Verteporfin Photodynamic Therapy Cohort Study: Report 1: Effectiveness and Factors Influencing Outcomes

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Purpose: To compare the visual outcomes after verteporfin photodynamic therapy (VPDT) administered in routine clinical practice with those observed in the Treatment of Age-related macular degeneration with Photodynamic therapy (TAP) trials and to quantify the effects of clinically important baseline covariates on outcome.

Design: A prospective longitudinal study of patients treated with VPDT in 45 ophthalmology departments in the United Kingdom with expertise in the management of neovascular age-related macular degeneration (nAMD).

Participants: Patients with wholly or predominantly classic choroidal neovascularization (CNV) of any cause with a visual acuity ≥20/200 in the eye to be treated.

Methods: Refracted best-corrected visual acuity (BCVA) and contrast sensitivity were measured in VPDT-treated eyes at baseline and subsequent visits. Eyes were retreated at 3 months if CNV was judged to be active. Baseline angiograms were graded to quantify the percentages of classic and occult CNV. Treated eyes were categorized as eligible or ineligible for TAP, or unclassifiable.

Main Outcome Measures: Best-corrected visual acuity and contrast sensitivity during 1 year of follow-up after initial treatment.

Results: A total of 7748 treated patients were recruited. Data from 4043 patients with a diagnosis of nAMD were used in the present analysis. Reading center determination of lesion type showed that 87% were predominantly classic CNV. Eyes received 2.4 treatments in year 1 and 0.4 treatments in year 2. Deterioration of BCVA over 1 year was similar to that observed in the VPDT arms of the TAP trials and was not influenced by TAP eligibility classification. Best-corrected visual acuity deteriorated more quickly in current smokers; with increasing proportion of classic CNV, increasing age, and better baseline BCVA; and when the fellow eye was the better eye.

Conclusions: Patients in the cohort who would have been eligible for the TAP trials demonstrated deterioration in BCVA similar to VPDT-treated TAP participants but with fewer treatments. Clinical covariates with a significant impact on BCVA outcomes were identified.

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Neovascular age-related macular degeneration (nAMD) is the most common cause of severe visual impairment in the developed world.[1,2] The main mechanism of visual impairment is the development of choroidal neovascularization (CNV), which occurs in 2 main forms as defined on fluorescein angiography (FA): classic and occult. The Treatment of Age-related macular degeneration with Photodynamic therapy (TAP) study, a large industry-sponsored phase 3 randomized controlled trial, reported a significant reduction of visual loss in eyes with classic CNV secondary to AMD treated with verteporfin photodynamic therapy (VPDT) when compared with eyes treated with a sham placebo.[3,4] Subgroup analyses reported greater benefit in lesions with larger proportions of classic CNV.

In 2003, the National Institute of Health and Clinical Excellence, the organization that advises the United Kingdom National Health Service on implementation of new health care technologies, recommended the use of VPDT in eyes with classic and no occult CNV (recommendation 1.1).[5] For those with some occult CNV present, treatment was only recommended providing robust data were collected on long-term outcomes, quality of life, and costs (recommendation 1.2). A longitudinal observational cohort study was established to provide evidence to inform a future review of VPDT by the National Institute of Health and Clinical Excellence and to allow a managed introduction of the technology.

The principle aims of this article are to report (a) how VPDT was provided in the National Health Service, (b) a

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comparison of the provision and outcomes of routine clinical practice with the findings of published randomized controlled trials, and (c) data on verteporfin infusion-related and ocular adverse events. We describe outcomes for patients who would have been eligible for the TAP trial, patients who did not fit these criteria, and patients in whom we had insufficient data to allow classification by TAP eligibility. An analysis of cost-effectiveness forms the content of a companion article. The study was designed to allow the results to be applied to other models of health service delivery.

Materials and Methods

Patients attending designated centers in the United Kingdom for consideration for VPDT were recruited into the study. The study population consisted of all patients treated with VPDT at participating centers irrespective of CNV cause. This article describes the visual outcomes for the subgroup with nAMD only. For participants who gave written informed consent, data characterizing clinical measures of vision, angiographic descriptors, and quality of life measures at baseline and follow-up were entered into a database. The study received research ethics committee approval (ref. MREC/03/11/103).

