Northern Treatment Advisory Group

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Verteporfin (Visudyne®) photo-dynamic therapy in the management of chronic central serous chorioretinopathy

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Summary

Background Central serous chorioretinopathy (CSCR) is a relatively common but usually self-limiting condition which can cause a variety of visual disturbances. It is caused by leakage of fluid from choroidal capillaries distorting the retina. In a small fraction of cases, the disease is prolonged or chronic. This is rare enough to be difficult to quantify, but estimates (with a high level of uncertainty) suggest around 30 patients per year in the North East of England. The disease typically affects men in middle age.

Treatment The standard treatment for chronic CSCR is laser photocoagulation, which is not suitable in many cases due to proximity to the macula, or watchful waiting. The treatment under review in this document is off-licence systemic infusion of verteporfin (a drug licenced for treatment of age-related macular oedema) followed by local activation at the affected part of the retina using fluence from a laser of a given wavelength (photodynamic therapy). This aims to reduce the leakage from choroidal capillaries. This is designed to be a one-off treatment, but some patients will have recurrent disease requiring further treatments: the proportion to which this applies is unclear, partly because of the heterogeneity between trial protocols.

Trials Approximately twenty trials have been published which assess the clinical outcome of visual acuity in patients; more have been published which assess the anatomical and morphological changes to the retina. All are relatively small, and there is considerable heterogeneity between trials in terms of the treatment regimen used (varying doses of verteporfin and fluence have been used, and patients have been treated at a wide variety of stages of disease). There are no studies with very long-term follow-up, though one small study (15 patients) had a mean follow-up time of almost seven years. Varying veteporfin PDT protocols have been adopted as standard practice in other health economies around the world.

Adverse events There have been no serious reported unexpected side effects of verteprofin PDT in the trials to date. The application received proposes use of half-dose verteprofin which may reduce the incidence of adverse events.

Cost Considerable uncertainty surrounds any estimate of the costs associated with this treatment: incidence of the condition is unclear; likelihood of recurrence and re-treatment is unclear; and comparisons with normal treatment regimens have not been done. A ball-park figure with a high degree of uncertainty suggests that introducing this treatment in the North East would cost £50,000 per annum.

Introduction

Central serous chorioretinopathy (CSCR) is an idiopathic eye disease in which fluid leaks from underneath the retina (the layer of sensory cells at the back of the eye). This fluid typically collects underneath the macula (the most sensitive part of the retina). This collection of fluid causes the macula to 'bulge', and this bulging causes visual disturbance. Depending on the severity of the condition, these disturbances could include: mild blurring of the central part of the visual field; a 'washed out' effect on colour vision; a 'shadowing' effect; or severe restriction of sight in the centre of the visual field.

CSCR has a 10:2 male predominance. Those aged 25-55 years are most frequently affected; the mean age of cases is around 50 years. 80% of cases occur in only one eye; bilateral disease is more common in those aged over 50. The annual incidence is estimated to be 6 per 100,000 population, giving a ballpark annual figure of 870 cases in the Northern Region (of which 166 are North East cases).

CSCR is usually self-limiting: around 85% of cases will spontaneously and completely resolve within six months (though 30-50% of these will recur at some point). A further 10% of cases will resolve within twelve months. However, the remaining 5% of cases will not resolve within 12 months: these patients are described as having 'chronic' CSCR.

For those patients with chronic CSCR, treatment options are limited. Laser photocoagulation can be used to burn the leak closed, but this has been proven not to result in visual gain but only maintain the level of vision at the time of treatment. Furthermore, it is reliant on the area to be treating being well-defined, and the danger of worsening the situation through 'collateral damage' means that it cannot be used when the leak is close to the centre of the macula.

Verteporfin is a drug which is usually used to damage and block off abnormal blood vessels which form in some eye diseases, such as the wet form of macular degeneration. Verteporfin is administered intravenously, collects in the abnormal blood vessels, and is then stimulated by light of a specific wavelength (photodynamic therapy - PDT). The light causes the verteporfin to react with oxygen in the blood to form short-lived chemicals which damage the blood vessel lining, and effectively block it off altogether. Since the light is required for the reaction to occur, the reaction is highly localised to the area exposed to the light.

In clinical trials and some individual cases, verteporfin PDT has been experimentally used (off licence) to treat chronic CSCR. The reasoning is that verteporfin PDT can be used to damage the 'leaky' vessels sufficiently to 'plug' the leak, but not to close them off altogether.

