

Baseline clinical measures and early response predict success in verteporfin photodynamic therapy for neovascular age-related macular degeneration

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CLINICAL STUDY

Abstract

Purpose To analyse the influence of baseline clinical characteristics on the outcome of verteporfin photodynamic therapy (VPDT) for neovascular age-related macular degeneration (nAMD).

Methods A total of 1008 patients commencing VPDT for nAMD in a single UK centre entered a prospective observational study between 1999 and 2006 and were followed for 2 years. Longitudinal linear mixed-effects modelling was applied to assess the influence of baseline covariates, such as best corrected visual acuity (BCVA), contrast sensitivity (CS), age, lesion size, and lesion type, on changes of BCVA over time in patients after VPDT. A logistic regression analysis was used to analyse clinical features significantly associated with treatment failure.

Results Study eye BCVA was significantly better on average throughout the course of treatment in patients with better baseline BCVA and CS in the study eye ($P < 0.001$ and $P < 0.01$, respectively) and lower age ($P = 0.01$). Mean BCVA showed a significant quadratic relationship between 0 and 6 months and with stabilisation between 6 and 9 months. Patients with better BCVA and worse CS at baseline, and those in whom BCVA dropped during the first 3 months of follow-up, were more likely to lose ≥ 15 letters after 12 months.

Conclusions Findings from our large longitudinal data set provide estimates of likely outcome based on baseline features and response at 3 months in patients commencing a course of VPDT for nAMD. Statistical modelling built up for this large data set can be applicable to other studies in ophthalmology research.

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Introduction

Neovascular age-related macular degeneration (nAMD) is the leading cause of severe visual impairment in the developed world in patients over 50 years of age.^{1–3} Verteporfin photodynamic therapy (VPDT) has been shown to be effective in randomised controlled clinical trials (RCTs) at reducing the likelihood of further visual loss when choroidal neovascularisation (CNV) is characterised on fundus fluorescein angiography (FA) as classic/no occult or predominantly classic.^{4,5} Similar effectiveness is observed in routine clinical practise.^{6,7}

RCTs have shown efficacy of intravitreal therapy with pegaptanib similar to VPDT but

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across all angiographic lesion types.⁸ For ranibizumab, there was an additional benefit shown with a gain of 15 or more letters for the 0.5 mg dose of between 33.8 and 40.4% of the patients at 12 months depending on lesion subtype leading to its introduction into routine clinical practise.^{9,10} However, long-term experience of anti-vascular endothelial growth factor (VEGF) therapy remains limited with uncertainty regarding ocular and systemic complications and the acceptability and feasibility of the required 4 weekly treatment regime. VPDT continues to be used as monotherapy in selected groups of patients such as those who do not adequately respond to anti-VEGF treatment or have concerns regarding an intraocular injection procedure, and in research settings as part of combined therapy protocols.¹¹ We analysed the value of clinical features at baseline and at the first review visit in predicting the outcome of VPDT for nAMD using a large data set collected from a single treatment centre. Descriptive data on outcomes at 12 and 24 months are published elsewhere.⁷ We derived a statistical model to provide useful information regarding factors influencing the response to treatment.

Materials and methods

After informed consent for data collection and analysis, patients commencing a course of VPDT for nAMD at St Paul's Eye Unit, Royal Liverpool University Hospital were recruited into a prospective observational study. Patients were observed every 3 months during 2 years, reduced to every 6 months in the second year if the lesion showed clinical features of inactivation. In cases of bilateral treatment, the first treated eye was considered as the study eye.

Study procedures are described in detail elsewhere.⁷ In brief, best corrected visual acuity (BCVA) was measured at each visit and contrast sensitivity (CS) at alternate visits using standardised refraction and testing protocols by accredited optometrists.⁷ BCVA and CS were recorded as letters read at one metre on an Early Treatment Diabetic Retinopathy Study (ETDRS) logMAR chart and Pelli-Robson chart, respectively.¹² Treatment was administered according to the TAP protocol⁴ and re-treatment guided by a locally produced protocol.⁶

Data were analysed using two methods. First, a linear mixed-effects model examined the relationship between baseline covariates and BCVA over time using the restricted maximum likelihood (REML) procedure. A second analysis used logistic regression to analyse explanatory variables associated with failure of treatment after 1 year. Failure was defined as a drop in absolute BCVA to below 20 letters and/or a loss of BCVA ≥ 15 letters from baseline.^{12,13}

The study was approved by the local institutional review board and conducted within the Declaration of Helsinki guidelines.

