Age related macular degeneration: from evidence based-care to experimental models

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Abstract: To describe the current aging population in China and globally, especially as it applies to age-related macular degeneration (AMD). To review the current standards of care for treating both wet (exudative) eAMD and dry (atrophic) aAMD. And to introduce a model for experimentation that is based on the Age-Related Eye Disease Study (AREDS) using eye bank tissue. A literature search that outlines current aging populations, standards of clinical treatment as defined by large, multicenter, randomized clinical trials that present level-I data with a low risk for bias. An experimental model system of AMD is presented that enables scientific analysis of AMD pathogenesis by applying grading criteria from the AREDS to human eye bank eyes. Analysis includes proteomic, cellular, and functional genomics. The standard of care for the treatment of eAMD is currently defined by the use of several anti-vascular endothelial growth (anti-VEGF) agents alone or in combination with photodynamic therapy. Monotherapy treatment intervals may be monthly, as needed, or by using a treat-and-extend (TAE) protocol. There are no proven therapies for aAMD. AMD that is phenotypically defined at AREDS level 3, should be managed with the use of anti-oxidant vitamins, lutein/zeaxanthin and zinc (AREDS-2 formulation). By understanding the multiple etiologies in the pathogenesis of AMD (i.e., oxidative stress, inflammation, and genetics), the use of human eye bank tissues graded according to the Minnesota Grading System (MGS) will enable future insights into the pathogenesis of AMD. Initial AMD management is with lifestyle modification such as avoiding smoking, eating a healthy diet and using appropriate vitamin supplements (AREDS-2). For eAMD, anti-VEGF therapies using either pro re nata (PRN) or TAE protocols are recommended, with photodynamic therapy in appropriate cases. New cellular information will direct future, potential therapies and these will originate from experimental models, such as the proposed eye bank model using the MGS, that leverages the prospective AREDS database.

Keywords: Age-related macular degeneration (AMD); age-related eye disease study (AREDS); eye bank model; evidence based review; epidemiology review

Introduction

According to the United Nations global demographic estimates, the number of individuals over 60 years of age is expected to double over the next 35 years from just under 1 billion in 2015 to over 2 billion by 2050 (1). The vast majority of this growth is expected to occur in Asia with much smaller percent increases in Europe and North America (1). Considering this rapid increase in the >60 year old demography globally, with disproportionate increases in Asia and China, the number of age-related macular degeneration (AMD) cases is expected to increase proportionately.

AMD has a profound effect on an individual's quality of life. Brown *et al.* have estimated that when the visual acuity is 20/50 or worse in the better eye, the quality of life decrease approximately 40%, equivalent to cardiac angina or a hip fracture (2). Furthermore, with more severe

AMD and a visual acuity in the better eye of 20/200 or worse, the quality of life is reduced 60% or equivalent to advanced prostate cancer, a catastrophic stroke, or being bed-ridden (2). Thus, AMD is common and the impact on quality of life is severe.

A leading modifiable risk factor for AMD is smoking (3-7). In China, there are an estimated 300 million smokers who are over age 15 (8,9). Thus, the burden of combining a rapidly aging population with a high prevalence of smoking, suggests that those who are over age 60, will be at even higher risk, albeit a preventable or modifiable risk factor. Yet another modifiable risk factor for progression of AMD is obesity (10). Childhood obesity is increasing rapidly in China with estimates from Shanghai of 4% in 1991 to 14% by 2005 (11). Thus, by combining increasing obesity with current smoking patterns in China, there will be a dramatic increase in the prevalence of AMD in the next 35 years for those over age 60. These factors will likely predict a tremendous burden of AMD in Asia, and particularly in China.

Current treatments for AMD has improved dramatically over the past 20 years and has shifted largely from laser based treatments for end-stage disease, to pharmacologic therapy and photodynamic therapy. Prevention has focused largely on life-style modification, such as smoking cessation, diet, and exercise. The use of anti-oxidant vitamins and zinc supplementation as defined by the Age-Related Eye Disease Study (AREDS) reduces the rate of progression in at-risk individuals (12). The treatments for exudative AMD (eAMD) largely rely on the use of multiple intravitreal injections with anti-vascular endothelial growth factor (VEGF) agents. A review of the studies that outline the various agents and their injection intervals is reviewed.

Literature review

When a clinician reviews the literature on a given topic and determines the best treatment plan or option for a given patient, awareness of the most relevant, published data and an understanding the quality of the data is critical. An excellent source of information that summarizes recent data on major topics in ophthalmology, such as AMD, is the preferred practice patterns (PPP) as published by the American academy of ophthalmology (AAO) (13). The PPP's are based on an updated Cochrane literature reviews of a particular topic that is then analyzed using the Scottish Intercollegiate Guidelines Network (SIGN) (14). These guidelines assess the level of study, then analyze the quality

of the work and summarize the evidence. Next, a team of clinicians provide the judgement, based on evidence combined with expertise in clinical practice, to issue a graded recommendation. The grade of the recommendation [grading of recommendations assessment, development and evaluation (GRADE)] (15), is based upon a recommendation that balances both the risks and benefits of the proposed therapy. The clinical group's combined knowledge on the topic provides relevant judgement from the clinical arena that adds further weight to the methodologically derived data in the literature.

