NONDAMAGING PHOTOTHERMAL THERAPY FOR THE RETINA

Initial Clinical Experience With Chronic Central Serous Retinopathy

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Purpose: To assess safety and clinical efficacy of the nondamaging photothermal therapy for the macula for the treatment of chronic central serous retinopathy.

Methods: Sixteen eyes of 16 patients with persistent central serous retinopathy (>4 months of duration) were treated with the PASCAL Streamline) at 577-nm wavelength, using 200-μm retinal spot sizes. Using Endpoint Management Software, the laser power was first titrated for a barely visible burn with 15-ms pulses, which was defined as 100% pulse energy. Treatment was then applied over the area of serous retinal detachment and adjacent nonthickened retina, using 30% pulse energy with the spot spacing of 0.25 beam diameter. Changes in subretinal fluid, Early Treatment Diabetic Retinopathy Study best-corrected visual acuity, and central macular thickness were measured over 6 months of follow-up. Pretreatment and posttreatment fluorescein angiography and fundus autofluorescence were also assessed.

Results: On average, 532 spots have been applied per treatment. No visible laser marks could be detected by clinical observation, optical coherence tomography, fundus autofluorescence, or fluorescein angiography. On average, 12 Early Treatment Diabetic Retinopathy Study letters gain was achieved at 2 months and was sustained by 6 months ($P < 0.001$). Central macular thickness decreased from 350 μm to 282 μm ($P = 0.004$). Subretinal fluid completely resolved in 37% of the patients after first treatment, whereas 44% of the patients required retreatment after 3 months because of recurrent fluid or incomplete resolution. The remaining 19% of the patients received a second retreatment. By 6 months, in 75% of the patients, the subretinal fluid was completely resolved, whereas in 25%, there was some minimal fluid left.

Conclusion: Photothermal therapy using 577-nm PASCAL laser with Endpoint Management graphic user interface was safe, and it improved visual acuity and resolution of subretinal fluid in chronic central serous retinopathy. Lack of tissue damage allows periodic retreatment without cumulative scaring, characteristic to conventional photocoagulation. This technique should be tested in the treatment of other macular disorders and may offer an alternative to conventional laser coagulation of the macula and to anti-vascular endothelial growth factor pharmacological treatments of macular diseases.

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Retinal photocoagulation, either alone or combined with pharmacological therapy, remains the standard of care for various retinal diseases, including proliferative diabetic retinopathy, diabetic macular edema, vascular occlusions, central serous retinopathy (CSR), and retinal tears. To minimize the side-effects while retaining the therapeutic benefits and to improve localization of the laser effects to specific retinal layers, various refinements in the treatment parameters have been introduced over the years, including variations in wavelength, pulse duration, and lesion intensity.

During the retinal laser therapy with visible and near-infrared wavelengths, light is absorbed primarily by melanin in the retinal pigment epithelium (RPE) and in pigmented choroid, and to a smaller extent by hemoglobin.[1] Energy deposition by light absorption results in tissue heating, with the maximum temperature in the RPE layer. Generated heat diffuses into the surrounding tissues, including the transparent neural

retina, and the depth of the retinal damage is governed by the laser power and pulse duration. Introduction of the pattern scanning approach to retinal photocoagulation (PASCAL)[2] has advanced the use of shorter pulses (10–30 ms), which limit heat diffusion, minimizing the inner retinal damage and pain.[3,4] As a result, less-damaging photocoagulation endpoints have been adopted,[5] which helped decrease residual scarring and improve restoration of the retinal structure and function over time.[6,7]

Selective and subvisible treatments have been developed to further minimize tissue damage, especially in the macula. These include selective RPE therapy with microsecond pulses, which allow destruction of the retinal pigmented epithelium without damage to the photoreceptors and choroid.[8] Retinal pigment epithelium cells proliferate and migrate from the surrounding areas, restoring complete coverage of the treated zone within days.[9] Clinical efficacy of selective RPE therapy has been demonstrated in applications to CSR and diabetic macular edema.[10]

A nondamaging approach to retinal laser therapy was initially attempted using near-infrared diode laser (810 nm) with very long exposures (60 seconds) and very large spot on the retina (800 μm).[11] This approach, termed transpupillary thermotherapy or TTT,[12] encountered difficulties with reliable titration, resulting in frequent occurrences of significant retinal damage.[13] Later, a pulsed version of a similar laser with smaller spot sizes (125 μm) has been applied for nondamaging retinal therapy. The "micropulse" laser delivers 100 ms and 300 ms bursts of pulses of 100 μs to 300 μs in duration, with the average power set below the clinically detectable tissue damage by adjustment of the pulse duty cycle and peak power. Clinical trials have shown that micropulse treatment of diabetic macular edema delivered with high-spot density is equally efficient or superior to the standard mETDRS protocol.[14] A smaller clinical trial demonstrated that the micropulse laser treatment reduced the subretinal fluid and improved visual acuity in patients with CSR compared with the untreated control group.[15] However, the lack of a well-defined titration procedure is reflected in the variable results of these studies.[16–18] In addition, high-density coverage of the macula with relatively small spots and long pulses requires lengthy treatment, which is difficult to perform without a scanner.

Significant advantages of the retinal phototherapy with a subvisible endpoint are the absence of scotomata and scarring, the ability to treat foveal areas, and improved preservation of color vision and contrast sensitivity.[18] The lack of chorioretinal damage permits high-density therapy, which greatly improves therapeutic outcomes, compared with conventional sparse laser treatment protocols in the macula.[14] Nearly confluent laser applications could be safely delivered over the entire edematous areas if short pulse treatment and pattern scanning would be applied. This approach would also allow retreatment of the same areas, even in proximity to the fovea.

