Collaborative Retrospective Macula Society Study of Photodynamic Therapy for Chronic Central Serous Chorioretinopathy

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Purpose: To assess the visual and anatomic outcomes of central serous chorioretinopathy (CSC) after verteporfin photodynamic therapy (PDT).

Design: Retrospective case series.

Participants: Patients with CSC who underwent PDT.

Methods: Members of the Macula Society were surveyed to retrospectively collect data on PDT treatment for CSC. Patient demographic information, PDT treatment parameters, fluorescein angiographic information, optical coherence tomography (OCT) metrics, pre- and post-treatment visual acuity (VA), and adverse outcomes were collected online using standardized forms.

Main Outcome Measures: Visual acuities over time and presence or absence of subretinal fluid (SRF).

Results: Data were submitted on 265 eyes of 237 patients with CSC with a mean age of 52 (standard deviation [SD] ± 11) years; 61 were women (26%). Mean baseline logarithm of the minimum angle of resolution (log-MAR) VA was 0.39 ± 0.36 (20/50). Baseline VAs were ≥20/32 in 115 eyes (43%), 20/40 to 20/80 in 97 eyes (37%), and ≤20/100 in 47 eyes (18%). Normal fluence was used for PDT treatment in 130 treatments (49%), half-fluence was used in 128 treatments (48%), and very low fluence or missing information was used in 7 treatments (3%). The number of PDT treatments was 1 in 89%, 2 in 7%, and 3 in 3% of eyes. Post-PDT follow-up ranged from 1 month to more than 1 year. Post-PDT VA was correlated with baseline VA (r = 0.70, P < 0.001). Visual acuity improved ≥3 lines in <1%, 29%, and 48% of eyes with baseline VA ≥20/32, 20/40 to 20/80, and ≤20/100, respectively. Subretinal fluid resolved in 81% by the last post-PDT visit. There was no difference in the response to PDT when analyzed by age, race, fluence setting, fluorescein angiography (FA) leakage type, corticosteroid exposure, or fluid location (subretinal or pigment epithelial detachment; all P > 0.01). Complications were rare: Retinal pigment epithelial atrophy was seen in 4% of patients, and acute severe visual decrease was seen in 1.5% of patients.

Conclusions: Photodynamic therapy was associated with improved VA and resolution of SRF. Adverse side effects were rare. Ophthalmology 2014;121:1073-1078 © 2014 by the American Academy of Ophthalmology.

*Supplemental material is available at www.aaojournal.org.

Central serous chorioretinopathy (CSC) is a disease in which there is serous exudative detachment of the retina, often associated with detachment of the retinal pigment epithelium (RPE). Fluorescein angiography (FA) in eyes with CSC generally reveals 1 or more focal areas of leakage from the level of the RPE, and indocyanine green angiography (ICG) shows multifocal choroidal vascular hyperpermeability.1 Historically, laser treatment has been applied with the intent of sealing the source of leakage into the subretinal or subretinal pigment epithelial space. In the era when only thermal laser was available, this treatment used to be applied in eyes with long-standing CSC or when it was deemed necessary to attempt rapid resolution of the subretinal fluid (SRF) for occupational reasons (e.g., airline pilots). Thermal laser was shown to result in the elimination of leakage in a proportion of eyes, but the final visual acuity (VA) outcome was no better than the untreated natural history.2 In addition, recurrence rates seen after laser treatment were no different compared with untreated eyes,3 and complications such as choroidal neovascularization could be devastating.

Photodynamic therapy (PDT) using verteporfin followed by exposure of the region of interest to a nonthermal laser was suggested as a viable option for chronic CSC because these eyes have primary choroidal hyperpermeability for which there is no effective treatment.4,5 In a pilot study of 20 eyes, Yannuzzi et al4 showed that after verteporfin PDT, 12 eyes had complete resolution of SRF and 6 eyes had improved VA. Another report of 26 eyes with CSC treated with focal laser or PDT5 found earlier recovery of vision and faster resolution of fluid with PDT than with focal laser. In addition to the lack of consensus on the
efficacy of PDT for this condition, there is a wide range of treatment parameters in use. These include standard and reduced fluence, reduced drug dosage, and shorter duration of laser application. To date, the reports in the literature regarding the management of CSC consist of small case series in which it has not been possible to explore the associations of interest adequately. This study was undertaken under the auspices of the Macula Society and involved 37 retinal specialists who contributed cases of CSC from their clinical practice repository. The aim of the study was to create a database of CSC that had been treated with PDT to describe the clinical outcomes.

