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Early detection of wet age-related macular degeneration (AMD)

Submission date
22/10/2014

Recruitment status
No longer recruiting

Registration date
18/11/2014

Overall study status
Completed

Last Edited
07/02/2022

Condition category
Eye Diseases

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Age-related macular degeneration (AMD) is a painless eye condition that leads to loss of vision. Neovascular AMD (nAMD) develops when abnormal blood vessels form underneath the macula (the part of the eye responsible for central vision) and damage its cells. Since 2008, drugs have been available to stop leakage into the macula in nAMD. The drugs are given as injections into the eye and their effects last for two months, therefore patients are seen usually every 8 weeks. At each visit there is an assessment to check if more treatment is required. It is usual practice to monitor the unaffected eye of these persons because many will develop the same condition. While the treatments are good at stopping decline of eyesight, restoration of normal sight is rare owing to pre-existing retinal damage. Therefore, detection of nAMD at a stage when damage to the retina is not permanent with prompt initiation of treatment could result in much better preservation of sight. Thus it is important to identify tests that will detect nAMD in its earliest stage. The aim of this study is to determine the best test or tests and the optimum frequency of testing to reliably detect the onset of nAMD with high specificity and sensitivity. To summarise we propose to restrict our study to those tests that are easily performed and routinely carried out in the NHS secondary care setting and which fall into two groups: functional and morphological. The functional tests are visual acuity, self-reported quality of sight in the unaffected eye, and the Amsler test. The morphological tests are a clinical examination to detect any signs of nAMD in the fundus (the part of the eye visible through the pupil using an ophthalmoscope), and optical coherence tomography (OCT).

Who can participate?
Patients aged over 55 attending eye clinics in NHS hospitals across the UK who have a recent diagnosis of nAMD in one eye only.

What does the study involve?
We will obtain information on the health of the unaffected eye from the regular examinations conducted in NHS clinics during follow up. We know that about a quarter of patients will develop nAMD in the second eye within 3 years of the first eye. We will compare the results of our portfolio of tests against the gold standard test, which is a fundus fluorescein angiogram (FFA). FFA involves injecting a dye into the blood stream and taking pictures of the fundus (the back of the eye) with a special camera to diagnose and locate the leaking blood vessels. FFA carries a

small yet finite risk of death due to severe allergic response to the dye (anaphylaxis), requires expensive equipment and specialist resources and is not suitable as a screening tool. Therefore, FFA is usually performed in secondary care in specialist hospital settings with access to resuscitation. We will collect results (positive or negative) as detailed above from each patient at each routine eye care appointment over a 3-year period. A positive test will trigger a FFA for confirmation of nAMD. Those patients who do not develop nAMD in the other eye during the study will have a FFA at 3 years from enrolment. From this information we will calculate the sensitivity and specificity of each assessment to diagnose nAMD. We will use this data to create a model to determine the best test and time-frame for early detection of nAMD.

What are the possible benefits and risks of participating?
The demonstration and validation of one or combinations of the above tests to rapidly, robustly and non-invasively detect the onset of nAMD will be of benefit to patients and providers of health care. It is unlikely that taking part will directly benefit you. However, it is possible that if subtle signs of wet AMD develop that are not detected at your clinic visit, and because the study team will be scrutinising your records in a systematic way, in a few people this might result in earlier detection of wet AMD. Taking part will also help us to develop more efficient ways of monitoring patients in the future. As there is no treatment or intervention involved we do not expect anything to go wrong as a result of taking part in this study.

Where is the study run from?
The study will be run from the Chief Investigators clinics in Belfast and Aberdeen. We aim to enrol approximately 16 participating sites from the following list: Belfast, Aberdeen, Edinburgh, Gloucester, Sheffield, Leeds, Liverpool, London, Bristol, Wolverhampton, Birmingham, Frimley Park, Southampton, Hull, East Yorkshire, Manchester, Hinchingbrooke, Cardiff, Leicester, Coventry and Southampton.

When is the study starting and how long is it expected to run for?
The study will run from January 2015 to March 2021.

Who is funding the study?
NIHR Health Technology Assessment Programme - HTA (UK).

Who is the main contact?
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Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
EDNA protocol v1.0; HTA 12/142/07

Study information

Scientific Title
Early Detection of Neovascular Age-related macular degeneration

Acronym
EDNA

Study objectives
There are highly effective therapies for neovascular AMD. However the optimum outcomes with preservation of vision is most likely to be achieved with early detection, i.e. at the time of onset of nAMD before fibrosis and atrophy can supervene and destroy the macular retina permanently. Although patients with nAMD can become symptomatic at the time of onset, a large proportion may miss the symptoms particularly when the first eye is involved as the second eye can compensate. Even when the second eye develops nAMD patients may not report these symptoms particularly if other pathology such as cataract is present. Therefore it is important to identify the best and the most robust test that can be used to identify the onset of nAMD promptly.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Health and Social Care Research Ethics Committee B, 20/11/2014, ref: 14/NI/1120

