Randomized Clinical Trial to Compare Micropulse Photocoagulation Versus Half-dose Verteporfin Photodynamic Therapy in the Treatment of Central Serous Chorioretinopathy

Florian T.A. Kretz, MD; Isabell Beger, MD; Frank Koch, MD; Katarrzyna Nowomiejska, PhD; Gerd U. Auffarth, MD; Michael J. Koss, MD

BACKGROUND AND OBJECTIVE: To evaluate sub-threshold diode-laser micropulse (SDM) versus half-dose verteporfin photodynamic therapy (hd-PDT) in central serous chorioretinopathy (CSC).

PATIENTS AND METHODS: 62 eyes of 62 patients were prospectively followed for changes in fluorescein angiography (FA), fundus autofluorescence (FAF), central macular thickness (CMT), best-corrected visual acuity (BCVA), and contrast visual acuity (CVA) after SDM (n = 20) or hdPDT (n = 24). CSC observation served as control group (n = 18).

RESULTS: Both treatment groups (60% SDM vs. 66.7% hdPDT) showed significant improvement in reduction of leakage activity compared to the control group (37.5%) at 16 weeks. CMT decreased by 69.7 µm (SDM), 109.8 µm (hdPDT), and 89 µm (control). BCVA improved by +6.7 (SDM group), +8.5 (hdPDT), and +1.5 ETDRS letters (control). CVA was best improved in the hdPDT group. No secondary RPE alterations could be detected by FAF after any intervention.

CONCLUSION: In comparison to the control group, hdPDT and SDM resulted in reduced leakage activity in FA and enhanced photopic and scotopic visual acuity in patients with CSC.


INTRODUCTION

Central serous chorioretinopathy (CSC) is an idiopathic disorder characterized by neuroepithelial serous detachment at the level of the retinal pigment epithelium (RPE). This is likely to be preceded by abnormal choroidal circulation.

We previously demonstrated that non-thermal subthreshold diode-laser micropulse (SDM) photocoagulation, with no visible burn endpoint and no discernable postoperative collateral damage, is superior to intravitreal injections of 1.25 mg bevacizumab (Avastin; Genentech, San Francisco, CA). The micropulse technique allows finer control of the photothermal effects at the RPE level.

In recent years, photodynamic therapy (PDT) with verteporfin (Visudyne; Novartis AG, Basel, Switzerland) has been used to treat CSC by counteracting the associated choroidal hyperperfusion with localized thrombosis and vasoconstriction. Several studies using a reduced dose of verteporfin have demonstrated convincing functional results in subretinal fluid resorption, as well as functional improvement in vision and microperimetry, especially for those studies using the half-dose verteporfin protocol (hdPDT).

To the best of our knowledge, this study represents the first comparative, prospective evaluation of SMD and hdPDT in the treatment of CSC with regard to visual outcome (central visual acuity and contrast vision), changes in subretinal fluid, and RPE in autofluorescence (FAF).
PATIENTS AND METHODS

Sixty-two eyes of 62 patients (50 men, 12 women) were included in this study during the period from September 2010 to October 2014. The eligibility criteria were a diagnosis of nonresorbing CSC, no more than two active leakage sites (ALS) on FA, and subretinal fluid that had been present for more than 3 months, as assessed by optical coherence tomography (OCT). Exclusion criteria included current use of exogenous corticosteroids (oral, topical, intranasal, or intravenous) in the previous 6 months, diabetic retinopathy, uveitis, any hereditary retinal/macular disease, or any history of intraocular surgery.

Ophthalmic examination at baseline and at 8 and 16 weeks after treatment included slit-lamp biomicroscopy, indirect ophthalmoscopy, measurement of intraocular pressure (IOP), ETDRS best-corrected visual acuity (BCVA), Amsler grid screening, contrast visual acuity (CVA), and central macular thickness (CMT), with OCT, FA, and FAF after initial treatment.

A computer-guided program, the Central Vision Analyser (Vimetrics, Media, PA), was used to analyze contrast vision. Six contrasts at different luminances were examined. For each contrast, the decimal visual acuity was calculated by the program.

