Macular Degeneration Foundation®

Our focus is your vision

Research Update 2010

Global research on the causes, genetics and treatment of Macular Degeneration continues at a hectic pace. In fact, no other area of ophthalmology is receiving as much attention at this time. Many Australian researchers are contributing substantially to the global effort and the MD Foundation is very proud of their efforts.

Major new Macular Degeneration Foundation research initiative

The MD Foundation will be 10 years old in 2011. As part of our 10 year celebrations, the Foundation will shortly be launching a major public appeal to raise $10 million over 10 years to support social and medical research into MD. The first round of our research grants will be made in 2011. If you would like to contribute to our new research fund, please contact us on 1800 111 709.

This update is a brief summary of some of the research programs occurring around the world.

Understanding research

Clinical trial phases

This update refers to clinical studies in different phases of development. A new drug or treatment must successfully pass from pre-clinical studies to phase 3 before it can be submitted for approval by regulatory authorities.

It is not unusual for drug development to take at least 10 to 12 years to move from phase 1 to registration.

Pre-clinical studies – initial testing of a treatment or drug in a laboratory setting using cell or tissue cultures, or animal models such as mice.

Phase 1 – a new drug or treatment is tested in a small number of humans (usually healthy volunteers) to test for initial safety, determine safe dosage and clarify how the treatment acts on the body.

Phase 2 – slightly larger patient numbers are involved to test for efficacy (whether the treatment works) and further clarify safety.

Phase 3 – the treatment is given to large numbers of patients to confirm efficacy, monitor side effects (including less common ones), compare the treatment to other commonly used treatments and gather information to allow the treatment to be used safely. Successful phase 3 studies allow the treatment to be submitted to the Therapeutic Goods Administration for registration.

Phase 4 – studies done after the treatment has been registered and made available to the public. These studies monitor the treatment's effect in different populations, or with different dosing schedules, monitor for very rare side effects, and any issues associated with long term use.

Glossary of key terms

MD: Macular Degeneration is damage to the macula, the central part of the retina, leading to a loss of central vision.

AMD: Age-related Macular Degeneration typically occurs in people over 50.

Early AMD: is characterised by the formation of **drusen**, which are small fatty deposits inside the retina. Patients with early AMD have minimal or no loss of visual acuity, but the disease can progress to late AMD.

Late AMD: can be split into two forms, 'Dry' & 'Wet'; both can lead to central vision loss.

Dry AMD: involves the breakdown of retinal tissue with scarring. It normally progresses slowly.

Wet AMD: the formation of new, leaky blood vessels in the retina. It can develop rapidly.

Diabetic retinopathy/macular edema: damage to the retina as a complication of diabetes. Can involve the formation of unwanted new blood vessels, similar to wet AMD.

Retinal vein occlusion: blockage of veins in the retina. Can also lead to the formation of unwanted new blood vessels and blindness.

VEGF: Vascular Endothelial Growth Factor is a protein which stimulates the growth of the new blood vessels seen in wet AMD.

PBS: Pharmaceutical Benefits Scheme is Australia's system to subsidise registered drugs that are proven to be safe, effective and cost-effective.

TGA: Therapeutic Goods Administration is Australia's regulatory agency for medical treatments.

FDA: Food & Drug Administration is the US regulatory agency for medical treatments.

"Off-label": the use of a treatment that has been registered (approved) for a particular disease but is being used for a different disease.

Treatments for wet AMD

Background

Lucentis is currently the most effective registered treatment for the management of wet AMD. It is reimbursed via the PBS for patients with wet AMD, providing certain medical criteria are met. In situations where Lucentis is not reimbursed, Avastin is sometimes used. The use of Avastin in the eye is considered "off-label" as it has not been approved by the TGA for this particular use.

Trials involving Lucentis and Avastin

Six large trials directly comparing the safety and efficacy of Lucentis and Avastin for wet AMD are now nearing the initial reporting stage. The largest is the CATT study, which is being conducted by the National Eye Institute in the US, and involves 1200 wet AMD patients at 44 sites. Twelve month results will be reported early in 2011.

Results for the British IVAN study, involving 600 patients are expected in 2011. The results for other smaller studies, including VIBERA, MANTA, LUCAS and GEFAL are also expected later in 2011 or 2012.

With the remarkable success of the anti-VEGF drugs such as Lucentis in the treatment of wet AMD, these agents have now been studied in other retinal conditions where new blood vessel formation is a problem. They have now been shown to help some patients with diabetic retinopathy/macular edema and retinal vein occlusions. Lucentis has recently been recommended for approval in Europe for treating diabetic macular edema.

VEGF Trap-Eye

The next AMD treatment likely to be introduced into regular use is VEGF Trap-Eye (aflibercept). This is an injection which blocks all forms of VEGF-A as well as some other growth factors which are known to encourage the growth of the abnormal blood vessels seen in wet AMD.

