Macular Disease Foundation AUSTRALIA

Macular Disease Research Update

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Could blood markers lead to new treatment options for AMD?

It's difficult to study macular degeneration as we can't biopsy the living eye. Associate Professor Gerald Liew, recipient of a 2015 MDFA Research Grant, and his team at Centre for Vision Research, University of Sydney, investigated whether a new technique could be used to study blood markers in people with age-related macular degeneration (AMD).

The retina is the most metabolically active tissue in the body with a high concentration of mitochondria (power stations of the cells) and lipids. A/Prof Liew and his research team hypothesised that a defect in mitochondrial function may result in some people developing disease such as AMD. One way of detecting mitochondrial dysfunction is through measuring the concentration of a group of molecules known as acylcarnitines. The study looked at whether the levels of acylcarnitines differed between patients with wet AMD and people without the disease.

"The research posed several challenges as the technique is new to the eye field, and in Australia generally, so we had to solve a few problems along the way," A/Prof Liew said.

The research team at Centre for Vision Research, University of Sydney.

The study showed that one type of the acylcarnitine molecules was significantly lower in patients with wet AMD than people without the disease, while another type of acylcarnitine was significantly higher. A/Prof Liew said he was thrilled with the final results.

"Our study suggested that mitochondria, the power stations of the cells, may not be working properly in macular degeneration. Even better, our findings suggested a way to correct this defect. We're now studying this in more detail and trying to develop a potential new treatment. All thanks to the MDFA funding our initial research!"

Clinical trials are studies in humans that 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.

Phase 1: early study to test intervention safety in a small number of people.

Phase 2: extended safety study with some tests of intervention effectiveness.

Phase 3: large trial of effectiveness and safety usually in comparison with standard care.

Phase 4: ongoing studies of safety and effectiveness in the general population once an intervention has been approved for use.

Early and Intermediate AMD

Luminate (Risuteganib)

Risuteganib, manufactured by Allegro Ophthalmics, is a new, small, synthetic peptide that blocks oxidative stress in the photoreceptor and retinal pigment epithelium (RPE) layer of the retina, reducing degeneration and inflammation. It's administered as eye injections. Risuteganib was investigated in a phase 2 clinical study and showed improved vision in patients with intermediate AMD and an acceptable safety profile. These initial results are encouraging as there's currently no approved treatment for intermediate AMD. The trial enrolled 39 patients; a larger trial is planned to further assess safety and effectiveness of the treatment.

Dry (atrophic) AMD

Pegcetacoplan (APL-2)

Pegcetacoplan, developed by Apellis, is an investigational molecule for the treatment of advanced dry AMD (geographic atrophy). It is designed to control excessive activation of the immune system, which is known to play a part in many diseases including dry AMD. Pegcetacoplan inhibits part of the immune system called complement component 3 (C3). Pegcetacoplan is being administered in clinical trials as a monthly or every-other-month eye injection. The results of a phase 2 trial in 246 patients were promising, with reduction in the progression of dry AMD and a good overall safety profile, however new onset wet AMD was reported more frequently in the pegcetacoplan treatment group. The treatment is now being investigated in two phase 3 trials: DERBY and OAKS. Each trial has now enrolled over 600 patients, including Australian participants. Initial results are expected in late 2021.

Zimura (avacincaptad pegol)

Zimura is a novel complement C5 inhibitor, which targets the excessive activation of the immune system in dry AMD. It is manufactured by Iveric bio. Positive results from the 18-month phase 3 trial, GATHER1, of Zimura in patients with dry AMD showed the treatment reduced geographic atrophy growth (disease progression) and was well tolerated. A second, 24-month, phase 3 trial, GATHER2, involving approximately 400 participants is underway. Zimura is administered as an eye injection either monthly or every other month. Pending positive results from the second trial, the manufacturer intends to apply for regulatory authorisation to the US Food and Drug Administration (FDA) and European Medicines Agency (EMA).