Study design
Multi-centre prospective cohort diagnostic accuracy study with 3-year follow-up

Primary study design
Observational

Secondary study design

Multi-centre

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Neovascular age-related macular degeneration

Interventions
Planned Interventions
Patients will attend regular monitoring visits for the fellow eye (with nAMD). The frequency of visits will be approximately every 8 weeks, as per local practice. We will use these regular monitoring visits for evaluating the candidate tests for the study eye (without nAMD). The following tests will be evaluated:
1. Clinical evaluation (with slit-lamp biomicroscopy and evaluation of patients symptoms) of the study eye.
Examination of the macula usually reveals fluid and or lipid (yellow deposition) and/or blood. Other features of AMD such as drusen and pigmentary irregularities may be observed. Sometimes these latter features are obscured by the exudative manifestations or may be absent in specific AMD phenotypes such as idiopathic polypoidal choroidopathy. However, their presence in the fellow eye is helpful in confirming the diagnosis of AMD.
Slit lamp biomicroscopy signs suggestive of nMAD are the following:
2. Subretinal or sub-RPE neovascularisation which may be visible as a dark grey lesion. Occasionally the lesion will have a dark pigmented edge which is thought to be due to proliferation of the RPE at the edge of the membrane.
3. Serous detachment of the neurosensory retina.
4. RPE detachment.
5. Haemorrhages- subretinal pigment epithelial, subretinal, intraretinal or preretinal. Breakthrough bleeding into the vitreous may also occur, indicating most often the presence of idiopathic polypoidal choroidal vasculopathy (IPCV).
6. Hard exudates (lipids) within the macular area related to any of the above, and not related to other retinal vascular disease. Epiretinal, intraretinal, subretinal or sub-pigment epithelial scar /glial tissue or fibrin-like deposits. Retinal angiomatous proliferations: microvascular proliferative lesions located within the retina Choroidal polyps: spherical lesions associated with choroidal vessels which cause the RPE to be focally elevated. For the purpose of this study, a positive clinical evaluation test is one as determined by an experienced ophthalmologist using (but not limited to) the above signs, and will trigger a reference standard test (FFA)
7. Patients subjective assessment of vision
The onset of exudative AMD is heralded by the appearance of central visual blurring and distortion.
Patients may complain that straight lines appear crooked or wavy when the lesion involves the central macula. During each follow-up visit patients will be given standard instructions to answer the following question: how is your vision in the (unaffected) eye? The patient will be prompted to answer one of the following four possibilities: about the same or better, a bit worse, worse, or

much worse. For the purpose of this study, a positive subjective report test is one where the patient reports much worse, deterioration and it will trigger a reference standard test (FFA).
8. Visual acuity
Patients with new onset nAMD will usually have a decrease in best corrected visual acuity (BCVA). Visual acuity is a measure of the spatial resolution of the visual processing system. It is a psychophysical test requiring a response from the person to be tested. Usually high contrast letters of diminishing size are displayed on a chart at a set distance. The most commonly used chart is the early treatment diabetic retinopathy study chart (ETDRS) which is based on a geometric progression of letter sizes with 5 letters in each row. A 3 line difference in either direction from any given line represents a halving or a doubling of the visual angle. For the purpose of this study a positive visual acuity test is one where there is a reduction of 5 or more letters in BCVA and this will trigger a reference standard test (FFA)
9. Amsler test
The Amsler chart or grid is a grid of horizontal and vertical lines used to monitor a person's central visual field. It is a simple, inexpensive, diagnostic tool that aids the detection of visual disturbances caused by changes in the retina, particularly the macula (e.g. macular degeneration). In the test, the person looks with each eye separately at the small dot in the centre of the grid printed on a paper. Patients with nAMD may see wavy lines or part of the pattern of lines may be missing. Patients will have a normal Amsler test in the study eye at baseline. For the purpose of this study a positive Amsler test is one where the patient reports any distortion which will trigger a reference standard test (FFA)
10. Optical Coherence Tomography (OCT)
11. Reference standard: fluorescein angiography (FFA)
Fluorescein angiography is currently the reference standard for diagnosing choroidal neovascularization (CNV) in AMD (i.e, nAMD). A fluorescein angiogram is a sequence of images of the fundus captured over a 10 minute period after injection of the non-toxic dye fluorescein isothiocyanate into a suitable peripheral vein. The diagnosis of neovascular AMD is by FFA. A technician or photographer performs the test, which is interpreted by an ophthalmologist. Pupils need to be dilated prior to the test. Neovascular AMD can be classified on the basis of the temporal and spatial features of the patterns of fluorescence as observed on the FFA:
Classic CNV is said to be present when an area of well delineated hyperfluorescence appears in the early phases of the FFA. Most commonly, classic CNV represents new vessels that have breached the RPE and lie in the subretinal space. Sometimes a typical lacy pattern of hyperfluorescence is observed in the very early phase of the angiogram which corresponds to the vascular profiles before the fluorescein has leaked out of these vessels and obscured the margins. Classic CNV also leak aggressively and hence there is considerable pooling of fluorescein dye in the sub-retinal space in late frames of the angiogram.
Multimodal imaging shows that these neovascular complexes lie between the RPE and the neurosensory retina and have a feeder vessel arising from the choroidal circulation.
Occult CNV, as its name suggests, refers to the presence of leakage without clear evidence of neovascular profiles in the early angiographic images. Two types of occult leakage are recognised. The first is a characteristic stippled hyperfluorescence which occurs early and is located at the level of the RPE. The RPE layer is elevated and in the later phases of the angiogram there is increasing hyperfluorescence and pooling of dye in the subretinal pigment epithelial space. The pattern of leakage suggests new vessels between Bruchs membrane and the RPE and it is therefore considered to be a fibrovascular pigment epithelial detachment (FPED). The second pattern of occult leakage is a more diffuse hyperfluorescence with poorly demarcated boundaries which occurs late in the angiographic phase generally after 2 minutes have elapsed since injection of dye. There is no corresponding hyperfluorescence in the early frames and there is shallow elevation of the RPE. This type of leakage is referred to as late leakage of indeterminate origin (LLIO). OCT has shed further light on these patterns of leakage and has revealed that the