Results

Of 1438 patients referred between November 1999 and October 2006 for possible treatment, 1008 met the eligibility criteria,⁷ were recruited for the study and commenced their course of VPDT. The study population was 706 at 12 months and 386 at 24 months, respectively. Distribution of patients is shown in Figure 1.

At baseline, the mean age was 77.2 years (range 47–102, SD 7.5) and 540 (54%) were women. The majority of patients had classic no occult (735 (72.9%)) or predominantly classic CNV (218 (21.6%)), with a small number of other lesion types (minimally classic: 41 (including RAP) and other: 14 (including PCV and occult/no classic)). Mean greatest linear diameter (GLD) at baseline was 3247 μm (range 322–7380, SD 1492).

Mean BCVA (SD) was 48.4 letters (11.1) at baseline falling to 38.3 (17.9) at 12 months. Mean CS (SD) was

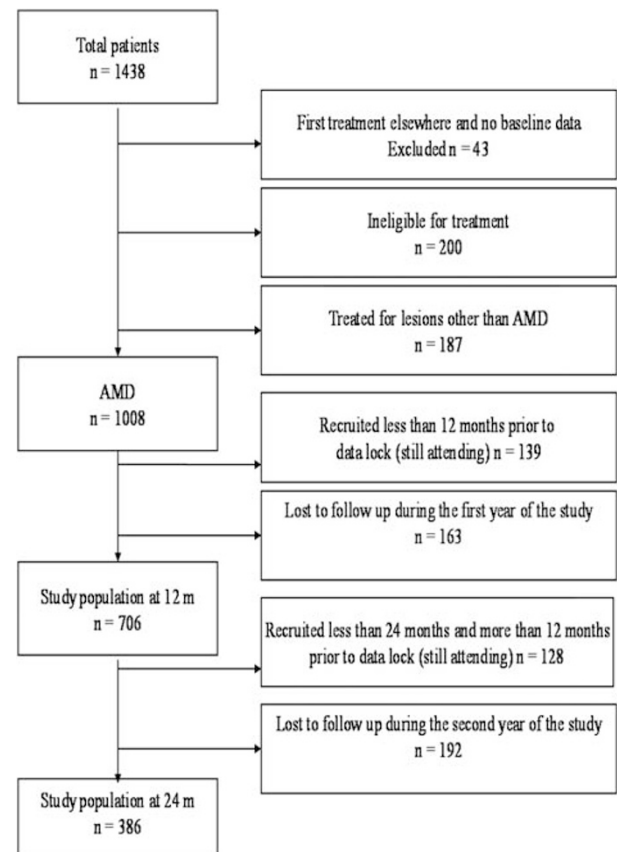


Figure 1 Flow chart illustrating distribution during follow-up of 1008 patients commencing a course of photodynamic therapy for neovascular age-related macular degeneration.

21.5 (6.8) at baseline and it remained constant at 12 months with values 21.5 (8.1). Mean total number of treatments (SD) was 2.91 (1.2) in year 1 and 0.54 (0.8), with 63% of the patients having no treatment, in year 2.

The change in mean BCVA over time is shown in Figure 2 together with the 5th, 10th, 25th, 75th, 90th, and 95th percentiles. After an initial fall, the mean BCVA stabilised between 6 and 9 months. There was a wide variation in BCVA curves of individual study eyes.

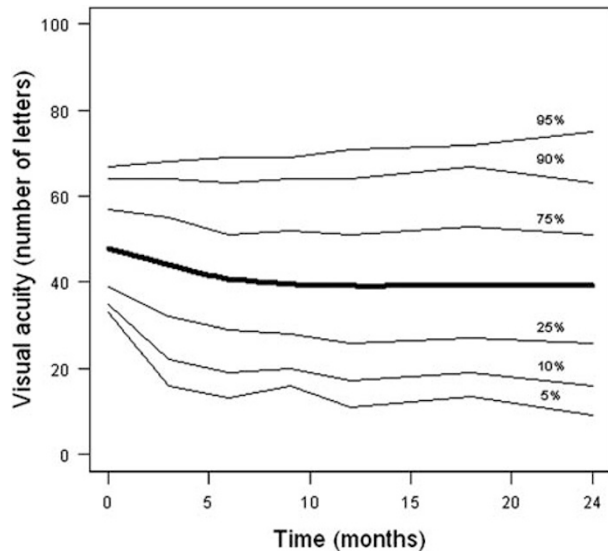


Figure 2 Mean visual acuities over 24 months follow-up of 1008 patients undergoing photodynamic therapy for neovascular age-related macular degeneration (thick black line). The 5th, 10th, 25th, 75th, 90th, and 95th percentiles are also plotted.