A manual describing the study design and methods, including standard protocols for all measurements, was prepared before recruitment started and updated periodically.[6] Only the main details of the methods are presented. Eligibility for treatment with VPDT was determined at each site by clinicians who specialized in the management of macular disease. Eligibility criteria were based on recommendations by the National Institute of Health and Clinical Excellence but were extended to include CNV due to other causes. At each visit, best-corrected visual acuity (BCVA) measured using Early Treatment Diabetic Retinopathy Study distance acuity charts[7] and contrast sensitivity measured using Pelli-Robson charts[8] were recorded as letters read. Information about adverse reactions (at the time of VPDT administration) and adverse events (at each subsequent visit, referring to the period between visits) was also collected. Adverse reactions included back pain during infusion, pain at the site of infusion, and extravasation into the injection site. Data on ocular adverse events (identified at the subsequent clinical visit) included a loss of $\geq$20 letters "suddenly" or within 7 days of treatment administration (patient report) and a new retinal pigment epithelial tear.

Stereoscopic color images and fluorescein angiograms were graded within the network of UK reading centers using definitions and protocols that have been published.[9,10] Grading involved the delineation and area measurement of classic and occult CNV and other lesion components contiguous to CNV. At the time of first treatment, eyes were classified into mutually exclusive categories based on the proportion of classic and occult CNV (predominantly classic, minimally classic, or occult no classic). We grouped patients into 3 categories according to whether the treated eye met the following eligibility criteria for the TAP trials: BCVA $>$33 and $<$74 letters at first treatment *and* evidence on FA of at least some classic CNV ($\geq$1% of lesion) *and* total CNV area $\geq$50% of the lesion *and* CNV under the geometric center of foveal avascular zone.[4] Thus, each treated eye was classified as follows:

1. meeting these eligibility criteria (eligible for TAP [EFT]);
2. not meeting the criteria (ineligible for TAP [IFT]); or
3. not classifiable because of the absence of gradable baseline FA (unclassifiable [UNC]).

Data Management and Statistical Analyses

Treating centers submitted data to an independent data management center at the London School of Hygiene and Tropical Medicine. Only data from the first eligible treated eye were analyzed, although some patients had both eyes treated during observation in the study; when both eyes were first treated at the same visit, 1 eye was selected at random. Some treated eyes with missing BCVA at baseline or no BCVA measurements after treatment could not contribute to the analysis and were excluded.

The protocol required sites to follow patients for 3 months during a course of treatment and 6 months once treatment had been discontinued, and to perform 12- and 24-month assessments. Years 1 and 2 of follow-up were defined as $\leq$350 days and $>$350 and $\leq$715 days, respectively, on the assumption that scheduled visits would tend to slip over time and were unlikely to occur at shorter time intervals than scheduled. Because of substantial loss to follow-up in year 2, we restricted our main analysis to report outcomes at 12 months for patients who had started treatment at least 1 year ($>$350 days) before the close of the study *and* who had at least 1 follow-up visit.

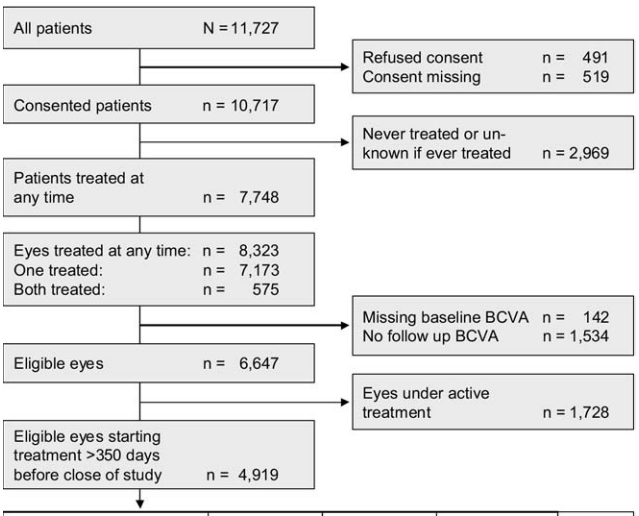
To investigate numbers of treatments administered, we had to distinguish clinical follow-up visits from visits solely for the purposes of the study. Treatment was defined as complete if $>$150 days ($\sim$5 months) had elapsed between subsequent visits, except when a gap of $>$150 days occurred between consecutive treatment visits, or if $>$150 days had elapsed after the last visit. Patients who had had their first treatment less than 12 months before the close of the study were not included in the 12-month analysis of treatments administered or BCVA outcomes.

