New Laser Technology and Techniques for Treating DME and PDR

By Prof. Paulo E. Stanga; With Dr. Maria Gil Martinez; and Dr. Salvador Pastor-Idoate

Diabetes mellitus is a chronic condition and although the management of systemic risk factors remains the first line of treatment it is often insufficient in controlling and preventing recurrences.

When treating patients with diabetic macular edema (DME) and/or proliferative diabetic retinopathy (PDR), the goal is to find the therapy with the best results and least side effects. We know that some patients respond to certain treatments differently than others, and this has been shown in the superior results that have been achieved with anti-VEGF agents when compared to argon laser.[1] In fact, there are several Level I studies providing evidence for intravitreal ranibizumab (Lucentis, Genentech), either alone or in combination with other treatments for DME.[1,2]

However, we also know that multiple injections of anti-VEGF agents are required for a lasting effect, and considering that DME is a chronic disease that affects the working population, this model is not sustainable. In fact, in the United Kingdom, where I practice, the National Institute for Health and Care Excellence has determined that ranibizumab is less cost effective than conventional laser treatment for DME and PDR and has recommended its use only when the central retinal thickness (CRT) is 400 µm or more at baseline.

The first reported randomized controlled trial on argon green laser panretinal photocoagulation in patients was published in 1977 by Hercules et al from Manchester Royal Eye Hospital.[3] As more experience was gained using argon green laser, data began to emerge that conventional laser treatment causes irreversible damage to the retina, including scars that expand over time, resulting in paracentral scotomas, loss of color vision, and even loss of central vision.[4]

The original Early Treatment for Diabetic Retinopathy Study (ETDRS) dates back to the 1980s and established panretinal laser photocoagulation (PRP) as the standard care for DR. The photocoagulation treatment regimen used in the ETDRS was adopted throughout the world and has since been modified per the mETDRS grid laser photocoagulation protocol. Indeed, a survey by the Diabetic Retinopathy Clinical Research Network (DRCR.net) revealed that the mETDRS protocol remains the most widely used treatment approach for DME.[5]

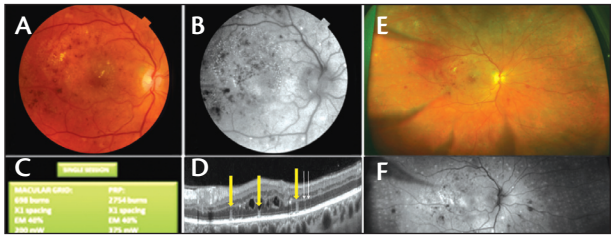

Figure 1. Subthreshold 40% EpM PASCAL single-session macular grid with PRP: Barely visible and invisible burns (A, E); burns visible on FAF (B,F); laser parameters (C); FD-OCT showing the landmark and the more intense sub-threshold burns (D; yellow and white arrows respectively).

However, a study has shown that multiple laser treatments with long-duration burns (100 ms) expand at a rate of 16.5% per year for up to 4 years and that, following ETDRS protocol PRP.[6] In addition, between 12% and 30% of patients may lose visual fields to the point where they are not able to drive.[7] The side effects of traditional PRP include loss of central vision, paracentral scotoma, and decreased color vision. These are mostly caused by the progressive enlargement of the laser scars consequent to the visible burn endpoint.

ADVANCED LASER TECHNOLOGY

With advancing laser technology and the advent of anti-VEGF and steroid injections for DME and PDR (as well as vitrectomy for some cases), visual field loss due to treatment effects is no longer acceptable. An example of newer laser technology is the PASCAL laser (Topcon). The PASCAL is a frequency-doubled Nd:YAG solid-state laser with a wavelength either 532 nm (green laser) or 577 nm (yellow laser).