Dynamic range of the retinal response to nondamaging hyperthermia has been established by monitoring expression of the heat shock protein (HSP70) in mouse.[19] However, the lack of a reliable titration protocol for reproducible subvisible treatment settings inhibited its adoption in clinical practice. If laser settings are too low, the treatment will be not only subvisible but also subtherapeutic, whereas if the settings are too high, there is a danger of excessive damage to the retina, especially with the nearly confluent coverage close to the fovea.

We developed a titration protocol for adjustment of the laser power and duration based on a retinal thermal model.[20] This protocol, called Endpoint Management (EpM), ties subvisible tissue effects to a visible titration point. For pulse durations exceeding 50 μs, thermal denaturation is the primary mechanism of cellular damage.[21,22] In this regime, the damage can be described with a first-order reaction kinetics (Arrhenius law) parameterized by an activation energy, corresponding to the denaturation of a single critical component, and assuming an absence of cellular repair during hyperthermia.[1]

Experiments with HSP expression after nondamaging retinal exposures in mouse[19] and a computational analysis of the clinical laser settings[23] indicated that nondestructive thermal therapy corresponds to Arrhenius values within the range of approximately $0.1 < \Omega < 1$.[19] In this regime, the RPE cells survive the hyperthermia and respond to the thermal stress by expression of the HSPs. Visible lesions produced at higher laser settings result in lethal damage to RPE and photoreceptors and have calculated values of $\Omega >> 1$, with the relevant range of Ω for retinal thermal therapy spanning several orders of magnitude. The 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 duration.[20] This protocol was calibrated in

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rabbits using optical coherence tomography (OCT), fluorescein angiography (FA), light microscopy, and transmission and scanning electron microscopy.[20]

In this article, we describe the first clinical experience with the application of the nondamaging EpM settings to the treatment of patients with chronic CSR.

Materials and Methods

Patient Selection

This was a prospective, nonrandomized, interventional case series approved by the Ethical Committee of the Hospital de Clínicas de Porto Alegre, Federal University of Rio Grande do Sul, and adhered to the tenets of the Declaration of Helsinki. Patients were older than 18 years, with chronic CSR and symptoms presented for more than 4 months. The CSR was confirmed by the presence of one or more leakage points in the fluorescein and/or indocyanine green angiography and subretinal fluid in the OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany) and increased choroidal thickness in enhanced depth imaging OCT mode. Best-corrected visual acuity (BCVA) measured by the Early Treatment for Diabetic Retinopathy Study protocol was in the range from 20/40 to 20/400. Patients included in the study did not have any other retinal or choroidal disease that could present with similar characteristics. They also did not have previous macular laser treatment or intravitreal steroids within the last 4 months or anti-vascular endothelial growth factor treatments during the last month before the laser treatment. Patients were not eligible if they had retinal thickening due to the epiretinal membrane or vitreomacular traction syndrome or had undergone major ocular surgery (including cataract surgery) within 6 months.

Treatment Procedures and Evaluation of the Therapeutic Effect

The baseline examination included ETDRS BCVA, slit-lamp examination of the anterior segment, indirect ophthalmoscopy, color fundus photography using CR-2 retinal camera (Canon), FA, and fundus autofluorescence using HRA-2 (Heidelberg Retina Angiograph; Heidelberg Engineering). Baseline macula and choroidal thickness and the presence of the subretinal fluid was evaluated by spectral domain OCT using Spectralis (Heidelberg Engineering). Patients eligible for the photothermal therapy received the laser treatment as described below. ETDRS BCVA and central macular thickness measurements by OCT were performed monthly for 6 months of the follow-up. Fluorescein angiography was repeated after 3 months and 6 months. Laser treatment could be repeated at 3 months or 6 months if the subretinal fluid persisted or recurred.

The effect of the laser treatment was measured by the improvement in visual acuity, assessment of serial retinal autofluorescence, resolution of the retinal detachment and/or subretinal fluid by OCT, and evaluation of leakage areas on FA. Potential adverse events have been monitored with visual acuity, clinical examination, FA, and OCT.

Laser Settings and Endpoint Management Algorithm

PASCAL laser (Topcon Medical Laser Systems, Santa Clara, CA) with 577-nm wavelength and 200-μm retinal spot size was applied by the Area Centralis HD contact lens (Volk). Treatment was based on OCT macular thickness map and on the increased autofluorescence area, which included areas of thickened and nonthickened retina. Retinal treatment begins with titration of the laser power to a minimally visible retinal lesion endpoint. As ophthalmoscopic visibility of the lesion changes over time, its appearance must be evaluated at a consistent time point after the laser application. For practical clinical usability, evaluation time point of 3 seconds was defined for this protocol. During titration, pulses of 15 ms in duration have been used. The titration pulse energy was assigned the 100% on EpM settings, and the treatment pulse energy was then defined as a percentage of this titration energy. Each energy level corresponds to a unique pair of laser power and pulse duration, as was described previously.[20]

Treatment was performed at 30% energy—the level established as the highest nondamaging setting in the animal studies.[20] Graphic user interface of the EpM allows keeping some of the corner spots of the pattern at 100% energy to produce visible landmarks for orientation. Treatment was initially applied using the macular grid pattern with landmarks on, using 0.25-diameter spacing between the laser spots (Figure 1). Inside the inner radius of the grid, additional 2×2 patterns were applied with landmarks off, and outside the grid, additional 3×3 patterns have been applied to expand the treated area, covering both the thickened and nonthickened retina in the posterior pole, as determined by the OCT and by increased autofluorescence. In retreatments, the landmarks have been turned off.

