EXTENDED REPORT

Recurrence of choroidal neovascularisation after photodynamic therapy in patients with age-related macular degeneration

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Aim: To determine the incidence of recurrence of choroidal neovascularisation (CNV) 18 months after cessation of photodynamic therapy (PDT) with verteporfin monotherapy in patients with age-related macular degeneration (AMD).

Methods: This was a prospective interventional cohort study. The sample consisted of 108 individuals with CNV secondary to AMD which was treated with PDT. Data on demographics, pre-PDT and post-PDT Early Treatment of Diabetic Retinopathy Study (ETDRS) acuity, pre-PDT lesion size and composition were collected for each participant. All participants returned for fundus photographs and ETDRS acuity measurements 18 months after their final PDT, which were compared with the same measurements from the final treatment session to determine recurrence status. Recurrences were classified primarily on the basis of haemorrhage and increased lesion size.

Results: Recurrences were observed in 36 of 108 (33%) eyes. 23 of 36 (64%) recurrences were clinically meaningful. Of the explanatory variables considered, only final PDT acuity was significantly different between those that recurred (45.5 ETDRS letters) and those that did not (38.4 letters; $p=0.03$).

Conclusion: CNV recurrences are common after PDT for AMD, occurring in 33% of eyes in this study. Visual acuity measured at the final PDT treatment visit may be a predictor of subsequent recurrence.

Age-related macular degeneration (AMD) is the leading cause of legal blindness in the Western world.¹ Severe visual loss in AMD is caused by the development of choroidal neovascularisation (CNV), which leads to scarring of the macula. Argon laser photocoagulation was shown to reduce vision loss for patients with subfoveal CNV secondary to AMD compared with placebo, but to result in immediate central visual loss.² Photodynamic therapy (PDT) with verteporfin monotherapy was demonstrated to significantly reduce the risk of severe vision loss secondary to CNV in selected patients with AMD in a series of large placebo-controlled trials.^{3–4} Improved results have been reported with the addition of intravitreal triamcinolone to PDT.⁵ Newer treatments, including inhibitors of vascular endothelial growth factor (VEGF), that show promise to reduce vision loss further, and indeed even improve vision in certain patients, are presently emerging.^{6–9}

As new treatments are emerging, there is an ongoing problem regarding the persistence and recurrence of CNV lesions. The Macular Photocoagulation Study (MPS) Group found that 52% of eyes treated with argon laser developed recurrences within 24 months of treatment.¹⁰ There are very little data on recurrence rates aside from those following thermal laser photocoagulation. The early detection of reactivation of CNV lesions may become a critical factor in preventing vision loss, regardless of treatment modality. The recurrence rate will also affect the total number of treatments and the long-term stability of visual acuity (VA), both of which are key issues in formulating treatment plans. The purpose of this study is to determine the incidence of recurrence of CNV activity 18 months after cessation of PDT monotherapy treatment in patients with AMD.

METHODS

Participants

Our study group consisted of men and women aged ≥ 50 years with CNV secondary to exudative AMD on fluorescein angiography (FA), treated with PDT with verteporfin by a

single retinal specialist (MJP). Eligible participants were consecutive patients living in one municipality (Greater Vancouver, Canada), who started receiving PDT between February 2001 and August 2003, and experienced treatment success after PDT for their CNV in AMD. We defined treatment success as cessation of leakage from a CNV lesion on FA for at least 9 consecutive months after receiving any number of PDT treatments¹¹; treatment success was not based on VA outcome. Potential participants were excluded if they had clinical signs of any other retinal disease (eg, myopic degeneration or ocular histoplasmosis syndrome), if they were non-English speaking, were not mentally competent to give informed consent or did not experience treatment success (stopped treatment for other reasons prior to cessation of leakage on angiography).

