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REVIEW

Photodynamic therapy for central serous chorioretinopathy

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Abstract

Purpose **Central serous chorioretinopathy (CSCR) is an idiopathic disorder characterised by detachment of the neurosensory retina due to serous fluid accumulation between the photoreceptor outer segments and the retinal pigment epithelium. There are currently no set guidelines or protocols on its treatment. This study was undertaken to assess the current literature on the the efficacy and safety of photodynamic therapy (PDT) as a treatment option for CSCR.**

Methods **Seven databases (PubMed, CENTRAL, MEDLINE, Web of Science, Embase, Scopus, and The Cochrane Database of Systematic Reviews) were searched without restrictions on time or location. We followed PRISMA guidelines and evaluated quality according to STROBE criteria. In total, 117 citations were identified and 31 studies describing 787 eyes were included for review. Data on indications for PDT in CSCR, dosing regimens of verteprofin PDT (which includes treatment dose of vertoporfin, treatment time, fluence, and spot size), number of treatment sessions, response to treatment, mean length of follow-up, and complications were extracted and analysed.**

Results **Since the introduction of PDT for the treatment of CSCR in 2003, there have been three randomised controlled trials (RCTs), one for acute and two chronic CSCR and 28 further studies that met the STROBE criteria that compared the use of PDT with other treatment options. All studies showed short-term efficacy of PDT in CSCR. The studies were of small sample size and lacked sufficient follow-up to draw conclusions on long-term efficacy and safety.**

Conclusions **There is sufficient scientific evidence to suggest that PDT may be a useful treatment option for chronic CSCR in the short-term. The review identifies a need for robust RCTs with longer follow-up to ascertain the role of PDT as a useful treatment option for CSCR.**

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Introduction

While the exact pathophysiologic mechanisms of central serous chorioretinopathy (CSCR) remains unknown, CSCR is thought to be a primary disorder of choroidal permeability from possible inflammation, ischaemia, or stasis.[1–3] The advent of fluorescein angiography (FA) and indocyanine green angiography (ICG-A) has helped in the diagnosis of this often debilitating condition. Typical FA findings include one or two areas of focal juxtafoveal focal leakage at the level of the RPE, with 'inkblot' or 'smokestack' hyperfluorescence. ICG-A, which facilitates evaluation of the choroidal vasculature, highlights mid-phase multifocal areas of choroidal hyperfluorescence in CSCR patients.[4,5] These areas are postulated to be caused by choroidal vascular hyperpermeability.[4,6–8]

Over the last two decades, numerous treatments for chronic CSCR have been investigated. These have included pharmacologic therapy, laser photocoagulation, photodynamic therapy (PDT) and most recently anti-vascular endothelial growth factor (anti-VEGF).[4,5,7–13] Each study with different treatment modalities has had its own drawbacks—small population size, treatment efficacy, and adverse event occurrence. In this review, we assess the studies that evaluated the use of PDT in the treatment of CSCR.[5,7,8]

In 1999, the treatment of age-related macular degeneration with photodynamic therapy (TAP) study group conducted a randomised control trial which showed superiority with the use of verteporfin vs placebo to treat wet age-related

macular degeneration ($P<0.01$). The standard regime consisted of a light sensitive drug, verteporfin, (6 mg/m^2) which is administered via intravenous infusion of 30 ml over 10 min. Fifteen minutes after the start of the infusion, a laser light at 689 nm delivered 50 J/cm^2 at an intensity of 600 mW/cm^2 over 83 s using a spot size with a diameter 1000 μm larger than the greatest linear dimension of the choroidal neovascularization (CNV) lesion.[9] Over the past decade, there have been various modifications of the PDT regime in terms of fluence, verteporfin dose and time that have been tried. To our knowledge, there has been only one systematic review by Karim and Adelman,[5] who assessed the use of various verteporfin doses in PDT as a treatment option for CSCR. Other variations of PDT treatment have not undergone a systematic review. The rationale of using various PDT modifications has been to reduce both the side effects of PDT and reduce the number of recurrences of CSCR. The main objective of this study was to evaluate whether current literature can guide us regarding PDT's efficaciousness in treating CSCR and what are the best PDT parameters to use.

Materials and methods

We conducted a systematic search of seven databases: PubMed, CENTRAL, MEDLINE, Web of Science, Embase, Scopus, and The Cochrane Database of Systematic Reviews (from 2003 to present) for randomised controlled trials (RCTs) and all other clinical studies with at least 1-month follow-up. All prospective and retrospective studies that met the STROBE criteria were included. The search strategy used both keywords and MeSH terms for the following terms or combinations: Central serous retinopathy, CSCR, PDT, verteporfin; anti-VEGF; ranibuzimab; bevacizumab.

All RCTs were included in our analysis. We included studies that met at least 70% of the STROBE standards (See table 1 below). Two reviewers assessed inclusion into this study and consensus was reached by discussion between reviewers.

The primary parameters of interest were as follows:

1. Indications for PDT based on various definitions of CSCR.
2. Dose of verteporfin, fluence, spot size, treatment time, and frequency of treatment.
3. Mean change in best corrected visual acuity (BCVA).
4. Change in macular thickness on optical coherence tomography (OCT).
5. Changes in choroidal thickness.
6. Changes of leakage on fundus fluorescein angiography (FFA).
7. Length of follow-up.
8. Complications such as choroidal non-perfusion and choroidal neovascularisation.

In the case of studies that sequentially reported longer follow-up of the same series of patients, the latest study with the longest follow-up was included. Data were entered into a Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) datasheet for tabulation and descriptive statistics.

Results

A thorough electronic database search yielded a total of 117 publications that reported the clinical outcomes of PDT in the treatment of CSCR.

PDT and CSCR

A total of 31 reports on clinical outcomes met the inclusion criteria for the use of PDT in CSCR/CSC treatment (see Figure 1).[11,14–44] These included three RCTs (Bae *et al*, Semeraro *et al* and Chan *et al*) that compared PDT with other treatment options as well as 28 STROBE-qualified studies, which also evaluated the efficacy of using PDT to treat CSCR.[11,15,17–39, 41–44] A summary of the three RCTs have been tabulated in Table 2. A meta-analysis could not be performed because of the heterogeneity of the studies.

