response
d. Classify the patient as an anti-VEGF nonresponder and proceed with full-fluence PDT

Photodynamic Therapy: Evolving Treatment Strategies and Keys to Effective Delivery

At one time, photodynamic therapy (PDT) was our only treatment for wet age-related macular degeneration (AMD).[1,2] However, when anti-VEGF injections became the standard of care for wet AMD, fewer PDT procedures were conducted. PDT is now experiencing a resurgence due to new indications and data on the effectiveness of combination PDT and anti-VEGF therapy in reducing the injection burden with good disease control and visual outcomes. PDT may be especially useful in patients with polypoidal choroidal vasculopathy (PCV), a subtype of AMD that has been shown to be more commonly associated with anti-VEGF resistance. The following roundtable brings together experts in PDT delivery to detail how it has evolved over the years and the evidence in support of its use.

— Rishi P. Singh, MD, Program Chair

DISEASE STATES BEST SERVED BY PDT

Q | **Dr. Singh:** PDT has been around for years for the treatment of AMD,[1,2] but its treatment indications have since expanded.[3-6] Dr. Kokame, how have you seen PDT evolve?

Gregg T. Kokame, MD, MMM: Initially, PDT was the only therapy we had for exudative macular degeneration. After the anti-VEGF therapies were introduced, we saw a significant improvement in the treatment of exudative macular degeneration, improved outcomes, and improved vision.[7,8] PDT has also been used in chronic central serous retinopathy (CSR) cases.[9-11] More recently, there's been renewed interest in using PDT to treat PCV, a subtype of exudative macular degeneration, in light of EVEREST II study results.[12] EVEREST II was a 2-year study from Asia that compared ranibizumab plus prompt PDT (n=168) versus ranibizumab monotherapy (n=154). Patients received PDT or sham PDT on day 1 and 3 monthly loading doses of ranibizumab, followed by as-needed ranibizumab, based on disease activity. EVEREST II showed PDT can decrease the need for injections and actually improve vision better than ranibizumab monotherapy. Patients in the combination treatment arm gained 9.6 letters versus only 5.5 letters in the anti-VEGF monotherapy group with fewer injections (6 vs 12). Combination therapy was also superior in terms of lesion regression.[12] Combination PDT and anti-VEGF is important to consider now for the PCV subtype of exudative macular degeneration.

Dr. Singh: Dr. Barakat, tell us about your initial PDT experience and how it's evolved.

Mark R. Barakat, MD: When I came out of training, PDT didn't have the role that it used to because it was largely supplanted by anti-VEGF therapy. However, I still find it useful as an adjunctive treatment. There will always be patients with AMD who are perhaps undertreated or where the frequency of treatment with anti-VEGF is not acceptable. For me, the gamechanger is with CSR because it seems to really work well in that, whereas other therapies don't seem to have as great a role. For example, the PLACE trial randomized 179 patients with chronic CSR to half-dose PDT (n=89) versus high-density subthreshold micropulse laser treatment (n=90). The first evaluation and primary endpoint was at 6 to 8 weeks, with a final evaluation at 7 to 8 months. At first evaluation, subretinal fluid resolved in half of patients who received PDT versus only 14% of patients who received the micropulse laser. At final evaluation, even more PDT patients had fluid resolution (67% PDT arm vs 29% micropulse arm).[9]

Jordana G. Fein, MD, MS: I find PDT useful in chronic CSR and in patients with nonresponding AMD. In patients with idiopathic PCV, we have good data that show combination PDT plus anti-VEGF therapy is superior to anti-VEGF therapy alone.[13,14] The EVEREST study was the first trial to investigate combination ranibizumab and PDT versus ranibizumab monotherapy in patients with symptomatic PCV.[14] The trial was designed to assess if PDT as a monotherapy or in combination with ranibizumab was more effective than ranibizumab monotherapy in achieving complete polyp regression at 6 months. At month 6, combination treatment resulted in more complete polyp regression than either PDT or ranibizumab monotherapy (77% combination therapy vs 71% PDT monotherapy vs 28% ranibizumab monotherapy).[14]

Dr. Singh: I've also used PDT in patients with peripapillary lesions.[15] It could also be beneficial for patients with juxtafoveal and extrafoveal choroidal neovascularization (CNV) with subfoveal component.[16]

Q | **Dr. Singh:** Dr. Fein, have you used PDT for juxtafoveal or extrafoveal CNV or peripapillary choroidal neovascular membrane (CNVM)?

Dr. Fein: The nice thing about PDT is it's a cold laser and does not create any permanent damage to the retina. I'm very comfortable using it for subfoveal, juxtafoveal, or extrafoveal CNV. I rarely use focal laser anymore because I find those patients do well with PDT and I do not have to worry about permanent scotomas from the treatment. Many patients with peripapillary CNVM do respond well to a low-burden of anti-VEGF, but in patients who don't, PDT is a very effective and safe option.

"I also try to categorize CNVM: type 1, which is below the retinal pigment epithelium (RPE); type 2, which is above the RPE; and type 3, which includes an intraretinal component of the CNVM."

—Dr. Kokame

Dr. Singh: Dr. Kokame, do you also consider PDT in peripapillary CNVM and extrafoveal or juxtafoveal neovascularization?

Dr. Kokame: I definitely consider it in peripapillary CNVM. PCV, at least in White patients, tends to be more frequently peripapillary, so it is very useful in this population. In juxtafoveal or extrafoveal neovascularization, I also use combination PDT and anti-VEGF and am more likely to consider full fluence in lesions that I can spare the fovea from treatment. I also try to categorize CNVM: type 1, which is below the retinal pigment epithelium (RPE); type 2, which is above the RPE; and type 3, which includes an intraretinal component of the CNVM. PCV is usually a type 1 CNVM, which has a higher risk of anti-VEGF resistance, whereas type 2 or type 3 have an excellent response to anti-VEGF agents. With PCV, a type 1 CNVM subtype, I would consider combination PDT and anti-VEGF as primary therapy, or if anti-VEGF monotherapy is begun, then consider combination PDT and anti-VEGF if there is a poor response.

Dr. Barakat: I agree with the previously mentioned sentiments. If it's outside the fovea, I think it's fair game. I think if you can decrease the treatment burden by using PDT on this, everybody wins.

USING PDT IN ANTI-VEGF NONRESPONDERS

Q | **Dr. Singh:** We talked about the use of PDT for anti-VEGF nonresponders. Dr. Kokame, how do you define the anti-VEGF nonresponder in your hands?

