Association Between the Efficacy of Half-Dose Photodynamic Therapy With Indocyanine Green Angiography and Optical Coherence Tomography Findings in the Treatment of Central Serous Chorioretinopathy

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• PURPOSE: To determine the efficacy of half-dose photodynamic therapy (PDT) in relation to indocyanine green angiography (ICGA) and optical coherence tomography (OCT) findings for treating chronic central serous chorioretinopathy (CSC).
• DESIGN: Observational case series.
• METHODS: Thirty-eight eyes of 37 patients with chronic CSC and symptoms for at least 6 months were recruited. PDT was performed using half the normal dose of verteporfin. A total light energy of 50 J/cm² over 83 seconds was delivered to the area of choroidal hyperfluorescence as observed on ICGA. The resolution of the subretinal fluid and recurrence rates were assessed in relation to the different degrees of choroidal hyperfluorescence and the distribution of fluid in the neuroepithelium, namely subretinal fluid or posterior retinal cystoid degeneration.
• RESULTS: After half-dose PDT a dry macula was obtained in 86.8% and 92.1% of the eyes at 1 month and at the last follow-up (14.2 ± 5.8 months) respectively. ICGA at baseline showed intermediate and intense hypofluorescence in 39.4% and 60.5% of the eyes respectively. All eyes with intermediate hyperfluorescence had only subretinal fluid at OCT and a dry macula was obtained in 87% and 100% at 1 month and at the last follow-up after half-dose PDT. In the intense hyperfluorescence group, 82.6% and 17.4% of the eyes had subretinal fluid only or both subretinal fluid and posterior retinal cystoid degeneration respectively. In the intense hyperfluorescence group with both subretinal fluid and posterior retinal cystoid degeneration, a dry macula was obtained in 75% and 25% of the eyes at 1 month and at the last follow-up respectively. Overall, of the 23 eyes with intense hyperfluorescence, 20 eyes (87%) had a dry macula starting from 1 month for the entire follow-up period.
• CONCLUSION: The half-dose PDT success rate in eyes with chronic CSC depends also on the distribution of fluid in the neuroepithelium. Half-dose PDT might not be effective or the recurrence rate might be high in eyes with posterior retinal cystoid degeneration. (Am J Ophthalmol 2011;xx:xxx. © 2011 by Elsevier Inc. All rights reserved.)

Central serous chorioretinopathy (CSC) is characterized by the development of serous neurosensory retinal detachment at the posterior pole. In the majority of patients, CSC is self-limiting and patients usually have a good visual prognosis.1 However, in cases of chronic CSC with persistent serous retinal detachment and chronic decompensation of the retinal pigment epithelium (RPE), progressive visual loss attributable to photoreceptor disruption and cystoid edema of the neurosensory retina might develop.1,2 The increasing use of indocyanine green angiography (ICGA) in CSC has improved the understanding of the pathogenesis of CSC and has demonstrated that during CSC choroidal circulation in addition to RPE is primarily affected, resulting in multifocal areas of choroidal vascular hyperpermeability.3,4

Treatment options for chronic CSC are thermal laser photocoagulation and photodynamic therapy. As direct thermal laser has the disadvantages of causing RPE damage and iatrogenic choroidal neovascularization (CNV), more effective and less harmful treatment modalities have been proposed. Photodynamic therapy (PDT) for CSC is reported to be efficacious in reducing subretinal fluid and increasing visual acuity in most patients.5,6 One of the strengths of PDT lies in its security and the assumed absence of side effects, although standard PDT can have some significant negative implications such as RPE atrophy, choriocapillaris ischemia, and secondary CNV.5,6

In order to avoid PDT-related complications, half-dose or low-fluence PDT has been suggested by different authors.7-9 Half-dose or low-fluence PDT with verteporfin is effective in inducing reabsorption of subretinal or intra-
TABLE 1. Central Foveal Thickness in 38 Eyes With Chronic Central Serous Chorioretinopathy Treated With Half-Dose Photodynamic Therapy

<table>
<thead>
<tr>
<th></th>
<th>Central Foveal Thickness ± SD</th>
<th>Resolution of Fluid</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>345.61 ± 101.00 μm</td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>—</td>
<td>86.8% (n = 33)</td>
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<tr>
<td>Last follow-up (14 months)</td>
<td>213.07 ± 47.20 μm</td>
<td>92.1% (n = 35)</td>
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*aP value was significant at the last follow-up (P = < .001).