Longitudinal mixed-effects analysis

The results of the longitudinal mixed-effects analysis are summarised in Table 1. The analysis was performed on data from 829 patients after excluding those patients for whom the values of one or more baseline covariates were missing (missing observations were considered to be missing completely at random). A random effect term with intercept and time slope was included in the model to account for a different baseline value and change of BCVA over time for each patient. A continuous auto-regression structure with parameter estimate $\phi = 0.58$ was chosen to model the within individual correlation based on the *best-fitting-model* (BIC criteria).

The statistical analysis revealed that changes in BCVA of the study eye were significantly associated with the value of BCVA at baseline (as one would expect due to their inherent correlation), as well as with the baseline covariates CS, age, and lesion size. In particular, BCVA was significantly better on average throughout the course of treatment in patients with better BCVA of the study eye at baseline ($P < 0.001$), better CS of the study eye at baseline ($P = 0.003$), lower age ($P = 0.01$), and smaller lesion size ($P = 0.003$).

Large values of BCVA at baseline were associated with large values of BCVA at any time point. However, patients with larger values of BCVA tended to lose more letters as indicated by the negative linear slope -0.04 . For example, if at baseline patient A had 20 letters more in BCVA than patient B, the negative linear term indicates that patient A would tend to lose approximately 0.8

Table 1 Effect of baseline covariates on BCVA over time ($n = 829$)

Fixed-effect parameter	Baseline covariates	Coefficient	Standard error	t-value	95%CI	P-value
Intercept	BCVAb	0.85	0.05	15.78	(0.74, 0.95)	<0.001
	CSb	0.27	0.09	2.99	(0.09, 0.45)	0.003
	BCVAbfe	0.01	0.01	0.33	(-0.02, 0.03)	0.74
	Age (years)	-0.16	0.06	-2.62	(-0.27, -0.04)	0.01
	Lesion size (mm)	-1.00	0.32	-3.00	(-1.57, -0.33)	0.003
	Lesion type	Classic/no occult (reference group)				
		Pred C	2.48	1.01	2.45	(0.50, 4.47)
	Min C	1.44	2.41	0.60	(-3.29, 6.16)	0.55
	Other	0.11	4.19	0.03	(-8.12, 8.34)	0.98
Linear slope ($t =$ time in months)	BCVAb	-0.04	0.01	-4.80	(-0.06, -0.02)	<0.001
	CSb	0.05	0.01	3.55	(0.02, 0.08)	<0.001
Quadratic slope (t^2)	BCVAb	0.0011	0.0003	3.50	(0.0005, 0.0017)	<0.001
	CSb	-0.0013	0.0005	-2.34	(-0.0023, -0.0002)	0.02
Random effect: SD intercept = 7.90; SD Slope = 0.44		Random error: SD Residual = 9.32		Continuous AR(1): Phi = 0.58		

BCVAb, best corrected visual acuity at baseline (letters); BCVAbfe, best corrected visual acuity in fellow eye at baseline (letters); CSb, best corrected contrast sensitivity at baseline (letters); lesion types: pred c, predominantly classic; min c, minimally classic.

Table 2 Logistic regression analysis of treatment failure at 1 year (BCVA <20 and/or loss of BCVA \geq 15 letters) in relation to corrected visual acuity, contrast sensitivity, age, and lesion type at baseline

Covariate	Model coefficient β (SE)	Odds ratio (95% CI)	P-value
BCVAb	0.05 (0.009)	1.05 (1.03, 1.07)	<0.001
CSb	-0.10 (0.015)	0.90 (0.88, 0.93)	<0.001
Age	0.03 (0.013)	1.03 (1.01, 1.05)	0.02
<i>Lesion type</i>			
Classic no occult		(reference)	
Predominantly classic	-0.54 (0.226)	0.58 (0.37, 0.90)	0.02
Minimally classic	-14.64 (638)	0 (0, inf)	0.98
Other	0.25 (0.779)	1.28 (0.28, 5.93)	0.81

BCVAb, best corrected visual acuity at baseline; CSb, best corrected contrast sensitivity at baseline.