STROBE-qualified studies

Twenty-eight studies met at least 70% of the STROBE criteria.[11,15,17–39,41–44] The total number of eyes in the studies varied from 5 to 82 (mean 25). Eleven of these studies used standard TAP protocol. The remaining seventeen studies assessed the effect of different parameter variations in the standard TAP protocol in treating CSCR: reduced fluence (eight studies), reduced dose verteporfin (eight studies), variation in exposure time (one study). Two studies[17,22] were noted to have more than one variation in standard TAP protocol both of which used half-dose verteporfin and decreased irradiation time.

Acute vs Chronic CSCR

Acute CSCR was diagnosed if symptoms lasted <3 months, whereas chronic CSCR was diagnosed if symptoms persisted over 3 months.[11,15,17–39,41–44] Three studies contained the use of PDT in treating acute CSCR ($n=3$), whereas the remaining 28 studies assessed the efficacy of using PDT to treat chronic CSCR ($n=28$).[11,15,17–39,41–44]

Table 1 The modified STROBE checklist of items for evaluation of observational studies

	Item no.	*Recommendation*
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any pre-specified hypotheses
Methods		
Study design	4	Present key elements of study design in the paper
Setting	5	Describe the setting or participating location
Participants	6	(a) Statement about institutional review board approval and consent (b) Give the inclusion and exclusion criteria (c) Describe the sources and methods of selection of participants (d) Describe methods of follow-up
Treatments	7	(a) Drug dose(s) defined
	8	(b) Drug administration described
Variables		Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers
Data sources/ measurement	9	
Visual acuity		(a) Define method of visual acuity measurement
OCT		(b) Describe technique for OCT data
Angiography		(c) Describe technique for fluorescein angiography/ICG-A data
Bias	10	Describe any efforts to address potential sources of bias
Study size	11	Explain how the study size was arrived at
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed
Results		
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Previous treatment for CSCR (c) Consider use of a flow diagram
Descriptive data	14	(a) Baseline vision and imaging data reported (b) Lesion type or size discussed (c) Indicate the number of participants with missing data for each variable of interest (d) Summarise follow-up time, eg, average and total amount
Main results	15	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
Adverse events	16	Adverse events reported
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

This table is modified from *Fung et al*.[45]

Acute CSCR. Of our three studies identified, one was an RCT and the other two were case series. Two studies used reduced dose of verteporfin (decreasing dose by 10% from 6 mg and half-dose verteporfin (3 mg)) compared with the standard dose (6 mg), whereas the other used half-fluence PDT (25 J/cm^2 compared with 50 J/cm^2).[16,32,39]

RCT: Chan *et al*[16] in 2008 compared the use of reduced dose verteporfin (3 mg) vs Placebo in 63 eyes. The other standard TAP parameters remained unchanged. The mean duration of CSCR was 6.4 ± 1.7 weeks. All patients had only one treatment session and the mean ± SD PDT laser spot size was 4200 ± 565 μm (range, 3400–4500 μm). Fifty-eight of the 63 patients (92.1%) completed 12-month follow-up.[16] (See Table 2 below.)

Outcome measures

Mean BCVA. Three months post treatment, the mean ± SD logMAR BCVA of the verteporfin group improved to 0.00 ± 0.11 (Snellen equivalent, 20/20), whereas the placebo group improved to 0.08 ± 0.11 (Snellen equivalent, 20/24) from 0.16 ± 0.19 (20/29) and 0.11 ± 0.12 (20/26), respectively ($P = 0.015$). The mean logMAR BCVA at 12 months was significantly better in the verteporfin group compared with the placebo group: – 0.05 ± 0.09 (Snellen equivalent, 20/18), *vs* placebo group of 0.05 ± 0.17 (Snellen equivalent, 20/22) ($P = 0.008$). The mean lines of BCVA improvement at 1 year for the verteporfin group was 1.8 lines, compared with 0.6 line for the placebo group ($P = 0.002$).[16]

Resolution of subretinal fluid (SRF). At the 3-month visit, 35 (89.7%) eyes in the verteporfin group had absence of subretinal fluid, compared with 8 (42.1%) eyes in the placebo group ($P = 0.001$). At 6 months, 36 (92.3%) eyes in the verteporfin group had absence of subretinal fluid, compared with 11 (57.9%) eyes in the placebo group ($P = 0.003$). Thirty-seven (94.9%) eyes in the verteporfin group compared with 11 (57.9%) eyes in the placebo group showed absence of subretinal fluid at the macula at 12 months ($P = 0.001$).[16]

Central foveal thickness (CFT) on OCT. The baseline mean ± SD OCT CFT for the verteporfin and placebo groups were 456 ± 223 μm and 452 ± 218 μm respectively. At 3 months, the mean ± SD OCT CFT of the verteporfin group reduced to 165 ± 82 μm, compared with 309 ± 182 μm for the placebo group ($P < 0.001$), while at 12 months, the mean ± SD OCT CFT for the verteporfin group remained significantly lower compared with the placebo group, with 161 ± 65 μm and 278 ± 192 μm, respectively ($P = 0.001$).[16]

