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PHOTODYNAMIC THERAPY IN 2020 AND BEYOND: CURRENT CONCEPTS FOR REAL-WORLD USE

Provided by evolve medical education

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CONTENT SOURCE

This continuing medical education (CME) activity captures content from a round table discussion.

ACTIVITY DESCRIPTION

Verteporfin for photodynamic therapy (PDT) has been in commercial use as a treatment for retinal disorders for several decades. Multiple studies have suggested a combination of anti-VEGF agents with PDT provides advantages over anti-VEGF monotherapy for polypoidal choroidal vasculopathy, but in wet age-related macular degeneration, the combination of PDT and anti-VEGF is not as clear-cut. This activity includes expert discussions on real-world clinical scenarios in which the use of PDT alone or in combination with anti-VEGFs can be a more efficacious treatment option than using anti-VEGFs alone, particularly in the setting of persistent disease activity.

TARGET AUDIENCE

This certified CME activity is designed for retina specialists and ophthalmologists involved in the management of retinal diseases.

LEARNING OBJECTIVES

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

- **Summarize** the clinical benefits of PDT in patients with retinal disorders and in those with persistent disease activity
- **Design** a treatment regimen based on a personalized medicine approach for patients who do not respond adequately to anti-VEGF injections
- **Identify** methods for effective PDT delivery in clinic settings, including dosing, infusion periods, and determination of treatment size
- **Differentiate** the benefits of half-fluence PDT and full-fluence PDT on a real-world population

GRANTOR STATEMENT

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PRETEST QUESTIONS

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

1. Please rate your confidence in your ability to use 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

2. Please rate how often you use PDT (based on a scale of 1 to 5, with 1 being never and 5 being always.)

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

3. In which diseases is PDT a reasonable treatment option?

a. Peripapillary choroidal neovascularization
b. Central serous chorioretinopathy
c. Choroidal neovascular membrane lesions
d. Ocular tumors
e. All of the above

4. All but which of the following statements is true?

a. Half-fluence PDT can be achieved by reducing power of laser.
b. Half-fluence PDT can be achieved by increasing the laser time.
c. Full-fluence PDT may be most appropriate for choroidal hemangioma treatment.
d. Half-dose PDT may reduce risks of severe vision decrease.

5. To determine the treatment size for PDT using traditional guidelines, how far beyond the greatest linear diameter of the lesion should you measure?

a. 4,000 µm
b. 3,000 µm
c. 2,000 µm
d. 1,000 µm

6. Post-PDT, what is the minimum number of days a patient should avoid direct sunlight?

a. 2 days
b. 3 days
c. 4 days
d. 5 days

7. The PLANET study evaluated PDT as a potential rescue therapy for patients with polypoidal choroidal vasculopathy (PCV) who had a suboptimal response to aflibercept. What did the findings suggest?

a. Ranibizumab is a better anti-VEGF agent to pair with PDT for patients with PCV.
b. Aflibercept/PDT combination was superior to aflibercept monotherapy, suggesting patients should be treated immediately with the combination particularly in the setting of an active hemorrhage.
c. Aflibercept monotherapy was shown to be noninferior to aflibercept/PDT, suggesting aflibercept may be an efficacious anti-VEGF therapy for PCV.
d. Patients with PCV do not benefit from rescue injections of PDT.

8. After 3 months, an elderly patient with anti-VEGF-resistant wet age-related macular degeneration treated with half-fluence PDT has had no response but vision has not worsened from the treatment. What is your next step(s)? *Select all that apply*.

a. Continue to watch the patient; they need more time for the treatments to be considered successful or nonrespondent.
b. Retreat the patient with full-fluence PDT.
c. Retreat the patient with partial-fluence PDT.
d. Treat the patient with a micropulse laser.

9. The Verteporfin in Photodynamic Therapy Study Group found _____ of patients could have acute vision loss after PDT.

a. 1%
b. 2%
c. 3%
d. 4%

10. What is a likely scenario for a patient who has undergone PDT for chronic central serous chorioretinopathy?

a. Immediate anatomic response
b. Anatomic response at 1 week, vision improvement within 1 to 2 weeks
c. Anatomic improvement after 2 months or longer; vision improvement is more variable
d. Vision improvement around 1 month; anatomic improvement is more variable

Photodynamic Therapy in 2020 and Beyond: Current Concepts for Real-World Use

Photodynamic therapy (PDT) using verteporfin has been used to treat retinal disorders, such as classic subfoveal choroidal neovascularization due to age-related macular degeneration, for several decades.[1-4] Now, PDT has many more uses in the retinal space, including central serous chorioretinopathy, polypoidal choroidal vasculopathy, choroidal tumors, and peripapillary choroidal neovascularization. Although safe and efficacious, PDT comes with many challenges, including office workflow considerations and insurance billing. The treatment itself is nuanced. Retina specialists must determine lesion size and treatment area, as well as the appropriate dosing for the clinical scenario at hand. The following roundtable discussion highlights these issues, and many others, with thought leaders in retina with extensive PDT experience.

—RISHI P. SINGH, MD, MODERATOR

CLINICAL SCENARIOS FOR PDT TREATMENT

Q | RISHI P. SINGH, MD: PDT has many uses in the clinic today, including subfoveal choroidal neovascularization, central serous chorioretinopathy (CSCR),[5-7] polypoidal choroidal vasculopathy,[8] ocular tumors,[9] and peripapillary choroidal neovascularization (CNV).[10] How do you use PDT in your practices?

JORDANA G. FEIN, MD, MS: I primarily use PDT for CSCR that is either chronic or recurrent that fails observation alone.[5-7] I also will use it for patients with recalcitrant age-related macular degeneration (AMD) who are getting monthly anti-VEGF therapy and still have persistent activity/edema. I also find it to be useful for patients with polypoidal choroidal vasculopathy (PCV).[8,11,12] Finally, less frequently, I use PDT for tumors such as choroidal hemangiomas. Multiple studies have demonstrated high rates of tumor control with minimal complications.[13-17]

DANTE PIERAMICI, MD: Most of the PDTs I peform are for patients with chronic CSCR. I also use PDT in patients with intraocular tumors such as choroidal hemangiomas and vasoproliferative tumors.[18] I use it more rarely for CNV[10,19] but do consider it in certain cases of polypoidal choroidopathy[20,21] or recalcitrant-type CNV lesions.

