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Photodynamic therapy for neovascular age-related macular degeneration (Review)

Wormald R, Evans J, Smeeth L, Henshaw K

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ABSTRACT

Background
In neovascular age-related macular degeneration, new vessels grow under the retina, distorting vision and leading to scarring. This is further exacerbated if the blood vessels leak. Photodynamic therapy, originally used in cancer treatment, has been investigated as a way to treat the neovascular membranes without affecting the retina.

Objectives
The aim of this review is to examine the effects of photodynamic therapy in the treatment of neovascular age-related macular degeneration.

Search strategy
We searched for trials in the Cochrane Central Register of Controlled Trials - CENTRAL (which includes the Cochrane Eyes and Vision Group trials register) on the Cochrane Library (Issue 4 2002), MEDLINE (1966 to November 2002) and EMBASE (1980 to November 2002). We used the Science Citation Index to search for reports that cited relevant study reports. We contacted experts in the field and we searched the reference lists of relevant studies for further trial reports.

Selection criteria
We included randomised trials of photodynamic therapy in people with choroidal neovascularisation due to age-related macular degeneration.

Data collection and analysis
Two reviewers extracted the data independently. Relative risks were combined using a fixed effect model after testing for heterogeneity using a chi-square test.

Main results
Two published trials were identified that randomised 948 participants to verteporfin therapy compared to 5% dextrose in water. Both trials were performed by the same investigators using largely the same clinical centres and funded by manufacturers of verteporfin. Outcome data were available at 12 and 24 months after the first treatment. Participants received on average five treatments over two years. The relative risk of losing three or more lines of visual acuity at 24 months comparing the intervention with the control group was 0.77 (95% confidence interval 0.69 to 0.87). The relative risk of losing six or more lines of visual acuity at 24 months comparing the intervention with the control group was 0.62 (95% confidence interval 0.50 to 0.76). The results at 12 months were similar to those at 24 months.

Authors' conclusions
Photodynamic therapy in people with choroidal neovascularisation due to age-related macular degeneration is effective in preventing visual loss. Outcomes and potential adverse effects of this treatment should be monitored closely. Further independent trials of Verteporfin are required to establish that the effects seen in this study are consistent and to determine important questions not yet addressed, particularly relating to quality of life and cost.
SYNOPSIS

Photodynamic therapy may reduce vision loss caused by one type of age-related macular degeneration, but more research is needed.

Age-related macular degeneration (AMD) affects the macula, the central area of the retina. One type is called ‘wet’ or neovascular AMD, as new blood vessels develop in the macula. These can leak and scar the eye, causing vision loss. Photodynamic therapy involves injecting chemicals, then radiating light as the chemicals flow through these new blood vessels. This aims to activate the chemicals enough to destroy the vessels, but not enough to hurt the eye. The review found evidence that this may reduce vision loss caused by neovascular AMD, but more research is needed.

BACKGROUND

Age-related macular degeneration (AMD) is a disease affecting the macula, the central area of the retina. The disease is defined as degeneration of the macula in older people (aged over 50) with no other apparent cause for the degeneration.

There are several signs in the retina that are associated with increasing age and increased risk of developing age-related macular degeneration. These signs, known as age-related maculopathy, include the presence of drusen (yellow spots beneath the retina) and pigimentary disturbance. In general age-related maculopathy is not associated with visual loss. Some people with age-related maculopathy will go on to develop age-related macular degeneration.

There are two main types of AMD. In geographic atrophy (dry) AMD, the retinal pigment epithelium is lost completely in localised areas. In neovascular (wet) AMD, sub-retinal neovascular membranes (new blood vessels) develop beneath the retina. These are associated with scarring of the retina that affects vision. The new vessels can leak causing haemorrhage that leads to larger scars or macular oedema and significant loss of vision. This review is concerned with treatment for neovascular age-related macular degeneration.

Sub-retinal neovascular membranes are defined as classic or occult according to their appearance on fluorescein angiography, in which fluorescent dye is injected intravenously and imaged as it passes through the blood vessels of the eye. Classic membranes are clearly delineated and leak fluorescein uniformly. Occult membranes are often hidden or their extent is hard to delineate, and fluorescein leakage is patchy. It is thought that these two angiographic patterns reflect the different extent to which the vessels have penetrated the retinal pigment epithelium, occult vessels lying underneath the retinal pigment epithelium. Some lesions may have both classic and occult components.

Trials have shown that early laser photocoagulation of classic extrafoveal membranes (those not directly underneath the fovea at the centre of the macula) could delay the loss of vision in a small number of patients (MPS 1994). However, most patients present with subfoveal membranes, and whilst photocoagulation can limit the extent of the subsequent visual loss, it causes immediate loss of central vision due to the concurrent destruction of the overlying retina.

Photodynamic therapy, originally used in the treatment of cancer, has been investigated as a way to treat the neovascular membranes without affecting the retina. Photoreactive chemicals are injected into the patient and irradiated with light as they pass through the neovascular membranes. This light is strong enough to activate the chemicals, causing them to emit free radicals that destroy the blood vessels, but is not strong enough to cause damage to the overlying retina.

OBJECTIVES

The aim of this review is to examine the effects of photodynamic therapy in the treatment of neovascular age-related macular degeneration.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies
We included randomised controlled trials.

Types of participants
We included trials in which participants were people with neovascular age-related macular degeneration as defined by the study investigators.

Types of intervention
We included any study in which photodynamic therapy was compared to another treatment, placebo or no treatment.

Types of outcome measures
The primary outcome for this review is prevention of visual loss. Any well-defined outcome based on visual acuity was used depending on the way in which authors presented trial data. Other validated measures of visual loss, such as contrast sensitivity, were used where available.

The secondary outcomes for this review are:
• new vessel growth,
• quality of life measures - any validated measurement scale which aims to measure the impact of visual function loss on quality of life of participants,
• any adverse outcomes as reported in trials.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: Eyes and Vision Group search strategy

Trials were identified from the Cochrane Central Register of Controlled Trials - CENTRAL (which contains the Cochrane Eyes and Vision Group trials register) on the Cochrane Library, MEDLINE and EMBASE.