OpRegen

OpRegen is a new retinal pigment epithelium (RPE) transplant therapy for treating dry (atrophic) AMD. RPE cells are located beneath the retina and are essential to a healthy retina. RPE cells are affected in AMD. OpRegen cell line is derived from human embryonic stem cells and administered as a cell suspension. OpRegen is being evaluated in a Phase 1/2a clinical study in patients with dry AMD. Seventeen of 21 patients have been enrolled so far. The company, Lineage Cell Therapeutics, has observed benefits in some patients, including reduction in the growth of geographic atrophy and improvement in vision, such as increased reading speed. One patient enrolled in a phase 1/2a study of OpRegen for dry AMD showed signs of retinal tissue regeneration, according to a media release. These observations are preliminary – the study is expected to be completed in 2024.

Wet (neovascular) AMD

Abicipar

Abicipar is a new anti-VEGF agent comprised of DARPin molecules, which are a type of antibody-like protein. It is administered as eye injections and works by binding to and blocking the activity of VEGF-A, preventing the formation of new blood vessels in wet AMD. The manufacturer, Allergan, made a decision to withdraw applications to the EMA and the Japanese Regulatory Agency following the FDA decision to deny approval of abicipar for wet AMD in the US due to the occurrence of intraocular inflammation. The manufacturer will continue working with regulatory agencies regarding further development of the treatment.

AKST4290

AKST4290 is newly developed, twice-daily oral treatment for patients with wet AMD. The treatment blocks CCR3, a mediator of inflammation thought to be important in AMD. Promising early data from a recent phase 2 trial involving 30 patients showed the treatment was well-tolerated and resulted in improved vision in most patients. A potential oral treatment represents a major step forward in reducing the treatment burden from anti-VEGF injections. Alkahest, the manufacturer, announced earlier this year the initiation of a phase 2b trial to further study the safety and efficacy of this treatment. The trial will assess the effects of AKST4290 on vision when combined with three loading doses of the approved eye injection treatment Eylea in previously untreated patients with wet AMD. The study will enrol approximately 150 patients.

Beovu (Brolucizumab)

Beovu (Brolucizumab) is an anti-VEGF agent which was approved by the TGA in Australia earlier this year. Beovu is administered via an eye injection but it is not currently reimbursed under the Pharmaceutical Benefits Scheme in Australia. In their recent review, the Pharmaceutical Benefits Advisory Committee (PBAC) considered that Beovu showed similar efficacy to Eylea (another anti-VEGF agent available in Australia), but did not accept that the evidence supported less frequent dosing. The PBAC considered that risk may be associated with Beovu with no additional benefit compared to the treatment options already available. The manufacturer, Novartis, is committed to returning the product to the PBAC with additional clinical evidence for further consideration at the earliest opportunity.

Faricimab (RG7716)

Faricimab is an antibody treatment that blocks the activity of both VEGF-A and Angiopoietin-2 – proteins involved in the formation of new blood vessels, inflammation and the disruption of blood vessel stability. It is administered as eye injections. Roche, the manufacturer, recently reported promising results of a phase 2 trial (STAIRWAY) in patients with wet AMD. The study showed that in the majority of patients in the one-year trial, dosing every 12 or 16 weeks resulted in maintenance of vision and anatomical improvements, similar to monthly injections with Lucentis. Faricimab was well tolerated. Two large, global, phase 3 trials, TENAYA and LUCERNE, are currently investigating the efficacy, safety and durability of Faricimab in patients with wet AMD administered every 16 weeks in comparison with Eylea, an approved anti-VEGF treatment, administered every eight weeks. It is hoped that the results will lead to longer treatment intervals with this drug compared with currently available therapies.