PRIYATHAM (PRITHU) S. METTU, MD: The primary place that PDT falls in my practice is for patients with anti-VEGF–resistant wet AMD.[22] My PDT use for these patients falls into two categories: (1) patients with persistent or progressive disease in spite of monthly anti-VEGF therapy; and (2) patients who initially were able to achieve quiescence on monthly injections but then have subsequent leakage on extension. I also utilize PDT for patients with acute episodic or chronic CSCR.

Q | DR. SINGH: Does anyone use PDT for extrafoveal lesions? When you see an extrafoveal CNV or even juxtafoveal CNV in a patient, what is your rationale for selecting between PDT, focal laser, and anti-VEGF therapy?

DR. FEIN: There is extensive evidence in the literature that PDT can stabilize juxtafoveal and extrafoveal CNV and improve vision.[23,24] For these lesions, I would however only recommend treatment if the patient was symptomatic with fluid through the fovea or with a significant scotoma from fluid in the peripapillary region. Even though I find PDT to be very effective, I still primarily rely on anti-VEGF injections as first-line therapy and consider PDT in a recalcitrant patient who was not responding to anti-VEGF.

DR. PIERAMICI: For me, it depends on the diagnosis. Some idiopathic peripapillary lesions seem to be recalcitrant to anti-VEGF therapy. However, I'd still try anti-VEGF therapy first; if I got a nice response, I might leave it at that. If it didn't respond well, then I might consider PDT or even laser photocoagulation if it was a well delineated area of CNV. PDT certainly would be safer, but it may be less effective, as well.

DR. SINGH: What's the evidence for PDT for polypoidal lesions? We now have multiple clinical trials evaluating PDT in combination with anti-VEGF for PCV versus anti-VEGF alone, including EVEREST, EVEREST II, and PLANET.[8,12,25,26] Does available evidence guide your use of anti-VEGF and PDT for these patients?

DR. METTU: To some extent it does. Let's dive a little deeper into these studies, which were all multicenter, randomized, double-masked trials, but asked slightly different questions.[8,25,26] In EVEREST, patients were randomized to verteporfin PDT, ranibizumab 0.5 mg, or the combination. Patients were administered with verteporfin PDT/placebo and initiated with three consecutive monthly ranibizumab/sham injections starting day 1, and retreated (months 3-5) as per predefined criteria, with endpoints assessed at month 6. The study met its primary endpoint, as verteporfin PDT combined with ranibizumab 0.5 mg or alone was superior to ranibizumab monotherapy in achieving complete regression of polyps. Mean change in visual acuity was comparable amongst the three groups.

EVEREST II included 322 patients across multiple centers in Asia, randomizing them to ranibizumab 0.5 mg monotherapy or combination ranibizumab and verteporfin PDT. All participants received three consecutive monthly ranibizumab injections, followed by a *pro re nata* (PRN) regimen. Participants also received vPDT/sham PDT on day 1, followed by a PRN regimen based on the presence of active polypoidal lesions. At 12 months, the combination regimen was not only noninferior to ranibizumab monotherapy for improvement in best-corrected visual acuity (BCVA), but actually superior in analyses of functional improvement (8.3 vs 5.1 ETDRS letters, respectively; mean difference, 3.2 letters) and complete polyp regression (69.3% vs 34.7%, respectively, $P < .001$). Furthermore, adding PDT minimized the ranibizumab injection burden (median of 4.0 vs 7.0, respectively).

These data provide compelling support for combination PDT and anti-VEGF therapy as a first line treatment for patients with polypoidal CNV lesions.

In contrast to the EVEREST studies, PLANET evaluated PDT not as a primary therapy but as a potential rescue therapy for patients with suboptimal response to aflibercept. In PLANET, 318 participants received three consecutive aflibercept 2-mg injections every 4 weeks. At week 12, participants with a suboptimal response were randomized 1:1 to receive either aflibercept plus sham PDT (aflibercept monotherapy) or a "rescue" of aflibercept plus rescue PDT (aflibercept/PDT). Participants who had optimal response and did not qualify for rescue received aflibercept every 8 weeks; those qualifying for rescue received aflibercept every 4 weeks plus sham/active PDT. When the rescue criteria were no longer met, injection intervals were gradually extended to 8 weeks. Using this study design, at 52 weeks, the aflibercept monotherapy group was noninferior to aflibercept/PDT combination therapy group, for the primary end point (+10.7 vs +10.8 letters, respectively; 95% CI, -2.9 to 1.6; P = 0.55), with few participants requiring rescue therapy (19 [12.1%] vs 23 [14.3%], respectively). At week 52, 49 (38.9%) and 60 participants (44.8%) had no polypoidal lesions observed on indocyanine green angiography in the aflibercept monotherapy and aflibercept/PDT groups, respectively.

These data suggest that aflibercept may be more efficacious as an anti-VEGF monotherapy choice for the treatment of PCV. Since there were not enough patients that met criteria of suboptimal response, the study could not evaluate the potential benefit of adding PDT in the setting of anti-VEGF resistance.

Taking all of this data together, I will try to start with aflibercept for patients with PCV whenever possible. That said, regardless of the specific anti-VEGF drug used for treatment, I will frequently consider adding PDT earlier, potentially even at treatment outset, if there is hemorrhage already present or I am concerned about the risk of bleeding, to try to achieve disease control as efficiently as possible.

SELECTING BETWEEN PARTIAL AND FULL FLUENCE

Q | **DR. SINGH:** When PDT first became available, we were giving full-fluence treatments for exudative AMD. Full fluence includes an IV of verteporfin (6 mg/m^2) for 10 minutes. The patient then receives PDT at the target lesion for 83 seconds with a wavelength of 689 nm and an energy of 50 mJ/cm^2.[27] Some of us have migrated to partial fluence over time.[28,29] What does the "partial fluence" mean to you? Do you use it, and, if so, at what frequency?

DR. PIERAMICI: The use of half fluence or even quarter fluence can be effective, and perhaps have fewer side effects, depending on the specific lesion treated.[28,30,31] Several studies have found reduced-fluence PDT to be equally effective as full-fluence.[28,30,32-34] Chan and colleagues[35] described good visual and anatomic results treating acute CSCR with half-dose PDT in a randomized controlled trial.

