Optical coherence tomography for the diagnosis, monitoring and guiding of treatment for neovascular age-related macular degeneration: a systematic review and economic evaluation

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Declared competing interests of authors: Andrew Lotery has received honoraria from Bayer, Novartis and Alcon and his institution has received educational grants from Novartis Pharmaceuticals. Winfried Amoaku has received personal fees from Alcon, Alimera Sciences, Allergan, Bayer, Novartis and ThromboGenics, grants from Allergan and Novartis, non-financial support from CenterVue SpA and Novartis, and other support from Pfizer.

Published December 2014
DOI: 10.3310/hta18690

Scientific summary

OCT for neovascular age-related macular degeneration

Health Technology Assessment 2014; Vol. 18: No. 69
DOI: 10.3310/hta18690

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Scientific summary

Background

Age-related macular degeneration is the most common cause of sight impairment in the UK. In neovascular age-related macular degeneration (nAMD), vision worsens rapidly (over weeks) due to abnormal blood vessels developing that leak fluid and blood at the macula. For patients with nAMD, it is common practice to initiate treatment with three consecutive (monthly) injections of antivascular endothelial growth factor therapy, and then the patient is reassessed to evaluate whether the disease is active or inactive. Many patients require monthly monitoring and treatment over a period of several years. Fundus fluorescein angiography (FFA), an invasive test, is considered the reference standard for detecting nAMD at initial presentation and it is also used for detecting recurrent activity at some monitoring visits. Optical coherence tomography (OCT) is a non-invasive test that can be used for detecting nAMD at initial presentation and is often used as the only imaging test for detecting recurrent activity during monitoring visits. The more recently introduced spectral domain optical coherence tomography (SD-OCT) incorporates a number of improvements over time domain optical coherence tomography (TD-OCT).

Objectives

This review aims to determine the optimal role of OCT in (i) the diagnosis of people newly presenting with suspected nAMD and (ii) in monitoring those previously diagnosed with the disease.

Methods

Electronic databases searched included MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Bioscience Information Service, Science Citation Index, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Medion, Health Technology Assessment database, PsycINFO, Applied Social Sciences Index and Abstracts, conference abstracts from the American Academy of Ophthalmology, the Association for Research in Vision and Ophthalmology, the European Association for Vision and Eye Research and current research registers. Searches were carried out from 1995 to March 2013 other than for conference abstracts (2009 to November 2012).

Types of studies considered included direct or indirect comparisons reporting diagnostic outcomes. The population was people with newly suspected nAMD or those previously diagnosed with the disease and under surveillance monitoring. The index test was TD-OCT or SD-OCT and comparator tests considered were clinical evaluation, visual acuity (VA), Amsler grid, colour fundus photographs, infrared reflectance, red-free images or blue reflectance, fundus autofluorescence (FAF) imaging, indocyanine green angiography (ICGA), preferential hyperacuity perimetry (PHP) and microperimetry. The reference standard was FFA.

Two reviewers independently screened the titles and abstracts of all reports identified by the search strategy and full-text papers were obtained for assessment. Data extraction was undertaken by one reviewer and checked by a second. Two reviewers independently assessed the risk of bias of the studies using the quality assessment of diagnostic accuracy studies, version 2 instrument.

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The results of the individual studies were tabulated and sensitivity, specificity and their 95% confidence intervals (CIs) presented for each test or combination of tests. The presence of heterogeneity was assessed by visual examination of forest plots of sensitivity and specificity. Summary receiver operating characteristic curves were derived. Meta-analysis models were fitted using hierarchical summary receiver operating characteristic (HSROC) curves. Summary sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratios were reported as median and 95% CI.

An economic model was developed to assess the cost-effectiveness of different strategies for diagnosis and monitoring of individuals with nAMD. Three strategies were selected for the diagnostic stage and three for the monitoring stage, giving a total of nine diagnosis–monitoring combinations.

Diagnostic strategies

(a) Stereoscopic FFA interpreted by an ophthalmologist. If positive (i.e. presence of nAMD), treat and monitor; if negative, discharge.
(b) OCT alone interpreted by an ophthalmologist. If positive, treat and monitor; if negative, discharge.
(c) VA, OCT and slit-lamp biomicroscopy (SLB) in all patients, performed/interpreted by an ophthalmologist. If positive or unclear, arrange for a FFA. If negative, discharge. This is the diagnostic strategy that best reflects standard practice.

Monitoring strategies

(a) OCT alone (interpreted by an ophthalmologist). If positive, treat. If negative or unclear, review in 1 month's time.
(b) VA, SLB and OCT interpreted together by an ophthalmologist. If positive, treat; if negative, review in 1 month's time. If unclear, then the ophthalmologist will arrange for a FFA. This is the monitoring strategy that best reflects standard practice.
(c) VA and OCT interpreted by a technician or nurse. If negative, review in 1 month's time. If positive or unclear, refer to an ophthalmologist for assessment (e.g. SLB and ophthalmologist interpretation of VA and SD-OCT test results). If positive, treat; if negative, review in 1 month's time; if unclear, arrange for a FFA.