Summary statistics were generated to show baseline characteristics. Treatment frequencies were cross-tabulated with TAP eligibility and tested for significance using chi-square statistics. We fitted a mixed regression model to estimate the BCVA trajectory during the first year, using data up to 2 years where available. We also examined the influence of the following covariates: age, gender, baseline BCVA, TAP eligibility, CNV composition, smoking status, and whether or not the fellow eye was the better-seeing eye. Better eye status was assigned on the basis of BCVA across the duration of the trial; if both eyes had similar BCVA, better eye status was classified as uncertain. Duration of follow-up ("time") was a covariate in the model; interactions of other covariates with time represented nonparallel trajectories.

Results

The flow of recruited patients in the study is shown in Figure 1. Between June 2004 and September 2007, data on 11,727 patients were submitted. A total of 7748 patients (8323 eyes) were treated at any time. Missing BCVA resulted in the exclusion of 1676 eyes (142 missing at baseline and 1534 at follow-up). Of the remaining 6647 eyes, 1728 had been first treated $\leq$350 days before the close of the study, leaving 4919. Restricting the analysis to 1 eye per patient excluded a further 8% of treated eyes. After excluding treated eyes with non-AMD cause, 4043 eyes remained. The baseline characteristics of these patients and eyes are shown in Table 1.

The numbers of treatments administered in years 1 and 2 are shown in Tables 2 and 3 by TAP eligibility status (i.e., groups EFT, IFT, and UNC). In year 1, among the entire cohort, fewer treatments were administered (average 2.35) than in the TAP trials (average 3.4; $\chi^2 = 615.2$, *df* 4, $P<0.0001$).[5,11] The average numbers of treatments for each of the TAP eligibility groups were 2.47 for EFT, 2.31 for IFT, and 2.29 for UNC ($\chi^2 = 364.3$, *df* 8, $P<0.0001$). In year 2, for the entire cohort, the average number of



	Eligible for TAP trials (EFT)	Ineligible for TAP trials (IFT)	Eligibility for TAP trials unclassified (UNC)	Total
All eyes	1,268	1,487	2,164	4,919
One eligible eye /patient	1,227	1,435	1,904	4,566
One eligible eye with nAMD /patient	1,227	1,187	1,629	4,043

Figure 1. Consolidated Standards of Reporting Trials-style diagram showing the patients and eyes treated in the VPDT cohort study. BCVA = best-corrected visual acuity; nAMD = neovascular age-related macular degeneration; TAP = Treatment of Age-related macular degeneration with Photodynamic therapy.

treatments was 0.40, compared with 2.2 in TAP.[11] The average numbers of treatments for each of the TAP eligibility groups were 0.40 for EFT, 0.37 for IFT, and 0.43 for UNC (χ^2 = 6.62, *df* 6, P = 0.36).

In the EFT group, predominantly classic CNV was present in 86.7% of patients (1064/1227) and minimally classic CNV was present in 13.3% of patients (163/1227). We compared the change in BCVA in the 2 angiographic subtypes in our study with those previously reported for treatment and sham treatment arms in the TAP trials (Figs 2 and 3).[4] The trajectory for predominantly classic lesions in the EFT group was similar to that of the TAP treatment arm. For the minimally classic lesions of the EFT group, the *trajectory* of BCVA was parallel to that observed for the minimally classic subgroup of the TAP treatment arm but showed less loss of BCVA.[4]

The coefficients from the regression model (Table 4) show that a number of baseline covariates influence BCVA. The rate of deterioration of BCVA was influenced by baseline acuity, with faster decline in BCVA over time in eyes with better starting acuity; a patient who read 5 letters more at baseline read only 2.7 letters more at 1 year. Best-corrected visual acuity deteriorated faster in older patients; after 1 year of follow-up, BCVA was 2 letters worse for a person 10 years older than average (88 vs. 78 years). Women presented with better baseline BCVA and maintained this difference during follow-up (+1.8 letters). Never- and ex-smokers presented with better baseline BCVA (+1.8 and +1.6 letters, respectively) and deteriorated more slowly when compared with current smokers. The decrease in BCVA by 1 year was 1 letter fewer in treated eyes of ex-smokers, and 3 letters fewer in treated eyes of never-smokers, than treated eyes of current smokers. If the fellow eye had better BCVA than the treated eye, BCVA in the treated eye was worse at baseline (+2.6 letters) and deteriorated faster; the decrease in BCVA by 1 year was 5 letters worse than if the treated eye was classified as the better-seeing eye.