Full-fluence PDT can be associated with a number of adverse events such as retinal pigment epithelium (RPE) tears, transient vision loss, and, rarely, severe loss of vision, which concerned the retina community; this is why many of us transitioned to half fluence.[36-40] PDT was associated with acute vision loss in about 4% of patients, according to the Verteporfin in Photodynamic Therapy Study Group.[40] Full-fluence PDT may result in more transient upregulation of VEGF and associated increased exudation. Therefore in many situations partial-fluence PDT is preferred intitally.[31] However, a recent study comparing half-fluence and full-fluence PDT using retrospective and comparative interventional studies found that after 1 year of treatment, full-fluence PDT reduced subfoveal choroidal thickness better than half-fluence PDT.[30] Lai et al reviewed 136 eyes (123 patients) with chronic CSCR who underwent half-dose PDT between 2005 and 2011.[41] They found patients could achieve long-term stable vision and resolution of serous retinal detachments, but that patients with bilateral CSCR were more likely to develop a recurrence after half-dose PDT.[41]

Reduced PDT can be achieved in two ways: reduced fluence and reduced verteporfin dose. Reduced fluence, using an energy of 25 J/cm^2 instead of 50 J/cm^2, can be achieved either by cutting the power of the laser from 600 mW/cm^2 to 300 mW/cm^2 or reducing the amount of laser exposure time. Some physicians have suggested the use of half-dose verteporfin (3 mg/m^2). These various methods probably achieve similar results though direct comparative studies are lacking.[42-44]

I start almost everyone with half-fluence PDT, be it for AMD, polypoidal choroidopathy, or central serous. However, I tend to start with full fluence for retinal/chorodial vascular tumors.

DR. FEIN: I also cut the power and not the time for half fluence. I usually start with half fluence, particularly for CSCR. For a choroidal tumor such as hemangioma or previously treated melanoma, I would use full fluency and full power initially.[45]

DR. METTU: I typically utilize full fluence for wet AMD cases. I use indocyanine green (ICG) angiography to specifically localize the pathologic CNV lesion in patients with wet AMD, which will allow me to reduce the effective spot size to target the base of a feeder arteriole in the case of an arteriolarized vascular complex or to target polyps in the case of a PCV subtype. This approach allows me to minimize potential effects on normal choroidal vasculature. If I am concerned my treatment is too close to the foveal center, then I will start with half fluence, which I do by adjusting the time to half duration, rather than adjusting the power. For CSCR, I will frequently start with half fluence, particularly if I'm aiming at a spot near the fovea.

Q | **DR. SINGH:** Realistically, how many times have you seen vision loss as a result of loss of choroidal blood flow following PDT, and do you think half-fluence reduces the risk?

DR. FEIN: I've never seen it. I completely understand the pathophysiology, and I still don't do full-fluence PDT when I think I can get away with half fluence. But I've never seen it in my practice.

DR. PIERAMICI: I've seen it, but it's been many, many years. In the last 10 or 15 years, I've mostly used half fluence except for tumor cases, so I haven't seen it recently.

DR. METTU: I've had one case that I can recall where the patient experienced acute vision loss afterward. It was a case where we initially tried half and went to full. There was some vision decrease on a repeat attempt of full fluence.

DETERMINING LESION SIZE AND TREATMENT AREA

Q | **DR. SINGH:** Lesion sizes are typically established through imaging such as fluorescein angiography (FA), ICG, or color fundus photography. When PDT first became available, we were taught that we should go a 1,000 µm beyond the greatest linear diameter of the lesion, take the measurements, provide those measurements back to someone, and then dial that into the machine. Does that have relevance for you now or do you estimate the lesion size yourself?

DR. PIERAMICI: Most cases I'm doing today are CSCR, and I measure the lesion on the FA with the image analytic software. When I sit down with the patient a few minutes before I start, I determine whether the laser aiming beam spot in real-time correlates with the premeasured image size. When they don't correlate well, I favor the real-time aiming beam size. Many of my CSCR patients have chronic disease, and it's difficult to know exactly the extent of active leakage. Sometimes, in the case of large lesions, I use a roaming spot to cover the entire lesion.

DR. METTU: For my wet AMD patients, as I mentioned, I'll typically use ICGA guidance to identify the spot size, and use choroidal vascular flow to assess dynamic filling of the CNV. I try to encompass the portion at the base of the feeder arteriole or where the polyps are and measure the lesion size. I'll typically add another 150 µm to that. Using this approach, my typical spot size is usually between 1,300 to 1,800 µm for the vast majority of these lesions. I'll usually have a technician print a color photo, and I will demarcate the photo and use it as a guide in the room for easy reference to ensure that I am targeting the laser spot accurately.

DR. FEIN: I look very carefully at the imaging and the ICG to determine the optimal location to treat. I have the FA/ICG images in the room displayed on a computer while I do my treatment in order to accurately target the areas of interest. In general, the smallest spot size I use in practice is 1,700 µm. For these smaller lesions, I'm essentially aiming directly on top of the active area. I usually allow for some minimal overlap to the surrounding areas, which I find to be helpful in case my alignment is not perfect.

MAXIMIZING OFFICE WORKFLOW FOR PDT

Q | **DR. SINGH:** How does scheduling PDT patients differ from your general routine clinical practice?

DR. FEIN: We have certain technicians in our office who are able to administer PDT, so we have to make sure that technician is scheduled to be in the office with me that day. Typically, I'll schedule a PDT appointment and then the front desk staff knows to forward that information to the lead technician in charge of technician assignments. That also alerts the front desk to get authorization for the verteporfin from the insurance carrier if required. Although we notate the patient is booked for PDT, these appointment slots are identical to our other types of appointments.

DR. PIERAMICI: Before anti-VEGF therapy, we used to do much more PDT. We'd have one day a week in the clinic when a nurse would come in and we'd schedule all the PDT cases and do them back to back.

Today we may schedule PDT once a month in certain offices. Most of the PDT cases I'm scheduling today are for patients with CSCR, and there may be an issue getting insurance coverage. The health care coverage logistics can take time. Treating CSCR is generally not an urgency like CNV, so they can wait a number of weeks for PDT without significant risk of visual loss.