Evidence based AMD guidelines and recommendations

In 2001, the AREDS, for the first time, clearly demonstrated that the use of anti-oxidant vitamins with zinc supplementation was beneficial for those over 55 years of age who had non-central geographic atrophy, extensive intermediate (63–125 micron) drusen, or at least one large druse (>125 micron) (12). More recently, in 2014, a report indicating that the beta-carotene component of the AREDS supplement could be effectively replaced with lutein/zeaxanthin (due to the cancer risk in smokers taking beta carotene) and the suggestion was to use the newer formulation of the AREDS supplement (AREDS 2) for those individuals who are at risk (16). Thus, such individuals should be advised to use supplements according to the criteria outlined in the AREDS. In the United States, estimates suggest that if those who should take the AREDS supplement actually followed these guidelines, that over 300,000 individuals, during a 5-year period, would avoid progression to more advanced AMD (17). If this data were extrapolated to the Chinese population, the order of magnitude is extraordinary. Thus, for those individuals who are over 55 years of age and have high-risk features, recommendation of using the AREDS 2 supplement is important. Furthermore, the use of beta-carotene in smokers should be avoided (18).

The role for the use of anti-VEGF agents in the management of eAMD has been addressed with very solid, high-quality data derived from numerous randomized clinical trials (19-23). Following the use of intravitreal anti-VEGF agents, the prior differentiation of occult or classic neovascularization criteria for determining treatment is no longer relevant for clinical management. Instead, the use of ocular coherence tomography (OCT) to determine the presence or absence of fluid in or under the

neurosensory retina is the key determinant for managing eAMD (24). Using SIGN and GRADE criteria, all of these four key studies (19-23) demonstrate high-quality, level-I data that have a high chance for reproducibility and demonstrate a rather dramatic, beneficial treatment effect. The comparison of anti-VEGF to either photodynamic therapy or observation clearly had a dramatically beneficial treatment effect that sets the basis for the current standards of care in eAMD. Is there bias in some of this data? The answer is quite likely "yes". However, given the size of the data-set, the dramatic and consistent treatment outcomes, the consistency found from multiple studies, and the unlikelihood that further studies would change the outcomes, all underscore the profound benefits of intravitreal anti-VEGF treatment.

In Asian populations, the incidence of idiopathic polypoidal choroidal vasculopathy (PCV) is higher than in Caucasian populations. The Everest study demonstrated that PDT combined with verteporfin was superior to monotherapy with ranibizumab (25). While a similar finding was not confirmed in Caucasian populations, combination therapy seems warranted in Asian patients who are suspected of having PCV (26).

The next topic surrounding the use of anti-VEGF therapy is dosing frequency. There are two basic patterns for treatment. The most recent, major study compared monthly to every other month (q8 weeks) (19). The agent that demonstrated equivalence at every 8 weeks was aflibercept, perhaps because of either advantageous pharmacokinetics of the agent or a higher binding affinity of the VEFG-trap molecule to the VEGF protein. Following the introduction of this frequent dosing regimen into clinical practice, clinicians began to shift to dosing schedules referred to as either pro re nata (PRN), or treat-and-extend (TAE). Using the PRN methodology, all patients returned monthly with an OCT that helps to guide therapy. If fluid is present within the neurosensory retina, between the neurosensory retina and the retinal pigment epithelium (RPE), or in some cases, under the RPE, anti-VEGF treatment continues. However, when using PRN treatment and the OCT does not demonstrate fluid, the injection is held for that visit with the patient returning in one month for re-assessment. In the major studies, caution was raised when using bevacizumab on a PRN basis as opposed to monthly injections because there was a greater chance of having persistent fluid and a lower chance for gaining visual acuity (27). Therefore, when using bevacizumab, PRN treatment is less favorable than monthly injections.

Many retina specialists are choosing to use the TAE protocol. The LUCAS study is a key study that analyzes the TAE method in a scientifically rigorous manner, comparing bevacizumab and ranibizumab using TAE (28). In this study, eyes were examined every 4 weeks until no fluid was detected on OCT imaging. At that point, an injection is administered as opposed to the PRN protocol when no treatment is given when there is absent fluid. However, in the TAE arm, the interval for follow-up is extended by 2 weeks at a time with injections given at each interval up to a maximum of 12 weeks. When there is a sign of recurrence, as assessed by the presence of fluid on OCT, the interval was then shortened by 2 weeks. At one year, more bevacizumab injections required 4 week injections while more ranibizumab treated eyes were able to TAE to 12 week intervals. Overall, the visual acuity benefits were similar between the two groups (28).

