Longevinex ® Improves Human Atrophic Aged-related Macular Degeneration (AMD) Photoreceptor / Retinal Pigment Epithelium Mediated Dark Adaptation[*]

Stuart Richer[1,2,3,4*], Lawrence Ulanski II[1,3,4], Anish Bhandari[4,5] and Natalia Popenko[4,5]

[1]Departments of Optometry and Ophthalmology, Preventative Ocular Medicine and Residencies, USA.
[2]Family Medicine, Chicago Medical School, Rosalind Franklin University of Medicine and Science (RFUMS), North Chicago, IL 60064-3095, USA.
[3]Department Surgery, UIC Eye and Ear Infirmary, Ophthalmology Retina Service 60612, USA.
[4]Captain James A Lovell Federal Health Care, North Chicago, IL, 60064-3095, USA.
[5]Chicago Medical School, Rosalind Franklin University of Medicine and Science (RFUMS), North Chicago, IL, 60064-3095, USA.

Authors' contributions

This work was carried out in collaboration between all authors. Authors SR and LUII identified suitable clinical candidates under medical center compassionate care guidelines. Authors SR and LU wrote the final version of the manuscript. Author AB gathered data, performed the statistical analysis, and wrote the first draft of the manuscript. Author NP performed all dark adaptation studies. All authors read and approved the final manuscript.

Article Information

Original Research Article

ABSTRACT

Aim: Gradual photoreceptor/ RPE deterioration/ vision loss in AMD is common, irrespective of US NEI AREDS I/II supplement risk reduction, or intra-vitreal anti-VEGF pharmacology. We evaluated dark adaptation (DA), a broad measure of photoreceptor / RPE health, with / without epigenetic modulation using a resveratrol–based caloric-restriction mimic (Longevinex ®www.longevinex.com).

_____

Corresponding author: E-mail: Stuart.richer1@va.gov;

Study Design: Case series, bi-ocular, clinical DA evaluation in deteriorating AMD, before and after supplementation, under medical center compassionate use guidelines.

Place and Duration of Study: Captain James A Lovell Federal Health Care Center, Illinois, USA, Optometry/Ophthalmology Departments between 4/2015 and 8/2016.

Methods: Baseline clinical DA threshold (log DB), time (min), and fixation (%) were taken for patients with established atrophic AMD (n=14 eyes; 6 M / 1 F; ages 64 - 89 years), using the AdaptDx ® (www.maculogix.com), with pupil dilation and best refraction. Following prescription of Longevinex® 1 capsule qd AM, DA was repeated, with each eye's response considered independent.

Results: All but 2 eyes improved in one or more DA parameters, with 3 cases showing improvement by retinal macula SD OCT. Expected vs. actual (worse vs. same/better), by eye, was significant by Chi Square, $P < .01$. Additional factors affecting DA: smoking, alcohol, elevated CRP and statins were retrospectively evaluated.

Conclusion: These first cases of epigenetic-induced DA stability / improvement are consistent with previous beneficial effects of Longevinex® such as enhanced choriocapillaris circulation. DA is the earliest functional AMD sign and a prime candidate for "AMD prevention". This work merits expansion to controlled studies.

Keywords: AMD; dark adaptation; epigenetics; Longevinex®; resveratrol.

1. INTRODUCTION

Dark adaptation (DA), as opposed to visual acuity, is a superior test for the presence and staging of AMD [1]. A MacuLogix AdaptDx® DA test result in excess of 6.5 minutes predicts future macular degeneration by at least 3 years before visual decline [2]. Furthermore, this clinical test, analogous to a glaucoma visual field, has a sensitivity and specificity of 90%, on par with the clinical performance of a retinal specialist [2]. Many articles provide evidence that resveratrol's biological activities include vasorelaxant activity, antiangiogenesis activity, anti-inflammatory activity, antioxidant activity, and so on through different molecular mechanisms using animal models and in vitro retinal cells. In this report, we evaluate DA using a resveratrol-based supplement.

Short and long term improvement in visual function and structure has previously been reported in AMD patients taking Longevinex® capsules (Resveratrol Partners, Las Vegas, NV USA), a nutraceutical supplement containing red wine solids (including 100 mg of stabilized laboratory grade microionized/microencapsulated low-dose trans-resveratrol), metal binding polyphenol red wine solids, vitamin D3 1200 IU, DNA repair nucleotides and a B cyclodextrin solubilizing agent. Longevinex ® has also been shown to increase the thickness of the choriocapillaris in normal and AMD patients [3,4]. B cyclodextrin have been shown to lower cholesterol/dissolve drusen by direct injection and bind, stabilize and remove lipofuscin bisretinoids from the retinal pigment epithelium [5].

The molecular mechanism of action of Longevinex ® is multi-modal involving reduction in hypoxia inducible factor (HIF) thru down-regulation of micro RNA 20b in turn controlling VEGF; 2) sequestration of labile iron and copper; 3) enhancement of the immune response by microglia and sensitization by vitamin D3 and 4) modulation of chemokine receptors. The mechanisms of actions and documentation of both short and long term clinical treatment, stem cell regeneration in 'treatment resistant' AMD, is found in a recent book chapter, *Advances in Ophthalmology and Optometry*, Beyond AREDS 2 [6].

Our basic clinical goal is stabilization and improvement of function and structure of AMD eyes (photoreceptor / RPE function), where no currently available treatment exists, under medical center compassionate care guidelines. Gradual deterioration of photoreceptor / RPE health in untreated and treated AMD patients is common, irrespective of risk reduction (AREDS I, II supplements) or current intra-vitreal anti-VEGF pharmacologic approaches. The first 7 consecutive clinical cases evaluating dark adaptation (DA), representative of photoreceptor / RPE health, are presented.

2. MATERIALS AND METHODS

2.1 AdaptDx® Protocol

The AdaptDx ® (MacuLogix, Middletown, PA, USA), with best refractive correction protocol was followed under scotopic conditions, based upon the manufacturers procedures and training

program. Briefly, photoreceptor / RPE (retinal pigment epithelium) mediated DA was measured psychophysically following photo-bleach. While viewing a red fixation LED and eye patch, the patient responds by a button press when detecting a 2-degree, 500-nm stimulus centered 5 degrees below the point of fixation in the vertical meridian. The stimulus is presented every 2s to 3s for duration of 200 msec. A 3-down, 1-up modified staircase threshold algorithm is used to determine threshold. After each threshold, the patient is provided a 15 second rest break. Threshold measurements repeat until the patient has recovered their threshold to 5×10^{-3} scotopic cd/m^2. Clinical DA was performed in all cases following pupil dilation using tropicamide 1% and phenylephrine hydrochloride 2.5% instilled no less than 15 min before the examinations. The fellow eye was occluded with an eye patch.