The following strategy was used to search CENTRAL Issue 4 2002:

#1 MACULAR-DEGENERATION:ME
#2 RETINAL-DEGENERATION:ME
#3 NEOVASCULARIZATION-PATHOLOGIC*:ME
#4 (((MACULA or MACULAR) or RETINA) or RETINAL) or CHOROID) or CHOROIDAL) near (DEGENERATION or NEOVASCULARIZATION))
#5 MACULOPATHY
#6 (((#1 or #2) or #3) or #4) or #5
#7 PHOTOCHEMOTHERAPY*:ME
#8 PHOTOSENSITIZING-AGENTS*:ME
#9 (PHOTOSENSITIZATION or PHOTOSENSITISING) or PHOTODYNAMIC) or PDT) or VERTEPORFIN or VISUDYNE
#10 (#7 or #8 or #9)
#11 (#6 and #10)

The following was used to search MEDLINE on SilverPlatter to November 2002:

#1 "MACULAR-DEGENERATION" all subheadings
#2 "RETINAL-DEGENERATION" all subheadings
#3 "NEOVASCULARIZATION-(PATHOLOGY)" all subheadings
#4 "SUBRETINAL-NEOVASCULARIZATION" all subheadings
#5 "MACULOPATHY"
#6 #1 or #2 or #3 or #4 or #5
#7 "PHOTODYNAMIC-THERAPY" all subheadings
#8 "PHOTOSENSITIZING-AGENT" all subheadings
#9 (PHOTOSENSITIZATION or PHOTOSENSITISING) or PHOTODYNAMIC) or PDT) or VERTEPORFIN or VISUDYNE
#10 (#7 or #8 or #9)
#11 (#6 and #10)

To identify randomised controlled trials, this search was combined with the Cochrane Highly Sensitive Search Strategy phases one and two as contained in the Cochrane Reviewers' Handbook (Clarke 2000).

The following strategy was used to search EMBASE on SilverPlatter to November 2002:

#1 "RANDOMIZED-CONTROLLED-TRIAL" all subheadings
#2 "CONTROLLED-STUDY" all subheadings
#3 "MULTICENTER-STUDY" all subheadings
#4 "PHASE-3-CLINICAL-TRIAL" all subheadings
#5 "PHASE-4-CLINICAL-TRIAL" all subheadings
#6 "DOUBLET-PROCEDURE" all subheadings
#7 "SINGLE-PROCEDURE" all subheadings
#8 "DOUBLET-PROCEDURE" all subheadings
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 (HUMAN or NONHUMAN) in DER
#11 (ANIMAL or NONHUMAN) in DER
#12 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9)
#13 #10 or #11

To identify randomised controlled trials, this search was combined with the following search:

#1 "RANDOMIZED-CONTROLLED-TRIAL" all subheadings
#2 "CONTROLLED-STUDY" all subheadings
#3 "MULTICENTER-STUDY" all subheadings
#4 "PHASE-3-CLINICAL-TRIAL" all subheadings
#5 "PHASE-4-CLINICAL-TRIAL" all subheadings
#6 "DOUBLET-PROCEDURE" all subheadings
#7 "SINGLE-PROCEDURE" all subheadings
#8 "DOUBLET-PROCEDURE" all subheadings
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#10 (HUMAN or NONHUMAN) in DER
#11 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9)
#12 #10 or #11

Photodynamic therapy for neovascular age-related macular degeneration (Review)
We used the Science Citation Index to search for reports that cited relevant study reports. We contacted experts in the field for information about further trials, and we searched the reference lists of relevant studies for further trial reports.

METHODS OF THE REVIEW

Selection of trials
Two reviewers independently scanned the titles and abstracts resulting from the electronic searches. We obtained full copies of all potentially or definitely relevant articles. Two reviewers assessed the full copies according to the 'Criteria for considering studies for this review'. Only articles meeting these criteria were assessed for quality.

Assessment of methodological quality
Two reviewers independently assessed study quality according to methods set out in Section 6 of the Cochrane Reviewers' Handbook. Reviewers were not masked to any trial details during the assessment. Four parameters of quality were considered: allocation concealment and method of allocation to treatment, masking of providers and recipients of care, masking of outcome assessment, and completeness of follow-up. Each parameter of trial quality was graded: A - adequate; B - unclear; C - inadequate. Disagreement between the reviewers on assessments was resolved by discussion. We contacted the trial authors for clarification on any parameter graded B - unclear, and we excluded any trial scoring C - inadequate on allocation concealment.

Data collection
Two reviewers independently extracted data using a form developed by the Cochrane Eyes and Vision Group (available from the editorial base). We resolved discrepancies by discussion. Two reviewers independently entered data into RevMan 4.1 and we checked any inconsistencies between the two against the study report.

Data synthesis
Our original data analysis plan was to summarise data from studies collecting similar outcome measures with similar follow-up times using the Peto method, after testing for heterogeneity between trials results using a standard chi-square test. The main outcome analysed, loss of three or more lines of visual acuity at 12 and 24 months follow-up, occurred relatively frequently in the trial cohort. The odds ratio, therefore, does not approximate to the relative risk. We present relative risks in this review. We planned to conduct sensitivity analyses to determine the effect of excluding studies given a grade of C - inadequate on any parameter of quality, but to date this has not been necessary.

DESCRIPTION OF STUDIES

The original electronic searches identified 76 reports. We found one randomised controlled trial (TAP 1999). Since the searches were updated in February 2001, May 2002 and January 2003, one further study has been identified and is included in this review (VIP 2001).

The TAP 1999 study was a multicentre study investigating the safety and effectiveness of verteporfin (Visudyne; CIBA Vision Corp, USA). It was conducted in 22 ophthalmology practices in Europe and North America. Participants were people with subfoveal choroidal neovascularisation (CNV) caused by age-related macular degeneration. The majority of participants were white (98%) with a mean age of 75 years. The VIP 2001 study was very similar to the TAP 1999 study. It was conducted in 28 practices, most of whom had also participated in the TAP 1999 study. As for the TAP 1999 study, the majority of participants were white (98%) with a mean age of 75 years.

In both trials, verteporfin (six milligrams per square metre of body surface area) was compared to placebo (5% dextrose in water) administered via intravenous infusion of 30 millilitres over 10 minutes. This was followed after 15 minutes by application of 83 seconds of laser light at 689 nm delivered 50 joules/square centimetre (cm²) at an intensity of 600 mW/cm² using a spot size with a diameter 1000 microns larger than the greatest linear dimension of the CNV lesion.

