

PASCAL Endpoint Management: Subthreshold Laser Therapy for Macular Diseases

Approaches with and without anti-VEGF: How we choose to treat our patients.

BY VICTOR H. GONZALEZ, MD, AND FRANCISCO J. RODRIGUEZ, MD

Half a century ago, argon laser photocoagulation was a welcome addition to the armamentarium of tools used in the treatment of retinal disease. Even as those conventional, single-spot argon lasers evolved, their well-known limitations—including scarring and pain—prevented them from being the ideal treatment for these conditions. Since then, pattern scanning lasers have emerged on the scene making retinal laser photocoagulation more comfortable, precise, and effective. The PASCAL (Pattern Scanning Laser; Topcon) is an OPSL laser that delivers multiple laser spots with a shorter pulse duration in a preset pattern. These shorter pulses use less energy and produce less choroidal heating, which results in less discomfort for the patient and is a viable option for the treatment of macular disease, along with—and sometimes instead of—anti-VEGF injections and steroids.



Victor H. Gonzalez, MD

Laser technology has advanced to the point where we can provide laser treatment and attain very meaningful outcomes for our patients who have vascular disease. That does not mean that anti-VEGFs do not still play a valuable role in our armamentarium; what it means is that a lot of these diseases will do very well being treated with a combination of laser and anti-VEGF—or in the right patients—laser alone. I use the PASCAL laser with Endpoint Management (EpM) for the treatment of select patients with almost all retinal vascular conditions.

With the PASCAL Laser, I find that my patients benefit from its short pulse duration and targeted burns, which result in increased comfort and less collateral damage. PASCAL's continuous laser pulse algorithm uses high speed galvanometers; they provide uniform pulses, and faster pattern delivery. The system's four-fiber beam delivery maintains a constant depth of field for all spot sizes resulting in consistent and predictable uptake. With EpM, the PASCAL can treat at subthreshold levels 30 times faster (10 ms to 15 ms) than

other subvisible technologies (200 ms to 300 ms).¹ EpM also provides Landmark Pattern technology, which enables me to treat lesions subvisibly while leaving visible markers for reference and documentation of the treatment region.

Perhaps most importantly, EpM has clear titration protocols; the program controls the power and exposure time of the laser using settings that are determined during titration; the software enables me to precisely adjust the treatment level from visible only with optical coherence tomography (OCT), fluorescein angiography (FA), or autofluorescence and even down to completely nondetectable levels, while still maintaining clinical efficacy.

ENDPOINT MANAGEMENT ADVANTAGES

EpM enables me to increase the therapeutic effect in patients who are not responding to anti-VEGFs, decrease the number of injections, and expand the number of patients that I can treat. This also decreases the treatment burden on those who respond best to a combination of injections and laser in several ways. First, laser treatment is not associated with certain risks that exist with intravitreal injections,

including infection or possibly inadvertently perforating the lens. In addition, patients treated successfully with laser require fewer office visits.

Another benefit is that my patients who are apprehensive or fearful about intravitreal injections will allow us to continue treatment for their disease. The injections are painful, so there is a significant noncompliance issue. Patients do not return for scheduled treatments because they do not want to face the needle again. The No. 1 comment I hear from my patients about intravitreal injections is that it is physically and psychologically painful when the needle enters the globe—no matter how well we numb the eye. Only those who have substantial visual acuity improvement return for additional injections; some are lost to follow-up. Again, one of the main advantages of the PASCAL Laser is that patients experience little to no discomfort with treatment.

When good candidates are given the option of further injections or laser, they overwhelmingly prefer the PASCAL. In addition to patient preference, conventional argon lasers are associated with increased risk and toxicity, as demonstrated in a number of diabetic macular edema studies.^{2,3} This adds to the reasons for why I prefer the subthermal tissue sparing alternative and use the PASCAL and EpM when treatment of the macula is required.

