Macular Disease Foundation AUSTRALIA

Macular Disease Research Update

November 2019

Could eating eggs reduce the risk of AMD?

An Australian study has shown that people who eat 2-4 eggs per week versus those who eat less than one egg per week had 49 per cent reduced risk of developing late AMD after 15 years.

Westmead Institute for Medical Research examined data from more than 3,600 Australian adults over the age of 49 who were followed over a period of 15 years.

For those adults whose age of onset of AMD was at the five or 10 year follow-up stage, eating 2-4 and 5-6 eggs per week was associated with 54 per cent and 65 per cent reduced risk of developing late stage AMD, respectively. Researchers say the beneficial impact of eggs comes from their yolks, which contain lutein and zeaxanthin.

These are both important nutrients for macular health and have anti-inflammatory and antioxidant properties. Further research is needed to validate the findings.

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.

They 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 and Intermediate AMD

Risuteganib

This new treatment is being studied in a Phase 2 trial involving 47 patients with intermediate AMD (medium-large drusen) from seven sites in the US. Risuteganib blocks the activity of integrin (a type of protein thought to be involved in AMD). Patients were randomised to receive Risuteganib by intravitreal injection or a placebo injection. At week 28, 48 per cent of patients who received Risuteganib had shown improvement in vision of at least eight letters. These initial results are encouraging considering there is currently no approved treatment for intermediate AMD.

Maculaser heat treatment

Maculaser heat treatment has recently been developed in Finland. It involves heating the retinal pigment epithelium (RPE) cells at the back of the eye with a near-infrared laser and precise temperature control. The treatment strengthens the defence mechanisms of the RPE and aims to stop the development of AMD in its earlier stages and prevent progression to either dry (atrophic) AMD or wet (neovascular) AMD. The potential success of this treatment relies on the ability to monitor the temperature of the RPE while administering the laser treatment. It's expected that testing of the Maculaser device in humans will begin in 2020.

Dry (atrophic) AMD

PRIMA

In MDFA's last research update, we reported positive initial findings in five patients with dry (atrophic) AMD who received the new wireless bionic implant called PRIMA. The device is surgically implanted under the atrophic macula. Recently announced data from the trial, one year after implantation showed that light perception was successfully re-established in the central retinal area of the five patients, with many able to identify letters as well as sequences of letters. Research is ongoing, however the manufacturer is evaluating the best pathway for regulatory approval.

OpRegen

OpRegen is a new RPE transplant therapy for treating dry (atrophic) AMD. RPE cells are essential to a healthy retina and become affected in AMD. Manufacturer BioTime Inc recently announced that it had treated its first patient in its ongoing Phase 1/2a trial by implanting RPE cells derived from human embryonic stem cells using the Orbit Subretinal Delivery System (Orbit SDS). The technology uses a new Thaw-and-Inject formulation, which would allow a rapid 'off the shelf' administration of RPE cells after thawing. The early trial will evaluate the efficacy and safety of the therapy in approximately 24 legally blind patients with dry (atrophic) AMD.

Wet (neovascular) AMD

Abicipar

Abicipar is a new anti-VEGF agent comprised of DARPin molecules, which are a type of protein. Apicipar works by binding to and blocking the activity of VEGF-A, preventing the formation of new blood vessels in wet AMD. Two Phase 3 trials (SEQUIOA & CEDAR) compared Abicipar with another agent Lucentis. The results so far show that Abicipar was just as effective after six to eight injections compared

with 13 Lucentis injections during one year of treatment. This new treatment option could potentially reduce the number of patient visits and injections. Allergan, the manufacturer, has filed a Biologics Licence Application (BLA) with the US Food and Drug Administration (FDA) and expects a decision in mid-2020.

AKST4290

AKST4290 is newly developed twice-daily oral treatment for patients with wet AMD. Promising early data from a recent Phase 2 trial involving 30 patients showed the treatment was safe, well-tolerated and resulted in improved vision in most patients. An oral treatment represents a major step forward in reducing the treatment burden from currently approved anti-VEGF injections. The encouraging results warrant further study.

