Longevinex® Improves Human Atrophic AMD Photoreceptor / RPE Mediated Dark Adaptation

Stuart Richer, OD, PhD; Lawrence Ulanski II, MD ; Anish Bhandari, MSc, MS1; and Natalia Popenko, MS3
Captain James A. Lovell Federal Health Care Facility & RFUMS, • North Chicago, IL ; UIC Eye & Ear Infirmary • Chicago, IL

ABSTRACT

PURPOSE: Gradual photoreceptor/ RPE deterioration in AMD is common, irrespective of AREDS I/II supplement risk reduction, or intra-vitreal anti-VEGF pharmacology. We evaluated dark adaptation (DA) in atrophic AMD patients, a broad measure of photoreceptor / RPE health, with / without an epigenetic caloric-restriction modulator (Longevinex ® www.longevinex.com).

OBJECTIVE: 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 <0.01. Additional factors affecting DA: smoking, alcohol, elevated CRP and statins were retrospectively evaluated.

CONCLUSION: These first cases of 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

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 AMD 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]

Short and long term improvement in visual function and structure has previously been reported by AMD patients taking Longevinex® capsules, a nutraceutical supplement containing red wine solids (including 100 mg of stabilized laboratory quality 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 has 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 and 'treatment resistant' AMD, is found in our recent book chapter, *Advances in Ophthalmology and Optometry*, Beyond AREDS 2.[6]

The 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.

Table 1:

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 D Centrum Silver Fish oil BID Mg Oxide 420mg
2 (RS)	64	F	5 years +	N	N	Retinal Pavingstone	20 mg lovastatin	Centrum®
3 (HJ)	82	M	8 years	N	N	no	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	1000IU Vit D AREDS2 500 mg Vit C, Fish oil
7 (DR)	84	M	New	N	N	N/A	N/A	Vitamin D

Table 1: Demographic Post-Hoc Clinical Review. 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. 1

Table 2:

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%

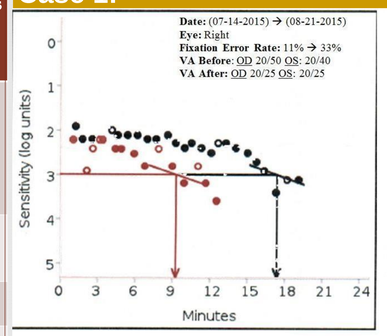
Table 2: Reduction in DA in Minutes (n=14 eyes, n = 8 same / improved and n= 4 worse, 2 unavailable. Fixation Errors (n=14 eyes, n= 8 same / improved +/- 3% and n =6 worsened). NA = non-applicable

Table 3:

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

Table 3: Clinical Dark Adaptation Clinical Data continued; #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).

Case 1:



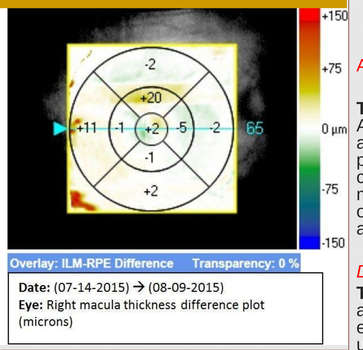
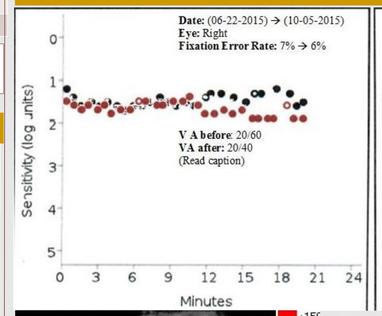
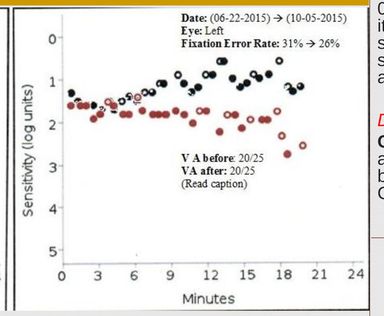
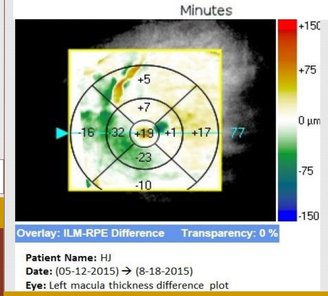


Figure 1a, b Longevinex ® x 5 weeks
Patent SN, an 86 y/o Caucasian male with atrophic AMD for 2 years w vascular component and abnormal R DA, was prescribed Longevinex®. Medical records note glaucoma suspicion R optic nerve vs optic neuropathy. **Figure 1a** DA shortened from ~17 to 8 min R retina, with 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) **Figure 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.

Case 4:







Legend:
Black: Dark Adaptation Before Longevinex Treatment
Red: Dark Adaptation After Longevinex Treatment

Figure #4a, b, c Longevinex® x 4 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.
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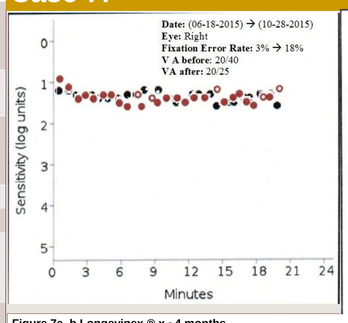
Case 7:



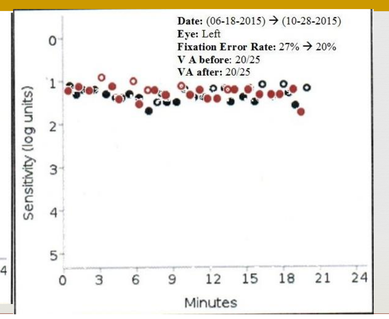


Figure 7a, b Longevinex ® x ~4 months
Patient RD, an 84 y/o Caucasian male with newly diagnosed advanced atrophic AMD prescribed Longevinex ® for ~4 month stable DA and no loss of retinal function, despite an additional 4 months of aging. VA improved 3 lines from 20/40 to 20/25 R eye and L eye remained the same at 20/25.

RESULTS

Adapt Dx® DA data was available for the first 7 patients

Table 1 tabulates 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.

Dark Adaptation Parameter Changes

Table 2 Tabulates 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

Table 3 Tabulates 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.

Dark Adaptation Graphs

Cases 1,4,7 show changes in DA of patients 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.

CONCLUSIONS

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. Longevinex® not only decreases cholesterol, but has been shown to restore myocardial dysfunction in hypercholesterolemic animals.16 In addition, it manifests: No cytotoxicity at high dose (no hormesis), whereas resveratrol at high dose does have toxicity; 2) Is beneficial against human metabolic syndrome; 3) Functions as an antidiabetic drug with insulin like sugar level reducing effects and 4) Promotes choroidal vasorelaxation and thickening. Combining MacuLogix AdaptDx ® screening with 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.

References

Available upon request

Contact Information

Dr. Stuart Richer, OD, PHD, FAAO
Capt. James A. Lovell FHCC Eye Clinic North Chicago, IL 60064
Tel: (224) 610-7145
Stuart.Richer1@va.gov