Choroidal Thickness Study Using Swept-source Optical Coherence Tomography

By Javier A. Montero, MD, PhD; and Jose M. Ruiz-Moreno, MD, PhD

The word "choroid" is derived from the Greek words for "forms" and "membrane." The choroid is a highly vascular and pigmented tissue that lies between the retina and sclera and that has a histologic thickness between 0.10 mm (anterior) and 0.22 mm (posterior pole). The vascular supply of the outer retina is maintained by the choroid, and changes to this structure can result in photoreceptor death; choroidal changes are also associated with diseases such as central serous chorioretinopathy (CSC), age-related macular degeneration (AMD), and Vogt-Koyanagi-Harada syndrome.

The in vivo thickness of the choroid has been understood via B-scan and Doppler imaging, but until spectral-domain optical coherence tomography (SD-OCT) imaging became available, very little was known about its in vivo structure.

The first time-domain (TD) OCT system, the Stratus (Carl Zeiss Meditec), provided little information about the choroid because most of the light emitted could not penetrate the retinal pigment epithelium (RPE); however, SD-OCT frequency settings improved upon the wavelengths used in TD-OCT to allow imaging deeper into the retina.

The most recent advance in OCT technology, known as swept-source OCT (SS-OCT), further improves upon the precision with which we can determine the inner and outer boundaries of the choroid, while also allowing examination of the choriocapillaris and larger choroidal vessels.

CHOROIDAL THICKNESS STUDY

In recent years, there have been several studies regarding changes in choroidal thickness, particularly in cases of high myopia,[1-5] CSC,[6-11] glaucoma,[12-16] AMD,[17-23] posterior uveitis,[24-28] and diabetic retinopathy.[29,30] Most of these, however, used conventional SD-OCT. We decided to perform our own study comparing results with SD-OCT vs SS-OCT to evaluate the differences between these technologies.

Our study was a cross-sectional, prospective study including 82 eyes of 46 healthy volunteers using the OCT
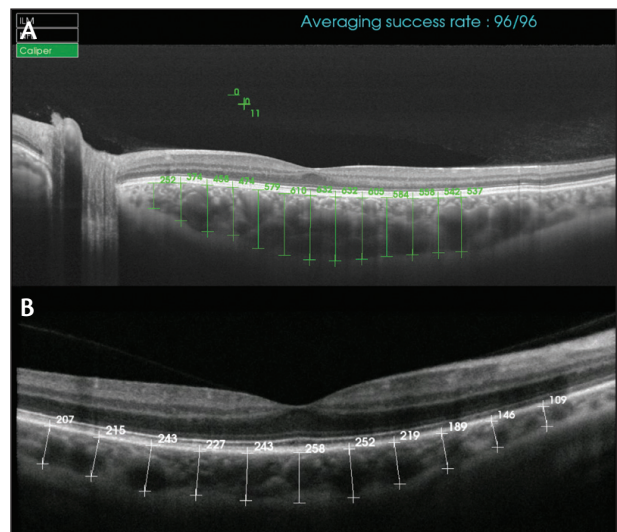

Figure 1. Manual determination of choroidal thickness at 6 different points nasal and temporal to the fovea and under the fovea. Top: Topcon SS-OCT prototype. Bottom: Topcon OCT 3D 2000 SD-OCT.

3D 2000 (Topcon) and an SS-OCT prototype system from Topcon. The mean age of patients in the study was 46 years of age (standard deviation, 23 years).[31]

The measurement of choroidal thickness perpendicular to the outer RPE was performed manually by 2 different observers at 13 different points: 1 under the fovea, 6 temporal to the fovea, and 6 nasal to the fovea, at 500 μm intervals.

The subfoveal choroidal thickness measurements were similar between both systems, with a mean value of 279.4 ±96.9 μm in the eyes measured with SD-OCT, and a mean value of 285.7 ±88.9 μm in eyes measured with SS-OCT (Figure 1). The ranges with both systems were very wide, with values from SD-OCT ranging from 84 μm to 506 μm and those from SS-OCT ranging from 130 μm to 527 μm. Comparing the average of all the choroidal thickness measurements did not reveal any significant differences, but, again, the ranges of values were large. The mean choroidal thickness with SD-OCT was 243.8

±78.8 µm (range, 103.6 µm–433.2 µm), and with SS-OCT it was 242.2 ±81.8 µm (range 97.6 µm–459 µm).