The IOP was measured using Goldman applanation tonometry, and CMT at the foveola was assessed by OCT in the automated mode (retinal thickness map mode, Model 3D OCT-2000, Topcon, Germany). After the acquisition of the FAF image (Carl Zeiss GmbH, Jena, Germany), standard FA (FF450 plus camera, Carl Zeiss Meditec, Jena, Germany) was performed with 2.5 cc of 10% fluorescein (Alcon Pharma GmbH, Freiburg, Germany). The images were then processed with a medical software system (Merge Eye Station, version 11; Jena, Germany) to identify changes in FA leakage and RPE. To determine possible harmful effects, such as therapy-induced RPE changes or atrophy caused by SDM or hdPDT, hyper- and hypoFAF areas were measured and compared using an image analysis software (WebViewer and PerfectView; CCS Pawlowski GmbH, Jena, Germany) at baseline and 16 weeks after initial treatment.

The same protocol was repeated at each follow-up visit. The quantitative assessment of leakage, hyper- and hypo-FAF areas, and changes in CMT were performed by a certified masked medical photographer (FL) and a masked retina specialist (FHK).

Written informed consent was obtained from each patient, adhering to good clinical practice regulations and the tenets of the declaration of Helsinki.

Patients were randomized by using a set of sealed

### Table 1

<table>
<thead>
<tr>
<th>Demographics and Baseline Characteristics of Patients With Central Serous Chorioretinopathy</th>
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<tbody>
<tr>
<td>Group (no. of patients)</td>
</tr>
<tr>
<td>Sex: M/F</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
</tr>
<tr>
<td>Eyes: R / L</td>
</tr>
<tr>
<td>Nicotine</td>
</tr>
<tr>
<td>Pack years</td>
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<tr>
<td>Duration of symptoms: Presumed duration of CSC in months</td>
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<tr>
<td>Mental stress</td>
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<tr>
<td>Prior steroid use</td>
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</tbody>
</table>

SDM = subthreshold diode-laser micropulse; hdPDT = half-dose verteporfin photodynamic therapy; CSC = central serous chorioretinopathy

Numbers are depicted as mean values ± standard deviation.

P values of the duration of symptoms between the groups (Mann-Whitney test):

- Group 1 vs. Group 2: P = .65
- Group 2 vs. Group 3: P = .03
- Group 1 vs. Group 3: P = .22
envelopes. Each letter contained one treatment option. Patients were asked to choose one envelope with the randomized study group assignment.

All patients in the SDM group received SDM photocoagulation treatment, performed with an 810 nm infrared diode laser (OcuLight SLx; IRIDEX Corp., Mountain View, CA) delivered through the Area Centralis 0.94x laser lens (Volk Optical, Mentor, OH). The laser was set in the micropulse emission mode and the laser power was adjusted to 1,000 mW with a duration of 300 msec and a 15% duty cycle. The spot size was set at 75 µm to 125 µm and applied on the active leakage site as described by Dorin G.5

In the hdPDT group, a half dose (3 mg/m²) of verteporfin was given as an intravenous injection over 10 minutes (180 mL/h).

After undergoing mydriasis and local anesthesia, each patient in the hdPDT group was treated, using the Area Centralis 0.94x laser lens and FA to guide the treatment over the full extent of the RPE leakage. Beginning 15 minutes after the start of the infusion, the leakage points were irradiated using a 689 nm laser (COHERENT Opal Photoactivator) over 83 seconds with a fluence of 50 J/cm² (irradiance: 600 mW/cm²).

Retreatment with either SDM photocoagulation or hdPDT was allowed at the discretion of the principal investigator (MJK) in the case of persistent, equal, or increased leakage activity with the presence of equal or greater subretinal fluid compared to baseline. After the last follow-up visit at 16 weeks, all patients were granted access to either treatment, regardless of their treatment group.

Statistical analyses were performed using Excel (Microsoft, Richmond, WA) and BiAS software (Version 8.2 for Windows, Epsilon-Verlag, Darmstadt, Germany). Distribution of the data was analyzed using the David’s test, whereas longitudinal changes were tested with Wilcoxon matched-pairs test within each group and the Mann-Whitney test for differences between the three groups.