The 2 standardized AdaptDx® protocols used were 'screening (maximum 6.5-minute duration)' and AMD staging (maximum 20-minute duration), depending upon clinical presentation. The early, linear part of the rod-mediated dark adaptation curve extracts the time required to reach a sensitivity of $5.0 \times 10(-3)$ cd/m2 (time to rod intercept) and the slope (rod adaptation rate). [2] The speed of DA was characterized by this rod-intercept value, with abnormal DA defined as rod-intercept of 6.5 minutes in the Rapid and Extend Protocols. [2] Baseline clinical DA threshold (log DB) at time=0, intercept time (min), and fixation quality (%) were taken for 7 consecutive AMD patients with established, progressive, atrophic AMD (n=14 eyes; 6 M / 1 F; ages 64 - 89 years). All were veterans at the James A Lovell Federal Health Care Center Optometry and Ophthalmology departments, examined between April 2015 and August 2016.

2.2 Consent /IRB and Safety/ Inclusion & Exclusion criteria

The use of a marketed product as part of medical practice for an individual patient does not require the submission of an IND (Investigational New Drug). However, oversight was requested and approved by the Chief of Staff and IRB (Hines DVA, Chicago, IL). The "medication" Longevinex® (Longevinex Partners, Las Vegas, NV) has exhibited excellent safety and freedom from side effect at the recommended dosage (1 capsule per day) among non-anemic subjects over 12 years (http://www.longevinex.com), with no reported hospitalizations during this extended time period. Animal and human toxicity data,

unusual for a dietary supplement, as well as fast track FDA petition has been submitted, and can be viewed on line [7].

Inclusion 1) Diagnosis of AMD; **2)** Potential clinical benefit in consultation with a retinal specialist (LU) in patients without conventional clinical options.

Exclusion 1) Anemia based on severe low RBC count / low hemoglobin as determined by medical record review (SR); **2)** Inability to perform the DA examination.

Notations were made in the chart regarding the patients' willingness to take a nutraceutical supplement pill every morning, as there were no additional clinical options according to retinal specialist consultation. Patients purchased Longevinex® on their own, except in the case of financial hardship, in which case it was provided by Longevinex® Partners.

2.3 Prescription and DA measurements

Based upon clinical recommendation, case by case (SR, LU); prescription of a single, capsule qd po AM apart from medications was prescribed in the presence of an abnormal DA of 6.5 minutes or longer. DA was repeated at varying clinical intervals. As these were clinical patients, and not research subjects, no attempt was made to standardize DA intervals or monitor / ascertain supplement use compliance between measurements.

2.4 Retrospective Medical Chart Review

For the purposes of this report, we acquired (post hoc) demographic data of several health and functional characteristics that the literature has suggested increase AMD risk and / or alter DA (e.g., BMI, smoking, alcohol use, family history, and chronic medical conditions) [8]. We acquired available "retrospective data", as abnormal DA has been associated with increased odds of elevated C-reactive protein (CRP), heavy use of or abstention from alcohol, high blood pressure, and drop in visual acuity under mesopic conditions. Statin medication use has also recently been shown to reduce drusen possibly improving dark adaptation [9].

2.5 Statistics

A positive result is considered to be a DA curve that remains the same or improved over time, in

one or more of the 3 DA parameters (baseline threshold, rod intercept and fixation accuracy). SDOCT (spectral domain ocular coherence tomography) macula images were taken with a Zeiss 4000 instrument (Carl Zeiss Meditec, Dublin, CA). Chi Square statistics were applied to this clinical sample post hoc using Microsoft Excel® Statistical Software, version 14.3.1. Independence between eyes was assumed. Owing to the limited clinical data set, and the preliminary nature of this report, we report only the DA (worse vs. same/better) Chi Square, P <0.05 considered significant. We assume independence by eye with any stability or improvement in rod intercept, baseline sensitivity and fixation accuracy to be consistent with a positive effect of the nutraceutical.

3. RESULTS

3.1 Demographics

DA data was available for the first 7 patients reported herein. Demographic post-hoc clinical review data (Table 1) represents the demographic data including age, gender, AMD diagnosis (years), current smoking (ppd), current alcohol (ounces per day), retinal dystrophy presence and pertinent medications and supplements. There were no current smokers or binge drinkers during the clinical measurement period. Five patients taking statins: case 1, 4 on simvastatin, case 2 on lovastatin and case 3, 5 on atorvastatin.

3.2 Dark Adaptation Parameter Changes

3.2.1 Summary of clinical dark adaptation data

(Table 2) shows DA data regarding DA reduction in minutes and fixation error rate at varying clinical intervals. Out of 14 eyes, 8 stayed the same/improved, 4 worsened, and 2 were unavailable.

3.2.2 Clinical dark adaptation clinical data continued

(Table 3) shows DA data regarding duration, log intercept, and baseline log sensitivity at varying clinical intervals and demonstrates overall DA improvement. Rod intercepts show improvement/ stability in 9/14 eyes, worsening in 4/14 eyes and

unavailable in 1/14. Baseline log sensitivity showed 11/14 eyes improved/ stabilized and 3/14 worsened. All but 2 eyes improved in one or more of the DA parameters across Table 2 and Table 3. Expected vs. actual (worse vs. same/better) Chi Square statistics shows a P value of P< 0.01, considered significant. With such a small sample size, it would be beneficial to repeat the study on a larger scale to strengthen statistical power. This pilot data provides further support for the clinical utility of Longevinex® in patients afflicted with atrophic AMD.

3.3 Dark Adaptation Graphs

Figs. 1-7 show the changes in DA of all patients by comparing the graphs before and after a given length of time on Longevinex® supplementation. All but 2 eyes improved in one more of the DA parameters. Cases 1, 4, and 6 show a stark improvement in SD OCT.

3.4 Demographic Post - Hoc Clinical Review

Table 1 shows demographic data obtained by medical chart post - hoc review. This included age, gender, smoking / alcohol use and presence of a retinal or corneal dystrophy. Potential DA improving medication and supplements were also tabulated.

Patients averaged 64-88 years of age, and 6 of 7 were male. There were no current smokers or alcohol users that could adversely affect the DA response. One patient had a peripheral retinal 'paving stone' dystrophy and another had a 'pellucid' type peripheral corneal dystrophy. some 5/7 patients used a statin and 6/7 patients were taking pabulum type supplementation.

3.5 Summary of Clinical Dark Adaptation Data

Table 2 shows the reduction in DA in minutes for n=14 eyes. n = 8 eyes had the same or improved DA, n= 4 eyes worsened with data from 2 eyes unavailable. The latter unavailable data was due to a mismatch between short and long DA versions, based on an error in the original physician order. For fixation quality, for n=14 eyes, most (n= 8 eyes) remained the same or improved by +/- 3%, and n = 6 eyes worsened.

3.6 Clinical Dark Adaptation Clinical Data Continued

Table 3 summarizes the number of eyes improved or remaining stable in at least one of the three DA parameters. For the 12 /14 eyes with available rod intercepts, n = 9/14 were the same or improved and n = 4/14 worsened with 1 unavailable. For baseline log sensitivity (+/- 0.2 log units), 11/14 were the same or improved, and only 3/14 worsened.

