

Looking to the future of AMD:

Mr Stephen Beatty and Dr John Nolan describe the challenges in delivering sight-saving therapy in age-related macular degeneration

We live in an ageing society, the importance of which is compounded by the fact that people are having smaller families. Consequently, the elderly section of the population is becoming an ever increasing proportion of the overall population.

It has been estimated that the 65-year-and-older section of society will account for 15 per cent of the Irish population by 2011, and 19 per cent by 2031, from a stable baseline of 11 per cent for the past 40 years (Irish Department of Health, 1999).

Of note, it is in the very old where the greatest increase in numbers will be seen (the number of those over 80 years of age is expected to increase by 66 per cent by 2035) [see figure across].

The macula is the specialised central part of the retina, which is responsible for central and colour vision. Age-related macular degeneration (AMD) is the leading cause of blind registration in the western world. Epidemiological studies carried out in different countries have been remarkably consistent, and all have demonstrated that the amount of vision loss and eye disease increases dramatically with increasing age. For each decade over the age of 40 years, the amount of blindness and vision-loss increases threefold.

Some 48 per cent of all cases of blind registration in persons aged 40 years and over is attributable to AMD. This is seen in about 2 per cent of the 70-to-80-year-old age group, 4 per cent in the 81-to-84-year-old (inclusive) group and 13 per cent in those aged 85 and older. Unsurprisingly, and since the ageing of society is an unprecedented phenomenon, AMD accounted for only a tiny proportion of blindness at the start of the 20th century.

It has been estimated that 80,000 people suffer from AMD in the Republic of Ireland (Fighting Blindness, Ireland, 2007), 417,000 people in the UK, and more than 1.75 million individuals in the US. These figures are expected to double by 2020.

The impact of vision loss secondary to AMD is manifested in an inability to drive, read, recognise faces or watch television, with a consequential loss of social independence in an era of declining family support and lengthening periods of retirement.

When asked what health condition they fear most, one third of people will identify blindness, another third will identify cancer, and the final third will identify a wide range of ailments or fears.

However, most people regard it as unlikely that they will ever develop blindness or vision loss. Indeed, health policy makers also regard vision loss as being of relatively minor importance or priority. It is worth emphasising that even small degrees of visual impairment have important adverse impacts on the quality and length of life.

For example, vision of 6/12 (~80 per cent) or less is associated with the following: loss of driving licence; increased risk of falls, hip fractures and depression; loss of social

independence; admission to nursing homes three years before their counterparts with normal vision; and a reduced ability to enjoy healthy and independent ageing.

The overall cost of sight loss in Ireland is approximately €400 million annually, with a significant part (33.3 per cent) of these costs attributable to AMD (report by Fighting Blindness Ireland, 2006). The cost of AMD to the Irish economy is estimated to be in the region of €133 million per annum.

The cost of vision loss and impairment to society and to healthcare providers cannot be overlooked. For example, the Global Burden of Disease, published in 2006, revealed that vision loss in aggregate ranks as the sixth most important cause of disability. The cost of vision loss and impairment may be classed as direct and indirect.

The indirect costs include the loss of earnings (by the patient), the cost of caregivers and nursing homes and other costs (e.g. transport). Direct costs include hospital care, outpatient and office visits, optometry costs, drugs and other direct medical expenses. For example, in Australia the direct costs of vision disorders cost as much as diabetes and asthma combined.

The number of people over the age of 65 years is expected to double in the next 20 years, when the overall population will increase only by about 20 per cent. Therefore, the number of Irish people with AMD-related vision impairment will increase from 80,000 to 160,000 over the next 20 years. Also, the cost of eye care will increase much faster than population growth because of the disproportionate increase in the elderly section of the population as a proportion of the overall population.

AMD may be classed as early or late, the former being asymptomatic and the latter causing loss of central vision if left untreated or if not amenable to treatment.

Relevant anatomy

The macula refers to the centre of the retina, and is the most sensitive part of the retina, and is responsible for colour vision and detailed central vision. The macula is essential for tasks that require good central vision such as reading, watching television, recognising faces and driving.

Early AMD

Early AMD is characterised by yellow white deposits (known as drusen) and/or pigmentary abnormalities (hyper- and/or hypo-pigmentation) at the macula, detected on ophthalmoscopy. Typically, early AMD is not associated with any subjective visual complaints on the part of the patient. However, early AMD represents the most important risk factor for late (and visually consequential) AMD.

Patients with early AMD should be warned of their increased risk of late AMD, alerted to the symptoms of late AMD (metamorphopsia, which refers to distorted central vision) and encouraged to attend their ophthalmologist on an urgent basis should such symptoms arise.

Successful management of late (neovascular) AMD depends on early presentation and intervention (see below). Novel and emerging technologies for the early detection of conversion to late AMD include microperimetry, relative sensitivity testing of photoreceptors and regular follow up with optical coherence tomography (OCT).

Also, patients with early AMD should be encouraged to reduce their risk of conversion to late AMD, and appropriate measures should include cessation of tobacco use, a healthy diet and supplementation with retinal antioxidants.

Late AMD

Late AMD is the result of choroidal neovascularisation (i.e. abnormal blood vessels growing from behind the retina) and/or atrophy (i.e. atrophy of the retina and choroid).

Late AMD is particularly frustrating because (if untreated or untreatable) it results in a loss of central vision. In other words, someone with late AMD can see everything except what he/she is looking at, and is therefore unable to read, watch TV, recognise faces or drive.

