Functionally Guided Retinal Protective Therapy for Dry Age-Related Macular and Inherited Retinal Degenerations: A Pilot Study

Jeffrey K. Luttrull1–3 and Benjamin W. L. Margolis2–4

1Private Practice, Ventura, California, United States
2Ojai Retinal Technologies, LLC, Ojai, California, United States
3EyEngineering, Inc., Ojai, California, United States
4Santa Clara University, Dynamics and Control Systems Laboratory, Santa Clara, California, United States

PURPOSE. To review the results of retinal function testing in eyes undergoing panmacular subthreshold diode micropulse laser (SDM) prophylaxis for chronic progressive retinal disease.

METHODS. The records of all patients undergoing prophylactic panmacular SDM for high-risk age-related macular degeneration (AMD) and inherited photoreceptor degenerations (IRDs) examined by pattern electroretinography (PERG), automated microperimetry (AMP), and Central Vision Analyzer (CVA) testing before and after treatment were reviewed.

RESULTS. A total of 158 consecutive eyes of 108 patients with AMD and 10 consecutive eyes of 8 patients with IRDs, evaluated both before and after SDM by PERG, were eligible for study. The IRD diagnoses included rod–cone degeneration (four eyes), cone–rod degeneration (three eyes), and Stargardt’s disease (three eyes). In AMD, AMP was performed in 40 consecutive eyes, and CVA in the subsequent 73 consecutive eyes concurrent with PERG. The SDM treatment consisted of 1800 to 3000 confluent spots throughout the retina circumscribed by the major vascular arcades, including the fovea (“panmacular”). Testing was performed 1 week before and by 1 month after treatment. Results indicated that 149/168 eyes were improved by primary PERG measures: 139/158 eyes with AMD by PERG low-contrast scan Magnitude D (MagD)(µV)/Magnitude (Mag)(µV) ratios (P = 0.0001) and 10/10 eyes with IRDs by 24° concentric ring scan MagD(µV)/Mag(µV) ratios (P = 0.002). Snellen visual acuity (VA) was unchanged, but macular sensitivity by AMP (P = 0.0439) and mesopic contrast VA by CVA (P = 0.006) were improved. There were no adverse treatment effects.

CONCLUSIONS. Our findings suggest a role for SDM as retinal protective therapy in chronic progressive retinal diseases. Pattern electroretinography enables (early, preventive) functionally guided, rather than (late, therapeutic) image-guided, disease management.

Keywords: laser, macula, pattern electroretinogram, microperimetry, age-related macular degeneration, retinitis pigmentosa, prophylaxis, retinal protection, retinal function testing, functionally guided disease management, prevention, central vision analyzer, contrast sensitivity

The complications of chronic progressive retinal diseases, such as diabetic retinopathy (DR) and age-related macular degeneration (AMD), constitute major causes of visual loss worldwide. Currently, retinal imaging and visual acuity (VA) testing guide management. As end-organ structural damage and vision loss are late disease manifestations, treatment instituted at this point must be intensive, often prolonged and expensive, frequently failing to improve VA, and rarely restoring normal vision.

Subthreshold diode micropulse laser (SDM) has been shown to be effective treatment for a number of retinal disorders without adverse treatment effects. By virtue of its safety and effectiveness, SDM has been proposed as preventive treatment for DR. Recently, the “Reset to Default” hypothesis for SDM action has been proposed. Reset Theory suggests SDM might protect the retina and slow progression of many chronic progressive retinal diseases. On the basis of morphologic data suggesting slowing of AMD progression following SDM (Luttrull JK, unpublished data, 2012), 15 years of clinical experience with SDM, the concepts of Reset Theory, and the absence of adverse treatment effects, SDM was offered in a retinal practice (JKL) as prophylaxis/retinal protection for high-risk AMD and inherited retinal degenerations (IRDs). Herein we report the results of retinal and visual function testing in a group of patients evaluated before and after SDM prophylaxis by pattern electroretinography (PERG), automated microperimetry (AMP), and Central Vision Analyzer (CVA) testing.