Dr. Kokame: We published a paper in *Ophthalmology Retina* in 2019 that showed PCV is more prevalent in patients who are resistant to anti-VEGF.[17] I look for patients to respond after a very short period of frequent injections, say 4 or 5. If they are still not responding well after that period, I recommend that clinicians look for PCV. PCV is the only clinical finding in exudative AMD that can predict anti-VEGF resistance. It is important to diagnose PCV as alternative therapy, such as combination PDT and anti-VEGF could be very helpful.

Dr. Barakat: I think labeling a patient as an anti-VEGF nonresponder is almost a misnomer for the majority of patients. There are some patients who have a high anti-VEGF burden; if you were to bring those patients in 1 or 2 weeks post injection, you'll likely see a response.[18] In a prospective study of 48 patients with wet AMD, two-thirds reached maximum central retinal thickness (CRT) reduction earlier than the standard 4-week interval, with some patients reaching it in as few as 1 or 2 weeks. It could be that many so-called nonresponders are actually short-term responders.[18]

The question is, what kind of frequency of injection is tolerated by you as a physician and by the patient? We've been conditioned to accept monthly treatment as okay and every 2 to 3 months as optimal. Hopefully, that interval will increase with our new agents in the pipeline. But in terms of the number of injections it takes to classify someone as a nonresponder, it's hard to say. If I give numerous injections and the retina stays dry, that's a responder and they're doing well. But if there's still fluid after 3 to 6 rounds of monthly injections, and that fluid is slightly increasing or getting closer to the fovea, that patient might be a nonresponder.

Dr. Fein: I define a nonresponder as someone who's had 3 anti-VEGF injections monthly and still has persistent fluid. I find that the patients who have persistent fluid at 3 months are often the ones that have persistent fluid at 1 year as well. There's some good data to suggest that the patients who do respond, respond early and quickly; the ones who don't respond, do not.

We have some different anti-VEGF agents in our arsenal. If I start with bevacizumab, I might switch the patient to aflibercept before classifying them as a nonresponder. But again, if there's persistent fluid after 3 anti-VEGFs treatments, I'd consider that patient a nonresponder. We do have some evidence that a low level of residual subretinal fluid may be tolerable, and that those patients may maintain good visual outcomes long-term.[19-21] For example, the FLUID study found that patients with wet AMD who were treated with ranibizumab using a treat-and-extend protocol and tolerated some fluid had comparable vision with fewer injections than patients who were treated until dry.[21] A recent Fight Retinal Blindness! Registry study in more than 700 eyes came to similar conclusions: some subretinal fluid can be tolerated with good visual outcomes.[22] Intraretinal fluid, however, is not ideal and associated with worse visual outcomes.[22] I agree with Dr. Barakat in that if you see a patient with worsening fluid or large amounts of subretinal fluid after 3 to 6 injections, that's certainly someone I would consider a nonresponder. I'd start thinking about adjunctive therapy in those patients.

KEYS TO EFFECTIVE PDT DELIVERY

Q | **Dr. Singh:** There's a lot of discussion around half-fluence or full-fluence PDT. What is the definition of half and full fluence? When would you choose half or full fluence at a given stage?

Dr. Kokame: It's important to differentiate between half and full fluence. Half fluence is 25 J/cm^2 of light at 300 mW/cm^2 for 83 seconds whereas full fluence is 50 J/cm^2 of light at 600 mW/cm^2 for 83 seconds. I do not recommend a decrease in the dose of injected

verteporfin or a decrease in the length of PDT laser treatment.[12,23] I consider full fluence for subfoveal lesions in patients with poor vision, 20/40 or 20/50 or worse, and extrafoveal lesions. I usually initially use half-fluence PDT in patients with subfoveal lesions and 20/20 to 20/30 VA. However, in the EVEREST II trial, investigators did more than 150 PDTs, and they used full fluence in every case.[12] They did not report a single case of vision loss, which may be related to the thicker choroid in PCV cases providing protection against choroidal ischemia.

"I agree we should use half fluence whenever possible on subfoveal lesions, however, I do find that I am more likely to get complete resolution of fluid using full-fluence PDT."

–Dr. Fein

Dr. Singh: How easy is it to achieve that in clinical practice? Do people know the settings?

Dr. Fein: If you have well-trained staff who are used to doing PDTs with you regularly, you can usually trust the settings knowing that full fluence is the 50 J/cm^2 and the half fluence is the 25 J/cm^2 over 83 seconds. I always confirm the settings with my staff, especially if I'm working with someone who is not as experienced. Luckily, the settings are relatively straightforward.

I did want to comment on something Dr. Kokame said. I think we're always trained to use the half fluence, especially for subfoveal lesions. However, data from EVEREST II is valuable because it demonstrates that we do not see the degree of vision loss with full-fluence PDT that is typically quoted from the original PDT literature.[24] In short, I agree we should use half fluence whenever possible on subfoveal lesions, however, I do find that I am more likely to get complete resolution of fluid using full-fluence PDT.

Dr. Barakat: I tend to stick with reduced fluence for most cases. I'd rather come back and do another treatment, especially since we have anti-VEGF injections to supplement in between. However, if you have something like a choroidal hemangioma, then I think full fluence would be a better option.

Q | **Dr. Singh:** Let's talk about PCV for a moment because this obviously is an area where we all use this therapy. Dr. Kokame, please take us through some salient features of a case that would indicate to you that it may be more PCV-related?

Dr. Kokame: Recent studies are looking at findings that allow the diagnosis of PCV without indocyanine green angiography (ICGA) because many practices don't have access for ICGA or rarely order ICGA. B-scan OCT, which is available in most practices, shows an inverted U-shape elevation of the RPE, which corresponds to the polypoidal lesion.[25,26] We showed that about 57% of the time we were able to diagnose PCV based on that lesion just on B scan OCT.[25] However, to make the diagnosis it is very important to go back and look at the OCT prior to anti-VEGF treatment, as after treatment this diagnostic finding is only seen in 25% of eyes. Important non-ICGA diagnostic criteria has recently been published by the Asia Pacific Ocular Imaging Society (APOIS) showing that in eyes with persistent disease activity 3 criteria were very helpful in diagnosing PCV, including the elevated sharply peaked elevation of the RPE, a ring-shaped lesion under the RPE within the sharply peaked RPE elevation, and a visible orange nodule on color fundus photographs.[27] En face OCT shows the OCT data in a cross sectional view and can be very helpful.[28,29] The PCV complex can be imaged and can look very similar to the image on ICGA.