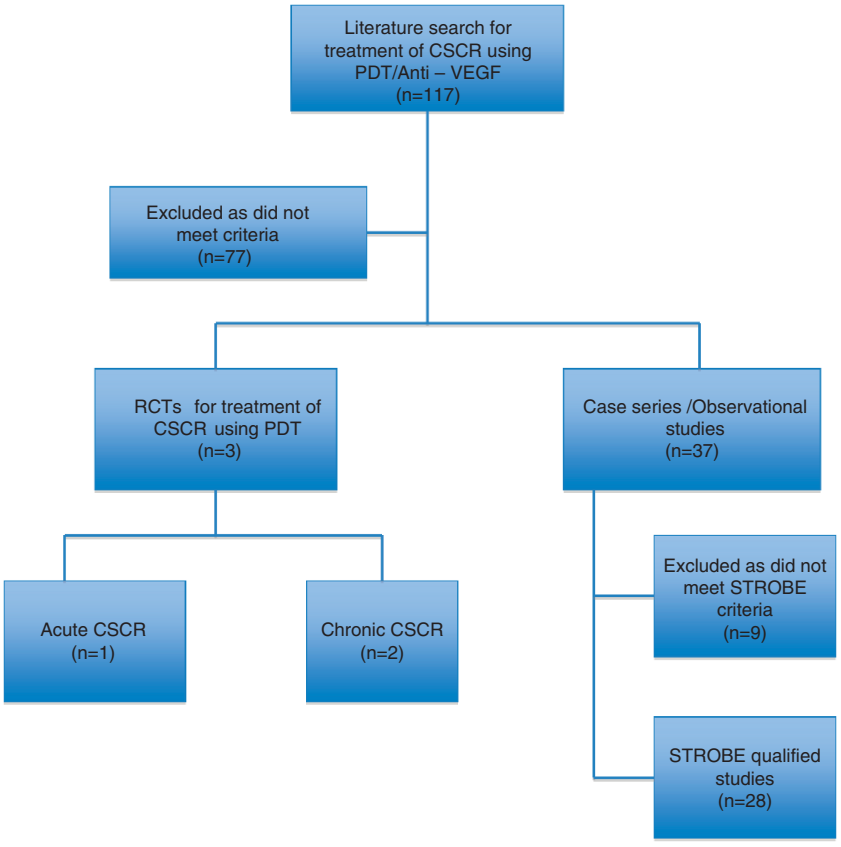

Figure 1 Flowchart showing selection of RCTs and STROBE-qualified studies.

Fluorescein leakage post PDT using ICG-A. At 3 months post PDT treatment, 34 (87.2%) of 39 eyes in the verteporfin group showed complete absence of fluorescein leakage compared with only 4 (12.8%) of 19 eyes in the placebo group ($P<0.001$).[16]

STROBE Studies: Zhao *et al*[39] assessed the use of decreasing dose of verteporfin in treating acute CSCR.15 eyes were assessed. The mean duration before treatment was 35 days (range, 5 days to 4.5 months). The mean follow-up was 11.8 months (range, 6–16 months). The mean number of treatment sessions was 1.25. The mean PDT laser spot size was 2400 μm (range, 500–3700 μm).

Smertsching *et al*[32] assessed the use of half-fluence PDT in treating acute CSCR. 19 eyes were assessed in the study. The duration of symptoms was 31.7 ± 38.1 days. Fifteen eyes were followed up to 12 months (79%). Only one treatment session was required.

Outcome measures

Mean BCVA. Both studies reported an improvement in the mean BCVA after treatment for acute CSCR, which were statistically significant. In Zhao *et al*[39] the mean ± SD logMAR BCVA improved from 0.47 ± 0.28 before PDT to 0.05 ± 0.19. A 4.1 ± 0.25 line improvement 12 months after follow-up was reported. Similarly, Smertsching *et al*[32] also reported an improvement in vision. Sixteen eyes were evaluated at month 3, and the BCVA score changed from baseline by a mean of 10 letters ($P<0.002$). Six months after PDT, 16 eyes were evaluated, and the BCVA score showed an improvement compared with baseline by a mean of 10 letters ($P<0.001$). At 12-month follow-up, 15 eyes were evaluated and BCVA score has changed by nine letters (from 47 to 56) on the ETDRS chart at 12 months ($P=0.003$).

CFT on OCT. One month post PDT treatment, Smertsching *et al*[32] reported complete resolution of SRF on spectral-domain OCT in all 19 patients. By the 12th month follow-up, CFT had decreased by a mean of 163 μm from 406 μm ($P<0.001$).

Chronic CSCR. Two RCTs and 26 STROBE-qualified studies were identified from our search.[11,15,17–39,41–44] Eleven of these studies used normal TAP protocol ($n=11$). The remaining fifteen studies assessed the effect of different parameter variations in the standard TAP protocol in treating CSCR: reduced fluence

Table 2 RCTs results summary

Paper	*Number of eyes*	*Parameter variation*	*Mean duration of CSCR (months)*	*Mean laser spot size (μm)*	*No. of treatment sessions*	*Mean duration of follow-up (months)*	*Baseline BCVA (LogMar)*	*LogMar BCVA*		
								3 months	*6 months*	*1 year*
Bae *et al*[40]	16	HF *vs* anti-VEGF	28.9 ± 23.6 months	1.778.94 ± 464.97	1.38	3–6	HF: 0.30 ± 0.37 Ran: 0.38 ± 0.25	HF: 0.18 ± 0.27 Ran:0.18 ± 0.22 *P* = 0.075	HF: 0.13 ± 0.17 Ran: NA	NA
Chan *et al*[16]	63	Verteporfin (3 mg) *vs* placebo	6.4 ± 1.7 weeks	4200 ± 565	1	12	PDT: 0.16 ± 0.19 Placebo: 0.11 ± 0.12	PDT: 0.00 ± 0.11 Placebo: 0.08 ± 0.11 *P* = 0.015	NA	PDT: – 0.05 ± 0.09 Placebo: 0.05v0.17 *P* = *0.008*
Semeraro *et al*[14]	22	anti-VEGF *vs* HF	>3 months	Not documented	HF: 1.6 ± 0.6 anti-VEGF: 3 ± 1	9	anti-VEGF: 1.3 HF: 1.2	NA	NA	Done at 9 months anti-VEGF: 0.84 (*P* = 0.032) HF: 0.90 (*P* = 0.028)

Abbreviations: BCVA, best corrected visual acuity; HF, half fluence; PD, standard Photodynamic therapy; Ran, ranibizumab; VEGF, vascuar endothelial growth factor.

(seven studies), reduced dose verteporfin (seven studies), variation in exposure time (one study). Two studies (Chan *et al* and Nicolo *et al*) were noted to have more than one variation in standard TAP protocol both of which used half-dose verteporfin and decreased irradiation time.

RCT: Bae *et al*[40] undertook a randomized study on the efficacy of half-fluence PDT *vs* intravitreal ranibizumab (0.5 mg/0.05 ml monthly for three months) to treat chronic CSCR in 16 eyes (eight eyes to each group). The mean duration of CSCR was 28.9 ± 23.6 months. The mean number of treatments was 1.25 sessions in the half-fluence group (a total of 1.38 sessions in both groups). Rescue treatments with a single session of low-fluence PDT for the ranibizumab group and ranibizumab injection for the low-fluence PDT group were conducted if there was re-accumulation or sustained SRF during the subsequent follow-up period and BCVA was <0.2 LogMar. The mean PDT laser spot size was 1778.94 ± 464.97 μm; range, 1500–3100 μm). All 16 eyes completed 6-months follow-up.