Methods

Macula Society members of the Research and Education Committee and the Website Committee collaborated with the Jaeb Center for Health Research to perform an investigator-reported retrospective, online study of outcomes after PDT in eyes with CSC. Macula Society members were invited to participate in an internet-based electronic survey. Patient demographic information, PDT treatment parameters, fluorescein angiographic information, optical coherence tomography (OCT) metrics, pre-treatment and post-treatment VA, and adverse outcomes after PDT were submitted by responding physicians using standardized, electronically submitted forms. Investigational review board (IRB) approval was obtained before the conduct of this study. Western IRB approval was obtained for all investigators in this study. In addition, individual institutional IRB approvals were obtained by those individuals whose institutions required their own institutional IRB approval for this project. Data entry was open for 4 months. Data queries were sent to participating physicians to obtain missing information noted on review of the forms.

Inclusion criteria included a diagnosis of CSC and follow-up of at least 3 months after PDT using verteporfin dye. Exclusion criteria included a report of any prior non-PDT therapy for CSC and the presence of a macular scar, prior retinal detachment, age-related macular degeneration, and active diabetic retinopathy. Visits were categorized into the following time periods based on the time from initial PDT treatment: 3 to 6 weeks, more than 6 and less than 12 weeks, and more than 12 weeks post-PDT. Visits were categorized into the following time periods based on the time from initial PDT treatment: 3 to 6 weeks, more than 6 and less than 12 weeks, and more than 12 weeks post-PDT.

Snellen visual acuities were converted to the logarithm of the minimum angle of resolution (logMAR) values for analyses. Point estimate for binary and continuous outcomes and corresponding 95% confidence intervals (CIs) were computed and calculated using generalized estimating equations to account for the correlated data from study participants with 2 study eyes. Association of baseline factors with outcomes was evaluated using analysis of covariance models adjusting for baseline VA with generalized estimating equations to account for the correlated data within participants with 2 study eyes when applicable. Given the number of exploratory subgroup analyses performed, a significance level of <0.01 was used to identify potential relationships. SAS software version 9.2 (SAS Inc., Cary, NC) was used for all analyses.

Results

Data were submitted on 237 patients with CSC from 11 countries and were submitted by 37 of 384 Macula Society members. By controlling for baseline VA, there was no effect of investigators on VA outcomes for investigators enrolling 10 or more eyes (P > 0.01). There were 110 patients from the United States, 47 patients from Italy, 17 patients each from Japan and the United Kingdom, 16 patients from Germany, 9 patients from Saudi Arabia, 6 patients each from Colombia and Northern Ireland, 4 patients from South Korea, 3 patients from Hong Kong, and 2 patients from Israel. By controlling for baseline VA, there was no effect of country on VA outcomes for countries with 10 or more eyes (P > 0.01). There were 176 men (74%) and 61 women with an average age of 52 years (standard deviation ± 11). Of the patients, 69% were Caucasian, 18% were Asian, 12% were Hispanic, <1% were black, and <1% were Hawaiian or Pacific Islander. Complete data were available on 237 of 239 patients, which serve as the population analyzed in this article. Thirty patients (13%) had a history of associated systemic corticosteroid use, but this history was not known in 9 patients (4%). There were 28 patients (12%) with bilateral CSC, resulting in a total of 265 study eyes. The median CSC disease duration was 12 months for the 212 eyes with a reported disease duration (mean, 24 months; range, 1 week to 8 years).

Full fluence (600 J/cm2) and half fluence (300 J/cm2) were the most commonly selected PDT treatment parameters. Approximately one half (130, 49%) had been treated with full fluence, and the majority of the remainder (128, 48%) had been treated with half fluence. The laser fluence was not recorded in 6 eyes (2.5%), and very low fluence was used (<1%) in 1 eye. The treatment duration was 83 seconds in 244 eyes (94%) and 40 seconds in 13 (5%) eyes. For those patients undergoing treatment of 40 seconds duration, 7 received full fluence and 6 received half-fluence laser. The number of PDT treatments was 1 in 236 eyes (89%), 2 in 19 eyes (7%), 3 in 8 eyes (3%), and not recorded in 2 eyes (<1%). During the first PDT treatment, the number of treatment spots used was 1 in 229 eyes (86%), 2 in 29 eyes (11%), 3 in 5 eyes (2%), and not recorded in 2 (<1%) eyes. Indocyanine green angiography guidance was used in 51% of eyes. Because this was a retrospective study, there was no standardized treatment protocol. The investigators were queried at the completion of the study about their treatment spot calculation. The investigators responded that the treatment spot was determined by using the diameter of the largest circle that covered the area of leakage (FA) or the area of hyperpermeability (ICG) or both. Investigators varied in the addition of zero to 1000 μm to the spot size. The foveal area was included if the leakage/hyperpermeability was in this area. The FA and ICG images were not reviewed in this retrospective study. Some investigators used multiple spots for their treatment.