The 12 month results of the phase 3 trials were announced in November 2010, and these show that the use of VEGF Trap-Eye injected either every month **or every 2 months** (after 3 initial monthly injections), produced similar results to the use of Lucentis. VEGF Trap-Eye also appeared to be well tolerated. The manufacturer is planning to submit it for registration in the US and Europe in the first half of 2011.

Studies are continuing to see if a treatment gap of up to 3 months in the second year is feasible. Studies are also being conducted to assess the value of VEGF Trap-Eye in diabetic macular edema (DME) and retinal vein occlusions.

Pazopanib

This is an eye drop which has an effect on several growth factors which are implicated in the development and progression of wet AMD. Pazopanib has already been shown to be very effective in reducing the formation of new blood vessels in mice, and initial human studies are promising. Phase 1 & 2 studies are now underway to assess safety, drug effectiveness and the correct dose to use. Pazopanib is intended to be used in conjunction with anti-VEGF injections, and it is hoped that its use will allow injections to be given less frequently.

E10030

This agent is also designed to work in conjunction with an anti-VEGF injection, to further improve the shrinkage of the new blood vessels that form in wet AMD. In a Phase 1 clinical study, patients treated with E10030 and Lucentis experienced a large decrease in the area of new blood vessel formation – more than has been seen with Lucentis given on its own. A larger phase 2 study has now commenced to further assess safety and efficacy.

Radiation treatment

1.Strontium-90
Because Macular Degeneration is a highly complex disease with many contributing factors, the use of combination treatment using different types of therapy may offer even better visual outcomes. The use of small, carefully targeted doses of radiation therapy (brachytherapy) using strontium-90 combined with anti-VEGF injections appears to offer improved outcomes compared to anti-VEGF treatment alone. Less collateral damage has been seen with this treatment compared to previous types of radiation treatment. Two large phase 3 trials are currently underway to further clarify the safety and efficacy of this treatment.

2. I-Ray
Another type of radiation treatment known as IRay, can be performed with the use of a robotically controlled x-ray device. The energy delivered is small and early results are promising. The treatment appears to be safe, and may allow fewer injections of an anti-VEFG drug to be used. A large study has commenced in Europe, and another is due to start in the US.

Treatments for dry AMD

At the moment, lifestyle modifications such as stopping smoking and dietary improvements are the only way to slow the progression of dry AMD. There is currently no treatment available for drusen or dry AMD.

The good news is that there are at least 20 new treatments that are being studied for the management of drusen and dry AMD, where the overall goal is to target the underlying cause of the disease. These approaches can be grouped into three main categories:

- drugs to promote survival of the photoreceptors and retinal pigment epithelium (RPE) in the retina
- drugs to prevent injury from oxidative stress and micronutrient depletion
- drugs to suppress inflammation.

Some examples of this research for dry AMD include:

Fenretinide

Fenretinide is a synthetic modification of Vitamin A, taken orally, which appears to have 3 important mechanisms on the development of both dry and wet AMD:

- it reduces some of the toxins which are known to accumulate on the macula, leading to the formation of drusen
- it has some anti-inflammatory properties
- it may also inhibit the formation of abnormal blood vessels.

The results of a major phase 2 trial in the US were announced in October 2010, which showed that fenretinide can slow down the formation of geographic atrophy (the advanced stage of dry AMD) and also reduce the rate of progression to wet AMD by more than 50% in some patients. The agent appeared to be well tolerated, although about 35% of patients experienced a slowed response to seeing in dark conditions. Phase 3 studies are now needed before the drug can be submitted for registration.

AL8309

This treatment is designed to protect the retina from oxidative damage due to certain wavelengths of light. AL8309 is given as an eye drop and it is hoped that it will slow the formation of the large scarred areas ("geographic atrophy") seen in later dry AMD. Several phase 2 & 3 studies are taking place, and we expect to hear the outcome of these in 2012.

ACU4429

This treatment, taken as a daily pill, works by decreasing the accumulation of toxic by-products on the retina which can lead to dry AMD. The drug has received "fast-track" status from the US FDA. This speeds up the development and review of new drugs that are aimed at serious conditions with unmet medical needs. A large phase 2 trial is now enrolled and results are expected in 2012.

Others

Other agents being investigated for dry AMD include:

Trimetazidine, alprostadil, encapsulated ciliary neurotrophic factor (CNTF), intravitreal brimonidine implant, anti-amyloid β antibody, OT-551 (piperidine derivative).

Stem cell research

PLEASE NOTE: The MD Foundation recognises and respects different points of view concerning stem cell research. The MD Foundation's role is simply to report on the key research for your information.

Stargardt's Disease

Following very successful initial animal trials, a US company has been granted "orphan drug" status by the FDA for a human embryonic stem cell (hESC) treatment for Stargardt's Disease, a childhood form of Macular Degeneration. In the US, "orphan drug" status is provided for promising new treatments in rare but important diseases, and provides additional incentives for the company to accelerate clinical testing. Animal studies showed that the stem cells successfully preserved vision in animals that would have otherwise gone blind. On November 22, 2010, the US FDA gave clearance for the first phase 1 human study to commence.