Semeraro *et al* undertook a randomized study on the efficacy of half-fluence PDT *vs* intravitreal bevacizumab (1.25 mg once off) to treat chronic CSCR in 22 eyes (12 eyes in bevacizumab group and 10 eyes in low-fluence PDT group). The mean duration of CSCR was >3 months. The mean number of treatments was 1.6 ± 0.6 sessions in the half-fluence group and 3 ± 1 injections in the anti-VEGF group. Fifty percent of all eyes seen had a recurrence of CSCR post initial treatment (seven eyes in anti-VEGF group and four eyes in low-fluence PDT group). Re-injections of bevacizumab or re-treatment with low-fluence PDT were scheduled at least 4 weeks after the initial treatment if one or both of the following criteria were met:

1. Decrease in BCVA of at least five letters on two repeated tests associated with an increase in the pooling area on FA; and/or
2. No decrease in intra-retinal fluid or pigment epithelial detachment (PED) documented by OCT.[14]

The mean PDT laser spot size was not documented and all 22 eyes completed 9-months follow-up. No complications were documented.

Outcome measures

Mean BCVA. Bae *et al*[40] showed that patients treated with low-fluence PDT had an improvement in the mean BCVA: improved from 0.30 ± 0.37 at baseline to 0.18 ± 0.27 at 3 months, but this was not statistically

significant ($P=0.075$) compared with their ranibizumab group. At the 6-month follow-up, there was further improvement in BCVA to 0.13 ± 0.17 in the PDT arm, yet this was still not statistically significant.

In Semeraro *et al*'s study, the mean visual acuity (VA) score (number of ETDRS letters read) improved from 20 ETDRS letters (SD11) to 43 letters (SD 14) at 9 months ($P=0.032$) in the anti-VEGF group. In the low-fluence PDT group, the mean VA score improved from 30 ETDRS letters (SD 8) to 40 letters (SD 12) at 9 months ($P=0.028$). Although the improvement in VA was greater in the anti-VEGF group compared with the low-fluence PDT group, the result was not statistically significant. ($P=0.59$).[14]

SRF. In 75% of the half-fluence group ([40]), there was complete resolution of SRF at 6 months compared with only 25% of eyes in the ranibizumab group.

CFT on OCT. In Bae *et al*'s[40] low-fluence PDT group, the mean excess foveal thickness was reduced significantly from $74.1 \pm 56.0\,\mu$m at baseline to $-35.4 \pm 44.5\,\mu$m at 3 months ($P=0.017$) compared with the ranibizumab group (mean excess foveal thickness decreased from $26.3 \pm 50.6\,\mu$m at baseline to $-23.1 \pm 56.5\,\mu$m at 3 months).

In Semeraro *et al*'s study, OCT revealed a decrease in the serous detachment and the focal areas of PED in both groups. The mean change over 9 months from baseline in central point thickness, defined as the distance between the Bruch membrane and the inner retinal surface, was $127\,\mu$m (SD 36) in the anti-VEGF group and $114\,\mu$m (SD 42) in the low-fluence PDT group ($P=0.0027$ and $P=0.0031$, respectively). Overall, the macular thickness in all patients significantly decreased during the follow-up period (from $345 \pm 85\,\mu$m in the anti-VEGF group to 218 ± 42 and from $361 \pm 108\,\mu$m in the low PDT group to $247 \pm 32\,\mu$m, respectively).[14]

Leakage on FFA. In Bae *et al*'s[40] study, 12 eyes were noted to have active leakage on FFA prior to treatment commencement in both groups: 6 in the low-fluence PDT group and 6 in the ranibizumab group. After completion of primary treatment, five eyes in the ranibizumab group showed persistent active leakage on FFA with only moderate reduction. At 6 months, persistent leakage was regressed in four eyes after an additional low-fluence PDT. All eyes in the low-fluence PDT group demonstrated complete resolution of active leakage after primary treatment, regardless of the presence of SRF.

In Semeraro *et al*'s study, the area of FA pooling decreased in both groups. The difference between FA area size at baseline and that at the nine-month-follow-up visit was statistically significant (anti-VEGF group: $P=0.001$; low-fluence PDT group: $P=0.01$), although the difference between the two groups was not significant. ($P=0.56$).[14]

STROBE studies: Pooled data from STROBE-selected studies showed the number of eyes in the studies varied between 5 and 82 eyes (mean: 24 eyes). The mean duration of chronic CSCR varied from 3 months to 16 years and the mean follow-up duration in these studies ranged from 1 to 56.8 months. Five studies (20.8%) had <6-month follow-up.[11,15,17–31,33–39,41,46,47] Table 3 below highlights key findings from the papers.

Variation in treatment parameters

Standard PDT. Eleven studies ($n=11$) used standard TAP protocol as discussed previously above to treat chronic CSCR. In all ten studies, there was a statistically significant improvement in BCVA after treatment ($P<0.05$).[23,25,26,30,33,34,36,37,41,43,44,46]

Fluence. Of the seven studies identified, three fluence-dosing regimens were identified: Standard fluence ($50\,J/cm^2$), half fluence ($25\,J/cm^2$) and quarter fluence ($12\,J/cm^2$). Two studies ($n=2$) compared standard fluence ($50\,J/cm^2$) with half-fleunce ($25\,J/cm^2$), whereas four studies ($n=4$) used half fluence ($25\,J/cm^2$) and one study ($n=1$) used a quarter fluence ($12\,J/cm^2$) alone to treat CSCR.[15,18,20,24,27,31]

Shin *et al*[27] and Reibaldi *et al* compared standard *vs* half-fluence PDT. Both authors reported better BCVA in the half-fluence group at the end of 12-month follow-up compared the standard group. However, Reibaldi *et al*[24] noted a further reduction CFT in the half-fluence group compared with the Standard fluence group, whereas Shin *et al*[27] noted the opposite. Similarly in the other four studies, BCVA improved and was statistically significant at the end of follow-up.