Beovu (Brolucizumab)

Beovu (Brolucizumab), also known as RTH258, has recently been approved by the US FDA to treat wet AMD. The approval was based on the positive results of two Phase 3 trials (HAWK & HARRIER), involving more than 1,800 patients worldwide. Beovu has been approved in the US for treatment commencing with monthly injections for the first three doses, followed by an injection once every eight to 12 weeks. It is the only anti-VEGF agent for wet AMD approved for the longer injection interval time. As yet, Beovu is not approved for use in Australia. The manufacturer, Novartis, is seeking regulatory approval.

Faricimab

Faricimab is a new treatment that neutralises the activity of both VEGF-A and Ang-2, proteins involved in the formation of new blood vessels. This year, Roche, the manufacturer, initiated two Phase 3 trials (TENAYA & LUCERNE). They will compare the safety, efficacy and durability of faricimab with Eylea for treating wet AMD. Almost 1,300 patients with wet AMD will be enrolled in the trial and randomly assigned to receive an injection of either faricimab up to every 16 weeks as indicated in the study protocol, or Eylea every eight weeks, following initial monthly loading injections. The main aim of both studies is to assess the change in vision at week 48 from baseline. It's hoped the results will show that faricimab will improve visual outcomes for patients and lead to longer treatment intervals. Also, two Phase 3 trials (YOSEMITE & RHINE) are currently underway to evaluate faricimab for the treatment of diabetic macular edema (DME).

PAN-90806

PAN-90806 is a new, once a day anti-VEGF eye drop for the treatment of wet AMD and other retinal diseases involving the formation of new blood vessels and fluid leakage. PanOptica, the manufacturer, reported positive results from its Phase 1/2 trial which began in 2018. More than 50 per cent of the 51 patients involved in the trial who received the once a day drop for 12 weeks completed the study without any need of a rescue anti-VEGF injection. Of those patients, 88 per cent showed either clinical improvement or stability of their wet AMD. Despite the small sample size, the results are encouraging. It's hoped this new form of treatment may lead to reduced burden associated with frequent anti-VEGF injections. Research into eye drops for the treatment of retinal diseases remains a challenge because of the need to deliver an adequate dose to the back of the eye.

Port Delivery System (PDS)

A refillable drug reservoir implant the size of a grain of rice called the Port Delivery System (PDS) can continuously deliver a concentrated version of Lucentis to patients with wet AMD, compared to frequent injections of the same drug. The Phase 2 trial (LADDER) involving 220 patients showed that the implanted drug reservoir is safe and effective in helping maintain vision and reduces the need for injections. When the drug reservoir is implanted, medication can be replenished without the need to remove the reservoir. The results also showed 60 per cent of patients went at least one year without needing a refill. A Phase 3 trial (ARCHWAY) involving up to 360 patients is currently underway comparing Lucentis delivered by the PDS implant (fixed 24-week intervals), to repeated monthly injections of Lucentis. The trial is expected to run until 2022.

OPT-302

Instead of blocking VEGF-A, OPT-302, a newly developed treatment in Australia, blocks two related proteins, VEGF-C and D, which also play a role in the formation of new blood vessels in wet AMD. MDFA reported in last year's update that initial studies showed the potential to improve vision and retinal swelling in patients with wet AMD when OPT-302 was given in combination with Lucentis. Further studies in a Phase 2 trial involving 366 patients who received different combinations of OPT-302 and Lucentis have shown positive results. Superior vision gains over 24 weeks were seen in patients receiving OPT-302 combination therapy compared to Lucentis alone. Further outcomes from this study are still being reviewed.