Statistical Analysis

For statistical analysis, the visual acuity data were converted to logarithm of the minimum angle of resolution (logMAR). The Wilcoxon signed-rank test was performed to assess change in the visual acuity

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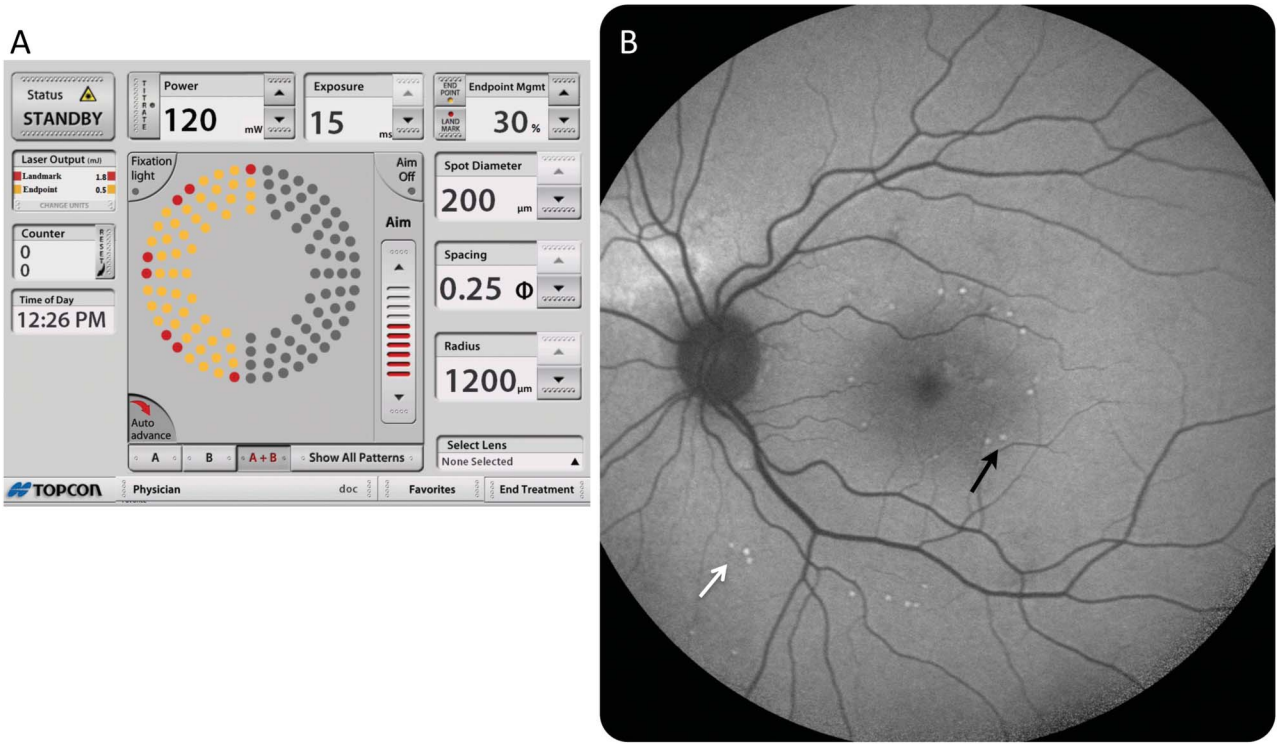

Fig. 1. A. Graphic user interface of the EpM software. Red dots indicate the landmarks (optional). Yellow dots indicate the locations to be treated at 30% energy. **B.** Fundus autofluorescence (FAF) after photothermal stimulation with landmarks (100% energy), which appear as spots with increased FAF (black arrows). Titration points are also visible in FAF outside the arcades (white arrows). The 30% treatment spots were not visible clinically by OCT of FAF.

and retinal thickness compared with the baseline. Average values of the retinal thickness and visual acuity are plotted, with the error bar representing the standard error of the mean.

Results

In this study, 16 eyes from 15 patients, 11 men and 4 women, with chronic CSR were enrolled. The mean duration of CSR was 10 ± 4 months. The average age was 55.68 ± 17.22 years.

Laser Settings

Typical power range in titration with 15-ms pulses was 90 mW to 150 mW, with the average of 126 ± 17 mW. Treatment was performed using 30% of the titration energy, with 0.25-diameter spot spacing in all the PASCAL patterns: macular grid, 2 × 2, and 3 × 3 square patterns. The average number of spots per treatment was 532 ± 190.

Therapeutic Effect

Representative cases are illustrated in Figures 2–5. Figure 2 illustrates a case of a 64-year-old man with decreased visual acuity for 8 months. Best-corrected visual acuity of 20/60 in the left eye and OCT showed discrete subfoveal serous retinal detachment with hyperreflective dots at the photoreceptor layer, suggestive of chronic disease (Figure 2, A and B). One month after the photothermal stimulation, there was a complete resolution of the subretinal fluid (Figure 2C), and visual acuity increased to 20/25.