We used to contract nurses to perform the verteporfin infusion, but have subsequently trained our angiographers to carry out most of the infusion tasks under our supervision. This has facilitated scheduling and cost.

DR. METTU: I usually schedule a separate PDT appointment. If it's a patient from my practice, we'll schedule their PDT 7 to 10 days after their last anti-VEGF injection. For patients who are referred to me, I'll coordinate with the referring doctor and schedule the PDT at a time that allows them to maintain their scheduled anti-VEGF regimen. We'll typically do imaging on the day of scheduled PDT, if they come to see me for the first time. We'll review the risks and benefits of PDT and then proceed. We have nurses who handle the administration of verteporfin and help coordinate the logistics and educate the patient on what to expect.

MANAGING PATIENT EXPECTATIONS AND POST-OPERATIVE CARE

Q | **DR. SINGH:** What do you discuss with the patient regarding preoperative care and postoperative care? How do you manage their expectations of PDT effectiveness?

DR. METTU: We have a system in place that involves the nurses calling patients a few days in advance and reviewing what to expect, specifically that patients need to avoid extensive exposure to sunlight and a lot of outdoor activity unless they're well covered. The US FDA recommends that patients avoid direct sunlight for 5 days after the procedure and our nurses recommend 3 to 5 days to patients.[46] Patients need to be extremely careful around the infusion site itself. I tell patients to err on the side of caution and avoid direct sunlight for at least 48 hours minimum.

In terms of what to expect, we talk about the risks, mostly the low risk of vision loss, and the benefits. We discuss the low incidence of symptoms like back pain.[47-49] That tends to be pretty infrequent in my experience, but we go over it as part of the informed consent process. Other risks include shortness of breath, elevated blood pressure, and pruritus.[48] Then the nurses reinforce the do's and don'ts after the procedure is over.

DR. FEIN: The other thing I make sure I discuss in the preoperative evaluation is appropriate expectations for the effectiveness of PDT, as well as the timing of this response. I tell patients they won't see an improvement for at least 6 to 8 weeks, and that maximal improvement may not be seen for several months. For instance, if it's an AMD patient, they're going to need to continue their regular monthly injections for the short term, even if the laser is effective. For CSCR patients who may be more concerned about the acute decline or scotoma in their vision, it's very important that he or she understands there will not be immediate improvement. If I have those conversations in advance, this saves me from extra phone calls 1 to 2 weeks after the procedure from patients concerned they haven't noticed an improvement yet.

I also review the sun precautions. I generally tell people I want them out of the sun for 3 days or 72 hours. If they have to go outside, they need to cover up completely with long sleeves, long pants, and a hat with a brim.

Q | **DR. SINGH:** Dr. Fein, you brought up a great point earlier that I want to touch on. In terms of clinical endpoints, there's not much of an improvement from the patient perspective. From a practitioner perspective, let's discuss how you know the patient is responding. What are you looking for, and when do you look for it?

DR. PIERAMICI: For a chronic CSCR patient, I'll usually see that patient back 4 to 6 weeks following treatment. I tell them upfront that we're hoping to see an anatomical improvement first and hopefully a visual improvement with time. There actually can be an acute reduction in vision during the first week, and I discuss this as well. When they come back in 4 to 6 weeks, I am encouraged when the optical coherence tomography (OCT) demonstrates the SRF is reducing or resolved. Surprisingly, in most cases of CSCR that I've treated, the fluid goes away eventually. However, the visual acuity response is much more variable. A lot of these patients, by definition, are chronic cases and even when the fluid resolves, the visual improvement may be modest. You have to prepare them for that possibility.

DR. METTU: I also bring my chronic CSCR patients back in about 6 weeks, hoping to see an anatomical response. Dr. Fein brought up a great point in terms of setting the expectation for vision. For the chronic patients, I usually say the goal is to try to maintain vision; if they see a visual improvement, that's a bonus. For the acute episodic patients, there's a good chance we may see visual improvement but that's typically delayed after the anatomical response. For wet AMD patients, I tell patients that the PDT isn't so much for the vision, it's to try to improve the long-term control of the disease and prevent their vision from getting worse.

In terms of seeing response, I will typically defer a repeat angiogram for those patients unless there's something specific that I want to see. When I was doing ICGAs more routinely after PDT for wet AMD patients, I found that many times I didn't have to achieve complete vaso-occlusion of the lesion in order to see resolution of disease activity. In many cases, a reduction in blood fluid was sufficient to achieve quiescent disease. However, it's likely that the most durable outcomes are obtained with CNV vaso-occlusion.

Q | **DR. SINGH:** Let's discuss retreatment intervals. When is the earliest time you'd consider retreatment?

DR. PIERAMICI: It depends on the disease process. If in 3 months a CSCR patient has seen no reduction in SRF, then I may try a full-fluence treatment. On the other hand, if a CSCR patient is starting to show some response after 3 months, say the fluid has reduced, then I'd give them more time before considering retreatment.

For AMD patients, a number of trials have examined the difference between early or late retreatment and none have showed much difference in safety or efficacy; they are both just as effective.[50] I'd personally consider additional anti-VEGF therapy first and then an additional PDT 6 months later if I'm not seeing a response.

DR. FEIN: I would not repeat a PDT before the 3-month mark. I'd consider retreating a CSCR patient after 3 months if there's been some improvement but there is residual fluid that remains. If I saw no response at all, I might consider trying something different, like a high-density subthreshold micropulse laser, depending on what the disease looked like angiographically. Brief micropulses to the RPE have been shown to stimulate RPE function without damaging the retina.[51-53] The "on" interval of the micropulse laser is typically 100 to 300 µs, followed by an "off" interval of 1,700 to 1,900 µs. The "off" interval allows the RPE to cool and return to baseline temperature before the next pulse is delivered, thereby eliminating heat build-up, decreasing damage to the retina, and preventing coagulative necrosis.[54] I also have a high retreatment threshold in wet AMD patients and would not repeat PDT for at least 4 to 6 months in those cases.

Q | DR. SINGH: What are some barriers to PDT treatment being used more often in clinical practice?

DR. METTU: The primary barrier is the availability of the laser. The other barrier is the lack of familiarity with PDT, particularly among many younger retina specialists who may know of PDT only from historical studies. If they didn't train at an institution where PDT was part of the approach, then it's quite foreign to them. There's a lack of awareness of the potential benefits.