4. DISCUSSION

Macular degeneration affects millions of senior adults. There is no proven remedy for the early stages of this insidious sight-robbing eye disease. This is the first report of an oral supplement that stabilizes / improves DA function (and hence retinal health) in primarily advanced cases using an FDA approved dark adaptation clinical instrument. In 5 of 7 cases the response was bilateral and occurred in as little as 1 month as in case 5. Three patients also exhibited improvement in their macula SD OCT pathophysiology (cases 1, 4, 6). Finally, in 4 of 7 patients there were profound multi-line improvements in their visual acuity (case 1 – both eyes improved, cases 3, 4, 5 - one eye improved).

Retrospective review suggests that none of our patients were current smokers or binge alcoholics between DA time point assessments. These 2 factors are known to *decrease* DA [8]. The majority (5 of 7) patients were taking a statin before, during and after the Longevinex® Rx time period, obviating this as a theoretical factor for the DA *stabilization / improvement* observed. Thus, our clinical observations appear robust.

As this is a *clinical observational case series*, the range of follow-up of individual AMD patients varied between 1 and 7 months depending upon individual circumstances, and the doctor's prior experience with Longevinex® efficacy. Some patients were taking other supplements that did not change during the intervention. No patient had other ophthalmologic treatment options. Notably, almost all patients (except case 2, age 64) were 80 years of age and older, similar to the aged veteran demographics in our previous Longevinex® publications [7].

The improvement in DA reported herein is consistent with the staging down (improvement) of AMD in several eyes, consistent with the Adapt Dx® literature. Dark adaptation is an energy-requiring process, as the outer retina is nourished by the profusely perfused choroid [10, 11]. This report is the first to find *improved fixation accuracy* as a 3rd AdaptDx® DA outcome measure in patients afflicted by AMD and is consistent with the improved structural changes noted on retinal imaging, and the improved visual acuity in 4 of 7 patients.

A provocative recent study noted resolution of drusen in 45% of n=23 patients placed on 80 mg Lipitor ® [9]. As well, Australian pulsed laser studies aimed at thinning Bruch's membrane, may potentially improve DA [12]. Whether the issue is cholesterol deposition between Bruch's membrane and the RPE or a thickening of Bruch's membrane, the putative mechanism for failing DA and worsened RPE health, in both cases, is believed to be translocation impairment of the essential vitamin A derivative "11-cis RAL" used in the "retinal cycle". Retrospective chart review– revealed no discontinuation or substitution, or change in statin dose during the DA time intervals during which Longevinex® was prescribed.

The expanding ophthalmologic use of statins against AMD appears to be a misdirection, as Cochrane meta- evaluation from currently available RCTs are "insufficient to conclude that statins have a role in preventing or delaying AMD onset or progression" [13]. Some statins, in some individuals, are also fraught with side effects [14]. Regardless, these findings support Mullins et al. that micro vascular changes are related to the pathogenesis of AMD and vascular endothelial cell loss occurs in association with sub-RPE deposit (including cholesterol) formation [10]. Whether micro vascular events are a cause or consequence of drusen or other deposit formation remains to be determined.

A recent cross sectional observation study involving 42 young healthy subjects mean age 25±2.0 years (29% men) evaluating choroidal thickness, found no detectable effect on rod-mediated DA, adjusted for age and gender [12]. Thus perhaps DA screening should begin with patients no younger than "baby boomers". Notably, MacuClear® 1% hydralazine eye drops are thought to work by increasing choroidal blood flow in early to intermediate AMD with the electroretinogram (ERGc) wave as a biomarker. Phase 2/3 results are pending, and it would be informative to evaluate MacuClear® and DA [15].

5

Table 1. Demographic post-hoc clinical review

Case (Figure # & initials)	Age	Gender	AMD duration	Current smoker	Current alcohol	Retinal /Corneal dystrophy? (yes / no)	DA improving medication?	Supplements
1 (NS)	86	M	2 years	N	N	N	40 mg simvastatin	1000IU Vit D3 Centrum Silver QD 1000 mg Fish oil BID 420 mg Mg Oxide
2 (RS)	64	F	5 years +	N	N	Retinal Pavingstone	20 mg lovastatin	Centrum®
3 (HJ)	82	M	8 years	N	N	N	40mg atorvastatin	
4 (HJ)	89	M	9 years+	N	N	N	20 mg simvastatin	MaxiVision® AREDS 2, Krill Oil
5 (CJ)	86	F	1 year	N	N	Corneal Pellucid	20 mg atorvastatin	Bright Eyes®
6 (KW)	88	M	1 year	N	N	N/A	N/A	1000 IU Vit D AREDS2 500 mg Vit C, 1000 mg Fish oil
7 (DR)	84	M	New	N	N	N/A	N/A	Vitamin D3

Age, gender, smoking, alcohol, retinal/corneal dystrophy presence, DA improving medication and supplements were tabulated. Ages 64-88 years, 6/7 male, no smokers or alcohol use. 2 patients have a retinal (pavingstone) and a corneal (pellucid) dystrophy, 5/7 statin use. 6/7 patients were taking a pabulum type supplement.

Table 2. Summary of clinical dark adaptation data

Case (Figure # & initials)	Reduction in minutes, % (OD)	Reduction in minutes, % (OS)	Fixation errors (OD)	Fixation errors (OS)
1 (SN)	(8, 53%)	(-3, NA%)	11%→33%	0%→59%
2 (SR)	(-3, NA%)	(-2, NA%)	9% → 46%	25%→28%
3 (JH)	(0, 0%)	(0, 0%)	0% → 11%	11%→12%
4 (JH)	(0,0%)	(0, 0%)	7% → 6%	31%→26%
5 (JC)	NA extended vs rapid, NA%	NA extended vs rapid, NA%	28%→0%	13%→0%
6 (KW)	(-8, NA%)	(0,0%)	29%→42%	14%→11%
7 (RD)	(0,0%)	(0,0%)	3%→18%	27%→20%

Reduction in DA in Minutes (n=14 eyes, n = 8 same / improved and n= 4 worse, 2 unavailable. Fixation Errors (n=14 eyes, n= 8 same / improved +/- 3% and n =6 worsened).
NA = non-applicable

Table 3. Clinical dark adaptation clinical data continued

| Case (Figure # & Initials)	Duration prescribed longevinex®	Rod intercept (OD)	Rod intercept (OS)	Baseline log sensitivity (OD)	Baseline log sensitivity (OS)	#Eyes improved OR remained stable in at least 1 DA factor
1 (SN)	5 Weeks	17.39→9.34	2.57 →6.10	~1.9→~2.2	2.8→2.1	1 (L eye parameters worse)
2 (SR)	7 Months	5.73→8.84	2.04→3.90	~1.3→~1.2	~2.1→~2.3	2 (L eye remains normal)
3 (JH)	4.5 Months	>6.5→>6.5	>6.5→N/A (Cannot be calculated)	~1.8→~2.3	~2.2→~2.6	2
4 (JH)	4 Months	>20→>20	>20→>20	~1.1→~1.4	~1.2→~1.6	2
5(JC)	1 Month	>20→>6.5	>20→>6.5	1.2→>1.2	1.0→1.1	2
6 (KW)	4 Months	11.9→19.85	>20→>20	~1.5→1.0	~0.9→~1.2	1 (R eye parameters worse)
7 (RD)	~4 Months	>20→>20	>20→>20	~1.1→~0.9	~1.0→~1.1	2