Verteporfin dose. The doses of verteporfin administered varied from $2\,mg/m^2$ to $6\,mg/m^2$, although most studies used a reduced dose of $3\,mg/m^2$ (n: 7).[17,19,21,22,28,35,42,47] All studies noted an improvement in the BCVA after treatment with verteporfin at the end of follow-up, as well as a reduction in CFT/ central macular thickness (CMT) on OCT. Uetani *et al*[35] in 2012 compared the use of $2\,mg/m^2$ *vs* $3\,mg/m^2$ verteporfin to treat CSCR in 16 eyes. At the end of the 3-month follow-up period, the BCVA was found to be better in the $3\,mg/m^2$ group compared with the $2\,mg/m^2$ group, although this was not statistically significant. From the studies analysed, we can deduce that 3 mg of verteporfin (half dose) produced the best results in terms of BCVA and reduction in CMT after a 6-month follow-up period.

Table 3 STROBE-qualified studies (Chronic CSCR) BCVA summary

Paper	*Number of eyes*	*Parameter variation*	*Mean duration of CSCR (months)*	*Mean laser spot size (μm)*	*No of treatment sessions*	*Mean duration of follow-up (months)*	*Baseline BCVA (LogMar)*	*BCVA (LogMar)*			
								1 month	*3 months*	*6 months*	*1 year*
Yannuzzi *et al*[37]	20	Standard PDT	111.6	4600	1	6.8	1.14	NA	NA	0.54	NA
Cardillo *et al*[46]	16	Standard PDT	>6	1300–4000	1.1	6–12	0.55	NA	NA	0.41	NA
Chan *et al*[41]	6	Standard PDT	9.8	3100	1	12.7	0.24 ± 0.09	NA	NA	NA	0.11 ± 0.13
Taban *et al*[33]	5	Standard PDT	192	6800	1	10	0.82	NA	NA	NA	0.48
Sakalar *et al*[26]	17	Standard PDT	>6	1760	1	13.06	0.26 ± 0.07	0.112	0.053	0.047	0.04 ± 0.02
Arevalo *et al*[44]	18	Standard PDT *vs* standard PDT + IVB/IVP	SPDT: 15.3 ± 7.5 PDT + IVB: 12.5 ± 14.2	Not stated	SDPT: 1.8 PDT + IVB: 1	12	SPDT: 0.60 PDT + IVB: 0.70	SDPT: 0.30 PDT + IVB: 0.62	SDPT: 0.34 PDT + IVB: 0.60	SDPT:0.38 PDT + IVB: 0.64	SPDT:0.20 PDT + IVB: 0.60
Silva *et al*[30]	46	Standard PDT	8.5	3390 ± 945	1.08	56.8	0.6	NA	NA	NA	0.4
Tarantola *et al*[34]	13	Standard PDT	26.7	Not stated	1.23	21.9	0.34	NA	NA	NA	0.24 at 21.9 month
Ruiz–Moreno *et al*[25]	82	Standard PDT	28	Not stated	1	12 ± 10	0.53 ± 0.43	0.51 ± 0.51	0.38 ± 0.41	0.48 ± 0.50	0.37 ± 0.45
Wali *et al*[36]	5	Standard PDT	8–23	Not stated	1	13.7	0.3	NA	NA	NA	0.18
Ozmert *et al*[23]	7	Standard PDT	15.3	Not stated	1	5.4	0.49	NA	NA	0.28	NA
Kim *et al*[43]	45	HF PDT *vs* IVB	HF: 29.4 ± 41.6 IVB: 25.7 ± 42.6	Not stated	HF: 1 IVB: 1.9 ± 1.3	HF: 8.4 ± 7.7 IVB: 10 ± 9	HF: 0.53 ± 0.31 IVB: 0.43 ± 0.34	HF: 0.32 ± 0.27 IVB: 0.35 ± 0.35	HF: 0.30 ± 0.23 IVB: 0.24 ± 0.18	HF: 0.1 ± 0.24 IVB: 0.31 ± 0.25	HF: 0.15 ± 0.24 IVB: 0.21 ± 0.20
Reibaldi *et al*[24]	42	Standard *vs* HF	8.5–9	Standard: 2500 ± 500 HF: 2800 ± 700	1.02	Standard: 8.5 ± 7.3 HF: 8.9 ± 7.8	Standard: 0.43 ± 0.1 HF: 0.46 ± 0.2	Standard: 0.27 ± 0.12 HF: 0.28 ± 0.17	NA	NA	Standard: 0.27 ± 0.12 HF: 0.16 ± 0.18
Smretschnig *et al*[31]	20	HF	>6	2233 ± 738	1	12	ETDRS40 ± 13 letters (range, 12–55 letters)	mean of four letters	Mean of six letters	mean of eight letters	mean of five letters
Shin *et al*[27]	67	Standard *vs* HF	24–38	HF: 3500 ± 1500 Standard: 2900 ± 900	1	HF: 12.6 ± 8.3 Standard: 13.4 ± 5.3	HF: 0.34 ± 0.27 Standard: 0.46 ± 0.42	HF: 0.26 ± 0.28 SF: 0.38 ± 0.38	HF: 0.18 ± 0.32 SF: 0.23 ± 0.41	NA	HF: 0.17 ± 0.32 SF: 0.21 ± 0.39
Inoue *et al*[18]	32	HF	>6	1829	1.1	15.5	0.31	0.26	0.23	NA	0.22
Butler *et al*[15]	5	Quarter fluence (12 J/cm2)	>3	Not stated	1.2	100 days	0.27	NA	0.02	NA	NA

Table 3 (Continued)