Figure 3 demonstrates the case of a chronic patient with CSR with baseline visual acuity of 20/100 and central serous retinal detachment (Figure 3A). Patient was treated by photothermal stimulation, and after 1 month, the central macular thickness decreased and visual acuity increased to 20/40 (Figure 3B). After 2 months, a complete resolution of subretinal fluid was observed (Figure 3C), and visual acuity was restored to 20/20.

A more extensive case of chronic CSR is illustrated in Figure 4. The baseline visual acuity was 20/25, but the serous retinal detachment was quite extensive, as shown in Figure 4A. One month after the treatment, the foveal region was reattached (Figure 4B) and visual acuity increased to 20/20. After 2 months, a complete resolution of the subretinal fluid was observed on OCT, although some discrete irregularities in the photoreceptors layer could be seen, as

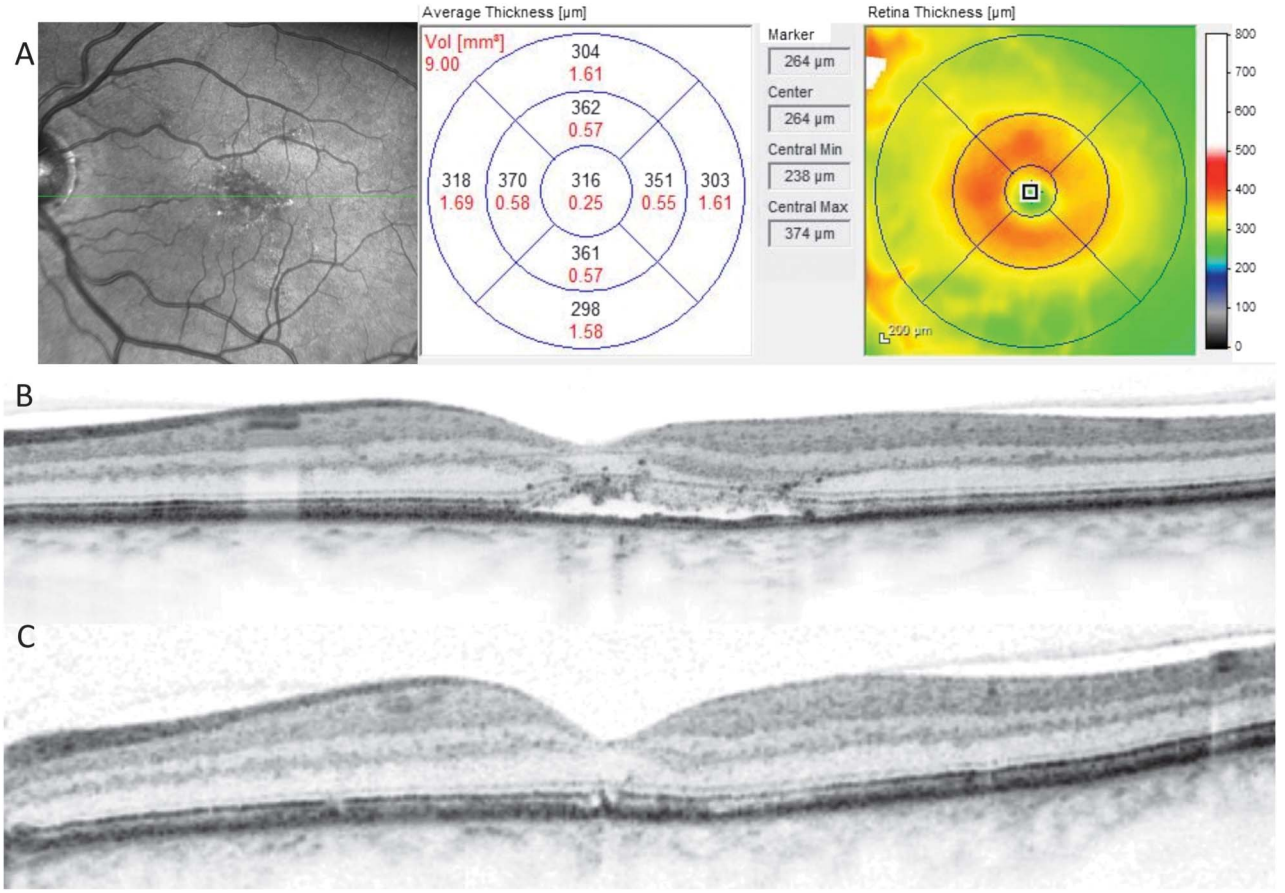

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Fig. 2. **A.** Chronic CSR, BCVA 20/60. **B.** Discrete subfoveal serous retinal detachment with hyperreflective dots at the photoreceptor layer suggestive of chronic disease. **C.** Complete resolution of the subretinal fluid and visual acuity (20/25) 1 month after the treatment.

pointed by the arrows in the Figure 4C. Visual acuity was 20/15.

Another case with extensive chronic CSR is illustrated in Figure 5. A 61-year-old woman with chronic CSR for >6 months had visual acuity of 20/60 and serous retinal detachment with RPE irregularities (Figure 5A). One month after the treatment, the central macular thickness significantly decreased (Figure 5B) and visual acuity increased to 20/30. Five months after the first treatment, vision improved to 20/25 but there was still some residual subretinal fluid (Figure 5C). Patient was retreated using the same protocol, and a complete resolution of CSR has been observed 3 months later (Figure 5D), with visual acuity restored to 20/20.