Participants in the TAP 1999 trial were reviewed every three months when visual acuity was measured and repeat fluorescein angiography performed. If the trial surgeon judged a recurrence of the membrane to be present or a persistence of the previous lesion, then repeat treatment was undertaken. In the phase one and two studies, it was concluded that up to five treatments were necessary to stabilise the situation (Miller 1999; Schmidt-Erfurth 1999). In the first year, a mean of 3.4 treatments were delivered to the treatment group and 3.7 to the control group. In the second year, a mean of 2.2 treatments were delivered to the treatment group and 2.8 to the controls group.

Visual acuity was measured in the VIP 2001 trial at 12 and 24 months. The report of the study did not indicate the mean number of treatments delivered for all participants. However, in the subgroup with occult CNV (76% of all participants) 3.1 treatments were given in the treatment group and 3.5 in the control group. In the second year, 1.8 and 2.4 treatments were given in the verteporfin and control groups respectively.

TAP 1999 was originally devised as two concurrent trials in order to comply with regulatory agency requirements. The study protocols were identical. Ten of the clinical centres were assigned to study A and 12 to study B. As the results of the trials were similar and the investigators analysed and presented the data as one trial, we have also assessed it as one trial.
Methodological Quality

Both TAP 1999 and VIP 2001 were high quality studies with a very similar study design.

Allocation of treatment group was by opaque serially numbered sealed envelopes and was stratified by clinical centre. The baseline characteristics of the participants by treatment group were published. The groups were well balanced with respect to a variety of demographic and clinical variables. Only one eye per person was treated.

Reasonable attempts were made to mask the ophthalmologist, participant, vision examiner and Photograph Reading Center personnel to the treatment assigned. As verteporfin and placebo were different colours (green versus colourless), the solutions and the intravenous tubing were covered with foil. The fundus appearance does not change during treatment to indicate whether verteporfin or placebo had been infused. There is no other physical evidence of treatment as verteporfin dye is excreted in the faeces and does not cause any colour change, and does not alter the colour of the skin or urine. It was therefore unlikely that participants were aware of their treatment status. In TAP 1999 the study investigators reported two instances where the participants were unmasked, and four cases where the ophthalmologists were unmasked, having noted a green solution.

Rates of follow-up were high in both studies. In TAP 1999 94% were seen at 12 months and 87% at 24 months. Follow-up was similar between the two treatment groups. The analysis was intention-to-treat and subgroup analyses were planned a priori (Bressler N, personal communication). In VIP 2001 93% were seen at 12 months and 86% at 24 months. All participants were included in the analyses and missing values were imputed using the method of last observation carried forward.

Results

The realistic aim of photodynamic therapy is to slow progression of age-related macular degeneration, not to produce normal vision. Outcomes are therefore expressed as risks of a poor outcome, rather than as improvements in vision. All results are based on the comparison of people randomised to receive verteporfin with those randomised to receive placebo (control).

Overall Analysis

Loss of three or more lines of visual acuity
A total of 948 patients from TAP 1999 and VIP 2001 studies were included in the meta-analysis. At 12 months, the pooled relative risk of losing three or more lines of visual acuity was 0.80 (95% confidence interval (CI) 0.70 to 0.91). The relative risk reduction was therefore 0.20 (95% CI 0.09 to 0.30). This analysis was done using a fixed effect model. A random effects model gave a non-significant result, largely because it placed more weight on the VIP study (pooled relative risk 0.82 (95% CI 0.64 to 1.04).

At 24 months, the pooled relative risk was 0.77 (95% CI 0.69 to 0.87) and the relative risk reduction was therefore 0.23 (95% CI 0.13 to 0.31). The random effects model gave a similar result.

Loss of six or more lines of visual acuity
At 12 months, the relative risk of losing six or more lines of visual acuity was 0.62 (95% CI 0.44 to 0.87) (TAP 1999 study only, data not reported for VIP 2001 study). The relative risk reduction was therefore 0.38 (95% CI 0.13 to 0.56). At 24 months, the pooled relative risk was 0.62 (95% CI 0.50 to 0.76) and the relative risk reduction was therefore 0.38 (95% CI 0.24 to 0.50).

Mean number of lines lost
In the TAP 1999 the mean number of lines of vision lost at 12 months was 2.2 in the intervention group and 3.5 in the control group. The difference was 1.3 with fewer lines lost in the intervention group. The P value for the difference in the mean number of lines lost was reported as P < 0.001 (Wilcoxon rank sum test). At 24 months, the mean number of lines of vision lost was 2.7 in the intervention group and 3.9 in the control group, a difference of 1.2 lines (P < 0.001).

The standard deviations for the mean numbers of lines lost were not reported and we therefore could not calculate confidence intervals.

Data on mean number of lines lost for the whole VIP 2001 study group was not reported.

Subgroup Analyses

Subgroup data are available only for the outcome 'loss of three or more lines of visual acuity' in the TAP 1999 study but for both outcomes (loss of three lines and loss of six lines) in the VIP 2001 study.

Evidence of occult choroidal neovascularisation
In the TAP 1999 study the relative risks of losing three or more lines of visual acuity at 12 months were 0.90 if occult choroidal neovascularisation (CNV) was present (95% CI 0.73 to 1.11) and 0.34 if occult CNV was absent (95% CI 0.22 to 0.51). At 24 months, the relative risks were 0.88 (95% CI 0.74 to 1.04) and 0.42 (95% CI 0.30 to 0.60) respectively.

The test for effect modification between these two subgroups was significant. Neither the 95% confidence intervals, nor the 99% confidence intervals, for these two subgroups overlap.

Lesion area composed of classic choroidal neovascularisation
In the TAP 1999 study, the proportion of the lesion comprised of classic CNV was estimated as 0%; greater than 0% but less than 50%; greater than 50%. The proportion was unknown in four participants (three in the treatment group and one in the control group). The subgroup analyses were therefore based on a total of 399 eyes.
In the VIP 2001 study, the majority of the participants (76%) had “occult with no classic CNV”. An additional 56 eyes had some classic CNV (less than 50% but greater than 0% as above). Only 19 eyes had predominantly classic CNV.

