Ophthalmol Ther (2023) 12:2199–2208
https://doi.org/10.1007/s40123-023-00739-4

BRIEF REPORT

# No-Dose Photodynamic Therapy Against Half-Dose Photodynamic Therapy for Treatment of Central Serous Chorioretinopathy

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Received: March 5, 2023 / Accepted: May 16, 2023 / Published online: June 8, 2023


## ABSTRACT

***Introduction***: This study aimed to describe the effects of no-dose full-fluence photodynamic therapy without verteporfin (no-dose PDT) and to compare no-dose PDT with half-dose verteporfin full-fluence photodynamic therapy (HDFF PDT) for managing chronic central serous chorioretinopathy (cCSC).

***Methods***: This retrospective study evaluated 11 patients with chronic recurrent CSC treated with no-dose PDT between January 2019 and March 2022. Most of these patients were also treated with HDFF PDT a minimum of 3 months before and were considered as the control group. We described the changes of best corrected visual acuity (BCVA), maximum subretinal fluid (mSRF), foveal subretinal fluid (fSRF), and choroidal thickness (CT) 8 ± 2 weeks after no-dose PDT, and we compared BVCA, mSRF, fSRF, and CT of no-dose PDT with those of the of same patients previously treated with HDFF PDT.

***Results***: Fifteen eyes of 11 patients (10 male, mean age 54 ± 12 years) received no-dose PDT; among these, 10 eyes of 8 patients (7 male, mean age 53 ± 12 years) also received HDFF PDT. Three eyes showed complete resolution of fSRF after no-dose PDT. No significant differences were disclosed between treatment with and without verteporfin comparing BCVA, mSRF, fSRF, and CT at baseline and 8 ± 2 weeks from the treatment ($p > 0.05$ in all analyses).

***Conclusion***: BVCA and CT significantly improved after no-dose PDT. Short-term functional and anatomical treatment outcomes for cCSC were similar for HDFF PDT and no-dose PDT. We hypothesize that the potential benefits of no-dose PDT may arise from thermal elevation that triggers and enhances photochemical activities by endogenous fluorophores, activating a biochemical cascade response that rescues/replaces sick, dysfunctional retinal pigment epithelial (RPE) cells. Results of this study suggest the potential value of a prospective clinical trial to evaluate no-dose PDT for managing cCSC, especially when verteporfin is contraindicated or unavailable.

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**Keywords:** Central serous chorioretinopathy; Choroid; Laser; Macula; Photodynamic therapy; Verteporfin

**Key Summary Points**

***Why carry out this study?***

Photodynamic therapy (PDT) with verteporfin has been used widely for the treatment of chronic central serous chorioretinopathy (cCSC) for two decades, but recent verteporfin shortages and verteporfin PDT's adverse effects prompted us to evaluate the PDT without verteporfin.

This study aimed to describe the efficacy of no-dose full-fluence PDT without verteporfin (no-dose PDT) in cCSC.

***What was learned from the study?***

No-dose PDT treated patients showed an improvement in functional and anatomical outcomes.

No-dose PDT may be a useful alternative or replacement for verteporfin PDT in managing cCSC.

## INTRODUCTION

Chronic central serous chorioretinopathy (cCSC) is characterized by persistent and recurrent serous retinal and retinal pigment epithelial (RPE) detachments with accompanying outer retinal and RPE degeneration [1–3]. Its multifactorial pathogenesis involves choroidal hyperpermeability, vasculopathy, and anastomosis [1, 4, 5]. cCSC complications causing serious vision loss include macular neovascularization, foveal atrophy, cystoid macular degeneration, and outer retinal disruption [2].

