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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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. 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 ≥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. 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 (≥1% of lesion) and total CNV area ≥50% of the lesion and CNV under the geometric center of foveal avascular zone. 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 ≤350 days and >350 and ≤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 (~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 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 ≤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; χ² = 615.2, df 4, P < 0.0001). The average number of treatments for each of the TAP eligibility groups were 2.47 for EFT, 2.31 for IFT, and 2.29 for UNC (χ² = 364.3, df 8, P < 0.0001). In year 2, for the entire cohort, the average number of
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, 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.
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 data analysis, which was taken into account by using a
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 2. Number of Photodynamic Therapy Treatments in Year 1 by Photodynamic Therapy Eligibility Subgroups

<table>
<thead>
<tr>
<th>Treatments in Year 1</th>
<th>Eligible for TAP Trials (EFT)</th>
<th>Ineligible for TAP Trials (IFT)</th>
<th>Eligibility for TAP Trials Unclassified (UNC)</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 1227</td>
<td>n = 1187</td>
<td>n = 1629</td>
<td>n = 4043</td>
</tr>
<tr>
<td>1</td>
<td>255</td>
<td>307</td>
<td>425</td>
<td>987 24.4%</td>
</tr>
<tr>
<td>2</td>
<td>377</td>
<td>400</td>
<td>571</td>
<td>1348 33.3%</td>
</tr>
<tr>
<td>3</td>
<td>364</td>
<td>292</td>
<td>384</td>
<td>1040 25.7%</td>
</tr>
<tr>
<td>4</td>
<td>224</td>
<td>181</td>
<td>229</td>
<td>634 15.7%</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>7</td>
<td>18</td>
<td>31 0.8%</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3 0.1%</td>
</tr>
</tbody>
</table>

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).

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

<table>
<thead>
<tr>
<th>Treatments in Year 2</th>
<th>Eligible for TAP Trials (EFT)</th>
<th>Ineligible for TAP Trials (IFT)</th>
<th>Eligibility for TAP Trials Unclassified (UNC)</th>
<th>Total Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 533</td>
<td>n = 478</td>
<td>n = 600</td>
<td>n = 1611*</td>
</tr>
<tr>
<td>0</td>
<td>392</td>
<td>348</td>
<td>425</td>
<td>1165 72.3%</td>
</tr>
<tr>
<td>1</td>
<td>90</td>
<td>89</td>
<td>112</td>
<td>291 18.1%</td>
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<tr>
<td>2</td>
<td>33</td>
<td>35</td>
<td>46</td>
<td>114 7.1%</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>4</td>
<td>14</td>
<td>32 2.0%</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>9 0.6%</td>
</tr>
</tbody>
</table>

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.
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
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. 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 and with previous findings of improvements in adult amblyopic eyes when vision in the fellow eye is lost. The modest size of the effect and its consistency across conditions suggest that it arises from a shift in decision criterion.

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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References


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