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CLINICAL STUDY

Comparison of visual acuity outcomes in predominantly classic *vs* occult lesions in age-related macular degeneration treated with photodynamic therapy

MJ Potter[1], SM Szabo[1,2] and WW Li[1]

Abstract

Purpose **To determine if patients with occult with no classic and predominantly classic (PC) choroidal neovascular membranes have clinically equivalent visual outcomes after treatment with photodynamic therapy (PDT) with verteporfin.**

Methods **This is a retrospective, observational cohort study. Two hundred and seventy-seven consecutive patients with occult or PC choroidal neovascularization secondary to age-related macular degeneration treated with PDT were included. The main outcome was the difference in mean change in Early Treatment of Diabetic Retinopathy Study (ETDRS) acuity lost from baseline in occult *vs* PC lesions, with the minimal clinically important difference (MCID) set at 7.5 letters.**

Results **At baseline, 131 patients had occult and 146 had PC choroidal neovascularization. Twelve-month follow-up data were available for 94 occult and 110 PC participants. Occult patients lost an average of 8.7 letters (1.9 lines), and patients in the PC group an average of 10.0 ETDRS letters (two lines) over 12 months. The mean letters lost at 12 months was not significantly different between the groups, and the MCID was not detected (difference = 1.3 letters; $P = 0.411$; 95% confidence interval (−2.3, 5.6)). Patients with occult lesions required a mean of 2.99 treatments *vs* a mean of 2.96 treatments in the PC group (out of a possible 4; $P = 0.172$).**

Conclusion **We were not able to detect a clinically important difference in mean change in visual acuity with PDT treatment between patients with occult and PC lesions.**

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Keywords: photodynamic therapy; age-related macular degeneration; choroidal neovascularization

[1]Department of Ophthalmology and Visual Sciences, University of British Columbia, Columbia, Canada

[2]Department of Health Care and Epidemiology, University of British Columbia, Columbia, Canada

Correspondence: MJ Potter, Department of Ophthalmology and Visual Sciences, University of British Columbia, 2550 Willow Street, Vancouver, British Columbia, Canada V5Z 3N9
Tel: +1 604 875 5733; Fax: +1 604 875 4243.
E-mail: mpotter@interchange.ubc.ca

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Introduction

Photodynamic therapy (PDT) with verteporfin (Visudyne; Novartis Ophthalmics, Duluth, GA, USA) remains the standard of care for the treatment of patients with predominantly classic (PC) choroidal neovascular membranes (CNV) in age-related macular degeneration (AMD).[1,2] The results of the Treatment of AMD with PDT (TAP) and Verteporfin in Photodynamic Therapy (VIP) Studies demonstrated the efficacy of this treatment for patients with PC and occult with no classic (OC) CNV lesions, although the magnitude of the separation between the treatment and placebo groups in OC lesions seemed to be less, and took longer to become apparent.[1–4] Practitioners, regulatory bodies, and reimbursement agencies have been slow to adopt PDT for OC lesions, based on the perception that it is less effective than for PC

lesions, and in many jurisdictions it is either available only at private clinics or not at all. Recent data on other treatment modalities, including Lucentis (ranibizumab; Genentech Inc.) and Macugen[5] (pegaptanib; Pfizer Ophthalmics), have generated controversy over whether fluorescein angiographic characteristics of CNV lesions in AMD influence the outcomes. Macugen was studied on a mixture of lesions, and Lucentis' results thus far have focused largely on occult lesions, leaving this question largely unanswered.

Treatment efficacy in the TAP and VIP Studies was compared by analysing the proportions of patients in each group avoiding moderate vision loss. The natural history of OC lesions, based on the placebo groups of the TAP and VIP Studies, seems to be worse than for PC lesions in terms of mean vision loss, although PC lesions may respond more favourably to PDT, resulting in a better apparent treatment effect in terms of proportions of patients avoiding moderate vision loss.[3,4] In addition, when OC lesions that are large ($\geq$4 Macular Photocoagulation Study Disc Areas (MPS DA)) and have good visual acuities ($>$65 Early Treatment of Diabetic Retinopathy Study (ETDRS) letters) are excluded, the results of the VIP Study showed equivalent outcomes with PC lesions from the TAP Study.