I began using the PASCAL laser at the Manchester Royal Eye Hospital back 2006, the first to do so in the European Union. We published several papers on the system and its clinical application, among them a safety review of the laser. Although pulse duration of PASCAL is shorter compared to traditional photocoagulation, it necessitates the use of a higher power, but we found that this higher power is not associated with adverse effects. Overall, we found that the PASCAL laser is safe and effective, and offers several advantages associated with shorter exposures including reduced pain, reduced inner

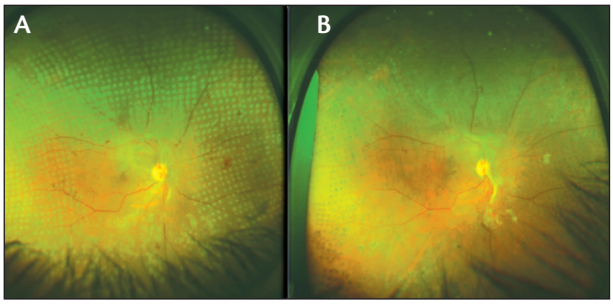

Figure 2. PRP appearance within 1 hour of treatment (A) and 1 month post treatment (B). Note the scarce carbonization or pigmentation of the retina and the fibrosis of the peripapillary neovascularization at 1 month.

retinal damage, and reduced scarring.[8]

One of the negative issues with conventional laser is the multiple sessions that are required. With PASCAL we can usually perform single session treatment. For example, a patient might come in 1 day and receive 600 burns, come back 2 weeks later and receive another 600 burns, and come back yet another time to receive 600 more burns. Conventional laser can be painful and the multiple sessions are inconvenient, and so some patients do not attend the follow-up laser visits. As a solution, I proposed in 2010 performing laser with the PASCAL in a single session. Some of my colleagues were initially worried about the possibility of side effects. However, our studies soon cleared this worries. We conducted at the Manchester Royal Eye Hospital the MAPASS Study, in which we compared single vs multiple-session PRP in regards to visual acuity, visual fields, and average central retinal thickness (CRT) on optical coherence tomography (OCT).[9] We found that after 1500 burns in a single session (ablation area 188 mm^2), the average CRT was lower than with multiple-session PRP (single-spot 100 ms). We hypothesized that this was because each session of PRP triggers an inflammatory response and obviously single session treatment induces a single inflammatory one.

We also showed a positive effect on PDR regression in 74% of patients undergoing a single session PRP vs 53% of those receiving multiple sessions ($P = 0.31$). There were no adverse outcomes (CRT, visual acuity, or visual field) from using multispot single-session PRP vs single-spot multisession PRP at 12-weeks post-laser.

Additionally, we reported that single session PASCAL induces in the patient lower levels of anxiety, headache, pain and photophobia compared to 100 ms single-spot multiple session PRP.

As it can be difficult to know where light intensity laser burns have been placed and for future treatment planning, we performed another study to evaluate the appearance of previously placed laser burns with OCT and fundus autofluorescence (FAF).[10]

We later evaluated the healing process with 10 ms PASCAL laser burns.[11] OCT at 1 year demonstrated that after laser with 10 ms burns, the outer retina recovers an almost normal anatomy, with the laser spot size reduction of 50%, suggesting that there was a novel healing response within the outer retina. Others have subsequently demonstrated in animal studies that this is because of retinal pigment epithelial (RPE) repopulation and photoreceptor infilling at the sites of these lesions.[12]

Another study that we performed evaluated the clinical effects and burn locations after barely visible 10-ms PASCAL laser.[13]

We found that barely visible laser produced an effect at the level of the inner and outer photoreceptor segments and apical RPE, with minimal axial and lateral spread of burns. SD-OCT confirmed spatial localization of FAF signal changes that correlated with laser-burn tissue interactions over 3 months. There was a reduction in CRT, suggesting that barely visible 10 ms PASCAL laser may reduce retinal edema within treated areas with minimization of scar formation.

