Chapter

Introductory Chapter: Advances in Management of AMD

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1. Introduction

The road from research to clinical care is a long one due to various reasons and is not entirely unjustified. In the urge for progress and "new science," one should remain vigilant in assuring that no harm is caused to the patients we serve. To this accord, the anti-VEGF therapy and the AREDS trials [1, 2] have been a game-changer in management of neovascular and atrophic macular degeneration (dry-AMD). The AREDS trials gave us evidence-based guidance on when and how to manage to prevent the progression of the disease. Whereas the neovascular AMD the vision loss is sudden, the dry-AMD the vision loss is slow and patients are unaware of the changes undergoing in their eyes. Like many other chronic diseases, dry AMD suffers from issues related to early diagnosis. The drusen that is so hallmark of dry-AMD are also seen in individuals that do not have AMD or at least not yet. How does one go about determining when the changes in retina are "normal" age-related changes or the onset of early dry AMD? The AREDS simplified grading scale [3] for AMD is a good start and the Beckman Classification System [4] improves upon the AREDS simple classification system. In the early stages of the disease dry-AMD does not show overt changes in visual function like visual acuity changes but if more challenging tasks are presented like visual function in dim illumination one indeed shows a decline. When an individual presents with a challenge in diagnosis or if the doctor would like to detect progression of the disease one could utilize extended functional testing to determine changes to visual function.

2. Functional testing and dry-AMD

Doctors have used screening color vision tests like red cap tests, Ishihara, and d-15 very successfully and they indeed have their place in our clinics. However, when investigating early visual dysfunction one may need quantifying threshold strategies. The Rabin Cone Contrast Test® is a threshold test that is helpful as an early detection strategy for various diseases. The use and benefits of color vision testing in early detection of disease and its progression is not a new concept. Numerous diseases such as diabetes cause changes to color vision prior to the onset of retinopathy [5]. The Duke University School of Medicine researchers used a variety of visual function tests and structural measurements to identify progression in early AMD and intermediate stage AMD [6]. The overarching goal was to detect progression in AMD in a short period of time and to identify useful endpoints for future clinical trials. They utilized Rabin Cone Contrast Testing® to isolate the three cone types and determine the cone contrast thresholds. This device uses precise calibration, and letter optotypes in red, blue, or green color that a patient is asked to recognize and report. This isolates and allows testing of the individual

cone system's integrity whilst assuring that the other cone types are suppressed. This longitudinal study of visual function in dry-AMD showed that the Rabin cone contrast testing was able to detect changes in color vision due to progression of dry-AMD within a period 12-month [6]. These results highlight the fact that detection of progression in a short duration allows possibility for early intervention and prevention of progressive vision loss.

3. Measuring macular pigment may be key to appropriate care

One does not expect a general physician or endocrinologist to manage diabetes without blood glucose measurements or A1c values and yet eye care providers often manage dry-AMD without knowing baseline macular pigment optical density (MPOD) values. It is true that low MPOD does not mean one has AMD, but a lower MPOD is a known alterable risk factor of AMD. It is postulated that early and intermediate stages of maculopathy are predominated by oxidative stress and low-grade inflammatory activation in aging retinae [7, 8]. Thus, it is not surprising that patients with dry-AMD benefit from treatment using antioxidant therapy. The MPOD is known to vary among various ethnicities [9] and its level depends upon the dietary intake of carotenoids as they cannot be synthesized in the human body [10, 11]. The supplementation of carotenoid-vitamin therapy has indeed shown benefits in dry-AMD however these benefits are not universal [1]. There could be various reasons for the difference in benefits observed, for example, the amount of damage to the retina or bioavailability of these supplements. Given that eye is the end organ that needs to benefit from these therapies, the levels of MPOD at the fovea must increase with these therapies. The current clinical gold standard in measuring MPOD is heterochromatic flicker photometry which is a psychophysical test [10, 12]. The measurement of MPOD clinically as a baseline and during clinical follow-up allows for assessing the patient compliance to taking the nutritional supplements and assuring that the nutritional supplements are bio-available, and carotenoids are indeed reaching the end organs. The AREDS trials [1], unfortunately, did not measure MPOD. This may be due to its difficulty and inability to obtain reliable measurements as advanced stages of dry-AMD which is accompanied by less-than-optimal visual acuity.