The TAP eligibility group and baseline lesion classification influenced outcome. Compared with EFT eyes with predominantly or minimally classic CNV, IFT eyes presented with better BCVA (+1.4 letters). The UNC eyes also presented with better BCVA +1.5 letters than EFT eyes and deteriorated more slowly (+1.50+0.77=+2.3 letters at 1 year). Within the EFT group, eyes with minimally classic CNV had better BCVA at baseline (+1.1 letters) and deteriorated more slowly compared with eyes with predominantly classic CNV (+1.13+2.08=+3.2 letters at 1 year). Eyes with occult only lesions (a subgroup of IFT eyes) were better by +3.4 letters at baseline and exhibited slower deterioration (+3.43+2.79=+6.2 letters at 1 year). The decrease in BCVA over 1 year was 8 to 16 letters depending on patient and lesion factors.

Adverse reactions were few. Rates varied from 0% to 4.3% (1.4% overall) across centers. Back pain was documented in 86 of 7748 first treatments (1.1%). Pain at the injection site (n = 2) and extravasation (n = 1) were rarely reported. Ocular adverse events were also few. Rates reported at the visit after first treatment (attributed to the period between first treatment and follow-up) varied from 0% to 5.2% (mean 2.0% overall) across centers. These included a sudden decrease in vision reported by the patient or a documented loss of ≥20 letters within 7 days of treatment in 25 of 7748 first treatments (0.3%), a tear of the retinal pigment epithelium in 5 patients (0.1%), and diverse other adverse events in 121 patients (1.6%).

Discussion

The VPDT Cohort Study is a large representative prospective study of the implementation between 2004 and 2007 of a new treatment modality into routine clinical practice in the management of nAMD, a disease that was not previously amenable to treatment. This study revealed functional visual outcomes at 1 year similar to those observed in the pivotal TAP trials but achieved with a lower retreatment frequency.

Strengths and Weaknesses

Despite its observational nature, the VPDT Cohort Study has many strengths. These include its size, pragmatic nature, and systematic collection of standardized data on acuity and lesion characteristics. Set against these strengths, there were a number of limitations.

Unlike the pivotal trials in which almost all patients were followed up for 24 months,[3,4,11] approximately half of the patients included in our analyses did not have 1-year follow-up. Because poor data quality is a well-recognized limitation of observational studies, we undertook computerized data-validation checks on an ongoing basis and when compiling the final dataset. We checked whether data were missing for some visits by (a) matching records from paper and electronic systems for collecting BCVA and (b) requesting centers to check explicitly whether additional visits had taken place for selected patients. The results from these checks implied that data had been submitted for >95% of completed visits.

Table 1. Baseline Characteristics of Patients Included in the Verteporfin Photodynamic Therapy Cohort Study

