THE ROYAL COLLEGE OF OPHTHALMOLOGISTS

Focus

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Age-related macular degeneration

Age-related macular degeneration (AMD) remains the leading cause of blindness in the developed world. Over the past few years, not only our understanding of the pathogenesis has significantly improved, Lucentis therapy has also altered the prognosis of neovascular AMD patients.

Genetics

The observation that siblings of AMD patients are at high risk of developing the condition, suggested that AMD is a genetic disease. It is only in 2005, this hypothesis is confirmed; the polymorphisms of complement factor H (CFH) were associated with AMD. This was followed by several genes in the complement pathways showing similar association. Another important genetic region is in the 10q26, it remains controversial whether it is the HTRA1 or LOC387715 is the real culprit. The functions of either of these genes are poorly understood, so it might not matter for the time being.

Environment

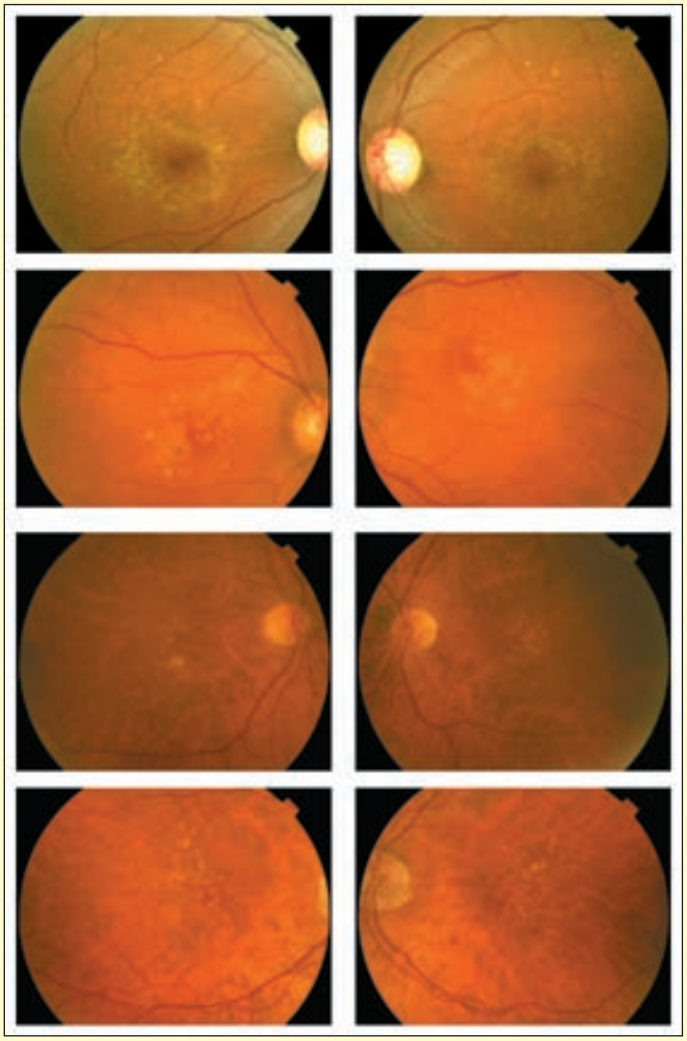
The most consistent environmental risk factor of AMD is smoking. There is evidence that smoking not only add to the risk of developing AMD but it multiplies the risk in those with "at risk" polymorphisms. One would argue no one should smoke, but smoking should be strongly discouraged in family members of AMD sufferers.

Lucentis

Lucentis is the first treatment in neovascular AMD that can significantly improve visual outcome. The pivotal trials used monthly injections. Over 1 year, over 40% of treated patients have significantly improved vision (>15 letters gain), about 75% have some improvement (>1 letter gain). About 5% have significant visual loss (>15 letters loss), most patients lose vision due to the deterioration of the atrophic component of the condition. Similar results maintained to 2 years.

It became clear that monthly injections are probably unnecessary, it is now usual practice to give 3 loading doses at monthly intervals, then patients are monitored monthly, patients are retreated if there are recurrences of fluids based on OCT, presence of new haemorrhage or further visual loss. At the moment, this scheme is not scientifically proven but there are several cases series support this scheme. There are controversies in the following areas:

- Does every patient need 3 loading doses?
- Do we need to review the patient monthly once the patient has been stabilised for a period of time?



Drusen – Many different types of drusen in different patients but the two eyes show remarkable similarities.

- Do we need to treat patient with subretinal fluid visible OCT but no visual loss?
- As the EMEA recommends retreatment of Lucentis only when there are more than 5 letter loss, do we need to do OCT at all?
- Can combination therapy with either PDT and/or steroid and most recently with local radiation, reduce treatment frequency and retain same efficacy?

At the time of writing (August 2008), the NICE guidance is still not issued. Nonetheless, it is likely that NICE will recommend the use of Lucentis based on the 3 loading doses and then as required. Both eyes can be treated. The drug will be provided for free by Novartis after 14 treatments on each eye. The transitional period could be problematic, as only new patients can join this dose capping scheme, anyone who was treated before either privately or NHS, they are not covered. One can argue that it might not matter as most of these patients will not need more than 14 treatments anyway.