METHODS

This study adhered to the tenets of the Declaration of Helsinki and was approved by an investigational review board (Western IRB). The records of all patients in a retina subspecialty practice...
who were receiving SDM prophylaxis for high-risk AMD (defined by the presence of multiple large, diffuse, or bilateral macular drusen; macular pigment disturbance; extrafoveal or subfoveal geographic pigmentation atrophy; and/or choroidal neovascularization in the fellow eye) and IRDs, tested by PERG before and after SDM, were reviewed. In many eyes with AMD, additional visual function testing using CVA and AMP was done as well. Exclusionary criteria included other obfuscating ocular disease including epiretinal membrane or prior membrane peeling; DR; macular edema (except in retinitis pigmentosa); current or prior macular retinal vascular occlusion; prior macular choroidal neovascular membrane (CNVM); optic atrophy or advanced glaucomatous nerve damage; poor PERG test quality and/or reliability indicated by poor electrical conductivity or excessive (five or more) testing artifacts; subfoveal CNVM in the treated eye; active CNVM in the fellow eye requiring anti-VEGF treatment within 1 month before SDM treatment, or between the time of SDM treatment and postoperative testing; and loss to follow-up before postoperative testing. Testing was performed within 1 week before SDM treatment, and within 1 month after treatment. As the setting for this pilot study was a solo private clinical retinal practice, the choice of testing modalities used reflected available technology, not necessarily ideal technology.

**Pattern Electoretinography Testing**

Pattern electoretinography was performed by using standard protocols of a commercially available system (Diopsys Nova-ERG; Diopsys Corp., Pine Brook, NJ, USA) according to International Society for Clinical Electrophysiology of Vision standards. Both eyes were tested simultaneously and recorded individually, undilated, and refracted for a 60-cm testing distance. For all visual stimuli, a luminance pattern occupying a 25° visual field was presented with a luminance reversal rate of 15 Hz.

For IRDs, a PERG “concentric ring” visual stimulus optimized for analyzing peripheral retinal sensitivity was used, presenting with a circle of 1 luminance and an outer ring with the contrasting luminance. The concentric ring stimulus used two subclasses of stimuli with an inner circle occupying a visual field of 16° and 24°. The concentric ring stimuli used a mean luminance of 117.6 cd/m² with a contrast of 100%.

For AMD, in addition to the CR scans, contrast sensitivity (CS) stimuli were used, presenting a “checkerboard” like-grid of 64 × 64 cells, alternating luminance levels, recording a high-contrast (HC) test with a mean luminance of 122 cd/m² and a contrast of 85%, and a low-contrast (LC) test with a mean luminance of 106.4 cd/m² and a contrast of 75%.

Patient and equipment preparation were carried out according to Diopsys guidelines. Signal acquisition and analysis followed a standard glaucoma screening protocol. Test indices available for analysis included “Magnitude D” (MagD[µV]), “Magnitude (µV)” (Mag[µV]), and the “MagD[µV]/Mag[µV]” ratio. Magnitude D is the frequency response of the time-domain–averaged signal in microvolts (µV). Inner retinal and/or ganglion cell dysfunction cause signal latencies resulting in magnitude and phase variability that reduce MagD[µV] by phase cancelation. Magnitude (µV) measures the frequency response of the total signal in microvolts (µV). Magnitude (µV) reflects the signal strength and electrode impedance of the individual test sessions, as well as a gross measure of inner retina and ganglion function. The MagD[µV]/Mag[µV] ratio thus provides a measure of patient response normalized to that particular test’s electrical quality. In the healthy eye, MagD[µV] should roughly equal Mag[µV]. Thus, the closer MagD[µV]/Mag[µV] is to unity, the more normal the macular function.

**Automated Microperimetry Testing**

Automated microperimetry (MAIA; Centervue, Inc., Fremont, CA, USA) testing was performed according to manufacturer recommendations. Following pupillary dilation, the patient was seated at the MAIA instrument with the head positioned and aligned to the testing screen. The patient was asked to maintain fixation on the fixation target and to signal notice of light points appearing on the instrument screen, projected at various thresholds and locations within the macular region, by depressing a hand-held button. Data thus recorded included percentage-reduced thresholds, average threshold, and percent initial and final fixation preferences (P1 and P2).

