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The 7th annual National Eye Health Week (NEHW) 2016 offers a great opportunity to shine a spotlight on a growing public health issue caused by a degenerative eye disease that is currently incurable and mostly untreatable. Age-related macular degeneration (AMD) in both its "wet" form and "dry" form (also known as Geographic Atrophy or GA) is the most common cause of sight loss in the developed world and the third most common globally.

The role of ageing, gene mutations, genetic susceptibility and the impact of the environment on genes, immune responses, lifestyle choices (including a poor diet, lack of exercise and smoking), inflammation, toxic proteins and debris in the eye in triggering AMD is generating some alarming statistics. Currently approx. 600,000 people wrestle with some form of AMD and 70,000 new patients join this group every year, leading to some predictions that by 2050 there will be around 1.3m patients in the UK with AMD.

It is projected that AMD will affect 196 million individuals globally by 2020, increasing to 288 million by 2040. The social, emotional and economic impact of this growing eye disease can only be imagined.

So, AMD is not only a touchstone for the remarkable and ongoing advances in eye research to prevent sight loss, treat eye disease and ultimately restore sight but also a crucible for the growing concerns amongst commissioners and NHS managers, patients, researchers and clinicians alike in the UK about the ability of eye clinics and hospitals to cope with the rising numbers of AMD patients, the cost of drugs and the optimum point at which to intervene to ensure that the sight of patients is saved.

Macular degeneration is emerging as a key battleground on which the growing array of weapons in the eye research armoury are targeted. These include Imaging and Artificial Intelligence, enhanced testing of visual fields and function, a better understanding of cell biology, proteins and the immune system, surgery, drug based treatments, genetics, gene and stem cell therapies, implants that provide vision enhancement and artificial sight, epidemiology and big data analysis, patient support and guidance on lifestyle issues including diet, obesity and smoking.

Indeed, if the relentless pursuit of academic researchers and clinician scientists is to be effective in improving the prediction and detection of AMD and enhancing our ability to better monitor and treat this eye disease and

ultimately restore sight lost to it, then we need to make an honest assessment of progress to date and devise future treatment strategies accordingly.

To illustrate this, VisionBridge has invited some leading experts to shine a light on their respective research and clinical activities to illustrate just some of the extraordinary innovation taking place across the UK in support of patients with either the wet and/or dry forms of AMD – the former is treatable but the latter is currently not.

Predicting AMD:

Research into prevention has been largely hampered by the lack of functional and structural biomarkers that can predict the development and progression of AMD. Professor Sobha Sivaprasad and Professor Alan Bird in the Institute of Ophthalmology and Moorfields Eye Hospital have been working on sub-phenotyping (understanding genetic characteristics influenced by inherited, environmental and developmental drivers) a heterogeneous group of patients with early AMD based on early functional and structural deficits to provide insight into the progression rates of different phenotypes and genotypes. In particular, dark adaptation, Medmont perimetry, handheld ERG and novel psychophysical measures are used to classify disease progression. This in turn will enable interventions to be developed that target each functional and structural phenotype. For example, Professor Glen Jeffery is evaluating the role of low light therapy in eyes with early AMD with functional deficits while novel lipid (fat insoluble in water) clearing agents will be evaluated in lipid-laden eyes manifesting with intermediate drusen.

Professor Sobha Sivaprasad
University College London
Consultant, Moorfields Eye Hospital

Detection and diagnosis:

Over the past 50 years, advances in retinal imaging have proven crucial to every advance in the diagnosis and treatment of age-related macular degeneration (AMD). In the 1960s, the advent of fundus fluorescein angiography (FFA) allowed researchers to determine the role of choroidal neovascularization (CNV) in the “wet” AMD. In the late 1990s, with the advent of photodynamic therapy (PDT), FFA became crucial to identifying those patients with AMD who would most benefit from treatment. Finally, in the past 10 years, optical coherence tomography (OCT) imaging has facilitated treatment with intravitreal injections therapies, in particular allowing for accurate assessment of disease activity and thus need for retreatment. Going forward, imaging technologies continue to rapidly advance. Advances in OCT hardware will allow devices that are smaller and more portable - this has the potential to allow people with AMD to monitor their condition from their own

homes or local communities. New imaging technologies will also likely prove crucial to the introduction of new therapies such as stem cell and gene therapies. In combination with hardware advances, advances in artificial intelligence will allow greatly improved analysis of retinal images, allowing for earlier detection of disease and providing new insights into its pathophysiology.

Dr Pearse A Keane
Clinical Lecturer in Ophthalmic Translational Research
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Gene therapy:

When compared to other therapy options, such as traditional drug based treatments, gene therapy is best suited at the early stages of disease, preferably prior to major physical changes. This can be achieved given the genetic nature of AMD and well developed algorithms that take into account a patients genes, diet, age and smoking to predict their level of risk. Other methods are best suited to later stage disease, such as stem cell therapies, that seek to replace the RPE cells already lost because of disease progression.'

