Northern Treatment Advisory Group

Verteporfin (Visudyne®) photo-dynamic therapy in the management of chronic central serous chorioretinopathy (CSCR) - new clinical evidence addendum

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Summary of research literature reviewed

The literature describing use of verteporfin for chronic CSCR has seen considerable growth, with many trials and case series reaching publication, mostly concentrating on the efficacy of smaller doses of verteporfin or fluence and/or combinations of the two. However, many published since the last review in 2015 have been retrospective studies, looking at populations treated over a number of years, which provides some statistical power to the number treated, an issue faced by the last review. However, due to the small numbers being treated, even 10 years of data within one hospital may only yield less than 100 patients.

The published studies do offer a reasonable proxy population in terms of demographics to the population which would receive treatment under this proposal: most patients are male and roughly middle-aged. The duration of symptoms varies between trials; the baseline before treatment reducing to less than 6 months (previous reviews have seen treatment starting at 6 months or greater).

The overall impact on acuity across all studies is positive. Since the baseline level of acuity is widely variable, it is unsurprising that the change in acuity is also widely variable. There are also few studies with long-term follow-up, which is an important omission given that recurrence is a well-described part of the natural history of the disease in many cases. Indeed, recurrence and re-treatment is described in a number of the included studies.

The table below sets out a numerical summary of the studies contained in this review, and the rest of this section gives a brief overview of the results, strengths and weaknesses of each included study.

Study	Number of		Mean duration before treatment; months (range)	% male	Mean age; years (range)	Verteporfin dose; mg/m^2	Mean visual acuity; LogMAR		
	eyes	patients					Baseline	12 months	End of follow up (length of follow up)
Young Joo Park et al (2019)[4]	94	88	8.4 (0.3–62)	68	47.9 (32-76)	6 & 3	0.34	0.16	0.19 (58m)
van Dijk EHC et al (2018)[2]		89‡	6 (3.76 – 11)	60	48 (40 – 57)	3	0.5†‡	-	(8m)
Cheng-Kuo Cheng, et al (2017)[5] half verteporfin dose cohort	20	20	At least 4 months	85	46.8 (38- 54)	3	0.39 ± 0.28		0.15 (6)
Cheng-Kuo Cheng, et al (2017) [5] half fluence cohort	20	20	At least 4 months	90	45.1 (37-53)	6	0.36 ± 0.41		0.12 (6)
Timothy Y. Y. Lai, et al (2015)	192	192	3	80	45 (36 – 53)	3	0.35 ±0.25 ‡	0.18 ‡	0.14 (36) ‡
Lim, et al (2014)[1]	265	237	24 (0.25-96)	74	52	See trial summary			

*Mean follow-up; cases varied †Approximate conversion to LogMAR - not reported
‡Only results from relevant arm(s) of study or cohort(s) of patients included

Clinical evidence supplied by requesting ophthalmologist:

Lim JI et al (2014)[1]

*This trial summary was from the previous assessment document, but placed here for completeness

This multicentre retrospective case series included 265 eyes of 237 patients. The duration of CSCR prior to treatment was not reported for all cases; for the 212 eyes with a reported disease duration, the mean was 24 months (range 1 week – 8 years). The median time was 12 months. The cohort of patients in this series was predominantly male (74%), with a mean age of 52 years (range not reported). The dose of verteporfin used is not reported.

Mean visual acuity at baseline was 0.39 LogMAR. The analysis was stratified into three groups: 115 eyes with baseline acuity of Snellen 20/32 (0.2 LogMAR) or better; 97 eyes with baseline acuity of Snellen 20/40 to 20/80 (0.3–0.6 LogMAR); and 47 eyes with baseline acuity of Snellen 20/100 (0.7 LogMAR) or poorer. The follow-up lengths varied considerably, from one month to more than one year. Mean change from baseline to follow-up was -0.5 LogMAR, -0.14 LogMAR and -0.23 LogMAR for each group respectively.

The multicentre retrospective nature of this case series, as well as the heterogeneity in treatment regimens used, makes it difficult to draw quantitative conclusions. However, all three groups showed improvement.

van Dijk EHC,et al (2018)[2] The PLACE trial

This open label, multicentre randomised controlled trial compared the use of half dose vPDT with high-density subthreshold micropulse laser treatment (HSML) in cases of CSC, of which 89 patients were randomised to the vPDT arm.

Patients had experienced visual symptoms for on average 6 months (range 3.76m – 11m) and were predominantly male (60%) with mean age of 48.9yrs. The dose of verteporfin was 3mg/m^2

For the vPDT cohort the baseline BCVA was 76.9 ±8.32. 6 to 8 weeks after the treatment, the change in BCVA was measured at +4.6 ±6.62 (n= 80) and at 7-8 months follow up the BCVA was +6.78 ±8.54 (n= 67). This was a superior result compared with the HSML cohort.

At 6-8 weeks following treatment, 51.2% of the vPDT cohort had a complete resolution of SRF with the 48.8% who had persisting SFR receiving a repeat treatment. Therefore, the cohort of patients who attended the final evaluation (n = 67) at 7 - 8months who demonstrated a 67% resolution of SFR comprised of patients who received either one or two treatments.