STANDARDIZED PARAMETERS

As we consider the benefits and advantages of EpM and PASCAL, we need to establish standardized parameters to help us decide when and in which patients it is appropriate to use this laser. For example, in my daily practice for patients with center-involved DME, I evaluate the patient's response to three anti-VEGF injections. If I have a good response, I do not use laser. I then follow with three more injections until the macula normalizes and the visual acuity no longer improves. I begin a treat-and-extend regimen on these patients. If after six injections there is not a significant reduction in center-involved DME, I re-evaluate and perform an FA. In these patients, if the visual acuity is better than 20/40 at baseline, I add a steroid and monitor the response. If the visual acuity is 20/50 or worse, I give a trial of three aflibercept (Eylea, Regeneron) injections. If the patient has a favorable response, I continue treatment until the macular anatomy normalizes and the visual acuity stabilizes. If I get no response and there is continued center-involved DME, I add a steroid. If there is still some edema that satisfies the ETDRS criteria and does not involve the center, I will use the PASCAL Laser in those areas of activity and only reinject if the macula center is involved. Multiple clinical randomized trials indicate that intravitreal anti-VEGF therapy, used alone or in conjunction with focal/

Case Study | Victor H. Gonzalez, MD

Patient: A 34-year-old female with a history of CSCR OS>OD; she was seen a year earlier and treated medically with eye drops, and her condition resolved.

Presentation: Visual acuity (VA) was 20/20 OD 20/25 OS (Figure 1).

Treatment: Two weeks after presentation, we performed laser treatment using PASCAL EpM.

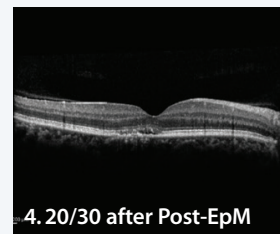
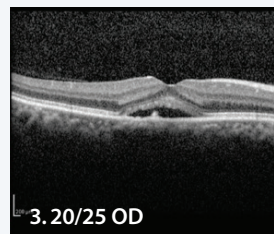
Results:

- Two weeks post laser VA was 20/25+2 OS, where it remained 2 months out (Figure 2).
- One year later, she returned with complaints of new metamorphopsia OD, with change in color vision. VA was 20/25 OD (Figure 3) and 20/20 OS.
- One week later, we performed focal laser OD. The patient was also started on ketorolac OD twice daily and advised to limit caffeine.

Outlook: OCT of the macula was repeated 1 week post laser (Figure 4). At that point, her visual acuity was 20/30 OD, and there was marked improvement in the serous retinal detachment (SRD). During her follow up, there has been complete resolution of the SRD, and VA was returned to baseline.



Figures 1 and 2. VA was 20/25 OS. Two weeks later, VA was 20/25+2 OS.



Figures 3 and 4. One year later, VA was 20/25 OD. During patient follow-up, there has been complete resolution.

Patient cases, parameters and techniques provided by the physician/author. Topcon assumes no responsibility for patient outcome or for physician oversight.

grid laser photocoagulation, is more effective than laser photocoagulation alone in improving visual acuity in DME. However, even with intensive treatment schedules and close patient monitoring typically employed in controlled clinical trials, more than 35% of patients with DME fail to achieve at least a 10-letter improvement in BCVA and more than 55% fail to achieve at least a 15-letter improvement after 2 years of first-line anti-VEGF therapy.⁴⁻⁶ Although anti-VEGF therapy is generally considered suitable first-line therapy for center-involved DME, not all DME patients respond satisfactorily to anti-VEGF agents.

STUDY RESULTS

I published a paper that retrospectively looked to determine the earliest interval when I could predict how well these patients would be doing at year 1, 2, and 3 after PASCAL Laser treatment.⁷ We performed this study because early identification of those patients who are likely to prove unresponsive or partially responsive to long-term anti-VEGF therapy enables more timely consideration of potential changes to their treatment regimens that might prove more effective in improving visual function and/or preventing vision loss. The important finding from this analysis was that after three injections, it is essential to reassess DME patients to ascertain whether other interventions need to be considered. We found that after three injections, if we stratified patients into BCVA gain from baseline, we could determine how the patient was going to do at 1, 2, and 3 years. The group that gained greater than 10 letters at 12 weeks did extremely well long term with anti-VEGF therapy. We found that the vision these patients gained after three injections was where they remained at 3 years. The group that gained less than 5 letters after three injections, with a few exceptions, remained at that poor level of vision after 3 years. We determined that continued intravitreal injections in most of those patients did not yield any significant benefit after 3 years.

These findings mimic my personal preference to reevaluate patients after three injections to ascertain whether continued injections will be effective alone or as adjunctive therapy, such as laser with PASCAL with EpM. Introducing the anti-VEGF first helps me identify which patients will do well with injections alone, as well as identifying those patients who are partial responders.