Despite the dramatic visual acuity improvements in the management of eAMD, multiple studies now demonstrate that with long-term follow-up, from 5 to 7 years, the visual acuity returns to baseline or worse than baseline (29-31). Thus, the pathogenesis of AMD is not due to neovascular growth and leakage alone and progresses despite treatment. Likely, the etiology is multifactorial with anti-VEGF addressing only one, yet a very important component, of end-stage eAMD. The search for treatments that address other pathways at earlier stages of AMD remains a current focus of research.

At this time, there are no proven therapies that address the slowly advancing forms of dry or atrophic AMD (aAMD). Proposed treatments include factors that address the complement system. The MAHALO phase II clinical trial investigated the role of an antibody to complement factor D (lampalizumab) (32). This early phase study demonstrated a possible reduction in progression of geographic atrophy as compared to sham therapy. However, recent phase III studies have failed to confirm these earlier findings.

The role of stem cells in the treatment of aAMD is at an even earlier stage in development, yet such therapy also holds future promise. Schwartz *et al*. (33). have performed a phase I/II clinical trial in a small number of patients who received subretinal injections of human embryonic stem cells (hESC). This data is too early and the number of cases are far too small to derive any further conclusions. However, cellular therapies my offer hope for the management of aAMD.

An experimental model

In our studies to investigate early mechanisms of AMD, we used human eye bank eyes both to study the pathogenesis of AMD and to look for early markers of disease. We developed a system that uses the AREDS grading criterial and enables an identical analysis that is performed on human eye bank eyes. We refer to this system as the Minnesota Grading System (MGS) (34). Since there is no animal model of AMD, we believe that this method of study, albeit non-interventional, is the best way to examine for early changes that are occurring at the cellular level. We found that gene expression data is valuable, when we replicated the process of eye bank tissue procurement in pig eyes. It is important to procure the eyes and preserve or freeze them within 6 hours of death (35). We tested various stages of the MGS using known anti-oxidant proteins and found that the quantitative expression of these proteins (i.e., superoxide dismutase) matched exactly what would be predicted by the stages in the AREDS (36). We have found many other proteomic changes in relevant stages of AMD progression. For example, there is an increase in the inducible subunits of the immunoproteasome (37), altered expression of proteins that are critical for mitochondrial function (38), and mitochondrial DNA mutations is differentially affected MGS 3 differently than in age-matched controls (39), Using the choroidal tissue, we've also worked with Dr. Chi-Chao Chan and her key investigators at the National Eye Institute to assess the genotype risks for polymorphisms of complement factor H and the *HtrA1* genes (40), macrophage polarization in the choroidal tissues (41), and expression of inflammatory mediators such as interleukin-17A (IL17A) (42).

We have further enhanced our tissue analysis of AMD eyes by obtaining fundus autofluorescence that enable us to assess the status of this clinically relevant imaging technology (43). Correlating fundus autofluorescence with biochemical analysis of human tissue ex-vivo will be useful for studying pathogenesis, especially for aAMD. Furthermore, we now have histopathology of the tissues as it corresponds to each of the four key AREDS stages as translated through the MGS (44). The histopathology links very closely to the know pathogenesis of the clinical condition and helps to validate this imaging methodology. Recently, we have refined the MGS grading system to achieve an even higher level of phenotypic risk as defined by the AREDS by dividing the stages into a 9-step severity scale (45,46). Thus, we believe that further studies, using either the current or an enhanced MGS system, will reveal pathways and potential targets for future intervention.

Conclusions

Managing patients with AMD requires a careful study of the available literature, sound judgement, and a working knowledge of the stages of AMD. The AAO produces regularly updated PPP's to help clinicians determine the best management strategies, as assessed using both professional methodologists combined with a group of clinical experts who review the available and relevant literature. This process involves a careful analysis to assess the overall study quality and minimizes the risk of bias.

In China, the incidence of AMD is likely to increase dramatically over the next 20–40 years. This increase is due to several key demographic factors that include an aging population, a high incidence of smoking, and increasing obesity. Thus, a working knowledge of this population and the evidence-based treatment options is critical to minimize the impact of AMD-related blindness. PCV is more common in this population and consideration should be given to combination anti-VEGF and PDT when appropriate.

Further studies are required to determine factors other than anti-VEGF treatments for AMD and these studies will facilitate a careful, scientific analysis of AMD pathogenesis. The AREDS is the largest clinical data base that gathers prospective, natural history of patients with AMD. The phenotype can predict, with a high level of accuracy, the 5-year risk for progression to more advanced forms of AMD. Using the MGS, we hope to leverage this large database in order to determine mechanisms and possible therapeutic targets that address earlier stages of AMD, and prevent the more advanced and blinding stages that leads to a dramatic decrease in overall quality of life for those affected.

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Footnote

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