The pooled relative risks for losing three or more lines of visual acuity at 12 months for the group with 0% CNV was 0.84 (95% CI 0.68 to 1.04). Results for three or more lines lost at 12 months were not reported for the other two subgroups in the VIP 2001 study. The results for the TAP 1999 study were as follows. The relative risk for losing three or more lines of visual acuity at 12 months in people with 0% but less than 50% CNV was 0.99 (95% CI 0.76 to 1.29) and 0.54 for greater than 50% (95% CI 0.40 to 0.71).

At 24 months the pooled relative risks for losing three or more lines of visual acuity were: 0.77 (95% CI 0.64 to 0.92), 0.93 (95% CI 0.77 to 1.14) and 0.60 (95% CI 0.48 to 0.75) respectively.

These results suggest there was a reduction in the risk of loss of vision when classic CNV was absent or when greater than 50% of the lesion was comprised of classic CNV. However there was very little reduction in risk when between 0% and 50% of the lesion was comprised of classic CNV. However the test for effect modification between these three subgroups was not statistically significant (p=0.066).

**NUMBERS NEEDED TO TREAT**

We calculated the numbers needed to treat (NNTs) to prevent one person losing three or more lines and, where possible, one person losing six or more lines of vision. These NNTs are derived from the study population, that is, people with subfoveal CNV and a baseline visual acuity of between 20/40 and 20/200 with approximately 5 treatments over two years.

The NNT to prevent one person losing three or more lines of vision at 24 months was 7.1 (95% CI 4.8 to 12.5). The NNT to prevent one person losing six or more lines of vision at 24 months was 7.1 (95% CI 5.0 to 12.5).

**ADVERSE EFFECTS**

Reports of visual disturbance (reports of “abnormal vision”, “decreased vision” and visual field defect) occurred in one in every four people taking part in the TAP 1999 and VIP 2001 studies. This is unsurprising as participants had neovascular AMD. However, people treated with verteporfin were more likely to report visual disturbance (pooled relative risk 1.61, 95% CI 1.24 to 2.09). Presumably this visual disturbance must have been reasonably transient as visual outcomes at 12 and 24 months were better in the treatment group. 2.4% of people treated with verteporfin experienced infusion-related back pain and 2.4% had photosensitivity reactions. Problems with the injection site occurred in 13.1% of people treated with verteporfin compared to 5.6% people in the control group. Few allergic reactions were seen and these were equally likely in treatment and control groups.

**DISCUSSION**

The absence to date of any effective treatment for neovascular age-related macular degeneration (except for the few in whom laser photocoagulation works) means that there will be intense interest in photodynamic therapy for the many millions of sufferers of the disease worldwide. Unfortunately, photodynamic therapy, like photocoagulation, can only be effective during the proliferative stage of the disease while the neovascular process is active. It cannot have any effect once sight is lost and the scarring process is complete. Therefore, like so many other degenerative processes of the neuroretina, nothing can be done to restore function once the damage is done. Most sufferers of the condition have established sight loss and, for these, the publicity surrounding the launch of Visudyne (verteporfin) will have raised false hopes. However, this review indicates that for people with active neovascular disease, photodynamic therapy can prevent vision loss.

A key question is how long the effect of treatment will last and whether repeated treatments would be required in the longer term. This review indicates that treatment benefits last for at least two years. An open-label extension of the TAP 1999 study indicated that vision outcomes remained relatively stable from 24 to 48 months (TAP 2002).

Another important issue is how many presenting patients will benefit from photodynamic therapy. In addition to the problem of accessing specialist services in time, there is the question of the proportion of lesions that will actually be treatable. The evidence reported here clearly suggests that purely classic neovascular membranes do well. Subgroup analysis of the TAP 1999 study suggested that photodynamic therapy is not effective when occult CNV is present. Occult vessels mean that the extent of the membrane cannot be clearly defined and so it is not surprising that treatment is found to be less effective because the laser cannot be aimed at the entire membrane. However, the VIP 2001 study recruited mostly patients with occult neovascularisation and demonstrated a treatment benefit of photodynamic therapy at 12 and 24 months. Pooled analysis of the TAP 1999 and VIP 2001 studies in this review showed no statistically significant difference in treatment effects in subgroups defined by the presence or absence of classic CNV.

We are not told in the available reports the extent to which clinicians and indeed the trial Photograph Reading Center personnel were able to agree about the subgroup classification of classic or occult lesions. It is likely that there is much variation in opinion on this. The necessary skill to report on fluorescein angiograms and recognise different lesion types is highly refined. Most experts assert that stereo images are required to be able to locate the position in depth of staining or fluorescein leaks. Stereophotography requires either a dedicated camera equipped to take simultaneous stereo images or a skilled photographer who takes sequential im-
Age-related macular degeneration is a bilateral disease although one eye is usually affected before the other. With a lesion present in one eye, the annual cumulative incidence of a lesion in the second eye is estimated to be about 15%. Clinicians now commonly advise patients with a lesion in one eye to be watchful for the onset of symptoms in the second eye, and to present as soon as those symptoms are noticed to improve the chances of catching the lesion in the second eye in time. This often entails the provision of an Amsler grid, a simple chart on which a number of gridlines are printed around a central fixation spot. The patient is instructed to examine the grid and to look for focal distortion of the lines in the grid which would indicate local elevation of the retina as a result of the growth of an underlying membrane. This strategy offers the best hope of saving sight with this new treatment at least in places where access to a qualified ophthalmologist can be slow.

It should also be recalled that this treatment does not restore sight but rather, prevents further deterioration. Sustaining numerous assessments which involve relative invasive treatments may have an adverse effect on the patient. Without patient orientated outcomes in this trial, we cannot comment on the patient’s perspective on the experience of Visudyne therapy. It is likely that in most cases, especially where loss of sight of the second eye is threatened, patients will be willing to undergo all the necessary interventions, even when the probability of success is small.

Adverse effects occurred infrequently with the exception of the rather vague “visual disturbance” which affected more people in the verteporfin group compared to the control group. However, this was not reflected in the visual acuity outcomes. Infusion-related back pain occurred in 2.4% which is substantially lower than in some other studies. For example, in a series of 250 people treated with verteporfin 9.6% experienced verteporfin associated pain, most of which was back pain (Borodoker 2002).