The systems were slightly different in measuring choroidal thickness in the most temporal region—SS-OCT was able to measure subfoveal choroidal thickness in 100% of patients in this area, whereas SD-OCT was able to obtain measurements in 74.4% of patients, the other percentage of volunteers being those with thicker choroids. The reproducibility with both systems was good.

Our conclusions were that both systems correlated well for the determination of choroidal thickness and that the best quality choroidal images were obtained with SS-OCT, which allowed higher rates of measurement, particularly in eyes with thicker choroids.

PEDIATRIC CHOROIDAL THICKNESS STUDY

It has been reported that choroidal thickness decreases with age. With this in mind, we sought to elucidate the changes that occur in a healthy pediatric population. This was a cross-sectional comparative, noninterventional study comparing the macular regions in a healthy pediatric population (<18 years of age) studied with the Topcon SS-OCT prototype vs measurements from normal healthy volunteers older than 18 years of age.[32] A horizontal choroidal thickness profile of the macula was manually created measuring choroidal thickness (from the posterior edge of RPE to the choroid-sclera junction) under the fovea, and measurements were taken by 3 independent observers. Three further determinations were performed every 750 mm temporally (T1, T2, and T3) and nasally (N1, N2, and N3) to the fovea.

There were 83 eyes in the pediatric group that were compared with 75 control (adult) eyes. The subfoveal choroidal thickness was not as different between the groups as expected, although we did find widely varying values for both subfoveal choroidal thickness and the average value of all macular thickness measurements (Figure 2).

We found that the profile of the choroid was thinner in areas closer to the optic disc and thicker closer to the fovea in both groups. Choroidal thickness decreased temporal to the fovea in the adult group and maintained a similar thickness in the pediatric group of eyes. We concluded that, although choroidal thickness was not significantly greater in younger eyes, the difference was statistically significant on the temporal side of the fovea.

HOW AGE AFFECTS THE CHOROID

When does this start to change? To find out, we performed another cross-sectional, noninterventional study to measure choroidal thickness in a healthy population of 276 eyes of 154 healthy volunteers ranging in age from 3 years to 95 years of age with the DRI OCT-1 system (Topcon).[33] A horizontal choroidal thickness profile of
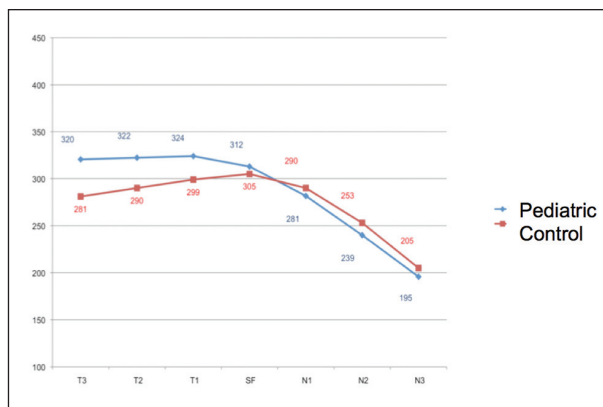

Figure 2. Choroidal thickness profiles in adult (red) and pediatric (blue) eyes as determined by Topcon SS-OCT prototype. The difference between profiles is more marked in the choroid temporal to the fovea.

the macula was manually created measuring choroidal thickness from the posterior edge of the RPE to the choroid-sclera junction under the fovea. Five further determinations were performed every 1000 mm temporally (T1, T2, T3, T4, and T5) and 3 more nasally (N1, N2, and N3) to the fovea. We grouped the eyes by age: 0 to 10 years (eyes, n=75); 11 to 20 years (n=48); 21 to 40 years (n=50); 41 to 60 years (n=40); and older than 60 years (n=63). The median age was 33.5 ±24.9 years and the median spherical equivalent was 0.10 ±1.36 D (from +3 D to -3 D). Two masked observers independently measured choroidal thickness.

The results in terms of variability were similar to what we had found in our previous studies, with a mean subfoveal choroidal thickness of approximately 300 µm. The mean macular choroidal thickness was approximately 260 µm. Additionally, when studying the choroidal thickness profile, we observed, as we did previously, that the choroid was thinnest closest to the optic disc and thickest in the foveal region.