Post-PDT follow-up ranged from 1 month to more than 1 year. Of these 265 eyes, follow-up data were available in 72% of eyes at 3 to 6 weeks post-PDT and in 98% of eyes within the first 14 weeks post-PDT. More than 65% of the eyes had a visit between 15 and 30 weeks after PDT treatment.

Visual Acuity Results

The mean logMAR VA at baseline was 0.39±0.36 (20/50). Baseline visual acuities were ≥20/20 in 21 eyes (8%), 20/25 to 20/32 in 94 eyes (35%), 20/40 to 20/80 in 97 eyes (37%), 20/100 to 20/200 in 34 eyes (13%), ≤20/320 in 13 eyes (5%), and missing in 6 eyes (2%). Change in VA over time for each group of eyes is shown in Table 1. The logMAR final VA was correlated with baseline VA (r = 0.70, P < 0.001). Because change in VA is significantly affected by baseline VA, all analyses were stratified by the following VA groups: ≥20/32, 20/40 to 20/80, and ≤20/100.

Improvement in VA was seen as early as 3 to 6 weeks post-PDT treatment; 11%, 32%, and 52% of eyes with baseline VA of ≥20/32, 20/40 to 20/80, and ≤20/100 gained ≥2 lines of VA. At the last follow-up visit available, post-PDT visual acuities were improved ≥2 lines in 26% (95% CI, 19–35), 55% (95% CI, 45–64), and
59% (95% CI, 44–71) of eyes with baseline visual acuities of ≥20/32, 20/40 to 20/80, and ≤20/100, respectively. Visual acuities improved ≥3 lines in <1%, 29%, and 48% of eyes with baseline visual acuities of ≥20/32, 20/40 to 20/80, and ≤20/100, respectively. Loss of ≥2 lines of VA at the last visit was seen in 7% (95% CI, 4–14) of eyes with ≥20/32, 5% (95% CI, 2–12) of eyes with 20/40 to 20/80 baseline VA, and 13% (95% CI, 6–26) of eyes with ≤20/100 baseline VA. Loss of ≥3 lines of VA was seen in 4% of eyes with ≥20/32, or 20/40 to 20/80 baseline VA, in contrast to 11% of eyes with ≤20/100 baseline VA. The mean changes in logMAR visual acuity from baseline were −0.5 (±0.16), −0.14 (±0.25), and −0.23 (±0.44) for eyes with baseline visual acuities of ≥20/32, 20/40 to 20/80, and ≤20/100, respectively. When the VA results of the subgroup of eyes with ≤20/40 baseline VA were analyzed (N = 142), 42% of these eyes had better than 20/40 VA at the final follow-up visit. After controlling for baseline VA, multivariate analysis showed no difference in the VA response to PDT when analyzed by age, race, fluorescence leakage type, steroid exposure, initial central subfield thickness (CST), ICG guidance of laser treatment, or fluid location (SRF or PED) (P > 0.01).

There were 18 patients who lost ≥3 lines of VA post-PDT at any time point during their follow-up after receiving PDT. Of these, 4 had increased CST on OCT within 15 weeks of the initial PDT. None of these 4 eyes had geographic atrophy. However, 1 eye was noted to have developed geographic atrophy at 40 weeks. There were 4 eyes that had acute severe visual decrease. Optical coherence tomography data were available for 1 of the 4 eyes. In this patient, initial VA decreased from 20/50 to 20/250 in the first month post-PDT treatment, and OCT showed macular thinning (baseline CST OCT was 361 μm and first month post-PDT CST OCT was 170 μm). When analyzed for older age (>50 years), no association was found for worse VA outcome at the first or last visit post-PDT.

### Retinal Findings and Ocular Imaging Results

Subfoveal SRF was reported as present in 220 eyes (83%), absent in 43 eyes (16%), and not recorded in 2 eyes (<1%) at baseline. For the eyes with baseline SRF on clinical examination, SRF was no longer detected in 75% of eyes at the first post-PDT visit and in 81% of eyes at the last post-PDT visit (Table 2). The initial presence and subsequent resolution of SRF on OCT were similar to the clinical examination.