#Eyes improved or remained stable in at least 1 DA factor.(12 /14) Rod Intercept data (n = 9/14 same/ improved; n = 4/14 worse, 1 unavailable. Baseline Log Sensitivity +/- 0.2 (11/14 = same / improved, 3/14 = worsened)
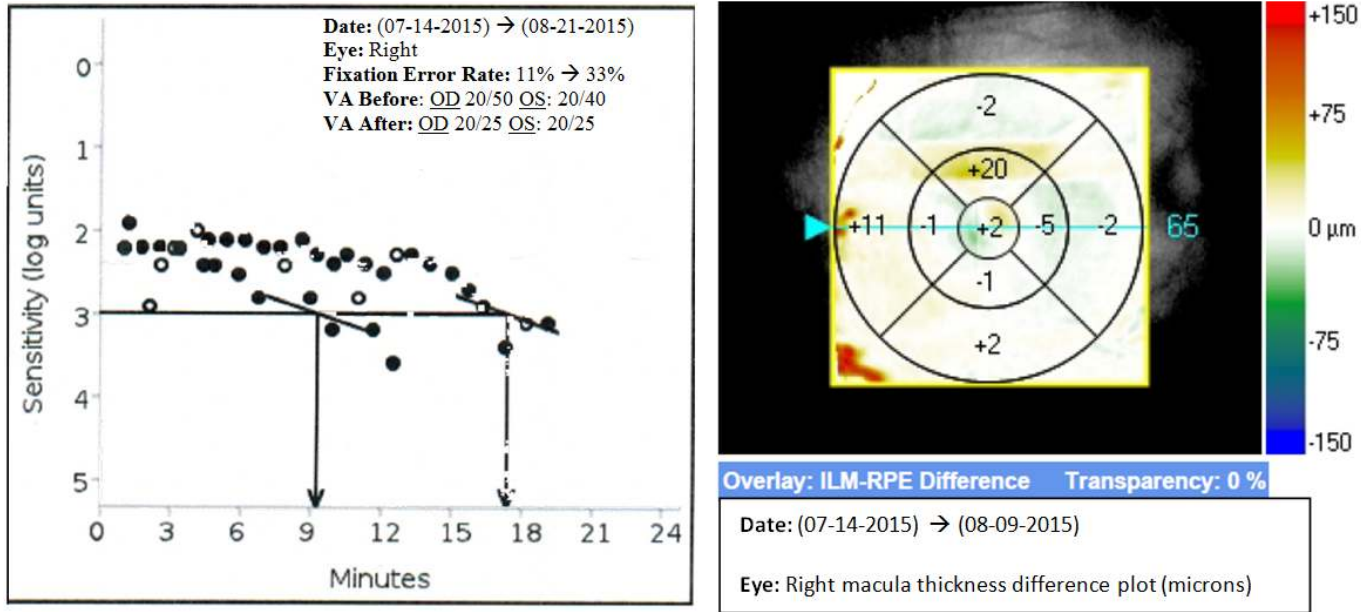
Fig. 1a, b. Longevinex ® x 5 weeks

Patent SN, an 86 y/o Caucasian male with atrophic AMD for 2 years w vascular component and abnormal R DA, was prescribed Longevinex®. Medical records note glaucoma suspicion R optic nerve vs optic neuropathy. Fig. 1a DA shortened from ~17 to 8 min R retina, with improvement in baseline log (db) sensitivity but not fixation and 3 line improved VA from 20/50 to 20/25. (His L retina DA was normal at baseline and follow-up (below 6.5 minutes), with 2 line improved VA from 20/40 to 20/25. (not shown) Fig. 1b shows significant improved registered macula SDOCT thickness DIFFERENCE at follow-up, with an increase in retinal thickness of 20 μm in the superior parafovea EDTRS quadrant, well beyond the 5u instrument axial resolution. This is the most vulnerable area of the retina in early AMD, and the location of the MacuLogix Adapt Dx® target stimulus
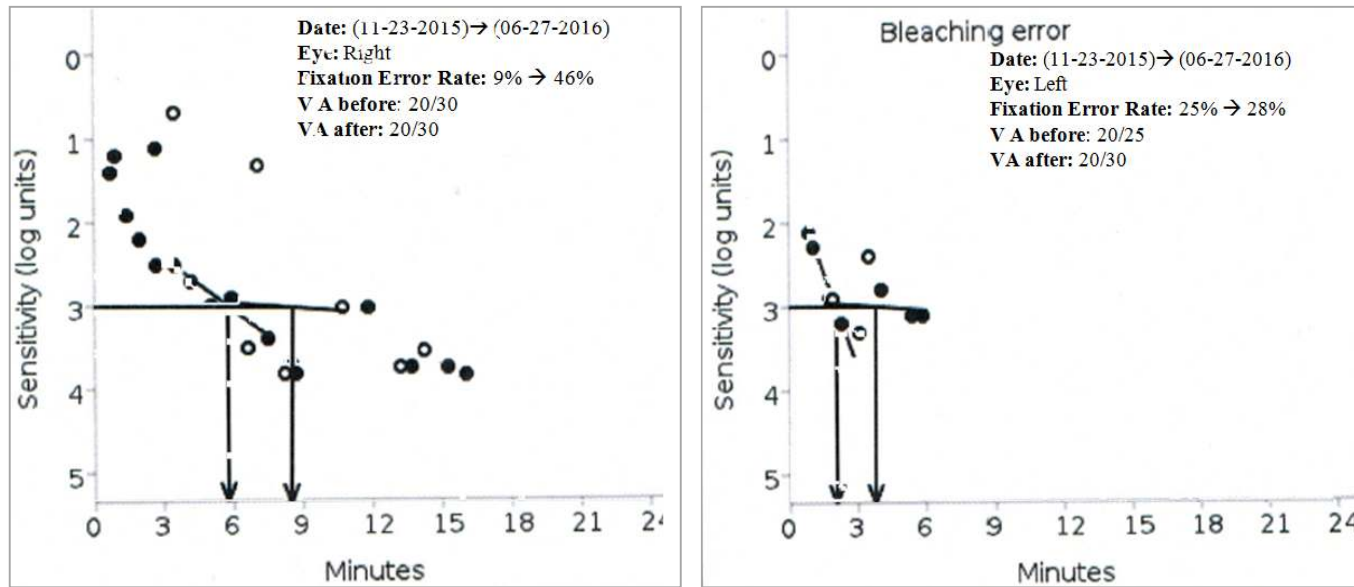
Fig. #2a, b. Longevinex® x 7 months

