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Macular Pigment Distribution Responses to High-Dose Zeaxanthin Supplementation in Patients with Macular Telangiectasia Type 2 (MacTel)

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Abstract

Purpose—Analysis of macular pigment (MP) amount and distribution in patients with macular telangiectasia type 2 (MacTel) receiving oral zeaxanthin supplementation in a randomized, open-label interventional trial.

Methods—Eight MacTel patients were randomized to 10 mg or 20 mg of zeaxanthin per day. At each visit, the subjects were examined including best corrected visual acuity (BCVA), contrast sensitivity (CS), fundus biomicroscopy, color fundus photography (CFP), autofluorescence imaging (AFI), optical coherence tomography (OCT), and serum carotenoid levels. Patients were assessed at baseline and after 6, 12, 18, and 24 months of zeaxanthin supplementation. MP concentration was analyzed and calculated from AFI obtained at 488 nm excitation wavelength. Serum carotenoid levels were obtained using high-performance liquid chromatography (HPLC).

Results—The majority of subjects had definite increases in intensity of the macular pigment's hypofluorescent ring, but none of them deposited macular pigment centrally at the fovea. Although some patients noted subjective improvements in vision, no objective improvements could be documented, and there were no changes in foveal OCT features. Yellowish, hypofluorescent crystals appeared in one subject's macular region with no change in visual acuity. These inner retinal crystals disappeared several months after discontinuing her 20 mg zeaxanthin supplement.

Conclusion—Based on our study, zeaxanthin supplementation does not result in any visual benefit in patients with MacTel, and does not re-establish a normal peaked distribution of macular pigment in the fovea. One subject developed a novel, reversible crystalline maculopathy in response to zeaxanthin supplementation that was reminiscent of canthaxanthin crystalline maculopathy.

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Keywords

retinal diseases; macular pigment; retinal vessels; telangiectasis; xanthophylls; zeaxanthin

Introduction

Macular telangiectasia type 2 (MacTel) is a rare disease entity initially characterized and classified by Gass and Blodi¹ based on histologic, slit-lamp biomicroscopic, and fluorescein angiographic findings. The staging classification was further refined by Yannuzzi et al². Patients with MacTel typically present with progressive decrease in vision in the fifth to seventh decades of life^{1,3}. The clinical findings include telangiectatic retinal vessels, loss of retinal transparency with parafoveal graying, telangiectatic retinal vessels, intraretinal crystalline deposits, right-angled vessels, foveal atrophy, hyperplasia of the retinal pigment epithelium, and retinal neovascularization^{1,3-5}. Despite extensive clinical characterization, the underlying genetic and physiological origins of MacTel have not yet been elucidated, but redistribution of the macular carotenoid pigments into a ring-shaped pattern is one of the earliest signs of the disorder⁶⁻⁸.

Carotenoids are ubiquitous pigments synthesized exclusively by plants and microorganisms. There are more than 15 different dietary carotenoids detectable in human serum; however, only lutein, zeaxanthin, and *meso*-zeaxanthin are found in the retina, typically in a peaked distribution centered at the fovea⁹⁻¹². Collectively, these are known as the macular pigment (MP). Previous studies have characterized unique changes in MP distribution using autofluorescence images and confocal blue reflectance in patients with MacTel¹³⁻¹⁵. Zeimer et al⁶ further classified a continuum of changes in macular pigment using 2-wavelength autofluorescence imaging. The most advanced class (Class III) described by their study was characterized by an oval effacement of macular pigment in the center of the fovea and a surrounding ring of macular pigment at 5° to 7° eccentricity. Supplementation with lutein and zeaxanthin has been shown to enhance central macular pigment optical density (MPOD) in patients with age-related macular degeneration¹⁶; however, high-dose lutein and low-dose zeaxanthin supplementation failed to increase macular pigment levels lost in the central fovea of Class III MacTel subjects⁷.

A comprehensive battery of *in vitro* and *in vivo* studies using high dosage zeaxanthin revealed no evidence for mutagenicity or target organ toxicity¹⁷. Human intervention studies indicate good systemic tolerance of zeaxanthin. Van de Kraats et al showed no systemic toxicity with a dose of up to 20 mg/day for up to 6 months¹⁸.

We sought to determine if high-dose zeaxanthin supplementation would be more successful in MacTel patients given that its distribution peaks more sharply at the fovea in normal eyes relative to lutein^{19,20}. Our main aim was to determine the amount and distribution of macular pigment in MacTel patients receiving oral zeaxanthin. Our next aim was to determine if high-dose zeaxanthin supplementation could preserve or enhance visual function as measured by visual acuity and contrast sensitivity. Lastly, we report a novel, reversible crystalline maculopathy in response to zeaxanthin supplementation that was reminiscent of canthaxanthin crystalline maculopathy.

Methods

Subjects

The study was conducted under clinical trials number NCT01354093 and IND112316 as part of the macular telangiectasis (MacTel) project (www.mactelresearch.org), which is the first longitudinal international multicenter trial to investigate the natural history of MacTel in a large patient cohort.

Eight patients with MacTel were recruited for this investigation. They had no prior history of lutein or zeaxanthin supplementation. The study was approved by the local medical ethics committee and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all subjects prior to the study.

Inclusion criteria for this investigation were as follows: either gender who have MacTel (as confirmed by the MacTel Central Study Reading Centre in London), age older than 18 years, ability to travel to the University of Utah for all study evaluations, and no history of lutein or zeaxanthin supplementation.