The model was run for a cohort of 65-year-old men for a lifetime time horizon. A 1-month cycle length was defined. Costs were expressed in 2011–12 pounds sterling and effectiveness in quality-adjusted life-years (QALYs). Costs and QALYs were discounted at 3.5%. Cost-effectiveness analysis results were reported using incremental cost-effectiveness ratios.

Uncertainty was explored by conducting one-way sensitivity analyses, scenario analysis and probabilistic sensitivity analysis. One-way sensitivity analyses were conducted on test sensitivity and specificity for diagnosis, the probability of ophthalmologist diagnosis or monitoring having unclear results, test sensitivity and specificity for monitoring, the probability of the nurse or technician assessment being unclear, and unit costs for OCT, FFA and ranibizumab [Lucentis®, Genentech Inc. (USA)/Novartis Pharmaceutical Ltd] treatment.

In addition, three scenario analyses were tested. All of these incorporated data favouring OCT (e.g. scenario 1 included the 95% CI upper limit for OCT sensitivity and specificity for diagnosis and monitoring, with £20.90 and £139 unit costs for OCT and FFA respectively). Scenario 2 assumed a cost per treatment injection of £50 instead of £742, and scenario 3 explored the effect of monitoring patients with OCT only, within the community, with referral to secondary care only for treatment.

Results

Number and quality of studies

Twenty-two diagnostic studies (20 full text, two abstracts) enrolling 2124 people and eight (full-text) monitoring studies enrolling 463 people were included. Only full-text studies were assessed for risk of bias. For both the diagnostic and monitoring studies, the domains in which the greatest number of studies were judged to be at high risk of bias were the patient selection domain (55%, 11/20; 25%, 2/8) and flow and timing domain (40%, 8/20; 25%, 2/8).

Summary of benefits and risks

Diagnostic studies

In a meta-analysis of diagnostic studies (four TD-OCT studies) sensitivity and specificity (95% CI) was 88% (46% to 98%) and 78% (64% to 88%) respectively.

In descriptive analyses, across the studies reporting other tests, median sensitivity was high for ICGA (93.2%, range 84.6–100.0%; four studies) and FAF (93.3%; one study), followed by PHP (81.5%, range 50.0–84.8%; three studies), colour fundus photography (70.0%; one study) and lowest for Amsler grid (41.7%; one study). Specificity was highest for colour fundus photography (95%; one study), followed by PHP (84.6% and 87.7%; two studies), and was low for FAF (37.1%; one study) and ICGA (36.8%; one study).

Monitoring studies

In a meta-analysis of monitoring studies (three TD-OCT, two SD-OCT studies), sensitivity and specificity (95% CI) was 85% (72% to 93%) and 48% (30% to 67%) respectively. For TD-OCT, sensitivity and specificity was 70% (56% to 80%) and 65% (48% to 79%) respectively. It was not possible to calculate pooled estimates using HSROC methodology for the two SD-OCT monitoring studies due to insufficient data. These studies reported high sensitivity of 94% and 90% but low specificity of 27% and 47%.

In the one monitoring study reporting ICGA, sensitivity of 75.9% and specificity of 88.0% was reported for detecting nAMD activity.

Summary of cost-effectiveness

The strategy that based its diagnostic decision on the results of FFA only, combined with VA and OCT interpreted together by a nurse or technician as a first monitoring step ('FFA & Nurse'), had the lowest total expected cost. This strategy dominated (i.e. lower total cost and higher QALYs) all others apart from one. Diagnosis based on FFA only, followed by ophthalmologist-led monitoring ('FFA & Ophthalmologist'), had a higher total expected cost and also produced higher total expected QALYs but at a cost per additional QALY > £30,000. Moreover, the 'FFA & Nurse' strategy had a 46.5% probability of being cost-effective at a £30,000 threshold value of willingness to pay for an extra QALY. Strategies using OCT alone for diagnosis or monitoring were unlikely to be cost-effective. This result seemed to be driven by the OCT low specificity that resulted in a high number of false positives (FPs).

Discussion

Strengths, limitations of the analyses and uncertainties

In terms of strengths, a systematic literature search was undertaken and non-English language studies were included. A HSROC model was applied, which takes account of the trade-off between true positives/FPs and models between-study heterogeneity. The evidence for diagnosis and monitoring was considered separately, as was the evidence for TD-OCT and SD-OCT. Regarding the economic model, multiple different pathways were developed and evaluated. In terms of limitations, very few studies provided sufficient information for inclusion in meta-analyses. Only a few studies meeting our inclusion

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criteria reported the performance of other diagnostic tests of interest; for some tests no studies were identified. The modelling was hampered by a lack of data on the diagnostic accuracy of strategies involving several tests (performed by ophthalmologists or other health professionals).