**Central Vision Analyzer Testing**

Central Vision Analyzer was performed in accordance with manufacturer guidelines (Visoptics, Mechanicsberg, PA, USA). The CVA is an FDA-approved measure of visual acuity. A thresholding algorithm is used to dynamically determine logMAR central VA at six different levels of contrast under mesopic testing conditions, ranging from 99% to 35%, and simulating real-world visual demands, using an interactive computer interface. Each eye was tested undilated and best corrected.

**Subthreshold Diode Micropulse Laser Treatment**

Following informed consent and pupillary dilation, topical proparacaine was applied to the cornea. A Mainster macular contact lens (magnification factor ×1.05; Ocular Instruments, Mentor, OH, USA) was placed on the cornea with the aid of viscoelastic. Under minimum slit-lamp illumination, the entire posterior retina circumscribed by the major vascular arcades was “painted” with 1800 to 3000 confluent spot applications of SDM (“panmacular” treatment). The laser parameters used were 810-nm wavelength, 200-μm aerial spot size, 5% duty cycle; and 1.4-W power and 0.15-second duration (Oculight SLx; Iris Medical/Iridex Corp., Mountain View, CA, USA).

**Statistical Analysis**

All data was de-identified before statistical analysis. All analyses were performed by using linear mixed models predicting the measure, with an indicator for time as a covariate, adjusting for left or right eye, and including a random patient intercept to correct for possible intereye correlation. Finally, univariate linear mixed models, predicting the difference (post-minus pretreatment) with pretreatment value as covariate, were performed. The coefficients and P values from six such models were compared.

**Definitions**

In the following, “macular function” and “retinal function” refer to the physiology and electrophysiology of the retina. In contrast, “visual function” is used to refer to measurements such as VA, visual fields, and CS.

**RESULTS**

In all, 220 eyes of 166 patients undergoing panmacular SDM prophylaxis for high-risk AMD and IRDs, between June 2012 and August 2015, were identified. These included 210 eyes of 158 patients treated for AMD; and 10 eyes of 8 patients treated for IRDs. Of these, 158 consecutive eyes of 108 patients with AMD, and 10 consecutive eyes of 8 patients with IRDs were evaluated before and after SDM by PERG and thus eligible for
TABLE 1. Comparison of Various Measured Values (Post- Minus Pretreatment), PERG Contrast Sensitivity Test Eyes, for High-Risk AMD in Response to Pannuscular SDM Laser Retinal Protective Therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MagD((\mu V))/Mag((\mu V)) ratio, high contrast</td>
<td>0.05 (0.19)</td>
<td>0.04 (−0.07, 0.17)</td>
<td>0.09</td>
</tr>
<tr>
<td>MagD((\mu V))/Mag((\mu V)) ratio, low contrast</td>
<td>0.08 (0.17)</td>
<td>0.08 (0.00, 0.17)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mag((\mu V)) measure, high contrast</td>
<td>0.05 (0.32)</td>
<td>0.05 (−0.17, 0.26)</td>
<td>0.37</td>
</tr>
<tr>
<td>Mag((\mu V)) measure, low contrast</td>
<td>0.08 (0.25)</td>
<td>0.07 (−0.06, 0.21)</td>
<td>0.02</td>
</tr>
<tr>
<td>Mag((V)) measure, high contrast</td>
<td>−0.04 (0.54)</td>
<td>−0.04 (−0.23, 0.14)</td>
<td>0.42</td>
</tr>
<tr>
<td>Mag((V)) measure, low contrast</td>
<td>−0.03 (0.35)</td>
<td>0.01 (−0.19, 0.17)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

The table shows the comparisons of interest for the PERG contrast sensitivity test data set. Each row shows the difference (post minus pretreatment) in MagD(\(\mu V\))/Mag(\(\mu V\)) ratio, Mag(\(\mu V\)) measure, or Mag(\(V\)) measure at the two contrast options. To test whether the mean difference is different from zero, linear mixed models predicting the measure were used, with an indicator for time as a covariate, also adjusting for intereye correlations. IQR, interquartile range.

Discussion

Any treatment that improves retinal function, and thus health, should also reduce disease severity, progression, untoward events, and visual loss. In this study, we found that pannuscular SDM improved retinal and visual function in dry AMD and IRDs without adverse treatment effects.