	Eligible for TAP Trials† (EFT)		Ineligible for TAP Trials (IFT)		Eligibility for TAP Trials Unclassified (UNC)		Total	
	n = 1227		n = 1187		n = 1629		n = 4043	
Mean age, yrs (SD)	78.8	(7.17)	78.3	(8.31)	78.7	(8.66)	78.6	(8.13)
Male, n (%)	513	(41.9%)	612	(42.8%)	768	(40.5%)	1893	(41.6)
Smoking status, n (%)								
Current smoker	170	(16.4%)	158	(16.5%)	211	(15.5%)	539	(16.1%)
Ex-smoker	437	(42.1%)	415	(43.5%)	574	(42.1%)	1,426	(42.5%)
Never smoked	432	(41.6%)	382	(40.0%)	579	(42.5%)	1,393	(41.5%)
BCVA (letters; SD)	50.6	(10.4)	50.2	(19.0)	48.7	(15.7)	49.7	(15.5)
BCVA group, n (%) >73 ETDRS letters	—	—	144	(12.1%)	79	(4.9%)	223	(5.5%)
73–34 ETDRS letters	1227	(100%)	766	(64.5%)	1,311	(80.5%)	3304	(81.7%)
<34 ETDRS letters	—	—	277	(23.3%)	239	(14.7%)	516	(12.0%)
CS, letters (SD)*	22.4	(6.89)	23.0	(7.67)	22.1	(7.59)	22.5	(7.38)
Lesion area, median mm^2 (interquartile range)								
All lesions	*n = 1215* 3.81	(1.8–6.8)	*n = 1158* 2.58	(0.9–6.4)	*n = 25* 4.20	(1.8–5.0)	*n = 2398* 3.28	(1.4–6.6)
Predominantly classic	*n = 1058* 3.46	(1.7–6.2)	*n = 621* 1.80	(0.6–4.7)				
Minimally classic	*n = 157* 6.66	(4.2–11)	*n = 537* 3.90	(1.6–8.4)				
Lesion area, DA, n (%)								
Predominantly classic	*n = 1064*		*n = 626*					
≤3 DA	868	(81.6%)	555	(88.7%)				
>3 DA ≤6 DA	152	(14.3%)	56	(9.0%)				
>6 DA ≤9 DA	28	(2.6%)	13	(2.1%)				
>9 DA	16	(1.5%)	2	(0.3%)				
Minimally classic	*n = 163*		*n = 559*					
≤3 DA	90	(55.2%)	389	(69.6%)				
>3 DA ≤6 DA	50	(30.7%)	114	(20.4%)				
>6 DA ≤9 DA	14	(8.6%)	35	(6.3%)				
>9 DA	9	(5.5%)	21	(3.8%)				
CNV location, n (%)	*n = 1227*		*n = 1187*				*n = 2414*	
Subfoveal	1227	(100%)	586	(49.4%)			1813	(75.1%)
Juxtafoveal	0	(0%)	349	(29.4%)			349	(14.5%)
Extrafoveal	0	(0%)	252	(21.2%)			252	(10.4%)
Lesion % classic CNV, n (%)	*n = 1227*		*n = 1187*				*n = 2414*	
≥50%	1064	(86.7%)	628	(53.0%)			1692	(70.1%)
>0% <50%	163	(13.3%)	351	(29.6%)			514	(21.3%)
0%	0	(0.0%)	208	(17.5%)			208	(8.6%)
Occult CNV present, n (%)	*n = 1227*		*n = 1187*				*n = 2414*	
	197	(16.1%)	303	(25.5%)			500	(20.7%)
Blood present in lesion	*n = 1227*		*n = 1187*				*n = 2414*	
	600	(49.9%)	532	(44.9%)			1132	(46.9%)
SPED present in lesion	*n = 1227*		*n = 1187*				*n = 2414*	
	11	(0.9%)	86	(7.3%)			97	(4.0%)

BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; CS = contrast sensitivity; DA = disc area; EFT = eligible for TAP; ETDRS = Early Treatment Diabetic Retinopathy Study; IFT = ineligible for TAP; nAMD = neovascular age-related macular degeneration; SD = standard deviation; SPED = serous pigment epithelial detachment; TAP = Treatment for Age-related macular degeneration with Photodynamic therapy; UNC = unclassified by eligibility for TAP; VPDT = verteporfin photodynamic therapy.

Summary statistics on the baseline characteristics of patients in the VPDT cohort study categorized by eligibility for inclusion in the TAP trials (EFT, IFT, UNC).

*Contrast sensitivity was only assessed by 18 centers. Therefore, the averages and standard deviations are calculated for a sample of 2289 patients (EFT 797, IFT 654, and UNC 838).

†Eyes classified as "eligible for the TAP trials" (the EFT subgroup) met the following eligibility criteria for the TAP trials: cause AMD; BCVA 73–34 letters; subfoveal CNV; CNV comprising ≥50% of lesion; classic CNV >0%.

The exact reasons for loss to follow-up are not known. Patients who were not followed lost the opportunity to be retreated if reactivation occurred; this may have led to worse BCVA outcomes with treatment in everyday practice compared with treatment in the licensing trials. However, the visual acuity outcome in the VPDT cohort study was generally similar to that observed in the treatment arm of the TAP trials.