Geographic atrophy

This is often forgotten as they are not commonly seen in clinic. In fact, for every 2 patients with wet AMD, there is 1 patient with end-staged GA, so about 12,000 new cases every year in the UK. This is the new frontier of AMD research. Over the past few years, it has become clear that GA is probably best monitored by autofluorescence (AF) imaging. This method gives high quality picture with well defined areas of atrophy. The difficulty of a drug trial in GA is that different patients might have different rate of progression. Several attempts had been made to predict progression but findings are inconsistent.

GA is generally believed to be caused by retinal pigment epithelial (RPE) dysfunction and eventually lead to cell death. One treatment strategy is to protect the cell by neuroprotection agents. Neuroprotective agents can be delivered by the encapsulated cellular technology, in which genetically modified cells that can produce growth factors are encapsulated inside an implant which is in turn surgical inserted into the vitreous cavity. As the cells are encapsulated, they do not interact with the host body and the immune cells cannot get into the implant to attack the foreign cells either. These agents can also be given as slow release biodegradable implant which can last 6 months or more. The whole implant is completely dissolved.

Fenretinide is an oral compound that decreases serum retinol by binding to retinol-binding protein, and promotes renal clearance of retinol. This in turn decreases the bio-availability of retinol for the RPE and photoreceptors. A2E, a retinoid by-product, is a major fluorophore in lipofuscin and a significant source of RPE cytotoxicity. It is hypothesized that by reducing toxic retinoid by-products of visual cycling, it can reduce GA progression.

Prevention of conversion to wet AMD

Despite Lucentis, patients with wet AMD have problems with reading, and most would not be able to drive. Furthermore, Lucentis is expensive; also the frequent visits to the hospital put a significant strain to the patient and the carers. There is no doubt that wet AMD prevention should be a research priority.

Biomarkers can be used to predict progression. Several biomarkers from complement factors, cytokines, matrix proteins and inflammatory markers had been identified in recent years. It remains unclear how to put that into clinical practice.

So far, the largest AMD treatment trial on prevention is the Alcon funded Anecortave Acetate Risk Reduction Trial. They studied whether anecortave acetate can reduce the conversion rate of the fellow eyes of patients with wet AMD. It was unfortunate that it has failed to meet the end point at 2 years and Alcon is no longer developing this drug further in the retinal area.

The original AREDS study can reduce conversion but it is plagued with controversy including the use of beta-carotene. There was also a media scare on the use of high dose vitamin E. More recently, excessive zinc accumulation is also found in AMD donor eyes. The take up rate of AREDS remains poor in most countries. Many epidemiological studies and laboratory studies supported the protective effect of macular pigment such as lutein and zeaxanthin. There is also evidence that omega-3 long chain polyunsaturated fatty acids can also prevent wet AMD. The AREDS2 study is now fully recruited and study both of these agents in combination with the original AREDS preparation.

Implantation surgery of advanced AMD

There are at least 2 implantation systems to be used in patients with advanced AMD. The implantable microscopic telescope (IMT) gives an x3 magnification, but a very restricted visual field. The implanted patient depends on the fellow eye for navigation but due to the high magnification, the patient can achieve very significant visual improvement. The IMT device is large and there is a risk of corneal damage during the surgery but the endothelial count appears to become stable after the initial loss. The IOL-VIP system is the only commercially available system; it gives a 1.3x magnification. It is based on 2 IOLs, one in the anterior chamber and the other in the posterior chamber, the company claims that there is a prismatic effect of the 2 IOLs allowing the image to be diverted to a healthier part of the retina. The benefit of this effect remains to be proven. The surgical risk is probably lower and it can be used in patients who are already pseudophakic. Personally, I found patients with poor vision in one eye and the implanted eye with pre-op vision in the range of 6/18 to 6/36 appears to do well. Patients with mid-range vision in both eyes would need binocular implantation.

Low vision support

Low vision support has a very low priority in the NHS. In most hospitals, it is not even an official service. Nonetheless it is a critical part of AMD management. There is going to be a Focus article on visual rehabilitation, so I am not going to discuss that further. However, we are starting a lobbying campaign to improve low vision support in the NHS and would value all your support.

Counselling and Emotional Support

Depression is extremely common in patients with AMD. The quality of life is often poor in AMD patients. It is often difficult for ophthalmologists to notice those problems during our rather brief consultation. Vision support workers in hospital departments are critical and often provide first line support when patients were told nothing can be done.

Charles Bonnet Syndrome

Visual hallucinations are very common in AMD patients, most patients do not dare to ask about it and often think that they have gone "crazy". In a recent Dutch survey of low vision units, that most units would not discuss Charles Bonnet Syndrome, despite it is in their National Low Vision Guideline. The Macular Disease Society and the RNIB are keen to increase the awareness of the syndrome. Most patients need to know the syndrome exists and it is common. Reassurance is what is usually need, and that can be done by an information leaflet or ask a direct question as part of the consultation.

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Victor Chong
Oxford Eye Hospital, University of Oxford