Current cCSC therapeutic options include monotherapy or combination treatment with verteporfin photodynamic therapy (PDT) [6, 7], subthreshold micropulse laser (SML) treatment [7, 8], transpupillary thermotherapy (TTT) [9–11], intravitreal anti-vascular endothelial growth factors (anti-VEGF) [12–14], and mineralocorticoid receptor antagonists [15, 16]. Verteporfin PDT has been used widely for the treatment of cCSC for two decades [1, 17]. Standard full-dose, full-fluence PDT is performed with a 6 mg/m$^2$ verteporfin dose (Visudyne®; Novartis, Basel, Switzerland) and an 83 s, 50 J/cm$^2$ exposure to 689 nm red laser light [6]. Full-fluence exposure produces a 0.6 W/cm$^2$ retinal irradiance (power/area) and a retinal temperature increase of roughly 2 °C [18–20].

Reduced dose and/or fluence PDT protocols were developed to decrease the adverse effects of PDT including choroidal ischemia, transient vision loss, RPE atrophy, and macular neovascularization (MNV) [6, 21–23]. Subthreshold (subvisible effects) thermal laser procedures were designed to reduce the adverse effects of standard retinal photocoagulation which include MNV, postoperative laser scar expansion, epiretinal fibrosis, and diminished central visual field sensitivity [8]. Subthreshold thermal laser procedures including SML and TTT use retinal irradiances higher than PDT [8, 19, 20]. Conversely, subvisible photochemical light-exposure procedures (photobiomodulation) use retinal irradiances lower than PDT [24].

Photobiomodulation therapy (PBT) is a non-thermal retinal light therapy that uses longer wavelength visible light or near-infrared radiation to produce photochemical reactions in endogenous retinal chromophores rather than PDT's intravenously administered exogenous retinal photosensitizers including verteporfin [24–26]. PBT was ineffective for center-involving diabetic macular edema in a phase 2 randomized clinical trial [27], but a pilot PBT study for non-neovascular age-related macular degeneration (AMD) [24, 26, 28] produced promising results.

Recently, Russo et al. compared long-term visual acuity and OCT outcomes between half-dose PDT and a near-infrared laser treatment (689-LT), which deliver 95 J/cm$^2$ via an intensity application of 805 mW/cm$^2$ over 118 s, for cCSC in a prospective, randomized, open-labeled, interventional pilot study and found that both treatments were effective [29].

These aforementioned studies, recent verteporfin shortages, the widespread availability of PDT laser systems, and our desire to decrease PDT's potential adverse effects prompted us to determine whether standard PDT full-fluence 693 nm red laser light was useful for managing cCSC without verteporfin. We refer to this treatment as "no-dose PDT," consistent with terminology used in other PDT laser equipment procedures.

## METHODS

This retrospective study adhered to the 1964 Helsinki declaration and its later amendments. All subjects signed an informed consent at the time of the treatment for retrospective studies. As a result of the retrospective nature of the study, the study does not require a specific ethics committee approval which is in line with Italian laws. We screened patients with a diagnosis of chronic CSC referred to the Medical Retina and Imaging Unit of San Raffaele Hospital (Milan, Italy) between January 2019 and March 2022. Patients were eligible for study inclusion study if they had cCSC, documented by the presence of subretinal fluid on OCT images and visual symptoms for more than 12 weeks, treated with no-dose PDT (full-fluence (50 J/cm2), full-time (83 s), 4-mm spot diameter). They were excluded from the study if they had (1) any treatment for retinal disease (including intravitreal injection, PDT, laser photocoagulation, or vitrectomy) less than 3 months before or after no-dose PDT or (2) low quality optical coherence tomography (OCT) images precluding good evaluation.

All patients who met the inclusion criteria were included in the no-dose PDT treatment group. Most of these patients were also treated with half-dose full-fluence PDT (HDFF PDT) with the spot location in the same plan, a minimum of 3 months before no-dose PDT (baseline) and were considered as a control group. Each patient underwent a comprehensive ophthalmic examination and multimodal imaging at baseline and 2 months after both no-dose PDT and, in a subset, HDFF PDT. Best corrected visual acuity (BCVA) was assessed using Snellen charts and the results were converted into the logarithm of the minimal angle of resolution (logMAR) for statistical analysis. Multimodal retinal imaging included fluorescein angiography (FA), fundus autofluorescence (AF), and spectral domain optical coherence tomography [SD-OCT; Spectralis HRA + OCT (Heidelberg Retina Angiograph + OCT; Heidelberg Engineering, Heidelberg, Germany) and swept-source OCT-A (PLEX Elite 9000; Carl Zeiss Meditec Inc., Dublin, CA, USA)].