METHODS

THIS STUDY WAS A RETROSPECTIVE, INTERVENTIONAL case series conducted in the Department of Neuroscience, Ophthalmology and Genetics of the University of Genova, Italy. Patients were offered treatment if they had persistent fluid involving the macula. Inclusion criteria were: 1) a 6-month history of CSC; 2) best-corrected visual acuity (BCVA) of 20/200 or better; 3) presence of subretinal fluid involving the fovea with or without posterior cystoid retinal degeneration on OCT; and 4) presence of active angiographic leakage on fluorescein angiography (FA) caused by CSC but not CNV or other diseases.

Indocyanine green angiography was performed on all patients in order to outline choroidal hyperpermeability areas. Patients who had received focal thermal laser photocoagulation for the treatment of CSC prior to this study were included, whereas patients previously treated with anti–vascular endothelial growth factor or steroid intravitreal injections were excluded. Snellen BCVA was measured at the baseline and post-PDT visits. Evaluation of macular detachment was performed using a spectral-domain optical coherence tomography (OCT) machine (Topcon 3D OCT-1000; Topcon, Capelle a/d IJssel, the Netherlands). Central foveal thickness was measured by way of the 12-radial scan protocols at baseline, at 1 month, and at the last follow-up visit. FA and ICGA were performed in all patients at baseline and at the last follow-up visit after PDT. Additional FA and ICGA were carried out on patients with persisting or recurring CSC during follow-up. PDT was performed by administering half the normal dose of verteporfin (Visudyne; Novartis AG, Lausanne, Switzerland) as previously described. Verteporfin was infused over 10 minutes followed by delivery of laser at 693 nm after 5 minutes from the commencement of infusion to target the area of choroidal hyperpermeability. A total light energy of 50 J/cm² over 83 seconds was delivered to the area of choroidal hyperfluorescence as observed in ICGA. Areas of choroidal vascular abnormality that were supposed to cause the serous detachment were considered to be treated.

In order to classify ICGA findings according to the criteria previously reported, 1 of the authors (M.N.) reviewed all baseline middle-phase ICG angiograms about 10 minutes after ICG injection. Revisions were masked with regard to outcomes in order to enhance objectivity. After treatment, patients were given protective glasses and instructed to avoid strong light for 2 days. The main outcome measures of the study included the percentage of patients with a dry macula at 1 month and at the last follow-up visit, BCVA, and central foveal thickness.

RESULTS

A TOTAL OF 38 EYES OF 37 PATIENTS WITH CHRONIC CSC received half-dose PDT. The mean ± SD age of patients was 48.5 ± 10.3 years (range 31–70) and 34 of the patients (91.8%) were male. Baseline mean ± standard deviation (SD) BCVA was 0.74 ± 0.19 (range 0.3–1.0). Mean follow-up was 14.2 ± 5.8 months (median 12, range 8–30). Baseline mean ± SD central foveal thickness was 345.61 ± 101.00 μm.
At baseline, 34 of the 38 eyes (89.5%) had subretinal fluid alone and 4 eyes (10.5%) had combined subretinal fluid and posterior cystoid retinal degeneration. Baseline FA showed 5 eyes (13.1%) with focal leakage and 33 eyes (86.8%) with diffuse leakage. On ICGA, choroidal hyperfluorescence was identified in all patients. Fifteen eyes (39.4%) showed an intermediate hyperfluorescence and 23 eyes (60.5%) showed an intense hyperfluorescence. All 15 eyes (100%) in the intermediate choroidal hyperfluorescence group had subretinal fluid only at OCT. Of the 23 eyes in the intense hyperfluorescence group, 19 (82.6%) had subretinal fluid only, while the remaining 4 (17.4%) also had posterior cystoid retinal degeneration.

