Treatments for dry age-related macular degeneration and Stargardt disease: a systematic review

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Scientific summary

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Scientific summary

Introduction

Age-related macular degeneration (AMD) is a progressive degenerative disease of the retina, in which the macula is most affected. It is the commonest cause of blindness in the UK. It affects mainly older people.

Advanced AMD takes two forms, wet and dry, both of which can lead to visual loss. Wet AMD, also called exudative or neovascular age-related macular degeneration (nAMD), is characterised by the development of abnormal new vessels [choroidal neovascularisation (CNV)]. Dry AMD refers to the progressive demise of retinal pigment epithelium (RPE) and photoreceptor cells (visual cells) of the retina resulting in geographic atrophy (GA). This report is concerned only with dry AMD, including progression to wet AMD, but not treatment of wet AMD or previously treated inactive wet AMD.

The first signs of AMD are the accumulation of yellowish deposits in the retina, called drusen. AMD goes through various stages, called early, intermediate and advanced. Advanced dry AMD is characterised by atrophy of the central retina (the macula) – it wastes away and patches of the retina and vision are lost. The central most detailed vision is lost, making it difficult to drive, read or recognise faces.

Stargardt disease (STGD) is a recessively inherited disease, wherein a defective gene has to be inherited from both parents. The disease is caused by mutations in the *ABCA4* gene, but different mutations are involved, and the age at onset varies according to the mutations, from childhood to adulthood. It affects mainly young people, often starting in late teens or early 20s. Older age at onset is associated with slower progression. STGD appears to be the commonest inherited retinal dystrophy.

There were two aims for this review. The first was to provide an up-to-date systematic review of treatments for dry AMD and STGD. The second aim was to identify treatments that were sufficiently promising for the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) and Efficacy Mechanism and Evaluation (EME) programmes to consider commissioning primary research.

Methods

We carried out a systematic review of treatments for dry AMD and STGD, using the standard search and review methods, looking first for systematic reviews and randomised trials, but with no restriction on study design because we were aware from scoping searches that many treatments were reported only by observational studies. We searched MEDLINE, EMBASE, Web of Science and The Cochrane Library from 2005 to 13 July 2017 for reviews, journal articles and meeting abstracts. Searches were limited to English language. The Association for Research in Vision and Ophthalmology (ARVO) website was also searched for meeting abstracts.

References of reviews were checked for relevant studies. ClinicalTrials.gov, the World Health Organization search portal and UK Clinical Trials gateway were searched for ongoing and recently completed clinical trials.

The methodological quality of the included studies was assessed using criteria based on those recommended by the Cochrane Collaboration and US National Institutes of Health.

The titles and abstracts of 7948 articles were screened by two reviewers and checked by a third. The full texts of 398 articles were obtained for further screening and checking of references, and 112 articles were included in the final report.

Principal findings: age-related macular degeneration

Physical treatments

Newer forms of laser treatment show promise but a large trial, the Laser Intervention in Early Stages of Age-Related Macular Degeneration (LEAD) trial, from a world centre of excellence in Melbourne, VIC, Australia, is ongoing (anticipated completion date June 2018), so we suggest waiting for their results.

Implantable telescopic lenses also show promise, but a NIHR EME study is under way (Efficacy of the Telescopic Mirror Implant for Age-related Macular Degeneration: The MIRROR Trial) in advanced AMD.

There is insufficient good-quality evidence to recommend the use of, or further research in, acupuncture, microcurrent stimulation or treatment with ozone.

There is some evidence on rheopheresis but the largest trial showed no benefit; most studies reporting positive results were small with only modest effect sizes and mostly uncertain risks of bias, and treatment would be inconvenient to older people. Therefore, we do not see rheopheresis as a research priority.

The evidence for the use of blue-light-filtering intraocular lenses after cataract extraction is currently insufficient to justify their routine use, but further research is under way.

Cell therapies

Two very small case series of cell transplantation were identified. Improvements in visual acuity (VA) were found in over half of treated eyes. The evidence base is still very sparse, but this seems a promising development and further research is under way.

Drug treatments

We think there is sufficient evidence to justify a trial of a potent statin, such as atorvastatin 80 mg daily.

Fenretinide (ReVision Therapeutics, San Diego, CA, USA) is a visual cycle inhibitor that may reduce the deposition of lipofuscin. One trial, with an unclear risk of bias, and written up by the manufacturer's staff as a 'proof of concept' study, had mixed results. Progression of GA was little different overall, but was less in the subgroup that responded best to the drug. Progression to wet AMD was halved by fenretinide. There were higher rates of adverse events with fenretinide. Overall, we think a trial in early dry AMD to slow progression might be considered.

An impressively large retrospective study from the USA found that people taking levodopa (L-dopa) were less likely to develop AMD, and that if they did develop it, it was about 7 years later than among people not taking L-dopa. Further research is needed, perhaps using one of the large UK general practice-based databases, in order to assess whether a trial assessing its use in treating AMD could be justified.

Large trials of lampalizumab are under way (sponsored by the manufacturer), so no new research is indicated in the meantime.

There is a little evidence of benefit from glatarimer acetate, but with only some shrinkage of drusen in two studies that had unclear risks of bias. The evidence is too sparse to justify NIHR research at present.

