New treatments for macular degeneration

What do actress Dame Judi Dench, author Stephen King and comedian Roseanne Barr have in common? The answer is that they have all been diagnosed with age-related macular degeneration (AMD), a condition in which the macula becomes damaged, resulting in visual impairment. As well as making everyday activities like reading and driving difficult, AMD can impair the quality of life in many ways. For example, AMD sufferers are at greater risk of injury and falls and are more likely to require supportive care. They are also at greater risk of depression compared with age-matched populations.

Given the medical need, it is not surprising that companies around the world are investigating new treatments for the disease, including small molecule and protein-based drugs, as well as gene and cell therapies. The targets for these drugs differ, depending on whether the disease is dry AMD or wet AMD. Competition is fiercest in the wet AMD sector, which also has seen the most recent innovation. This is a new single-chain antibody fragment developed by Novartis for wet AMD that was approved by the US Food and Drug Administration in October 2019. Beovu (brolucizumab) targets vascular endothelial growth factor (VEGF), a signal protein that stimulates the growth of blood vessels in the eye.

While wet AMD has featured the most recent innovation, dry AMD is by far the more common of the two diseases. Dry AMD accounts for between 85% and 90% of all cases and is associated with the development of small yellow deposits – known as drusen – under the retina. Drusen are made up of lipid material and while they are not thought actually to cause AMD, their presence is considered to be a risk factor for developing AMD, particularly the so-called 'soft' drusen. There is some evidence that a diet rich in carotenoids such as lutein and zeaxanthin, or dietary supplements containing these pigments, may slow the growth of drusen and hence the development of AMD.

In a small proportion of dry AMD patients the condition will progress to wet AMD, although some patients develop wet AMD without any prior macular disease. In some ways, wet AMD can be seen as a defensive response to dry AMD, whereby new blood vessels start to grow in the retina as the body attempts to reverse the damage. However, as these blood vessels grow under the macula they can cause local swelling and bleeding (hence the term 'wet' AMD). This leads to further damage and even scarring of the macula. It is possible for both types of AMD to exist in the same patient, with dry AMD in one eye and wet AMD in the other.

Besides a lack of dietary carotenoids, a number of risk factors for AMD have been recognised, including older age, the presence of AMD in the other eye, a family history of AMD, smoking, hypertension and obesity[1]. A recently published study even found a correlation between exposure to nitrogen dioxide and carbon monoxide in traffic fumes and the risk of developing AMD[2].

At present there is no cure for dry AMD, although a number of possible treatments have been investigated. Broadly speaking, the main categories of treatment being examined are anti-inflammatory agents, neuroprotective agents, agents that modulate the visual cycle, and treatments that restore choroidal blood flow. Choroidal and retinal blood flow are decreased in patients with AMD, and this may be a contributory factor in the development of new blood vessel formation[3].

Prominent among inflammatory targets being studied is the complement system. Genentech (Roche) has carried out trials of intravitreal lampalizumab, a humanised monoclonal antibody against complement factor D, with a view to slowing the chronic, progressive degeneration of the macula, known as geographic atrophy, secondary to AMD. However, in the Chroma and Spectri trials in 2017, lampalizumab failed to meets its primary endpoints[4]. UK-based Gyroscope Therapeutics Ltd is currently recruiting patients into a Phase 1/2 trial of GT-005, a recombinant adeno-associated virus vector encoding a human complement factor. Earlier this year, Gyroscope merged with specialist UK medical device company Orbit Biomedical Ltd to create "the first fully-integrated retinal gene therapy company with clinical, manufacturing and delivery capabilities"[5]. More recently, Gyroscope raised £50.4 million in Series B financing to support the development of GT-005, among other projects.

Meanwhile Potentia Pharmaceuticals Inc, based in Kentucky, US has successfully completed a Phase 1 study of POT-4, a C3 inhibitor that is administered by intravitreal injection, while US-based Ophthotech has carried out a Phase 1 study of intravitreal injections of ARC-1905, an anti-C5 aptamer. Ophthotech has since switched its focus to gene therapy products and changed its name to IVERIC bio Inc.

Another US company, Hemera Biosciences Inc, is studying CD59, a naturally occurring protein that protects cells from over-activity of the complement system. Hemera says that patients with AMD have less CD59 in the retina to protect cells from damage caused by complement. The company has developed a gene therapy product to restore normal levels of CD59.

Neuroprotective therapy

In the area of neuroprotective therapy, Neurotech Pharmaceuticals Inc, based in Rhode Island, US, is exploring the use of ciliary neurotrophic factor 501 (CNTF), a member of the interleukin-6 family of cytokines, using the company's proprietary ECT (encapsulated cell therapy) technology. The product comprises a small capsule that contains human retinal pigment epithelium cells, modified to produce CNTF, that is implanted into the back of the eye. A Phase 2 trial is underway to study its safety and effectiveness in dry AMD and other neurotrophic ocular diseases including macular telangiectasia.