On average, central macular thickness decreased from 350 μm to 282 μm ($P = 0.004$) (Figure 6A). In 75% of the patients, the subretinal fluid was completely resolved, and in 25%, there was some minimal fluid left. Patients gained, on average, 12 ETDRS letters in BCVA at 2 months, which remained steady by 6 months (Figure 6B; $P < 0.001$). Patients gained, on average, 12 ETDRS letters in BCVA at 3 months, which remained steady by 6 months (Figure 6B). Subretinal fluid resolved in 37% of the patients after first treatment, whereas 44% required retreatment after 3 months because of either a recurrent fluid or incomplete fluid resolution. The remaining 19% of the patients received second retreatment, as summarized in the Table 1. Patients with complete resolution of subretinal fluid on OCT had no leakage on FA. In patients with partial resolution of the fluid, some residual hyperfluorescence could still be observed.

Adverse Events

There were no adverse events related to the treatment. No visible laser marks at the 30% treatment settings could be detected by clinical observation, OCT, fundus autofluorescence, or FA. During the follow-up, there was no cumulative damage to the retina and no visible burns could be detected after the second or third treatment. The only visible signs of the treatment were the landmarks (100% energy), which appear as small spot of increased autofluorescence of the RPE in the titration area (white arrow in

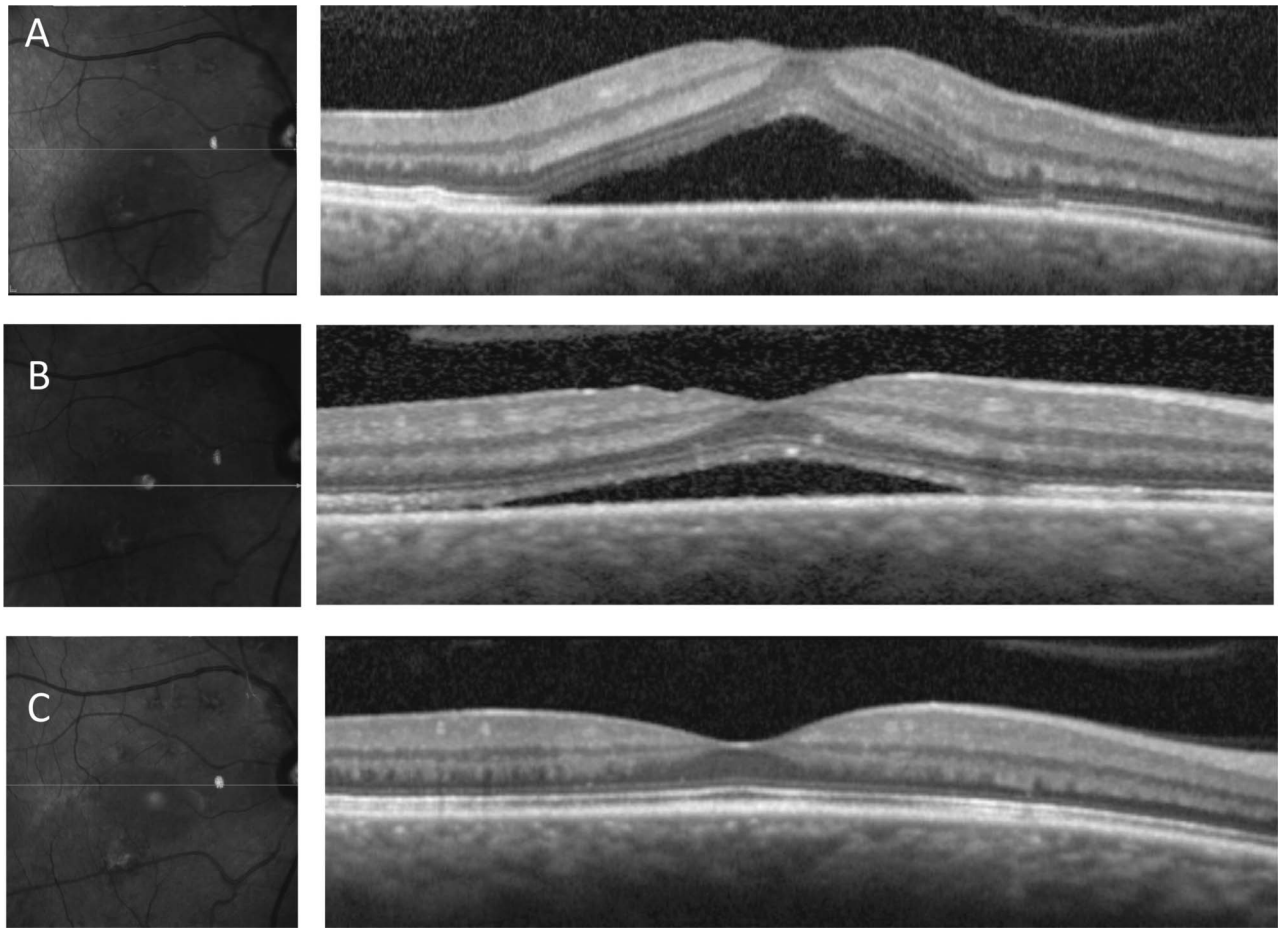

Fig. 3. A. Chronic CSR, BCVA 20/100. **B.** One month after treatment, the central macular thickness decreased and visual acuity increased to 20/40. **C.** After 2 months, the subretinal fluid was completely resolved and visual acuity restored to 20/20.

Figure 1B) or at the corners of the treatment patterns (black arrow in Figure 1B).