Patient SR, a 64 y/o Caucasian female with atrophic AMD for 5 years, was prescribed Longevinex (R) for 7 mo. Fig. 2a: DA lengthened from ~6 min to ~9min R retina but with significantly decreased fixation from 46 % to 9 %, and decreased baseline sensitivity. Fig. 2b: Normal DA, increasing slightly from ~ 2.75 min to 3.5 min. VA stayed the same at 20/30 each retina
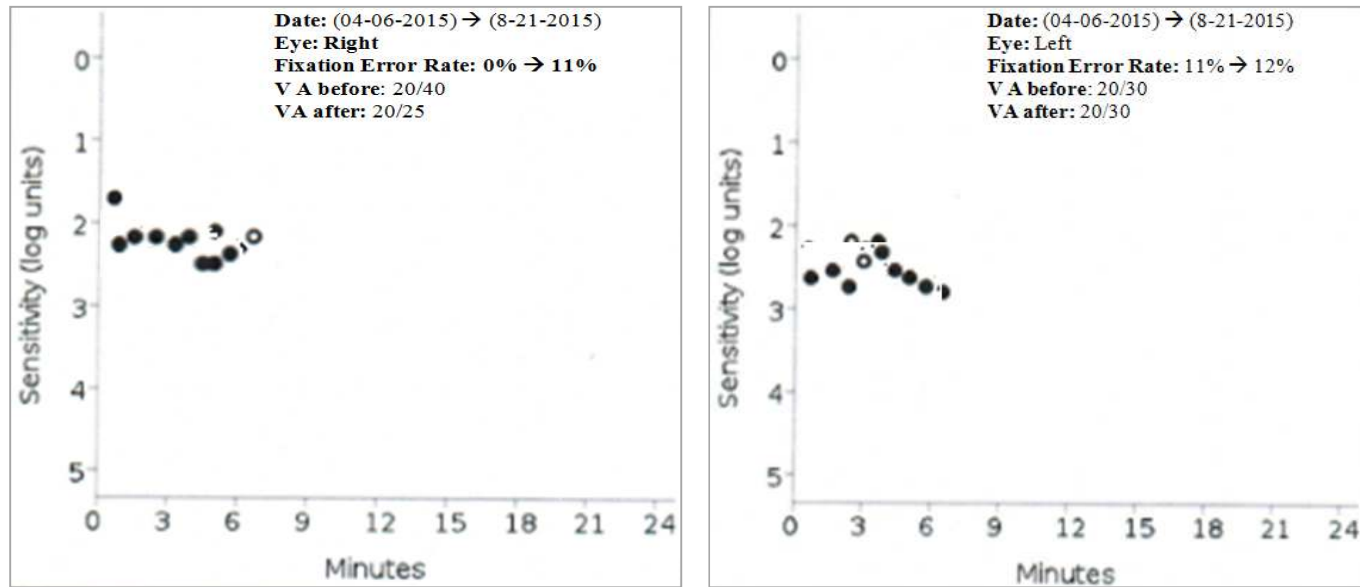
Fig. #3a, b. Longevinex® x 4.5 months

Patient JH, an 82 y/o Caucasian male with severe atrophic AMD for 8 years was prescribed Longevinex® and followed for 4.5 mo. Bilateral DA improvement in baseline sensitivity, without significant change in or DA (min) or fixation in standard clinical testing mode (actually worse R eye). VA R retina improved from 20/40 to 20/25 (3 lines). Unfortunately, 20 minute extended AMD DA staging exam was not ordered. This patient noted that his R eye has improved, and his L eye showed no signs of further visual deterioration.

Overlay: ILM-RPE Difference   Transparency: 0 %
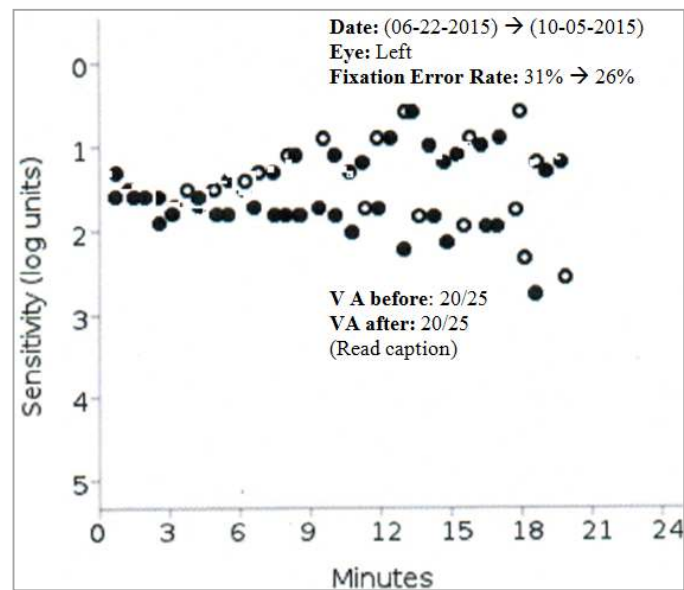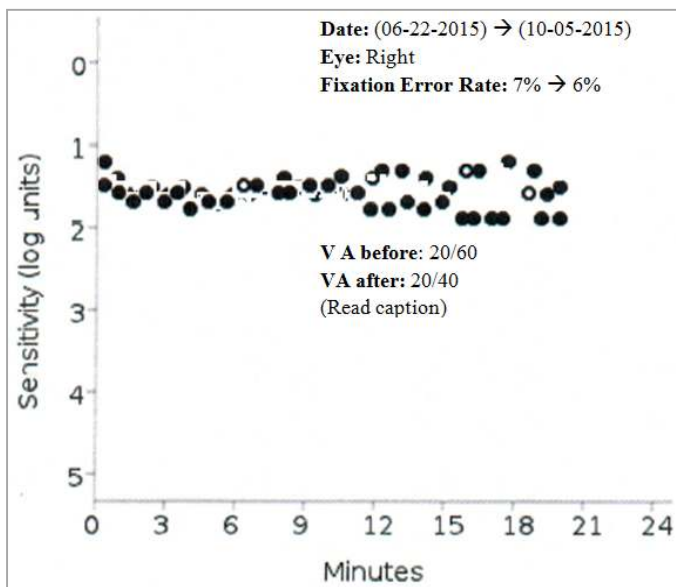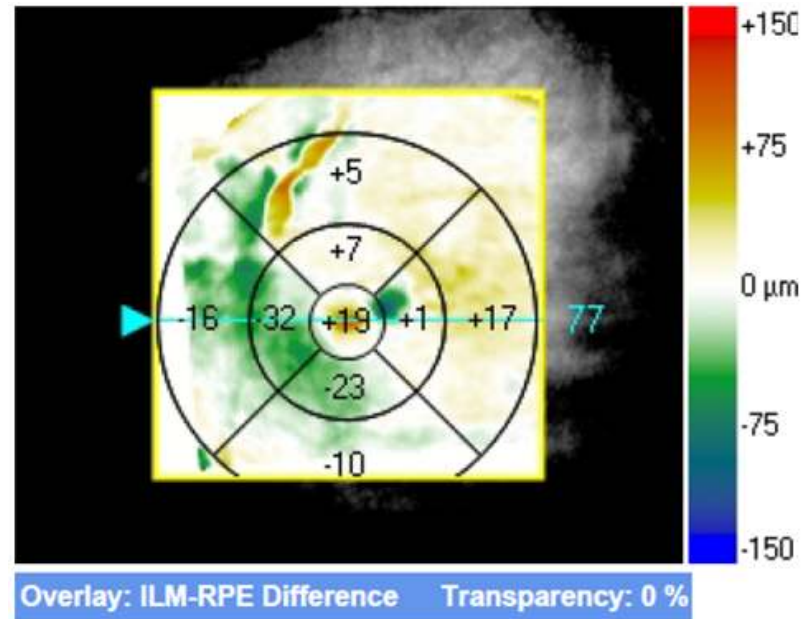
Patient Name: HJ
Date: (05-12-2015) → (8-18-2015)
**Eye:** Left macula thickness difference plot