Comparing the sexes in this population, we observed that the differences were not significant in the average thickness, although subfoveal choroidal thickness was slightly lower in females. Although this difference was insignificant, this may be explained by the fact that, on average, the females included in this study were older.

In comparing age groups, the average choroidal thickness appeared to decrease as age increased. Similar changes could be observed in subfoveal choroidal thickness measurements. Differences were more significant in the temporal aspect of the fovea (Figure 3). Our conclusion was that choroidal thickness seems to decrease with age.

SUMMARY

Thus far, we have evaluated only eyes of healthy volunteers, but our results may help us to understand what happens in the presence of pathology. For example, we

have previously been unable to determine subfoveal choroidal thickness in patients with high myopia, and now, using SS-OCT, we can determine the extent to which the choroid has thinned. Alternatively, we can perform the same evaluation in terms of how thick the choroid is in the presence of CSC or diabetic retinopathy.

SS-OCT permits a wider range of imaging with a detailed examination of the ocular structures from the vitreous gel to the sclera. The high penetration of the light at 1050 nm enables choroidal examination under serous or fibrovascular RPE detachments.

The high-speed scanning capabilities facilitate patient cooperation, even among children, and, because the patient cannot detect the light at these high speeds, the eye is less likely to move. ■

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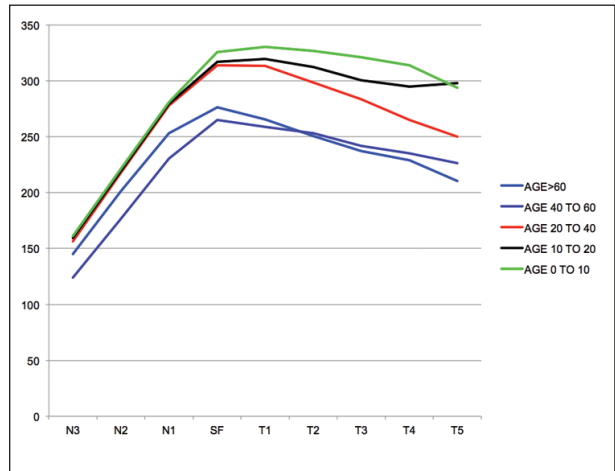

Figure 3. Choroidal thickness profiles in different age groups, determined by Topcon SS-OCT prototype. The difference between age groups is more marked in the choroid temporal to the fovea.

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Swept-source OCT: Taking Imaging Deeper and Wider

By Zofia Michalewska, MD, PhD

Over the past decade we witnessed a marvelous change in optical coherence tomography (OCT) techniques as we moved from time-domain to spectral-domain (SD) OCT. Many of us in the retina subspecialty, however, believed that these advances were only the tip of iceberg and that continued improvements in OCT would allow us to see even further into the eye.

The latest development of choroidal imaging was born from the understanding that retinal function is dependent on the choroid. Choroidal thinning and loss of vascular tissue leads to damage to the retinal pigment epithelium (RPE) and photoreceptors. Conversely, dilatation of choroidal vessels or choroidal vascular hyperpermeability increases the hydrostatic pressure within the choroid, inducing thickening. Choroidal abnormalities, such as hyperpermeability, vascular changes, loss, or thinning, are critical in the onset and progression of age-related macular degeneration (AMD), polypoidal choroidal vasculopathy (PCV), central serous chorioretinopathy (CSC), chorioretinal atrophies, Vogt-Koyanagi-Harada syndrome, and others.

In 2008, Spaide et al[1] were the first to visualize the choroid by inverting SD-OCT images, and in 2009, Heidelberg introduced the first commercially available device to enable choroidal visualization (Spectralis, Heidelberg Engineering). SD-OCT images are highest in resolution near the zero-delay line. Thus, when the image is inverted, even if some resolution is lost at the vitreous and the retina, the resolution at the choroid is excellent.

Swept-source (SS) OCT (DRI-OCT, Topcon) is a completely new technology that enhances the visualization of the choroid and, for the first time, enables us to visualize the vitreous, retina, and choroid in high resolution on the same scan. The technology uses a laser sweeping through different wavelengths up to 1050 nm, which is much higher than the conventional 850 nm used in SD-OCT. This enables a scanning speed of 100 000 A-scans/sec, which leads to single B scans with a 1-µm axial resolution and 12-mm width.. For the first time, it is possible to obtain automatic choroidal volume and thickness measurements by using the software included in this device.