One small study reported benefit from oral prednisolone but it scored poorly on quality assessment so there is insufficient evidence to justify its use. If steroids were to be used, a localised one would seem better. The results of a trial of an implanted steroid, fluocinolone (Alimera Sciences, Alpharetta, GA, USA), are awaited (NCT00695318).

For nine drugs, there was some evidence showing no or very little benefit, or even harm, so we do not recommend further consideration. They are alprostadil, eculizumab, dorzolomide, OT 551 eye drops, sirolimus, tandospirone, trimetazidine, visaline and emixustat (Acucela, Seattle, WA, USA).

Nutrients

There are many studies of nutritional supplements but some had too few participants, were of poor quality, were of too short duration or were of combinations of compounds, making it difficult to assess the relative contributions of each. Supplements used include lutein and zeaxanthin, in combination or individually, or combined with a variety of other minerals and/or vitamins: omega-3 fatty acids, folic acid, various vitamins, ginkgo biloba, curcumin (from turmeric), saffron and zinc. The first AREDS trial showed the benefit of supplements in patients with intermediate or advanced AMD, which persisted for 7 years, with a modest but useful slowing of progression. It could mean that 30% of people expected to progress to advanced AMD over a 5-year period would not. The trial did not have enough power to confirm, or not confirm, effects in the earliest stages. The AREDS 2 trial showed that beta-carotene should be replaced by lutein and zeaxanthin, and that the dose of zinc could be reduced. We therefore think that there is already good evidence that the AREDS 2 supplement should be used for patients meeting the AREDS 3 and 4 categories.

Saffron extracts have been reported to show some benefits in VA and might justify further research.

There is currently insufficient evidence to recommend any other nutritional supplements.

Principal findings: Stargardt disease

At present, the most promising treatments for STGD appear to be:

- Prevention of lipofuscin accumulation. Several drugs may have potential, including fenretinide, deuterated vitamin A (ALK-001; Alkeus Pharmaceuticals, Boston, MA, USA) and emixustat. Early trials of ALK-001 and emixustat are under way. Fenretinide has shown promise in dry AMD and we think a trial in STGD may be justified. A vignette has been written for the HTA programme.
- Gene therapy is at an early stage, but a study (StarGen NCT01736592) is under way in Oregon and Paris.
- Cell transplantation to replace the RPE has been tried in one small study in only nine people with STGD, but looks promising. Further research is under way.

There are three other possible interventions that seem worth further research. One is light reduction with glasses or contact lenses, as reported in one very small trial in which progression in the light-protected eye was reported to be less in four out of the five participants. Second, there is a plausible rationale for the benefits of lutein and zeaxanthin supplementation to protect the macula (perhaps especially the fovea) but insufficient evidence.

The evidence for the third comes, so far, only from animal work, in which fenofibrate appears to have some activity as a visual cycle inhibitor. Fenofibrate is an old, cheap and safe drug used for lipid-lowering, but is currently being trialled in diabetic retinopathy, in which it has shown some benefit in past studies.

Limitations: age-related macular degeneration

The main limitation came from the poor quality of much of the evidence. Many studies were of too short duration. Many studies used VA as their main outcome despite not having sufficient duration to observe changes.

Limitations: Stargardt disease

The evidence on treatments for STGD is sparse. Most studies tested interventions with no comparison group, were far too short term and the quality of some studies was poor. There has been very little research into the treatment of STGD compared with AMD.

Outcomes in future research

Visual acuity is often preserved until a late stage in patients with AMD and in those with late-onset STGD. We would like to see interventions at earlier stages, when people may have few symptoms, as it is likely that treatment at earlier stages would be more effective. Research at earlier stages of AMD may require earlier identification, for example by optometrists at annual eye examinations. The most important outcomes are those that matter to patients: distant and near VA, contrast sensitivity, reading speed, ability to drive, adverse effects of treatment, health-related quality of life, progression of disease and patient preference. Central visual loss is a late event, especially in atrophic AMD, and predictors and early biomarkers of future central visual loss, such as macular sensitivity, should be sought for use in clinical trials if there is good evidence that they are strong predictors of subsequent visual outcomes. These will include changes detectable by investigation, such as by microperimetry, but not necessarily by people with AMD. These biomarkers might make it feasible to reduce the length of follow-up, and possibly sample sizes, in clinical trials, and might speed to discovery of new treatments.

One possibility is dark adaptation, which may be an early sign of developing AMD. Several studies have reported that dark adaptation may be impaired in AMD before best corrected VA is affected.

So another recommendation is for research into predictors of later visual outcomes which can be used in trials of early interventions, starting with a systematic review of predictors and biomarkers, and then longitudinal population-based cohort studies.

Conclusions

Taking into account the considerable amount of research that has been done or is under way, we suggest that, in AMD, the NIHR programmes should consider:

- a trial of a potent statin
- a trial of fenretinide.

In STGD, we suggest:

- a trial of fenretinide
- a proof of concept trial of lutein and zeaxanthin supplements.

We also suggest that there should be an epidemiological study into the relationship between treatment with L-dopa (for Parkinson's disease) and the incidence of AMD. This may be more within the remit of the MRC.

Study registration

This study is registered as PROSPERO CRD42016038708.

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HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

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