The following features were evaluated: changes of BCVA, maximum subretinal fluid (mSRF), foveal subretinal fluid (fSRF), and choroidal thickness (CT) between baseline and $8 \pm 2$ weeks after no-dose PDT. Furthermore, we evaluated BCVA, mSRF, fSRF, and CT before (T1) and after treatment (T2) between no-dose PDT and HDFF PDT. mSRF, fSRF, and CT were measured manually by two expert graders (AS and RS) and the mean value was used for the analysis. Maximum SRF was defined as the highest vertical distance between the end of the outer segment and the RPE; foveal SRF was defined as the vertical distance between the end of the outer segment and the RPE at the foveal center; subfoveal CT was defined as the vertical distance between the hyper-reflective line of Bruch's membrane and the chorio-scleral interface.

Data were analyzed by Shapiro test to investigate the normal distribution. Parametric data were presented as mean and standard deviation and non-parametric data as median and interquartile range. Changes in BVCA, mSRF, fSRF, and CT comparing data before and after no-dose PDT and HDFF PDT were analyzed using the Student paired *t* test. Comparisons of BCVA, mSRF, fSRF, and CT between no-dose PDT and HDFF PDT groups at baseline and follow-up were performed using the Wilcoxon signed rank test and involved only patients that received both treatments. *P* values less than 0.05 were considered statistically significant. Analyses were performed with the open-source software R (R Foundation for Statistical Computing, Vienna, Austria).

**Table 1** Comparative analysis between no-dose PDT and HDFF PDT groups

| | Baseline | | | 2-month follow-up | | |
|---|---|---|---|---|---|---|
| | **No-dose PDT** | **HDFF PDT** | ***p* value*** | **No-dose PDT** | **HDFF PDT** | ***p* value*** |
| BCVA (logMAR) | 0.4 (0.3–0.8) | 0.4 (0.4–0.5) | 0.685 | 0.4 (0.3–0.5) | 0.3 (0.3–0.5) | 0.928 |
| mSRF (μm) | 101 (67–133) | 111 (77–171) | 0.489 | 73 (65–91) | 73 (53–94) | 0.965 |
| fSRF (μm) | 67 (0–105) | 22 (0–143) | 0.822 | 24 (0–68) | 8 (0–42) | 0.644 |
| CT (μm) | 392 (351–463) | 375 (343–383) | 0.353 | 412 (331–419) | 331 (324–374) | 0.085 |

Data are presented as median (IQR)

*PDT* photodynamic therapy, *HDFF* half-dose full-fluence, *BCVA* best corrected visual acuity, *logMAR* logarithm of the minimal angle of resolution, *IQR* interquartile range, *mSRF* maximum subretinal fluid, *fSRF* foveal subretinal fluid, *CT* choroidal thickness

*Comparison performed using the Wilcoxon signed rank test

## RESULTS

Fifteen eyes of 11 Caucasian patients (1 female, 10 male) with a mean age of 54 ± 12 years (range 38–75) met the inclusion criteria and were included in this study. All eyes were included in the no-dose PDT treatment group, while 10 eyes of 8 patients (1 female, 7 male) with mean age of 53 ± 12 years (range 38–75) also received HDFF and were included in the control group. Five eyes of the control group had no SRF reduction after HDFF, while the remaining five eyes showed an improvement of SRF with subsequent recurrence. No treatment-naïve patients were included in the study and no systemic condition that might play a role in the development of CSC affected any patients in either group, including steroid use, pregnancy, or other systemic diseases related to the disease pathogenesis.