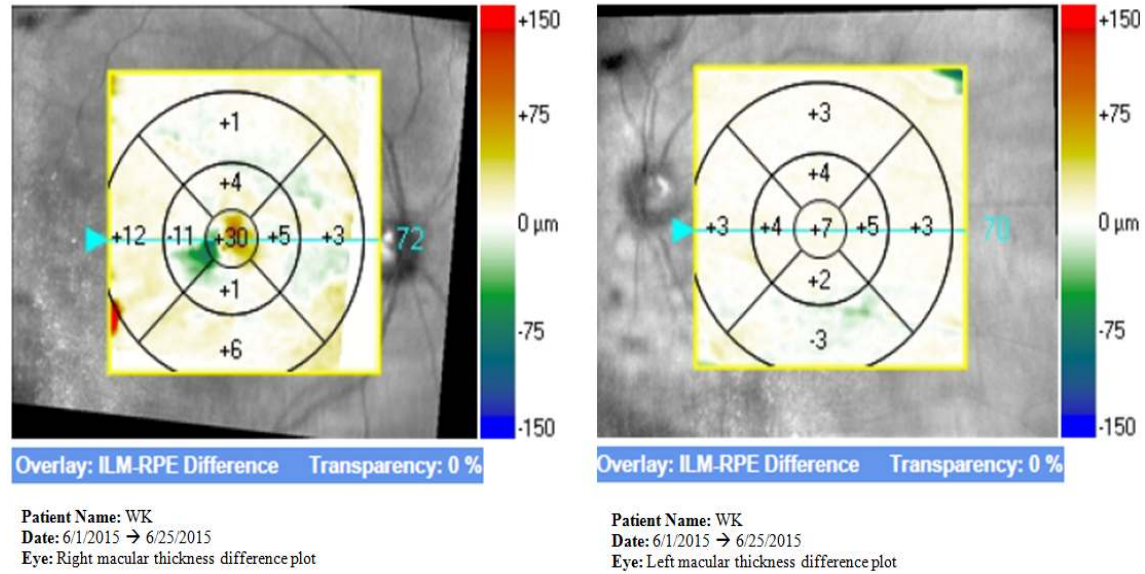**Fig. #4a, b, c. Longevinex® x4 months**

A second patient JH, an 88 y/o Caucasian male with atrophic AMD for at least 9 years , showing improvement L eye > R eye in extended time – frame DA, after 1 month of prescribed Longevinex ®. Retinal sensitivity improved as clearly evident in his L eye beginning at 6 min. The L retina DA slope is steeper with ending sensitivity ~ 1 log unit more sensitive (lower curve). VA R improved from 20/60 to 20/40 (2 Snellen lines). VA stayed the same in his left eye. Fig. C. There was a significant 19u increase in L SDOCT retinal foveal thickness of 19μm, and 7u superior parafovea L retina explaining better fixation and improved DA log sensitivity
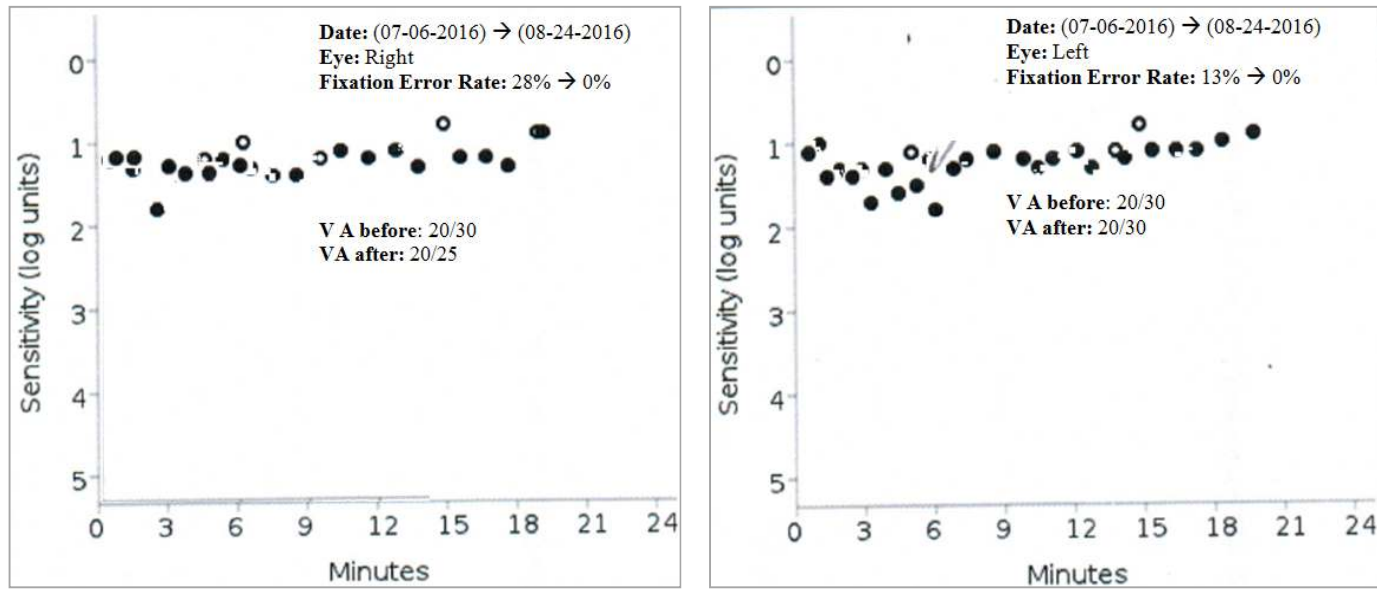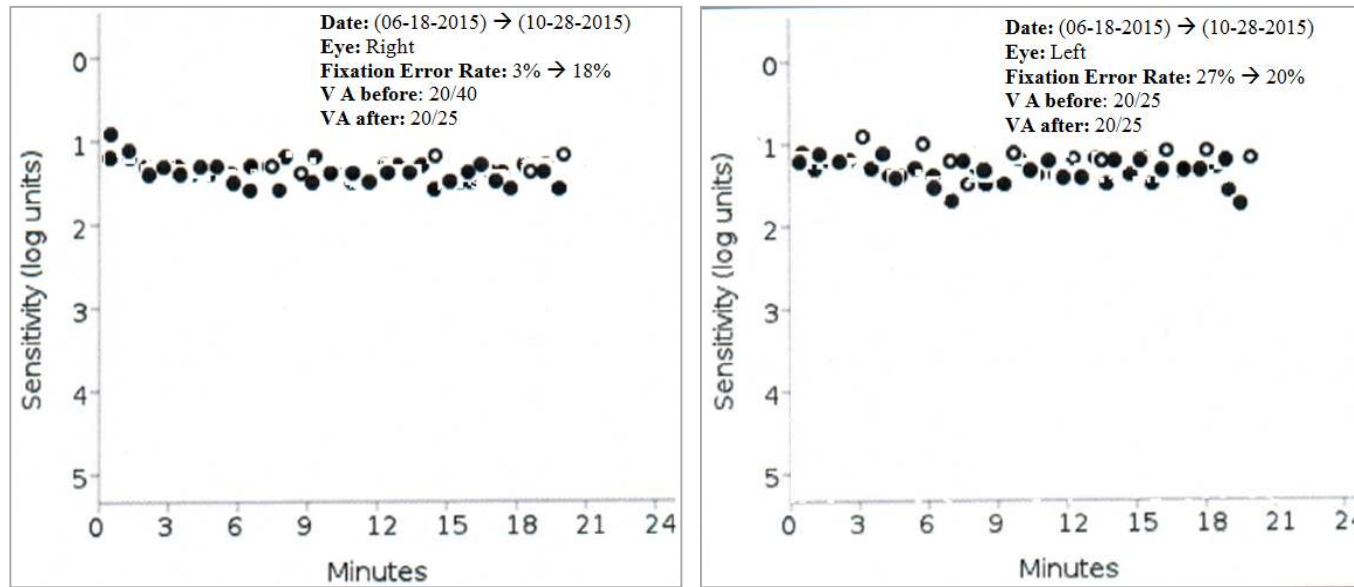
Fig. #5a, b. Longevinex® x 1 month