Paper	*Number of eyes*	*Parameter variation*	*Mean duration of CSCR (months)*	*Mean laser spot size (μm)*	*No of treatment sessions*	*Mean duration of follow-up (months)*	*Baseline BCVA (LogMar)*	*BCVA (LogMar)*			
								1 month	*3 months*	*6 months*	*1 year*
Lim *et al*[20]	30	HF	Intense hyperfluroescence: 13.2 ± 11.3 Weak hypofluorescence: 11.9 ± 9.0	Intense hyperfluorescence: 2796.7 ± 1017.5 Weak hyperfluorescence: 3007.9 ± 767.7	1	6	Both combined 0.39 ± 0.21 Intense: 0.43 ± 0.28 Weak: 0.36 ± 0.24	NA	NA	Both combined 0.18 ± 0.17 Intense: 0.20 ± 0.27 Weak: 0.21 ± 0.23	NA
Shinojima *et al*[28]	17	Half-dose verteporfin	32.6 ± 36.2	Not stated	1.1	12	0.15	NA	0.07	0.02	0
Nicolo *et al*[22]	38	Half-dose verteporfin	>6	Not stated	1.13	14.2 ± 5.8	0.13 ± 0.72	NA	NA	NA	0.08 ± 0.70
Maruko *et al*[21]	20	Half-dose verteporfin	> 6	6288 ± 872	1	1	0.37	0.27	NA	NA	NA
Uetani *et al*[35]	16	Half-dose *vs* one-third dose verteporfin	30.5	Half dose: 3000 ± 213 1/3 dose: 2775 ± 268	1	3	ETDRS HD 76.0 ± 3.1 ATD 72.7 ± 4.0	HD 78.7 ± 2.5 ATD 74.3 ± 4.0	HD 81.4 ± 3.0 ATD 74.3 ± 4.4	NA	NA
Maruko *et al*[47]	13	Half-dose Verteporfin	>6	5450 ± 1839	1	12	0.4	NA	0.29	NA	0.22
Koytak *et al*[19]	8	Half-dose Verteporfin	12.50 ± 9.20	2125 ± 1042	1.25	12	0.69 ± 0.27	0.38 ± 0.27	NA	NA	0.38 ± 0.27
Chan *et al*[17]	48	Half-dose Verteporfin	8.2 ± 7.1	3935 ± 276	1.2	12	0.31 ± 0.26	NA	0.2	NA	0.15
Pyrds *et al*[42]	16	Half-light exposure	8.81	1638	1	1.93	0.13	0.06	NA	NA	NA

Abbreviations: ATD, one-third-dose verteporfin; BCVA, best corrected visual acuity; HD, half-dose verteporfin; IVB, intravitreal bevacuzimab; PD, standard photodynamic therapy; VEGF, vascular endothelial growth factor.

Time. Only one study ($n=1$) had a variation in time: Pyrds *et al*[42] with a light exposure time of only 42 s (as against 83 s). Complete resorption of the subretinal fluid was documented in all eyes at the 1-month follow-up. BCVA improved from 0.13 LogMar to 0.06 LogMar following a treatment after a 1-month follow-up period. Fourteen patients reported subjective visual improvement in the form of reduction or elimination of the relative central scotoma and or metamorphopsia. Choroidal thickness in the area where PDT was applied decreased from 407 μm (mean; 95% confidence interval (CI) 356–458 μm) to 349 μm (mean; CI95 300–399 μm; $P<0.0001$), and subfoveal choroidal thickness was reduced from 421 μm (mean; CI95 352–489 μm) to 346 μm (mean; CI95 278–414 μm; $P=0.0001$). Initially, subfoveal choroidal thickness was significantly increased in the treated eye compared with the healthy fellow eye (mean 324 μm; CI95 273–376 μm; $P=0.0003$), but after treatment, the difference was not significant.

Combination of treatment parameters. Chan *et al*[17] and Nicolo *et al*[22] had more than one variation in standard TAP protocol: both used half-dose verteporfin and decreased irradiation time. Both studies reported a significant improvement in BCVA and mean decrease in CFT after treatment with PDT.

Laser spot size. Mean laser spot size ranged between 1300 and 6800μm.[15,17–27,29–31,33–37,39,41–44,46,47] Thirteen studies ($n=13$, 54.2%) used a mean spot size <4500 μm. The spot size was not mentioned in seven studies.

Treatment sessions. The mean number of treatment sessions varied from 1 to 1.8 sessions. Fifteen studies ($n=15$, 62.5%) had only one PDT treatment session and five ($n=5$, 20.8%) had 1.1 sessions. The mean number of sessions was 1.1. Recurrence of SRF was the main indicator for the second treatment. The time to recurrence ranged from 3 to 22 months in all studies analysed, with most recurrences happening 3–6 months after initial PDT treatment. Other important factors contributing to re-treatment were persistent SRF and development of CNV following the first treatment, as seen in Reibaldi *et al*'s study. Time to second treatment in eyes undergoing re-treatment was on average 6 months (range from 3 to 12 months).[15,17–27,29–31,33–37,39,41,42,46,47]

Outcome measures

BCVA. Although studies are heterogeneous, from Table 1 we can deduce an improvement in BCVA at 1,3, 6, and 12 months in all groups. At 21.9 months, Tarantola *et al*[34] found an improvement in LogMar BCVA from 0.34 to 0.24.

SRF. At 1 month post PDT treatment, the percentage of SRF resolution varied from 70 to 100%. Only three studies reported complete SRF resolution at 1 month. At 12 months, SRF resolution had improved to 75–100% in all studies. All the other studies had >90% SRF resolution at 12 months.[15,17–27,29–31,33–37,39,41–44,46,47] Below is an analysis of the variations in PDT treatment parameters and the effects on SRF resolution.

Standard PDT group: Of the 11 studies analysed, 4 (36%) had complete resolution of SRF and no recurrence of SRF during the follow-up period. In Chan *et al*'s study, one juxtafoveal CNV developed 3 months post standard PDT treatment.[23,25,26,30,33,34,36,37,41,46]

Variation in verterporfin dose: The variation in verteporin dose PDT group had the best results in terms of resolution of SRF and improvement of BCVA post PDT treatment. In the half-dose verterporfin group, complete resolution of SRF was seen in three out of seven studies (42.9%) at the end of each study's follow-up period. Uetani *et al* reported 70% resolution of SRF in the half-dose verterporfin group compared with only 33% in the 2 mg/m^2 verterporfin group 1 month after treatment with PDT. 100% resolution of SRF was seen in both half-dose and one-third-dose verterforin though, 3 months after treatment. In Koytak *et al*'s study, complete resolution of SRF was noticed in six of eight eyes (75%) at the end of 12 months. No complications were noted in the decreased-dose verterporfin group following PDT treatment.[17,19,21,22,29,35,47]

Variation in Fluence: It is interesting to note that all of the studies with a variation in fluence had a recurrence of CSCR post PDT treatment within a 1-year-follow-up period. Recurrence rate of CSCR varied from 3 to 24%.[15,18,20,24,27,31] Shin *et al*'s[27] reported the best results in terms of resolution of CSCR with a 91.1% resolution of SRF in the half-fluence group compared with 97.0% in the standard fluence group at 1 month. There was only one (3%) recurrence of CSCR in the half-fluence group during the 10-year follow-up period. Inuoe *et al*[18] had the worst CSCR recurrence rates. SRF had completely resolved in 29 eyes (91%) at 3 months after one application of PDT but recurrence of CSCR 12 months post CSCR was seen in 7 of 29 eyes (24%). In Reibaldi *et al*'s[24] study, a juxtafoveal CNV developed 3 months after treatment in one standard-fluence-treated eye.