In the no-dose PDT treatment group, BVCA and CT significantly improved during the follow-up, from 0.59 ± 0.43 logMAR at baseline to 0.50 ± 0.36 logMAR after 2 months ($p = 0.038$) and from 389 ± 56 μm to 363 ± 62 μm ($p = 0.026$), respectively. Although not statistically significant, mSRF and fSRF showed a trend of reduction during the follow-up (from 141 ± 77 to 111 ± 120 μm ($p = 0.334$) and from 101 ± 79 to 87 ± 129 μm ($p = 0.565$) for mSRF and fSRF, respectively).

Also in the HDFF PDT treatment group, BVCA and CT significantly improved during the follow-up, from 0.54 ± 0.32 logMAR at baseline to 0.46 ± 0.27 logMAR after 2 months ($p = 0.035$) and from 372 ± 35 to 345 ± 37 μm ($p = 0.008$), respectively. Although not statistically significant, mSRF and fSRF showed a trend of reduction during the follow-up (from 138 ± 88 to 87 ± 81 μm ($p = 0.283$) and from 71 ± 81 μm to 33 ± 56 μm ($p = 0.144$) for mSRF and fSRF, respectively).

Comparison of no-dose PDT group (i.e., treatment group) and HDFF PDT group (i.e., control group) showed that BCVA was not statistically different at baseline ($p = 0.685$) and at the 2-month follow-up ($p = 0.928$) (Table 1). No significant difference was also observed between the two groups in mSRF at baseline and ($p = 0.489$) at the 2-month follow-up ($p = 0.965$), in fSRF ($p = 0.822$ and $p = 0.644$ at baseline and 2-month follow-up, respectively), and in CT ($p = 0.353$ and $p = 0.085$ at baseline and 2-month follow-up, respectively) (Table 1, Fig. 1). Three eyes treated with no-dose PDT showed a complete resolution of SRF and two eyes of other patients treated with HDFF PDT showed complete resolution of SRF (Fig. 2).

## DISCUSSION

This retrospective study demonstrated a significant increase of BCVA and a significant