**RESULTS**

Patient demographics and baseline characteristics are summarized in Table 1.

We detected significant differences in the pretreatment duration of symptoms between groups 2 and 3 ($P = .03$ only. All other baseline characteristics were comparable between the groups. During the study, no patient was using any oral, topical, inhaled, or injected corticosteroids. Two patients (3.2%) in the control group dropped out of the study without explanation at the 8-week visit.

Eyes in the SDM group received an average of 101 shots with an average power of 1,494 mW. Ten patients (50%) at 8 weeks after baseline and four patients at study end required a second treatment. Two patients received three treatments over the 16-week follow-up because of non-resolving FA and OCT-documented active RPE leakage. No tissue reactions (ie, tissue heating) were observed at any point during the micropulse laser treatment.

After the initial hdPDT session, two patients received a second hdPDT treatment at 8 weeks, and four received another at 16 weeks because of persistent or increasing subretinal fluid on FA and OCT.

The changes in CMT, BCVA, and CVA are shown in

**TABLE 2**

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline (T0)</th>
<th>8 Weeks After Treatment (T1)</th>
<th>16 Weeks After Treatment (T2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (SDM; n = 20)</td>
<td>86.9 ± 14.3; 86.5 (76.8-100)</td>
<td>92.7 ± 12.0; 92.5 (82.8-104.8)</td>
<td>93.6 ± 10.9; 96 (84.8-101.8); §A</td>
</tr>
<tr>
<td>Group 2 (hdPDT; n = 24)</td>
<td>82.8 ± 11.5; 86.0 (75-91.5)</td>
<td>86.8 ± 13.9; 89.5 (71.8-98)</td>
<td>91.3 ± 13.8; 96 (87-98.8); §B</td>
</tr>
<tr>
<td>Group 3 (control; T0/T1: n = 18, T2: n = 16)</td>
<td>96.4 ± 8.8; 94 (90-105.5); 96 ± 10.0; 94 (88.5-107)</td>
<td>97.9 ± 10.7; 98 (87.5-108.8)</td>
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</tbody>
</table>

SDM = subthreshold diode-laser micropulse; hdPDT = half-dose verteporfin photodynamic therapy

Best-corrected visual acuity in mean values ± standard deviation. Median values with value range. All values in number of total letters read.

Significant differences within the groups (Wilcoxon matched-pairs test) are described as follows:

Group 1: §A T2 vs. T0: $P = .0078$; Group 2: §B T2 vs. T0: $P = .012$

Significant differences between the groups (Mann Whitney test) are described as:

$\partial$ Group 2 vs. Group 3: T0, $P = .019$
Tables 2 to 4, where significant comparisons are provided with appropriate P values.

Leakage on FA, suggesting as a sign of disease activity, improved significantly (P = .03) in the SDM group, with 12 patients (60%) showing no persistent leakage at the 16-week visit. In the hdPDT group, 16 patients (66.7%) had obtained significant improvement (P = .008) at the end of the study (Figure 1). In contrast, only six patients (33.3%) in the control group showed decreased leakage activity. Table 5 shows the hyper- and hypoFAF areas at baseline (T0) and 16 weeks (T2).

After therapy, no significant RPE changes could be detected in any group with FAF (Table 5). The comparisons T0 vs. T2 of the mean complete FAF area was in group 1 (0.23 ± 0.26 mm² vs. 0.25 ± 0.30 mm²; P = .86); in group 2 (0.46 ± 0.44 mm² vs. 0.43 ± 0.46 mm²; P = .51), and in group 3 (0.32 ± 0.34 mm² vs. 0.31 ± 0.3 mm²; P = .34). The comparisons T0 vs. T2 of the mean hyperFAF area was in group 1 (0.15 ± 0.19 mm² vs. 0.22 ± 0.28 mm²; P = .88); in group 2 (0.46 ± 0.44 mm² vs. 0.43 ± 0.46 mm²; P = .51), and in group 3 (0.32 ± 0.34 mm² vs. 0.31 ± 0.3 mm²; P = .34). The comparisons T0 vs. T2 of the mean hypoFAF area was in group 1 (0.09 ± 0.01 mm² vs. 0.10 ± 0.08 mm²; P = .90); in group 2 (0.09 ± 0.03 mm² vs. 0.08 ± 0.04 mm²; P = .54), and in group 3 (0.07 ± 0.04 mm² vs. 0.06 ± 0.03 mm²; P = .65).

