Subthreshold Retinal Treatment With Yellow 577-nm PASCAL Laser

BY PAULO STANGA, MD

Laser has been the gold standard for diabetic macular edema (DME) since the first publication from the ETDRS in 1985. Conventional laser, however, can lead to scarring. For instance, a standard laser burn enlarges by 16% per year for up to 4 years. Additionally, recent data on the use of anti-VEGF therapy for DME has brought the role of laser as first-line therapy into question. There is reason to question the rationale for using anti-VEGF treatment for DME.

First, the CATT study showed some evidence that frequent injections of anti-VEGF agents may be associated with a higher risk of geographic atrophy (GA). The proportion of study eyes with GA at 2 years among eyes without apparent GA at enrollment ranged from 25.8% in the ranibizumab (Lucentis, Genentech) monthly group to 12.9% in the bevacizumab (Avastin, Genentech) as-needed group. GA at 2 years was greater among patients treated monthly ($P = .007$).[1]

Also, intravitreal anti-VEGF injections have a short duration of effect, as seen in the experience with ranibizumab for age-related macular degeneration (AMD), where deviating from the monthly injection schedule has proved challenging. Monthly injections for a chronic disease that often affects patients at a much earlier age than AMD can present a significant burden for patients and for the health care system. Additionally, in DME, multiple injections of anti-VEGF agents over a long period of time has been shown to lead to enlargement of the foveal avascular zone and resulting decreased visual acuity.[2-5] Because of these factors, laser will most likely remain an important component in the treatment of DME.

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Patients with proliferative diabetic retinopathy (PDR), however, undergo multiple laser treatments during their lifetimes. The annual scar expansion rate (16.5%) continues for up to 4 years following panretinal photocoagulation (PRP).[6] We know that the adverse events of visible endpoint photocoagulation are caused by thermal damage to areas adjacent to the target retinal pigment epithelium (RPE).[7-9]

Because laser will continue to be a critical treatment option for our patients with PDR, the current perception of laser treatment must change. Additionally, we may see the greatest benefit with earlier treatment. Thus, new laser technology has been developed in recent years to minimize effects to the surrounding structures and to minimize photoreceptor injury. Micropulse is one treatment modality that has shown

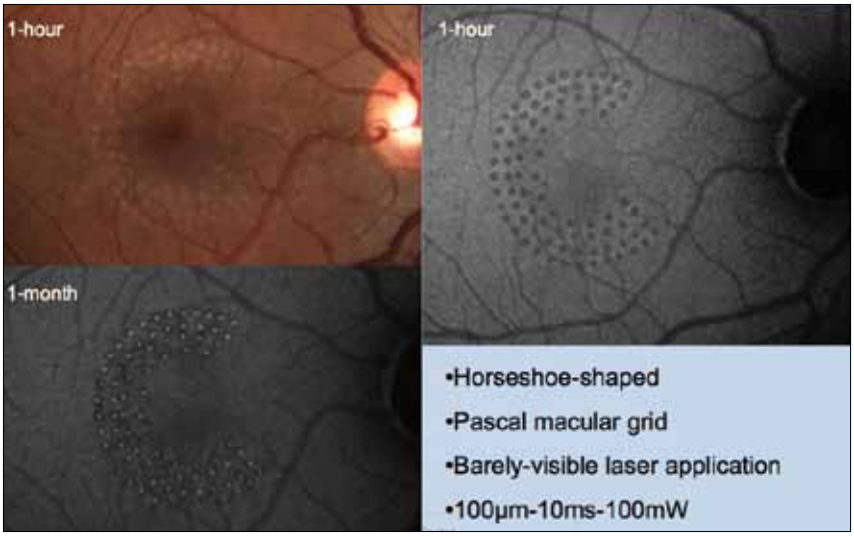

Figure 1. Confirmation of the Pascal 10 ms laser burn placement and laser-induced tissue reaction.