Dr. Singh: Dr. Barakat, do you have any other thoughts about PCV?

Dr. Barakat: I don't get the same volume of PCV patients like Dr. Kokame, but I'd say that PCV tends to be underdiagnosed. Some people come in thinking they have AMD, and a large part of my level of suspicion is to see the response or lack thereof. My take-home point is, if you have what seems to be a regular neovascularization case and they're just not budging, ICG is a good tool to use, if available, to help delineate that.

Dr. Fein: Even if we don't have access to ICG, we can look to certain factors on our fundus exam and fundus photography. We're much more likely to see exudates, serosanguinous, and retinal pigment epithelial detachments in PCV cases. ICG, however, remains the gold standard for diagnosis.

Dr. Kokame: Serous detachment is more likely to be seen in PCV, whereas intraretinal edema is more likely seen in typical exudative AMD. A higher height of the subretinal fluid is also an indicator of PCV, as is a bigger subretinal hemorrhage.

Dr. Singh: Is PDT useful in treating retinal angiomatous proliferation (RAP) lesions? There is some evidence that combination PDT and ranibizumab may provide long-term regression.[30]

Dr. Kokame: RAP lesions are extremely responsive to anti-VEGF,[31] so I haven't used PDT for those.

Dr. Singh: I agree; I've found RAP lesions to be incredibly responsive to most anti-VEGF treatments.

Dr. Fein: Many RAP lesion patients are excluded from current clinical trials because of their exquisite anti-VEGF responsiveness, which can make it hard to tell whether the addition of another agent is helpful or not.

Q | **Dr. Singh:** How do you incorporate PDT into your busy retina practices?

Dr. Barakat: I know exactly when a PDT patient is coming in. I like to have the fluorescein angiography (FA) and ICG done ahead of time so I can measure the spot size in advance. But if that didn't happen, then you can do it in between patients. It's really about having a staff that's very comfortable and familiar with the PDT. I keep seeing other patients and then excuse myself when my staff comes to get me for the PDT. It's 83 seconds plus me getting ready, and then we move on. It works pretty well as long as you get the timing right.

Dr. Fein: My office has created PDT timeslots in our schedule so that we're not booked for an 8 AM and an 8:15 AM PDT back to back. We try to have one morning slot and one afternoon slot. Like Dr. Barakat, I try to get everything measured and prepared for ahead of time. I'll typically write the treatment plan on the chart (half fluence, full time, 1.5 mm spot size, etc) so that the technician knows what I want and can get everything set up ahead of time.

Q | **Dr. Singh:** Is everyone comfortable doing FA or ICG on the same day as the PDT?

Dr. Kokame: In Hawaii where I practice, we often have patients diagnosed with exudative AMD come in from another island. We do diagnostic testing including ICGA followed by combination PDT and anti-VEGF injection on the same day. The PDT is done at the hospital and the anti-VEGF injection is done in the office. We haven't had problems performing the FA or ICG in the morning and then the PDT in the afternoon.

Dr. Singh: I have a similar setup. I have them scheduled for a certain period of time, and we are all aware of when a PDT patient is coming in. The patient comes in and the nurse preps the PDT appropriately for the weight-based dosing. We deliver the medication intravenously, and then I show up when it's already infused. That brings up another question around the timing of the infusion. Do you think it matters if you start it right after the infusion is completed? Or do you have a window by which you can complete the infusion and actually perform the procedure?

Dr. Kokame: Once the verteporfin infusion over 10 minutes is complete, I usually wait 5 minutes and then perform the laser treatment. This allows the verteporfin dye to clear through the retinal vessels.

Dr. Fein: I also try to treat the patient immediately after the PDT timer goes off, however, there is no evidence to suggest that if you're delayed by 20 or 30 minutes after the timer that the procedure won't work as well.

Dr. Barakat: I agree. There's a grace period.

Q | **Dr. Singh:** One of the most controversial topics related to PDT is spot size determination. I was under the impression for a while that the spot size needed to be 1,000 µm on each side of the lesion. Is that something you're commonly doing in practice?

Dr. Barakat: I still keep my spot size relatively generous to get all the edges.

Dr. Fein: The smallest spot size that I can get on my current machine is about 1.5 mm. I sometimes wish I had the capability to use an even smaller spot size, but because I try to treat the area with some overlap along the border, usually this is adequate.

Dr. Kokame: For PCV, the PDT spot size is much smaller than the initial spot size based on the leakage on the FA plus a 1,000 µm border utilized initially in exudative AMD. For PCV, the lesion size is based on the ICGA and not the FA, and I usually only add a 300 to 500 µm border around the PCV lesion.

Q | **Dr. Singh:** Is there any reason to do more than one treatment at the same sitting, either for the same eye or the fellow eye?

Dr. Fein: I've done it in patients who are uninsured and paying out of pocket. Verteporfin is very costly. I had a patient with bilateral chronic CSR where normally I would have had them come back to treat the fellow eye but in that particular case, because of insurance issues, I did opt to do a bilateral treatment, which is not my standard.

Dr. Kokame: I do bilateral treatments. In that situation, I start maybe 30 seconds early in the primary eye and then immediately treat the fellow eye. I'm very comfortable with that approach. I haven't had any problems with bilateral PDT ever since we started PDT therapy in 2000. I also do two treatments in the same eye for two different locations of PCV lesions.

Dr. Singh: I've done it in a patient with a large peripapillary lesion and it's hard to get it as a circular object, obviously getting all of the lesion. Sometimes I've had to retreat the area next to it just because I had a smaller spot size. Obviously, it's a circle and it's harder to arrange it in a way that would be next to the nerve head.

Dr. Kokame: Dr. Ursula Schmidt-Erfurth presented a study at the Macula Society Meeting in 2015 that looked at whether PDT was safe to use over the optic nerve, and interestingly she found it to be safe.

Q | **Dr. Singh:** Dr. Barakat, what do you tell patients to do after the procedure to assure that they have a good outcome?

Dr. Barakat: I typically explain the precautions about wearing long sleeves, a hat, and staying out of direct sunlight for approximately 3 days. These precautions are important everywhere, but I would argue that it might be even more important in Arizona,

where I practice. Although it is very rare for PDT to result in choroidal ischemia, I also tell them to let me know if they have any vision issues.

