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## EpM TISSUE-SPARING LASER THERAPY — A DISCUSSION WITH PASCAL EXPERTS

Scientists responsible for Endpoint Management (EpM), Topcon's tissue-sparing retinal laser therapy, and an international cadre of EpM users gathered to discuss the current state of lasers in the treatment of retinal disease, the appropriate place for intravitreal injections in the forward-thinking retinologist's practice, the vanishing role of traditional photocoagulation, and the growing use of tissue-sparing alternatives such as EpM.

They reached the following conclusions:

- Using high-energy standard lasers is counterintuitive and potentially destructive when treating macular diseases — particularly when close to the central macula.
- Physicians want to reduce the number of intravitreal injections used to treat vascular disease.
- Current practice trends rely more on tissue-sparing laser treatments such as EpM.
- Combination treatment remains a viable option.

The data we have now suggest that initiating a lower energy laser treatment with EpM helps alleviate the negative consequences associated with laser photocoagulation and photodynamic therapy (PDT). The data also suggest that low-energy laser treatments can be used effectively in conjunction with anti-VEGF injections, as well as alone, in some cases — such as non-center involved diabetic macular edema (DME). Randomized multi-center trials are in the planning stages to further elucidate out EpM treatment plans, and the discussion helped shape standardized treatment protocols that will foster our ability to compare EpM study outcomes and define clear-cut treatment protocols.

– Victor H. Gonzalez, MD

# THE STATE OF LASER TREATMENT OFFERINGS



BY VICTOR H. GONZALEZ, MD

When anti-VEGFs became available, they were important to diabetic patients because they represented an alternative to high-energy lasers that were associated with collateral tissue damage. Approximately 25% of my patients have diabetes, so anti-VEGFs became an important part of my armamentarium as I built my practice. The honeymoon did not last long, because we quickly realized that a large percentage of these patients were not going to be cured by anti-VEGFs, that the capabilities of the anti-VEGFs were limited, and that we needed to start looking for alternative treatments.

The concept of having a safer way to apply laser treatments emerged early in the process in the form of low-energy laser treatments. The problem was that we did not know how to apply the concept from a scientific perspective. Thanks to the work done by researchers at Stanford University, including Daniel Palanker, PhD, we gained a much better understanding of how and why we must apply these low-energy treatments a certain way in order to maximize patient outcomes.

## TREATMENT OPTIONS AND OUTCOMES

With the availability of low-energy, tissue-sparing laser treatment, questions remain regarding their application alone and in conjunction with anti-VEGFs. The DRCR.net, of which I am a member, produced Protocol I for diabetes treatment. Protocol I showed the following: Laser by itself with modified Early Treatment Diabetic Retinopathy Study (ETDRS) parameters resulted in visual improvement over time. Deferred laser and prompt laser in combination with a ranibizumab (Lucentis; Genentech) injection (as well as prompt laser with a sham injection) resulted in the following: At 1 year the visual acuity gains were similar for the two ranibizumab arms, however, as we followed these patients over time, there was an important difference in terms of the final visual outcomes between the prompt and delayed laser. We wondered if perhaps there was something about the way the laser was being applied that was having a negative impact on the visual outcome over the long term.

**“IN MY HANDS, LOW-ENERGY SUBTHRESHOLD LASER TREATMENT WITH EpM IS A GREAT ADDITION TO MY ARMAMENTARIUM FOR THE TREATMENT OF CSR, DME, AND BRANCH RETINAL VEIN OCCLUSION.”**

Similarly, the aflibercept (EYLEA; Regeneron) DA VINCI analysis looked at microperimetry at 6 months in patients who received laser or aflibercept.<sup>1</sup> Even though the visual acuity was similar between the two groups, there was a noticeable difference in retinal sensitivity between the group that received the laser versus the group that received only the drug.