Salehi M, et al (2015) [3]

This meta-analysis looked at 25 RCT's which had evaluated varied forms of treatment for CSC including: anti-VEGF (ranibizumab, bevacizumab), PDT (full-dose, half-dose, 30%, low-fluence), laser treatment (argon, krypton and micropulse laser),beta-blockers, carbonic anhydrase inhibitors, helicobacter pylori treatment, and nutritional supplements (Icaps, lutein).

The majority of the trials were of low power due to numbers treated and/or design. The authors concluded: "CSC remains an enigmatic condition in large part due to a natural history of spontaneous improvement in a high proportion of people and also because no single treatment has provided overwhelming evidence of efficacy in published RCTs. While a number of interventions have been proposed as potentially efficacious, the quality of study design, execution of the study and the relatively small number of participants enrolled and followed to revealing endpoints limits

the utility of existing data. It is not clear whether there is a clinically important benefit to treating acute CSC which often resolves spontaneously as part of its natural history. RCTs comparing individual treatments to the natural history would be valuable in identifying potential treatment groups for head-to-head comparison. Of the interventions studied to date, PDT or micropulse laser treatment appear the most promising for study in future trials"

Other clinical evidence published since 2015

Young Joo Park et al (2019) [4]

This single centre retrospective study included 94 eyes of 87 patients. The patients selected to be included had undergone vPDT between March 2003 and February 2015 and had been seen in the same clinic for at least 3 years after treatment. These patients had previously been diagnosed with CSCR via fluorescein angiography and regarded as chronic when their symptoms persisted for longer than 6 months. The mean age of the patients was 47.9 years (range 32.6yrs – 76.6yrs) with males making 68% of the cohort.

A varied regime of fluence and verteporfin dosage was used across the cohort, 76 patients received half-fluence with standard dose verteporfin, 12 received full-fluence with half dose verteporfin and 6 patients received full-fluence with a standard dose of verteporfin.

Mean follow-up duration was 58.1 months± 20.3 months.

Mean best-corrected visual acuity improved by 0.15 ± 0.31 logMAR (pre-treatment mean BCVA was 0.34 ± 0.33 logMAR, with mean BCVA at the last visit 0.19 ± 0.36 logMAR).

Eight-five eyes (90%) had resolution of subretinal fluid 1 month after treatment. Nine eyes (10%) showed nonresponse i.e. continued SRF leakage persisting beyond 6 months post vPDT. There were 23 (24.5%) patients of the initial responder cohort who showed recurrence of symptoms, with the mean time elapsed being 28.6 months ± 20.8 (range 1.1 to 86.3 months).

The limitations of this study include its retrospective design and the small population. Selection and attrition bias may have occurred because patients without recurrence are less likely to re-visit the clinic, hence, the rate of recurrence and non-response may have been overestimated in the present study. Nevertheless, this study included long-term follow-up data, as well as analysis of the outcome of secondary treatment for patients who were nonresponsive or had recurrence.

Cheng-Kuo Cheng, et al (2017) [5]

This prospective, randomized, observer-masked comparison study compared the efficacy of half dose verteporfin/standard fluence with standard verteporfin/half dose fluence. 40 eyes from 40 patients were randomised into the two groups to be treated in a single centre over the period July 2008 to December 2012. All the patients had been experiencing symptoms for at least 4 months.

Patients were seen for regular follow-up visits at 1 week before and at post-treatment Week 1, Month 1, Month 3, and Month 6 after treatment.

Both regimens resulted in high percentages of resolution of SRF (100% in the half-dose group and 95% in the half-fluence group) and comparable improvement in visual acuity outcomes. However, the small number of cases in this study does not provide sufficient statistical "power" to detect smaller differences between these two groups. In addition, a 6-month follow-up alone may not be able to detect the long-term efficacy and adverse effect such as recurrence of leakage and the occurrence of late complications.

Timothy Y. Y. Lai, et al (2015) [6]

This single centre retrospective study included 192 eyes of 192 patients and was designed to compare the effects of half dose vPDT treatment versus natural disease progression. Seventy-five eyes with CSC were treated with half-dose verteporfin PDT, and 117 eyes were in the untreated control group.

The mean ± SD logMAR visual acuity at baseline for the half dose verteporfin PDT and untreated control groups was 0.35 ± 0.25 and 0.28 ± 0.28, respectively. At 3 years, and the mean ± SD logMAR visual acuity of the half-dose verteporfin PDT and untreated control groups improved to 0.14 ± 0.20 and 0.23 ± 0.28, respectively. The mean visual improvement at 3 years was significantly higher in the half-dose verteporfin PDT group compared with the untreated control group.

Eyes treated with half-dose verteporfin PDT had significantly faster complete resolution of subretinal fluid compared with untreated controls. At the last follow-up, five eyes (6.7%) in the half-dose verteporfin PDT group had persistent subretinal fluid, compared with 11 eyes (9.4%) in the untreated control group. During the follow-up period, recurrence of CSC developed in 15 eyes (20.0%) in the half-dose verteporfin PDT group, compared with 62 eyes (53.0%) in the untreated control group

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