The loss to follow-up introduced uncertainty to the data analyses, which was taken into account by using a

Table 2. Number of Photodynamic Therapy Treatments in Year 1 by Photodynamic Therapy Eligibility Subgroups

Treatments in Year 1	Eligible for TAP Trials (EFT) n = 1227		Ineligible for TAP Trials (IFT) n = 1187		Eligibility for TAP Trials Unclassified (UNC) n = 1629		All Patients n = 4043	
	N	%	*N*	%	*N*	%	*N*	%
1	255	20.8%	307	25.9%	425	26.1%	987	24.4%
2	377	30.7%	400	33.7%	571	35.1%	1348	33.3%
3	364	29.7%	292	24.6%	384	23.6%	1040	25.7%
4	224	18.3%	181	15.3%	229	14.1%	634	15.7%
5	6	0.5%	7	0.6%	18	1.1%	31	0.8%
6	1	0.1%	0	0.0%	2	0.1%	3	0.1%

EFT = eligible for TAP; IFT = ineligible for TAP; TAP = Treatment for Age-related macular degeneration with Photodynamic therapy; UNC = unclassified by eligibility for TAP.
Numbers of treatments in year 1 (≤350 days) in patient groups categorized by eligibility for the TAP trial (EFT, IFT, UNC).

mixed regression model to predict BCVA at 1 year in different subgroups. This approach allows all of the available data to be modeled but does not prevent attrition bias. We observed that patients who were lost to follow-up tended to have poorer BCVA at baseline (data available from the authors). Because follow-up data were more likely to be missing with increasing duration after first treatment, the model will have tended to underestimate deterioration in BCVA over time. However, the regression model for BCVA trajectory assumed that BCVA deteriorated steadily (on the principles of parsimony and "best-fit"); this assumption is unlikely to be valid when BCVA is poor because the neovascular process burns out, causing a "floor" effect. Attrition bias and a floor effect would have affected the results in opposite directions; therefore, in our judgment, the model did not markedly underestimate deterioration in BCVA over time.

Although loss to follow-up is a scientific limitation, our experience also demonstrates vividly the difficulties associated with follow-up when treatments requiring multiple visits over an extended period of time in an older age group are introduced into routine clinical practice. Such data are invaluable to health service planners and are rarely available. We believe that patients and clinicians became disheartened with eyes that showed deterioration of vision during treatment and follow-up, causing treatment to be discontinued before the recommended time point of 2 years. We did not attempt to predict outcome at 2 years because data were sparse.

A further limitation of the study was the inability to classify 40% of the lesions at baseline with respect to TAP eligibility (eyes classified as UNC), either because an angiogram was not submitted or because the submitted angiogram could not be graded. This group was retained in the model; parameter estimates tended to lie between those for EFT and IFT groups, and between those for predominantly and minimally classic lesions. Thus, there was no reason to believe that these eyes represented a biased selection with respect to eligibility for the TAP trials or their lesion composition.

Table 3. Number of Photodynamic Therapy Treatments in Year 2 by Photodynamic Therapy Eligibility Subgroups

Treatments in Year 2	Eligible for TAP Trials (EFT) n = 533		Ineligible for TAP Trials (IFT) n = 478		Eligibility for TAP Trials Unclassified (UNC) n = 600		Total Patients n = 1611*	
	N	%	*N*	%	*N*	%	*N*	%
0	392	73.6%	348	72.8%	425	70.8%	1165	72.3%
1	90	16.9%	89	18.6%	112	18.7%	291	18.1%
2	33	6.2%	35	7.3%	46	7.7%	114	7.1%
3	14	2.6%	4	0.8%	14	2.3%	32	2.0%
4	4	0.8%	2	0.4%	3	0.5%	9	0.6%

EFT = eligible for TAP; IFT = ineligible for TAP; UNC = unclassified by eligibility for TAP.
Numbers of treatments in year 2 (>350 and ≤715 days) in patient groups categorized by eligibility for the TAP trial (EFT, IFT, UNC).
*Total number of patients (1611) represents those among the 4043 patients who had their first treatment >2 years before the date of last data submission.

