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Management of age-related macular degeneration: what is the choice in the new millennium?

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There are few other diseases in ophthalmology, if any, as intriguing and controversial as age-related macular degeneration (AMD) in respect of pathogenesis or management. The disease may present as a dry atrophic form or a wet exudative form with choroidal neovascularization (CNV). It is usually thought that AMD affects Caucasians more than Asians, although this condition has been increasingly recognized in Asians in recent years.^{1,2} In Hong Kong, AMD became the fourth commonest cause of new registration for permanent blindness in 1998, accounting for 11.3% of cases (Table 1).³ As life expectancy increases, more and more patients will present with this condition in the coming years; similar findings have been observed in other countries.⁴

Despite the huge amount of effort and resources put into the research of AMD, its pathogenesis is still not fully understood. Genetic and twin studies suggest a genetic predisposition which may explain the varying incidence and presentation in different races.^{5,6} Epidemiological studies demonstrate possible risk factors such as smoking, ultra-violet exposure or cardiovascular disease.⁷⁻¹⁰ Several case-control and experimental studies have supported the theory that antioxidants may play a protective role against the development or progression of AMD, but the findings have been inconsistent and conflicting.¹¹⁻¹⁴

Laser photocoagulation is still the only treatment with proven benefit for patients with exudative AMD.¹⁵⁻¹⁷ However, only

a small proportion of these patients have well-defined CNV in the extra-foveal or juxta-foveal location which can be treated without dramatic harm to the remaining vision. The great majority of patients have poorly defined or occult membranes which are not amenable to laser treatment. Patients with subfoveal CNV have to risk an immediate drop in their central vision after laser treatment and their relative scotoma converted to a more disturbing absolute scotoma in the hope of having more stable vision after a few years.¹⁸ The Macular Photocoagulation Study shows that only 13% of patients who have fluorescein angiography (FA) done are actually eligible for laser treatment and the recurrence rate is as high as 50%; only about 6.5% can be successfully treated. Recent studies with indocyanine green (ICG) guided photocoagulation demonstrates that an additional 25% of

Table 1. Major causes of new permanent blindness registration in Hong Kong, 1997 to 1998

Cause	Percentage of patients
Glaucoma	19.5
Diabetic retinopathy	14.0
High myopic macular degeneration	12.1
Macular degeneration (other than myopic degeneration)	11.3
Cataract and related complications	8.4
Corneal pathology	7.7
Others	27.0

patients can be treated by laser according to the 'hot spot' shown in ICG.^{19,20} However, recurrence occurs in almost two thirds of the patients. This means that, by combining FA and ICG guided treatments, about 15% can be successfully treated at present.²¹

Limitations in laser therapy have stimulated interest in other modes of treatment for AMD. Different forms of medical treatment have been studied based on various theories. First of all, avoidance of possible risk factors such as smoking and ultraviolet exposure, or control of cardiovascular diseases is a simple and logical approach and offers additional benefits to the general health of elderly patients. Pharmacological therapy is an attractive and theoretically sound mode of therapy and may act as a prophylactic treatment. The first agent that has been intensively studied is interferon α -2a because of its antiangiogenic effect. A number of preliminary reports suggested its usefulness in treating subfoveal CNV. However, although the agent has been shown to be effective in treating hemangiomas in infants and the vascular Kaposi sarcoma in acquired immunodeficiency syndrome, a randomized, placebo-controlled, parallel, multicenter double blind trial demonstrates that it provides no benefits over placebo for treating AMD.^{22,23} Other antiangiogenic agents have been studied, such as amiloride, thalidomide and triamcinolone, but no clinical usefulness has been shown.

Micronutrients are another attractive form of treatment for AMD and may be the only form of treatment for the atrophic type of AMD. In some places, there is widespread use of commercially available vitamins and minerals to treat AMD without definitive study on their safety and efficacy. It is hypothesized that light exposure causes liberation of oxygen free radicals which damage the outer retina and, by oral ingestion of micronutrients and minerals which have inherent antioxidant capabilities, peroxidation of long-chain polyunsaturated fatty acid in the photoreceptor membrane is inhibited and degenerative changes of AMD could be prevented.²⁴ This theory is supported by animal studies which show that antioxidants can prevent retinal degeneration;²⁵ case-control studies also suggest that people with higher plasma level of antioxidants are less likely to develop AMD.²⁶ However, some of the data do not reach statistical significance and other studies produce inconsistent findings.^{11,14} Currently, a long-term multicenter prospective study, the Age Related Eye Disease Study, is being conducted in the USA to address specific questions as to the benefits and risks of micronutrients for AMD. It is hoped that this study will provide more solid evidence for the role of micronutrients in AMD. In a review paper in this issue, Dr Wolfgang Schalch thoroughly discusses the possible role of carotenoids in reducing the risk for AMD and the readers will find it very interesting.

Several experimental surgical therapies for AMD have also been studied in recent years; these include surgical excision of CNV,^{27,28} retinal pigment epithelium (RPE) or iris pigment epithelium transplantation,²⁹ various forms of macula translocation,³⁰⁻³² and even use of a macula buckle.³³ Although

surgical excision of CNV is technically feasible and has attracted strong interest from vitreo-retinal surgeons, visual results are usually disappointing.^{27,28} These may be due to surgical trauma to the photoreceptor or RPE, RPE removal along with CNV removal with inadequate repopulation after surgery, subretinal scarring in the dissection bed, secondary choriocapillaris atrophy, or recurrence of CNV.³⁴ It is believed that RPE plays an important role in the function of photoreceptors and pathogenesis of AMD. Such belief leads to research on RPE transplantation²⁹ and macula translocation, which is receiving great attention as a treatment for subfoveal CNV. Several surgical techniques of macula translocation have been reported including peripheral retinotomies from 180° to 360°, or scleral shortening or outpouching without large peripheral retinotomies.³⁰⁻³² The surgical results so far are unpredictable with a high incidence of complications; however, in some successful cases, significant visual improvement has been reported which is rare with other forms of treatment.