The Northern Treatment Advisory Group has received an application to conduct an appraisal of and make a recommendation for the use of verteporfin PDT in chronic CSCR according to specific criteria described in the following section. A similar application was reviewed by NETAG in March 2011. In response, the evidence was

reviewed by the Lead Pharmacist for NETAG, William Horseley. This review is an update of this earlier document.[1]

Lead author's note on visual acuity scales

The commonest scale used for reporting visual acuity in the research literature is the **Log**arithm of the **M**inimum **A**ngle of **R**esolution (LogMAR). This is measured using a LogMAR chart, on which the typeface of a consistent number of letters per line decreases in a geometric pattern. In LogMAR terms, a larger number indicates worse vision. The scale is calibrated with 0 as plumb normal vision, and 2.0 as near-blindness. Values below zero indicate supranormal vision. It may be useful to think of this as the level of "magnification required" to achieve normal vision.

For the purposes of comparison throughout this review, the values in all studies have been converted to LogMAR. It should be noted, however, that this is not a precise conversion, since difference visual acuity scales rely on different methods of measurement (e.g. the Snellen scale uses the Snellen chart, rather than LogMAR). Hence, such conversions cannot be made with absolute accuracy.

Since LogMAR is not a clinically familiar measurement for many physicians in the UK, a conversion chart for a variety of scales is provided on page 20; this should be interpreted with a degree of caution due to the limitations outlined above.

Clinical evidence

There are a number of different scales used to describe visual acuity, which can cause confusion for non-specialists. The commonest scale used in research is the LogMAR scale. This is a logarithmic scale describing the degree of magnification required to achieve normal (20/20) vision. Hence, higher LogMAR values indicate higher levels of visual impairment. For ease of understanding, this discussion includes calculated LogMAR conversions even where this notation system was not used by the original authors. A conversion chart for other common notation systems is given in Appendix 1.

The application for verteporfin PDT in chronic CSCR relates to the following specific criteria:

1. Chronic CSCR present for at least three months
2. Active disease diagnosed by fluorescein and ICG angiography, and optical coherence tomography
3. Baseline visual acuity of 6/60 (1.00 LogMAR) or 35 letters (1.30 LogMAR) or better
4. No evidence or history of allergy to treatment

In addition, the application refers to the use of verteporfin at half the dose used for its licenced indication in age-related macular degeneration: 3mg/m^2 body surface area as opposed to the usual 6mg/m^2.

A similar application was received by the North East Treatment Advisory Group (NETAG) in March 2011, and a report was produced by William Horsley (Lead Pharmacist for NETAG) in response. The following description of the evidence is based on this earlier assessment, plus new literature indexed in Medline and published between 2011 and 2014.

The search for evidence relating to this topic was restricted to papers published in English between 2011 and 2014. Papers tagged with the keyword ‘verteporfin’ and the Medline topic index ‘Chronic serous chorioretinopathy’ were included in an initial review; those which were irrelevant to the clinical question (including those which discussed only acute CSCR), or which did not discuss clinical outcomes (e.g. reported exclusively on structural changes in the eye rather than changes in vision) were excluded. Papers which reported on combined therapies (e.g. verteporfin PDT plus intravitreal anti-vascular endothelial growth factor therapy) were also excluded, as they were considered to be out-with the remit of this review. A further search was conducted for papers published prior to 2011; this confirmed that all relevant papers published before this date were included in the earlier NETAG assessment.

Summary of research literature reviewed

The literature describing use of verteporfin for chronic CSCR has seen considerable growth in the last three years, with a large number of trials and case series reaching publication. However, a most of these studies are small: of the 17 to be discussed in this review, 9 had 25 patients or fewer, and only one included more than 100 patients. Complicating the picture further is the heterogeneity of treatment regimens: only 7 of the 17 studies described herein used the same verteporfin dose as is proposed in the North East. Furthermore, the dose of fluence – that is, the laser used to activate the verteporfin – varies between trials. There is also considerable variation between trials in severity of disease, from an average of “mild vision loss” in some studies to “severe vision loss” in others.

The trials discussed herein describe changes in visual acuity, but this does not fully capture the patient impact of chronic CSCR. As the retina is distorted, the image as since is also distorted – but not necessarily in a way which affects acuity. A patient can have severely distorted vision (e.g. in which straight lines appear curved), yet normal acuity (i.e. ability to perceive objects at a given distance). The converse is also true. There is a wealth of further literature describing the anatomical changes in response to verteporfin CSCR, but this is even further removed from the patient experience.