Treatment

All study participants had CNV in exudative AMD treated with at least one session of PDT monotherapy. CNV was classified as predominantly classic (PC), minimally classic (MC) or occult (OC) in composition, based on baseline fluorescein angiograms, reviewed in a masked fashion by MJP. This reviewer has been certified as a treating ophthalmologist by the Digital Angiography Reading Center, New York, USA, the Wisconsin Center, Madison, USA and Wilmer Reading Center, Baltimore, USA. Fluorescein angiographic criteria for eligibility for PDT treatment were adapted from the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study,¹² Verteporfin in Photodynamic Therapy Trial³ and Verteporfin Roundtable Guidelines.¹¹ FA 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

Abbreviations: AMD, age-related macular degeneration; CNV, choroidal neovascularisation; ETDRS, Early Treatment of Diabetic Retinopathy Study; FA, fluorescein angiography; MC, minimally classic; MPS, Macular Photocoagulation Study; OC, occult; PC, predominantly classic; PDT, photodynamic therapy; VEGF, vascular endothelial growth factor

Table 1 Summary of clinical characteristics of the study group (n = 108), in counts (proportion) or mean (SD), as appropriate

Characteristic	n (%) or mean (SD)
Female	75 (69.4%)
Treatment eye = OD	47 (43.5%)
Age at final study visit (years)	78.1 (6.7)
Pre-PDT lesion size (µm)	3650 (1450)
RAP lesion present at baseline	5 (4.6%)
Pre-PDT subfoveal lesion location	95 (88%)
Pre-PDT lesion composition = OC	42 (38.9%)
Pre-PDT lesion composition = PC	44 (40.7%)
Pre-PDT lesion composition = MC	22 (20.4%)
Pre-PDT visual acuity (ETDRS letters)	50.4 (13.2)
Final PDT visual acuity (ETDRS letters)	38.5 (16.2)
Final study visit visual acuity (ETDRS letters)	36.2 (16.6)
Mean number of PDT treatments	3.8 (1.8)
Duration of AMD, from diagnosis to final study visit (months)	28.7 (6.5)

AMD, age-related macular degeneration; ETDRS, Early Treatment of Diabetic Retinopathy Study; MC, minimally classic choroidal neovascularisation; OC, occult with no classic choroidal neovascularisation; OD, right eye; PC, predominantly classic choroidal neovascularisation; PDT, photodynamic therapy with verteporfin; RAP, retinal angiomatous proliferation.

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 <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 (≤ 4 MPS disc areas) or associated with poor (< 65 letters on the ETDRS chart) VA, and with presumed recent (< 16 weeks duration) disease progression or haemorrhage, were considered for treatment. Prior to treatment, all patients underwent VA testing using the ETDRS chart, measured by a trained vision examiner and scored according to the standard protocol.¹³ 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 Treatment of Age-Related Macular Degeneration With Photodynamic Therapy (TAP) Report no 1.¹² Patients were reassessed 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 FA. VA, 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 VA was stable, without an increase in lesion size, mainly when fibrosis was present. Severely decreased vision or fibrosis, and stable VA were also considered to be factors weighing against treatment. All clinic patients regularly returned for follow-up for consideration of PDT every 3 months until three consecutive no-treatment decisions had been achieved.¹¹ At that point, patients were discharged to their referring eye care professional.

Current clinical practice guidelines recommend ceasing PDT treatment when there is minimal or no fluorescein leakage on angiography, there is little or no subretinal fluid, and the biomicroscopic appearance as well as vision is stable or improved.¹¹ No guidelines for following patients further to monitor recurrences or consider further treatment have been established. VA and fundus biomicroscopy are non-invasive methods of screening for potential recurrences, and, if they are stable, FA does not seem to be warranted.

Primary outcome measure

To determine the incidence of recurrence of CNV activity after cessation of PDT monotherapy, we asked clinic patients meeting the inclusion criteria to return for a follow-up visit (termed the study visit). Study visits consisted of an ETDRS VA measurement and colour fundus photography, and were performed 18 months after their last visit at which PDT was delivered (termed the final PDT treatment, and determined retrospectively). We defined recurrence of CNV activity as showing increased lesion size on fundus photography, with the presence of haemorrhage, subretinal fluid and VA data used as corroborating information. Recurrences therefore occurred between 9 and 18 months after an individual's final PDT treatment. Recurrences were confirmed by FA. Since the current standard of clinical practice is not to perform FA in patients who are stable on clinical examination and VA testing for more than a year and a half following the cessation of treatment, we used fundus photography as a non-invasive method of screening for recurrence, with FA as the gold standard.

The incidence of CNV recurrence was determined by comparing photographs and ETDRS acuity measurements obtained at the study visit with the same measurements from the final PDT treatment visit. Recurrences were classified as clinically meaningful if they were associated with a decrease of ≥ 2 lines from the final PDT VA, or if the VA at the study visit had dropped to $\leq 20/400$. Data on demographics, pre-PDT ETDRS acuity, pre-PDT lesion size and composition, final treatment ETDRS acuity and time since diagnosis of AMD in the study eye were also collected on each participant.