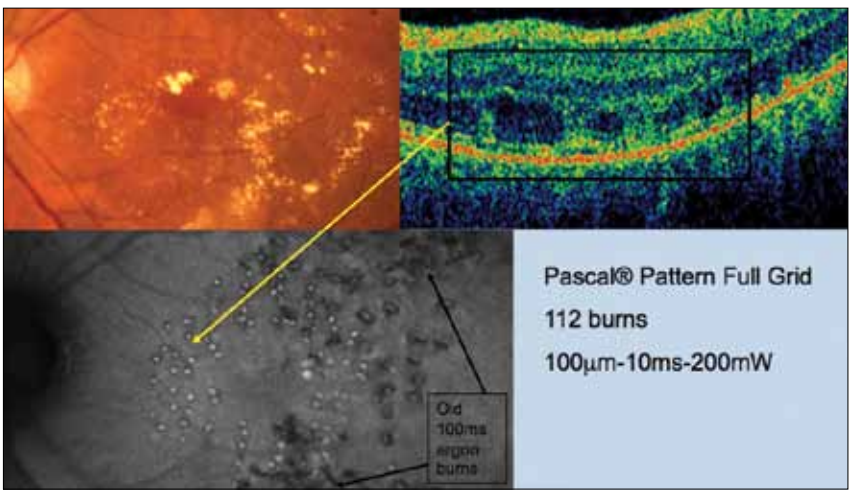

Figure 2. Laser-tissue interaction with subvisible 10 ms laser burns.

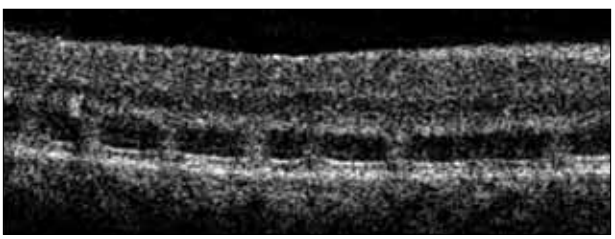

Figure 3. Over time, Pascal burns have corresponded on FD-OCT to localized defects at the junction of inner and outer segments of photoreceptors and apical RPE.

promise to limit laser damage, but my concern with this technique is that, because you cannot see where you have treated, there is a risk for retreatment of the same areas.[10]

APPLICATION OF PATTERN LASER

Another solution is pattern laser. I began using the PASCAL laser (Topcon) in 2006. Over time, we have developed a Fourier-domain optical coherence tomography (FD-OCT) and fundus autofluorescence (FAF) technique with the PASCAL laser.[11] We use FAF and OCT to image the burns to discern the effects of the PASCAL—the FD-OCT confirming that burns from the PASCAL are confined and localized to the outer retina, and the FAF showing the burns that are not always visible on fundus biomicroscopy. Figure 1 shows the confirmation of PASCAL 10-ms laser burn placement and laser-induced tissue reaction. We used a horshoe-shaped macular grid pattern and applied barely visible 100-µm laser spots at 100 mW. Figure 2 demonstrates the laser-tissue interaction with subvisible 10 ms laser burns using a PASCAL pattern full grid for 112 burns, 100 µm in size, at 200 mW power. We have found that threshold PASCAL 10 ms burns remain highly localized in the outer retina, with no significant reflectivity changes in adjacent RPE cells or inner neuroretina. Over time, PASCAL burns have corresponded on FD-OCT to localized defects at the junction of photoreceptor inner and outer segments (IS/OS) and apical RPE (Figure 3).

We then evaluated how well these burns heal over time. In Figure 4, from a study on healing of laser burns,[12] FD-OCT performed 1 hour postlaser shows multiple vertical bands of increased optical reflectivity within the outer plexiform layer (Figure 4A). At 12 months, FD-OCT shows normal hyperreflective layer of the IS/OS, with the laser burns localized to the photoreceptor outer segment tips and apical RPE layers (Figure 4G). In this study, we observed a significant 50% reduction in outer retinal burn size for 10-ms pulse laser over 1 year, suggesting that a novel healing response occurs within the outer retina. The laser was targeted to the outer photoreceptor segment layer, and