These retrospective subgroup analyses have been subject to much debate, which raises the question as to how they translate into clinical practice. There is a common perception that OC lesions follow a less severe course, and that they respond less well to PDT than PC lesions. Indeed, the comparison of the proportions of patients treated with PDT who lose vision with respect to placebo suggests this outcome. Both TAP and VIP used the proportions of patients avoiding moderate vision loss as the main outcome measure. However, mean change in vision per group was also presented. Patients with OC lesions treated with PDT lost 6.5 letters less than placebo over 24 months, *vs* a loss of 5.8 in those with PC treated with PDT compared to placebo.[2,3] The OC placebo group actually lost more vision, on average, than the PC group, indicating that the course of OC lesions may not actually be less severe than PC lesions. OC and PC lesions may actually behave similarly in response to PDT, when mean changes in visual acuity are examined.

No study has yet been performed with the express purpose of comparing the outcomes of PDT treatment in PC *vs* OC lesions in terms of mean change in visual acuity. If indeed patients with OC and PC lesions experience similar benefits from PDT, then it is reasonable to treat them in the same manner from a clinical standpoint. Furthermore, if these lesion types need not be separated in future clinical trials, it would greatly speed the development of new therapies, particularly combinations of drugs that act by different mechanisms. The purpose of our study is to determine whether AMD patients with OC and PC CNV lesions have clinically equivalent visual acuity outcomes after treatment with PDT with verteporfin, when patients with OC lesions that are large and have good visual acuities are excluded.

Materials and methods

This retrospective cohort study was approved by the Institutional Review Boards of the University of British Columbia and the Vancouver Coastal Health Research Institute. PDT treatment is available at no cost to patients, as it is covered under the Medical Services Plan of British Columbia. There was no pharmaceutical company sponsorship during the course of this study.

Two hundred seventy-seven consecutive patients with PC or OC CNV secondary to AMD were assessed and treated by one physician (MJP), and underwent their baseline PDT treatment between July 2000 and September 2003. A higher proportion of PC lesions were included at the beginning of this period as OC lesions were not treated until the release of the results of the VIP Study[3] in 2001.

Patients included in this study had to be at least 50 years of age, with evidence of a new subfoveal CNV lesion on fluorescein angiography, secondary to exudative AMD. If patients presented with bilateral subfoveal CNV lesions owing to AMD, one eye was randomly assigned by coin toss to inclusion in the study. If CNV developed later in the fellow eye of a patient already included in the study, the fellow eye was not followed for research purposes.

CNV was classified as PC or OC based on baseline fluorescein angiograms, reviewed in a masked manner by MJP. MJP has been certified by the Digital Angiography Reading Center, the Wisconsin and Wilmer Reading Centers. Fluorescein angiographic criteria for eligibility for PDT treatment were adapted from the TAP Study,[1] VIP Trial,[3] and Verteporfin Roundtable Guidelines.[6] Fluorescein angiography was performed using a Topcon 50EX camera with an OIS MegaVision digital capture device and viewed using OIS WinStation XP software V 10.0.80. Patients treated with PDT had angiographic evidence of CNV that extended under the geometric centre of the foveal avascular zone. Features obscuring the identification of classic or occult CNV on angiography, including blood, hypofluorescence not from blood, or a serous detachment of the retinal pigment epithelium, could be present, but had to occupy less than 50% of the total lesion area. The area of CNV had to occupy at least 50% of the total lesion area. PC CNV lesions and OC lesions that were either small ($\leq$4 MPS DA) or associated with poor ($<$65 letters on the

ETDRS chart; Snellen equivalent = 20/50-1) visual acuity, and with presumed recent (<16 weeks duration) disease progression or haemorrhage, were considered for treatment. Before treatment, all patients underwent visual acuity testing using the ETDRS chart, measured by a trained vision examiner and scored according to the standard protocol.[7] All patients had had recent refractions at their referring doctors' offices, and all vision testing was performed using patients' habitual corrections.

PDT was performed using the standard protocol, as outlined in the TAP Report No. 1.[1] Patients were re-assessed in follow-up every 3 months ± 2 weeks, including repeat vision examinations. Re-treatment was performed primarily on the basis of the presence of leakage on fluorescein angiography. Visual acuity, the presence of blood, subretinal fluid, and fibrosis were used as ancillary data to assist with clinical decision-making regarding re-treatment. Cessation of leakage was the primary basis for ending treatment. Treatment was also withheld if leakage was present on FA, but the visual acuity was stable, without an increase in lesion size, principally when fibrosis was present. Severely decreased vision or fibrosis, as well as stable visual acuity were also considered to be factors weighing against treatment.