OCT and Anatomic Changes after PDT using CFT or CMT measurements

Table 4 below shows the results of resolution of SRF in the STROBE-qualified studies. From our

Table 4 STROBE-qualified studies CFT, recurrence and complications summary

Paper	*Number of eyes*	*CFT before Rx (μm)*	*CFT after Rx (μm)*				*Recurrence of CSCR (%)*	*Complications*
			1 month	*3 months*	*6 months*	*1yr*		
Yannuzzi *et al*[37]	20	NA	NA	NA	NA	NA	2 of 20 eyes (10%)	None
Cardillo *et al*[46]	16	241	NA	NA	142 μm	NA	12.5% (2 eyes)	None
Taban *et al*[33]	5	NA	NA	NA	NA	NA	None	None
Sakalar *et al*[26]	17	383.35 ± 29.61	237.82 ± 18.9	188.82 ± 10.66	172.24 ± 5.38	169.24 ± 5.04	None	None
Silva *et al*[30]	46	CMT 316 ± 114	NA	NA	At 48 months	169.7 ± 41.1	4 eyes (8.6%)	None
Tarantola *et al*[34]	13	375 ± 62 (in only four eyes)	NA	NA	NA	231 ± 94 at 24 months	3 eyes (23%) (recurrences occurred at 4, 6, and 22 months)	None
Ruiz–Moreno *et al*[25]	82	325 ± 95	229 ± 70	206 ± 68	202 ± 76	NA	2.4% (2 eyes)	2 eyes Secondary CNV 9 eyes Reactive RPE hyperplasi*a*
Wali *et al*[36]	5	NA	NA	NA	NA	NA	None	None
Arevalo *et al*[44]	18	PDT + IVB 288.4 ± 79.8 PDT: 332.9 ± 85.6	NA	NA	NA	PDT + IVB 163.1 ± 25.9 ($P = 0.005$) PDT: 213.1 ± 54.2 ($P = 0.002$)	Not clearly documented	1 CNV in SDPT group
Ozmert *et al*[23]	7	Retinal elevation mean 152.1 (range 45–272).	0	NA	NA	NA	None	None
Reibaldi *et al*[24]	42	Standard; 324 ± 83 HF: 315 ± 95	Standard:198 ± 73 Half:174 ± 32	NA	NA	NA	2 in standard-fluence (at 3 and 6 months) 1 in low-fluence (at 3 months)	1 standard-fluence-treated eye, juxtafoveal CNV developed 3 months after treatment.
Smretschnig *et al*[31]	20	325 ± 94.7	197 ± 30	215 ± 39.40	204 ± 42.8	222 ± 98.61	3 of 20 eyes (15%)	None
Shin *et al*[27]	67	HF: 291.5 ± 78.6 SF: 307.2 ± 96.6	HF: 175.0 ± 55.1 SF: 164.1 ± 60.8	HF:178.9 ± 60.1 SF: 156.4 ± 23.4	NA	HF: 172.7 ± 49.0 SF: 154.4 ± 23.6	1 of 33 eyes in HF group (3.0%)	None
Inoue *et al*[18]	32	NA	NA	NA	NA	NA	7 of 29 eyes (24%)	None
Butler *et al*[15]	5	0.82μl	NA	0	NA	NA	1 of 5 eyes (20%)	None
Lim *et al*[20]	30	Intense: 362.7 ± 86.6 Weak: 335.8 ± 72.5	NA	NA	NA	NA	1 of 14 eyes (7.1%) 6 months after PDT in weak hyperfluorescence group.	None
Shinojima *et al*[28]	17	NA	NA	NA	NA	NA	5 of 17 eyes (29.4%)	None
Nicolo *et al*[22]	38	345.61 ± 101.00	NA	NA	NA	213.07 ± 47.20	5 of 38 eyes (13.2%)	None
Maruko *et al*[21]	20	SRF height: 199 ± 92μm	22 ± 40μm	NA	NA	NA	None	None
Uetani *et al*[35]	16	HD: 357 ± 26 ATD: 325 ± 21	HD 70% ATD 33%	100% resolution in both groups	NA	NA	None	None
Maruko *et al*[47]	13	397 ± 108 μm	323 ± 120 μm	312 ± 117 μm	317 ± 117 μm	321 ± 122 μm	None	None
Koytak *et al*[19]	8	CMT 366 ± 95 μm	217 ± 32 μm	NA	NA	NA	None	None
Chan *et al*[17]	48	320 ± 142	197 ± 64	175 ± 50	NA	NA	4 of 48 eyes (8.3%)	None
Kim *et al*[43]	45	NA	NA	NA	NA	NA	HF: 1 (4.8%) IVB: 4 (16.7%)	None

Abbreviations: ATD, one-third-dose verteporfin; BCVA, -best corrected visual acuity; HD, half-dose verteporfin; HF, half fluence; IVB, intravitreal bevacuzimab; PTD, standard Photodynamic therapy; SF, Standard fluence.

research, 19 studies assessed the resolution of SRF using CFT ($n=16$) or CMT ($n=3$) as a marker. In all studies although not heterogeneous, there was a statistically significant reduction in either CMT or CFT after treatment with PDT at 1, 3, 6, and 12 months. Tarantola *et al* also noticed SRF resolution and a reduction in CFT at 24 months ($231 \pm 94\,\mu$m from $375 \pm 62\,\mu$m). A similar pattern was noticed in Silva *et al* at 48 months with a reduction in CMT from 316 ± 114 to $169.7 \pm 41.1\,\mu$m.[15,17–27,29–31,33–37,46,47]