We recently published the results of the first randomized study investigating the short-term effects of targeted PASCAL retinal photocoagulation (TRP) versus reduced fluence or minimally-traumatic panretinal photocoagulation (MT-PRP) versus standard-intensity PRP (SI-PRP) in PDR.[14] All patients underwent 2500 laser burns in a single session. The results showed that 20-ms PASCAL TRP and MT-PRP using 2500 burns showed comparable efficacy to SI-PRP with no increase in macular thickness in the short term and no laser-related complications.

There are clear benefits with low-intensity burns, both in the macula as well as outside it. The PASCAL system allows more controlled and precise application of arrays with predetermined parameters and we have demonstrated a 50% reduction in the size of 10 ms outer retinal burn over the course of 1 year.

TISSUE REMODELING DATA

We subsequently gained a better understanding of the laser-induced tissue remodeling that takes place within the outer retina and the reasons for the reduction in size of the burn.

Animal histopathology studies have shown the decreasing width of the retinal damage zone suggesting that photoreceptors and RPE cells migrate from the immediate unaffected areas to fill in the gap in the photoreceptor layer.[15,16] In these studies, retinal lesions produced by barely visible burns at short exposures (10 ms to 30 ms) decreases in size over time. The photoreceptors destroyed with laser are gradually replaced by photoreceptors shifting from the undamaged adjacent areas, thereby restoring visual sensitivity in the former lesion,

leading us to believe that, over time, the RPE and the retina fully recover, leaving no permanent damage.[15-18]

All of these data show that barely visible or subthreshold laser may work when applied to the macular area or as PRP, and now that the proof of concept has been shown, new laser technology is required to easily apply this concept to clinical practice.

ENDPOINT MANAGEMENT

Topcon has developed Endpoint Management (EpM). EpM is a method of precise control of laser energy relative to titration level. It is particularly important for treatment at low energies. EpM begins with titrating laser power to a barely visible burn, then the clinician selects the percentage of that energy to be delivered to the treatment locations. EpM can be used for both the 532-nm and 577-nm laser wavelengths for macular treatment and for PRP.

The EpM approach to laser therapy allows the physician to consistently operate in the realm of therapeutic relevance for subvisible treatments. When no burns are visible, the biggest risk becomes lack of therapeutic effect.

Fundus autofluorescence can easily and noninvasively demonstrate the spatial distribution of new and old burns that are not visible on biomicroscopy.

TREATMENT ALGORITHMS

Focal laser remains my first option for focal macular edema, as the response is generally good and we can usually avoid multiple anti-VEGF injections. When performing grid laser for cases of diffuse DME, however, it is important to treat all the area of macular thickening.

When treating diffuse macular edema with laser, I pretreat significantly thick maculas with either anti-VEGF bevacizumab (Avastin, Genentech), ranibizumab, or triamcinolone acetonide to reduce the macular thickness prior to applying laser, and I do FAF imaging prior to repeating laser procedure on order to avoid overtreating the same area.

I use 10 ms duration burns within the macula and 20 ms outside the macula. I perform 2500 to 3000 light-intensity burns in single-session PRP and retreat 2 to 3 months later, if necessary. I perform macular laser and PRP combined in the same treatment session.

I am currently using the PASCAL laser almost exclusively with EpM, which makes it significantly easier to titrate the burns and allows for a good tissue healing response and a higher level of confidence for working close to the fovea.

SUMMARY

With the current laser technology that we have available, we no longer need to burn the full thickness of the retina with treatment. Because we are able to treat patients with subvisible, nondamaging laser, we should be treating earlier, before vision loss occurs, and macular edema or new vascularization becomes significant. With EpM, we should be able to safely treat close to the fovea.

Diabetic retinopathy is a complex disease that is rarely effectively controlled with monotherapy; rather, a multipronged approach may be more effective.

Large clinical trials using subthreshold treatment must be conducted. However, animal and pilot clinical studies in humans have provided so far compelling evidence for the clinical efficacy of this treatment modality. ■

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