Discussion

Despite a wide use of retinal photocoagulation in clinical practice, physiological pathways of the retinal laser therapy have never been well established. Panretinal photocoagulation is believed to help reduce production of angiogenic factors by reducing the number of photoreceptors in peripheral retina. Photoreceptors are the most numerous cells in the retina and metabolically the most demanding cells in the body, with multiple mitochondria per cell. Therefore, significant reduction in the number of photoreceptors (by about one third) in panretinal photocoagulation is believed to help reduce metabolic load on the diseased retinal vasculature, and thereby decrease hypoxia with associated production of angiogenic factors. Focal grid coagulation was rationalized as a means to seal the leaking microaneurysms, and thereby decrease the fluid influx into the retina. However, therapeutic pathways of the macular scatter photocoagulation, where much smaller area is treated than in PRP and no leakage is directly addressed, remain unexplained.

We hypothesize that the mechanism of action might involve upregulation of the HSPs by the thermal stress in RPE and choroid, which help boost their cellular functions, including the enhanced capability of the fluid pumping from the retina. Protein misfolding and aggregation is a fundamental component of the aging process in cells.[24] Heat shock proteins refold the damaged proteins and thereby protects cells from protein aggregation, proteotoxicity, and apoptosis.[25] Aging cells undergo a decline in transcriptional pathways, including heat shock factor (HSF1) potency, and thus lose capacity to synthesize HSP.[26] Decreased HSP concentrations lead to a decline in protein quality control, which in turn contributes to protein aggregates formation in cells, commonly observed in neurodegenerative diseases.[27]

It has been shown that induction of HSP in aging cells helps maintain protein homeostasis by refolding the damaged proteins, which accumulate during aging

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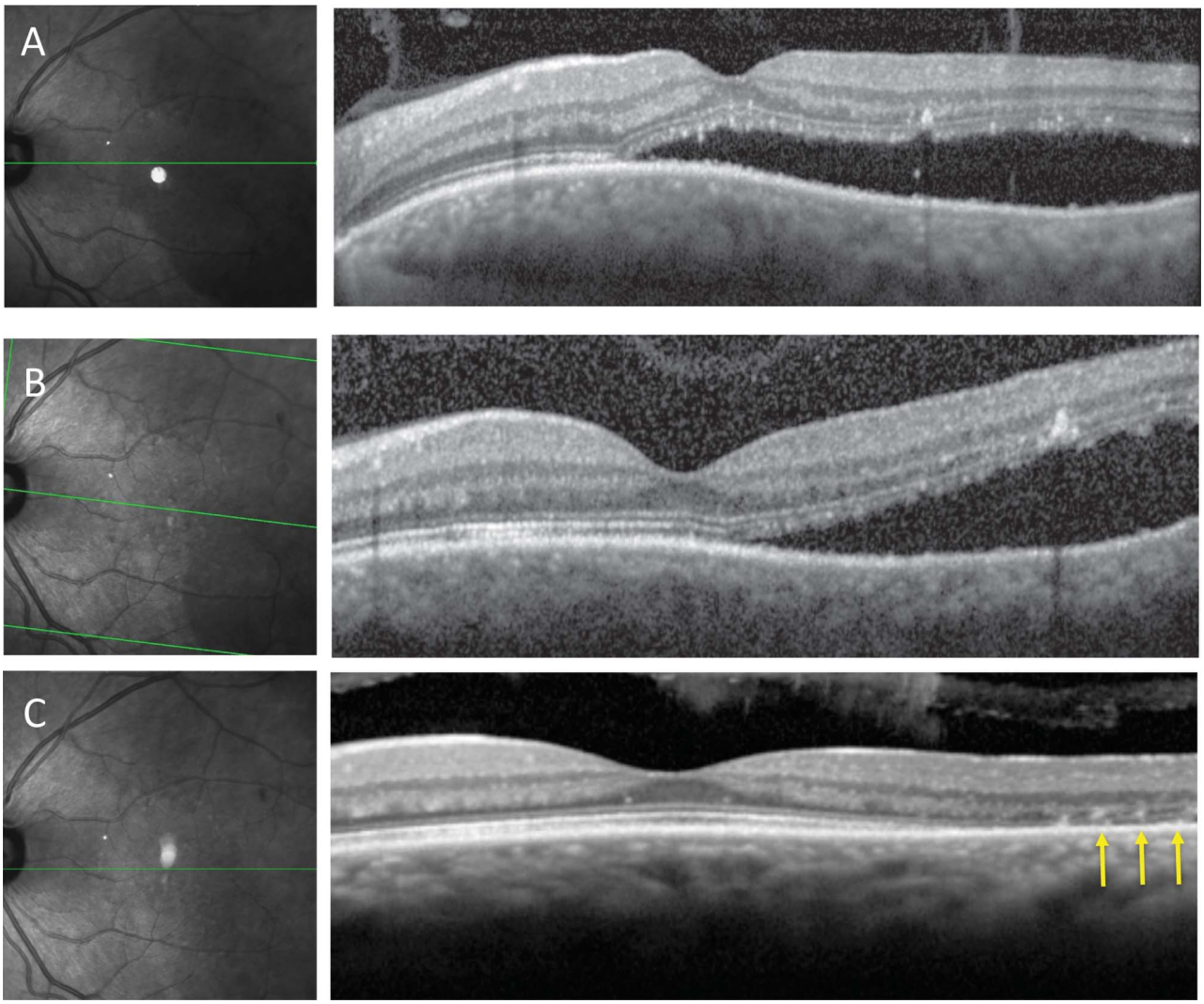