A second neuroprotective agent being studied is Allergan's beta-2 agonist brimonidine tartrate, which is otherwise used to treat open-angle glaucoma and ocular hypertension. Brimonidine has been found to have a neuroprotective effect on retinal cells in animal models[6]. Allergan, which is currently being acquired by AbbVie Inc, has announced positive results in the Phase 2b BEACON trial of intravitreal brimonidine for geographic atrophy secondary to AMD: mean geographic atrophy area growth was significantly reduced at 24 and 30 months. Phase 3 studies are pending.

Compared with neuroprotective therapy, modulation of the retinal cycle has attracted relatively little attention. Acucela, a subsidiary of the Japanese company Kubota Pharmaceutical Holdings, has reportedly completed a Phase 2/3 trial of emixustat (ACU-4429), which inhibits the conversion of all-trans-retinol to 11-cis-retinalin (part of the visual cycle), in patients with geographic atrophy, although no results have been posted. Acucela previously had an agreement with Otsuka Pharmaceutical Co for the co-development of emixustat, but this was terminated in 2016.

Blood flow

On the other hand, a number of companies have investigated choroidal blood flow as a target for the treatment of dry AMD. One of the first to adopt this approach was UCB SA, which has carried out a trial of intravenous alprostadil with the aim of improving visual acuity in dry AMD patients. Interim analysis indicated that the results did not reach statistical significance, and the trial has not been repeated.

Also, a company called MacuCLEAR, subsequently acquired by Healthcare of Today Inc, carried out Phase 2/3 studies of MC-1101, which it said was "previously approved by the FDA as an oral antihypertensive drug." However, no results of these studies appear to have been published.

As well as these, a handful of drug candidates are being investigated that do not fit into the above categories. Probably the most advanced is Allegro Ophthalmics LLC's risuteganib, which successfully completed a Phase 2 trial in patients with intermediate non-exudative AMD (intermediate dry AMD). Results, announced in June 2019, showed that the trial met its primary endpoint, with 48% of patients in the risuteganib arm gaining at least eight letters of visual acuity at 28 weeks compared with baseline[7]. The company says that risuteganib interferes with integrin functions that have been implicated in retinal diseases, giving it the potential for a broad-spectrum effect on different pathways of oxidative stress.

Cell Cure Neurosciences, a subsidiary of US cell therapy company Lineage Cell Therapeutics Inc, is currently recruiting patients into a Phase 1/2a study of OpRegen, a formulation of human embryonic stem cells and derived retinal pigmented epithelial cells, for the treatment of advanced dry AMD with geographic atrophy. OpRegen has been granted fast track designation by the FDA, and its development has been partially supported by more than $14 million in grants from the Israel Innovation Authority. Another company investigating cell therapy for dry AMD is Astellas Pharma Inc, whose MA09-hRPE product, which comprises human embryonic stem cell-derived retinal pigment epithelial cells, has been the subject of Phase 2 studies.

Lastly, Pfizer Inc is carrying out early clinical trials with RN6G, a monoclonal antibody that targets amyloid-beta, the protein implicated in Alzheimer's disease.

In contrast with dry AMD, several products have been approved for the treatment of wet AMD. In terms of mechanism of action, they all target VEGF which stimulates the growth of blood vessels and is implicated in the aetiology of wet AMD.

The first VEGF-based product on the market was Macugen (pegaptanib), a pegylated anti-VEGF aptamer, which was discovered by NeXstar Pharmaceuticals Inc and licensed to EyeTech Pharmaceuticals Inc for marketing in the US. Macugen was approved in the US in 2004 and in the EU in 2005, where it was marketed by Pfizer, and subsequently in other countries. In 2006, Macugen was joined on the market by Genentech's Lucentis (ranibizumab) which is a humanised monoclonal antibody fragment against VEGF. Several studies have shown that treatment with ranibizumab yields greater improvements in vision than treatment with pegaptanib[8]. Both products are administered by intravitreal injection.

Anti-VEGF agents that inhibit the formation of new blood vessels were originally developed as antitumour agents: the growth of tumours is dependent on a plentiful blood supply, so inhibiting the development of new blood vessels effectively curbs tumour growth. As a leader in this sector, Genentech also developed the VEGF inhibitor Avastin (bevacizumab) as an antitumour agent. Avastin was originally approved by the FDA in 2004 for the treatment of metastatic colorectal cancer, with its indications subsequently being extended to include breast, lung, renal and brain cancers.

The fact that both ranibizumab and bevacizumab act via the same mechanism, and the fact that Avastin is considerably cheaper per dose than Lucentis, led ophthalmologists to experiment with intravitreal Avastin as a treatment for wet AMD about 10 years ago. However Avastin has not been formally approved by the FDA for treating AMD, and Genentech has not carried out any clinical trials of the drug in AMD. The issue is still being litigated in the UK.