When I think about treating central serous retinopathy (CSR), I remember using the anti-VEGFs and photodynamic therapy (PDT), which were the two developing drugs during my training. I did a lot of work with the photosensitizers, in tumors primarily, and then later on in wet age-related macular degeneration (AMD). What we have learned from those studies is that damage can be done with PDT and can be significant and unpredictable. Therefore, extreme care needs to be taken. Now, anytime I treat CSR, I am very careful to not treat the fovea and to consider the very negative outcomes that can occur when the subfoveal area is included in PDT.

My treatment of DME has evolved over time. All of the major studies — VIVID/VISTA, RISE/RIDE, as well as all of the European studies — support the use of anti-VEGFs in center-involved DME. We do not yet have anti-VEGF treatment data, on a large scale, for non-center involved DME. In my hands, at this time, for non-center involved DME that meets the ETDRS criteria, I will still use laser as first-line therapy. If there is center-involved DME, I will always use

the anti-VEGFs first for three injections. Then depending on the patient's progress, I may alter my treatments using the EARLY analysis as follows: If vision is 20/20 and central retinal thickness normalizes, I will continue the drug *pro re nata* (PRN, as needed). If there is persistent center-involved DME, I will continue with three or more injections and consider adding steroids or laser or both if edema and poor vision persist. If the central macula normalizes, and there is persistent ETDRS disease, I will add laser.

### PROTOCOL I — EARLY ANALYSIS RESULTS

We published the EARLY analysis in 2016.<sup>2</sup> In the EARLY analysis, we were looking for the earliest way to predict how Protocol I patients — treated PRN — would do over time. We found a strong correlation between stratifying visual acuity after three injections into three groups: Those that gain greater than 10 lines, those that gain fewer than 5 lines, and those who fall in between those two groups. When we followed them over time we saw that, for the most part, they remain in the same group. The important take-home message is not to use only three injections; the message is that after three injections, if you stratify the patients using these three visual acuity gains, then you can predict how that patient will do going forward if you continue the treatment. It can be useful to counsel patients. At that point, it is a good idea to discuss with the

patient what the potential outlook is for their condition using anti-VEGFs, and depending on which group they are in, discuss the addition of EpM.

In response to the question, “Where does laser treatment fit into the paradigm of macular disease management today?” the answer is simple. In my hands, low-energy subthreshold laser treatment with EpM is a great addition to my armamentarium for the treatment of CSR, DME, and branch retinal vein occlusion. I still use an anti-VEGF as first-line treatment for DME and other retinovascular conditions. I will introduce low energy (EpM) for patients that are not responding to anti-VEGF therapy and will continue to do that while I gain more knowledge of this tissue-sparing laser technology. ■

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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.

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# PATIENT OUTCOMES WITH EpM



BY DANIEL LAVINSKY, MD

We have a lot of excellent clinical experience using Endpoint Management (EpM) in the tissue-sparing treatment of various types of retinal pathology. I will share our early clinical study data and several patient case studies — some with short-term outcomes and others with results as far out as 3 years.

## CENTRAL SEROUS RETINOPATHY CASE STUDIES CASE STUDY | CHRONIC SUBFOVEAL DETACHMENT

This patient case study exemplifies the use of the PASCAL laser with EpM (Figure 1A and 1B). In this case, a 61-year-old female with 20/60 vision was experiencing symptoms of subfoveal leakage for over 6 months (A). After treatment with EpM this resolved, and after 3 years she has had no recurrence (B). Most recent optical coherence tomography (OCT) shows no fluid and no signs of any side effects, burns, or thinning in the photoreceptor layer. See *Treatment Parameters* chart for more detail.

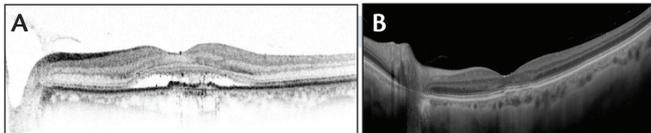


Figure 1. A patient presents with 20/60 vision and subfoveal leakage over 6 months (A). After treatment with EpM this resolved. The patient has no recurrence after 3 years (B).