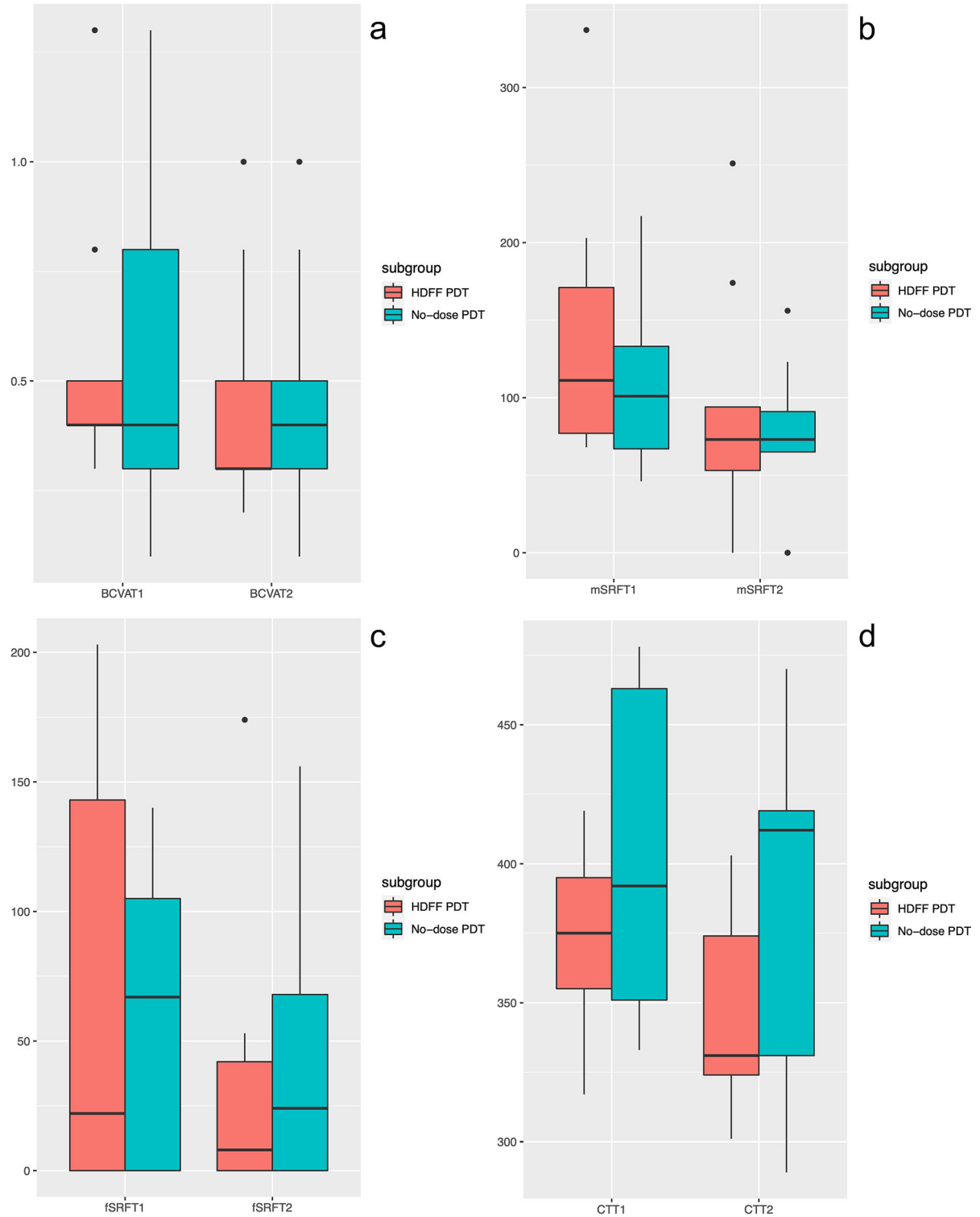


**Fig. 1** Box plots for best correct visual acuity (BCVA) (**a**), maximum subretinal fluid (mSRF) (**b**), foveal subretinal fluid (fSRF) (**c**), choroidal thickness (CT) (**d**) for both groups at different timepoints. Data were expressed as median and range interquartile. *PDT* photodynamic therapy

decrease of CT after no-dose PDT (more specifically after no-dose PDT and HDFF PDT for 10 on 15 eyes) and we observed an improvement trend of mSRF and fSRF after the treatment. Similar improvement was recorded in HDFF PDT. These results are in line with current literature [1]. In addition, we found no significant differences at 2-month follow-up in functional and anatomical results between the no-dose PDT and the HDFF PDT groups. Overall, we observed that BCVA, mSRF, fSRF, and CT improved in both groups without significant differences between patients treated with no-dose PDT and their prior HDFF PDT. Complete resolution of SRF occurred in three eyes treated with no-dose PDT compared to two eyes with HDFF PDT (Fig. 2). Three patients had an immediate worsening of exudation 24–48 h after no-dose PDT treatment, which resolved with an improvement compared to baseline (Fig. 3). This temporary complication has been also observed in patients treated with conventional PDT with verteporfin [30, 31].