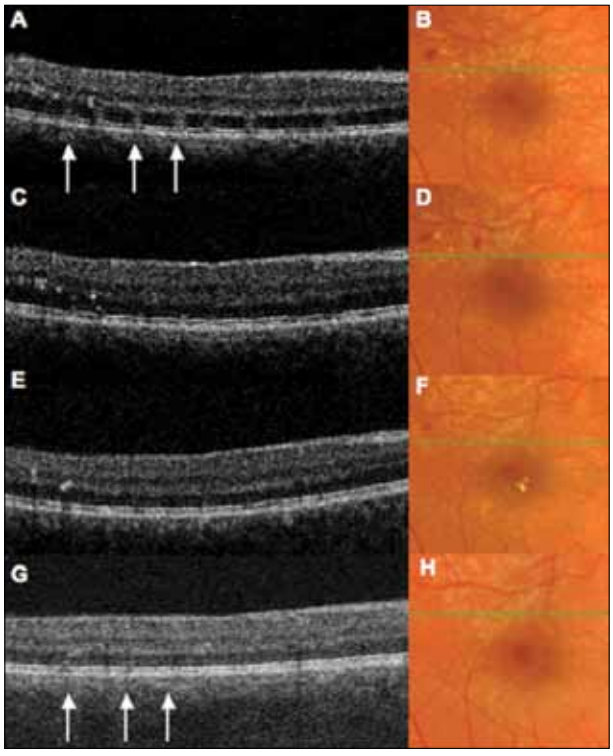

Figure 4. FD-OCT performed 1 hour postlaser shows multiple vertical bands of increased optical reflectivity within the outer plexiform layer (A). At 12 months, FD-OCT shows normal hyperreflective layer of the IS/OS, with the laser burns localized to the photoreceptor outer segment tips and apical RPE layers.

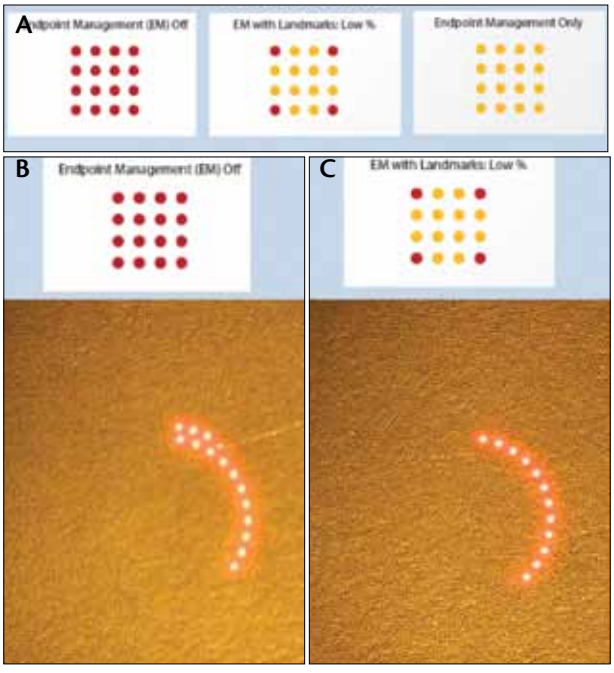

Figure 5. Endpoint Management indicators: (A) The red spots represent the burns at 100% laser power, while laser burns represent a percentage of the power. For example, red spots can be set at 100% (B) and yellow ones at 70% (B), achieving a more subtle burn but maintaining a landmark.

there may be greater RPE repopulation and photoreceptor in-filling at the sites of these lesions. In DME, the healing responses in the outer retina may reduce photoreceptor loss and maintain therapeutic effects.

In another study, we examined the laser titration of burns from the PASCAL 532-nm laser applied to diabetic retinas, using FD-OCT and FAF to evaluate laser-tissue interactions at subclinical and low-fluence levels.[13] We found that there were significant healing responses with reduction in burn size at lower levels of clinical visibility using a 20-ms pulse laser. We also found that longer pulse duration produced increased disruption of IS/OS and RPE layers, greater perilesional photoreceptor atrophy, and variable changes in lesion size over time.

In yet another study, we showed that barely visible 10-ms PASCAL laser burns produced an effect at the level of the IS/OS and apical RPE, with minimal axial and lateral spread of burns.[14] FD-OCT confirmed spatial localization of FAF signal changes that correlated with laser-burn–tissue interactions over 3 months. The PASCAL laser showed promise in reducing retinal edema within the affected sectors of the retina to effectively treat DME with minimized scarring.

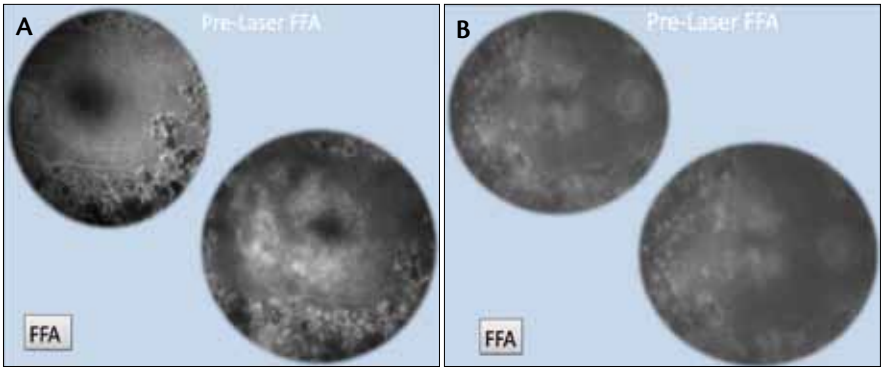

Figure 6. Patient with diffuse DME who had been treated previously with standard laser photocoagulation.