## CENTRAL SEROUS RETINOPATHY | STUDY DATA

We conducted a pilot study<sup>1</sup> of EpM for central serious retinopathy (CSR) (Figure 2). We included 21 eyes of 20 patients, and we have 12 months of follow-up. We found that visual acuity improved after 1 month and remained stable for 1 year. Complete resolution of fluid was achieved in 81% of eyes (17 out of 21) and only four eyes had partial fluid retention after 1 year. With respect to fluid resolution, there were no non-responders. Central macular thickness improved and then remained stable after 1 to 3 months. Measurement of subfoveal choroidal thickness indicated that choroid got thinner by between 50 to 100  $\mu\text{m}$ . We suspect that amount of reduction may be enough for the choriocapillaris to decrease the hyperpermeability. Most patients (58%) required a retreatment, 16% achieved a stable outcome with one treatment, 16% required three treatments, and 10% had four treatments. In comparison to

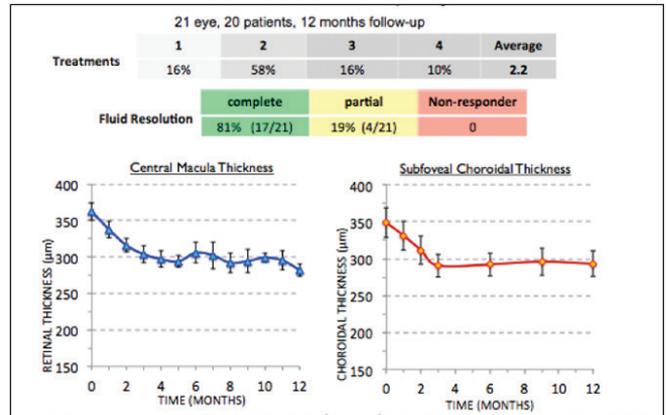


Figure 2. A pilot study of EpM for CSR.

## TREATMENT PARAMETERS FOR CSR CASE (FIGURES 1A AND 1B)

**Average Power:** 120 mW for titrated burn (100%)  
**Exposure:** 15 ms  
**Spot Size:** 200  $\mu\text{m}$   
**Spacing:** 0.25 spot diameter  
**EpM Setting:** 30%  
**Total Spots:** 520

other CSR treatments, we consider these good outcomes. Plans for a randomized clinical trial looking at EpM in CSR are in the works.<sup>1</sup>

## DIABETIC MACULAR EDEMA CASE STUDIES CASE STUDY | DIABETIC PATIENT WITH SEVERE NPDR AND MACULA EDEMA OU

This case shows a 64-year-old female with Type 2 diabetes for more than 20 years (Figure 3A through 3C). She had severe nonproliferative diabetic retinopathy (NPDR) with macular edema OU (A). She had 20/60 visual acuity OD and 20/80 visual acuity OS. She submitted to one anti-VEGF injection and had a panic attack; after that, she refused to undergo additional injections. We started EpM, using 30% energy and 120 mW, 200  $\mu\text{m}$  spot size, and 736 burns. In 2012, the year she first had EpM, she had 20/60 visual acuity (A). In 2013, she had 20/40 visual acuity (B), and in 2017, 4

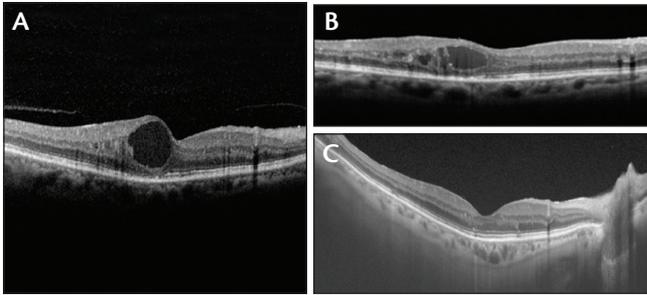


Figure 3. A patient presents with severe NPDR and 20/60 visual acuity OD in 2012 (A). After EpM treatment, she has 20/40 visual acuity in 2013 (B). In 2017, she has 20/20 visual acuity (C).

years after her initial EpM treatment, she was stable with 20/20 visual acuity and no additional injections (C). We are repeating EpM every 3 to 4 months with good results.