Dr. Singh: Dr. Kokame, obviously with the sun exposure in Hawaii, are you concerned about that exposure risk with patients?

Dr. Kokame: Yes, I was very concerned about it early on, but now I tell my patients I've been doing this for 23 years and we haven't had a single patient develop a problem in Hawaii. Usually that helps make them feel more comfortable.

"I advise patients that the effects of PDT are going to take 6 to 8 weeks for early effect and 3 to 4 months for optimal effect, and that they shouldn't expect to see immediate improvement."

—Dr. Fein

Dr. Fein: I always like to discuss expectations. Some patients imagine that PDT will be like cataract surgery, where there's a magic response after 1 day. I advise patients that the effects of PDT are going to take 6 to 8 weeks for early effect and 3 to 4 months for optimal effect, and that they shouldn't expect to see immediate improvement.

Dr. Singh: Has anyone had patients with acute reactions to the drug? I know the most common reaction that has been reported is back pain during the infusion procedure.[32]

Dr. Barakat: I've had very few issues during the procedure itself. The biggest thing I worry about is patient anxiety because it's difficult to hold still for 83 seconds. The patient can become antsy and worry something is going wrong. I tend to coach them through those 83 seconds, but as far as negative side effects, I've had very few.

Q | **Dr. Singh:** How about in regard to the guidance. Are you going by the fundus photograph, the ICG, or the FA?

Dr. Barakat: I try to go by the ICG but many times I find myself going by the FA because that's a little bit clearer and easier to lineate.

Dr. Fein: ICG is the gold standard in terms of how we determine our treatment spot size. But I do use the FA as well, and I prefer to have the FA/ICG side-by-side in movie format to select my treatment size and location. I also think it's important to look at the OCT and to see if there's a small pigment epithelial detachment in the area corresponding to the area of leakage. I want to confirm that the imaging all matches up and makes sense.

Dr. Kokame: I agree with Dr. Fein. It's important to use many different modalities to identify PCV. The best and most sensitive modality is ICG using the scanning laser ophthalmoscope. However, I make sure that the spot size from the ICG includes all areas of active leakage on the FA. En face OCT, OCT B-scan, and OCT angiography can also provide collaborative diagnostic data to diagnose PCV. When following PCV lesions long term I often use OCT angiography in those cases, as it prevents the need to do multiple and frequent dye injections.

Q | **Dr. Singh:** What do you recommend for follow-up after PDT?

Dr. Fein: In a patient who's receiving monthly anti-VEGF injections, I would continue their monthly injections. However, in the case of a CSR patient who isn't getting injected, I'd typically see them back 6 to 8 weeks after the PDT is performed. I will follow with an OCT because at that point in time I'm assessing for clinical improvement. In 3 to 4 months following treatment, I would consider repeating the ICG and FA if I'm not seeing clinical improvement to assess whether another treatment would be warranted.

Dr. Barakat: My follow-up period depends on the patient pathology. If I have someone who is already on an injection schedule that we've tried our best to optimize, then I will try to get the PDT in between that cadence and follow up and continue with the anti-VEGF treatments. In terms of CSR, it's a different story; I wait 2 to 3 months before seeing them again, and I tend to follow with OCT. If they are dry on OCT, I think the PDT achieved what it needed to. If I see some lingering fluid, then I would consider reimaging them with FA and ICG.

Dr. Kokame: For patients with PCV or wet AMD, I follow-up the combination PDT and anti-VEGF at 6 weeks. I usually do FA, ICG, and OCT again at this first visit to make sure the treatment worked. I want to see if the polypoidal lesions have regressed and if the branching vascular network has decreased. If there is no fluid, I don't inject an anti-VEGF agent. But if there is subretinal fluid even with regression of the polypoidal lesions, I will continue with anti-VEGF injections, as the branching vascular network can also cause leakage.

Q | **Dr. Singh:** A new photodynamic laser is in development specifically designed for use with verteporfin for injection. What do we know about this laser? What do you hope to see from it when it comes to market?

Dr. Kokame: I haven't seen the device yet. We know that the FDA is planning to do a factory inspection, but they haven't

approved it yet. I think it's very important that we get a PDT laser FDA approved in the United States as most PDT lasers currently in use are more than 20 years old. Most of the rest of the world has access to a PDT laser, but there currently is not an approved PDT laser for sale in the United States.

Dr. Fein: I had the opportunity to demo the new laser last month. It's very exciting because right now, if our laser breaks, it's very complicated to get it fixed. You can't really order new units and parts. The new laser is much smaller and more portable. It has a mini-tablet interface unit that allows you to use your finger to set fluence time, irradiance, etc. It has its own computer system that actually houses the information. You can store the patient's medical record number with the date of treatment and the treatment details. It's really exciting, and I am hopeful that the technology will be available soon in the United States for purchase and usage.

Dr. Barakat: The lasers we have are at the end of their life, so I am very much looking forward to a new option. It would be a shame to lose out on a therapy for patients because we don't have the technology available.

CASE 1: BILATERAL CHRONIC CSR TREATED WITH PDT

Dr. Fein: Our first case is a 66-year-old woman who I initially saw in June 2021. She reported decreased vision for about a year in her right eye. She had no complaints in the left eye at the time of presentation. Previously she was treated with thermal laser in the right eye by a physician outside of our practice. Past medical history was notable for gastroesophageal reflux disease, and she was on lansoprazole. Her VA was 20/25 OU, and her intraocular pressures are 15 and 17 mm HG. Anterior segment examination is notable only for minimal nuclear sclerosis OU. Figure 1 shows her OCT. You can see subretinal fluid in the right eye, CRT of 454 µm. Although her left eye was not symptomatic, she has some subretinal fluid with a CRT of 473 µm. Notably, it's very difficult on the right eye OCT to see the base of the choroid given choroidal thickening.

Figure 2 shows the FA. On the right eye, we see a focal hotspot with late leakage present. Interestingly in the left eye, it's difficult to discern where the leakage initiates. There are few small punctate areas of hyperfluorescence but no obvious focal leakage. Figure 3 shows the ICG bilaterally. On the right eye, there's an area that's hypercyanescence like the area on FA, but we're not catching any focal hotspot. On the left eye, we do see this focal punctate area of hypercyanescence.