Statistical methods

The primary outcome measure at 12 months was the difference in mean change in visual acuity from baseline in the PC and OC groups. The minimal clinically important difference (MCID) is defined as the smallest change in score in visual acuity over 1 year that would be clinically meaningful.[8] If no significant difference were detected with the MCID set at three lines,[1] it might still be possible to detect finer differences between the groups, if present, with a more stringent MCID of 1.5 lines. We therefore chose to define the MCID for the purposes of our study at a difference in mean change between the groups of 7.5 letters (1.5 lines) of ETDRS acuity.

Secondary outcome measures included the proportion of eyes that lost less than or equal to 15 letters (three lines) on the ETDRS chart from baseline, the proportion of eyes that lost less than 30 letters on the ETDRS chart (six lines) from baseline, and the proportion of eyes that maintained (±4 letters) or improved (>4 letter increase) ETDRS acuity from baseline. Data were extracted from prospectively completed data forms, and was tested using an 'intent-to-treat' analysis (all participants eligible at baseline were included), the results of which were compared to a 'completers' analysis (only those completing month 12 were included).[9] The last observation carried forward method was not used to impute missing data, as this would likely overestimate subsequent visual acuity measurements.

Statistical significance for comparison of the mean letters of vision lost between the OC and PC groups was performed using Student's *t*-test. A χ^2 test was used to compare the proportion of patients in the OC and PC groups that lost less than 15 or 30 letters, or who experienced a gain in vision. The Mann–Whitney U-test was used to compare differences in mean number of treatments between groups. To detect the MCID of 7.5 letters of mean vision change between the OC and PC groups, with a power (β) of 0.8 and error (α) of 0.05, would require a minimum of 81 eyes finishing 12 months of follow-up per group. All statistical testing was performed using S-PLUS® 6.2 for Windows, 2003.

Results

We included all eligible patients in our study. Two hundred and seventy-seven consecutive patients over 50 years of age with subfoveal PC or OC CNV secondary to AMD, treated with PDT with verteporfin (Table 1) were included. One hundred and thirty-one patients had OC CNV, and 146 had PC CNV lesions at baseline. The mean age was 78.7 (range, 60–93) in the OC group and 77.9 (range, 54–95) in the PC group. Mean baseline ETDRS visual acuity was 48.5 letters in the OC group (approximate Snellen equivalent = 20/100-2) and

Table 1 Patient demographics of the study group

	PC n (%), n = *146*	*OC n (%),* n = *131*
Gender		
Male	67 (45.9)	51 (38.9)
Female	79 (54.1)	80 (61.1)
Age (years)		
50–64	6 (3.4)	2 (1.5)
65–74	40 (27.4)	36 (27.5)
75–84	75 (51.4)	64 (48.9)
>85	25 (17.1)	29 (22.1)
Mean	77.9	78.7
Treatment eye		
OD	76 (52.1)	61 (46.6)
OS	70 (47.9)	70 (53.4)
Baseline ETDRS Va		
≥74 (≥20/32)	6 (3.4)	1 (0.75)
54–73 (20/80–20/32)	42 (28.8)	47 (35.9)
34–53 (20/200–20/80)	64 (43.8)	65 (49.6)
≤33 (≤20/200)	34 (23.2)	18 (13.7)
Mean	45.42	48.49

PC = predominantly classic choroidal neovascularization; OC = occult with no classic choroidal neovascularization.

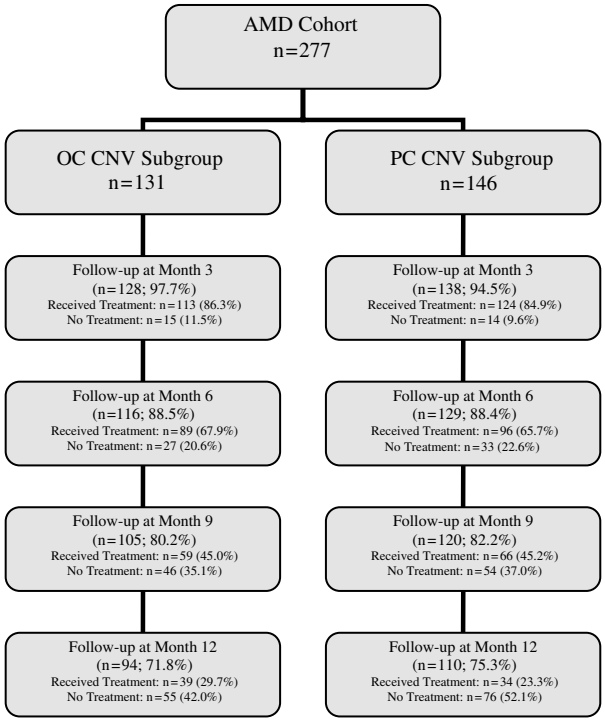

Figure 1 Profile of patients with OC or PC CNV lesions receiving PDT treatment, and completing follow-up, over 12 months.