Subjective Amsler grid evaluation in all groups revealed a diminution of metamorphopsia in 14 patients (70%) from the SDM group, 18 patients (75%) from the hdPDT group, and eight patients in the control group (44%). Persistent or worsened metamorphopsia was noticed in six SDM (30%) patients, six hdPDT patients (25%), and 10 (56%) control patients.

No ocular adverse events were observed. The recurrence rates were distributed similarly, with 20% in the SDM group and 16.6% in the hdPDT group. In the hdPDT group, two patients experienced a new leakage, whereas other patients had a recurrence of the original leakage points.

**DISCUSSION**

CSC is characterized by idiopathic serous detachment of the neurosensory retina.

The 16-week results of our study indicate superior

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**Table 3**

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<thead>
<tr>
<th>Group</th>
<th>Baseline (T0)</th>
<th>8 Weeks After Treatment (T1)</th>
<th>16 Weeks After Treatment (T2)</th>
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<tbody>
<tr>
<td>Group 1 (SDM; n = 20)</td>
<td>CMT; 273.9 ± 76.8; 260.5 (218.5 - 324.8)</td>
<td>CMT; 180.7 ± 62.8; 169 (130.3 - 221.5); ¥B</td>
<td>CMT; 204.2 ± 87.6; 195.5 (140.5 - 257.3); ¥A</td>
</tr>
<tr>
<td>Group 2 (hdPDT; n = 24)</td>
<td>CMT; 330.1 ± 131.3; 333.5 (198.3 - 459)</td>
<td>CMT; 205.6 ± 97.6; 164.5 (128.3 - 304.5); ¥D</td>
<td>CMT; 220.3 ± 120.1; 165 (154 - 255.5); ¥C</td>
</tr>
<tr>
<td>Group 3 (control; T0/T1: n = 18, T2: n = 16)</td>
<td>CMT; 325.5 ± 153.6; 402 (149 - 439)</td>
<td>CMT; 274.1 ± 132.6; 211 (171.5 - 378)</td>
<td>CMT; 236.5 ± 118.9; 188.5 (152.5 - 341.5); ¥E</td>
</tr>
</tbody>
</table>

SDM = subthreshold diode-laser micropulse; hdPDT = half dose verteporfin photodynamic therapy; CMT = central macular thickness.

Significant differences within the groups (Wilcoxon matched-pairs test) are described as follows:

Group 1: GMT - ¥A T2 vs. T0: P = .014; ¥B T1 vs. T0: P = .012
Group 2: GMT - ¥C T2 vs. T0: P = .05; ¥D T1 vs. T0: P = .034
Group 3 GMT - ¥E T2 vs. T0: P = .039

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**Figure 1.** Leakage activity measured with fluorescein angiography in patients with central serous chorioretinopathy before (T0) and after treatment (T1-2). Significant differences within the groups (Wilcoxon matched-pairs test): Group 1: T2 vs. T0: P = .03; Group 2: T1 vs. T0: P = .015; T2 vs. T0: P = .0078.
subretinal fluid resolution and a significant increase of VA at 8 weeks and at 16 weeks after either treatment compared to observation when looking at leakage on FA (Figure 1). The CMT decreased also significantly in the control group similar to the treatment groups (Table 3), but was still associated with 66.7% persistent leakage activity in FA, versus 40% in the SDM and 33.3% in the hdPDT group. This is reflected by the fact that VA and contrast VA (Tables 2 and 4) improved significantly in both treatment groups. Comparison between each group for VA was not significant, which could be an effect of the better VA in the control group at the screening visit.

Sixteen weeks after treatment, the eyes of the SDM group showed a reduction of leakage activity in 60% ($P = .03$), an increase of visual acuity by 6.7 letters ($P = .0078$), a decrease in macular thickness by 69.7 µm ($P = .014$), and a reduction of metamorphopsia by 20%.