Figure 1 shows the difference between SD-OCT and SS-OCT imaging. It demonstrates that in eyes with cataract or other media opacities, SD-OCT might not present
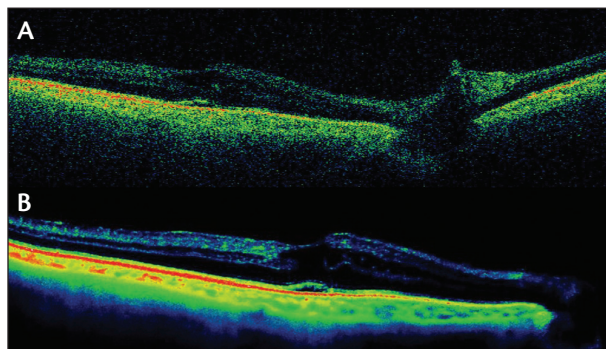

Figure 1. An eye of a patient with diabetic macular edema and cataract imaged with SD-OCT (A). The poor scan quality is due to cataract. The same eye of the same patient on the same day was recorded with SS-OCT (B). Despite the poor fundus view on indirect ophthalmoscopy, SS-OCT enables clear visualization of the posterior pole.

good quality images of the retina. However, due to the longer wavelength used, SS-OCT overcomes this problem and enables us to achieve high-quality retinal images even if the fundus view is impeded due to media opacities.

Longer scans (12 mm vs 7 mm to 10 mm in conventional SD-OCT) and deep choroidal imaging are especially important in depicting optic disc pit maculopathy. SS-OCT clearly captures the flow of fluid from the optic disc to the subretinal space.

NEW FINDINGS WITH SS-OCT

To evaluate the outer choroidoscleral boundary, we performed a study that included 180 eyes of patients with varied states of retinal health (among them full-thickness and lamellar macular holes, epiretinal membranes, dry and wet AMD) who were imaged with the DRI-OCT. The aim of the study was to visualize the outer choroidoscleral boundary, which succeeded in all cases.

SS-OCT enables us to precisely image retinal details. Figure 2 shows the additional areas that can be seen with this technology, including the external limiting membrane, inner segment of the photoreceptors, Voerhoff membrane, RPE, choriocapillaris, Sattler layer (medium choroidal vessels), and the large-diameter choroidal vessels of Haller layer. Beneath the hyperreflective line between the choroid and sclera, SS-OCT reveals the lamina suprachoroidea.

Additionally, in some eyes, we observed suprachoroidal space (Figure 3), which had not previously been observed in healthy eyes. This is a virtual space between the choroid and sclera that expands in some conditions, such as choroidal effusion in severe hypotony. Some research has been conducted on introducing anti-VEGF drugs into this space.[2] Suprachoroidal buckling has also recently been described. In this technique, a substance is introduced into the suprachoroidal space, exactly over a retinal break, in order not only to close the break, but also to relieve traction. This substance resolves after a few months, which eliminates the myopic shift that is quite common in conventional buckling surgery.[3] In the future, enhanced visualization of the suprachoroidal space may help in the application of suprachoroidal drug delivery.

VITREOMACULAR INTERFACE APPLICATIONS

As retina specialists, we are used to the idea that diseases such as vitreomacular traction syndrome (VMT syndrome), macular holes, and epiretinal membranes are grouped together as *vitreomacular interface diseases*. The latest advances in choroidal imaging question this grouping. There are many patients with VMTs that release after a few months, and many who do not experience release but are not candidates for surgery. In 2011, we published a paper suggesting that the reason for the different outcomes is the size of the vitreous adherence to the retina: The smaller the area of adherence, the more likely that release will occur.[4] VMT may also proceed to epiretinal membranes, full thickness macular holes (FTMHs) or lamellar macular holes (LMHs), and it appears that when traction is transmitted through the retinal layers to the photoreceptor layer, forming a triangular elevation of the photoreceptors, patients are more likely to develop FTMHs. Conversely, those patients in whom this force is not transmitted through the retinal layers are more likely to develop LMHs.[5]

What is the role of the choroid in vitreoretinal disease? Some authors have suggested that thinner choroids may contribute to the development of macular holes.[6,7] Further studies are needed as to whether choroidal thickness will add new information on the progression of VMT.