The published studies do offer a reasonable proxy population in terms of demographics to the population which would receive treatment under this proposal: the majority of patients are male and roughly middle-aged. The duration of symptoms varies, but most studies include only cases suffering symptoms for more than six months.

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. In several studies, while the change is statistically significant, the clinical significance is suspect (e.g. improving from a severe vision loss of Snellen 6/95 to Snellen 6/75). 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, despite relatively short follow-up.

The table overleaf 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)
Ruiz-Moreno et al (2010)[2]	82	72	28 (3–38)	78	46 (29–70)	6	0.53	0.37*****	0.37 (12m*****)
Chan et al (2008)[3]	48	48	8 (3–40)	90	46 (32–73)	3	0.31	0.15	0.15 (12m)
Lai at al (2006)[4]	20	18	7 (3–24)	94	46 (38–62)	3	0.3†	-	0.2† (1m)
Maruko et al (2010)[5]‡	8	8	>6 (-)	88	60 (46–70)	3	0.37	-	0.27 (1m)
Reibaldi et al (2010)[6]	42	42	8.5 (-)	81	49 (37–64)	6	0.45	0.21	0.21 (12m)
Zhao et al (2009)[7]‡	8	8	1 (0–2)	75	57 (35–66)	1.8	0.59	-	0.09 (12m*)
Koytak et al (2010)[8]	8	8	12.5 (6–34)	88	41 (33–66)	3	0.69	0.30	0.30 (12m)
Lim et al (2014)[9]	265	237	24 (0.25-96)	74	52 (-)	-	*Refer to text below*		
Nicoló et al (2014)[10]	60	56	>6 (-)	85	49 (-)	*Refer to text below*			
Butler et al (2011)[11]	5	5	>3 (-)	-	- (-)	6	0.3†	-	0.1† (100d*)
Bae et al (2014)[12]‡	18	-	13.3 (-)	83	51 (-)	6	0.38	0.12	0.12 (12m)
Ohkuma et al (2013)[13]	22	21	44 (3–187)	95	54 (44–76)	6	0.22	0.08	0.08 (12m)
Jirarattanosopa et al (2012)[14]	27	27	- (-)	-	- (-)	3	0.32	0.18	0.18 (12m)
Smretschnig et al (2013)[15]	20	19	>6 (-)	-	- (-)	6	1.2†	1.1†	1.1† (12m)
Vasconcelos et al (2013)[16]	17	15	>6 (-)	94	48 (32–65)	6	0.7†	0.6†	0.6† (81m*)
Karakus et al (2013)[17]	27	24	12 (6–24)	71	44 (29–61)	3	0.19	0.07	0.07 (21m*)
Rouvas et al (2012)[18]	29	27	>6 (-)	70	43 (29–61)	3	0.45	-	0.08 (20m*)

*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

Ruiz-Moreno et al (2010)[2]

This multi-centre case series included 82 eyes of 72 patients. The mean duration of CSCR before treatment was 28 months (range 3–38). The cohort of patients in this case series was predominantly male (78%), with a mean age of 46 years (range 29–70). In contrast to the regimen under consideration in this review, the intervention in this study was verteporfin PDT at full-dose (6mg/m^2) rather than half-dose (3mg/m^2).

Mean visual acuity improved from 0.53 LogMAR to 0.48 LogMAR after six months, and 0.37 LogMAR by the end of follow-up ($p < 0.0001$). The change can also be described in terms of the number of extra lines the patient was able to read on the ETDRS vision chart. In this case, the mean change was an increase of 1.9 lines, with 20% of eyes gaining five or more lines. 27% of eyes could read no extra lines, and 6% of eyes worsened.

Given the nature of the disease, progress can also be measured in terms of central foveal thickness (that is, the amount the centre of the macula is 'bulging' forward). In this case, mean thickness decreased at each follow-up point to nearly half its original thickness by the end of follow-up.

84% of eyes required only one treatment; the others required 2–4 treatments.

Chan et al (2008)[3]

This case series included 48 eyes of 48 patients. Compared to the Ruiz-Moreno study, the mean duration of CSCR before treatment was much shorter, at 8 months (range 3–40). The cohort was predominantly male (90%) with a mean age of 46 years (range 32–73). 40% of the cohort had suffered previous episodes of CSCR. This case series used the same verteporfin dosage as is under consideration in this review (3mg/m^2).