Fig. 4. A. Chronic CSR with extensive serous retinal detachment, BCVA 20/25. **B.** Reattachment of the foveal region and improved visual acuity (20/20) 1 month after treatment. **C.** Complete resolution of subretinal fluid with visual acuity (20/15) 2 months after treatment. Some discrete irregularities in the RPE and photoreceptors layers are pointed by the yellow arrows.

and are toxic to cells. It has been also demonstrated that when reactive oxygen species or heat stress denature native proteins, the heat shock response is activated and HSPs become engaged in chaperoning the damaged proteins.[24] The ability of HSP to counteract the proteotoxic effect in tissues can promote longevity and rejuvenate cellular functions. Increase in life span and decrease of aging-related proteotoxicity associated with the expression of HSPs has been observed in model organisms such as *Caenorhabditis elegans*. In addition, molecular chaperones such as HSP27 and HSP70 have antiapoptotic functions and therefore can prevent depletion of essential cell populations in degenerative processes.[28] Enhanced synthesis of HSP and cochaperones in response to sublethal thermal stress of RPE can bring back the normal physiology of these cells in aging and disease. After the same logic, it well may be that cellular exposure to mild reactive oxygen species stress during photochemical therapy (e.g., at the edges of the damage zone in photodynamic therapy) has beneficial effect similar to the sublethal thermal stress.

With this hypothesis, we optimized the retinal photothermal therapy to operate within the range limited from below by the threshold of HSP expression (Arrhenius integral $\Omega = 0.1$) and from above by the thermal damage to RPE cells (Arrhenius integral $\Omega = 1$).[19] We also assumed that the efficacy of the treatment would increase if more RPE cells in the diseased areas are exposed to thermal stress. Therefore, the treatment was applied at high density, with 0.25-diameter spot spacing corresponding to 50% of

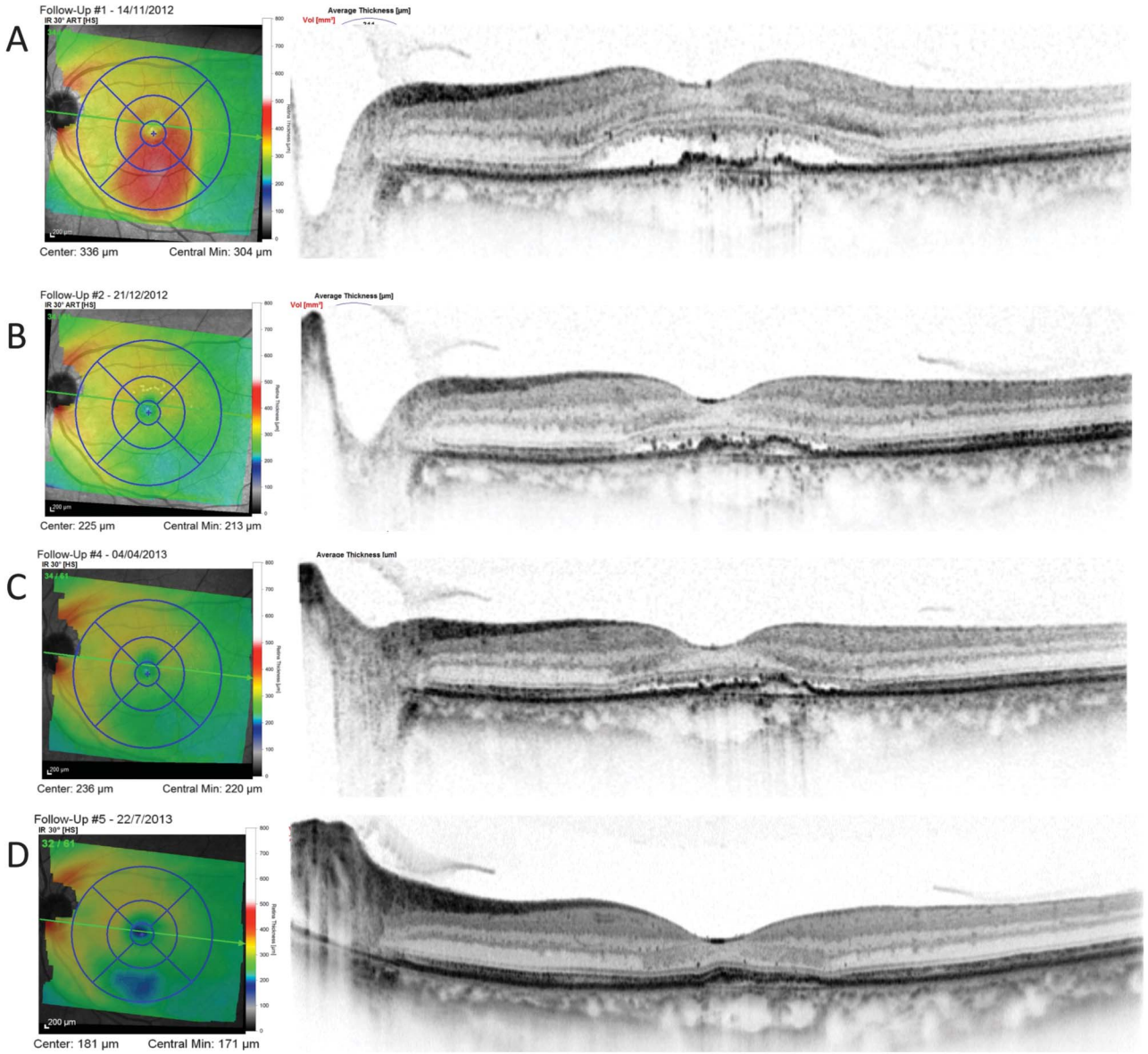

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Fig. 5. A. Chronic serous retinal detachment with RPE irregularities, visual acuity of 20/60. **B.** Decrease in central macular thickness and increase of visual acuity (20/30) 1 month after treatment. **C.** Residual subretinal fluid and visual acuity (20/25) 5 months after the first treatment. **D.** Complete resolution of CSR and visual acuity (20/20) 3 months after retreatment.