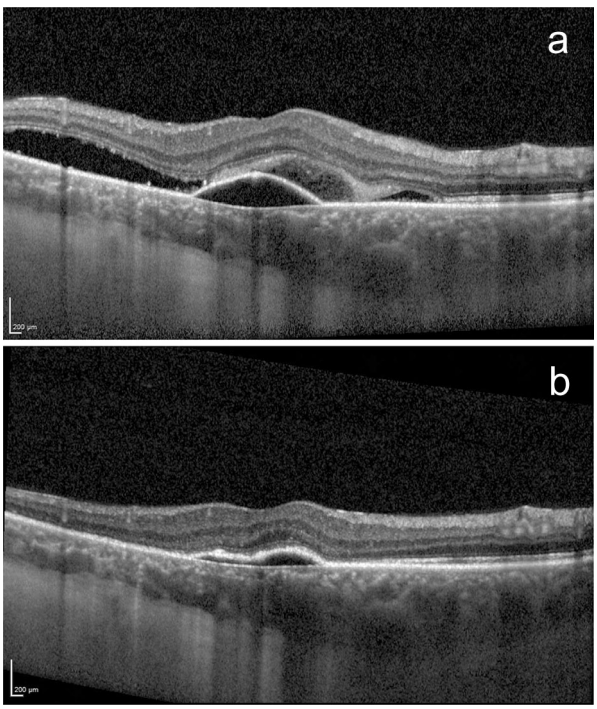


**Fig. 2** Image shows complete resolution of SRF after no-dose PDT. *PDT* photodynamic therapy, *SRF* subretinal fluid

To the best of our knowledge, no-dose PDT for the treatment of cCSC has not been investigated or reported previously. Other nonvisible endpoint therapies that have been used previously for cCSC include SML [7, 8] and TTT [9–11]. Hypothetical mechanisms for nonvisible endpoint laser light therapy have been analyzed and reviewed exhaustively in numerous publications [19, 24, 28]. Challenges of subvisible endpoint therapy that have limited its widespread acceptance include lack of documentable treatment effects and variability in ocular media and retinal light absorption that interfere with treatment parameter selection.

Full-fluence no-dose PDT uses 689 nm red laser light to produce a retinal irradiance of 0.6 W/cm$^2$ with an accompanying non-damaging retinal temperature rise, which could be computed as a 2 °C increase [18–20]. This irradiance is roughly one-tenth that of the 5 W/cm$^2$, 810 nm laser irradiance used previously to treat cCSC with TTT [10] or 10 times greater than the 0.065 W/cm$^2$, 660 nm red light irradiance used in PBT for non-neovascular AMD [24]. In essence, no-dose PDT could be classified as thermally enhanced PBT or reduced-dose TTT.

Various studies explored the mechanism of action and rationale of PBT treatment for AMD [1]. Irradiation with their spectral light combination induces a photochemical reaction on the cellular level, activating cytochrome *c* oxidase (complex IV) as the first chromophore [2, 3]. Complex IV increases the respiratory chain function and mitochondrial respiration, raising protein synthesis, antiapoptotic pathways, antioxidants, cell metabolism, and various anti-inflammatory processes [2, 3].

Furthermore, the effects of TTT in the treatment of cCSC have been reported in several publications [4–7]. TTT raises the temperature at the level of RPE and its deep and prolonged hyperthermia induces hyper-expression of heat shock proteins (HSP) [8]. Hyperthermia elicits an adequate stress response to trigger an immediate and short-term cytokine release leading to monocyte recruitment and activation of biological activities in decompensated dysfunctional RPE cells [8]. Although no-dose PDT uses less power than TTT, spot diameter is larger