Rather than addressing choroidal hyperperfusion, nonthermal and nondamaging SDM photocoagulation allows application of laser energy to subfoveal and extrafoveal lesion sites by stimulating a biological response in compromised RPE cells. This technique may induce the resolution of subretinal fluid by improving these cells’ tight junctions and pumping functions mediated by upregulation of metalloproteinase enzymes. One difficulty of SDM photocoagulation is finding the optimal laser dose and verifying the localization and the total amount of laser applications due to the absence of visible treatment endpoint. Because of the lack of visibility of a focal burn point associated with conventional laser photocoagulation, it is difficult to choose the energy level that is sufficient to stimulate the RPE cells for rehabilitation of the defect without causing thermal damage. In our study, however, therapeutic benefits were obtained without any observable intraoperative tissue reaction or collateral damage discernable at any time postoperatively. Using FAF, we can examine the distribution of fluorescent lipofuscin in RPE cells and, thus, damage as reduced FAF.11,12

In our study, FAF demonstrated no significant alterations in the size of hypo- or hyperFAF areas (Table 5). This supports the safety aspect of the dose-finding technique applied here. We speculate that a higher laser energy, a denser treatment with a higher number of confluent applications over the entire area of decompensated RPE cells, and repetition of treatment would likely lead to even better final results, but further studies of the optimal dosage of SDM are needed to determine its full safety potential. According to Yannuzzi et al., PDT treatment addresses directly the origin of subretinal fluid development in CSC, but collateral damage can include choroidal ischemia, RPE changes, secondary neovascularization, or PDT/laser-induced scotoma. In a direct comparison of hdPDT and standard PDT, Shin et al. showed minimal retinal damage with hdPDT but the same effectiveness. Others described a sufficient effect even when the verteporfin dose was reduced to 30% of the normal dose. However, the optimal PDT technique, in terms of dosage, laser activation time, fluence, indocyanine green angiography-guid-

### Table 4

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<tr>
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<th>Contrast Visual Acuity (M1–M3, G1–G3) in Mean Values ± Standard Deviation</th>
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<tbody>
<tr>
<td></td>
<td>M1</td>
</tr>
<tr>
<td>Group 1</td>
<td>0.57 ± 0.42</td>
</tr>
<tr>
<td>Group 2</td>
<td>0.41 ± 0.26</td>
</tr>
<tr>
<td>Group 3</td>
<td>0.77 ± 0.33</td>
</tr>
<tr>
<td>G1</td>
<td>0.58 ± 0.31</td>
</tr>
<tr>
<td>G2</td>
<td>0.44 ± 0.31</td>
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<tr>
<td>G3</td>
<td>0.80 ± 0.38</td>
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</table>

Significant differences within the groups (Wilcoxon matched-pairs test): Group 1: G3: $P = .049$; Group 2: G2: $P = .006$; G3: $P = .002$
Because the exact mechanism of action of PDT in CSC is still unknown, the standard protocol should be carefully modified. By the end of our study, the patients in the hdPDT group had reached a reduction of leakage activity, as shown by FA, of up to 66.6% \( (P = .0078) \) an increase of visual acuity of 8.5 letters \( (P = .012) \), a decrease in macular thickness by 109.8 \( \mu \text{m} \) \( (P = .052) \), and a reduction in metamorphopsia of 41.7%. The rapid response of these patients is remarkable. At the 8-week visit, this group showed a significant decrease in leakage activity of 36.4% \( (P = .015) \). In addition, the eyes of patients in the hdPDT group showed the strongest increase in contrast visual acuity, particularly at high light levels and low contrast.