Eyelea (aflibercept), developed by Regeneron Pharmaceuticals Inc, is another wet AMD treatment. Approved by the FDA in 2011, it is a recombinant fusion protein that targets VEGF-B and placental growth factor as well as VEGF-A; Lucentis targets mainly VEGF-A. In addition, Eyelea has a much longer systemic half-life than Lucentis, which may confer a therapeutic advantage.

Market competition

Competition in the anti-VEGF market increased even further in October 2019 with the US approval of Novartis' follow-up product Beovu (brolucizumab). Originally developed by the University of Zurich, Switzerland spin-out ESBATech, brolucizumab targets VEGF-A. According to Novartis, "Beovu is the first FDA-approved anti-VEGF to offer both greater fluid resolution versus aflibercept and the ability to maintain eligible wet AMD patients on a three-month dosing interval immediately after a three-month loading phase"[9]. Observers expect Beovu to take market share from Lucentis, especially as Novartis has initiated a rebate scheme to support patients. The European Medicines Agency adopted a positive opinion for Beovu in December 2019.

Besides the anti-VEGF products already mentioned, several others are in advanced clinical trials, including one which is already being marketed in China. This is Conbercept, a fusion protein developed by Chengdu Kang Hong Biotech that targets VEGF-A, VEGF-B and placental growth factor, like Eyelea. It is already marketed in China for the treatment of neovascular AMD, while in the US patient recruitment for two multicentre Phase 3 trials is currently underway. The product reportedly has fast-track status.

Other anti-VEGF products currently in clinical trials include:

- Abicipar, being developed by the Swiss company Molecular Partners AG and exclusively licensed to Allergan on a

worldwide basis in the field of ophthalmology. The product is based on Molecular Partners' DARPin platform which comprises single-domain proteins, much smaller than a full antibody, with a constant framework and a randomised target binding surface. The company says that abicipar has been engineered for a long half-life in the eye and highest potency: Phase 3 results have demonstrated that quarterly injections are equivalent to monthly injections of Lucentis.

- Besides Lucentis, Regeneron has developed Zaltrap (ziv-aflibercept), an identical fusion protein to aflibercept which is marketed by Sanofi SA in the US for the treatment of metastatic colorectal carcinoma. By analogy with the situation regarding Avastin, trials are underway to investigate whether ziv-aflibercept could form the basis of a treatment for AMD in countries where aflibercept is unavailable or financially prohibitive. Data from the Phase 2 ZEBRA (Ziv-aflibercept Efficacy in Better Regulating AMD) trial, which compares intravitreal ziv-aflibercept with intravitreal bevacizumab, ranibizumab, or aflibercept are expected in 2020.
- Roche has commenced several Phase 3 trials of faricimab, a bispecific monoclonal antibody that targets angiopoietin-2 and VEGF-A, in wet AMD patients. It is also being studied in diabetic macular oedema.
- In September 2019, the Australian company Opthea Ltd announced positive results from a Phase 2b trial of OPT-302, a soluble form of vascular endothelial growth factor receptor 3 (VEGFR-3) that blocks the activity of VEGF-C and VEGF-D. Opthea is developing OPT-302 for use in combination with inhibitors of VEGF-A such as Lucentis or Eyelea: combination therapy with OPT-302 and a VEGF-A inhibitor achieves more complete blockade of members of the VEGF family, the company says[10]. This includes mechanisms contributing to sub-optimal responses to selective VEGF-A inhibitors.

Apart from anti-VEGF agents, there is some interest in gene therapy as a possible treatment for wet AMD. A potential advantage of gene therapy over traditional anti-VEGF therapies is that it would require fewer intravitreal injections, which may increase patient compliance and thus improve clinical outcomes. At the American Academy of Ophthalmology meeting in October 2019, Adverum Biotechnologies Inc, a clinical-stage gene therapy company targeting ocular and rare diseases, presented data from the first six patients taking part in its Phase 1 trial of the company's gene therapy product, ADVM-022. Over a median 34-week follow-up, no patients required rescue anti-VEGF injections (for example for complications such as vision-threatening haemorrhage), improvements in visual acuity were maintained, and the product was safe and well tolerated[11].

Elsewhere, the University of Texas Southwestern Medical Center, US is conducting preclinical studies of potential gene therapies that target mechanisms of disease apart from VEGF. This approach could reduce the need for frequent intravitreal injections, according to UT Southwestern's Dr Rafael Ufret-Vincenty. Also, the US National Institutes of Health is conducting trials in which researchers are using patient-derived induced pluripotent stem cells with the aim of growing new retinal cells to replace those damaged in AMD. In addition, Novartis recently announced a collaboration with Microsoft to explore the use of artificial intelligence in drug development, including personalised therapies for macular degeneration[12].

Age-related macular degeneration can have a major impact on a patient's quality of life, and while considerable progress has been made in the management of wet AMD, much remains to be achieved, including better treatments for dry AMD.

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