## CONCLUSION

In conclusion, our goal is to expand our focus beyond case series to evidence-based, well-designed clinical trials with the aim of identifying common concepts and patterns in EpM's usefulness in the treatment of retinal disease. ■

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- Financial disclosure: Consultant (Topcon)

# EXPERT DISCUSSION AND CONSENSUS

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**W**ith today's laser technology, we can attain meaningful outcomes for our patients who have vascular disease without the damaging effects associated with traditional lasers. While anti-VEGF therapy continues to be first line therapy for most retinovascular disease, a combination of laser and anti-VEGF — or in the right patients — laser alone may also be effective. I use the PASCAL laser with Endpoint Management (EpM) for the treatment of select patients with almost all retinal vascular conditions. My patients benefit from PASCAL's short pulse duration and targeted burns, which result in increased comfort and less collateral damage. EpM 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 down to completely undetectable levels, while still maintaining clinical efficacy.

Below, retinal surgeons from around the globe discuss tissue-sparing lasers, EpM, and anti-VEGFs, in relation to issues germane to daily clinical use.

– Victor H. Gonzalez, MD

**VICTOR H. GONZALEZ, MD:** How do subthreshold lasers impact anti-VEGF use in your practice?

**KISHIKO OHKOSHI, MD, PhD:** In my practice, anti-VEGF injections are administered first, and EpM is applied for residual edema. In this method, anti-VEGF injection is administered until macular thickness becomes stable; then we apply the laser for residual edema. EpM has changed the concept of laser therapy for me. In my practice, tissue-sparing EpM laser has now completely replaced conventional laser treatment for most macular diseases.

Anti-VEGF therapy has changed the role of retinal laser therapy for management of diabetic macular edema (DME). Although studies have shown the efficacy of anti-VEGF and treatment, repeated injections impose a large financial burden on patients. Moreover, anti-VEGF drugs have been shown to be ineffective in certain cases. Combination therapy using anti-VEGF and laser treatment decreases the number of injections for DME patients. Therefore, laser treatment is expected to save money and lessen the financial burden on patients. However, conventional laser treatment is destructive, with risks of retinal scarring. Fortunately, today we do not have to be concerned about unfavorable laser scarring because subthreshold laser is available.

**MIHO NOZAKI, MD, PhD:** We did a prospective multisite study in Hong Kong, Korea, and Japan led by principle investigator Ian Wong, MD, looking at anti-VEGF alone and in combination with EpM. EpM was performed within 4 weeks after initial anti-VEGF injection, and we followed patients for 6 months. Patients were excluded if their central retinal thickness was more than 500  $\mu\text{m}$  after initial anti-VEGF injection. Preliminary results indicate combination therapy can reduce one injection in 6 months.

**DR. GONZALEZ:** Why are EpM standard treatment protocols necessary?

**DANIEL PALANKER, PhD:** Unlike pharmacological treatments, until recently, lasers lacked a common titration and treatment protocol; there was no consistency. Laser users felt that they were entitled to their own recipe: applying different energies, pulse durations, spot sizes, and number of spots without any preclinical data supporting these setting selections. Therefore, comparing results of the laser treatment between different users was nearly impossible. We decided to find the range of tissue response below damage threshold and to develop a uniform protocol for treatment within this range in every patient. With EpM, everything except for titration power is preset: spot diameter, spacing, energy relative to titration, and pulse duration. All the physician needs to do is to titrate power to a barely visible burn, switch the setting to 30% energy on the EpM scale, and treat. If everyone follows this recipe, physicians will be able to compare treatments that are done in exactly the same way. Topcon made a convenient EpM user interface to enable users to follow this recipe. This standard is based on preclinical studies, and it was established to help with consistency of use and to facilitate comparisons of outcomes in clinical trials.