Pigment epithelial detachment (PED) was present in 73 eyes (28%), absent in 190 eyes (72%), and not recorded in 2 eyes (<1%) at baseline. On clinical examination, 56 eyes (21%) had SRF and PED, whereas neither SRF nor PED was observed in 26 eyes (10%). For the eyes with baseline PEDs on clinical examination, the initial post-PDT visit dilated fundus examination showed absence of the PED in 55% of eyes and the final visit showed absence of the PED in 65% of eyes. Similar proportions were seen by OCT imaging.

Several OCT acquisition systems were used to image these patients with CSC. These OCT systems included the Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany) (N = 76), Zeiss Stratus (Carl Zeiss Meditec Inc., Dublin, CA) (N = 60), Zeiss Cirrus (Carl Zeiss Meditec Inc., Dublin, CA) (N = 41), Topcon (Oakland, NJ) (N = 41), Opko (Miami, FL) (N = 5), and Optovue (Fremont, CA) (N = 2). To meaningfully compare pre-PDT and post-PDT OCT scans, only OCT measurements obtained with the same machine at various time points for the same patient were analyzed.
For this subset of data, post-PDT CST thickness was on average smaller than the baseline pre-PDT CST measurements for each machine (Table 2). Of the 175 eyes with OCT data available at both the baseline and the last follow-up visit, the CST measurements decreased by a mean value of 114 μm (95% CI, −97 to −130). At the final visit, 59 eyes (79%) improved by 25 μm or more and 7 eyes (4%) worsened by 25 μm or more. There was no association between baseline VA and change in CST measurements.

Focal leaks on FA were noted to be present in 180 eyes (68%) at baseline. The presence of post-PDT focal leaks was assessed for those eyes with baseline focal leaks. At the first post-PDT visit FA, 78% of those with focal leakage in the baseline FA no longer had leakage (80/180 eyes with focal leaks had an FA at the first follow-up visit). At the last post-PDT visit, 81% of those with focal leakage on a baseline FA showed no leakage (62/180 eyes with baseline focal leaks had an FA at the final visit) (Table 3). Similar results (78% at the initial post-PDT and 76% for the final post-PDT visit) were seen for areas of diffuse fluorescein angiographic leakage. Retinal pigment epithelium atrophy was seen in 10 eyes (4%), and acute severe visual decrease was reported to have occurred post-treatment in 4 eyes (1.5%).

### Study Limitations

Central serous chorioretinopathy is known to resolve spontaneously and there was no control group in our study. In addition, the data are retrospective and thus carry the risk of selection bias. Because the study was investigator reported in design, we cannot exclude the possibility that clinicians selectively included cases with favorable outcomes. In addition, we did not verify data against source documents. Nonetheless, our study has strength in the inclusion of large numbers of cases from diverse clinical practices from around the world.

### Discussion

This retrospective investigator-reported study represents the largest collection of cases with chronic CSC treated with verteporfin PDT. In our study, PDT therapy resulted in improved VA, resolution of SRF (on both clinical examination and OCT), and reduction in fluorescein angiographic leakage in the majority of the treated eyes. There was no association between VA outcome and fluence setting, baseline ocular characteristics, gender, age, or lesion type. Adverse side effects were uncommon, and post-treatment acute severe VA decreases occurred rarely (1.5% of cases). Therefore, in accord with prior reports of PDT for CSC, our study suggests that PDT results in the resolution of the exudative manifestations of chronic CSC.

Although PDT caused the resolution of SRF in the majority of patients (81%), improvements in VA of a similar magnitude were not observed. Improvement by 2 or more lines occurred in approximately half of the eyes with an initial acuity of ≤20/100 and in 30% of eyes with baseline acuities between 20/40 and 20/80. This discrepancy between resolution of fluid and improvement in VA has been seen in other studies, including the first pilot study using PDT for chronic CSC. Possible explanations include irreversible damage to the photoreceptors or underlying RPE or both. In the present study, the chronicity of CSC of 24 months (median, 12 months) may have led to a combination of irreversible photoreceptor loss, photoreceptor dysfunction, or RPE loss in some eyes. This would explain the lack of more significant gains in vision in approximately half of the eyes with 20/200 baseline visual acuities despite the resolution of fluid. Morphologic studies suggest that damage to the photoreceptor mosaic remains despite resolution of SRF.
the cone mosaic and cone densities of eyes with resolved CSC compared with normal eyes.\(^8\) These abnormalities also were associated with visual loss. Another explanation for the lack of more robust VA improvement despite resolution of fluid is the ceiling effect.\(^9\) This applies to eyes with \(\geq 20/30\) VA, in which it may be difficult if not impossible to achieve a 3-line improvement. This group of eyes also is less likely than eyes with better VA to have VA loss post-PDT therapy.