This patient was symptomatic in her right eye and had previously been treated, so we did elect to do PDT for her right eye, which was performed in July 2021. Because the origin of the fluid seemed to be multifactorial, I treated with full fluence but did

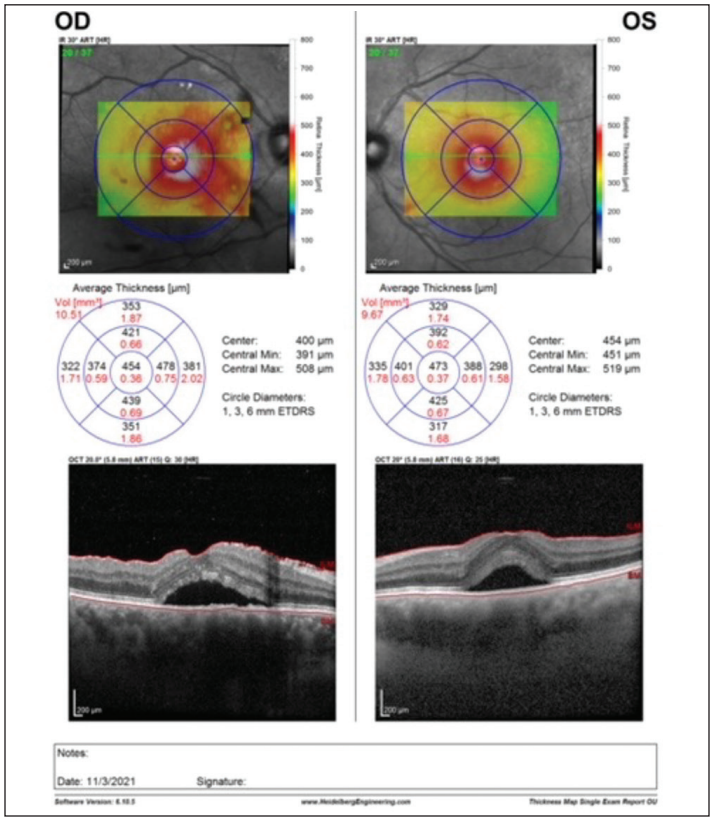

Figure 1. Case 1: Baseline OCT.

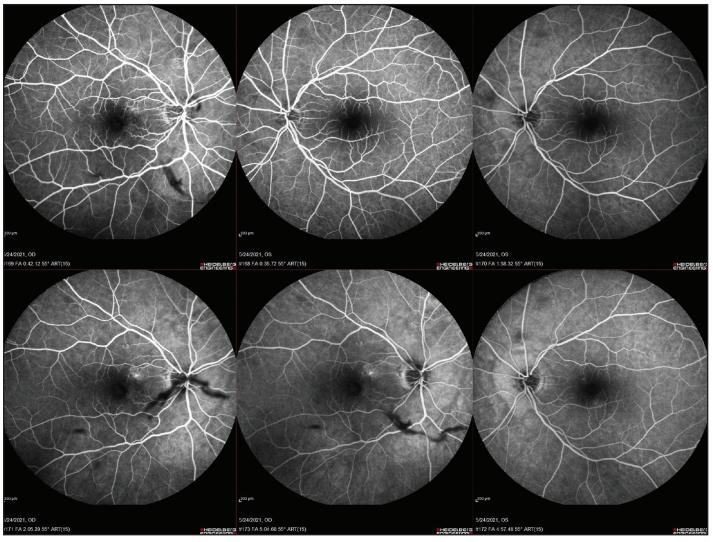

Figure 2. Case 1: Baseline FA.

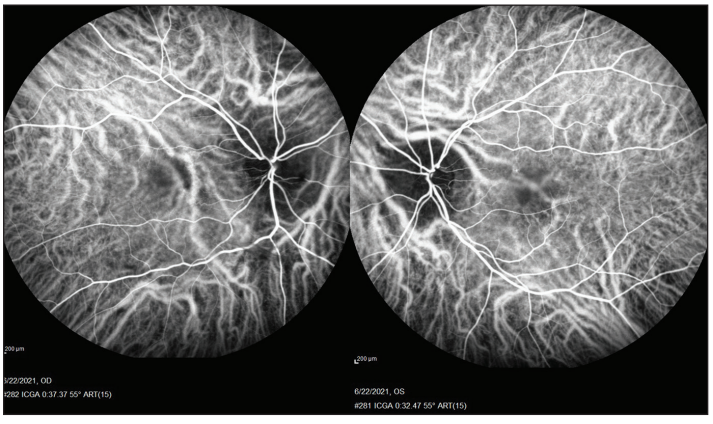

Figure 3. Case 1: Baseline ICG.

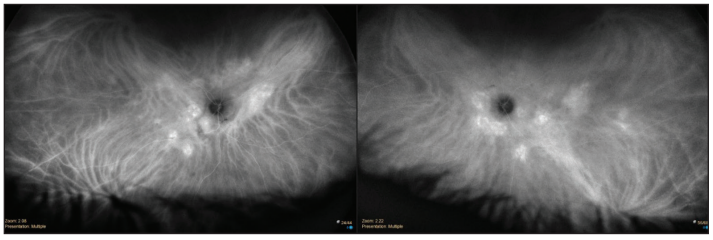

Figure 4. Case 1: Imaging 3 months post PDT OD.

two separate treatment areas each for half of the total treatment time. Figure 4 shows the ICG 3 months post-PDT and is more revealing than the previous imaging, with later frame present, making it clearer where the areas of leakage are originating. Right eye OCT demonstrates CRT is 343 µm, so there has been some response to treatment, but there's still persistent subretinal fluid.

Following treatment in the right eye, the left eye acutely worsens and CRT increases to 598 µm with decreased visual acuity and micropsia noted. I recommended a PDT on the left eye, and given her suboptimal response in the right eye, elected to treat with full fluence. Left eye PDT was performed October 26, 2021, and the right eye PDT was repeated on November 30, 2021. Figure 5 shows the most recent follow-up from December 10, 2021 (6 weeks after repeat PDT OD and 1 week after PDT OS), demonstrating improvement in both eyes in subretinal fluid. We will continue to monitor her and hope for continued reduction in subretinal fluid.