Patient JC, an 86 y/o Caucasian male, with atrophic AMD for 2 years, prescribed Longevinex ® for ~ 6 wks. Fig. 5a: No improvement in DA sensitivity or slope, but dramatically improved fixation with a 2 line improvement in VA R eye (20/30 to 20/20) Fig. 5b: Improvement in L retinal sensitivity and fixation is evident
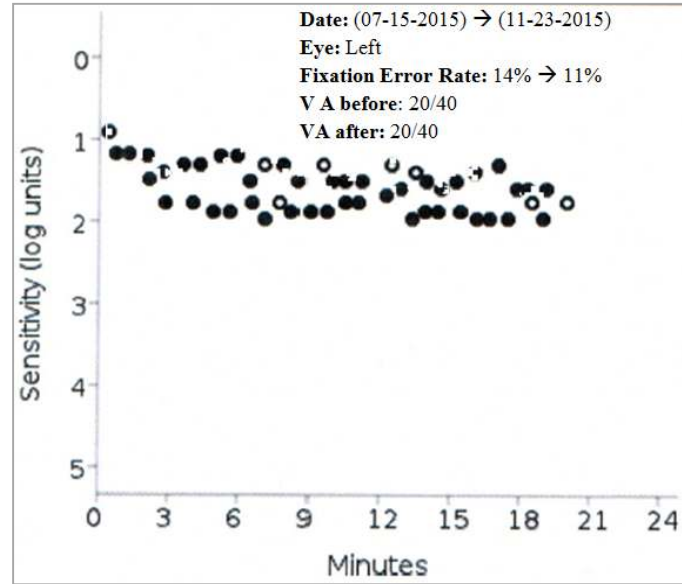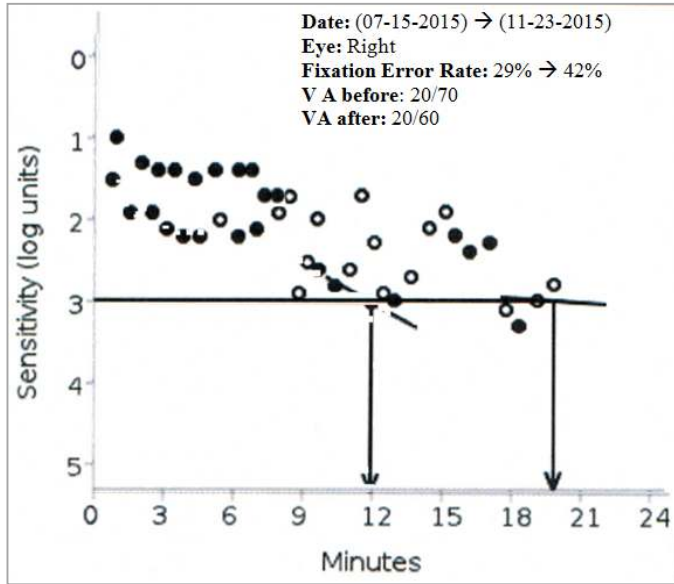
Fig. #6a, b, c, d. Longevinex® x 4 months

Patient KW, 88 y/o male, with atrophic AMD for 1 year and prescribed Longevinex® for 4 mo. Fig. 6a Worsened DA R retina by all 3 DA attributes. Fig. 6b Improved L retina baseline and extended retinal sensitivity and fixation. VA was approximately the same at 20/60 R and 20/40 L. Fig. 6c, d Patient KW shows significant increase in his retinal thickness R retina by 30µm in the center and in his L retina by 7µm in the center

Fig. 7a, b. Longevinex ® x ~4 months

Patient RD, an 84 y/o Caucasian male with newly diagnosed advanced atrophic AMD prescribed Longevinex ® for ~4 month stable DA and no loss of retinal function, despite an additional 4 months of aging. VA improved 3 lines from 20/40 to 20/25 R eye and L eye remained the same at 20/25.

Compared with statins, Longevinex® has several key advantages with lack of side effects, after 12 years in the marketplace. The benefits to the vascular system extend beyond resveratrol and include:

- Decreased inflammation (COX-2, CRP)
- Decreased HIF-1 and VEGF gene expression (miRNA 21, 20b, 539)
- Increased expression of Nrf2 mediated endogenous antioxidants (GSH)
- Decreased blood clotting (platelet adhesiveness)
- Increased vasodilation (the nitric oxide beneficial effect on the choriocapillaris)
- Increased divalent metal chelation (against labile oxidant Fe^{++}, Cu^{++})
- Decreased oxidation and peroxidation
- Decreased cell adhesion (of platelets, microbes and tumors)
- Decreased calcification (i.e., of arterioles and Bruch membrane) [5]

Longevinex® not only decreases cholesterol, but has been shown to restore myocardial dysfunction in hyper-cholesterolemic animals. [16] In addition, it manifests:

1) No cytotoxicity at high dose (no hormesis), whereas resveratrol at high dose has toxicity; 2) Is beneficial against human metabolic syndrome [17,6]; 3) Functions as an anti-diabetic drug with insulin like sugar level reducing effects and 4) Promotes choroidal vasorelaxation and thickening [4,5].