neovascular complexes of FPED and LLIO patterns are present in the sub-retinal pigment epithelial space causing irregular elevation of the RPE.
Retinal angiomatous proliferation (RAP). This type of neovascularisation is consists of intraretinal telangiectatic blood vessels that are strongly associated with serous pigment epithelial detachments and a form of drusen known as reticular drusen.
Idiopathic polypoidal choroidal vasculopathy (IPCV). Polyps are seen as focal, round areas of abnormal dilated choroidal vessels, often associated with large areas of lipid deposition and haemorrhage. The presence of haemorrhagic PED is highly suggestive of the presence of this phenotype. These polyps are best visualised by indocyanine green angiography which is recommended if the combination of FFA and OCT features suggest presence of this variant of nAMD (Age-related macular degeneration guidelines 2009 Royal College of Ophthalmologists).
We will use multimodal imaging to classify the nAMD lesion into the 4 categories of subretinal neovascularisation, sub-retinal pigment epithelial neovascularisation, RAP lesions and polypoidal choroidopathy.
For the purpose of this study, a positive FFA test is one showing typical changes of nAMD as determined by an experienced ophthalmologist, regardless of the category or type of lesion.

Intervention Type
Other

Phase
Not Applicable

Primary outcome measure
1. The primary diagnostic outcome measures are the sensitivity and specificity of each of the five candidate tests (fundus examination, patients subjective assessment of vision, visual acuity, Amsler test, OCT) on any diagnosis of nAMD confirmed by FFA in the study eye over 3 years of monitoring.
2. The primary economic outcome measure will be the incremental cost to the health service per quality-adjusted life-year (QALY) gained for each candidate test used as a diagnostic tool. We will use the complete cohort data at 3 years follow-up to estimate total monitoring and treatment costs to 3 years, and to model the longer-term cost effectiveness of the alternative monitoring strategies through their impact on the timing of treatment initiation.

Secondary outcome measures
Secondary diagnostic performance outcomes:
1. Diagnostic odds ratio, likelihood ratio, diagnostic performance (sensitivity and specificity) of combinations of tests: measured from candidate test results compared to reference standard (FFA) over 3 years.
2. Proportion of indeterminate tests: over 3 years of monitoring

Other outcomes:
1. Time gain of early detection: measured using economic decision analytic model for each candidate test as a diagnostic tool
2. Visual acuity at diagnosis of nAMD (by FFA) within 3 years of follow-up
3. Performance of a risk predictor algorithm according to baseline characteristics
4. Establishment of a well characterised cohort of clinical and biological data for future research

Overall study start date
01/01/2015

Completion date
31/03/2020

Eligibility

Key inclusion criteria
1. Newly diagnosed nAMD in one eye and an unaffected second eye
2. Aged 55 years or over

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
560

Total final enrolment
552

Key exclusion criteria
1. Age less than 55 years old
2. Patients who cannot give informed consent
3. Patients with a history of nAMD in both eyes
4. Unable to undergo a fundus fluorescein angiography (FFA) test
5. Not undergoing regular monitoring in standard of care

Date of first enrolment
01/01/2015

Date of final enrolment
31/07/2016

Locations

Countries of recruitment
Northern Ireland

United Kingdom

Study participating centre

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University/education

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ROR
https://ror.org/00hswnk62

Funder(s)

Funder type
Government

Funder Name
NIHR Health Technology Assessment Programme - HTA (UK); Ref: 12/142/07

Results and Publications

Publication and dissemination plan

Planned publication in a peer reviewed appropriate journal.

Intention to publish date
31/12/2020

Individual participant data (IPD) sharing plan
Not provided at registration.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		28/07/2021	30/12/2021	Yes	No
Results article		01/01/2022	07/02/2022	Yes	No
HRA research summary			28/06/2023	No	No