The standard error (SE) of the coefficient estimators, the odds ratios (per unit change in the covariate) with the corresponding 95% confidence intervals and P-values are provided.

letters more per month than patient B. The positive quadratic slope (0.0011) implies that the loss of letters because of large values of BCVA at baseline becomes less important as time increases. The opposite effect was observed with CS: patients with larger values of CS at baseline tended to gain more letters over time (positive linear slope equal to 0.05). For example, if the CS of patient A is at baseline 20 letters greater than patient B, patient A will tend to gain approximately one letter more than patient B per month. The negative value for the quadratic slope (-0.0013) indicates that this effect becomes less strong over time.

Table 1 also shows that older patients and those with larger values of lesion size tend to show a worse outcome with more letters of BCVA lost, although the size of these effects was small and was not clinically significant. Finally, lesion type classified as predominantly classic showed a slightly better outcome than classic/no occult. BCVA of the fellow eye at baseline and gender were not statistically significant and do not seem to influence BCVA changes over time.

We also analysed whether the number of treatments was significantly associated with changes in visual acuity. This question was addressed by taking into account that patients had different lengths of follow-up and no significant association was detected.

Logistic regression analysis

Table 2 shows the result of the logistic regression analysis for treatment failure after 1 year as a function of baseline BCVA, CS, age, and lesion type. Patients with large values of BCVA at baseline were more likely to experience treatment failure ($P < 0.001$). In particular, the odds of treatment failure increased by 65% for every 10 letters increase of BCVA at baseline (odds ratio (OR): $\exp(10 \times 0.05) = 1.65$, $P < 0.001$). This effect can be explained by taking into account the definition for

treatment failure adopted (see Materials and methods section) and that patients with larger BCVA at baseline tend to lose more letters as deduced from the longitudinal analysis. In addition, patients with low values of CS at baseline were more likely to experience treatment failure ($P < 0.001$). When taking into account CS at baseline, the odds of treatment failure decreases approximately three times for every 10 letters increase of CS at baseline (OR: $\exp(10 \times (-0.10)) = 0.37$, $P < 0.001$). Younger patients and patients with predominantly classic CNV were less likely to fail treatment (both $P = 0.02$, see Table 2).

Change in BCVA at 3 months

To analyse the effect of change in BCVA at the first follow-up visit, the proportions of patients maintaining vision (<15 letters lost and BCVA \geq 20 letters) at 12 months was calculated as a function of BCVA at baseline and of change of BCVA at 3 months. Both variables were segregated in ordinal steps as shown in Table 3.

As expected, because of the mathematical correlation, as the number of letters lost at first follow-up increased there was a greater chance of patients experiencing treatment failure at 12 months. The proportion of patients experiencing a treatment failure was only 20.8% (82/394) if ≤ 5 letters were lost at 3 months compared with 79.8% (95/119) if 15 or more were lost at 3 months. The threshold change in BCVA at 3 months to give a 70% chance of no treatment failure was -15 letters.

Discussion

Our results provide useful information regarding the influence that baseline clinical features have on change in visual function over time in patients undergoing VPDT. The mixed-effects linear regression model applied here

Table 3 Proportions of patients maintaining vision (<15 letters lost) at 12 months for different values of BCVA at baseline and change of BCVA after 3 months (the numerator indicates the number of patients maintaining vision at 12 months and the denominator indicates the total number of patients)

	Change in BCVA after 3 months						n_m	n	%
	$\geq +15$	+14 to +6	+5 to -5	-6 to -14	-15 to -29	≤ -30			
<i>BCVA baseline</i>									
≥ 60	1/1	14/16	43/58	10/29	1/14	0/9	69	127	54.3
50–59	7/7	29/34	48/67	15/36	7/31	0/9	106	184	57.6
40–49	8/11	12/17	67/87	25/47	8/25	1/6	121	193	62.7
<40	14/14	11/13	58/69	22/35	7/23	0/2	112	156	71.8
n_m	30	66	216	72	23	1			
n	33	80	281	147	93	26			
%	90.9	82.5	76.9	49.0	24.7	3.8			

The sample size (n), the number of patients maintaining vision (n_m), and the percentage of patients maintaining vision (%) are given for each of the categories based on BCVA at baseline (last three columns) and change of BCVA after 3 months (last three rows).

shows that patients with better BCVA and CS at baseline have a better outcome and that these findings are both clinically and statistically significant.