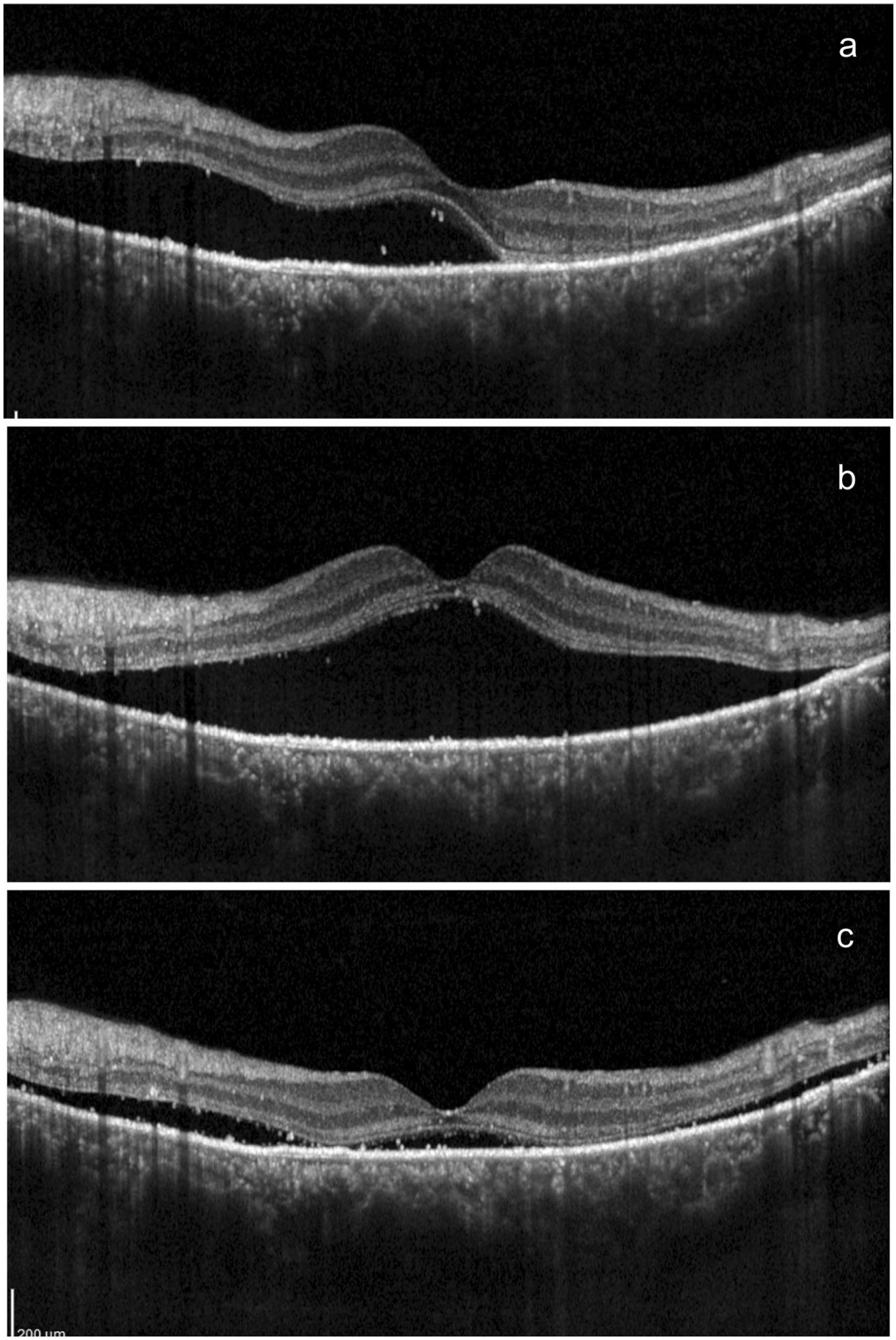


**Fig. 3** Image shows an immediate worsening of exudation 24–48 h after no-dose PDT treatment (**b**), which resolved with an improvement (**c**) compared to baseline (**a**). *PDT* photodynamic therapy

and irradiation time is longer than with TTT. Moreover, melanin absorption coefficient is slightly higher at 689 nm in no-dose PDT than at 810 nm in TTT. Thus, the original calculations could underestimate the biological effects of no-dose PDT. Therefore, we hypothesized that the mechanism of our no-dose PDT treatment is elicited by a non-lethal photothermal rise in all targeted RPE cells due to laser energy absorption by the endogenous chorioretinal chromophores. This thermal elevation triggers and enhances photochemical activities by endogenous fluorophores, activating a biochemical cascade response that rescues/replaces sick, dysfunctional RPE cells. It aims to heal a decompensated outer blood-retinal barrier that results in restored impermeability, transport, and trophic functionality. In addition, secondary to the hyper-expression of the HSP, TTT leads to apoptosis of endothelial cells and consequently vascular thrombosis, mainly expressed in the choroid [4–7]. According to this mechanism, TTT also induces a choriocapillaris closure which results in blood flow stasis and decreased leakage, similar to PDT. Interestingly, this may reasonably explain the immediate worsening in three patients in our series.

