Updates in the Management of Age-Related Macular Degeneration

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Introduction

Age-related macular degeneration (AMD) is the leading cause of visual impairment and blindness among elderly patients in western countries and its prevalence is increasing due to aging of the population.1-4 In the United Kingdom, it has been estimated that around 3.5% of the population aged 75 years or older are visually impaired due to AMD.4 Due to westernisation of the Asian populations, the prevalence of AMD is also rising in various Asian countries. Therefore, clinicians should be aware of the recent developments in the management of AMD. This review aims to summarise some of the advancements in order to assist clinicians to have a better understanding in the management of this sight-damaging disease.

Classification of AMD

AMD can be broadly classified into the dry (non-exudative) and the wet (exudative) forms. Early AMD is characterised by the presence of drusens with or without pigmentary changes of the retinal pigment epithelium (RPE) or the neurosensory retina. Drusens are acellular debris within the RPE basement membrane and are seen as yellow spots at the macula on ophthalmoscopy. Small drusens are commonly seen in normal individuals as signs of aging, whereas higher number of large drusens are associated with AMD (Figure 1). In more advanced non-exudative AMD, patients may develop severe visual loss due to localised area of RPE atrophy known as geographic atrophy. The wet or exudative form of AMD is also known as neovascular AMD and is characterised by the development of choroidal neovascularisation (CNV) (Figure 2), pigment epithelial detachment (PED), and disciform scar formation in advanced cases. Although neovascular AMD only occurs in around 10% of patients with AMD, it disproportionately accounts for 90% of patients with severe visual loss caused by AMD.

The diagnosis of exudative AMD with CNV is established on fundus fluorescence angiography which involves intravenous injection of fluorescence sodium solution followed by a series of retinal photographs obtained using a special fundus camera. Visual prognosis of patients with neovascular AMD depends on the location and classification of the CNV. The Macular Photocoagulation Study (MPS) has previously demonstrated that direct laser photocoagulation may be useful in the treatment of CNV located outside the fovea (extrafoveal CNV).5,6 However, the visual prognosis of patients with CNV located at the central fovea (subfoveal CNV) is very guarded since 70% of patients with subfoveal CNV will have visual acuity of 20/200 or worse within two years.5,7 Laser photocoagulation is also not useful in these cases since the recurrence rate of CNV is high and patients will develop immediate loss of central vision after treatment.5,6 Therefore, until the development of photodynamic therapy (PDT) recently, there has been no effective treatment for patients with subfoveal CNV due to AMD.

Figure 1. Fundus photograph of a patient with dry (non-exudative) AMD characterised by drusen at the macula.

Figure 2. Fundus photograph of a patient with wet (exudative) AMD characterised by choroidal neovascularisation and scar formation at the macula.
Photodynamic therapy for neovascular AMD

Photodynamic therapy (PDT) is a two-steps procedure involving infusion and activation of a photosensitiser. It has the advantage over conventional direct laser photocoagulation due to its selective damage on the CNV while sparing any damage to the overlying neurosensory retina and RPE. This selective action is caused by preferential binding of the photosensitising agent to the low-density lipoprotein receptors present on CNV endothelial cells. After infusion of the photosensitising agent, a low-energy diode laser is used for activation of the drug, resulting in generation of highly reactive oxygen species such as free oxygen radicals and singlet oxygen molecules, thereby causing thrombosis and damage to the CNV.

The drug which is currently available for PDT in the treatment of CNV is verteporfin (Visudyne, Novartis, Switzerland). Treatment involves infusion of the 6mg/m² verteporfin over 10 minutes, followed by application of low-energy laser to the area of CNV for 83 seconds at 15 minutes from the commencement of infusion for drug activation. Repeat PDT with verteporfin is usually performed at 3-monthly intervals in patients with active CNV on fluorescein angiography. On average, patients will require two to three treatments in the first year and around one to two treatments in the second year. PDT with verteporfin is generally well tolerated and complications associated with PDT are uncommon. Around 3% of patients however might develop acute severe visual loss following PDT. Nonetheless, PDT with verteporfin remains the treatment of choice in patients with neovascular AMD at present.

Newer treatment modalities for neovascular AMD

Despite the efficacy of PDT with verteporfin, a substantial proportion of patients with CNV due to AMD will still develop significant visual loss. Another limitation of PDT is the high number of retreatment in some patients. Therefore, adjunctive and newer treatments have been proposed to improve the outcome in these patients. Studies have shown that combined PDT with verteporfin and intravitreal injection of triamcinolone acetonide may have a beneficial role in treating CNV due to AMD. Preliminary results in using inhibitors of vascular endothelial growth factor (VEGF) such as pegaptanib and ranibizumab for the treatment of neovascular AMD are also encouraging and these agents will certainly increase the armament for the treatment of neovascular AMD in the near future.

Prevention and prophylaxis for AMD disease progression

As the visual outcome following treatment of AMD is generally poor, management of AMD should also include controlling the risk factors for disease progression as well as early detection of disease progression. Patients with high risk clinical features of AMD like large number of soft drusens or neovascular AMD in the fellow eye should be educated with the symptoms of AMD progression such as new onset of scotoma or metamorphopsia. An Amsler grid is a simple but useful tool for self-examination and all patients with AMD should be taught how to use the grid to detect new onset of symptoms which might be indicative of CNV or disease progression (Figure 3). When new symptoms arise, patients should seek specialist care as soon as possible for dilated fundus examination and further investigations since early detection of CNV might allow better visual outcome after treatment.

Figure 3. Amsler grid for self-examination

Various epidemiological studies have also evaluated the risk factors for the development of AMD. Cigarette smoking is one of the most important risk factor for AMD and the risk of both non-exudative and exudative AMD development is higher in current smokers than ex-smokers. Therefore, all patients with AMD regardless of type should be advised to stop smoking. Recent evidence has also suggested that exposure to second-hand smoke will also increase the risk of AMD by nearly two-fold. Systemic hypertension is also an important risk factor for the development of neovascular AMD and patients with hypertension should be followed more carefully for the development of advanced AMD.
Other modifiable risk factors for AMD include hyperlipidemia and cardiovascular diseases and these co-morbidities should be kept under optimal control.25

Antioxidants have been proposed to have an important role in the development of AMD and might be useful for prophylaxis of AMD. The Age-related Eye Disease Study (AREDS) is a multi-center randomized controlled clinical trial which investigated the role of high dose vitamin antioxidant supplementations in the prevention of AMD progression.26 The results showed that high dose supplements of vitamin C (500mg), vitamin E (400 IU), beta-carotene (15mg), zinc (80mg) and copper (2mg) could delay the progression of intermediate AMD to advanced AMD. It was also beneficial in delaying AMD progression in the good eye in patients with advanced AMD in the fellow eye. This antioxidant formulation should therefore be considered in patients with moderate AMD or with advanced AMD in one eye for prophylaxis treatment of AMD. Patients who smoke should be warned of the potential risk of beta-carotene supplements due to increased risk of lung cancer among smokers found in previous randomized controlled trials.27

Conclusions

The impact of AMD in our society is likely to increase in the near future due to aging and westernization of the population. In view of the substantial burden of disease caused by visual impairment, it is important for all clinicians to be aware of the disease as early detection of AMD especially neovascular AMD may improve the visual outcome after treatment. More effective treatment modalities are becoming available and will have the potential to further improve the visual outcome in these patients who were untreatable just less than a decade ago.

References