

Verteporfin photodynamic therapy for neovascular age-related macular degeneration: cohort study for the UK

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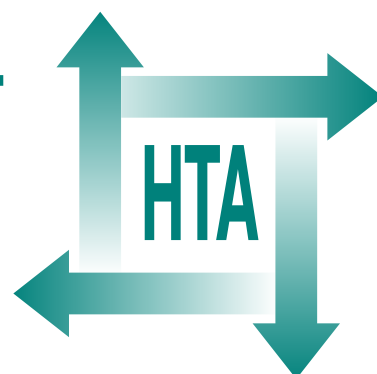
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Executive summary

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Executive summary

Introduction

In 2003, the National Institute for Clinical Excellence (NICE; now the National Institute for Health and Clinical Excellence) issued guidance to the NHS for a new, expensive treatment for 'wet' or neovascular age-related macular degeneration (nAMD) called verteporfin photodynamic therapy (VPDT). The guidance recommended treatment for the subtypes of nAMD for which the benefit from VPDT had been observed to be largest in phase 3 licensing trials [the 'TAP' (Treatment of Age-related macular degeneration with Photodynamic therapy) trials] but mandated the collection of robust information on vision, quality of life and the costs of having and treating nAMD for subtypes for which the cost-effectiveness of VPDT was less certain. The VPDT cohort study was set up to provide evidence to inform a future review of VPDT by NICE, to monitor compliance with the NICE guidance and to allow treatment of some subtypes of nAMD in compliance with the 'only-in-research' recommendation of the NICE guidance.

Objectives

The VPDT cohort study aimed to answer the following questions:

- (a) Is VPDT in the NHS provided as in randomised trials?
- (b) Is 'outcome' the same in the NHS as in randomised trials?
- (c) Is 'outcome' the same for patients who would have been ineligible for randomised trials?
- (d) Is VPDT safe when provided in the NHS?
- (e) How effective and cost-effective is VPDT?

Methods and participants

Study design

Treatment register/longitudinal case series.

Setting and participants

All hospitals providing VPDT in the NHS and all patients attending VPDT clinics, that is including baseline data for patients found to be ineligible for VPDT.

Outcomes

The primary outcome was logarithm of the minimum angle of resolution monocular best-corrected distance visual acuity (BCVA) in the VPDT-treated eye. Secondary outcomes were adverse reactions (ARs) and adverse events (AEs), contrast sensitivity (CS), generic and visual health-related quality of life (HRQoL), resource use and morphological changes in treated nAMD lesions.

Follow-up

The protocol specified that patients should be followed every 3 months during treatment or active observation (a treatment episode) and, at the end of a treatment episode, every 6 months up to 2 years and annually thereafter. Clinicians were advised to base decisions to retreat on criteria used in the TAP trial. The protocol also specified key data which should be collected [BCVA, fundus colour photography and fundus fluorescein angiography (FA)] at

each visit during a treatment episode and at least annually thereafter. CS, HRQoL and resource use data were collected at 6-monthly intervals but only in a subset of hospitals chosen to provide a representative sample of patients. The treatment costs of VPDT were obtained from reference sources.

Grading of neovascular age-related macular degeneration lesions

Colour photographs and FAs were graded by independent, externally accredited personnel within a network of reading centres established for the study. The proportion of classic and occult choroidal neovascularisation (CNV) was measured and lesions were classified into mutually exclusive categories namely predominantly classic, minimally classic or occult no classic. Treated eyes were then classified into one of three categories based on whether or not the treated eye met four key eligibility criteria for the TAP trials (presenting BCVA > 33 and < 74 letters, presence of some classic CNV, total CNV area \geq 50% of the lesion and CNV under the geometric centre of the foveal avascular zone). Thus, each treated eye was classified as (a) meeting these eligibility criteria ('eligible for TAP'; EFT); (b) not meeting the criteria ('ineligible for TAP'; IFT); or (c) not classifiable owing to the absence of a gradable baseline FA ('unclassifiable'; UNC).

Analyses

Objectives (a)–(d) are descriptive and were addressed by relevant statistical summaries of the data set. Objective (e) required comparisons to be made with untreated patients similar to those treated in the study. We proposed three methods to do this, although only one was possible, namely quantifying the associations between BCVA and HRQoL, and between BCVA and health and social service costs, and combining these associations with information about BCVA benefit from the TAP trials and from the cohort study. Except for objective (d), for which all treated patients were included, the main analyses included only one treated eye per patient for patients with CNV from nAMD who had > 1 year of follow-up or who had completed their treatment.

Results

Data were submitted by 47 participating hospitals for a total of 8323 treated eyes in 7748 patients. Key missing data (e.g. baseline BCVA, no follow-up data) reduced these numbers to 6647 eyes in 6223 patients. Only eyes which were treated > 350 days (1 year) before the most recent data submission, or which had completed treatment, were analysed; 4919 eyes in 4566 patients met this criterion. The number of eyes classified against eligibility for the TAP trial were 1227 EFT, 1187 IFT and 1629 UNC. Responses to at least one HRQoL and resource use questionnaire were submitted for about 2000 patients (the number varied by questionnaire).

(a) Is verteporfin photodynamic therapy in the NHS provided as in randomised trials?

The percentages of treated eyes receiving one, two, three or more than three treatments in year 1 was 25%, 34%, 25% and 16%, falling to 18%, 7%, 2% and 1%, respectively in year 2. The mean number of treatments in years 1 and 2 was 2.3 and 0.4 much lower than in the 'TAP' phase 3 trial on which NICE guidance was mainly based. About 50% of patients had completed their treatment by the end of year 1. Follow-up was incomplete because hospitals discharged patients owing to the introduction of local policies that limited the number of outpatient reviews. Therefore, analyses of outcomes at 1 year (for comparison with 1-year outcomes in the TAP trial) required complex statistical modelling to take into account the missing follow-up data and to allow comparison with 1-year outcomes in the TAP trial.