Francisco J. Rodriguez, MD

DME is a chronic complex disease that can be effectively treated with a variety of management strategies. Treatment for DME has become gradually more refined, effective, and safe as new wavelengths and treatments have entered clinical practice including, PASCAL's EpM and other lasers, intravitreal anti-VEGF agents, and corticosteroids. A

body of evidence in the literature shows that anti-VEGF is commonly selected as a first-line of treatment for DME; that laser treated patients tend to sustain a reduction in macular thickness and remain stable, and that a combination of anti-VEGF and laser or steroids improve visual acuity and central macular thickness (CMT) and may reduce the number of intravitreal injections required.⁴⁻⁶ Subthreshold laser treatment for DME, such as that delivered with PASCAL EpM, has similar effects on BCVA as threshold macular laser, but with lower energy, fewer side effects, and less or no scarring.⁸ Most patients with DME that I see in my practice have chronic disease, and in these cases it is appropriate to combine the laser with anti-VEGF or steroids. I like to use a combination of anti-VEGF and PASCAL EpM because I do not like to inject these patients over the long term; my aim is to reduce the number and frequency of intravitreal injections. It is quite expensive for us to treat these patients indefinitely with injections to try to stop the progression of diabetic retinopathy, and it is quite uncomfortable for patients and family members to come frequently for tests, examinations, and treatments. In my practice, in addition to using PASCAL EpM for combination treatment along with intravitreal anti-VEGF injections for patients with DME, I also use this combination for central serous chorioretinopathy (CSC) cases, and I use the PASCAL Laser alone for panretinal photocoagulation. EpM is a nondamaging retinal laser therapy that uses a unique algorithm to control laser power and pulse duration, optimizing the therapeutic effect of the laser at subvisible levels. Combined with the PASCAL Laser, which utilizes predetermined patterns for more homogeneous and precise laser spot delivery, EpM provides rapid pattern scanning and nondamaging laser therapy. EpM is available as an optional upgrade on all PASCAL Lasers and can be used with 532-nm and/or 577-nm wavelengths.

PATIENT OBSERVATIONS

Patients appreciate being treated with PASCAL EpM because the time of intervention is shorter, and there is less pain. Even diabetic patients favorably compare their experience with PASCAL to previous conventional laser photocoagulation; with conventional laser treatment they would be so uncomfortable that we had to administer pain medication prior to treatment. There are additional advantages of PASCAL EpM compared with other subthermal laser methods. First, the titration protocol for producing predictable and reproducible outcomes is exemplary. Second, the duration of the pulse with EpM is shorter than the duration of the other subvisible technologies such as micropulse. Third, the EpM has the Landmark Pattern feature, which allows us to treat lesions subvisibly, while leaving visible markers for reference and documentation of the treatment region. Another advantage of PASCAL EpM is that it can be repeated as often

Case Study | Francisco J. Rodriguez, MD

Patient: A 66-year-old pseudophakic male with diabetic retinopathy.

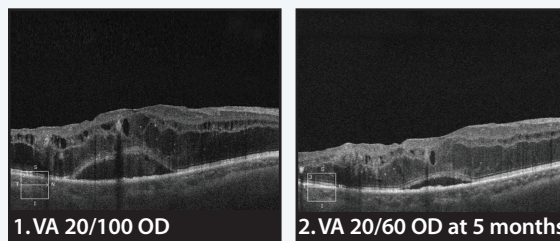
Presentation: 20/100 OU; edema and central serous detachment (Figure 1).

Treatment Plan: Protocol I – antigenic injections to dry the patient, followed by laser treatment.

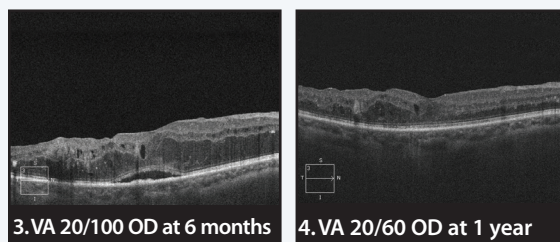
Results:

- Visual acuity (VA) improves to 20/60 after five ranibizumab injections (Figure 2), but worsens to 20/100 after the sixth injection. Patient is lost to follow up.
- Patient returns, and I administer PASCAL EpM laser treatment to reduce the number of injections and improve VA.
- Patient achieves some reduction in edema following the PASCAL EpM, but VA remains at 20/100 (Figure 3). Patient is once again lost to follow up.
- When he returns, I recommended steroid (Ozurdex) injections followed by PASCAL EpM. His VA improves to 20/80 after the injections. After undergoing PASCAL EpM, he experiences retinal thickening and further VA improvement to 20/60 (Figure 4).