Mean visual acuity was markedly better at baseline in this group than in the Ruiz-Moreno group: 0.31 LogMAR. Despite this, mean visual acuity still showed considerable improvement after one year: 0.15 LogMAR ($p < 0.001$). The mean number of ETDRS lines gained was 1.6 (range -5–8). Two eyes lost vision as measured by ETDRS lines.

The Chan case series included a sub-group analysis based on presence or absence of pigment epithelial detachment (PED) at baseline. PED is a disease process in which the pigmented layer of the retina becomes detached from the underlying anchoring layer. Those with PED at baseline (27%) showed no significant improvement following treatment.

Lai et al (2006)[4]

This case series is described as the pilot study for the Chan et al (2008) case series[3], though it is not clear whether the patients included in this pilot study were also included in the Chan et al (2008) series. This case series included 20 eyes of 18 patients. The mean duration of CSCR before treatment was 7 months (range 3–

24). The cohort was predominantly male (94%) with a mean age of 46 years (range 38–62). 72% of the cohort has suffered previous episodes of CSCR. This case series used the same verteporfin dosage as is under consideration in this review (3mg/m^2).

Mean visual acuity at baseline was Snellen 20/40 (equivalent to 0.3 LogMAR). Follow-up lasted only four weeks, at which visual acuity has improved to Snellen 20/30 (0.2 LogMAR; $p < 0.001$). As with the Chan et al study, those with PED at baseline showed no significant improvement in visual acuity.

Maruko et al (2010)[5]

This comparative case series reports the results of therapy in 12 eyes (of 12 patients) of 'classic' CSCR treated with laser photocoagulation and 8 eyes (of 8 patients) of 'chronic' CSCR for which laser treatment was not considered suitable and which were treated with verteporfin PDT. The mean duration of CSCR before treatment is not reported beyond stating that it was greater than six months in all patients in the verteporfin PDT arm.

The mean age of the laser photocoagulation group was 55 (range 38–65), compared with 60 (range 46–70) in the verteporfin PDT group. Both groups were predominantly male (75% of laser photocoagulation group; 88% of verteporfin PDT group). This study used the same verteporfin dosage as is under consideration in this review (3mg/m^2).

The main outcome measure for the study was choroidal thickness. After four weeks, there was no significant reduction in choroidal thickness in the laser photocoagulation group, compared with a small but significant reduction in the verteporfin PDT group.

Visual acuity is also reported at baseline and four-week follow-up. The mean acuity in the laser photocoagulation group changed from 0.10 LogMAR to 0.06 LogMAR. In the verteporfin PDT group, the change was from 0.37 LogMAR to 0.27 LogMAR.

While the comparison between the groups is limited in this study by the different patient characteristics between the groups, the 8 patients in the verteporfin PDT arm of the study add further data to the evidential picture.

Reibaldi at al (2010)[6]

This non-randomised comparative case series included 42 eyes of 42 patients with chronic CSCR. These were non-randomly split into two groups for a study of the specific parameters associated with the laser therapy applied after receiving verteporfin. This variation is not material to the question of whether verteporfin should be used, and indeed there were no significant differences in outcome between the groups, so for the purposes of this review, we will treat the 42 patients as a homogenous group.

This study used a verteporfin dose of 6mg/m^2 – twice that under consideration in this review. The mean duration of CSCR before treatment was 8.7 months. The cohort was predominantly male (81%), and had a mean age of 49 years (range 37–64). The mean visual acuity at baseline was 0.45 LogMAR, improving to 0.28 LogMAR after one month and 0.21 LogMAR after twelve months ($p < 0.05$ in both cases). Central foveal thickness also decreased significantly.

As with the other studies, the 8 patients with PED at baseline showed no significant improvement in visual acuity.

Zhao et al (2009)[7]

This study of 15 eyes in 15 patients with acute (not chronic) CSCR used a variety of doses of verteporfin in order to determine the smallest effective dose. Seven patients were given one of seven doses of verteporfin, varying from 4.2mg/m^2 to 0.6mg/m^2 by 0.6mg/m^2 intervals. The lowest effective dose was found to be 1.8mg/m^2; the researchers used this for the next seven patients, and re-treated those who had been undertreated using this dose.

For the 8 patients who received only 1.8mg/m^2, the mean visual acuity at baseline was 0.59 LogMAR. This improved to 0.09 LogMAR by the end of follow-up, which varied from 7 to 15 months after treatment (mean 12.6 months). This cohort was predominantly male (75%), with a mean age of 57 years. As these were acute patients, their mean duration of symptoms was short: mean 4 weeks (range: 6 days–2 months).