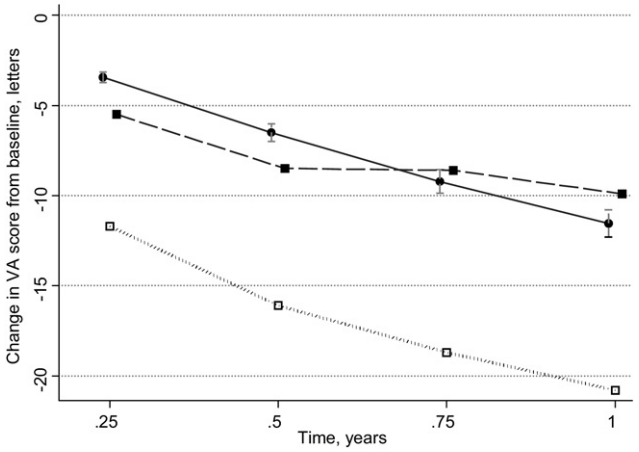


Figure 2. Change in BCVA from baseline in eyes with predominantly classic CNV. *Solid circles, solid line:* VPDT cohort study. *Solid squares, dashed line:* TAP[11] study-treated group. *Hollow squares, dotted line:* TAP[11] study sham group. Confidence intervals are not shown for TAP study-derived data because they were not reported. VA = visual acuity.

Comparison of Outcomes in the Verteporfin Photodynamic Therapy Cohort Study versus Treatment of Age-related Macular Degeneration with Photodynamic Therapy

A striking feature of the VPDT Cohort Study was the smaller number of treatments delivered. In the TAP trials, 3.4 treatments were administered in the first year and 2.2 treatments were administered in the second year on the basis of a protocol that required retreatment in the presence of any leakage on FA.[11] The protocol for our study required clinicians to retreat as in the TAP trials. However, substantially fewer treatments were administered in the VPDT cohort. Despite this difference, we observed a visual outcome that was comparable to that seen in the TAP trial. Thus, our findings suggest that clinicians do not adhere to protocols that are used in key licensing trials and that retreatment decision making is influenced more by subsequent experience gained from treating large numbers of patients. Changes in practice after a drug has been licensed need to

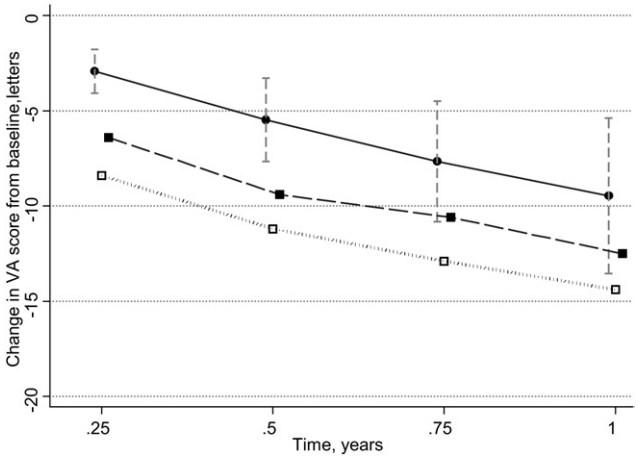


Figure 3. Change in BCVA from baseline in eyes with minimally classic CNV. *Solid circles, solid line:* VPDT cohort study. *Solid squares, dashed line:* TAP[11] study-treated group. *Hollow squares, dotted line:* TAP[11] study sham group. Confidence intervals are not shown for TAP study-derived data because they were not reported. VA = visual acuity.