The trials included in this review appear to have been performed to high standards and were closely supervised by the Food and Drugs Administration of the USA. Both trials were sponsored by the manufacturers of the drug (CIBA Vision & Novartis Ophthalmics) and declared potential conflicts of interest exist for a number of the trialists who hold interests in the manufacturer of the laser technology. This makes detailed scrutiny of reports of the trial essential. Of concern are the numerous protocol revisions that were registered with the Institutional Review Bodies throughout the study and after completion of follow-up. Although we have not yet had access to the main protocol or to the revisions, a CIBA representative has assured us that the changes were not substantive and, in particular, that there were no changes to the a priori determinants of the primary outcomes.

**Authors’ Conclusions**

**Implications for practice**

This review provides evidence that photodynamic therapy in people with classic and occult choroidal neovascularisation due to age-related macular degeneration is effective in preventing visual loss. Approximately seven people need to be treated with approximately five treatments over two years to prevent one person losing three or more lines of visual acuity.

Two trials were included in this review. Both trials were performed by the same investigators using largely the same clinical centres and funded by manufacturers of verteporfin. As for all new technology, outcomes and potential adverse effects need to be monitored when introduced into clinical practice.

There are major implications for health services, both in terms of potential expenditure and organisation, if photodynamic therapy is to be introduced. Where referral to an ophthalmologist is through a primary care network, facilities for the recognition of this condition in its early stages are needed. There is potential for an enormous increase in referral of people with early age-related maculopathy for assessment, in case an early treatable lesion is present. This could swamp already overstretched facilities at the secondary care level. Extra resources will be required at the secondary care level to manage increased referrals, for the necessary technology to diagnose treatable lesions and to deliver treatment.

**Implications for research**

Two trials were included in this review. Both trials were performed by the same investigators using largely the same clinical centres and funded by manufacturers of verteporfin.

Further independent trials of verteporfin are required to establish that the effects seen in this study are consistent and to determine important questions not yet addressed - particularly relating to quality of life and cost. Descriptive epidemiology on the population at risk and the numbers likely to benefit is essential to estimate the impact of this new treatment on health service resources. We need to establish how people in need of treatment can access it in time. Surveillance for possible rare but severe adverse effects will be required.
POTENTIAL CONFLICT OF INTEREST

None known.

ACKNOWLEDGEMENTS

The Cochrane Eyes and Vision Group developed and executed the electronic searches. We would like to thank Neil Bressler, Simon Harding and Javed Bhatti (CIBA Vision) for providing information about the TAP study. Usha Chakravarthy (Queens University, Belfast) and Bob Thompson (Macular Disease Society) provided useful comments on the review.

SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- Moorfields Eye Hospital NHS Trust UK

REFERENCES

References to studies included in this review

TAP 1999 {published and unpublished data}


TAP 2000 {published and unpublished data}


References to studies excluded from this review

Schmidt-Erfurth 1999
References to ongoing studies

ADD-V
Addition of an anti-inflammatory called Voltaren Ophthalmic®. Ongoing study Starting date of trial not provided. Contact author for more information.

Japan
Visudyne for CNV due to AMD. Ongoing study Results expected at end 2003.

VALIO
Altered light treatment using delayed light after Visudyne in occult AMD. Ongoing study Starting date of trial not provided. Contact author for more information.

VER
Visudyne in Early Retreatment Phase IIIB clinical trial. Ongoing study Results expected at end 2003.

VIM
Visudyne in Minimally Classic study. Ongoing study Starting date of trial not provided. Contact author for more information.

VIO
Visudyne therapy in Occult Phase III trial. Ongoing study Starting date of trial not provided. Contact author for more information.

Additional references

Borodoker 2002

Clarke 2000

Fine 1999

Miller 1999

MPS 1994

TAP 2002

Yusuf 1991

*Indicates the major publication for the study

TABLES

Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>TAP 1999</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised controlled trial: one eye per patient was randomised in a 2:1 (treatment:control) ratio</td>
</tr>
<tr>
<td>Participants</td>
<td>609 people with subfoveal CNV lesions caused by AMD with evidence of classic CNV and best corrected acuity of approximately 20/40 to 20/200</td>
</tr>
<tr>
<td>Interventions</td>
<td>Photodynamic therapy following verteporfin injection versus photodynamic therapy following intravenous 5% dextrose</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Visual acuity at 12 and 24 months</td>
</tr>
<tr>
<td>Notes</td>
<td></td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>VIP 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised controlled trial: one eye per patient was enrolled. Randomisation in sealed envelopes stratified by clinical centre.</td>
</tr>
</tbody>
</table>
### Characteristics of included studies (Continued)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Details</th>
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</thead>
<tbody>
<tr>
<td>Participants</td>
<td>339 people with subfoveal CNV caused by AMD</td>
</tr>
<tr>
<td>Interventions</td>
<td>Photodynamic therapy following verteporfin injection versus photodynamic therapy following intravenous 5% dextrose</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Visual acuity at 12 and 24 months</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Secondary outcomes include contrast sensitivity and changes in angiographic outcomes</td>
</tr>
<tr>
<td>Notes</td>
<td>Randomised 2:1 to verteporfin treatment</td>
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</table>

**Allocation concealment:** A

AMD - age-related macular degeneration
CNV - choroidal neovascularisation

### Characteristics of excluded studies

- Schmidt-Erfurth 1999: Non randomised open-label phase I and II trial

### Characteristics of ongoing studies

#### Study: ADD-V
- **Trial name or title**: Addition of an anti-inflammatory called Voltaren Ophthalmic®
- **Participants**
- **Interventions**
- **Outcomes**
- **Starting date**
- **Contact information**
- **Notes**

#### Study: Japan
- **Trial name or title**: Visudyne for CNV due to AMD
- **Participants**
- **Interventions**
- **Outcomes**
- **Starting date**: Results expected at end 2003
- **Contact information**: Nic Gwatkin, Head of Marketing, Novartis Ophthalmics
- **Notes**