DR. FEIN: Another barrier is the cost of verteporfin. It's difficult to get the authorization from certain insurance carriers, and that likely prohibits people in a solo retina practice or a small group that may not have the infrastructure in place to deal with the billing and prior authorization. The staff required can also be an issue. Private practices generally don't employ nurses, but rather technicians. The technicians who do PDT must be well trained, and must do the procedure often enough to be comfortable with all of the necessary steps. Getting the proper staff assembled, the authorization from insurance companies, and buying and billing the drug make the process more complex.

DR. PIERAMICI: Many private practice groups have multiple offices with one laser between them to share. You have to pack up the laser and ship it to the office or the patient has to travel to another office, which they often won't do. Anti-VEGF injections are a much easier regimen, logistically. Offices have become very efficient with injections while PDT requires more organization.

DR. SINGH: What are the most important pearls for a retina specialist new to PDT? How might they get started?

DR. FEIN: There are many variables that can impact the effectiveness of PDT, including verteporfin dosing, fluence level, infusion periods, and the accurate determination of lesion size.[28,30,31,55,56] The most important part about PDT is the planning. If you know where the leakage is, and where you need to treat, firing the laser is easy. It's the preparation and patient discussion that is difficult. Figuring out where you're going to treat on the retina is step No. 1. An excellent resource available to retina specialists who are just starting out with PDT can be found on the American Academy of Ophthalmology's EyeWiki site.

RECENT TRIALS IN PDT

Q | DR. SINGH: Are there any recent data that are helpful for PDT?

DR. PIERAMICI: Eplerenone has been suggested as an alternative to PDT for chronic CSCR. However, a recent randomized, double-blind, placebo-controlled trial found that visual results at 12 months were not significantly different between the groups. This study group concluded that eplerenone was not superior to placebo and that ophthalmologists who currently prescribe eplerenone for CSCR should discontinue this practice.[57]

A randomized open-label trial of half-dose PDT versus high-density subthreshold micropulse laser (PLACE Trial) demonstrated the superiority of PDT over micropulse in the treatment of chronic central serous retinopathy.[52] Visual and anatomic outcomes were significantly better with PDT and these differences were clinically relevant.

A recent paper from the Wills Eye Ocular Oncology group compares choroidal hemangioma treatment in the era prior to PDT (defined as 1967–2001) versus PDT (defined as 2002–2018).[58] A total of 458 tumors were treated during a 51-year period. It showed much better results for vision and fluid reduction from PDT. Hemangiomas treated in the PDT era showed also improved tumor regression and better control of cystoid macular edema.

CASE 1: CHOROIDAL HEMANGIOMA

DR. PIERAMICI: This case is a 44-year-old healthy man who had an acute change in vision. On the exam, an orange discoloration was visible deep to the retina, but also a larger area of SRF and some subretinal lipid at the leading edge (Figure 1).

The FA reveals a speckled hyperfluorescence, which could be consistent with an occult area of choroidal neovascularization (Figure 2). However, based on the ultrasound, there was an area of localized choroidal thickening, SRF over the choroidal lesion, and then SRF extending into the macular region (Figure 3). These findings suggested a choroidal hemangioma, and we treated it with full-fluence PDT. He had a very positive response and within 6 weeks had resolution of the SRF following just one therapy (Figure 4) and has remained stable for years.

Patients with choroidal hemangiomas respond very well to PDT. I've had patients with choroidal osteomas who seem to do less well, and I'll use anti-VEGF in addition to PDT in those patients. Vasoproliferative tumors can also respond to PDT, however multiple treatments may be necessary and given their peripheral location can be hard to reach. Vasoproliferative tumors may be easier to address with cryotherapy. The hemangioblastomas (retinal capillary hemangiomas), may be targeted with PDT as well depend-

Figure 1. Case 1: 44-year-old male with choroidal hemangioma at baseline.

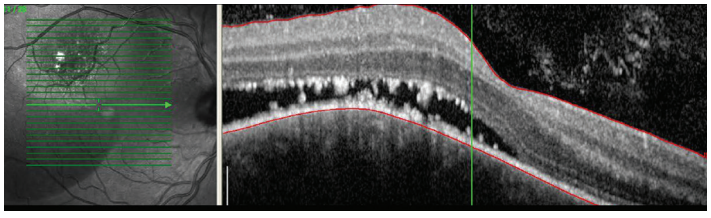

Figure 2. Case 1: Fluorescein angiogram at baseline.

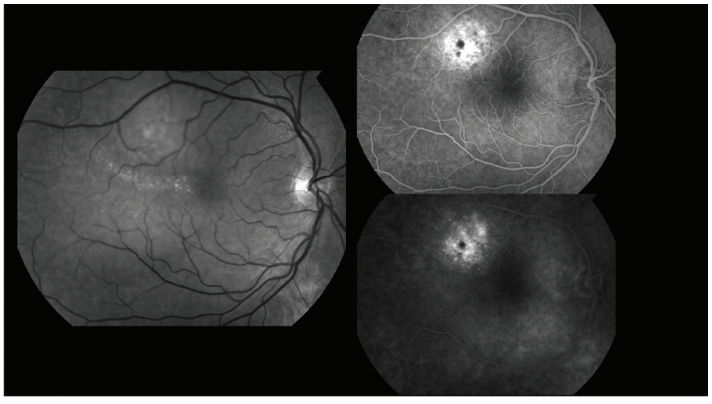

Figure 3. Case 1: Showing subretinal fluid over the lesion.

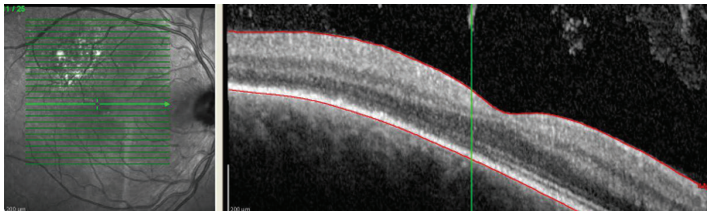

Figure 4. Case 1: Post-PDT at 4 weeks.

ing on size and location. Again, many of these are more easily addressed with laser photocoagulation when smaller or cryotherapy when larger and more peripheral. Larger peripapillary hemangioblastomas are good cases for which to consider PDT.