Koytak et al (2010)[8]

This small study included 8 eyes of 8 patients. The mean duration of CSCR prior to treatment was 12.5 months (range 6–34). The cohort of patients in this case series was predominantly male (88%), with a mean age of 41 years (range 33–56). This case series used the same verteporfin dosage as is under consideration in this review (3mg/m^2).

Mean visual acuity at baseline was 0.69 LogMAR: considerably poorer than the other studies discussed thus far. After one month, mean acuity increased to 0.38 LogMAR ($p = 0.017$). At twelve-month follow-up, it had increased further to 0.30 ($p = 0.018$ for change against baseline). There were also significant improvements reported in mean central macular thickness.

The single patient with pigment epithelial detachment (PED) at baseline showed no significant improvement in acuity following treatment.

Lim et al (2014)[9]

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, it is clear that all three groups showed improvement.

Nicoló et al (2014)[10]

This Italian multicentre retrospective study compared 31 eyes of 28 patients who received half-fluence PDT with 29 eyes of 28 patients who received half-dose PDT. The disease duration prior to treatment was not reported for all patients, but the inclusion criteria for the study included disease duration of at least six months. The cohort of patients was overwhelmingly male (85%), with a mean age of 49 years (range not reported). There were no notable demographic differences between the two groups. The 'half-fluence group' received 25 J/cm^2 fluence and 6mg/m^2 verteporfin, and the 'half-dose group' received 50 J/cm^2 fluence and 3mg/m^2 verteporfin.

Visual acuity at baseline was 0.19 LogMAR in the 'half-fluence' group, and 0.13 LogMAR in the 'half-dose group'. Both groups saw improvement at 12 months, with no statistically significant difference between the groups (to 0.08 LogMAR in the 'half-fluence group' and 0.07 LogMAR in the 'half-dose' group).

Importantly, this study reports that 14 of the 31 eyes had at least one recurrence of subretinal fluid during the study period; several had multiple recurrences. A total of 20 extra treatments were given to patients. Fewer recurrences and re-treatments were needed in the 'half-dose' group compared with the 'half-fluence' group. The time period over which these recurrences and additional treatments were given is not made clear in the paper, though may be around 12 months, as this was the most frequently reported follow-up time within the paper.

Butler et al (2011)[11]

This very small case series described five eyes of five patients with chronic CSCR treated with 6mg/m^2 verteporfin PDT with a 'very minimal' dose of fluence. All patients showed improvement, including one who had normal visual acuity at

baseline and supranormal visual acuity following treatment. The authors conclude that more research is needed to determine the best possible fluence dose.

Bae et al (2014)[12]

This South Korean study compared verteporfin PDT with intravitreal ranibizumab for the treatment of chronic CSCR. The detail of the comparison is beyond the scope of this review, which will concentrate only on the verteporfin arm, though the ultimate conclusion was that verteporfin PDT outperformed intravitreal ranibizumab. The verteporfin dose used was 6mg/m^2.

The relevant arm of the study included 18 eyes of an unspecified number of patients. The eyes were predominantly male (83%), with a mean age of 51 years (range not reported). The mean duration of symptoms prior to treatment was 13.3 months (range not reported). Baseline visual acuity was 0.38 LogMAR, improving to 0.12 LogMAR at 12 months. It should be noted that two of the patients who received verteportfin PDT went on to receive 'rescue treatment' consisting of 3 injections of ranibizumab, so the mean improvement cannot be entirely attributed to verteporfin PDT.

Ohkuma et al (2013)[13]

This Japanese study used reduced-fluence PDT to treat 22 eyes of 21 patients. The cohort was predominantly male (95%) with a mean age of 54 years (range 44–76). The mean duration of symptoms prior to treatment was 44 months (range 3–187). The study used a verteporfin dose of 6mg/m^2.

At baseline, the best corrected visual acuity was 0.22 LogMAR, which improved to 0.08 LogMAR after 12 months, representing statistically significant improvement. However, the authors point out that only 6 eyes showed *clinically* significant improvement (defined as an improvement of at least 2 lines on a vision chart); the remaining 16 eyes remained *clinically* unchanged.

Jirarattanasopa et al (2012)[14]

This Thai study has been published only in abstract form. It was a retrospective case series involving 27 eyes of 27 patients with chronic CSCR treated with verteporfin PDT at a 3mg/m^2 verteporfin dose. The patient demographics and duration of symptoms prior to treatment are not reported. Mean visual acuity improved from 0.32 LogMAR at baseline to 0.18 LogMAR at 12 months.