Analysis

Mean pre-treatment and post-treatment visual acuities, baseline lesion size, duration of AMD and number of PDT treatments were compared between groups of individuals with and without CNV recurrence using Student's *t* test. Differences in proportions of patients in each group, by lesion composition, were compared using the χ^2 test. The distributions of continuous explanatory variables were examined by scatterplot, and collinearity between explanatory variables was assessed. Univariate and multivariate logistic regression was used to model the relationship between putative explanatory variables and a recurrence event.

This prospective study was approved by the institutional review boards of the University of British Columbia and Vancouver Hospital.

RESULTS

We contacted 127 consecutive potential participants, 10 of whom were too ill to participate, 2 of whom had moved and 7 of whom were not interested in participating. Our study population therefore consisted of 108 men and women with CNV secondary to AMD in whom cessation of fluorescein leakage from their CNV lesion was noted after their final treatment with PDT. Table 1 shows the clinical characteristics of the study group.

No association was seen between baseline lesion size and composition by χ^2 test ($\chi^2 = 108.5455$, degrees of freedom = 92, *p* value = 0.115). Recurrences were observed in 36 of the 108 (33.3%) eyes by the end of the 18-month period of follow-up. Figure 1 shows a sample series of fundus photographs depicting a CNV recurrence. Of the recurrences, 21 (58%) were judged to be clinically meaningful on the basis of VA and FA. Of the 36 recurrences, 14 (38.9%) were still followed in the clinic 18 months after their final PDT treatment for treatment in their fellow eye, and 2 (5.6%) were re-referred due to complaints of visual changes. The remaining 20 (55.6%) recurrences, 12 of

Figure 1 Recurrence fundus photos. Fundus photography of a representative participant showing (A) an inactive lesion after the final photodynamic therapy visit, and (B) a recurrence of choroidal neovascularisation activity after 18 months.

which were judged to be clinically meaningful, would have gone undetected without additional FA or clinical investigation.

Mean pre-PDT, final PDT, final study visit ETDRS VA, duration of AMD, number of treatments and baseline lesion size were compared between those with recurrence of CNV and those without. The proportion of patients with OC, PC or MC lesions was also compared between groups. Only final PDT VA was significantly different between those with recurrence (45.5 ETDRS letters) and those without (38.4 letters; $p = 0.03$). Table 2 shows the summary statistics for selected putative explanatory variables, based on recurrence status.

Only final PDT VA was a significant predictor of recurrence on logistic regression. The odds ratio (95% CI) for developing a recurrence, based on final PDT VA, is 1.03 (1.01 to 1.06), taking into account the effect of age. Thus, for every one-letter increase in final PDT VA, the odds of having a CNV recurrence increases by 3%.

DISCUSSION

We found that CNV recurrences are very common in patients treated with PDT for CNV in AMD within the first 1.5 years of follow-up. Indeed, one-third of the participants in our study experienced a recurrence within this time frame. Poor final PDT VA was found to be a significant predictor of recurrence in our study, but the effect size was small. This observation is in accordance with the prediction that as macular health deteriorates, there is less likelihood of a clinically meaningful recurrence in scarred tissue. We did not observe significant effects of other variables, including baseline lesion size or composition, on the recurrence rate.

Although newer therapies are currently in use for the treatment of CNV secondary to AMD, the large number of patients treated with PDT worldwide could well make rescue strategies for recurrences a major concern. This number could increase if combination therapy including PDT and VEGF inhibitors comes into widespread use. Understanding the recurrence rate is not only helpful for post-PDT patients but also establishes a benchmark against which the recurrence rates for other treatment modalities may be compared. Although direct comparison with the MPS data is difficult due to differences in study design and duration of follow-up, 52% of eyes treated with argon laser were noted to have recurrences within 24 months of treatment cessation.¹⁰