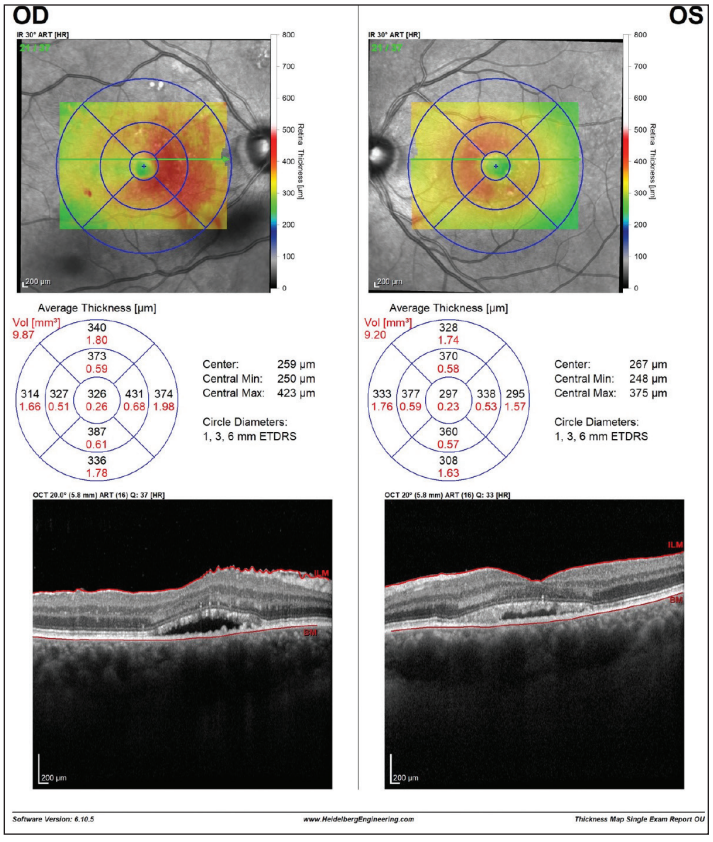

Figure 5. Case 1: Six weeks after repeat PDT OD and 1 week after PDT OS.

Dr. Singh: If you go back to your initial ICG images, I was impressed that you didn't find a particular area of treatment and yet you applied it broadly to that.

Dr. Fein: So there's that obvious area of hyperfluorescence supranasally, which I thought definitely needed to be treated. I was not sure about the area inferonasally and whether there was any leakage there. The initial ICG images were not very helpful especially in the right eye and may have been more illustrative if later images were obtained. This was a case in which I decided to do full-fluence treatment but split the treatment into 2 spots, which effectively made each treatment half fluence. I'd be curious to get others' thoughts on that. What do you do when you feel like the ICG is not giving you a complete picture?

Dr. Singh: I would say that I think this is where the benefits of PDT come in. You can treat broadly, move your spot around to wherever you need to, and even encompass the fovea. This is especially helpful in diseases like this where you don't have a subfoveal lesion per se with neovascularization. I think this is really where PDT shows its true value. It also doesn't cause adverse events when you choose a broad approach. I think it's a fantastic application, and you did a nice job with this case.

CASE 2: PCV CAN PREDICT ANTI-VEGF RESISTANCE

Dr. Kokame: Our next case is a 96-year-old man who presented with 20/40 VA and a vascularized pigment epithelial detachment, subretinal fluid, and macular edema with occult leakage on FA. He had received 15 aflibercept injections and still had persistent disease activity with subretinal fluid. Due to his age he was ready to give up and not continue with therapy. Figure 6 shows how his imaging looked after monthly aflibercept. In the fundus photo there is persistent subretinal fluid, but no subretinal hemorrhage. The OCT shows that there is still intraretinal cystic changes and subretinal hyperreflective material (SHRM). The ICG shows a polypoidal complex. You can see inferiorly that there are multiple dilated polypoidal lesions at the terminal ends of the PCV complex or within the PCV complex. The FA on the right of Figure 7 illustrates an early phase above and a late phase below showing definite persistent occult leakage.

Dr. Singh: It's interesting because when you showed that lesion, it doesn't have the particular OCT appearance you discussed beforehand, does it?

Dr. Kokame: No, it doesn't, but there's SHRM in that OCT image. With the Heidelberg scanning laser ophthalmoscope you can actually scroll to a specific area on the ICGA that shows the polypoidal lesion and with point-to-point correlation between the ICG and the OCT, this will show the corresponding inverted U-shaped lesion on the B scan OCT. Most of the polypoidal lesions are inferior so we didn't actually cut through the lower part of the lesion in this OCT image.

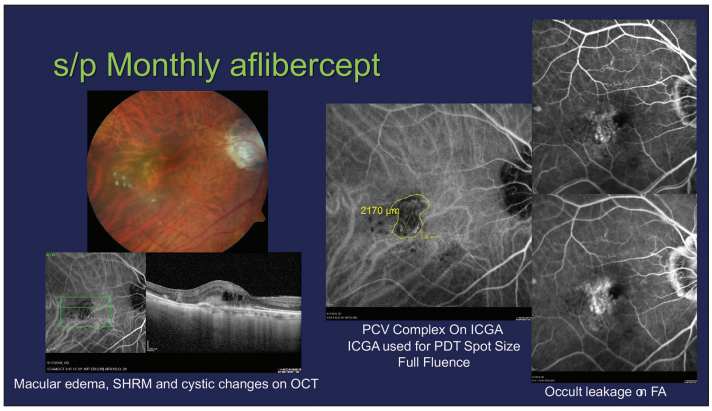

Figure 6. Case 2: Imaging after 15 monthly aflibercept injections.

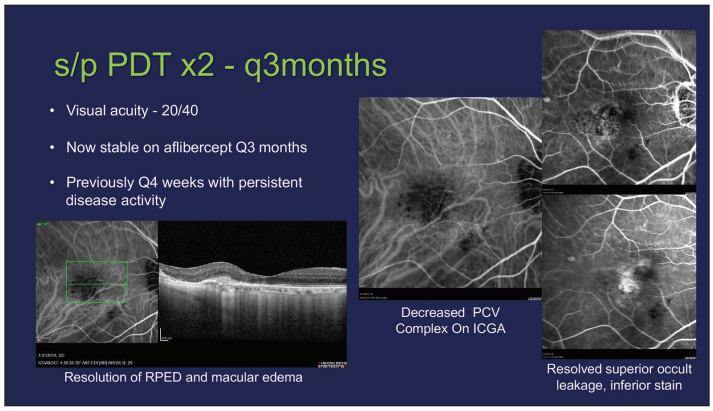

Figure 7. Case 2: Imaging after 2 rounds of PDT.