RBM-007

While current anti-VEGF treatments show considerable visual benefits for patients with wet AMD, some patients don't respond as well. They may lose vision with the formation of fibrosis under the macula. RBM-007 is a newly developed agent targeting fibroblast growth factor 2 (FGF2), which is involved in new blood vessel formation as well as fibrosis in several diseases. The Phase 1/2a trial (SUSHI) evaluates the safety and tolerability of a single intravitreal injection of RBM-007 in nine patients with wet AMD who responded poorly to previous anti-VEGF treatment with injections. Initial results were positive in seven of the nine patients, and there are plans for a Phase 2 trial.

Gene therapy

ADVM-022

In MDFA's last update we reported on positive results from very early studies which evaluated a newly developed gene therapy to treat wet AMD delivered as a single injection into the eye. Research progressed to a phase 1 trial (OPTIC) involving 30 patients across four cohorts. Adverum Biotechnologies Inc, the manufacturer, has announced data from the first cohort of this trial, showing this gene therapy was safe and well tolerated. Patients also showed improvement in retinal structure over 24 weeks and did not require anti-VEGF rescue injections. Before enrolling in the study these patients needed repeated and ongoing injections to maintain vision. Patients in the second cohort of the trial are being evaluated with a lower dose of ADVM-022. Although in its early stages, the results are encouraging and research is ongoing.

RGX-314

This single injection under the retina shows promise as a new gene therapy for wet AMD. Recent data from a Phase 1/2a trial involving 42 patients across five dose cohorts showed promising results. Patients received the single injection of RGX-314 followed by monthly reviews. Twelve patients in the higher dose cohort showed positive clinical and visual responses to the treatment. Of these 12 patients, 75 per cent were injection-free during 5-6 months of follow-up. Based on these results, research will progress to a Phase 2b study.

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.

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This information is a summary only and further information is available from MDFA. Discussion of a project does not constitute MDFA endorsement of that product or treatment.

Eyes on Research

$600,000 awarded to Australian researchers on World Sight Day

MDFA awarded a further $600,000 to three leading Australian researchers in a prestigious event held at Admiralty House, the Governor General of Australia's residence in Sydney, on World Sight Day (10 October). The successful recipients of MDFA's Research Grants Program, which aims to reduce the incidence and impact of macular disease, were announced by His Excellency the Honourable David Hurley, Governor-General of Australia. With the generous support of the community, MDFA has now committed $4.2 million to cutting-edge research since the program's launch in 2011.

This year's grant recipients are:

Professor Alex Brown
South Australian Health and Medical Research Institute
Project title: Defining the **R**isk and **E**pidemiology of **A**boriginal Australian **M**acular Disease: The **DREAM** Project

Dr Audra Shadforth
Griffith University and Queensland Eye Institute
Project title: Investigating the potential for scar-less wound healing in age-related macular degeneration (AMD)

Dr Zhichao Wu
Centre for Eye Research Australia
Project title: Novel prognostic imaging biomarkers for improved risk stratification in the early stages of AMD

Image: L-R front row – Robert Kaye SC (Chairman), Dr Shadforth, His Excellency General the Honourable David Hurley, Her Excellency Mrs Hurley, Dee Hopkins (CEO). Back row – Professor Brown, Dr Wu

CURRENT MDFA FUNDED PROJECTS

Using stem cells to understand the causes of dry (atrophic) AMD

Innovative studies are needed if we are to prevent AMD progression. Human induced pluripotent stem cells (iPSCs) are a valuable tool for investigating the causes of disease. In 2017, Professor Alice Pébay from the University of Melbourne was awarded a MDFA Research Grant of $300,000 over two years to undertake research to better understand the mechanisms causing geographic atrophy (GA).

Her research involves the use of a large cohort of patient stem cell-derived retinal cells to establish the genetic signature that leads to GA development and progression. Her team has successfully guided 120 patient-specific iPSCs into becoming the retinal cells affected in GA (60 controls and 60 patients) and have investigated how their genes behave in each sample using new technology called single cell RNA sequencing.

The data that has been collected are currently being analysed to identify the genetic differences associated with the GA samples to help uncover new pathways involved in the development of GA, and ultimately paving ways for new treatments. Her project is due to be completed at the end of this year.