(b) Is 'outcome' the same in the NHS as in randomised trials?

Analyses of BCVA outcome at 1 year found no difference in the rate at which vision was lost in patients in the different eligibility groups. Patients in the EFT group lost 11.6 letters

(95% confidence interval 10.1 to 13.0 letters) by 1 year compared with 9.9 letters in the TAP trial subgroup.

(c) Is ‘outcome’ the same for patients who would have been ineligible for the TAP trial?

Given that there was no difference in the rate at which vision was lost in the different eligibility groups, patients in the IFT and UNC groups also lost 11.6 letters by 1 year. Note that this does not mean that VPDT is equally effective in these other groups, as the study had no data for the rate of deterioration in BCVA over time without VPDT, which may differ by eligibility group. After adjusting for covariates, patients in the EFT group had, on average, poorer BCVA at baseline (a difference of just over two letters) than patients in the IFT and UNC groups.

(d) Is VPDT safe when provided in the NHS?

Frequencies of ARs (immediately following treatment) and AEs (recorded at the subsequent visit, covering the interval between visits) decreased dramatically after the first treatment visit, either because local investigators did not record adverse effects of the same kind on repeat visits or because adverse effects deterred patients or their ophthalmologists from continuing treatment. ARs were reported on 1.4% of first visits and AEs following 1.9% of first visits; these frequencies were lower than those reported for patients treated with VPDT in the TAP trial.

(e) How effective and cost-effective is verteporfin photodynamic therapy?

Associations between the best BCVA in either eye with (i) HRQoL and (ii) health and social care resource use in the community were estimated from data for visits for which BCVA and HRQoL data were available. These associations allowed the 11-letter difference in BCVA between VPDT and sham treatment in the TAP trial to be ‘translated’ into a utility difference of 0.012 and into a health and social service resource use difference equivalent to £60 in year 1 and £92 in year 2. The cost-effectiveness of VPDT was estimated on the basis of these quality-adjusted life-years (QALYs) and community cost differences derived for the TAP trial and the costs of the lower frequency of treatment observed in the cohort study, giving an incremental cost per QALY over 2 years’ treatment of £170,000.

Comment and conclusions

The main findings were that (i) VPDT was administered much less frequently in routine clinical practice than in the TAP trial; (ii) in routine clinical practice, patients were followed much less frequently than in the research setting of the TAP trial, with attendance tending to stop once BCVA had dropped; (iii) for the EFT group, deterioration in BCVA over time was similar to that in the TAP trial; (iv) there was no evidence that safety was worse than in the TAP trial; and (v) the estimated cost per QALY was similar to the highest previous estimate.

The main limitation was the exclusion and early loss to follow-up of some patients, who are likely to have been those with a worse than average outcome; this limitation would have led treatment frequency to be overestimated and deterioration in BCVA and cost per QALY to be underestimated.

A number of observations on the introduction of this technology into routine clinical practice can be made: (i) there was wide variation in the readiness of centres to follow a proscribed protocol including follow-up; (ii) there was variable engagement by centres with the collection of data, with improvement in data quality occurring over time only at centres with highly committed research-focused staff; (iii) provider organisations had varying degrees of difficulty in establishing and maintaining consistent provision to the service specification required by the national commissioning and professional bodies.

Implications for practice

Implications for practice do not relate to the use of VPDT to treat nAMD because VPDT has now been superseded by the introduction of new treatments.

- The small number of treatments administered suggests that treatment regimens receiving marketing authorisation may overestimate the intensity of treatment required. This is potentially an important consideration in relation to other new health technologies.
- This limitation of loss to follow-up should be carefully considered in the design of similar studies for interventions requiring treatment or follow-up over many months, especially if the effectiveness of an intervention is not dramatic.
- Use of VPDT should be limited to (a) circumstances in which newer technologies are contraindicated or refused by patients or (b) categories of age-related macular degeneration such as polypoidal choroidopathy or other diseases with neovascularisation arising from the choroid.
- Appraisal of a technology that benefits one eye should evaluate the benefit at the level of a person, not an eye.
- The consequences of the shallow gradients of relationships (a) between BCVA and European Quality of Life-5 Dimensions utility and (b) between BCVA and health and social services resource use/cost need to be considered carefully when appraising other technologies to treat eye diseases that impair vision.

Research recommendations

Similarly, our research recommendations are outside the context of nAMD:

- Further studies are required to investigate the effectiveness and cost-effectiveness of VPDT for neovascularisation due to myopia, inflammation and other choroidal diseases including central serous chorioretinopathy.
- Modification of the effectiveness of new interventions for nAMD by covariates found to influence effectiveness in this study should be studied.
- The relationships between BCVA and HRQoL/health and social services resource use are important for modelling cost-effectiveness. Further research should investigate how widely these relationships can be applied, for example to other diseases that reduce BCVA.

Conclusions

The VPDT cohort study model was successful in establishing a network of research expertise, expanding research capacity, engaging professional bodies and developing purchaser-provider relationships around research and development. It formed a structure for the managed introduction of the technology including the necessary training and service specification development. The success of the model was limited by the freedom of providers to divert investment into other services and to revise care pathways. Improvements in models of the introduction of costly new technology into the NHS are recommended.

Publication

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NIHR Health Technology Assessment programme

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 03/36/01. The contractual start date was in December 2003. The draft report began editorial review in December 2010 and was accepted for publication in June 2011. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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