DR. SINGH: Are you ever concerned that there will be more lipid after these treatments or is that something that reabsorbs, meaning you weren't concerned about collapsing the lesion?

DR. PIERAMICI: This case was a super responder. I wouldn't say most patients respond like this; some require more than one treatment. However, there is a potential for an initial exudative response to therapy and temporary worsening. This is much more common with cryotherapy.

DR. FEIN: This is a great case of SRF associated with a choroidal hemangioma that responded beautifully to PDT. I have also had success with other types of choroidal tumors such as choroidal melanoma (previously treated with brachytherapy) with persistent SRF and/or metastatic choroidal lesions with SRF causing symptomatic visual changes.

DR. PIERAMICI: That's a great point. I've had a patient with metastatic breast cancer and multiple lesions in the retina. Although the patient's life expectancy wasn't long and had already received maximum radiation treatment, PDT resolved much of the fluid and helped maintain some of her vision for many months. Repeat therapy could be applied as well.

CASE 2: HYPERLIPIDEMIA, HYPOTHYROIDISM, HALF-FLUENCE PDT

DR. FEIN: This case is a 67-year-old man with a history of hyperlipidemia and hypothyroidism. He had decreased visual acuity in his right eye for several months, and had no significant past ocular history or surgery. He was taking aspirin, rosuvastatin, and levothyroxine daily. He was referred to me by one of my partners for consideration of PDT. By the time I saw him in November 2019, he had been having symptoms for 3 or 4 months. The OCT shows a cuff of SRF directly under the fovea, and the FA shows a focal area of late leakage (Figure 5).

His vision was good, so I suggested we observe him for another month prior to any treatment. He returned a month later and remained symptomatic with persistent fluid (Figure 6) and we decided to proceed with PDT treatment. PDT was delivered at the following parameters to the target site: Fluence: 25 J/cm^2; Power: 300 mw/cm^2; Time: 83 seconds; Spot size: 1,500 µm; Height: 69 inches; Weight: 182 lbs; and Calculated BSA: 2.0 m^2.

Eight weeks after the PDT, a resolution of the SRF occurred, but there was still significant RPE disruption at this point (Figure 7). His vision was 20/20. Remember, these patients will look a lot better anatomically before their visual symptoms improve. I explain to patients that the visual improvement often lags significantly behind the anatomic improvement we may see on OCT.

DR. SINGH: When you perform these treatments, do you do ICG as well? Does that factor into your overall treatment plan, or does FA guide you?

DR. FEIN: I often do both FA and ICG. However, in this case, the patient had only an FA with one of my partners, which

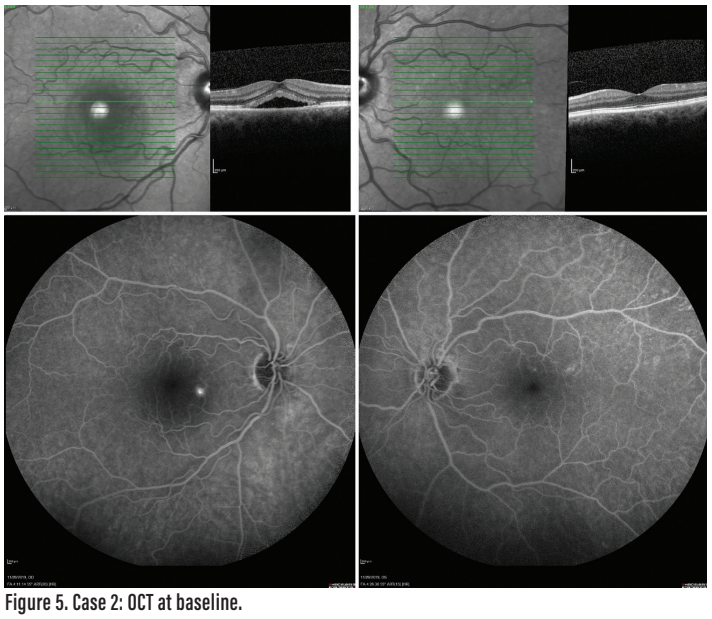

Figure 5. Case 2: OCT at baseline.

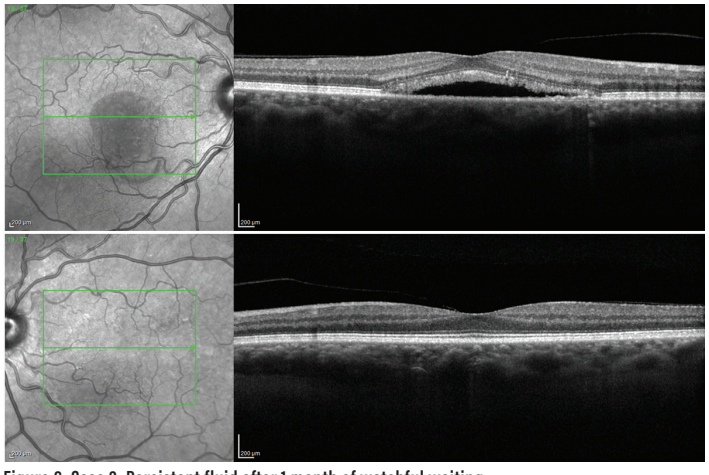

Figure 6. Case 2: Persistent fluid after 1 month of watchful waiting.

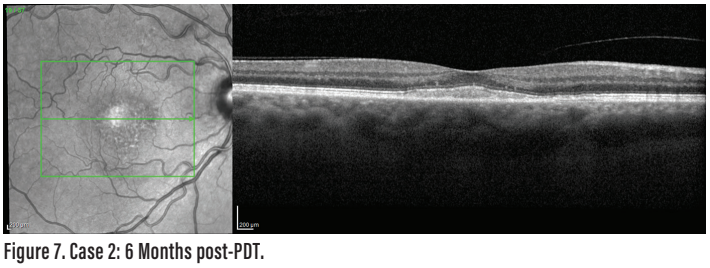

Figure 7. Case 2: 6 Months post-PDT.

demonstrated a very clear area to treat, so I did not feel it necessary to perform additional ICG imaging.

DR. METTU: In your experience, do you typically see a resolution of the RPE disruption over time, and what timeframe do you expect to see that? Does it correlate with any vision improvement?