Recurrence rates have also been studied for a number of other treatments for CNV due to AMD, with various sample sizes and observation periods. Despite the initial enthusiasm about limited macular translocation as treatment for CNV in AMD, persistence and recurrence of CNV lesions remain a major cause of vision loss; recurrence rates vary from 19% to 52% over 1–2 years of follow-up in several studies.^{14–16} One study looked retrospectively at recurrence rates after PDT with verteporfin and found that 17% of followed patients experienced recurrences; however, as they had follow-up on less than half of their study sample, some bias may be present in their estimate.¹⁷ Currently, there is insufficient information on VEGF inhibitors, including pegaptanib (Macugen), ranibizumab (Lucentis) and bevacizumab (Avastin),^{5–9} to determine whether recurrences after the cessation of treatment are as frequent as with PDT and argon laser. It is plausible, but unproven, that the larger treatment size for a given lesion size has a protective effect

Table 2 Comparison of clinical characteristics of those with recurrence of choroidal neovascularisation ($n = 36$) and those without recurrence ($n = 72$), in counts (proportion) or mean (SD), as appropriate

Characteristic	No recurrence ($n = 72$)	Recurrence ($n = 36$)	p Value
Age at final study visit (years)	78.2 (6.75)	78.2 (6.67)	0.928
Pre-PDT lesion size (μm)	3635 (1515)	3660 (1290)	0.936
Pre-PDT lesion composition = OC	29 (40.3%)	13 (36.1%)	0.915
Pre-PDT lesion composition = PC	30 (41.7%)	14 (38.9%)	0.962
Pre-PDT lesion composition = MC	13 (18.1%)	9 (25.0%)	0.914
Pre-PDT visual acuity (ETDRS letters)	49.0 (12.1)	53.3 (15.0)	0.113
Final PDT visual acuity (ETDRS letters)	38.4 (14.2)	45.5 (18.9)	0.031
Final study visit acuity (ETDRS letters)	35.0 (12.1)	38.4 (17.5)	0.322
Number of PDT treatments	3.9 (1.9)	3.7 (1.6)	0.552
Duration of AMD, from diagnosis to final study visit (months)	29.3 (6.6)	27.6 (6.2)	0.212

AMD, age-related macular degeneration; ETDRS, Early Treatment of Diabetic Retinopathy Study; MC, minimally classic; OC, occult with no classic choroidal neovascularisation; PC, predominantly classic choroidal neovascularisation; PDT, photodynamic therapy with verteporfin.

upon recurrences, when PDT is compared to argon laser. Uniform criteria for stopping treatment with the newer modalities need to be established in order to allow gauging the recurrence rate, as well as to permit patients and doctors to judge clinical success. Accordingly, the recurrence rate will become increasingly important not only when comparing new treatments but also for healthcare planning, as more individuals are treated and become at risk for experiencing recurrences.

Recurrence events after PDT may depend on the length of time since cessation of treatment, as well as on the fact that treatment has stopped. We felt that an 18-month window of follow-up should probably be sufficient to capture early recurrences after PDT. Our study is strengthened in that our clinical practice patterns and results, in terms of the mean number of PDT treatments administered, well-represent previously published clinical practice effectiveness studies on PDT,^{18, 19} although the rate of re-treatment in the large randomised trials was slightly higher.^{3, 12} In addition, the prospective nature of our study enabled us to capture data on a large number of patients who would otherwise be unlikely to come to follow-up.

A potential limitation of our study is selection bias in the inclusion of patients. An attempt was made to capture all eligible patients, however, and only 7 (5.5%) individuals were not interested in participating. It is unlikely that this small proportion of individuals could have changed the direction of the results, even if all of them had or had not experienced recurrences. A small number of patients were too ill, and one may expect that recurrence might be distributed among them without regard to systemic illness, and in the same manner as that in the study group.

The definition of recurrence included leakage on FA, although 7% of our patients were classified as such without an angiogram. Biomicroscopy could have missed small edge recurrences, although these would have been unlikely to result in a drop in central acuity. Further, if any recurrences were missed, the true recurrence rate would have been larger than reported here, so our calculated rate is a conservative estimate.

CNV recurrences are relatively common in patients treated with PDT for CNV in AMD within 1.5 years of follow-up. Most of these patients may benefit from additional treatment to prevent further vision loss. Long-term surveillance to detect recurrences after the cessation of treatment may be clinically important, since the underlying predisposition to develop CNV persists in these patients. It is highly probable that recurrences will become an even more frequent clinical problem as more vision is preserved due to further advances in this field. Hopefully, early detection of recurrences will result in the preservation of more vision, and as therapeutic strategies shift towards prevention, the tendency to recur will become modifiable.

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