HIGH MYOPIA

Choroidal imaging distinguishes several new conditions not observed with earlier devices. Additionally, it allows better explanation of details of previously known diseases.

Dome-shaped macula was for a long period of time an unexplained phenomenon of high myopia, as the disease usually coexists with lengthening and stretching of the eyeball. Originally it was considered that the phenomenon is due to choroidal thickening in macular area or scleral infolding due to collapse of the posterior eyeball. Choroidal imaging with enhanced-depth imaging SD-OCT revealed that sclera, and not the choroid is

Figure 2. Top: SS-OCT 12-mm scan using the DRI-OCT visualizes the optic nerve head and macula in a healthy eye. Bottom: enlargement from the box.
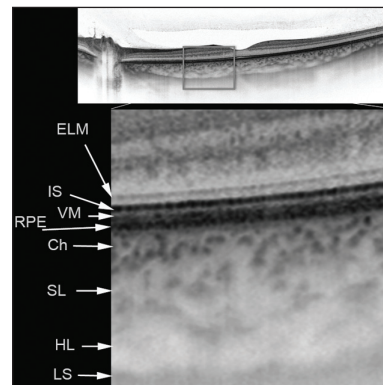
ELM: external limiting membrane; IS: ellipsoid inner segments of photoreceptors; VM: Voerhoff membrane; RPE: retinal pigment epithelium; Ch: choriocapillaris; SL: Sattler layer; HL: Haller layer; LS: lamina suprachoroidea.
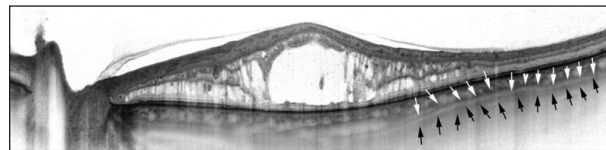

Figure 3. SS-OCT scan of a patient with diabetic macular edema. The white and black arrows indicate suprachoroidal space.

thickened in this condition.[8]

Optic disc pits were usually thought to be only congenital, but SS-OCT reveals optic disc pits or conus pits in 16.2% of highly myopic eyes. In most cases, these changes are not visible ophthalmoscopically. In myopic eyes, optic disc pits usually develop in superior or inferior parts of the disc, unlike congenital optic pits, which usually develop at the temporal edges.[9]

SUMMARY

SS-OCT has allowed us to learn more about the outer choroidoscleral boundary, which may be useful in developing surgical and medical strategies for treatment. Additionally, it may enable us to see deeper into the eye to further explore many retinal diseases. ■

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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]
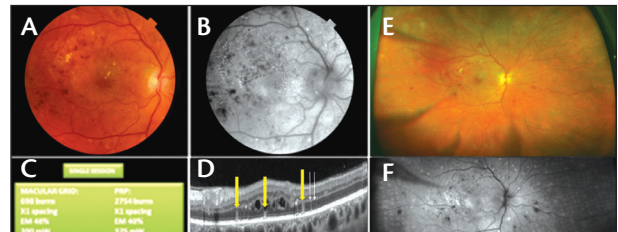

Figure 1. Subthreshold 40% EpM PASCAL single-session macular grid with PRP: Barely visible and invisible burns (A, E); burns visible on FAF (B,F); laser parameters (C); FD-OCT showing the landmark and the more intense sub-threshold burns (D; yellow and white arrows respectively).

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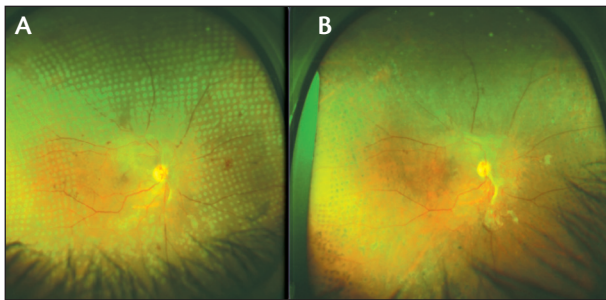
Figure 2. PRP appearance within 1 hour of treatment (A) and 1 month post treatment (B). Note the scarce carbonization or pigmentation of the retina and the fibrosis of the peripapillary neovascularization at 1 month.

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 multi-pronged 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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