Other forms of treatment for AMD that have been widely studied in recent years include laser photocoagulation of macula drusen,³⁵⁻³⁷ radiation therapy³⁸⁻⁴⁰ and photodynamic therapy (PDT).^{41,42} It has been observed that laser photocoagulation induces resolution of drusen treated directly as well as those located away from the laser scars. The mechanism involved is uncertain, but may be due to destruction of degenerating RPE cells, stimulation of macrophages and other phagocytic cells that remove the directly or indirectly treated drusen, or opening up channels that facilitate transport of RPE debris.³⁵ However, large scale studies showed that the disappearance of drusen is not associated with a lower incidence of CNV or visual loss in the treated eyes.^{36,37}

The scientific rationale for using radiation therapy for CNV is based on evidence that proliferating endothelial cells are susceptible to radiation. Several pilot studies suggested that patients treated with radiation for CNV may experience less visual acuity loss,^{38,39} but recent prospective multicenter randomized clinical trials show that radiation therapy has no benefit as a treatment for subfoveal CNV⁴⁰ and some patients may develop a bleb-like choroidal neovascular complex called radiation-associated choroidal neovascularopathy.⁴³

PDT appears to be a promising new form of treatment for subfoveal CNV. A photosensitizer dye that accumulates in actively growing neovascular tissue is injected intravenously followed by activation with a non-thermal laser. The therapy is effective in stabilizing subfoveal CNV in more than half of the patients treated without causing damage to the overlying neurosensory retina. However, fluorescein leakage from the CNV usually reappears by 4 to 12 weeks requiring repeated treatment.^{41,42} The results for occult CNV are also less satisfactory. Moreover, the cost of the currently available drug is quite high, limiting its use in many places.

With the wide array of possible treatment options available, none of which is really curative, ophthalmologists are facing

a dilemma as to what to do and how to advise patients with AMD. To whom should the general ophthalmologists refer their patients? Vitreo-retinal surgeons may wonder if it is time to translocate a macula or whether it may be safer to start PDT first. Such uncertainties would make it difficult to give fair and sound advice to patients. On the other hand, with ready access to the latest information through the internet and mass media, coupled with the widespread dotcom frenzy, the more intelligent patients would possess more knowledge of their disease than the busy practicing ophthalmologists and demand the 'latest breakthrough' treatments, which their doctors have not heard of.

The solution to this dilemma lies in the profession's effort to run and coordinate properly conducted research studies and trials to give more conclusive evidence of the pathogenesis, natural course and benefits of various forms of treatment. It is also important to be prudent in interpreting data from research studies to avoid bias leading to confusing results. In Chinese and Asians, relatively little information is available on the natural course, presentation, or treatment response of AMD patients. In this issue, Dr K.W. Wu presents a report on the angiographic findings and outcome of patients with AMD in Hong Kong. It is believed that genetic predisposition and environmental influences interact in a complex manner to produce the disease. Chinese in Hong Kong frequently lead a western style of living. A comparison of the manifestation of AMD in Chinese patients in Hong Kong with those living in rural China or Western countries would give clues as to the importance of environmental influences. While genetic predisposition probably could not be altered by medical means in the near future, environmental influences may be controlled and treatment measures can focus on this. Instead of sophisticated and expensive treatment, it is possible that AMD can be prevented or delayed by simple means or measures. Dr K. W. Lam, in his paper on the nutritional value of *Gou Qi Zi*, discusses the interesting structure and function of the seed *Gou Qi Zi*, which has been said to be beneficial in improving vision in traditional Chinese medicine for thousands of

years. Its high zeaxanthin content has only been elucidated in recent years and further research will be useful to prove its value in preventing retinal degeneration.

In the past decade, a distinct form of disorder causing hemorrhage or exudation in the macula similar to exudative AMD has been described as idiopathic polypoidal choroidal vasculopathy (IPCV). This disorder can occur in any race, age or sex, but is more commonly seen in middle-aged non-white female patients, with a marked variation in the morphology and natural course.^{44,45} In Dr K. W. Wu's report, two such cases were identified of the 14 ICGs performed. Although its pathogenesis and relation with AMD is still uncertain, IPCV tends to have a spontaneous resolution of exudation and hemorrhage, and a better visual prognosis. Furthermore, IPCV can be more effectively treated by direct laser photocoagulation than CNV. Such findings are important for the management and counseling of our patients, suggesting that ICG should be done more routinely in patients with exudation or hemorrhage of the macula.

Macula degeneration was once thought to be rare in East Asians. This is now shown to be wrong; or at least has become untrue. The increase in its incidence is unlikely to be due to the aging of the population alone, and may indicate the influence of environmental pressures. The expenses incurred for investigation, treatment, and rehabilitation of these patients will place a great burden on society. The poor outcome with current management indicates that there is an urgent need to undertake further research in this area to test the importance of genetic factors, life-style or nature of environmental influences. With modern molecular genetic techniques, the genes responsible for AMD or IPCV may soon be identified. Because of the differences in genetic predisposition, characteristics, and natural history of the disease between Asians and Caucasians, the results from studies undertaken in Western societies cannot be assumed to pertain to East Asia. In the quest for an effective treatment for AMD, it is also time for us to think hard and reassess our role in the development of medicine.

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