**DANIEL LAVINSKY, MD:** Even with the standard interface, if you want to increase the effect, it's possible. You don't need to increase the power too much; instead you should increase treatment density. This means you increase the number of the spots so the sum of the energy being delivered to the treatment area is sufficient to induce proper retinal pigment epithelium stimulation. This is very important to consider because increasing the power could be damaging.

**DR. GONZALEZ:** So basically, there are two ways to increase the

treatment effect: Either you increase the energy, or you increase the number of applications; and the safest way to increase the number of applications is to leave the energy stable so that we don't run into potentially damaging levels. When is it ideal to use EpM solo versus combination EpM with anti-VEGF?

**JOSE CARDILLO, MD:** Approximately 50% of patients don't respond to anti-VEGF, another 25% are partial responders. Depending on the stage of DME, patients may respond differently to treatment. It's hard for us to pharmacologically address this disease because it might be a different disease depending on the stage. In the early phase, it may respond better to anti-VEGF; in the late/chronic phase, it may respond better to steroids. In my clinic, I have DME patients who do not respond to laser alone or in combination, whereas I have patients with central serous retinopathy who respond so well to EpM that it's my first and only line of treatment for that pathology.

**DR. GONZALEZ:** Just like with anti-VEGF, we are learning which are going to be the ideal patients. One of the tasks moving forward is to develop those parameters and surrogate markers that could possibly help guide us toward those patients who are going to be ideal for EpM, and which ones will need combination therapy. I think that most of us who use pharmacologic therapy for DME realize now that identifying those ideal patients from the beginning is not easy. The three injection litmus test that we published in what we called the EARLY analysis is a step in the right direction in helping us begin to divide those patients into effective treatment groups.<sup>1</sup>

**DR. GONZALEZ:** When is it safe to retreat using EpM?

**DR. LAVINSKY:** A critical piece of information is that PASCAL with EpM is photothermal stimulation, not photocoagulation. Instead of coagulating the tissue, we are stimulating the cell to defend itself from the oxidative damage, from the hyperglycemia, or whatever is causing damage in diabetes or other diseases. So, the cell itself is capable of producing cytokines to decrease the edema or the fluid, but this effect is not everlasting, and that is why we need

to treat again. In my experience, the effect of the laser will decrease over time. I explain to patients that it is like a drug; they will need the laser treatment again. In DME, I evaluate every 3 months, and I analyze the trend. If I see a clear trend of decreased edema, sometimes I wait another 3 months. If I see that it's the same or the trend is not as good, or even if it's worse, then I retreat at the 3-month mark. It's very important for us to have clear retreatment criteria. First of all, don't wait too long because then the effect could be gone, and it would be almost as if you are starting from zero.

**IAN WONG, MD:** I think the issue with retreatment is that it is unclear when to retreat because we don't really see any visible burns at the end of the treatment. So, it's not like conventional old-style laser where you really see a white burn or a faded gray burn, which gave us a sign that we had actually done something. With EpM, you don't see what you've done so you just have to be confident based on your prior experience and observations with other patients that the laser is working. Fortunately, the laser can be repeated because of its tissue-sparing properties. I think it's very important to say retreatment is only relevant if we're doing real tissue-sparing therapy. If you see burns, either on autofluorescence or on OCT, it's by definition not tissue-sparing retinal therapy, and I wouldn't consider doing a retreatment after 3 months. Before we retreat, we should take an autofluorescence or an OCT, see if we have damaged anything, and if there is damage, do not retreat.

**DR. GONZALEZ:** I retreat at 3 months, and I analyze the trend. If I see a clear trend of decreased edema, sometimes I wait another 3 months. If I see that it's the same or the trend is not as good, or even if it's worse, then I retreat at the 3-month mark.

## CONCLUSION

A variety of macular diseases can be effectively treated with lasers in the anti-VEGF era.