Table 2 Reasons for patients not completing 12 months of follow-up

	PC patients (%), n = *146*	*OC patients (%),* n = *131*
Deceased	2 (1.4)	1 (0.8)
Illness	6 (4.1)	5 (3.8)
Repeated no treatments with stable Va	14 (9.6)	18 (13.7)
Severe vision decrease	1 (0.7)	1 (0.8)
Travel distance	7 (4.8)	4 (3.1)
Did not want to follow up	3 (2.1)	2 (1.5)
Lost to follow up	2 (1.4)	4 (3.1)
Moved	1 (0.7)	0 (0.0)
Side effects	0 (0.0)	2 (1.5)

45.4 letters in the PC (20/125) group ($P = 0.080$). Mean baseline lesion size (in greatest linear dimension) was larger in the OC (4135 μm; range, 1500–6000 μm) than in the PC (3505 μm; range, 1000–6200 μm) group ($P = 0.0001$).

Twelve-month follow-up data were available for 94 participants in the OC group (71.2%) and 110 participants in the PC group (75.3%). The proportion of patients completing each follow-up visit is outlined in Figure 1, with reasons for losses to follow-up outlined in Table 2.

Data analysis was performed using all available information for all 277 patients entered in the study (intent-to-treat analysis). Mean letters lost in each of the OC and PC groups at each 3-month time point are illustrated in Figure 2a, shown with 95% confidence intervals (CIs) in Figure 2b and c for the OC and PC groups, respectively. Patients in the OC group lost an average of 8.7 letters (1.9 lines), and patients in the PC group lost an average of 10.0 ETDRS letters (two lines) over 12 months. The mean letters lost at 12 months between the groups was not significantly different ($P = 0.411$; 95% CI (−2.3, 5.6)). The MCID in mean change of 7.5 letters lost was not detected (difference, 1.3 letters between the OC and PC groups).

Results from those who completed 12 months of follow-up ($n = 204$; completers analysis) were examined by inspection and found to be similar to those from the intent-to-treat analysis. A *t*-test was not performed since all participants in one group were contained within the other. In the completers analysis, participants in the OC group lost an average of 8.5, and PC patients 11.5 ETDRS letters over 12 months. The mean letters lost at 12 months between the groups was not significantly different ($P = 0.186$) and the minimal clinically significant difference of 7.5 letters lost between groups was not found (difference in treatment effect between groups, three letters).

A subgroup analysis was performed for patients in the OC group, where lesions were stratified by baseline lesion size <4 MPS DA ($n = 24$) or ≥ 4 MPS DA ($n = 107$).

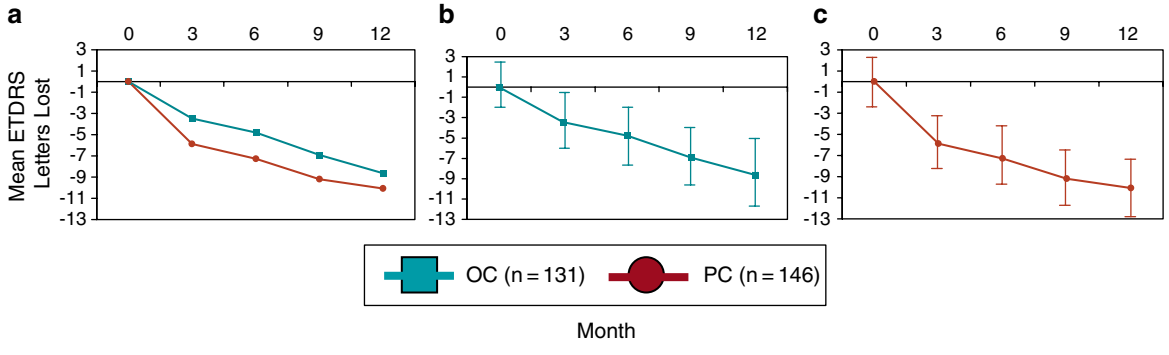

Figure 2 (a) Mean letters lost over time, by baseline lesion composition category, for all study patients (intent-to-treat population). (b) Mean letters lost over time for OC patients, with 95% CI. (c) Mean letters lost over time for PC patients, with 95% CI.