Because we wanted to see how well the PASCAL works in the macula area, we performed

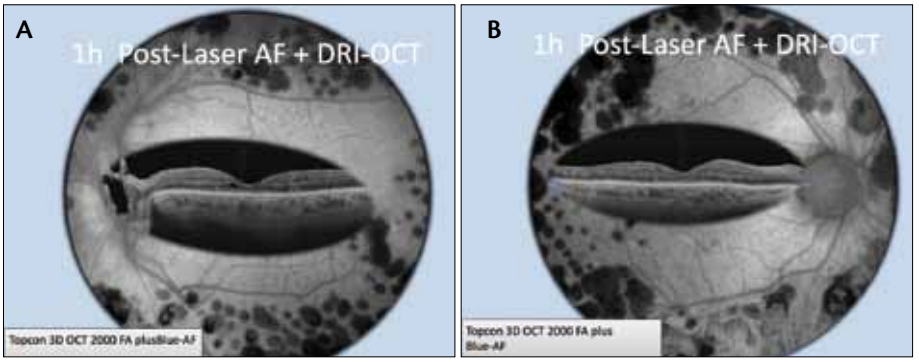

Figure 7. One hour after PASCAL 577-nm laser was applied.

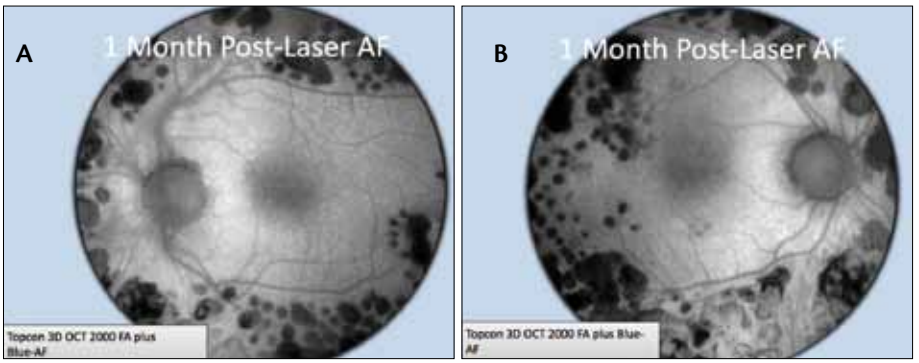

Figure 8. One month after laser; tissue response is apparent.

the Peter Pan Study, which is currently in press.[15] In this study, we found that barely visible subthreshold laser may work when applied in the macular area or as PRP.

ENDPOINT MANAGEMENT AND PASCAL 577-NM LASER

We believe that we have shown proof of concept that pattern laser can be applied, but new laser technology is necessary to apply these concepts to clinical practice. To answer this need, Topcon has developed Endpoint Management, which utilizes the 577-nm yellow PASCAL laser rather than the older 532-nm green laser; this allows titration of power. The visible titration endpoint can be referenced throughout the course of treatment by enabling the landmark feature, which creates reference lesions at the titration dose at the corners of the square pattern (Figure 5).

Figure 6 shows a patient with diffuse DME who had been treated previously with standard laser photocoagulation. Figure 7 is the patient's FAF and deep range imaging (DRI)-OCT (Topcon) images 1 hour after the PASCAL 577-nm laser was applied. We had set the Endpoint Management at 70% for this case, and the DRI-OCTs show that the laser damage is very confined and localized. Figure 8 shows the FAF images from the patient 1 month following laser, in which a tissue response is clear from the hyperfluorescence indicating that we have successfully targeted the RPE.

SUMMARY

There is evidence that barely visible laser photocoagulation can work within the macula as primary therapy for DME. Endpoint Management allows more accurate titration of the energy within the subthreshold range, creating the potential for significant reduction in collateral damage and allowing a good tissue healing response. Doctors may feel more confident using laser earlier in the treatment process, particularly when treating close to the fovea. ■

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