Koytak et al. used hdPDT in eyes with chronic CSC (> 6 months’ duration of symptoms), with the same protocol described in the current paper and described a resorption of subretinal fluid in 75% with a significantly better VA and a significant decrease of macular thickness after 12 months.\(^\text{17}\) The effect of hdPDT in acute CSC (defined as 3 months) has been demonstrated in a randomized, controlled trial with 63 patients and a greater absorption of fluid (94.9% of patients) compared with the placebo group (57.9% of patients).\(^\text{18}\)

In their pilot study of SDM treatment for CSC, Lanzetta et al. reported an improvement in liquid absorption of 2/3 after 1 month and 3/4 at the end of the study (14 months) without secondary retinal damage.\(^\text{19}\) The effect of SDM photocoagulation on chronic CSC (defined as > 6 months’ duration) has been described in a case report of seven patients. Subretinal fluid was reduced and VA was enhanced in all seven patients. Five eyes experienced a complete resorption within 8 weeks.\(^\text{20}\) Chen et al. conducted a prospective observation of 26 eyes with juxtafoveal CSC leaks, especially in relation to the different types of CSC. The patients were divided into three groups: Group A had leakage without associated RPE atrophy, group B had leakage with RPE atrophy, and group C had diffuse RPE decompensa-

### Table 5

Size of Hyper- and/or Hypo-Fundus Autofluorescence (FAF) Area in Patients With Central Serous Chorioretinopathy Before and After Treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline (T0)</th>
<th>16 Weeks After Treatment (T2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1: (SDM; n = 20)</td>
<td>0.23 ± 0.26; 0.11 (0.01 - 0.93)</td>
<td>0.25 ± 0.30; 0.14 (0.01 - 1.17); §A</td>
</tr>
<tr>
<td>Group 2: (hdPDT; n = 24)</td>
<td>0.50 ± 0.54; 0.12 (0.05 - 1.54)</td>
<td>0.45 ± 0.51; 0.20 (0.04 - 1.56); §B</td>
</tr>
<tr>
<td>Group 3: (control; T0/T1: n = 18, T2: n = 16)</td>
<td>0.36 ± 0.37; 0.16 (0.06 - 1.00)</td>
<td>0.32 ± 0.34; 0.11 (0.05 - 0.92); §C</td>
</tr>
</tbody>
</table>

SDM = subthreshold diode laser micropulse; hdPDT = half-dose verteporfin photodynamic therapy

No significant differences within the groups (Wilcoxon matched-pairs test):
- Group 1: §A T2 vs. T0: \( P = .86 \)
- Group 2: §B T2 vs. T0: \( P = .38 \)
- Group 3: §C T2 vs. T0: \( P = .25 \)

No significant differences between the groups (Mann-Whitney test)

![Figure 2. Hyper- and hypo-fundus autofluorescence (FAF) areas and optical coherence tomography of patient 31 (subthreshold diode micropulse therapy) before (T0) and after treatment (T2). The outer area (area 2) demonstrates the liquid bubble and detachment of retinal pigment epithelium (RPE). In the inner area (area 1) the size of diffuse hyper/hypoFAFs in terms of RPE changes is visible. Sixteen weeks after treatment (T2) RPE changes even show a slight decline.](image)
tion. Interestingly, all patients in group A and 89% of those in group B had complete resorption of the subretinal fluid, but only 45% of the patients in group C achieved a resorption. It supports the observation that those patients with single focal leakage and short symptom duration (because they often show no RPE atrophy) are especially likely to benefit from SDM photocoagulation. Among the patients treated with SDM, 70% had chronic CSC as shown by FA, which may have anatomic or a more affected RPE. Although we cannot relate our outcome to Chen’s work, in light of our results, SDM therapy appears to be a good choice for patients with acute CSC and/or shorter time from the onset of the disease, before the loss of IS, OS, and visual functions become irreversible, whereas PDT seems to be a good treatment possibility in both the chronic progressive and acute forms of CSC.

A major limitation of the study is our short follow-up time of only 16 weeks. Especially the chronic version of CSC shows a high recurrence rate, which could not be observed in our short follow up. Still our results over 16 weeks prove the improvement of both treatment groups compared to the control group.

In conclusion, in this 16-week randomized, prospective, controlled study, compared with the control group, both hdPDT and SDM photocoagulation resulted in reduced leakage activity in FA, enhanced visual acuity, and resolution of subretinal fluid in OCT in patients with CSC, with no detected side effects of treatment.

REFERENCES