Although baseline visual acuity was significantly higher in the small lesion size group compared to the large lesion group (56.2 *vs* 46.8 ETDRS letters, $P=0.01$), the mean change in vision over time was not different. Patients with smaller OC lesions at baseline lost a mean of 7.77, and those with larger OC lesions, 8.97, ETDRS letters from baseline.

Significant differences were not found between patients in the PC and OC groups for any of the secondary outcome measures. Sixty-two per cent of patients in the PC ($n=68$) and 70.2% of patients in the OC ($n=66$) groups lost ≤ 15 letters of ETDRS acuity at the month 12 visit ($P=0.267$). The proportion of patients losing ≤ 30 letters of ETDRS acuity was 93.6% ($n=88$) in the OC group and 86.4% ($n=95$) in the PC group ($P=0.14$). Similarly, with respect to the proportion of patients who maintained or improved ETDRS acuity from baseline, significant differences were not seen between the OC (38.3%; $n=36$) and PC (37.3%; $n=41$) groups ($P=.996$). Patients with OC lesions required a mean of 2.99 treatments (out of a possible 4) *vs* a mean of 2.96 treatments (out of a possible four) in the PC group ($P=0.172$).

Discussion

We found the clinical effectiveness of PDT with verteporfin for PC and OC lesions, measured by the difference in mean change in vision over 1 year, to be remarkably similar. The baseline and final visual acuities were well matched between the groups and the overall mean change in visual acuity over 1 year was almost identical. Our secondary outcomes, including the proportions of patients losing less than 15, or 30 letters, or having no change in vision between the OC and PC groups, support our hypothesis. Our MCID between the PC and OC groups was set at 7.5 letters, to set the comparison at a relatively stringent level. We believe that smaller differences are unlikely to be meaningful in clinical practice.

There are several differences between our results and the previously published data from multicenter trials. It must be borne in mind, however, that our study was designed to compare clinical effectiveness between OC and PC lesions, rather than the absolute efficacy compared to placebo. These differences preclude direct statistical comparison, although some observations are of interest. First, a large clinical study may reflect the general population of patients presenting for treatment of AMD better than earlier studies, where patients were recruited with long commitments to rigorous randomized trials. The TAP and VIP Studies had hard ceilings on lesion sizes (less than 5400 μm greatest linear dimension), and visual acuities (better than 20/200), and therefore excluded some patients whom we included. Second, our OC patients had larger mean baseline lesion sizes and lower mean baseline visual acuities, both of which were worse prognostic factors in the VIP Study. Nonetheless, our patients with OC lesions did not seem to deteriorate at a faster rate than the PC lesions, as shown in the decay curves. Thus, our study provides independent confirmation of the observation from the VIP Study that the visual outcomes of OC patients appear to be equal to the outcomes of the PC lesions in the TAP Study, when large lesions with good vision are excluded.

Limitations of our study include the loss to follow-up of some patients. Nonetheless, the proportion of patients who did not complete 12-month follow-up and the reasons for the losses to follow-up were very similar between the OC and PC groups in our study. We compared the intent-to-treat analysis with the completers analysis,[9] and found little difference in the outcomes. Almost 90% of the patients completed the 9-month visit, and the vast majority the 12-month visit. Seventy-five per cent of the vision loss in such patients appears to occur in the first 6 months.[2,3] These are excellent reasons to believe that we have observed our patients during the time interval in which differences, if present, in the decay of visual acuities in PC *vs* OC lesions should be observed.

One potential source of bias in our study is the interpretation of fluorescein angiograms. It is known that the inter-rater reliability is generally within 20%, so we would expect a group of expert graders to vary within this amount.[10] Our reader has been trained by multiple reading centres, and the agreement rate in multiple multicentre trials has been well within this standard. Another potential source of bias in our study is in the outcome measurement of visual acuity. All visual acuities were measured by an independent assessor, who was not aware of the lesion classification for each patient. The fact that our results follow similar decay curves to the TAP and VIP PC and OC groups, respectively, suggests, but does not prove that we are observing results that would be expected from the multicenter trials, if they had shared our study objectives.

The absence of a difference between OC and PC lesions in the effectiveness of PDT with verteporfin has a number of implications for patient care. The current reluctance among practitioners to treat OC *vs* PC lesions is not based upon a study of relative effectiveness, and perhaps should be reconsidered. These perceptions are often reflected in recommendations made to patients, taking into account the scarcity of resources. If indeed these patients benefit in the same manner as those with PC lesions, it seems reasonable to consider them for treatment as well. Finally, if it is not necessary to separate

OC and PC lesions, it may be reasonable to incorporate this information into the design of certain types of clinical trials, which would greatly speed the development of new therapies for AMD.

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