DR. FEIN: The RPE continues to change its appearance on the OCT for another 3 to 6 months after the PDT. I do think that some of the visual improvements correspond with the RPE healing. The No. 1 contributing factor to the distortion or micropsia these patients experience has to do with the SRF, but certainly the RPE disruptions contribute significantly as well.

DR. PIERAMICI: The only thing I'd add to this is that depending on whether PDT was available, this is a patient I might even consider for focal laser photocoagulation. We also have a micropulse laser in some offices, and we'll use that in some cases as well when PDT is not readily available. I find that the micropulse is not as reliable as PDT, and recent clinical research indicates this as well. If they don't respond to the micropulse, then you can still proceed with a PDT.

CASE 3: PERSISTENT PED AND FULL-FLUENCE PDT

DR. METTU: The next case is a 75-year-old white female with wet AMD who was referred for persistent serous pigment epithelial detachment (PED) in spite of three consecutive monthly aflibercept treatments. There was some associated macular hemorrhage as well. OCT demonstrated a large macular serous PED and a smaller PED in the nasal peripapillary area, immediately adjacent.

The ICG showed an ill-defined polypoidal lesion with a branching vascular network (BVN). We treated with full-fluence PDT because it was extrafoveal, covering the polyps and the BVN. One month post-PDT, there was complete closure of the polyps, collapse of the PED, and a resolution of the SRF.

This case nicely illustrates that when you are able to achieve vaso-occlusion, you frequently see an immediate anatomical response. It illustrates the efficacy of PDT for achieving polyp closure and polyp regression.

This patient maintained quiescent disease without any recurrence of the polyps for the subsequent year, receiving anti-VEGF on a treat-and-extend basis. Following PDT, I continue anti-VEGF treatment and try to extend treatment interval, to minimize the risk of recurrent disease.

CASE 4: OCCULT LESIONS AND REPEAT PDT

DR. METTU: The last case is a 79-year-old white female who was referred to me after receiving monthly anti-VEGF for about 16 months. There is some evidence of disease chronicity, with macular fibrosis temporal to the fovea (Figure 8), with OCT demonstrating subretinal hyperreflective material that corresponds to the area of fibrosis. OCT also demonstrated cystic intraretinal fluid and some SRF as well. The FA showed an occult CNV leakage pattern, especially temporal to the fovea. The ICGA demonstrated a branching arteriolar vascular complex (indicated by the red outline in the figure).

If we were to apply conventional FA-guided parameters for PDT, we would outline the full extent of the occult leakage pattern by FA and try to capture the portions that are temporal and super temporal to the foveal. But as seen in Figure 8, the feeder artery

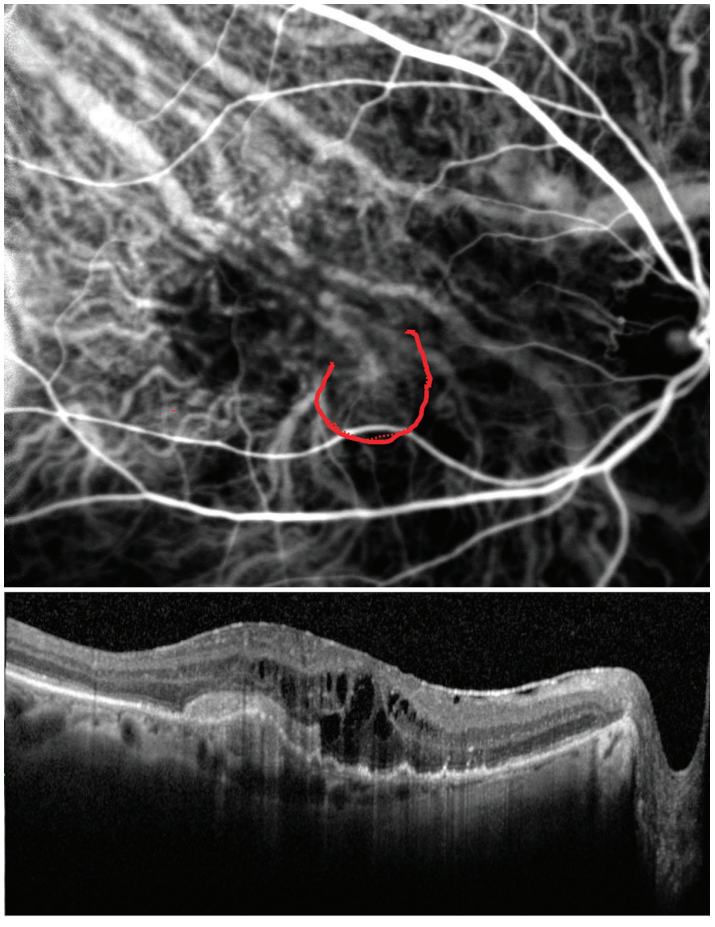

Figure 8. Case 4: A 79-year-old with wet AMD, persistent disease, and arteriolar CNV.

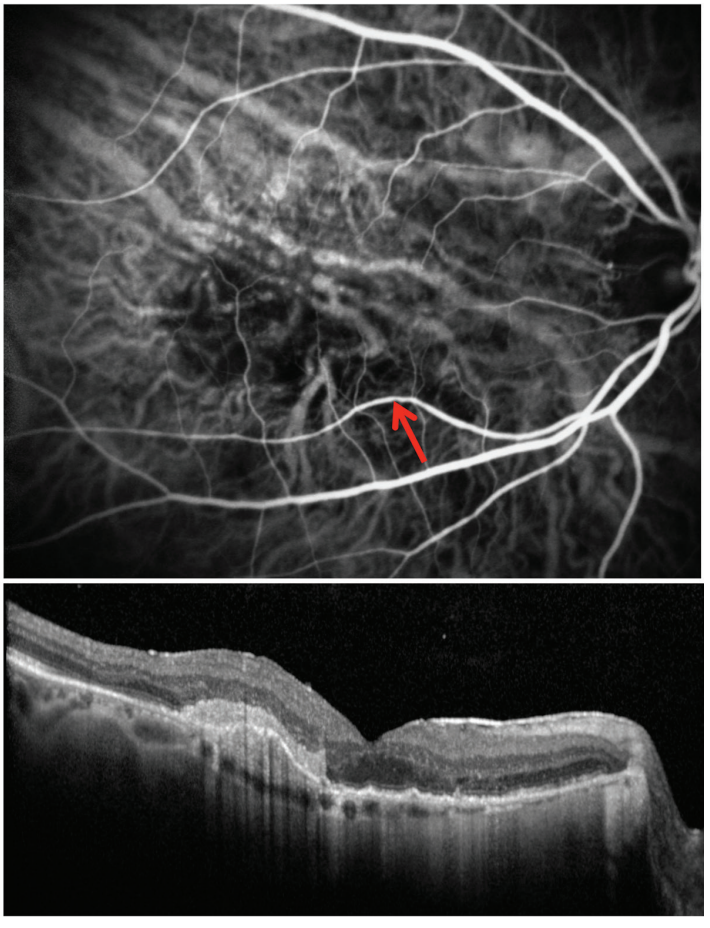

Figure 9. Case 4: Post-PDT imaging.