#### Study: VALIO
- **Trial name or title**: Altered light treatment using delayed light after Visudyne in occult AMD
- **Participants**
- **Interventions**
- **Outcomes**
- **Starting date**
- **Contact information**: Nic Gwatkin, Head of Marketing, Novartis Ophthalmics
- **Notes**
### Characteristics of ongoing studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>VER</th>
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<tbody>
<tr>
<td><strong>Trial name or title</strong></td>
<td>Visudyne in Early Retreatment Phase IIIB clinical trial</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>People with predominantly classic CNV</td>
</tr>
<tr>
<td></td>
<td>321 people at 31 sites enrolled</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Visudyne therapy every 3 months (standard) vs more frequent regimen</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Starting date</strong></td>
<td>Results expected at end 2003</td>
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<td><strong>Contact information</strong></td>
<td>Nic Gwatkin, Head of Marketing, Novartis Ophthalmics</td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>VIM</th>
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<tbody>
<tr>
<td><strong>Trial name or title</strong></td>
<td>Visudyne in Minimally Classic study</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Visudyne therapy vs visudyne therapy with reduced light intensity vs placebo</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Starting date</strong></td>
<td></td>
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<td><strong>Contact information</strong></td>
<td>Nic Gwatkin, Head of Marketing, Novartis Ophthalmics</td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>VIO</th>
</tr>
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<tbody>
<tr>
<td><strong>Trial name or title</strong></td>
<td>Visudyne therapy in Occult Phase III trial</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>People with occult but no classic CNV due to AMD</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Starting date</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Contact information</strong></td>
<td>Nic Gwatkin, Head of Marketing, Novartis Ophthalmics</td>
</tr>
</tbody>
</table>

### Graphs

**Comparison 01. PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO**

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
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</thead>
<tbody>
<tr>
<td>01 Overall effect: &gt;=3 lines lost at 12 mths</td>
<td>2</td>
<td>948</td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>0.80 [0.70, 0.91]</td>
</tr>
<tr>
<td>02 Overall effect: &gt;=3 lines lost at 24 mths</td>
<td>2</td>
<td>948</td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>0.77 [0.69, 0.87]</td>
</tr>
<tr>
<td>03 Overall effect: &gt;=6 lines lost at 12 mths</td>
<td></td>
<td></td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>04 Overall effect: &gt;=6 lines lost at 24 mths</td>
<td>2</td>
<td>948</td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>0.62 [0.50, 0.76]</td>
</tr>
<tr>
<td>05 Classic CNV subgroups: &gt;=3 lines lost at 12 mths</td>
<td></td>
<td></td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>06 Classic CNV subgroups: &gt;=3 lines lost at 24 mths</td>
<td>6</td>
<td>942</td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>0.77 [0.69, 0.87]</td>
</tr>
</tbody>
</table>
07 Adverse effects: Visual disturbance 2 948 Relative Risk (Fixed) 95% CI 1.61 [1.24, 2.09]
08 Adverse effects: Injection site 2 948 Odds Ratio (Fixed) 95% CI 2.54 [1.50, 4.31]
09 Adverse effects: Infusion-related back pain 2 948 Odds Ratio (Fixed) 95% CI 8.40 [1.11, 63.58]
10 Adverse effects: Allergic reactions 2 948 Odds Ratio (Fixed) 95% CI 0.94 [0.34, 2.56]
11 Adverse effects: Photosensitivity reactions 2 948 Odds Ratio (Fixed) 95% CI 5.37 [1.01, 28.60]

INDEX TERMS

Medical Subject Headings (MeSH)
Glucose [therapeutic use]; Macular Degeneration [drug therapy]; Neovascularization, Pathologic; Photochemotherapy; Photosensitizing Agents [therapeutic use]; Porphyrins [therapeutic use]; Randomized Controlled Trials; Retinal Neovascularization [drug therapy]

Medical MeSH check words
Humans

COVER SHEET

Title
Photodynamic therapy for neovascular age-related macular degeneration

Authors
Wormald R, Evans J, Smeeth L, Henshaw K

Contribution of author(s)
RW participated in protocol development, study selection and assessment and writing up of the original and update of the review.
JE participated in protocol development, study selection and assessment, data abstraction and entry and writing up of the original and update of the review.
LS participated in protocol development, study selection and assessment, data abstraction and entry and writing up of the original and update of the review.
KH abstracted data and entered data into RevMan for the update of the review and participated in the updating of the review text.

Issue protocol first published /
Review first published 2000/2
Date of most recent amendment 21 September 2003
Date of most recent SUBSTANTIVE amendment 25 February 2003
What’s New
Information not supplied by author

Date new studies sought but none found
Information not supplied by author

Date new studies found but not yet included/excluded
Information not supplied by author

Date new studies found and included/excluded 03 January 2003

Date authors’ conclusions section amended 30 May 2001

DOI 10.1002/14651858.CD002030
Fig. 1.  Comparison 01. PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

01.01 Overall effect: >=3 lines lost at 12 mths

Review: Photodynamic therapy for neovascular age-related macular degeneration
Comparison: 01 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO
Outcome: 01 Overall effect: >=3 lines lost at 12 mths

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Relative Risk (Fixed)</th>
<th>Weight</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI (%)</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>TAP 1999</td>
<td>156/402</td>
<td>111/207</td>
<td>64.0</td>
<td>0.72</td>
<td>[0.61, 0.86]</td>
</tr>
<tr>
<td>VIP 2001</td>
<td>114/225</td>
<td>62/114</td>
<td>36.0</td>
<td>0.93</td>
<td>[0.75, 1.15]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>627</td>
<td>321</td>
<td>100.0</td>
<td>0.80</td>
<td>[0.70, 0.91]</td>
</tr>
</tbody>
</table>

Total events: 270 (Treatment), 173 (Placebo)
Test for heterogeneity chi-square=3.23 df=1 p=0.07 I²=69.0%
Test for overall effect z=3.26 p=0.001

Fig. 2. Comparison 01. PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

01.02 Overall effect: >=3 lines lost at 24 mths

Review: Photodynamic therapy for neovascular age-related macular degeneration
Comparison: 01 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO
Outcome: 02 Overall effect: >=3 lines lost at 24 mths

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Relative Risk (Fixed)</th>
<th>Weight</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI (%)</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>TAP 1999</td>
<td>189/402</td>
<td>129/207</td>
<td>62.8</td>
<td>0.75</td>
<td>[0.65, 0.88]</td>
</tr>
<tr>
<td>VIP 2001</td>
<td>121/225</td>
<td>76/114</td>
<td>37.2</td>
<td>0.81</td>
<td>[0.68, 0.96]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>627</td>
<td>321</td>
<td>100.0</td>
<td>0.77</td>
<td>[0.69, 0.87]</td>
</tr>
</tbody>
</table>