Patient cases, parameters and techniques provided by the physician/author. Topcon assumes no responsibility for patient outcome or for physician oversight.



Figures 1 and 2. VA was 20/100 OD at presentation and improves to 20/60 OD after five injections.



Figures 3 and 4. VA remains at 20/100, but improves to 20/60 after injection followed by PASCAL EpM. During patient follow-up, there has been complete resolution.

Outlook: Following EpM treatment, the patient’s ellipsoid zone and external limiting membrane is intact, suggesting that there is a positive outlook for additional VA improvement.

as necessary with no concern of toxicity.

ENDPOINT MANAGEMENT COMBINATION TREATMENT

There are instances where a combination of PASCAL EpM and anti-VEGF therapy is ideal, instances where anti-VEGF alone is adequate, and still others where laser alone is effective. For DME cases, I essentially follow a protocol that shows the benefits of anti-VEGF combined with laser. Based on this, I typically perform a series of four to six injections, repeat FA, and then perform PASCAL EpM. Next, I follow the patient and try to extend the length of time between visits and injections. In the instance of CSC, I use the PASCAL as first-line therapy. We have observed numerous benefits based on our use of PASCAL EpM. I appreciate that the PASCAL system is user friendly, with a brief learning curve. It saves time and improves efficiency, enabling us to see more patients. Treatment of retinal breaks and pan-retinal photocoagulation for vascular diseases takes a few minutes. I believe that the PASCAL Laser with EpM has a meaningful role to play in the management of macular disease, and EpM is advantageous for both acute and chronic DME. PASCAL EpM is minimally invasive, results in limited collateral damage, and can be repeated due to the precision of the Landmark Pattern feature. ■

1. Data on file.
2. Gonzalez VH, Campbell J, Holekamp NM, et al. Early and long-term responses to anti-vascular endothelial growth factor therapy in diabetic macular edema: Analysis of Protocol I data. *Am J Ophthalmol.* 2016;172:72–79.
3. Do DV, Schmidt-Erfurth U, Gonzalez VH, et al. The DA VINCI Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema. *Ophthalmology.* 2011;118:1819–1826.
4. Elman MJ, Bressler NM, Qin H, et al. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology.* 2011;118(4):609–614.
5. Rajendram R, Fraser-Bell S, Kaines A, et al. A2-year prospective randomized controlled trial of intravitreal bevacizumab or laser therapy (BOLT) in the management of diabetic macular edema: 24-month data: report 3. *Arch Ophthalmol.* 2012;130(8):972–979.
6. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology* 2012;119(4):789–801.
7. Gonzalez VH, Campbell J, Holekamp NM, et al. Early and late Anti-VEGF Response in diabetic macular edema. *Am J Ophthalmol.* 2016;172:72–79.
8. Pei-Pei W, Shi-Zhou H, Zhen T, et al. Randomised clinical trial evaluating best-corrected visual acuity and central macular thickness after 532-nm subthreshold laser grid photocoagulation treatment in diabetic macular edema. *Eye (Lond).* 2015;29(3):313–21.

Victor H. Gonzalez, MD

- founder of the Valley Retina Institute in McAllen, TX.
- financial disclosure: Research support: Topcon
- maculadoc@aol.com

Francisco J. Rodriguez, MD

- chairman of the Department of Ophthalmology, University of Rosario, Bogotá
- director of Fundacion Oftalmologica Nacional
- financial disclosures: Consultant: Novartis/Alcon, Allergan, Bayer. Speakers Bureau: Novartis/Alcon, Allergan, Bayer, Topcon, Nidek. Research Support: Novartis
- fjrrodriguez@fon.org.com

PASCAL is a registered trademark and Endpoint is a trademark of Topcon. © TOPCON 2017. All other brand/product names are the trademarks of their respective owners.