Macular Disease Foundation AUSTRALIA

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Macular Disease Research Update

December 2018

Flavonoids & Vegetable Nitrates

An Australian study has shown that people who eat oranges daily have a 61% reduced risk of developing AMD than people who don't eat oranges regularly.

Westmead Institute for Medical Research examined data from more than 2,000 Australian adults over 15 years and found a particular flavonoid (powerful antioxidant) in oranges called hesperidin appears to help protect against the disease.

Researchers speculate that the beneficial impact of flavonoids on macular health comes from their antioxidant and anti-inflammatory properties. Further research is needed to validate the findings.

Another study from the same research institute has shown that eating 100 to 142mg of vegetable nitrates found in leafy green vegetables could help reduce the risk of developing early AMD by 35%.

The researchers analysed data on more than 2000 Australian adults over the age 49 who were followed over a period of 15 years. If confirmed in other studies, these findings could have positive implications for the prevention of AMD.

Clinical trials are studies in humans which aim to find a better way to manage a particular disease, while establishing correct dosage, safety and efficacy and comparisons to other treatments.

Trials are designed in a way to minimise the possibility of bias or incorrect conclusions.

Key:

- 🔴 Early studies with positive initial findings.
- 🟠 Studies with indication of a potential clinical effect.
- 🟢 Advanced studies with evidence of a significant clinical effect.

Early AMD

2RT laser 🟢

Results of the pivotal three-year clinical trial (LEAD trial) on the use of the ultrafast (nanosecond) laser called 2RT showed a promising trend in reducing the rate of progression to late stage AMD in carefully selected patients with earlier stages of the disease (large drusen). The 2RT laser uses ultra-short laser bursts to cause changes in the outer pigment layer of the retina, and slow down the degenerative process.

The trial found patients with less severe signs of AMD showed a nearly four-fold decrease in the progression rate of their disease, whereas patients with more severe signs at the beginning of the trial had a doubling of their progression rate to late stages of AMD when compared to patients who were not treated. It is the first time in more than 20 years of AMD laser research, that a laser intervention has successfully addressed disease progression.

Further studies need to be conducted and, at this stage, treatment with the 2RT laser should only be conducted within a clinical trial setting.

Dry (atrophic) AMD

PRIMA 🟠

A new wireless bionic implant called PRIMA, designed for patients who have lost sight from late-stage dry AMD, has shown positive initial findings in five patients. The device, developed by Pixium Vision, is surgically implanted under the atrophic macula and acts like a tiny solar panel powered by pulsed infrared light through a tiny projector that connects to a pair of glasses and mini-camera. All five patients were able to perceive light and identify several visual patterns such as bars, letters and numbers. Further overseas trials are expected. There are also plans to test PRIMA on patients with retinitis pigmentosa.

Complement inhibition 🟠

Overactivity of part of the body's immune system, known as 'complement', has been shown to play a role in the development of AMD. A number of proteins are being developed to inhibit (block) different complement pathways in an attempt to reduce the development of dry AMD.

APL-2: An inhibitor targeting the complement protein C3 showed positive results in a phase 2 trial (FILLY). The treatment, given as an injection into the eye, was shown to reduce the progression of dry AMD by 29% over one year and the effect of the drug was greatest in the second six months of treatment. Two international, multi-centre phase 3 trials (OAKS & DERBY) have begun to assess the safety and efficacy of multiple injections of APL-2 into the eyes of patients with geographic atrophy.

Zimura: Another inhibitor, targeting the complement protein C5, is currently being investigated in an ongoing Phase 2b clinical trial for patients with geographic atrophy. A Phase 2b trial using the same drug began this year for patients with Stargardt disease, the most common form of childhood macular degeneration. Also, a phase 2a trial using Zimura in combination with anti-VEGF therapy (Lucentis) has begun for the treatment of wet (neovascular) AMD.

Wet (neovascular) AMD

Brolucizumab (RTH258) 🟢

Follow-up data from two large phase 3 (registration) trials (HAWK & HARRIER) for a newly developed anti-VEGF injection called Brolucizumab were recently announced.

Over a period of 48 weeks, both studies compared Brolucizumab with Eylea, an existing registered treatment. The safety of Brolucizumab compared favourably and more than 50% of patients on Brolucizumab were able to maintain 12-week intervals between injections until week 48, compared to the typical eight- week intervals for Eylea.

Follow-up data analysis showed retinal fluid, a key marker of disease in wet AMD, was detected less often in patients treated with Brolucizumab versus Eylea. As yet, there is no approval for the use of Brolucizumab in Australia. It's expected that regulatory approval will be sought in due course.

Abicipar 🟢

Two phase 3 trials (SEQUOIA & CEDAR) evaluating the use of Abicipar for patients with wet AMD have shown encouraging results. The trials compared eight and 12 weekly dosing of Abicipar with monthly treatment with Lucentis. Allergan, the manufacturer, plans to file Abicipar with the FDA in 2019.

Port Delivery System 🟠

A new study shows a refillable drug implant the size of a grain of rice called the Port Delivery System can continuously deliver a concentrated version of Lucentis to patients with wet AMD over a longer period of time, compared to frequent injections of the same drug. The phase 2 trial (LADDER) exceeded expectations in terms of durability. Most participants maintained the full effect of the drug for six months or more without the need for a refill. A phase 3 trial (ARCHWAY) will begin this year.

PAN-90806 🔴

A phase 1/2 trial began in April to evaluate this once a day eye drop for the treatment of wet AMD and other eye conditions such as diabetic retinopathy, where abnormal blood vessels grow under the retina. Previous research showed that this drug was safe, tolerable and effective in suppressing the formation of new blood vessels. The overseas trial, expected to run until March 2019, will look at the use of the drug in patients across a higher and broader dose-range. The challenge will be delivering an adequate dose to the back of the eye.