Table 4. Parameter Estimates from the Regression Model

Covariate	Regression Coefficient	95% CI	*P* Value
Time (per year)	−15.68	−17.78 to −13.59	<0.0001
Time^2 (per year)	3.33	2.74–3.92	<0.0001
TAP eligibility:			
EFT group	0.00	—	0.026
IFT group	1.42	0.17–2.67	
% of lesion classified as classic			0.014†
≥50%	0.00	—	—
>0% and <50%	1.13	−0.44 to 2.70	0.158
0%	3.43	1.04–5.83	0.005
Unknown % classic	1.50	0.29–2.72	0.016
% of lesion classified as classic × time*			0.031†
≥50%	0.00	—	—
>0% and <50%	2.08	0.38–3.77	0.016
0%	2.79	0.20–5.38	0.035
Unknown % classic	0.77	−0.45 to 1.98	0.218
Age (yr)	−0.20	−0.26 to −0.14	<0.0001
Age × time*	−0.29	−0.36 to −0.22	<0.0001
Baseline ETDRS (per letter)	0.743	0.70–0.77	<0.0001
Baseline ETDRS (per letter) × time*	−0.20	−0.23 to −0.16	<0.0001
Gender:			
Male	1.00	—	—
Female	1.76	0.85–2.67	0.0002
Smoking status:			0.091†
Never smoked	1.00	—	—
Ex-smoker	1.89	0.34 to 3.44	0.017
Current smoker	1.59	0.01 to 3.18	0.049
Unknown smoking status	2.03	0.10 to 3.96	0.039
Smoking status × time*			0.002†
Never smoked	1.00	—	—
Ex-smoker	1.09	–0.66 to 2.83	0.223
Current smoker	3.03	1.28–4.78	0.0007
Unknown smoking status	1.21	–0.78 to 3.20	0.233
BCVA in fellow eye			<0.0001†
Fellow worse	1.00	—	—
Fellow similar to treated eye	−2.12	−3.46 to −0.77	0.002
Fellow better	−2.57	−3.73 to −1.40	<0.0001
BCVA in fellow eye × time*			<0.0001†
Fellow worse	1.00	—	—
Fellow similar to treated eye	−1.53	−3.04 to −0.02	0.0471
Fellow better	−5.16	−6.52 to −3.79	<0.0001

BCVA = best-corrected visual acuity; CI = confidence interval; EFT = eligible for TAP; ETDRS = Early Treatment Diabetic Retinopathy Study; IFT = ineligible for TAP; TAP = Treatment for Age-related macular degeneration with Photodynamic therapy.
Influence of covariates on baseline visual acuity and change in acuity over time.
*Interactions with time, implying that the rate of change in BCVA over time was influenced by the baseline line covariate.
†*P* value for overall factor (i.e., across multiple categories).

be considered by providers and purchasers of health care when implementing any new technology requiring frequent retreatment and by researchers when designing pragmatic phase 3 trials.[12] Our findings also highlight that treatment protocols evaluated in commercial phase 3 trials may recommend more treatment than necessary or a treatment frequency that is not deliverable across the whole eligible population.

Even though the method of collection of adverse reactions and events were different from the pivotal trials, the findings of our study support the assertion that VPDT is generally a safe procedure because injection-related adverse reactions were mild and transient and sudden loss of vision attributable to the treatment itself was rarely reported.

Factors Influencing Change in Best-Corrected Visual Acuity in the Verteporfin Photodynamic Therapy Cohort Study

The large and representative nature of our cohort allowed us to investigate the influence of a range of baseline covariates. Several factors contributed to deterioration in acuity, including older age, poorer BCVA at commencement of treatment, being a current or ex-smoker, and having a fellow eye with better vision than the treated eye. Although our findings are consistent with clinical wisdom, experience, and intuition, this is the first study to quantify the effects of these factors on visual change. For example, eyes of older participants tended to deteriorate faster than those of younger participants with better BCVA. The magnitudes of the interactions between smoking status and vision in the fellow eye with time, estimated here for the first time, are striking. Also, our finding of a better outcome when the treated eye is the better-seeing eye is important and has been overlooked in previous studies. This finding is consistent with a previous report that suggested that an eye with nAMD does not achieve its full visual potential unless it is the better-seeing eye[13] and with previous findings of improvements in adult amblyopic eyes when vision in the fellow eye is lost.[14] The modest size of the effect and its consistency across conditions suggest that it arises from a shift in decision criterion.[15]

In conclusion, the VPDT cohort study yielded visual acuity outcomes similar to that seen in the treatment arm of the TAP trials. The most notable finding was that these outcomes were achieved despite a considerably lower retreatment frequency. Even though VPDT is no longer the first line of treatment for nAMD, our findings continue to have relevance to clinical practice. In particular, the quantification of the influence of key covariates of age, cigarette smoking, and status of the fellow eye on the trajectory of vision loss has added to our knowledge and suggests that these factors should be considered in the design and analysis of trials of treatments for nAMD.

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Footnotes and Financial Disclosures

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