Dr. Fein: Do you think it also makes a difference because the patient has had treatment before and some of the neovascularization has regressed?

Dr. Kokame: That's true, as we discussed previously, polypoidal lesions do resolve after anti-VEGF treatment, but in this B-scan image we just did not choose a cut through the inferior polypoidal lesions. We did 2 PDT treatments 3 months apart, and his VA improved to 20/40. The patient is now stable on aflibercept every 3 months whereas he was previously treated every 4 weeks with persistent disease activity and ready to quit treatment.

Figure 7 shows his imaging after 2 rounds of PDT. On the OCT, you can see resolution of the pigment epithelial detachment, intraretinal cystic changes, and edema. On the ICG, you can see a remarkable decrease in the polypoidal lesions. You can still see the branching vascular network, but the polypoidal lesions have remarkably regressed. And on the FA on the right, there's staining but not the significant leakage that was present before the PDT. This is a good example of anti-VEGF resistance on PCV, and a good response to combination PDT and anti-VEGF injection.

Dr. Barakat: That's a great case. It makes me want to do ICGs after PDTs now. That ICG response is wonderful.

Dr. Fein: This is a great example of how PDT can be so effective in reducing the treatment burden for patients with anti-VEGF resistance. If you can get them on a Q3 month anti-VEGF schedule after PDT, patients are much happier. The burden is so much less. This is a beautiful example of that.

CASE 3: PDT IN AN ANTI-VEGF SHORT-TERM RESPONDER

Dr. Barakat: Our last case is an 80-year-old White man with an interesting ocular history in his right eye. About 5.5 years earlier he had cataract surgery and was very symptomatic with glare and vitreous debris. Six months after cataract surgery he had an intraocular lens exchange with a vitrectomy. He did not have a membrane peel at the time, just the vitrectomy. Then 3 years prior, which was 2 years after the vitrectomy, he was diagnosed with wet AMD. At the time that we are joining the story, he had received 19 ranibizumab injections during that 3-year period. Initially, he was receiving injections every 3 months, then the interval was decreased to monthly.

He continued to receive monthly injections and his VA tended to fluctuate between 20/25 and 20/40. You still see some subretinal fluid in the temporal periphery, threatening the fovea but not in the fovea. He was becoming pretty frustrated with the monthly injections and fluctuating vision. We extended him to 2 months

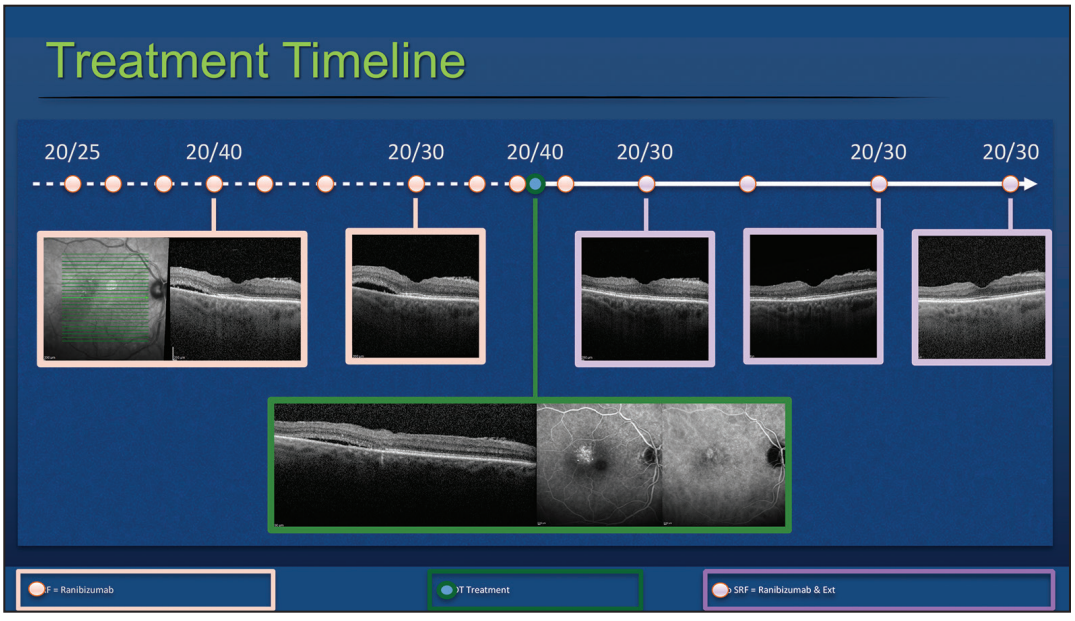

Figure 8. Patient treatment timeline.

and saw his subretinal fluid worsen, possibly unable to extend due to the previous vitrectomy. He received another monthly injection and the decision was made to bring him in for a PDT a week after his last ranibizumab injection. He looked almost dry on that day, with very little fluid. Figure 8 shows a timeline of his treatment. This illustrates my point that we know anti-VEGF treatments work well. I think the term nonresponder is probably a little bit generous; these are just people who need a lot of anti-VEGF.

He receives the PDT at half fluence. He comes in about a month later and gets another anti-VEGF injection. This is the first time he's been dry in quite a while. I was tempted to go to a PRN treatment plan, but we extended him. His vision is stable and there's no fluid. One year later, his VA is 20/30 with stable vision and no fluid. Instead of 9 injections a year, he's now at Q3 months. For me, this case highlights that PDT can help you achieve more durability and improve the quality of life for our patients. It may not completely get them off the anti-VEGF therapy, but it's certainly a nice adjunct therapy to offer them.

Dr. Singh: I'm impressed with the response.

Dr. Kokame: That was a great case. Even though we have some evidence that a bit of subretinal fluid may not be a bad thing, it is much better to have a result of no fluid and good vision than to keep treating a patient with persistent fluid. I think retina specialists should consider combination PDT and anti-VEGF injection because the posttreatment anatomy can be so much better.

Dr. Fein: That was a great case; thanks for sharing it with us. I think ICG is particularly helpful here, given how much treatment the patient has already received. The FA starts to look diffusely hyperfluorescent, and it's difficult to determine where to treat. The ICG provides a clearer spot of where the neovascularization is coming from.