OPT-302 🟠

Current injections for wet AMD block the protein VEGF-A. A new treatment in Australia called OPT-302 blocks two related proteins, VEGF-C and D, which are also thought to play a role in the formation of new blood vessels. A phase 1/2a trial using OPT-302 to target anti-VEGF-C/D with and without Lucentis to target anti-VEGF-A showed positive results of improving vision and retinal swelling. This suggests that combination therapy is a promising strategy to treat wet AMD and other retinal vascular diseases. Further phase 2 trials are currently being conducted.

Gene therapy: ADVM-022 🔴

A newly developed gene therapy for the treatment of wet AMD delivered as a single-injection into the eye showed positive results in laboratory studies. The therapy will now be tested in humans in a phase 1 clinical trial (OPTIC) in the US. Researchers believe ADVM-022 gene therapy has the potential to provide sustained VEGF inhibition thereby minimising the burden of frequent injections. The trial will run for two years.

Stem cell research 🟠

Two research groups, one in the UK and the other in the US, reported preliminary findings in early-phase clinical trials of stem cell-based treatments for AMD. The studies involved two different implants both designed to replace the retinal pigment epithelium (RPE), a cell layer that degenerates in patients with AMD.

The tiny implants consist of a single layer of up to 100,000 stem-cell derived RPE cells on an ultrathin synthetic membrane designed to mimic the membrane in the eye that supports the RPE.

The UK trial involved two patients with advanced wet AMD who were monitored for 12 months after receiving the implant and reported significant improvements in vision. The implants were well-tolerated, the cells remained stable and neither patient showed signs of rejection.

The US trial involved four patients with late-stage dry AMD who successfully received implants, which were also well-tolerated.

The retina of each implanted patient showed structural changes consistent with the replacement of the RPE layer. None of the implanted eyes showed progression of vision loss, one eye showed improvement in vision and two eyes showed an improvement in visual fixation.

Further clinical trials are needed before stem cell therapy can be considered standard treatment.

Diabetic retinopathy: Emixustat hydrochloride

An experimental oral medication for the treatment of proliferative diabetic retinopathy (DR) showed positive results in a phase 2 trial.

The results show the potential for the drug to decrease retinal thickness in patients with DR, and suggest the possibility of slowing the progression of DR. The manufacturer is pursuing research partnerships and preparing to launch further trials needed for regulatory approval.

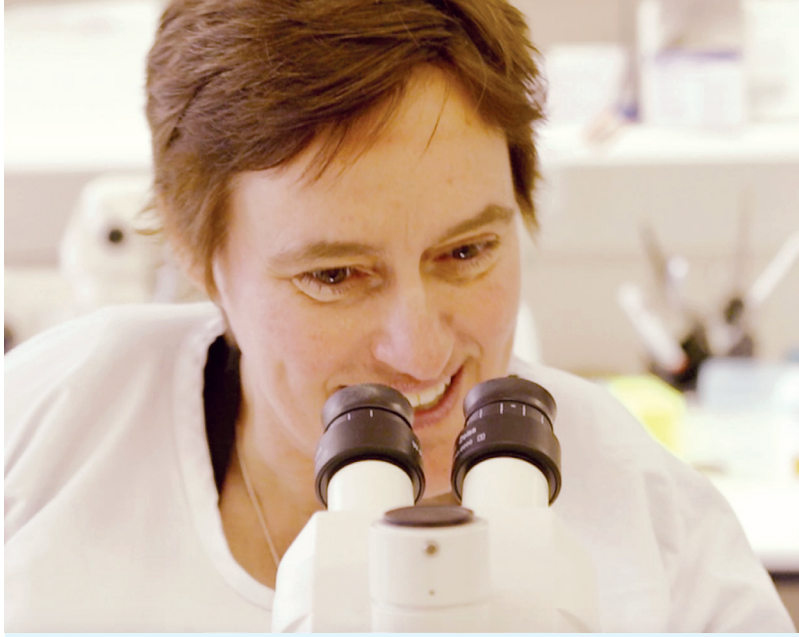
Diabetic Macular Edema (DME)

Faricimab

Two phase 3 trials (YOSEMITE & RHINE) have started to evaluate the use of faricimab for the treatment of DME. Faricimab is a specialised antibody which inhibits both VEGF-A and Ang-2, proteins involved in the formation of new blood vessels (angiogenesis).

The drug is to be injected into the eye at eight-week intervals and compared with an injection of Eylea, also administered once every eight weeks. The trial is expected to run until mid-2022.

Faricimab is also being evaluated in a phase 2 trial (STAIRWAY) given either every 16 weeks or every 12 weeks to patients with wet AMD. Initial results show the potential for this drug to allow fewer injections while achieving the same results as current treatments. A phase 3 trial for faricimab in wet AMD is expected to begin in 2019.



Research Grants Program

To date, MDFA has committed $3.6 million to Australian research through its grants program.

Ten research projects are underway, and the next round of grants will open from **1 March 2019**, for research commencing in 2020. Expressions of interest can be made via an online form, available on the MDFA website.

If you would like to donate to the MDFA Research Grants program call 1800 111 709 or donate online at www.mdfoundation.com.au

For further information and support, please call the MDFA Helpline on 1800 111 709.

Please note: Research is a lengthy, expensive and high-risk process. Some of these projects may not result in treatments, and others are years from completion. MDFA does not accept liability for out of date, misinterpreted or incorrect information.

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