OPT-302

OPT-302, a new treatment developed in Australia, blocks proteins VEGF-C and D, which play a role in the formation of new blood vessels in wet AMD. It is administered as eye injections. In last year's update MDFA reported that the phase 2 trial, involving 366 patients who received different combinations of OPT-302 and the approved anti-VEGF agent Lucentis, showed positive results. The manufacturer, Opthea, recently announced it has successfully completed meetings with the FDA and EMA to obtain guidance on the phase 3 clinical trials of OPT-302 for wet AMD. The company will conduct sham-controlled clinical studies evaluating OPT-302 in combination with ranibizumab (Lucentis) or aflibercept (Eylea). At least 900 patients will be enrolled in each trial.

Port Delivery System (PDS)

The PDS is a permanent refillable drug reservoir implanted via an operation and can continuously deliver a modified version of the approved anti-VEGF agent ranibizumab (Lucentis) to patients with wet AMD. Trials of the PDS have compared safety and efficacy with monthly intravitreal injections of Lucentis. Positive phase 2 trial (Ladder) results were published last year and 40-week results from the phase 3 Archway study were reported this year by the manufacturer, Roche. These data showed that patients using the device had similar outcomes to patients treated with monthly Lucentis. The study results included 248 patients who were implanted with the device, which was refilled at 24-week intervals. The remaining 167 patients in the study received monthly intravitreal injections of Lucentis. Safety findings were similar between the two groups. The study is ongoing and is expected to be completed in 2022.

RBM-007

RBM-007, manufactured by RIBOMIC, is a newly developed agent targeting fibroblast growth factor 2 (FGF2), which is involved in new blood vessel formation as well as fibrosis (scarring) in several diseases, including wet AMD. RBM-007 is administered as monthly eye injections. The initial results of the phase1/2a trial, SUSHI, were positive. This molecule has now progressed to a phase 2 clinical trial, TOFU. The study will investigate the use of RBM-007 alone or in combination with the approved anti-VEGF treatment Eylea, compared to Eylea alone in patients with wet AMD. Approximately 81 patients will be enrolled into the study, which is expected to be completed in mid-2021.

Gene therapy

ADVM-022

ADVM-022 is a single injection gene therapy that delivers aflibercept to the retina. Aflibercept (Eylea) is an anti-VEGF medication used routinely in patients with wet AMD. Following injection of the gene therapy, the transfected cells of the eye produce the aflibercept protein continually, potentially doing away with the need for further eye injections. The company, Adverum, is conducting a phase 1 trial (OPTIC) of the therapy in 30 study participants. Interim findings indicate a sustained treatment response with an acceptable safety profile. Additional study results are expected at the end of 2020 and the study will continue until mid-2022. An additional trial is planned to commence mid-2021 to investigate the safety and efficacy of this treatment in a larger group of people.

GT005

GT005 is an investigational one-time gene therapy that is delivered under the retina and is intended to slow the progression of geographic atrophy in patients with dry AMD. The treatment aims to increase the production of complement factor 1 (CF1), a natural inhibitor of inflammation, by cells of the retinal pigmented epithelium. GT005 is being evaluated in a phase 1/2 clinical trial called FOCUS, and a phase 2 clinical trial called EXPLORE. The company plans to enrol approximately 75 patients in the EXPLORE trial, including some in Australia. The FDA granted expedited review designation to GT005 for the treatment of geographic atrophy secondary to dry AMD, in patients with specific genetic mutations that mean that they have low levels of CF1. The company, Gyroscope Therapeutics, plans to begin a phase 2 trial in a larger group of patients before the end of the year.

RGX-314

RGX-314 is an inhibitor of the VEGF pathway which is a key cause of new blood vessel formation and leakage in wet AMD. This single injection under the retina shows promise as a gene therapy for the disease. Following the release of positive one-year data from a phase 1/2a trial, the manufacturer, REXENBIO, recently announced the start of a phase 2 trial that will enrol 40 patients with wet AMD. Patients will either receive a single injection of RGX-314 or repeated injections of the approved anti-VEGF treatment Lucentis. Interim data are expected later this year.