In terms of uncertainties, there was substantial disagreement between OCT and FFA specificity, especially for monitoring. As FFA was considered the reference standard it was not possible to assess whether or not OCT might have better sensitivity or specificity than FFA. It was unclear why the specificity was lower for SD-OCT compared with TD-OCT.

The model was based on one eye status and outcomes, as this is the approach most commonly used in this health area. The so named 'one eye models' can underestimate resources used due to a proportion of nAMD individuals having active nAMD in both eyes in one particular visit. In the current model, this would increase the cost for those strategies with a higher number of FPs (i.e. lower specificity) and therefore would be unlikely to modify the general conclusions of this report. In addition, the model did not consider effects on utility due to treatment injections and frequent monitoring. Anxiety in nAMD individuals was believed to occur at each monitoring visit mainly due to uncertainty of the underlying condition rather than the effects of treatment injections. Limited evidence was available on the probability of nAMD active individuals becoming inactive when under treatment or inactive nAMD individuals becoming active. Short-time follow-up data were extrapolated to a lifetime time horizon.

Generalisability of the findings

From the populations evaluated in the primary studies, the results of this report are broadly generalisable to the NHS. One of the UK-based diagnostic studies evaluated a nurse-led, fast-track screening clinic, which may not be representative of current UK practice. In addition, 55% of the diagnostic and 25% of the monitoring studies were considered to be at risk of selection bias due to either pre-selection of participants and/or inappropriate exclusions.

Conclusions

Implications for service provision

In terms of OCT test performance, this review found that, based on a relatively small body of evidence of variable quality:

- For diagnosis of newly suspected nAMD, OCT had high sensitivity (88%) and moderate specificity (78%) (meta-analysis).
- For monitoring of those previously diagnosed with nAMD, OCT had high sensitivity (85%) but low specificity (48%) (meta-analysis).
- OCT had higher sensitivity than TD-OCT but lower specificity (monitoring studies).

The strategy that based its diagnostic decision on the results of FFA only, combined with a nurse- or technician-led stepwise approach for monitoring, had the lowest expected total cost and a 47% probability of being cost-effective at a £30,000 threshold value of willingness to pay for an extra QALY. Strategies using OCT test results alone to make diagnosis and/or monitoring treatment decisions were unlikely to be a cost-effective use of resources.

There has already been a shift in the diagnostic and monitoring pathways for nAMD caused by the adoption of OCT. At the diagnostic stage, OCT is currently used in addition to FFA (reference standard), whereas for monitoring it has virtually replaced FFA, which is only used in selected circumstances. The evidence suggests that using OCT as the only test for monitoring patients with nAMD and detecting activity would, potentially, result in a substantial proportion of patients receiving treatment unnecessarily.

The continuing rise in the ageing population, with increasing numbers of people being diagnosed with nAMD and moving on to monitoring for renewed disease activity, will continue to present challenges for ophthalmology departments to have sufficient capacity to provide timely testing and treatment.

Suggested research priorities

- Regarding monitoring of nAMD, OCT is routinely used in current practice, while FFA is used only in particular scenarios. There is a substantial disagreement between OCT and FFA. There is a need to research that OCT (without FFA) is an acceptable way of detecting active nAMD and guiding treatment. As there is the theoretical possibility of OCT being better in some cases than the current reference standard, such studies might be designed to include a 'fair umpire' test, if available, to examine differences between OCT and FFA, or be designed to incorporate sufficient follow-up to assess the consequences of the tests in terms of clinical effectiveness outcomes (e.g. VA).
- Regarding diagnosis of nAMD, current practice consists of FFA (as reference standard) associated with OCT. Further research should be considered to establish the added value of OCT, and whether OCT (associated with SLB and VA) can fully replace FFA. As above, such studies might be designed to include a 'fair umpire' test, or the evaluation of the consequences of the diagnostic intervention.
- Regarding the different phenotypes of nAMD, further evidence on the diagnostic performance of OCT according to phenotype of nAMD is required.
- For both diagnosis and monitoring of nAMD, prospective studies are required to assess the diagnostic accuracy and clinical effectiveness of strategies involving possible different combinations and sequences of tests (e.g. VA, SLB, FAF imaging, OCT), including a comparison of their interpretation by ophthalmologists compared with other health professionals.
- To strengthen the evidence base used to develop the economic model, it would be important to explore the likelihood of active and inactive nAMD individuals becoming inactive or active respectively. In addition, a preference-based study to assess utility weights (e.g. decrements) associated with treatment and frequent monitoring is needed.
- Further research is needed to evaluate health status (utilities) in patients with nAMD, taking into consideration the visual function and spectrum of disease in both eyes and exploring the value added by inclusion of fellow eye information.

Study registration

This study is registered as CRD42012001930.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

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Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 5.116

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index and is assessed for inclusion in the Database of Abstracts of Reviews of Effects.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 10/57/22. The contractual start date was in February 2012. The draft report began editorial review in July 2013 and was accepted for publication in February 2014. 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 reviewers 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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