Therefore, PBT and hyperthermia could explain the improvement in BVCA, mSRF, fSRF, and CT also observed in patients with cCSC treated with no-dose PDT.

The benefits of no-dose PDT include its low cost, patient comfort, non-proprietary status, and the widespread availability of PDT laser systems.

The limitations of our no-dose PDT study include its retrospective design, small size, the short follow-up duration, and dependence on patients treated previously with HDFF PDT. Furthermore, the absence of a sham group does not allow one to evaluate the placebo effect, which may be significant in patients with CSC. However, the means of morphological and anatomical characteristics (BCVA, CT, mSRF, fSRF) before no-dose PDT and HDFF PDT were not statistically different; thus, the effects of these two treatments were absolutely comparable. Moreover, including eyes with SRF that have already undergone HDFF PDT may imply that these are much more resistant eyes, underestimating the efficacy of the no-dose PDT.

## CONCLUSIONS

In this retrospective study we demonstrated a significant increase of BCVA and a significant decrease of CT after no-dose PDT. Furthermore we found that no-dose PDT and HDFF PDT had similar short-term functional and anatomical results. We hypothesize that the mechanism of action for no-dose PDT is thermally enhanced photobiomodulation or low irradiance transpupillary chorioretinal thermotherapy. A prospective clinical trial (currently under design by our group) is needed to prove the efficacy of no-dose PDT vs. PDT in the management of recurrent cCSC and determine whether no-dose PDT is effective for managing cCSC in treatment-naïve patients.

## ACKNOWLEDGEMENTS

We thank the participants of the study.

***Funding.*** No funding or sponsorship was received for this study or publication of this article.

***Author Contributions.*** Giuseppe Querques, Giorgio Dorin, Martin Mainster, Francesco Bandello: concept and design. Andrea Servillo, Riccardo Sacconi, Ilaria Zucchiatti, Giorgio Dorin, Martin Mainster, Lea Querques. Francesco Prascina: drafting the manuscript. Riccardo Sacconi, Andrea Servillo: statistical analysis. Andrea Servillo, Elena Grachova, Beatrice Tombolini: collecting data.

***Disclosures.*** Andrea Servillo, Ilaria Zucchiatti, Elena Grachova, Lea Querques, Francesco Prascina, Beatrice Tombolini, Giorgio Dorin, Martin Mainster have nothing to disclose. Riccardo Sacconi has the following disclosures: Allergan Inc, Bayer Shering-Pharma, Medivis, Novartis, Zeiss. Giuseppe Querques has the following disclosures: Alimera Sciences, Allergan Inc, Amgen, Bayer Shering-Pharma, Heidelberg,

KBH, LEH Pharma, Lumithera, Novartis, Sandoz, Sifi, Sooft-Fidea, Zeiss. Francesco Bandello has the following disclosures: Alcon, Alimera Sciences, Allergan Inc, Farmila-Thea, Bayer Shering-Pharma, Bausch and Lomb, Genentech, Hoffmann-La Roche, Novagali Pharma, Novartis, Sanofi-Aventis, Thrombogenics, Zeiss.

***Compliance with Ethics Guidelines.*** This retrospective study adhered to the 1964 Helsinki declaration and its later amendments. All subjects signed an informed consent at the time of the treatment for retrospective studies. As a result of the retrospective nature of the study, the study does not require a specific ethics committee approval which is in line with Italian laws.

***Data Availability.*** The data sets used and/or analyzed during the current study available from the corresponding author on reasonable request.



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