Patients with late atrophic AMD should be encouraged to take measures to reduce risk of disease progression, and such measures should include cessation of tobacco use, a healthy diet and supplementation with retinal antioxidants. However, it should be borne in mind that, currently, there are no known beneficial therapeutic interventions for the atrophic form of late AMD.

Fortunately, and in contrast, patients who are diagnosed with late neovascular AMD can be successfully treated, but need immediate and rapid referral to an ophthalmologist equipped to manage this condition. Indeed, appropriate treatment of neovascular AMD consists of intravitreal injections of a pharmacologic agent (anti-VEGF therapy) and is associated with a 90 per cent chance of improving or stabilising vision (40 per cent actually improve). This compares to 98 per cent risk of visual loss if left untreated.

Neovascular AMD is the result of overproduction of vascular endothelial growth factor (VEGF) in and behind the retina.

Anti-VEGF agents (such as ranibizumab), injected directly into the vitreous cavity, have been shown to dramatically reduce the risk of visual loss in neovascular AMD, and to result in visual improvement in 40 per cent of cases, and stabilisation of vision in a further 50 per cent. In contrast, the natural history of neovascular AMD is associated with a 98 per cent risk of permanent and irreversible visual loss.

Indeed, the ability of ranibizumab therapy to limit and/or reverse fluid accumulation at the macula as a consequence of neovascular AMD, and therefore to preserve and/or restore vision, has been proven. Two randomised, placebo-controlled, double-masked, clinical trials of ranibizumab (commercially known as Lucentis, Novartis) – the ANCHOR and MARINA studies – have demonstrated that intravitreal administration of this anti-VEGF therapy is associated with clinically and statistically significant benefits in terms of vision and in terms of the angiographically demonstrable lesions.

Successful treatment of neovascular AMD depends on the following conditions:

- I Treatment is instituted very early after the onset of neovascularisation, and before sub-retinal fibrosis (scar tissue) causes irreversible visual loss;
- I Treatment should consist of injections into the eye, spaced no more than one month apart;
- I Injections into the eye should continue in accordance with the evidence base, and should not be discontinued prematurely;

Of note, a diagnosis of neovascular AMD can only be made following fundus fluorescein angiography (FFA), consistent with the Guidelines of the Royal College of Ophthalmologists.

In other words, any ophthalmologist attempting to treat neovascular AMD should have immediate and direct access to FFA, and it is somewhat unsatisfactory if the ophthalmologist does not have direct access to FFA, because arranging, performing and interpreting the angiogram (without direct and immediate access) will often result in a delay of two weeks or more before appropriate anti-VEGF treatment can be instituted.

In other words, and given that speed of treatment is the most important determinant of visual outcome in neovascular AMD, any retinal specialist intent on treating neovascular AMD in the absence of immediate and direct access to FFA will find it very difficult to deliver best practice for these patients.

It is also crucial to understand that FFA should only be undertaken in a hospital environment, where a cardiac team is readily available because of the (albeit unlikely) possibility of an anaphylactic reaction.

Finally, access to FFA must be direct, immediate and available to patients at their initial consultation for suspected neovascular AMD, in an environment where a booking system is employed for scheduling the patient (there and then) for his/her intravitreal injection (if indicated).

A system where the patient is expected to return on another day for FFA is most unsatisfactory:

- I the FFA staff may be over-booked, and it might be two or three weeks before an FFA can be performed;
- I it involves yet another administrative link in the clinical pathway, which can lead to missed appointments;
- I it involves yet another journey for the patient and his/her family to the diagnostic/treatment centre;
- I the clinician will be unable to make a clinical decision at the initial consultation;
- I the clinician will be unable to demonstrate, using FFA images, the nature of the condition to the patient and his/her family;
- I the clinician will be interpreting the images days or weeks after the consultation, when the clinical context is no longer fresh in his/her mind;
- I a date for the injection of the therapeutic agent, if indicated, cannot be arranged at the initial consultation, thus adding further administrative links (e.g. phone calls, letters) to the patient's clinical journey;
- I an inevitable delay, and therefore clinical compromise, in the intravitreal administration of the therapeutic agent (if indicated).

It is important to note that, in order to have direct and immediate access to FFA, four things are required: a) a room to house the FFA; b) a nurse/technician to capture and archive the images; c) the FFA equipment; d) a cardiac arrest team.

Beyond FFA, OCT is also required for management and follow-up of patients with neovascular AMD. OCT allows the treating ophthalmologist to capture cross-sectional images of the retina, and therefore to monitor response to treatment.

In summary, the management of neovascular AMD (which involves monthly injections into the eye for at least one year, and in an elderly population), in the midst of the current epidemic of this condition, represents an unprecedented administrative and logistical burden on healthcare providers, patients and families.

Meeting the challenge of this burden is imperative, because the advantages of treatment versus non-treatment are well established, accepted and beyond dispute. Healthcare providers must create an environment where the diagnosis can be made at initial consultation, so that intervention can be rapidly scheduled when the patient and his/her family can agree a suitable date for treatment.

Furthermore, the healthcare provider must provide an environment where the intravitreal injections can be administered in a safe and efficient manner. Finally, ongoing follow-up care and appropriate administrative support are essential for successful visual outcomes in neovascular AMD.

The Institute of Eye Surgery at Whitfield Clinic, Waterford, has pioneered this patient-centred strategy in Ireland, and has an established AMD Treatment Centre which is meeting the logistical and administrative challenges of delivering best care to patients with AMD. References on request.

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