Total events: 310 (Treatment), 205 (Placebo)
Test for heterogeneity chi-square=0.32 df=1 p=0.57 I²=0.0%
Test for overall effect z=4.41 p=0.0001
### Fig. 3. Comparison 01. PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

**01.03 Overall effect: >=6 lines lost at 12 mths**

Review: Photodynamic therapy for neovascular age-related macular degeneration

Comparison: 01 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

Outcome: 03 Overall effect: >=6 lines lost at 12 mths

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Relative Risk (Fixed)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>TAP 1999</td>
<td>59/402</td>
<td>49/207</td>
<td>0.62 [0.44, 0.87]</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square=0.03 df=1 p=0.86 I²=0%

Test for overall effect z=4.65 p<0.00001

<table>
<thead>
<tr>
<th>0.1</th>
<th>0.2</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favours treatment</td>
<td>Favours placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Fig. 4. Comparison 01. PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

**01.04 Overall effect: >=6 lines lost at 24 mths**

Review: Photodynamic therapy for neovascular age-related macular degeneration

Comparison: 01 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

Outcome: 04 Overall effect: >=6 lines lost at 24 mths

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Relative Risk (Fixed)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
<td>(%)</td>
</tr>
<tr>
<td>TAP 1999</td>
<td>73/402</td>
<td>62/207</td>
<td>0.61 [0.45, 0.81]</td>
<td>53.3</td>
</tr>
<tr>
<td>VIP 2001</td>
<td>67/225</td>
<td>54/114</td>
<td>0.63 [0.48, 0.83]</td>
<td>46.7</td>
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<tr>
<td>Total (95% CI)</td>
<td>627</td>
<td>321</td>
<td>0.62 [0.50, 0.76]</td>
<td>100.0</td>
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</tbody>
</table>

Total events: 140 (Treatment), 116 (Placebo)

Test for heterogeneity chi-square=0.03 df=1 p=0.86 I²=0%

Test for overall effect z=4.65 p<0.00001

<table>
<thead>
<tr>
<th>0.1</th>
<th>0.2</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favours treatment</td>
<td>Favours placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Comparison 01. PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

**01.05 Classic CNV subgroups: >=3 lines lost at 12 mths**

#### Outcome: 05 Classic CNV subgroups: >=3 lines lost at 12 mths

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Relative Risk (Fixed)</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
<td></td>
<td>95% CI</td>
</tr>
<tr>
<td>01 No classic CNV</td>
<td>TAP 1999</td>
<td>14/38</td>
<td>13/19</td>
<td>100.0</td>
<td>0.54 [0.32, 0.90]</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>38</td>
<td>19</td>
<td>100.0</td>
<td>0.54 [0.32, 0.90]</td>
</tr>
<tr>
<td></td>
<td>Total events: 14 (Treatment), 13 (Placebo)</td>
<td></td>
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<tr>
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<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect z=2.35 p=0.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>02 Classic CNV &gt; 0 to &lt; 50%</td>
<td>TAP 1999</td>
<td>89/202</td>
<td>46/103</td>
<td>100.0</td>
<td>0.99 [0.76, 1.29]</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>202</td>
<td>103</td>
<td>100.0</td>
<td>0.99 [0.76, 1.29]</td>
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<tr>
<td></td>
<td>Total events: 89 (Treatment), 46 (Placebo)</td>
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<td>Test for heterogeneity: not applicable</td>
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<tr>
<td></td>
<td>Test for overall effect z=0.10 p=0.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>03 Classic CNV &gt; 50% (predominantly classic)</td>
<td>TAP 1999</td>
<td>52/159</td>
<td>51/84</td>
<td>100.0</td>
<td>0.54 [0.41, 0.71]</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>159</td>
<td>84</td>
<td>100.0</td>
<td>0.54 [0.41, 0.71]</td>
</tr>
<tr>
<td></td>
<td>Total events: 52 (Treatment), 51 (Placebo)</td>
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</tr>
<tr>
<td></td>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect z=4.31 p=0.000002</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
### Fig. 6. Comparison of PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

**01.06 Classic CNV subgroups: >=3 lines lost at 24 mths**

**Review:** Photodynamic therapy for neovascular age-related macular degeneration

**Comparison:** PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

**Outcome:** Classic CNV subgroups: >=3 lines lost at 24 mths

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Relative Risk (Fixed)</th>
<th>Weight</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
<td>(%)</td>
<td>95% CI</td>
</tr>
<tr>
<td>01 No classic CNV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAP 1999</td>
<td>18/41</td>
<td>14/20</td>
<td>7.0</td>
<td>0.63 [ 0.40, 0.98 ]</td>
<td></td>
</tr>
<tr>
<td>VIP 2001</td>
<td>91/166</td>
<td>63/92</td>
<td>30.0</td>
<td>0.80 [ 0.66, 0.97 ]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>207</td>
<td>112</td>
<td>37.0</td>
<td>0.77 [ 0.64, 0.92 ]</td>
<td></td>
</tr>
<tr>
<td>Total events: 109 (Treatment), 77 (Placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity chi-square=0.95 df=1 p=0.33 I^2=0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z=2.89 p=0.004</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>02 Classic CNV &gt; 0 to &lt; 50%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAP 1999</td>
<td>106/202</td>
<td>58/104</td>
<td>28.4</td>
<td>0.94 [ 0.76, 1.17 ]</td>
<td></td>
</tr>
<tr>
<td>VIP 2001</td>
<td>19/38</td>
<td>10/18</td>
<td>5.0</td>
<td>0.90 [ 0.53, 1.52 ]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>240</td>
<td>122</td>
<td>33.4</td>
<td>0.93 [ 0.77, 1.14 ]</td>
<td></td>
</tr>
<tr>
<td>Total events: 125 (Treatment), 68 (Placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity chi-square=0.02 df=1 p=0.88 I^2=0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z=0.66 p=0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>03 Classic CNV &gt; 50% (predominantly classic)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAP 1999</td>
<td>65/159</td>
<td>57/83</td>
<td>27.7</td>
<td>0.60 [ 0.47, 0.75 ]</td>
<td></td>
</tr>
<tr>
<td>VIP 2001</td>
<td>10/16</td>
<td>3/3</td>
<td>1.9</td>
<td>0.63 [ 0.43, 0.91 ]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>175</td>
<td>86</td>
<td>29.6</td>
<td>0.60 [ 0.48, 0.75 ]</td>
<td></td>
</tr>
<tr>
<td>Total events: 75 (Treatment), 60 (Placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity chi-square=0.06 df=1 p=0.81 I^2=0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z=4.54 p&lt;0.00001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>622</td>
<td>320</td>
<td>100.0</td>
<td>0.77 [ 0.69, 0.87 ]</td>
<td></td>
</tr>
<tr>
<td>Total events: 309 (Treatment), 203 (Placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity chi-square=10.36 df=5 p=0.07 I^2=51.7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z=4.41 p=0.00001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Favours treatment Favours placebo
Fig. 7. Comparison of PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