The standard dose of drug (6 mg/m\(^2\) of body surface area) and the laser parameters (50 J/cm\(^2\), 600 mw, 83 seconds) were originally intended for managing neovascular age-related macular degeneration.\(^10\) However, because the aim of treatment for CSC is not neovascular vessel closure, but rather closure of leakage from existing vessels and subsequent resorption of fluid, investigators have experimented with the dose of the drug (3.0 mg/m\(^2\) body surface area) and the laser fluence settings. An aim in treatment of CSC is to restore the choroidal/RPE/Bruch’s membrane complex morphology to something approaching normality. Reducing the energy output to between 35 and 25 J has been used by various studies.\(^11\) After these adjustments to drug dose and fluence levels, some studies have reported a trend toward better outcomes and fewer side effects. Furthermore, these alterations to treatment protocol were found to reduce retinal and choroidal thinning, but the significance of these findings is unclear.

In our study, which had a larger sample size, multivariate analyses found no association of outcome with respect to fluence; however, our investigators who had various preferences did not rely on a defined protocol. Thus, although we cannot directly compare outcomes on the basis of these 2 parameters, the statistical model used in our study suggested an absence of association between laser fluence settings and VA outcomes. In this context, our findings are in accord with a number of small clinical studies. A prior study compared 19 eyes with chronic CSC treated with full-fluence PDT with 23 eyes with chronic CSC treated with half-fluence PDT in a prospective, multicenter, masked, nonrandomized trial. In most of the eyes, both full- and reduced-fluence PDT resulted in SRF resorption with VA improvement. No retinal atrophy or systemic adverse events were noted.\(^18\)

Our study found that 65% of PEDs resolved after PDT, a smaller proportion in response compared with other studies. One prospective study of 15 eyes receiving low-dose PDT found that 93% of PEDs resolved.\(^13\) However, another study showed recurrence of PEDs within 1 year of treatment in 31% of eyes with chronic CSC that initially had detachment of the PED at 6 months.\(^19\) Further work is needed in this area.

The use of PDT addresses the choroidal vascular hyperpermeability. Photodynamic therapy results in decreased hyperpermeability and reduced choroidal thickness in treated eyes with CSC.\(^20\) In a retrospective comparative series of laser photocoagulation (\(n = 12\)) with PDT (\(n = 8\)), both groups showed resolution of SRF, but only the PDT eyes showed decreased choroidal thickness on OCT enhanced depth imaging and decreased hyperpermeability on ICG angiography.\(^20\) A retrospective study has shown that although subfoveal choroidal thickness decreased after both spontaneous resolution of CSC and low-fluence PDT, the choroidal thickness decreased to the normal levels only in the PDT-treated eyes.\(^21\)

Alternatives to PDT include focal thermal laser, vascular endothelial growth factor antagonists, and oral corticosteroid blockers. In a prospective comparative interventional study of 22 patients, no significant difference in visual and anatomic outcomes was noted between eyes treated with bevacizumab and eyes treated with low-dose PDT.\(^22\) A prospective pilot study showed poor anatomic response rates with ranibizumab compared with PDT for CSC.\(^20\) After a single session of PDT, 6 eyes (75%) achieved complete resolution of SRF and reduction of choroidal hyperpermeability, whereas only 2 (25%) ranibizumab-treated eyes achieved this result after consecutive ranibizumab injections. A small pilot study of 16 patients with chronic CSC who received daily oral mifepristone showed that 7 patients had improved VA and 7 patients had resolution of SRF on OCT.\(^23\) Potential side effects include skin rash, nausea, dizziness, fatigue, reversible liver transaminase elevation, and endometrial hyperplasia. Rifampin also has been tried because it increases the metabolism of endogenous corticosteroids through its induction of the enzyme cytochrome P450. Side effects include gastrointestinal problems, drowsiness, dizziness, flu-like symptoms, easy bruising, joint pain, and liver toxicity.

In conclusion, this study has demonstrated that PDT with verteporfin can result in resolution of morphologic changes associated with CSC and improve vision in some cases. Data from large, appropriately controlled and bias-free studies will be necessary to fully define the best treatment regimen, treatment response rates, visual efficacy, and side effects of this promising therapy. However, an important barrier to such a trial would be the enormous cost because the number of potential variables is large with implications for the size of study. The present study provides useful estimates for the design of future trials, and given the large sample size, the data collected in this study reflect real-world outcomes that could be expected for PDT of chronic CSC.

References


Footnotes and Financial Disclosures

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*A list of members of the Macula Society CSC Collaborative Study Group, Research and Education Committee and Website Committee appear in Appendix 1 (www.aaojournal.org).

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