At 1 month from PDT, the resolution of the fluid was complete, partial, or absent in 86.8% (33/38), 10.5% (4/38), and 2.6% (1/38) of eyes respectively. At the last follow-up visit the resolution of the fluid was complete, partial, or absent in 92.1% (35/38), 2.6% (1/38), and 5.3% (2/38) of the eyes respectively. Overall, there was a significant \( P < .001 \) decrease of the central foveal thickness (Table 1). BCVA was unchanged or had improved by 3 lines in 57.8% (22/38) and 39.5% (15/38) of the eyes respectively. Only 1 eye lost 3 lines at the last follow-up visit. Overall BCVA improved significantly (0.83 ± 0.2, \( P = .001 \)). The rates of resolution of subretinal fluid based on ICGA and OCT findings are reported in Table 2. In the intermediate hyperfluorescence group, subretinal fluid recovered completely in 87% (13/15) and 100% (15/15) of eyes at 1 month and at last follow-up respectively. In the intense hyperfluorescence group with subretinal fluid only, a dry macula was obtained in 89.5% (17/19) and 100% (19/19) of the eyes at 1 month and at the last follow-up respectively. In the intense hyperfluorescence group with posterior cystoid retinal degeneration, a dry macula was obtained in 75% (3/4) and 25% (1/4) of the eyes at 1 month and at last follow-up visit respectively. Overall, in the intense hyperfluorescence group, 87% (13/15) of eyes had a dry macula starting from 1 month after treatment and lasting throughout the follow-up period (Figures 1 through 3).

Two eyes, in the intermediate hyperfluorescence group, had received focal thermal laser photocoagulation prior to this study. The mean number of PDT treatments required during follow-up was 1.13 treatment sessions. One single session of half-dose PDT achieved treatment response in 33 of 38 eyes (86.8%). Five of 38 eyes (13.2%), either with persistent or recurrent serous macular detachment, underwent a second half-dose PDT on average after 6.6 months (range 3–12 months). Four of the 5 eyes had an intense hyperfluorescence pattern and of these, 2 had subretinal fluid plus posterior cystoid retinal degeneration. Retreatment led to a complete resolution of exudation in 3 of the 5 eyes at last follow-up visit. Two eyes with persistent subretinal fluid and/or posterior cystoid retinal degeneration at last follow-up visit also presented an intense hyperfluorescence. None of the patients developed any
systemic adverse event associated with verteporfin infusion including infusion site complications and low back pain. None of the patients had any subjective or objective drop in vision immediately after PDT.

DISCUSSION

IN THE CURRENT STUDY OF 38 EYES, DRY MACULA WAS obtained in 33 eyes (86.8%) at 1 month and in 35 eyes (92.1%) at the last follow-up visit after half-dose PDT. At baseline, the findings on ICGA were intense hyperfluorescence in 60.5% \( (n = 23) \) of the eyes and intermediate hyperfluorescence in 39.4% \( (n = 15) \) of the eyes. We did not find eyes without hyperfluorescence area on ICGA.

The effectiveness of half-dose PDT differed depending on the variations not only in the choroidal hyperpermeability as previously described\(^\text{12}\) but also in the distribution of the fluid underneath the neuroepithelium. If we take into consideration the ICGA pattern only, then a dry macula was obtained in 87% of the eyes with intense hyperfluorescence starting from 1 month post half-dose PDT, while a dry macula was obtained in 87% and 100% of the eyes with intermediate hyperfluorescence at 1 month and at last follow-up respectively. Such results were not consistent with previous results in which all eyes with intense hyperfluorescence had a complete resolution of subretinal fluid.\(^\text{12}\) Based only on ICGA findings, we should then conclude that eyes with intense hyperfluorescence treated with half-dose PDT show a lower number of dry macula when compared to eyes with intermediate hyperfluorescence. If, however, we analyze the same 2 groups based also on OCT findings (Table 2), we find that 19 of the 23 eyes in the intense hyperfluorescence group had only subretinal fluid, and of these, 89.5% and 100% had a dry macula at 1 month and at last follow-up respectively. Of the 4 remaining eyes in the intense hyperfluorescence group with posterior cystoid retinal degeneration, only 1 had a dry macula at the last follow-up, although some intraretinal cysts persisted not involving the fovea. No posterior cystoid retinal degeneration was found in the intermediate hyperfluorescence group.