Recently, the mechanism of retinal laser treatment has been proposed and its clinical behavior described in "Reset to Default Theory." We believe the results of this study are supportive of Reset Theory. Fundamental to Reset Theory are certain predictions. First, SDM treatment should produce prompt improvement in retinal function. Second, SDM treatment should be without any adverse effect by any measure. Third, SDM treatment should produce disease-specific benefits in a wide variety of disorders, including most, if not all, chronic progressive retinal disorders, regardless of etiology. Fourth, SDM treatment should be "pathoselective," improving dysfunctional tissue while having negligible effect on normal tissue. Thus, the more dysfunction present, the more measured improvement anticipated after treatment. Fifth, SDM treatment-induced improvements in retinal function, or "retinal protection," might wear off, needing periodic retreatments to maintain maximum clinical benefits. Our study did not address the final prediction. However, we found that PERG may be useful for monitoring retinal function and preventive treatment responses, and it can be complemented by AMP and CVA testing. Regarding the first four claims, our findings support Reset Theory. Because there are few similarities between AMD and various IRDs, we report both to examine Reset Theory’s prediction of SDM as a nonspecific trigger of disease-specific retinal repair. Reset Theory predicts both the positive treatment response across these different diagnoses, as well as the distinctive PERG responses observed in this study.

Pattern electroretinography was introduced in 1964 by Riggs and associates. Unlike ganzfeld and focal electroretinography (ERG) that use flash stimuli to measure photoreceptor function, PERG uses projected temporally and spatially alternating patterned stimuli of constant illumination to generate a neuroretinal electrophysiologic response that is either a series of transient responses at slow reversal rates (<5 Hz), or a periodic steady-state response at faster reversal rates (>5 Hz). Originally thought to be simply an alternate form of ERG, PERG was recognized in the 1980s to arise from different sources, principally the inner retina and ganglion cell layer. Pattern electroretinography has since been shown to be an objective, sensitive, and highly reproducible indicator of both macular and ganglion cell function. Performed in a single
center by experienced personnel, PERG has been shown to be reliable and highly repeatable.\textsuperscript{18–25} As ours was a clinic-based pilot study, the diagnostic technologies we used are not necessarily ideal, but simply the technologies available to us. Of these, we found PERG the most informative. In the absence of optic nerve disease, PERG responses reflect macular function, measured at the inner retina and ganglion cell layer and reflecting input from the outer retina.\textsuperscript{18–25} Pattern electroretinography is a sensitive test that can be difficult to perform well.\textsuperscript{20} However, as noted above (Odom et al.\textsuperscript{20}), we also found that PERG done in a single location on the same machine by the same technician with the same technique can provide useful and consistent information.\textsuperscript{20,21}

As one of the earliest detectors of ganglion cell dysfunction, PERG is a sensitive predictor of glaucoma and progression, anticipating visual field loss by years, and improves following

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{infrared_and Autofluorescence}
\caption{Infrared (left) and fundus autofluorescence photographs (right) of right eye (top) and left eye (bottom) of a patient with AMD and geographic pigmentary atrophy 3 months after panmacular SDM treatment. Visual acuity of right eye before and after treatment, 20/100. Visual acuity of left eye before treatment, 20/70; after treatment, 20/50. Note absence of retinal laser lesions.}
\end{figure}
normalization of intraocular pressure. As a measure of macular function, PERG is reduced by AMD and other maculopathies and responsive to therapies for neovascular AMD. However, the result of any testing method will vary in a particular patient over time, even in the absence of clinical change. At times, such variability may make interpretation of test results difficult or even misleading. This is also true for PERG, but less so than for tests requiring higher levels of patient cooperation, such as visual field testing. Thus, it may be difficult to make a judgment on a particular patient, on a particular day, based on a single test result, particularly in a novel test application. Constrained by economic considerations and patient fatigue, serial testing in clinical practice for result averaging is impractical. Thus, it is reassuring that the SDM treatment effects, detected most sensitively by PERG, were consistent, robust, highly significant, and appear to be sustained for at least 6 months postoperatively in most patients. We expect that prospective trials will reveal the duration of the typical treatment response and indicate the ideal times to consider retreatment in order to maintain the maximum treatment benefits, reducing reliance on individual episodic testing results.