London Eye Project

The London Eye Project to Cure Blindness is a 5 year project designed to develop a treatment to use human embryonic stem cells to produce retinal cells for transplantation into damaged eyes. In 2010, the project has been able to take a line of stem cells from a single human embryo and produce the precise retinal tissue they require. Pending regulatory approval, human clinical trials will commence in 2011.

Adult Stem Cells

In August 2010, researchers from Nebraska USA reported the first demonstration that a patient's own adult stem cells could potentially be used to repair damaged retinal cells. This is different from other research such as the London Eye Project which is focusing on the use of the transplantation of embryonic stem cells, which have many potential issues such as rejection and the source of cells.

The adult stem cell research has been performed on rats and mice and involved the activation of adult stem cells using a combination of small proteins called peptides. Some of the activated cells moved to the location of the dying retinal cells and then changed into retina-like cells, with a transient but significant improvement in light perception. If this work can be duplicated in humans, it will help overcome the concerns of some people about the use of stem cells from other sources including embryos.

Other treatments

Laser for dry MD

A new laser for the management of dry AMD is being developed in Australia, known as the Ellex 2RT. This laser uses extremely short (nanosecond) pulses of laser light to treat drusen, without appearing to cause damage to surrounding retinal tissue. The Royal Victorian Eye and Ear Hospital in Melbourne recently reported 6 month results in 14 patients showing a decrease in drusen in 70% of treated eyes; central visual function improved in 50%.

Retinal imaging confirmed there was no evidence of laser damage to photoreceptor cells. A new trial, involving centres in Australia, Europe and the USA is planned to commence in 2011 to confirm the safety, efficacy and longer term effects of the treatment.

The laser is also being studied for the management of diabetic macular edema, and initial results are promising.

Sub-retinal implant

A new sub-retinal implant is being developed in Germany which is showing promise for people with total blindness as a result of diseases such as retinitis pigmentosa. This implant is unlikely to be of benefit for AMD patients, at least initially, since even legally blind MD patients will usually already have better vision than this implant will provide, particularly at the side.

The implant sits underneath the retina, directly replacing lost or damaged light receptors.

In a pilot study published in November 2010, the device allowed three totally blind people to detect shapes and objects within days of treatment. One patient was able to find and identify objects on a table and walk around a room independently.

These initial trial results were considered a proof of concept and the implant will now be further developed and tested in Europe in a larger patient population. If these trials prove successful, the device could be available in about 5 years.

Other retinal implants are being developed, including programs in Australia, however the German implant appears to be the most developed at this stage.

Implantable telescope

A miniature implantable telescope made by VisionCare Inc received US FDA registration and EU CE approval in 2010. This telescope is about the size of a pea and is implanted inside the eye in a similar location to where an intraocular lens is implanted in cataract surgery. The telescope is intended for use in people with end-stage AMD who have minimal remaining sight. The telescope is currently being evaluated by an Australian company for possible registration and importation.

Genetics and gene therapy

Significant progress is being made with the identification of genes which are linked to the increased risk of AMD. Some genes have also been identified which may be protective, and other genes may help predict how someone will respond to a treatment. It is now increasingly clear that AMD results from a chronic inflammatory response, involving a disruption to the “complement” system, which is a biochemical chain of reactions which normally helps our immune system. Certain gene variations have been shown to be associated with these complement changes. New treatments have been designed to block this disruption to the complement system and are now in phase 1 trials.

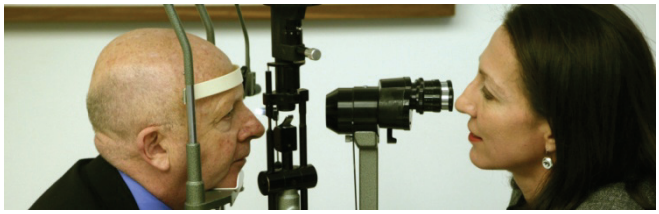
Gene therapy

A phase 1 trial is now underway in which a viral vector “delivers” a gene which will stimulate a protein that will bind to, and inactivate the VEGF molecule. The gene therapy approach theoretically only requires one injection.

Nutrition

It is now considered to be standard practice that patients with moderate to advanced AMD take a supplement conforming to the AREDS formula (zinc 80mg, Vitamin C 500mg, Vitamin E 400IU, Copper 2mg per day), as this can slow the progression of MD by 20 to 25%.

The next generation of supplement is being studied in the AREDS2 trial, which is now expected to be reported on in 2012. This study evaluates the effect of lutein, zeaxanthin and/or omega-3 supplements in addition to the removal of beta-carotene (high levels of which are known to be harmful to smokers) and the effect of differing levels of zinc.



Please note:

Research is a lengthy, expensive and high risk activity. It must be recognised that many of these projects are still years away from completion, and some treatments may not make it through the rigorous development process.

Discussion of a project does not constitute the MD Foundation’s endorsement of that product or treatment.

The Foundation is unable to recommend or facilitate the entry of any clients into a particular trial as clinical trials have strict inclusion and exclusion criteria.