Smretschnig et al (2013)[15]

The full text of this study is currently unavailable; however, the abstract appears to describe a study which is not dissimilar to others discussed herein. It is notable, however, for including patients whose visual acuity at baseline is considerably worse than the other papers discussed. The authors followed 20 eyes of 19 patients who

had suffered symptoms of CSCR for six months or more. They were treated with verteporfin PDT, at a 6mg/m^2 verteporfin dose. Visual acuity improved from 40 letters (approximately 1.2 LogMAR) to 44 letters (approximately 1.1 LogMAR) at 12 months. While this improvement was statistically significant, it is difficult to interpret the degree of clinical relevance of such an improvement: both 1.2 LogMAR and 1.1 LogMAR represent severe vision loss.

Vasconcelos et al (2013)[16]

This small study is notable for its long period of follow-up. The study included 17 eyes of 15 patients who were almost all male (94%) and had a mean age of 48 years at treatment (range 32–65). The duration of symptoms prior to treatment is not recorded, but the inclusion criteria require symptoms of at least six months' duration. The study used a verteporfin dose of 6mg/m^2.

At baseline, the mean best corrected visual acuity was 63 letters (approximately equivalent to 0.7 LogMAR). At 12 months, this improved to 71 letters (approximately 0.6 LogMAR), and this improvement was maintained to final follow-up. Final follow-up occurred at a mean time of 81 months (range 62–104). Two of the 17 eyes underwent second treatments during the follow-up period (one at 2 years and one at 7 years), and hence the sustained improvement cannot be fully attributed to the original intervention.

Karakus et al (2013)[17]

This small study, too, has a longer period of follow-up than is typical, and has an increased relevance to the clinical question under consideration as it uses half-dose verteporfin (3mg/m^2). The study followed 27 eyes of 24 patients. Again, the majority of patients were male (71%). The mean age was 44 years (range 29–61), and the mean duration of symptoms prior to treatment was 12 months (range 6–24).

At baseline, mean best corrected visual acuity was 0.19 LogMAR. This improved to 0.07 LogMAR by 12 months, 0.09 LogMAR at 24 months, and 0.07 LogMAR at final follow-up (mean 29 months, range 12–36). Retreatment for recurrence was necessary in 2 eyes.

Rouvas et al (2012)[18]

This retrospective analysis considered 29 eyes of 27 patients with chronic CSCR. The majority of patients were male (70%), and the mean age was 43 years (range 27–59). The duration of symptoms before treatment is not reported, but an inclusion criterion was that symptoms must have been present for at least 6 months.

Mean best corrected visual acuity at baseline was 0.45 LogMAR, which improved to 0.08 LogMAR at the end of follow-up (mean follow-up time 20 months, range 12–40). Results at 12 months are not reported. Notably, and atypically among similar studies, 12 patients had a 0.0 LogMAR at end of follow-up (that is, vision which is

fully correctable to normal). Four eyes required second treatments during the follow-up period. It is unclear why the patients in this study had such notably improved outcomes compared with similar studies already discussed.

Chan et al (2010)[19]

This review article discussed several non-standard indications for verteporfin PDT. In the case of CSCR, it concluded that – while the outcomes reported in prior studies were promising – "randomised control trials that are sufficiently powered for confirming efficacy outcomes at twelve months are needed".

Karim et al (2013)[20]

This additional, more recent, review article concentrated entirely on the treatment of chronic CSCR with verteporfin. It concluded: "While the body of evidence supports PDT as an efficacious and relatively safe treatment for CSCR, further evaluation of the long-term efficacy and safety of PDT, as well as protocol improvements are required."

Safety

Verteporfin in combination with PDT has been in clinical use for several years in many markets, although use in this specific indication is limited and outside of the product licence. Nevertheless, the treatment has demonstrated consistent safety outcomes in large randomised studies and clinical use. The most common adverse effects are known to be hypercholesterolemia, back pain due to infusion, photosensitivity, visual defects and impairment, and nausea, each affecting around 10% of patients.

Studies of chronic CSCR that used the half-dose verteporfin regiment have reported no unexpected safety issues, although even the trials with the longest follow-ups only reach 21 months. It is unclear from the comparative studies whether the half-dose regimen decreases the incidence or severity of side effects, but – conversely – the limited evidence available does not indicate that the half-dose regimen presents any additional safety issues.