The measurement of MPOD in poor test-takers and individuals with suboptimal visual acuity may be addressed by objective techniques of measurement of MPOD which do not depend on or require too much subjective input. There are various objective measures used in research laboratories that could provide a quick and reliable measure of MPOD. These include dual-wavelength autofluorescence techniques [13], resonance Raman imaging [14], and Macular Pigment reflectometry [12, 15]. The Macular Pigment Reflectometry not only can provide a repeatable MPOD, but also lutein and zeaxanthin optical density values [12, 15]. The MPOD values measured using the Macular Pigment Reflectometry technique closely match heterochromatic flicker photometry [12]. The measurement of an individual's lutein and zeaxanthin optical density in-vivo in a period of 30-seconds approximately offers significant clinical advantages when applied to individualized or personalized medicine. It could help answer various fundamental questions and enhance our understanding of both physiological and pathological states. When personalized medicine becomes reality, we may find that supplementing with carotenoid vitamin therapies that are needed by an individual than "one size fits all" approach may lead to better clinical outcomes.

4. Does carotenoid vitamin therapy only help intermediate stage AMD?

The AREDS trials showed that supplementation with carotenoid vitamin therapy prevented progression from intermediate to advanced stages of AMD. Further, the AREDS-2 trial [1] showed that the carotenoid supplementation with lutein and zeaxanthin indeed favored treatment, particularly in those that had low serum levels at baseline. It's a fair question to ask if the carotenoid vitamin therapy does benefit other stages of AMD? An equally important question is what other benefits can be seen in individuals with dry-AMD with carotenoid vitamin therapy? These are big questions, and it would be ideal if there were additional large-scale trials like AREDS that give us all the answers for early diagnosis, prognostic, and new treatments when they become available. This aspiration may be in part impractical for all scientific questions and when such large trials are not available doctors will need to evaluate all tiers of evidence available to derive clinical guidelines for disease states. Numerous reports have shown clinical benefits, by raising the levels of xanthophylls in the retina through dietary supplementation, thus, adjunctive carotenoid vitamin therapy may offer enhanced neuroprotection by augmenting MPOD and subsequently preventing further injury [16, 17]. Higher levels of MPOD are thought to preserve retinal tissue, specifically, the layers containing photoreceptors in the fovea, through two primary mechanisms: (1) serving as an innate optical filter against blue light; and (2) as protective antioxidants, by neutralizing free radicals and reducing consequent oxidative injury [16, 17]. In a recent systematic review of carotenoids in the management of AMD showed that there are at least 20 epidemiological studies and 35 randomized controlled trials that have evaluated this topic [17]. These studies evaluated various facets of the topic: supplementation and increase in serum carotenoids, MPOD, and changes in visual function. Whereas improvements in BCVA were seen in six out of eighteen (6/18) trials, remarkable benefits in contrast sensitivity were demonstrated in ten out of fifteen (10/15) randomized controlled trials [17]. Improvements were also seen in glare disability, photostress recovery time, and improvements in multifocal electroretinogram results [17]. Thus, it was concluded that consistent evidence from large-scale epidemiology studies, and several randomized clinical trials, substantiate the synergic neuroprotective benefits afforded by carotenoid vitamin therapy in eyes with any stage of AMD [17]. It is important to note that these visual benefits may be decreased in late-stage AMD compared to early or intermediate stage AMD [17, 18]. A dose-response relationship with stronger effect and greater serum carotenoids and MPOD levels is seen with supplementation of a greater dose of carotenoids [19]. In a recent RCT [20] we found that six-month supplementation with a greater amount of ocular carotenoids (28mg) and omega 3 supplement (675 DHA and 230 EPA), when compared to AREDS-2 formulation soft-gels (12 mg) not only provided greater serum carotenoid levels but also led to significant improvements in measured contrast sensitivity in individuals at risk of AMD. Indicating that quicker and greater visual benefits can be seen if a larger dose of ocular xanthophylls is supplemented to patients. There are numerous questions that remain to be answered for example do potent antioxidants like astaxanthin reach retinal layers? Are there any synergistic effects of these carotenoids? Scientists have answered a lot of questions and a lot more remain.

Roughly one in eight individuals aged 60 or greater is suffering from AMD; it is fair to say that it deserves our special attention. It was long believed that in the chronic disease of dry-AMD not much occurs or is needed until much later in disease state; we can confidently say, that is not true. With the advancement in clinical testing like Rabin Cone Contrast testing, we can detect this disease easily and along

with devices that can measure MPOD we can better manage the disease and monitor its progression. The objective technology of Macular Pigment Reflectometry to measure MPOD, and individual carotenoid optical density shows promise in personalized medicine. Also, there is sufficient data from various RCTs to recommend carotenoid vitamin supplement at all stages of AMD, which may prevent its progression but definitely provides an improvement in vision, and who does not like an improved vision!

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