Dr. Singh: Wonderful comments. Thank you to the faculty for your participation in this discussion on using PDT in 2022. ■

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PHOTODYNAMIC THERAPY: EVOLVING TREATMENT STRATEGIES AND KEYS TO EFFECTIVE DELIVERY

Release Date: March 2022
Expiration Date: April 2023

INSTRUCTIONS FOR CREDIT

To receive credit, you must complete the attached **Pretest/Posttest/Activity Evaluation/Satisfaction Measures Form** and mail or fax to Evolve Medical Education LLC, 353 West Lancaster Avenue, Second Floor, Wayne, PA 19087; Fax: (215) 933-3950. To answer these questions online and receive real-time results, please go to http://evolvemeded.com/course/2156-supp. If you experience problems with the online test, email us at info@evolvemeded.com. *NOTE: Certificates are issued electronically.*

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DEMOGRAPHIC INFORMATION

Profession
___ MD/DO
___ OD
___ NP
___ Nurse/APN
___ PA
___ Other

Years in Practice
___ >20
___ 11-20
___ 6-10
___ 1-5
___ <1

Patients Seen Per Week (with the disease targeted in this educational activity)
___ 0
___ 1-15
___ 16-30
___ 31-50
____ >50

Region
___ Northeast
___ Northwest
___ Midwest
___ Southeast
___ Southwest

LEARNING OBJECTIVES

Did the program meet the following educational objectives?	**Agree**	**Neutral**	**Disagree**
Summarize the mechanism of action and the clinical benefits of PDT in patients with retinal disorders	_____	_____	_____
Design a treatment regimen based on a personalized medicine approach for patients who do not respond adequately to anti-VEGF injections	_____	_____	_____
Critique methods for effective PDTdelivery in clinic settings, including dosing, using and administering reduced fluence protocols, infusion periods, determination of treatment size, and posttreatment care	_____	_____	_____
Describe the benefits of half fluence PDT or full fluence PDT on a real-world population	_____	_____	_____

POSTTEST QUESTIONS

Please complete at the conclusion of the program.

1. Based on this activity, please rate your confidence in your understanding of photodynamic therapy (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

a. 1
b. 2
c. 3
d. 4
e. 5

2. Based on this activity, please rate your confidence in your ability to apply key concepts of photodynamic therapy (PDT) in the clinic (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

a. 1
b. 2
c. 3
d. 4
e. 5

3. What were the key findings of EVEREST II?

a. PDT monotherapy is more effective than anti-VEGF monotherapy in the complete regression of PCV at 6 months
b. Combination PDT and ranibizumab can decrease the need for anti-VEGF injections and improve vision in patients with PCV
c. Patients with PCV can have some amount of subretinal fluid with good long-term visual outcomes
d. Ranibizumab monotherapy is only slightly more effective at improving vision than PDT, therefore PDT is preferred due to the reduced treatment burden

4. PDT can be used to successfully treat the following retinal diseases EXCEPT:

a. Chronic central serous retinopathy
b. Retinal angiomatous proliferation lesions
c. Retinitis pigmentosa
d. Juxtafoveal or extrafoveal choroidal neovascularization

5. Which statement provides the most accurate description of an anti-VEGF nonresponder?

a. Nonresponder is a misnomer; they are really short-term responders
b. Nonresponders are patients who don't respond after 3 loading doses of anti-VEGF
c. Nonresponders are patients who don't respond after 5 to 6 monthly injections of anti-VEGF
d. Nonresponders are patients who have persistent fluid after 4 monthly injections of anti-VEGF

6. Identify the correct settings for half-fluence PDT.

a. 50 J/cm^2 of light at 600 mW/cm^2 for 83 seconds
b. 50 J/cm^2 of light at 300 mW/cm^2 for 83 seconds
c. 25 J/cm^2 of light at 300 mW/cm^2 for 41 seconds
d. 25 J/cm^2 of light at 300 mW/cm^2 for 83 seconds

7. A 75-year-old patient presents with predominately occult subfoveal lesions and a VA of 20/100 OU. _____ would be an appropriate first-line treatment.

a. Half-fluence PDT
b. Full-fluence PDT
c. Monthly aflibercept injections
d. Three loading doses of ranibizumab followed by PRN

8. The same patient from Question 7 has not responded to anti-VEGF after 6 rounds of monthly treatment. What is your next step?

a. Continue with monthly aflibercept injections
b. Classify the patient as an anti-VEGF nonresponder and proceed with half-fluence PDT
c. Switch the patient to another anti-VEGF agent to initiate a response
d. Classify the patient as an anti-VEGF nonresponder and proceed with full-fluence PDT

ACTIVITY EVALUATION

Your responses to the questions below will help us evaluate this activity. They will provide us with evidence that improvements were made in patient care as a result of this activity.

Rate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low_____

Rate your knowledge/skill level after participating in this course: 5 = High, 1 = Low_____

This activity improved my competence in managing patients with this disease/condition/symptom. _____ Yes _____No

Probability of changing practice behavior based on this activity: _____High _____ Low _____No change needed

If you plan to change your practice behavior, what type of changes do you plan to implement? (check all that apply)

Change in pharmaceutical therapy _____
Change in nonpharmaceutical therapy _____
Change in diagnostic testing _____
Choice of treatment/management approach _____
Change in current practice for referral _____
Change in differential diagnosis _____
My practice has been reinforced _____
I do not plan to implement any new changes in practice _____

Please identify any barriers to change (check all that apply):

_____ Cost
_____ Lack of consensus or professional guidelines
_____ Lack of administrative support
_____Lack of experience
_____ Lack of time to assess/counsel patients
_____ Lack of opportunity (patients)
_____ Reimbursement/insurance issues
_____ Lack of resources (equipment)
_____ Patient compliance issues
_____ No barriers
_____ Other. Please specify: _____

The design of the program was effective for the content conveyed	___ Yes	___ No
The content supported the identified learning objectives	___ Yes	___ No
The content was free of commercial bias	___ Yes	___ No
The content was relative to your practice	___ Yes	___ No
The faculty was effective	___ Yes	___ No
You were satisfied overall with the activity	___ Yes	___ No
Would you recommend this program to your colleagues	___ Yes	___ No

Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced through your participation in this activity:

_____ Patient Care
_____ Practice-Based Learning and Improvement
_____ Professionalism
_____ Medical Knowledge
_____ Interpersonal and Communication Skills
_____ System-Based Practice

Additional comments:

_____

_____ I certify that I have participated in this entire activity.

This information will help evaluate this activity; may we contact you by email in 3 months to inquire if you have made changes related to this activity? If so, please provide your email address below.

_____

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