Overall, in our series of cases with chronic central serous chorioretinopathy we found 2 different patterns of fluorescence on ICGA. All patients with intermediate choroidal hyperfluorescence responded to half-dose PDT. Patients with OCT shows the complete resolution of posterior cystoid retinal degeneration and subretinal fluid. (Fourth row) At the last follow-up visit (14 months) FA (Fourth row, right) shows persistent diffuse retinal pigment epithelial decompensation; ICGA (Fourth row, left) shows a slight reduction in choroidal hyperfluorescence. (Bottom row) OCT shows recurred posterior cystoid retinal degeneration and subtle subretinal fluid detachment.
intense choroidal hyperfluorescence were further divided into 2 subgroups. Those cases with posterior cystoid retinal degeneration responded very poorly to half-dose PDT, while those without posterior cystoid retinal degeneration had an excellent response to PDT. We therefore hypothesize that posterior cystoid retinal degeneration might be another, and probably more reliable, predictive factor of PDT effectiveness. It has been suggested that posterior cystoid retinal degeneration originates from chorioretinal adherent lesions derived from atrophic RPE areas and is favored by the presence of fibrin attributable to long-standing RPE decompensation as well as choroidal hyperpermeability.7 In such areas, fluid from the choriocapillaris exudes directly in the retina, causing cystoid degeneration. Though a relationship is probable, based on our data we cannot establish a direct relationship between the extent of chronicity and the presence of cystoid changes. We therefore speculate that the occurrence of posterior cystoid retinal degeneration might be considered a negative predictive factor of half-dose PDT effectiveness and should probably advise to modify PDT parameters or to investigate new treatment modalities, although similar results were obtained in 3 cases with cystoid macular degeneration using standard PDT.5

FIGURE 2. Right eye of a 41-year-old man with chronic central serous chorioretinopathy. (Top, left and right) At baseline, middle- and late-phase indocyanine green angiography shows intense choroidal hyperfluorescence. (Second row) At baseline, optical coherence tomography (OCT) shows only subretinal fluid. (Bottom row) At the last follow-up visit (24 months), OCT shows a complete dry macula. (Insert) Color photograph shows scan line.
As hyperfluorescence areas on ICGA were found in all eyes of this case series, we cannot draw conclusions about the effectiveness of half-dose PDT in eyes with no hyperfluorescence area on ICGA. In association with ICGA and OCT findings, recurrence was another noteworthy finding in the current study. The recurrence rate in this study was 13.2% (5 out of 38 eyes), which is in line with the recurrence rate of previous reports (9%-21%).5,6,8 Four out of the 5 eyes that recurred were in the intense hyperfluorescence group and 2 of the latter 4 also had posterior cystoid retinal degeneration, which persisted at the last follow-up after retreatment. Of the remaining 3 eyes (2 eyes with intense hyperfluorescence and 1 eye with intermediate hyperfluorescence) with subretinal fluid only, retreatment led to a complete resolution of the exudation. Based on our results, previous focal laser treatment does not appear to impact negatively on the outcomes after half-dose PDT. No eyes in the current study had choroidal ischemia or progression of RPE atrophy after PDT. Thus, our results confirm once again that half-dose PDT is a

FIGURE 3. Left eye of a 49-year-old man with chronic central serous chorioretinopathy. (Top left) Baseline late fluorescein angiography shows multifocal retinal pigment epithelial leakage areas. (Top right) Baseline late indocyanine green angiography shows intermediate choroidal hyperfluorescence. (Second row) Baseline optical coherence tomography (OCT) shows wide subretinal fluid. (Bottom row) At the last follow-up visit (19 months), OCT shows a complete dry macula.
safe and effective treatment for chronic CSC leading to a complete resolution of retinal exudation in about 90% of cases, but it would be palliative for minor cases of CSC.

Limitations of this study are the relatively small number of patients with posterior cystoid retinal degeneration. Although our data might have been influenced by subjectivity in the evaluation of the indocyanine pattern, it appears that choroidal hyperpermeability is a necessary condition, though failure of the PDT effect or recurrence could be better explained with the exudation status within the retina instead of the intensity degree of choroidal hyperfluorescence.

In conclusion, the resolution of exudation might be expected in eyes with subretinal fluid regardless of the intensity of choroidal hyperfluorescence after half-dose PDT. We should, however, be aware of persistence or recurrences of the disease in eyes with posterior cystoid retinal degeneration.

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REFERENCES

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