Cost analysis

The dose of verteporfin is based on patient body surface area, therefore the dose administered may vary considerably from patient to patient. Verteporfin is available in single-use 15mg vials and the dose required for the proposed regimen is 3mg/m^2. Therefore, a single vial will provide sufficient drug for a patient with a body surface area of up to 5m^2 – which far exceeds the plausible range for body surface area. Hence, for the purposes of this cost analysis, we shall assume that each patient requires one vial.

It would theoretically be possible to 'pair up' patients to share one vial, which would reduce the number of vials needed for treatment and hence an element of the cost. However, given the relative rarity of the condition and the practicality of doubling up in this manner, it seems unlikely to occur in practice.

Verteporfin, as Visudyne®, costs £1020 per vial (inc VAT). In addition to the cost of the drug, it is assumed that a day-case admission is required for administration by intravenous infusion followed by laser therapy. It is assumed that this treatmed will be carried out under the payment-by-results tariff code BZ24C (non-surgical ophthalmology with length of stay 1 day or less and age 19 years or over) at £341 per admission (excluding the market forces factor uplift, typically between 1 and 3% for Trusts in the North East). Thus, the total cost of one treatment episode is around £1360.

Due to the highly specific nature of the target patient group it is difficult to reliable estimate the number of patients that might require treatment within the North East. The prevalence of CSCR is estimated at 5.8 per 100,000 population, but most of these will resolve spontaneously within a short period of time. A workable estimate based on audit activity for the previous version of this review was that approximately 30 patients per annum within the North East would qualify for verteporfin PDT. This would generate a cost for newly diagnosed patients of circa £40800 per annum.

However, there is considerable heterogeneity among studies of the frequency with which repeat treatments are required due to recurrence or initial treatment failure. A conservative estimate based on these studies suggests that around 15% of patients require one or more further treatments; it seems reasonable to suggest a minimum 20% additional cost to account for this (circa £8000). It should be noted, however, that this may represent a considerable underestimate, especially as most of the studies published to date have relatively short periods of follow up.

Currently, verteporfin treatment is available on an individual basis for patients who demonstrate exceptionality. This process has attendant delays, which clinicians suggest is likely detrimental to outcomes: this position is supported by a small amount of evidence in some of the studies discussed.

Other treatments that may be used for chronic CSCR include laser photocoagulation or conservative management with no active treatment. Long term follow-up (11 to 15 years) for these alternative strategies indicates that good visual acuity is achievable

for most patients, with only 5% experiencing severe deterioration in visual acuity. The rate of recurrence was circa 40% in untreated patients and nil in patients treated with laser photocoagulation. Although visual acuity was good, almost all eyes had some residual abnormal vision such as colour or contrast sensitivity. Additionally, some patients are not suitable candidates for laser photocoagulation due to the proximity of the lesion to the macula.

The level of uncertainty around the patient group and outcomes means that it is not possible to perform a cost-effectiveness analysis of verteporfin PDT versus laser photocoagulation or no treatment. Laser photocoagulation would probably attract similar admission costs, but without the drug costs associated with verteporfin PDT, so it could be assumed that the incremental cost per patient of verteporfin PDT versus laser photocoagulation is of the order of £1000.

Follow-up outpatient appointments are about £70 per visit. The treatment application includes three-monthly outpatient follow-up appointments, the total cost of which would be £210 per annum. However, this may not be a true incremental cost compared with other treatments (or, indeed, no treatment) which may also require follow-up.

Patient impact

Patient impact is very difficult to quantify. It is self-evident that loss of vision, typically in middle-age, will be distressing, and may have important occupational and economic implications. However, it is not clear what impact treatment with verteporfin PDT will have for patients. There is only a handful of cases in which return to pre-morbid visual acuity is reported. In several studies, improvements which are statistically but not clinically significant are reported. The long-term effects of treatment are not yet described, but it is clear that recurrence remains a strong possibility.

Hence, it is not clear that verteporfin PDT will result in an outcome which is substantially beneficial to patients, and the small number of heterogenous published studies makes it difficult to estimate the number of patients who would experience a real-world benefit.

Yet, it is clear from all of the studies that verteporfin PDT almost always produces some degree of improvement in visual acuity.

It is important to consider that visual acuity represents only one element of the visual disturbance in central serous chorioretinopathy: other visual disturbances are common but more difficult to measure and so rarely reported in the literature. There is a considerable volume of literature which reports on the anatomical and morphological changes to the retina which are caused by this treatment in an attempt to capture a broader picture, but it is clear that change in morphology is not always accompanied by change in visual symptoms (and the converse is also true).

Therefore, it may be that the literature review herein underplays the real-world impact of treatment, though the degree to which this is true is impossible to quantify.