"Given the localised nature of AMD, gene therapy represents a very real opportunity to deliver therapeutic potential right in the part of the eye we here it is needed. Altering the way the retinal pigment epithelium (RPE) cells contribute to inflammation, lipid synthesis and blood vessel growth means a patient would have a therapy constantly maintained in their eye. This may be delivered by a single sub retinal injection, removing the need for monthly eye clinic appointments currently endured by patients receiving anti-VEGF.

While the anti-VEGF era has seen a tremendous advance in our approach to AMD, the window of opportunity for initiating this therapy is very short. In some senses, anti-VEGF therapy is palliative medicine. Patients are observed until they have the most advanced form of AMD before injecting an eye with drugs that actually fail to target the underlying disease process. Significant tissue damage and visual loss may have already taken place and, further, some patients respond poorly to these treatments.

A note about VEGF: VEGF, or Vascular endothelial growth factor for those in the know, is a small protein that promotes blood vessel growth. Given that excessive blood vessel growth is a major feature of wet AMD it is perhaps not surprising that therapies directed against VEGF were quickly employed. Anti-VEGF is an antibody that perturbs VEGF function, thus stopping blood vessel growth when applied directly to the site of disease. One problem, however, is the transient nature of this treatment and explains why patients are constantly needing injections to keep up the levels of anti-VEGF, or face the consequences of the blood vessels growing again. Herein lies the greatest criticism of anti-VEGF treatments, that it only slows down, or stops the final

stages of the disease, and does nothing to address the underlying problem or prevent it in the first place.'

Furthermore, with a new delivery method come new opportunities for therapies and treatment may no longer be the preserve of the wet form of AMD.

However, we still have no treatments in routine use for geographic atrophy, which is thought to affect over 8 million people worldwide. We need to understand that dry AMD is a multi faceted disease, which can only be cured if treated in its very early stages and indeed linked to the underlying disease process and a patient's specific genotype.

Dr. Simon Clark
Centre for Ophthalmology & Vision Sciences
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Surgery with lasers:

Micropulse laser for drusen removal - "Drusen" is the name given to small yellow deposits in the retina, which is often described as the first signs of AMD. They sit between the vascular supply of the retina (choroid) and the light sensitive photoreceptors for vision. Increase number and volume of drusen increases the risk of significant visual loss and common symptoms include difficulty with reading and adapting to changes in light.

The concept of using laser to remove drusen is not new as it has been used since the 1990's. However, traditional laser causes scarring and can lead to conversion to wet AMD. Unfortunately, the current "rejuvenation laser" 2RT laser is also understood to cause scarring albeit much reduced compared to previous procedures. So another laser is in use by a growing number of consultant ophthalmologists, the "micropulse" laser, which is used extensively in diabetic patients and patients with serious central retinopathy for many years. The Micropulse laser delivers the laser energy in short pulses, and the treatment parameters have been tested in diabetic patients for over 10 years leading to the biological benefit without any scarring. The assumption is that drusen removal will have short term benefit in improving nutrient supply for the photoreceptors, but the long term benefits remain unclear.

Victor Chong MD, FRCS, FRCOphth Consultant Ophthalmic Surgeon Oxford Eye Hospital Oxford University Hospital

A drug based treatment:

A novel drug treatment "Lampalizumab" may well be the answer for some of those patients with the advanced form of macular degeneration or "dry" AMD also known as "Geographic Atrophy" (GA). It is designed to target the

complement genes and suppress the overactive complement defence system, which can lead to inflammation and associated tissue and cellular damage. However it might simply slow down the progression of GA rather than improve vision.

This novel treatment injected into the eye is currently being tested in a Roche sponsored Phase 3 clinical trial supervised by Roche Chief Investigator Professor Andrew Lotery and his team in Southampton University and this work could lead to personalised treatments that are based on individual patient's genetic tests.

Professor Andrew Lotery
Professor of Ophthalmology Southampton University

Converting light into new vision:

It has long been thought fanciful that it might be possible to restore some degree of visual perception to patients who had lost their sight. However, alongside the remarkable and emerging clinical trial data relating to stem cell and gene therapies is the growing awareness of neuro-prosthetic devices.The breadth and depth of the understanding about micro and nano-electronics neurobiology required to bring together the two worlds of the eye and the brain and build a world of bionic vision for those who have lost their sight is immense. Visual neuro-prostheses or Bionic Vision Restoration technologies aim to provide those who have lost their sight to retinal dystrophies like retinitis pigmentosa, useful visual perception with independent locomotion and improve their quality of daily living. These retinal prostheses are specifically designed for patients having lost their photoreceptors but with functional optic nerve. The loss of photoreceptors can either result from hereditary genetic retinal diseases such as retinitis pigmentosa or more complex diseases such as age-related macular degeneration. Bionic Visual perception can be achieved by electrically stimulating the residual retinal circuit. Pixium Vision and its partners are developing two bionic vision systems: an epi-retinal IRIS®II for retinitis pigmentosa and a wireless photovoltaic sub-retinal system.

Dr Mahi Muqit
Consultant Vitreoretinal Surgeon Moorfields Eye Hospital