Our findings can be illustrated for the aid of clinical interpretation from the model coefficients shown in Table 1. For each 10 letters of better BCVA at baseline (two lines on an ETDRS chart or 0.2 logMAR) there was, on average, 5.3 letters better outcome in BCVA in the study eye after 12 months (where $5.3 = 10 \cdot (0.85 - 0.04 \cdot 12 + 0.0011 \cdot 12^2)$). Patients with better BCVA at baseline experienced greater loss of BCVA over time as shown by the negative slope and this relationship was statistically significant. Therefore, for every 10 letters better BCVA at baseline there was, on average, a 4.7 letter greater loss in BCVA at 12 months. This appears to suggest that VPDT is of less benefit for patients with better levels of baseline vision and is supported by our patients final BCVA being limited to a relatively small range of absolute values. Patients with lower BCVA at the commencement of therapy are likely to have more longstanding and advanced disease. PDT may be of greater benefit at this stage when neovascular lesions are more established and the biological effect of vessel closure is more relevant.

Our results on the relationship between change in vision at 3 months and outcome at 12 months show that the initial response to VPDT can give some information regarding the final outcome. There was a 70% probability of no treatment failure in our cohort if BCVA had dropped <15 letters at 3 months. Loss of ≥ 15 letters at 3 months has been termed by us as ‘primary non-response’ and indicates that clinicians should consider switching to an alternative treatment option. Our results suggest that only a small proportion of patients who have lost 15 or more letters at month 3 benefit from continued treatment. For such patients alternative treatment strategies should therefore be considered at that stage.

In contrast to the findings of better BCVA being predictive of greater visual loss, there was an inverse relationship between CS and drop in BCVA. On average, for each six letters better CS at baseline (two triplets on the Pelli–Robson chart) there was a 6.8 letter gain in BCVA over 12 months (where $6.8 = 10 \cdot (0.27 + 0.05 \cdot 12 - 0.0013 \cdot 12^2)$). Our finding of a better CS at baseline being associated with better BCVA during follow-up raises questions regarding the differential predictive effect of different types of visual function. Our findings, supported by others,^{14–17} suggest that CS should be used to a greater extent in assessing the efficacy of treatment of AMD.

CS arises from a summation of input from receptive fields of ganglion cells, which are further processed in the lateral geniculate nucleus.¹⁸ The photoreceptor origin of these fields is likely to extend laterally beyond the lesion boundary in nAMD. Patients with better CS at baseline may have a healthier retina surrounding the lesion, and consequently, better anatomical and functional reserve allowing a better response to therapy, either with VPDT or other treatment modalities. It is also possible that better CS may be an indicator of a less aggressive lesion more likely to respond to treatment.

Older patients experienced a worse outcome. For example, for each 10-year increment in age, BCVA was on average 1.6 letters worse at 12 months. However, this effect was not considered to be clinically significant despite being statistically significant.

The relationship between BCVA and CS at baseline and changes of BCVA over time was similar to the results observed in the TAP study indicating that our findings could be generalised to patients receiving VPDT in routine clinical practise.

The statistical longitudinal model we derived provides novel information regarding the linear and quadratic changes of BCVA over time and the effect that values of BCVA and CS at baseline have on these changes. Missing

data has been assumed to be lost completely at random and although we expect that the absence of these data has not affected the main findings, a more complex statistical model in which missing values are recovered using the existing data set is under investigation.

The results of VPDT observed in our cohort and in RCTs are generally inferior to those reported with ranibizumab therapy in the ANCHOR trial.⁹ However, some groups of patients cannot manage the frequent injections required with anti-VEGF therapy. For these patients in whom 50% or more of their lesion comprises classic CNV it would appear reasonable to consider VPDT to reduce the frequency of visits and treatments. Our findings indicate that this is particularly applicable in patients with lower BCVA but better CS at baseline. At the 3 month follow-up visit, clinicians may wish to use our results to recommend switching to another therapy if BCVA has dropped by more than 15 letters. Various combinations of anti-VEGF therapy with VPDT are currently being analysed. Our results provide a reference point for the selection of VPDT therapy for these patients.

Summary

What was known before

- Verteporfin photodynamic therapy has been shown to be effective in randomised controlled clinical trials at reducing the likelihood of further visual loss.

What this study adds

- We show the influence of several baseline covariates, such as contrast sensitivity, on the changes in best corrected visual acuity over time and identify that early response is significantly associated with treatment success/failure. These findings, as well as the methodology used, are relevant for longitudinal studies that are based on other treatments and in other retinal diseases.

Conflict of interest

The authors declare no conflict in interest.

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