01.07 Adverse effects: Visual disturbance

Review: Photodynamic therapy for neovascular age-related macular degeneration
Comparison: PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO
Outcome: 07 Adverse effects: Visual disturbance

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Relative Risk (Fixed)</th>
<th>Weight</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI (%)</td>
<td>(%)</td>
<td>95% CI</td>
</tr>
<tr>
<td>TAP 1999</td>
<td>89/402</td>
<td>32/207</td>
<td></td>
<td>53.0</td>
<td>1.43 [ 0.99, 2.07 ]</td>
</tr>
<tr>
<td>VIP 2001</td>
<td>94/225</td>
<td>26/114</td>
<td></td>
<td>45.0</td>
<td>1.83 [ 1.26, 2.66 ]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>627</td>
<td>32</td>
<td>100.0</td>
<td>1.61 [ 1.24, 2.09 ]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 183 (Treatment), 58 (Control)
Test for heterogeneity chi-square=0.85 df=1 p=0.36 I²=0%
Test for overall effect z=3.59 p=0.0003

Fig. 8. Comparison of PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

01.08 Adverse effects: Injection site

Review: Photodynamic therapy for neovascular age-related macular degeneration
Comparison: PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO
Outcome: 08 Adverse effects: Injection site

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Odds Ratio (Fixed)</th>
<th>Weight</th>
<th>Odds Ratio (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI (%)</td>
<td>(%)</td>
<td>95% CI</td>
</tr>
<tr>
<td>TAP 1999</td>
<td>64/402</td>
<td>12/207</td>
<td></td>
<td>64.5</td>
<td>3.08 [ 1.62, 5.84 ]</td>
</tr>
<tr>
<td>VIP 2001</td>
<td>18/225</td>
<td>6/114</td>
<td></td>
<td>35.5</td>
<td>1.57 [ 0.60, 4.06 ]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>627</td>
<td>32</td>
<td>100.0</td>
<td>2.54 [ 1.50, 4.31 ]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 82 (Treatment), 18 (Control)
Test for heterogeneity chi-square=1.34 df=1 p=0.25 I²=25.1%
Test for overall effect z=3.46 p=0.0005

Photodynamic therapy for neovascular age-related macular degeneration (Review)
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### Fig. 9. Comparison 01. PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

**01.09 Adverse effects: Infusion-related back pain**

**Review:** Photodynamic therapy for neovascular age-related macular degeneration

**Comparison:** 01 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

**Outcome:** 09 Adverse effects: Infusion-related back pain

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Odds Ratio (Fixed)</th>
<th>Weight (%)</th>
<th>Odds Ratio (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAP 1999</td>
<td>10/402</td>
<td>0/207</td>
<td>49.8</td>
<td>11.10</td>
<td>[0.65, 190.40]</td>
</tr>
<tr>
<td>VIP 2001</td>
<td>5/225</td>
<td>0/114</td>
<td>50.2</td>
<td>5.71</td>
<td>[0.31, 104.21]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>627</td>
<td>321</td>
<td>100.0</td>
<td>8.40</td>
<td>[1.11, 63.58]</td>
</tr>
</tbody>
</table>

Total events: 15 (Treatment), 0 (Control)

Test for heterogeneity chi-square=0.10 df=1 p=0.75 I²=0.0%

Test for overall effect z=2.06 p=0.04

---

### Fig. 10. Comparison 01. PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

**01.10 Adverse effects: Allergic reactions**

**Review:** Photodynamic therapy for neovascular age-related macular degeneration

**Comparison:** 01 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

**Outcome:** 10 Adverse effects: Allergic reactions

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Odds Ratio (Fixed)</th>
<th>Weight (%)</th>
<th>Odds Ratio (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAP 1999</td>
<td>8/402</td>
<td>3/207</td>
<td>49.7</td>
<td>1.38</td>
<td>[0.36, 5.26]</td>
</tr>
<tr>
<td>VIP 2001</td>
<td>3/225</td>
<td>3/114</td>
<td>50.3</td>
<td>0.50</td>
<td>[0.10, 2.52]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>627</td>
<td>321</td>
<td>100.0</td>
<td>0.94</td>
<td>[0.34, 2.56]</td>
</tr>
</tbody>
</table>

Total events: 11 (Treatment), 6 (Control)

Test for heterogeneity chi-square=0.90 df=1 p=0.34 I²=0.0%

Test for overall effect z=0.13 p=0.9
### Fig. 11. Comparison 01. PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

#### 01.11 Adverse effects: Photosensitivity reactions

**Review:** Photodynamic therapy for neovascular age-related macular degeneration

**Comparison:** 01 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

**Outcome:** 11 Adverse effects: Photosensitivity reactions

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Odds Ratio (Fixed)</th>
<th>Control Odds Ratio (Fixed)</th>
<th>Weight (%)</th>
<th>95% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAP 1999</td>
<td>14/402 32.5</td>
<td>0/207 15.49</td>
<td>92, 260.96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIP 2001</td>
<td>1/225 67.5</td>
<td>1/114 0.50</td>
<td>0.03, 8.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>627 100.0</td>
<td>321 5.37</td>
<td>1.01, 28.60</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 15 (Treatment), 1 (Control)

Test for heterogeneity chi-square=3.32 df=1 p=0.07 I² =69.9%

Test for overall effect z=1.97 p=0.05