the area covered by the laser pattern. Radiation was applied not only in edematous area identified by OCT but also in the areas of enhanced autofluorescence indicating chronic RPE damage. As the confidence in the lack of retinal damage will be gained with experience, the pattern density can be further increased to cover up to 100% of the treated area. High-density coverage of the macula requires large number of spots, typically between 400 and 700. Because each spot is irradiated with a pulse shorter than 10 ms,[20] such a large number of spots can be quickly placed using pattern scanning, especially with automatic pattern advancement option, built into the new software of Synthesis laser (Topcon Medical Laser Systems).

Previous studies using subvisible micropulse laser treatment demonstrated a success rate of approximately 70% in patients with chronic CSR, and a retreatment rate of approximately 50%,[29,30] similar to this study. However, the use of Endpoint Management software has several advantages compared with micropulse laser treatment: 1) proper titration protocol provides appropriate energy level to stimulate RPE in every patient, 2) shorter pulses and the use of patterns allow faster and more reproducible treatment, and 3) possibility of placing the barely visible

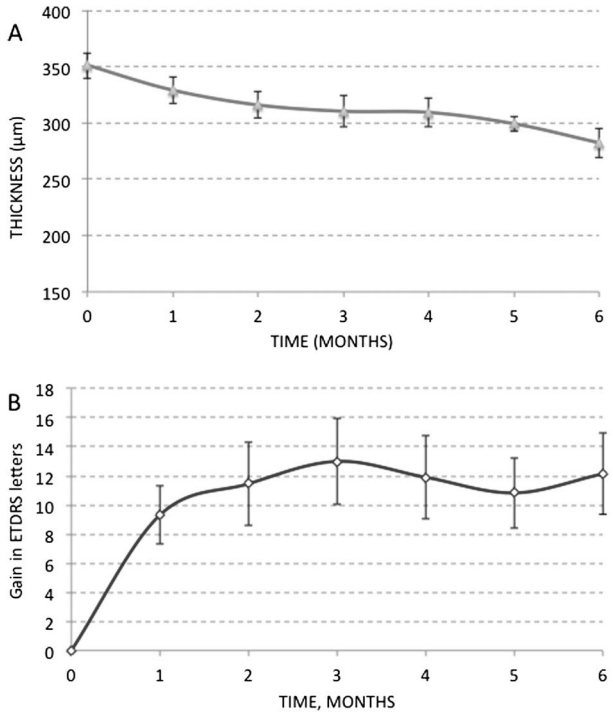

Fig. 6. A. Average central macula thickness over the 6 months of follow-up. **B.** Gain in ETDRS letters over the 6 months of follow-up in the same cohort of patients. Error bars represent the standard error of the mean.

landmarks helps with the documentation of the treatment location.

Limitations of this study include a small number of patients, short follow-up time, and the absence of a control group. It is important to note, although, that the patients treated in this study had chronic CSR, with persistent conditions for at least 4 months before the treatment and increased choroidal thickness in enhanced depth imaging OCT. Previous studies with an observation-only control group demonstrated that chronic CSR has a very limited resolution rate, with 92% of persistent leakage in the control group, and therefore a treatment is warranted after confirming chronicity of the disease.[15,31]

Our results demonstrate significant reduction, and in a majority of patients with CSR, a complete resolution of subretinal fluid, with corresponding improvement in visual acuity. The treatment produced no observable retinal damage at any of the follow-up time points, except for the visible landmarks.

Table 1. Number of Treatments and Fluid Resolution in Patients During the Follow-up Period

Fluid resolution	Complete (75%)	Partial (25%)	None (0%)
Treatment (n)	1 (37%)	2 (44%)	3 (19%)

Recurrence of the intraretinal fluid after a few months in some cases indicates that the improvement provided by the photothermal stimulation may fade over time. Retreatment with the same parameters was found safe and no cumulative retinal damage was detected over the follow-up period. Very encouraging was the observation that the retinal response to retreatment was as strong as that of the first treatment, and in some cases even better than the initial result, which could represent a cumulative therapeutic effect of several treatments.

Photothermal therapy might also be efficient in the treatment of other outer retinal disorders associated with RPE deficiency, such as drusen and dry age-related macular degeneration. Tight integration of the pigmented microvilli of the RPE with outer segments of photoreceptors allows efficient heating of the outer segments. Such thermal stress might stimulate HSP expression in photoreceptors, helping to reduce aggregation of misfolded proteins that occurs in neurodegenerative diseases. Availability of the EpM software for PASCAL lasers on the market enables immediate testing of the nondamaging photothermal therapy for various macular disorders.

Key words: retinal laser therapy, retinal photocoagulation, photothermal stimulation, central serous retinopathy.

Acknowledgments

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