from which the arteriolar complex arises is actually inferonasal to the fovea, apparent as a central hyperfluorescent focus with radial arteriolar vessels emanating in a spoke-like pattern.

We identified this central part of the feeder and then targeted the PDT to that spot accordingly. After the PDT, we achieved vaso-occlusion of the feeder artery in association with resolution of fluid by OCT (Figure 9). This case demonstrates the utility of targeted PDT application to achieve vaso-occlusion while reducing risk of potential adverse effects on the choriocapillaris.

This patient had a durable response for about 6 months and was referred back for repeat PDT for disease recurrence. We were able to achieve similar results on the repeat PDT at that visit and again following a third PDT 8 months later.

DR. FEIN: This is a nice example of how helpful ICG can be in terms of figuring out treatment location. You did a beautiful job isolating a focal area to treat based on the ICG, whereas if you're just looking at the FA, it would be very difficult to ascertain where to perform a focal PDT.

DR. SINGH: I agree. I'm impressed with the anatomical response. You can reduce the number of anti-VEGF injections in some of these lesions through PDT treatment. We're not having to monitor these patients as much as we necessarily could, and this is a great example of that.

That concludes our roundtable on PDT in 2020 and beyond. Many thanks to the panel for their time and expertise. ■

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PHOTODYNAMIC THERAPY IN 2020 AND BEYOND: CURRENT CONCEPTS FOR REAL-WORLD USE

Release Date: June 2020
Expiration Date: June 2021

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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

Setting
___ Solo Practice
___ Community Hospital
___ Government or VA
___ Group Practice
___ Other
___ I do not actively practice

Models of Care
___ Fee for Service
___ ACO
___ Patient-Centered Medical Home
___ Capitation
___ Bundled Payments
___ Other

LEARNING OBJECTIVES

DID THE PROGRAM MEET THE FOLLOWING EDUCATIONAL OBJECTIVES?	AGREE	NEUTRAL	DISAGREE
Summarize the clinical benefits of photodynamic therapy (PDT) in patients with retinal disorders and in those with persistent disease activity.	_____	_____	_____
Design a treatment regimen based on a personalized medicine approach for patients who do not respond adequately to anti-VEGF injections.	_____	_____	_____
Identify methods for effective PDT delivery in clinic settings, including dosing, infusion periods, and determination of treatment size.	_____	_____	_____
Differentiate the benefits of half-fluence PDT and 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 ability to use 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

2. Based on this activity, please rate how often you intend to use PDT (based on a scale of 1 to 5, with 1 being never and 5 being always).

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

3. In which diseases is PDT a reasonable treatment option?

a. Peripapillary choroidal neovascularization
b. Central serous chorioretinopathy
c. Choroidal neovascular membrane lesions
d. Ocular tumors
e. All of the above

4. All but which of the following statements is true?

a. Half-fluence PDT can be achieved by reducing power of laser
b. Half-fluence PDT can be achieved by increasing the laser time
c. Full-fluence PDT may be most appropriate for choroidal hemangioma treatment
d. Half-dose PDT may reduce risks of severe vision decrease

5. To determine the treatment size for PDT using traditional guidelines, how far beyond the greatest linear diameter of the lesion should you measure?

a. 4,000 µm
b. 3,000 µm
c. 2,000 µm
d. 1,000 µm

6. Post-PDT, what is the minimum number of days a patient should avoid direct sunlight?

a. 2 days
b. 3 days
c. 4 days
d. 5 days

7. The PLANET study evaluated PDT as a potential rescue therapy for patients with polypoidal choroidal vasculopathy (PCV) who had a suboptimal response to aflibercept. What did the findings suggest?

a. Ranibizumab is a better anti-VEGF agent to pair with PDT for patients with PCV.
b. Aflibercept/PDT combination was superior to aflibercept monotherapy, suggesting patients should be treated immediately with the combination particularly in the setting of an active hemorrhage.
c. Aflibercept monotherapy was shown to be noninferior to aflibercept/PDT, suggesting aflibercept may be an efficacious anti-VEGF therapy for PCV.
d. Patients with PCV do not benefit from rescue injections of PDT.

8. After 3 months, an elderly patient with anti-VEGF-resistant wet age-related macular degeneration treated with half-fluence PDT has had no response but vision has not worsened from the treatment. What is your next step(s)? *Select all that apply.*

a. Continue to watch the patient; they need more time for the treatments to be considered successful or nonrespondent.
b. Retreat the patient with full-fluence PDT.
c. Retreat the patient with partial-fluence PDT.
d. Treat the patient with a micropulse laser.

9. The Verteporfin in Photodynamic Therapy Study Group found _____ of patients could have acute vision loss after PDT.

a. 1%
b. 2%
c. 3%
d. 4%

10. What is a likely scenario for a patient who has undergone PDT for chronic central serous chorioretinopathy?

a. Immediate anatomic response
b. Anatomic response at 1 week, vision improvement within 1 to 2 weeks
c. Anatomic improvement after 2 months or longer; vision improvement is more variable
d. Vision improvement around 1 month; anatomic improvement is more variable

ACTIVITY EVALUATION

Your responses to the questions below will help us evaluate this CME 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
_____ Medical Knowledge
_____ Practice-Based Learning and Improvement
_____ Interpersonal and Communication Skills
_____ Professionalism
_____ System-Based Practice

Additional comments:

_____

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

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

_____


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