The patients in our study were 80 years of age, or older. The literature is consistent with the conjecture that DA extension to children of AMD patients is desirable. These patients, who have not lost measurable vision, may nonetheless benefit from "AMD detection combined with epigenetic prevention" via small molecular weight nutrient intake [6]. To wit, some 22 -23% of naïve subjects have impaired dark adaptation and hence impaired photoreceptor / RPE health [8, 18]. According to Owsley et al, these patients are more likely to have elevated CRP (c reactive protein), smoke, use alcohol, have hypertension and have poor mesopic and low luminance vision [7].

There are ~48 million Americans over the age of 65 and if the above figures translate to the entire population (22% of ~50 million), dark adaptation testing could uncover ~11 million senior Americans with near-perfect visual acuity who will develop macular degeneration in their near future. This is exactly the time to intervene, or in theory, prevent AMD.

The greater application of this dark adaptation vision test is also among younger family members of individuals who have been diagnosed with macular degeneration since prolonged dark adaptation time can predict future onset of this dreaded eye disease up to 4 years before it can be clinically diagnosed. Forty-five percent (45%) of the population who have a parent with macular degeneration will develop the disease in their lifetimes.

5. CONCLUSIONS

Prolonged dark adaptation time is a marker of the future onset of a dreaded vision problem - macular degeneration. Subclinical AMD is a highly prevalent disease that in theory causes avoidable vision loss years before an eye doctor can see visible changes within the retina. DA is the new biomarker for AMD detection for both diagnosis and staging. Prevention and not mere detection is the ultimate public health goal. Combining MacuLogix AdaptDx ® screening with resveratrol based therapies such as Longevinex ® supplementation may alter the natural time course of AMD. Our observations should be validated in a controlled manner as it is an efficient and cost effective strategy for large populations of at risk patients. Moreover, proven medical, laser or surgical treatment for the common early form of macular degeneration is lacking.

PATIENT CONSENT

Informed consent was noted in the medical chart based upon the patient / doctor consent process for compassionate use of Longevinex® at the James A Lovell FHCC, per medical center guidelines.

ETHICAL APPROVAL

It is not applicable.

ACKNOWLEGEMENT

REFERENCES

1. Jackson GR, Edwards JG. A short-duration dark adaptation protocol for assessment of age-related maculopathy. J OculBiol Dis Infor. 2008;1:7–11.
   DOI: 10.1007/s12177-008-9002-6

2. Jackson GR, Scott IU, Kim IK, Quillen DA, Iannaccone A. Diagnostic sensitivity and specificity of dark adaptometry for detection of age-related macular degeneration. Invest Ophthalmol Vis Sci. 2014;55:1427–1431.
   DOI: 10.1167/iovs.13-13745

3. Nociari MM, Lehmann GL, Perez-Bay AE, Radu RA, Ryan S, Shelby G, et al. Beta cyclodextrins bind, stabilize and remove lipofuscin bisretinoids from retinal pigment epithelium. Proceedings of the National Academy of Sciences of the United States; 2014.
   DOI: 10.1073/pnas.1400530111

4. Richer S, Patel S, Sockanathan S, Ulanski LJ, Miller L, Podella C, et al. Resveratrol based oral nutritional supplement produces long-term Beneficial effects on structure and visual function in human patients. Nutrients. 2014;6(10):4404–4420.
   DOI: 10.3390/nu6104404

5. Wang S, Moonasar N, Xiao X, Yin T, Weinreb RN, Sun X. Effect of resveratrol-based nutritional supplement on choroidal thickness: A pilot study. Curr Eye Res. 2016;41(10):1339-1345.
   Available:http://dx.doi.org/10.3109/027136 83.2015.1119282

6. Richer, Ulanski, Popenko, et al. AMD beyond AREDS II, in: Myron Yannuzzi, MD Editor. Advances in Ophthalmology and Optometry. Elsevier Press, Philadelphia. 2016;335-369.

7. AMDFD; 2012.

   Available:http://www.longevinex.com/pdf/L ongevinexAMDFDAPetition.pdf Accessed 06.20.2016.

8. Owsley C, Huisingh C, Jackson GR, Curcio CA, Dashti N, Clark M, et al. Associations between abnormal rod-mediated dark adaptation and health and functioning in older adults with normal macular health. Invest Ophthalmol Vis Sci. 2014;22;55(8):4776-89.
   DOI: 10.1167/iovs.14-14502

9. Vavvas DG, Daniels AB, Kapsala ZG, Eliott D, Gragoudas ES, Kim IK, et al. Regression of some high-risk features of age-related macular degeneration (AMD) in patients receiving intensive statin treatment. E. Bio. Medicine. 2016;4(5):198-203.
   DOI: 10.1016/j.ebiom.2016.01.033

10. Mullins F, Johnson MN, Faidley EA, Skeie JM, Huang J. Choriocapillaris vascular dropout related to density of drusen in human eyes with early age-related macular degeneration. Invest. Ophthalmol, Vis. Sci. 2011;52(3):1606-1612.
    DOI: 10.1167/iovs.10-6476

11. Munch IC, Altuntas C, Li XQ, Jackson GR, Klefter ON, Larsen M, et al. Dark adaptation in relation to choroidal thickness in healthy young subjects: A cross-sectional, observational study. BMC Ophthalmol. 2016;11:105.
    DOI: 10.1186/s12886-016-0273-6

12. Sekiyama E, Saint-Geniez M, Yoneda, K, Hisatomi T, Nakao S, Maruyama K, et al. Heat treatment of retinal pigment epithelium induces production of elastic lamina components and antiangiogenic activity. FASEB J. 2012;26(2):567-75.
    DOI: 10.1096/fj.11-184127

13. Gehlbach P, Li T, Hatef E. Statins for age-related macular degeneration. Cochrane Database Syst Rev. 2016;4(8).
    DOI: 10.1002/14651858.CD006927

14. Barrett B, Ricco J, Wallace M, Kiefer D, Rakel D. Communicating statin evidence to support shared decision-making.BMC Fam Pract. 2016;17(41).
    DOI: 10.1186/s12875-016-0436-9

15. McCP; 2014.
    Available:https://clinicaltrials.gov/ct2/show/ NCT02127463
    (Accessed 12.23.16.15-16)

16. Juhaz B, Das DK, Kertesz A, Juhasz A. Reduction of blood cholesterol and ischemic injury in the hypercholesteromic rabbits with modified resveratrol,

Longevinex. Mol Cell Biochem. 2011;348: 199–203.
DOI: 10.1007/s11010-010-0615-2

17. Fujitaka A, Otani H, Jo F, Jo H, Nomura E, Iwasaki M, et al. Modified resveratrol Longevinex improves endothelial function in adults with metabolic syndrome receiving standard treatment. Nutr Res. 2011;31(11):842–847.
 DOI: 10.1016/j.nutres.2011.09.028

18. Owsley C, McGwin G, Clark ME, Jackson GR, Kline LB, Witherspoon CD, et al. Delayed rod-mediated dark adaptation is a functional biomarker for incident early age-related macular degeneration. Ophthalmol. 2016;123(2):344-51.
 DOI: 10.1016/j.ophtha.2015.09.041

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/19286