Choroidal thickness on OCT

Three studies assessed the choroidal thickness before and after PDT treatment (See Table 5 below).[22,41,42] Both Maruko *et al*[21] and Pyrds and Larsen[42] demonstrated that choroidal thickness in the area treated with PDT initially increased after treatment, then decreased. Pyrds and Larsen showed that choroidal thickness in the area where PDT was applied decreased from 407 μm (mean; 95% CI 356–458 μm) to 349 μm (mean; CI 95% 300–399 μm; $P<0.0001$), and subfoveal choroidal thickness was reduced from 421 μm (mean; CI 95% 352–489 μm) to 346 μm (mean; CI 95% 278–414 μm; $P=0.0001$). They also demonstrated that initially, subfoveal choroidal thickness was significantly increased in the treated eye compared with the healthy fellow eye (mean 324 μm; CI 95% 273–376 μm; $P=0.0003$), but after treatment, the difference was not significant. A similar result is seen in Maruko *et al*'s[21] study where the mean choroidal thickness in the PDT group increased significantly from $389 \pm 106\,\mu$m at baseline to $462 \pm 124\,\mu$m ($P=0.008$) by 2 days after treatment, and then reduced rapidly to $360 \pm 100\,\mu$m ($P=0.001$) at 1 week and $330 \pm 103\,\mu$m ($P=0.001$) after 4 weeks as compared with baseline. In Chan *et al*[41] 3 months after PDT, where the mean diameter of the dilated choroidal vessel reduced from 546 μm to 371 μm ($P=0.028$) in the six eyes analysed.

Recurrence of CSCR

From Table 2, ten studies ($n=10$) recorded no recurrence of SRF after treatment with PDT in a 12-month follow-up period. We can also deduce that the recurrence rate of CSCR once treated with PDT varied from 0 to 24% despite previous complete resolution of SRF after first treatment ($n=14$). Recurrence of CSCR resulted in another session of PDT treatment in most studies.[15,17–27,29–31,33–37,39,41,42,46,47] There was no pattern to timing of recurrence in any of the studies.

Complications

Eighty-five percent of studies ($n=22$) reported no ocular or systemic complications from the administration of PDT in the treatment of CSCR.[15–23,26–28,30,31,33–37,43,44,46,47] Four studies, however, reported ocular complications.[24,25,41,44] Ruiz–Moreno *et al*[25] reported secondary CNV in two eyes (2.4%) post PDT treatment. Arevalo *et al* as well as both Chan *et al*[41] and Reibaldi *et al*[24] also noted the development of juxtafoveal CNV in one eye each (5.6%, 16.7%, and 2.4% respectively) three months after PDT treatment.

Discussion

Chronic and recurrent CSCR can be a debilitating condition, often affecting the working age group. There is currently no gold standard therapy for its treatment. In this systematic review, we evaluated the efficacy of using standard and varied PDT treatment modalities from various RCTs and STROBE-qualified observational studies over the last 10 years. All these studies had small sample sizes, different inclusion criteria, different methods of examination, short follow-up and lacked matched controls. All treatment modalities led to an improved BCVA and a resolution of SRF to varying degrees of success; however, no correlation could be established between BCVA and CFT before or after PDT in any study. This lack of correlation may be because of the fact that majority of our studies analysed had a mean duration of CSCR >6 months prior to PDT therapy, by which time photoreceptors may have been damaged.

There are two RCTs that compared PDT with other treatment modalities in treating CSCR in both the

Table 5 Choroidal thickness analysis pre and post PDT treatment

Paper	*Number of eyes*	*Choroidal thickness before Rx (μm)*	*Choroidal thickness after Rx (μm)*				*Recurrence of CSCR (%)*	*Complications*
			1 months	*3 months*	*6 months*	*1 year*		
Chan *et al*[41]	6	546 ± 67	NA	371 ± 56	NA	NA	None	1 Juxtafoveal CNV @ 3 months
Pyrds *et al*[42]	16	407 (356–458)	349 (300–399)	NA	NA	NA	None	None
Maruko *et al*[21]	20	LP: 345 ± 127 PDT: 389 ± 106	LP 340 ± 124 PDT 330 ± 103	NA	NA	NA	None	None

Abbreviations: LP, Laser photocoagulation; PTD, standard Photodynamic therapy.

acute and chronic forms at six months. Although the verteporfin and fluence doses varied between these two studies, the mean BCVA at 3 months was better in both groups ($P = 0.015$ and $P = 0.075$ respectively). This effect was maintained at 6 months in both studies. A similar effect was also noted in the STROBE-qualified studies.

Our review suggest a lower rate of side effects and reduction in CSCR recurrence for eyes treated with half-dose verteporfin PDT. In the half-dose verterporfin group, complete resolution of SRF without recurrence was seen in three out of seven studies (42.9%) at the end of each study's follow-up period. A converse effect was seen in the variable-fluence group, where all of the studies with a variation in fluence had a recurrence of CSCR post PDT treatment within a 1-year-follow-up period. Recurrence rate of CSCR varied from 3 to 24%.

In most of our analysed studies, the laser treatment spot size was selected based on angiographic leakage in the FA and not on choroidal abnormality as demonstrated on ICG-A, hence, why a smaller laser spot was used in treating majority of cases. This approach was to avoid overtreatment of the choroidal vasculature and prevent choroidal ischaemia. However, it may be argued that the pathological level of CSCR is actually at the choroidal level, so treatment may be better guided by ICG-A findings and not by leakages sites on FA.

PDT treatment is known to be associated with certain rare but serious complications: such as secondary RPE changes, choriocapillaris hypoperfusion, choroidal ischaemia, choroidal infarction, and CNV development related to the hypoxic damage caused by choriocapillaris occlusion at the site of PDT, all of which can potentially reduce the VA.[11,16,46,48] As CNV is a known complication of CSCR, it is difficult to assess the role of PDT in the development of CNV. In three of our analysed studies, two patients developed juxtafoveal CNV 3 months after PDT treatment. A further two patients developed secondary CNV during follow-up. In these cases, a decrease in choroidal perfusion could have increased the risk of CNV development by promoting release of vascular endothelial growth factor. There were no documented cases of choroidal non-perfusion.

Conclusion

Our systematic review demonstrates that a modified half-dose PDT protocol remains the safest and most effective method of treating chronic CSCR based on a heterogeneous collection of studies. Ideally, a randomised controlled clinical trial is warranted to evaluate the efficacy of modified PDT regime using half-dose verteporfin in treating patients with chronic CSRC with other available treatment options to better understand the relative effects of the various options available for this condition.

Conflict of interest

The authors declare no conflict of interest.

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