Of note is that many treated AMD eyes, and both eyes with Stargardt’s disease, had extensive macular geographic atrophy included in confluent panmacular SDM treatment (Fig. 1). These eyes had the poorest preoperative testing responses. However, linear regression analysis showed that these eyes also had the greatest improvements after treatment, by all measures. While a discussion of the implications of this observation is beyond the scope of this article, it is clear that

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MagD(μV)/Mag(μV) ratio, 24°</td>
<td>0.02 (0.21)</td>
<td>0.01 (−0.09, 0.12)</td>
<td>0.44</td>
</tr>
<tr>
<td>MagD(μV)/Mag(μV) ratio, 16°</td>
<td>0.05 (0.22)</td>
<td>0.07 (−0.10, 0.20)</td>
<td>0.07</td>
</tr>
<tr>
<td>Mag(μV) measure, 24°</td>
<td>0.04 (0.38)</td>
<td>0.02 (−0.20, 0.25)</td>
<td>0.52</td>
</tr>
<tr>
<td>Mag(μV) measure, 16°</td>
<td>0.04 (0.26)</td>
<td>0.05 (−0.15, 0.21)</td>
<td>0.27</td>
</tr>
<tr>
<td>Mag(μV) measure, 24°</td>
<td>0.01 (0.36)</td>
<td>0.00 (−0.18, 0.20)</td>
<td>0.86</td>
</tr>
<tr>
<td>Mag(μV) measure, 16°</td>
<td>−0.04 (0.36)</td>
<td>−0.03 (−0.21, 0.15)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

The table shows the comparisons of interest for the PERG concentric ring test data set. Each row shows the difference (first post- minus pretreatment) in MagD(μV)/Mag(μV) ratio, MagD(μV) measure, or Mag(μV) measure at 24° and 16°. To test whether the mean difference is different from zero, linear mixed models predicting the measure were used, with an indicator for time as a covariate, also adjusting for left or right eye. The P values are those associated with the time (pre versus post) regression coefficient. A significant P value indicates that the mean difference is significantly different from zero. The table shows that all comparisons are not statistically significant. This method accounts for intereye correlation.
functional tissue responsive to therapy remains within areas of geographic atrophy (Figs. 1, 2, 6; Table 6).

Paralleling the PERG responses, we found that VA measured by CVA testing significantly improved in AMD eyes, along with macular sensitivity measured by AMP. Improvements in visual function captured by AMP and CVA are important, indicating a benefit from SDM treatment in the overall quality of visual function that is not revealed by conventional chart VA testing. As loss of CS is the earliest visual abnormality in AMD, and thus a sensitive indicator of disease, it is notable that the improvements in dry AMD following SDM were reflected most by measures of CS. The SDM-elicited improvements in visual function, particularly measured by CVA testing under mesopic conditions, suggest a practical benefit for patients with dry
A summary of calculated difference (post- minus pretreatment) for eyes with age-related and inherited retinal degenerations treated with panmacular SDM retinal protective therapy, AMP eyes accounting for possible intereye correlation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced threshold (Nmiss = 8)</td>
<td>2.72 (16.98)</td>
<td>0.00 (−6.75, 6.75)</td>
<td>0.8487</td>
</tr>
<tr>
<td>Average threshold</td>
<td>11.12 (28.02)</td>
<td>0.35 (−0.85, 2.65)</td>
<td>0.0439</td>
</tr>
<tr>
<td>P1</td>
<td>−4.85 (33.30)</td>
<td>0.50 (−12.00, 7.50)</td>
<td>0.4664</td>
</tr>
<tr>
<td>P2</td>
<td>−0.08 (21.04)</td>
<td>0.00 (−5.50, 5.00)</td>
<td>0.9049</td>
</tr>
</tbody>
</table>

The table shows the comparisons of interest for the AMP data set. Each row shows the difference (follow-up minus preoperation) in reduced and average threshold as well as P1 and P2. To test whether the mean difference is different from zero, linear mixed models predicting the measure were used, with an indicator for time (preoperative versus follow-up) as a covariate, also adjusting for left or right eye. The P values are those associated with the time (preoperative versus follow-up) regression coefficient. A significant P value indicates that the mean difference is significantly different from zero. Only average threshold is significantly different preoperatively versus follow-up. Nmiss, number of missing data points for the reduced threshold measure; P1, initial fixation preference; P2, final fixation preference.