- There is scientific evidence to support EpM as a tissue-sparing therapy for the treatment of macular disorders based on work conducted by scientists and doctors such as Drs. Palanker, Lavinsky, and others.<sup>2-6</sup>
- Using the parameters developed by the consensus, we can conclude EpM is safe and effective. See *Treatment Parameters* chart for more detail.
- Tissue-sparing treatment, such as EpM, can be used safely and effectively as first-line therapy. ■

1. 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.  
 2. Lavinsky D, Sramek C, Wang J, et al. Subvisible retinal laser therapy: titration algorithm and tissue response. *Retina*. 2014; 34(1):87-97.  
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### EpM TREATMENT PARAMETERS BASED ON EXPERT MEETING

**Average Power:** 120 mW for titrated burn (100%)

**Exposure:** 15 ms

**Spot Size:** 200 µm

**Spacing:** 0.25 spot diameter

**EpM Setting:** 30%

4. Lavinsky D, Palanker D. Nondamaging photothermal therapy for the retina: initial clinical experience with chronic central serous retinopathy. *Retina*. 2015;35(2):213-222.
5. Wood E, Karth P, Sanislo S, et al. Nondamaging retinal laser therapy for treatment of central serous chorioretinopathy: what is the evidence? *Retina*. 2016:1-13.
6. 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*. 2015;29:313-322.

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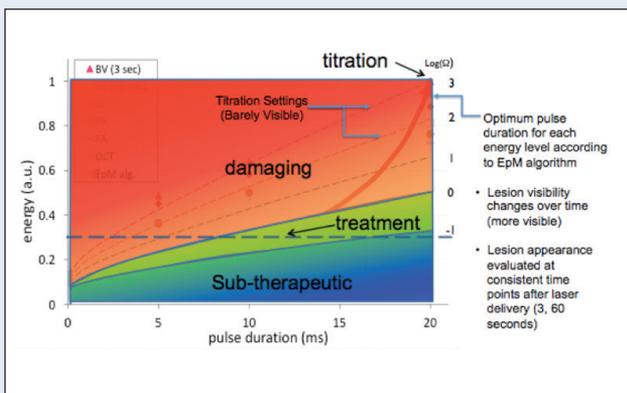
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## EpM — WHAT YOU SHOULD KNOW

### WHAT IS IT?

Endpoint Management (EpM) is a proprietary tissue-sparing therapy that uses a unique algorithm to control laser power and pulse duration (Figure), optimizing the therapeutic effect of the laser at subthreshold levels.

Combined with the PASCAL laser, EpM provides rapid pattern scanning and tissue-sparing therapy. EpM is available as an optional upgrade on all PASCAL lasers and can be used with 532-nm and/or 577-nm wavelengths.



**Figure. Scientifically-developed algorithm based on the Arrhenius Equation — a formula for the dependence of tissue reaction rates on temperature (“time-temperature curve”).** Image courtesy of Daniel Palanker, PhD.

### HOW DOES IT WORK?

- EpM software automatically adjusts laser energy (power and pulse duration) applied to the eye to deliver tissue-sparing laser energy at a predetermined percentage of the titrated “barely visible” energy level.
- Maximizes the “therapeutic window” by targeting the margins between visible and subvisible treatment endpoints
- Balances power and pulse duration to automatically provide the best “path” between treatment endpoints
- EpM algorithm maps a range of calculated Arrhenius integral values to linear steps in pulse energy, normalized to a titration dose specified at a particular pulse duration.

### THE ADVANTAGES

- Safe and effective: establishes a treatment baseline and visible treatment boundary
- Simple to treat: physician titrates until a slight burn is seen. EpM option is selected on the laser and the physician treats.
- Allows periodic retreatment without cumulative scarring
- Faster treatments: Since EpM is coupled with PASCAL technology, treatment is more rapid resulting in greater patient comfort.
- Takes the guesswork out of subvisible treatment as it automatically provides the best “path”

*Patient cases, parameters, and techniques provided by the physician/author.*

*Topcon assumes no responsibility for patient outcome or for physician oversight.*