Points to consider

The majority of cases of CSCR resolve spontaneously, often within three months of diagnosis. However, there is a small cohort of patients for whom symptoms will persist, producing chronic CSCR. Treatment options currently consist of either laser photocoagulation – which is not suitable for all cases – or conservative supportive care with no active treatment.

Verteporfin PDT, using a half-dose regimen, has been investigated as a potential treatment option for chronic CSCR. While a large number of studies have now been published in this field, only a small minority report on the clinically relevant outcome of visual acuity, and still fewer use the treatment regimen proposed (others use varying doses of verteporfin or fluence).

All studies consistently demonstrated improvements in vision upon treatment with verteporfin PDT that strengthen the case for the observed effects being treatment related as opposed to spontaneous. However, it is notable that not all of the improvements described would be particularly clinically relevant, even where they are statistically significant. There are also no direct randomised comparisons with current standard therapies. No safety issues have been identified from this off-licence use of verteporfin to date.

Treatment with verteporfin PDT is costly, at an estimated £1360 per treatment. Some patients require more than one treatment, though the proportion of patients this affects is unclear (especially in the long-term). However, the number of patients in the North East who might require treatment is estimated to be only 30 per annum. It should be noted that all of these estimated costs and patient populations rely on untested assumptions.

Since the publication of the NETAG review in March 2011, a number of new studies have been published. However, these are all small, vary widely in the treatment regimen used, and typically have relatively short follow-up periods. There are a number of small trials cited in grey literature which do not vary widely from those that have been discussed in this review, and have not been included herein as the lack of detailed methods and results makes assessment of their findings impossible.

Several papers make reference to verteporfin PDT for chronic CSCR being funded as a standard treatment in some health economies, yet the relative rarity of the condition makes it difficult to find details of funding policies in this area.

In the US health economy, verteporfin PDT is funded by the health insurer Aetna after four months of CSCR symptoms, provided the patient is not legally blind and that the area covered by the lesion is less than or equal to 6.4mm.[21] Verteporfin PDT for chronic CSCR is not covered by the national Medicare system, but nor is it nationally barred: local discretion is allowed.[22]

Visual acuity scales conversion chart

ICD-9-CM ranges		Decimal	US	Snellen fraction		Minimum angle of resolution		Visual acuity score
				6m	1m	MAR (1/V)	LogMAR	Letter count
(Near-) Normal vision	Range of normal vision	1.6	20/12.5	6/3.8	1/0.63	0.63	**-0.2**	110
		1.25	20/16	6/4.8	1/0.8	0.8	**-0.1**	105
		1.0	**20/20**	**6/6**	**1/1**	**1.0**	**0**	**100**
		0.8	20/25	6/6.75	1/1.25	1.25	**0.1**	95
	Mild vision loss	0.63	20/32	6/9.5	1/1.6	1.6	**0.2**	90
		0.5	20/40	6/12	1/2	2.0	**0.3**	85
		0.4	20/50	6/15	1/2.5	2.5	**0.4**	80
		0.32	20/63	6/19	1/3.2	3.2	**0.5**	75
Low vision	Moderate vision loss	0.25	20/80	6/24	1/4	4	**0.6**	70
		0.20	20/100	6/30	1/5	5	**0.7**	65
		0.16	20/125	6/38	1/6.3	6.3	**0.8**	60
		0.125	20/160	6/48	1/8	8	**0.9**	55
	Severe vision loss	0.10	20/200	6/60	1/10	10	**1.0**	50
		0.08	20/250	6/75	1/12.5	12.5	**1.1**	45
		0.063	20/320	6/95	1/16	16	**1.2**	40
		0.05	20/400	6/120	1/20	20	**1.3**	35
	Profound vision loss	0.04	20/500	6/150	1/25	25	**1.4**	30
		0.03	20/630	6/190	1/32	32	**1.5**	25
		0.025	20/800	6/240	1/40	40	**1.6**	20
		0.02	20/1000	6/300	1/50	50	**1.7**	15
(Near-) blindness	Near-blindness	0.016	20/1250	6/380	1/63	63	**1.8**	10
		0.0125	20/1600	6/480	1/80	80	**1.9**	5
		0.01	20/2000	6/600	1/100	100	**2.0**	0
	Blindness	No light perception (NLP)						

Adapted from http://precision-vision.com/Introduction-to-Visual-Acuity-Measurement/a-visualacuity.html

Author's declaration

The lead author has no relevant interests to declare.

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