AMD, who often note difficulty reading and functioning in low-light and low-contrast settings, common activities of daily living.26–29

Identifying a benefit from prophylactic treatment of chronic progressive retinal diseases morphologically is inherently problematic. Abnormal retinal (physiologic) function precedes anatomic derangement and loss of visual function. It is initially asymptomatic and associated with normal retinal imaging. Abnormal visual function, by contrast, is generally symptomatic, resulting from anatomic derangements such as loss of photoreceptors, or the development of macular edema. Thus, reflecting advanced disease and end-organ damage detectable by retinal imaging, visual loss may be difficult to treat and is often irreversible. Likewise, retinal degeneration in chronic disease usually develops slowly, often over decades of retinal dysfunction, making morphologic detection of preventive treatment effects difficult, and then only after the fact. As current retinal disease management is predicated on the results of retinal imaging, treatment is necessarily offered late in the disease process. Treatment of advanced disease is most difficult and least rewarding, needing to be more potent, intensive, prolonged, usually more expensive, and still unlikely to restore normal VA. Interventions before visual loss and abnormalities detectable by retinal imaging thus offer the best prospect for preservation of normal visual function. Therefore, preventive treatments must necessarily be guided by retinal function testing rather than retinal imaging or VA testing. We call this “functionally guided (disease) management” (FGM). By allowing early diagnosis and disease monitoring before the onset of retinal anatomic changes, we expect FGM to improve visual outcomes when compared to current practices.

High-density/low-intensity SDM was developed in 2000 and first reported in 2005 as effective treatment for diabetic macular edema without laser-induced retinal damage.4 Subthreshold diode micropulse laser applies sublethal thermal laser stimulation selectively to the RPE and has been reported to be effective for a number of retinal disorders without adverse treatment effects. In addition to DME, these include severe nonproliferative and proliferative DR, branch retinal vein occlusion, and central serous chorioretinopathy.10–12 Unlike conventional photocoagulation for DME, SDM improves macular sensitivity by AMPE.27 Based on these observations, the “Reset to Default Theory” of SDM action was proposed to
describe the clinical behavior of SDM. Reset Theory suggests RPE heat-shock protein (HSP) activation as the principal therapeutic mechanism of SDM and all other forms of retinal laser treatment (other than cautery). By triggering HSP-mediated RPE repair, RPE function, and thus health, is improved, leading to normalization of RPE cytokine expression and retinal autoregulation. Although HSP activation has long been theorized as one possible mechanism of retinal laser treatment, Reset Theory suggests the primacy of this pathway (via SDM’s elimination of prior models, which theorized benefits from retinal photocoagulation) and provides a framework for understanding the resultant clinical implications arising from this mechanism. The power of any theory rests in its ability to predict. Reset Theory has successfully predicted the unprecedented observation that SDM could reverse drug tolerance in neovascular AMD. Reset Theory also predicted the treatment responses in dry AMD and IRDs we report here.
TABLE 5. Summary of Calculated Difference (Post- Minus Pretreatment), Visual Acuity on LogMAR Scale Measured by the Central Visual Acuity Analyzer in Eyes With Age-Related and Inherited Retinal Degenerations Treated With Panmacular SDM Retinal Protective Therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>99% Contrast</td>
<td>73</td>
<td>-0.146 (0.511)</td>
<td>-0.073 (-0.356, 0.114)</td>
<td>0.02</td>
</tr>
<tr>
<td>75% Contrast</td>
<td>73</td>
<td>-0.148 (0.488)</td>
<td>-0.058 (-0.301, 0.107)</td>
<td>0.01</td>
</tr>
<tr>
<td>65% Contrast</td>
<td>73</td>
<td>-0.151 (0.458)</td>
<td>-0.109 (-0.301, 0.067)</td>
<td>0.006</td>
</tr>
<tr>
<td>53% Contrast</td>
<td>73</td>
<td>-0.107 (0.444)</td>
<td>-0.032 (-0.248, 0.097)</td>
<td>0.049</td>
</tr>
<tr>
<td>45% Contrast</td>
<td>73</td>
<td>-0.103 (0.370)</td>
<td>0.000 (-0.250, 0.058)</td>
<td>0.02</td>
</tr>
<tr>
<td>35% Contrast</td>
<td>73</td>
<td>-0.104 (0.416)</td>
<td>-0.044 (-0.248, 0.105)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

The table shows the difference (post- minus pretreatment) in logMAR visual acuity at six levels of contrast measured under mesopic testing conditions. To test whether the mean difference is different from zero, linear mixed models predicting the visual acuity were used, with an indicator for time as a covariate, also adjusting for left or right eye. The table shows significant improvement at all contrast levels. This method accounts for intereye correlation.

FIGURE 6. Scatterplots of the linear regression analysis of the dry AMD PERG MagD(μV)/Mag(μV) (top) and MagD(μV) (bottom) ratios. Note the negative slope, statistically significant in each, indicating that the worse the preoperative value, the greater the degree of postoperative improvement.
In principle, improved retinal function and health, if maintained, should produce long-term benefits, reducing both the rate of disease progression and incidence of adverse events. Our findings support the Reset Theory suggestion that, as a nonspecific stimulus of disease-specific retinal repair, SDM may produce salutary effects in a number of unrelated chronic progressive retinopathies. Further study is needed to confirm our findings and will reveal whether such effects, which may be thought of as “homeotrophic” as they normalize tissue function, will lead to long-term clinical benefits in AMD and IRDs. Longer experience with SDM for complications of DR is encouraging in this regard5,8–10,12 (Fig. 7).

Primary immutable disease factors such as age, diabetes mellitus, or inherited genetic defects are not amenable to HSP-mediated retinal repair. However, it is interesting to note that the presence of such abnormalities alone is generally insufficient to cause visual loss, as patients with chronic progressive retinopathies may enjoy normal or near-normal visual function for decades before developing clinical retinopathy and experiencing visual loss. This suggests that it may be secondary abnormalities, caused by the immutable defect, accumulating over time both “upstream” and “downstream” from the primary defect, that cause the cell death and anatomic derangement that result in visual loss. These secondary abnormalities are the ones most amenable to SDM-stimulated HSP-mediated repair.5,9–12,10,11 By mitigating the effects of such secondary defects, retinal degeneration and visual loss might thus be delayed if not prevented. Only controlled long-term studies can determine if SDM retinal protective therapy will be helpful in this regard. However, before long-term treatment benefits can be hoped for, early improvements, such as those we reported here in dry AMD and IRDs, must be achieved.

This study had limitations common to pilot studies. It reported a small group of patients from a single center receiving a novel treatment assessed in a novel way. The data were obtained by retrospective review of medical records developed in the course of clinical patient care, rather than through a controlled prospective experimental protocol. However, while the data were limited and imperfect, they are not uninformative or unimportant.31 The primary outcome measure derives from a well-known, objective, and reproducible measure of macular function, PERG, and is echoed by measures of visual function including AMP and CVA. Consistent with 15 years of clinical experience and prior reports, we reported here in dry AMD and IRDs, must be achieved.

The table shows the post minus pretreatment differences of various measures among the PERG contrast sensitivity testing of eyes with dry age-related macular degeneration. Paired t-tests were performed to determine whether each measure differed significantly pre treatment versus post treatment. MagD(μV)/Mag(μV) ratio, high and low contrast, were both significantly (P = 0.03 and P < 0.0001, respectively) higher, on average, post treatment. MagD(μV), low contrast, was also significantly (P = 0.006) higher post treatment.

* Paired t-tests.

FIGURE 7. Intravenous fundus fluorescein angiograms of eye with severe nonproliferative diabetic retinopathy before (left) and after (right) panretinal SDM. Note decreased micro- and macrovascular leakage, with reperfusion of local ischemia.
those without. These results may provide initial benchmarks. Further research is warranted.

**Acknowledgments**

The authors thank Taylor Blachley, MS, and David C. Musch, PhD, MPH, of the Department of Biostatistics, University of Michigan Medical School, for their assistance in the statistical analysis of study data; and Stephen H. Sinclair, MD, for his editorial assistance. The authors alone are responsible for the content and writing of the paper.

Disclosure: J.K. Luttrull, None; B.W.L. Margolis, None

**References**