The eight study subjects were aged between 38 and 79 years. The male to female ratio was 1:7. Best corrected distance visual acuities were tested at 4 meters with standard Early Treatment Diabetic Retinopathy Study (ETDRS) protocols and converted to Snellen equivalents. These values were then transformed to logarithm of the minimum angle of resolution values for statistical analysis. Contrast sensitivity was tested with the CSV-1000 (Vector Vision; Dayton, OH) contrast sensitivity testing instrument. A contrast sensitivity (CS) curve comprised of 4 rows (A, B, C, D) was plotted for each patient, specifically testing 3, 6, 12, and 18 cycles per degree, respectively.

At each visit, all patients were dilated using 0.5% tropicamide and 2.5% phenylephrine. Afterwards, slit-lamp biomicroscopy, color fundus photography, optical coherence tomography (OCT), and single-wavelength autofluorescence imaging with the Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany) was performed. Blood was also drawn to assess serum zeaxanthin levels.

Classification of macular pigment distribution was carried out by a single investigator (PSB) from fundus autofluorescence images. All eight subjects were graded as Class III, as per the classification scheme proposed by Zeimer et al⁶.

The patients were randomly assigned to receive 20 mg or 10 mg of zeaxanthin a day (EyePromise Zeaxanthin; ZeaVision, LLC). Every 6 months, serum levels of zeaxanthin, visual acuity, contrast sensitivity, fundus biomicroscopy, OCT, and macular pigment concentration by autofluorescence were analyzed. After 24 months, supplementation was stopped at the conclusion of the study.

Macular Pigment Measurements Using Single-Wavelength Autofluorescence Imaging (AFI)

For the determination of macular pigment levels and their spatial distributions, the Heidelberg Spectralis image files were exported into and processed with ImageJ software

(NIH, Bethesda, MD). As described in detail in Sharifzadeh et al²¹, individual image pixels were first grouped into small discrete circular pixel areas, with each “disk” containing 30 pixels, and each disk chosen at strategic AFI image regions lying on the macular pigment ring and outside the ring, respectively. For each disk, the individual autofluorescence pixel intensities, I , were averaged, resulting in a corresponding average local disk intensity value, I_{ave} . Next, a disk from on the ring was identified that had lowest autofluorescence intensity, $I_{min(ave)}$ resulting from the highest carotenoid absorption for the excitation light. In a third step, 10 “reference” disks with highest autofluorescence intensities, I_{max} , were selected at eccentricities greater than 7 degrees, image locations where carotenoid absorptions are virtually absent. Areas with blood vessels or other retinal abnormalities, such as retinal holes, hemorrhaging, RPE atrophy or RPE hypertrophy were excluded in the selection of the reference disks.

The maximum obtainable image contrast is calculated as the ratio between the averaged high autofluorescence intensities of the 10 reference disks, $I_{max(ave)}$, and the lowest autofluorescence intensities of the disk on the ring, $I_{min(ave)}$. This ratio, $I_{max(ave)} / I_{min(ave)}$, is proportional to the MPOD according to the relation²¹

$$MPOD = 1.4 \times \log \left(\frac{I_{max(ave)}}{I_{min(ave)}} \right)$$

where 1.4 is a calibration factor taking into account the spectral mismatch between the MP absorption band maximum at 460 nm²² and the excitation wavelength at 488 nm. Images and data from only one eye from each patient were used for analysis at all time points as determined by a masked reviewer based on the eye with the best quality set of autofluorescence images.

Serum Carotenoid Assessment

Standards of lutein, zeaxanthin, α -carotene, β -carotene, lycopene, 3'-oxolutein, and β -cryptoxanthin, were from Kemin Health (Des Moines, IA), DSM (Kaiseraugst, Switzerland) and Dr. Fred Khachik, (University of Maryland, Baltimore, MD). Organic solvents were HPLC grade from Fisher Scientific (Hampton, NH).

Serum (0.2mL) was extracted using ethanol containing 0.1% butylated hydroxytoluene (BHT): ethyl acetate (4:10), followed by hexane extraction. The organic extracts were evaporated to dryness by flushing with inert gas, and the residues were reconstituted in methanol: methyl tert-butyl ether (MTBE) (80:20, v/v) and centrifuged at 2000g before analysis.

Separation of carotenoids was carried out on a Surveyor Plus HPLC system (Thermo Scientific) equipped with an autosampler and photodiode array (PDA) detector, on a C30 column (YMC Europe GmbH, Germany) (250 × 4.6 mm i.d) at a flow rate of 1.0 ml/min²³. A linear gradient of methanol and MTBE (%methanol @ min: 95 @ 0; 70 @ 20; 40 @ 30; 5 @ 40; 95 @ 45; 95 @ 50) was used as mobile phase, and the column was maintained at

room temperature with the PDA detector operated at 450 nm. Peaks were identified and confirmed using PDA spectra and by co-elution with authentic standards as necessary. Standard solutions of each individual carotenoid with known concentrations were calculated spectrophotometrically using published extinction coefficients^{24,25} and were injected in different volumes so as to achieve final injected amounts ranging from 0.1 to 100 ng. The carotenoid content was quantitated using standard curves of available standards.

Results

Serum Zeaxanthin Levels: Response to Supplementation

All patients were compliant with oral zeaxanthin supplementation as assessed by >98% compliance by pill counts. Supplementation resulted in an increase in serum zeaxanthin levels from baseline in all patients but with wide variability. The initial levels of increase and time dependent profiles of serum zeaxanthin levels for the next 24 months are shown for all the patients (Figure 1). Patient D was taken off of supplementation at 6 months because of the formation of retinal crystals, which explains the sharp decrease in zeaxanthin levels at 8 months (Figure 1). The patient was restarted on 10 mg/day of zeaxanthin supplementation at 10 months once the retinal crystals disappeared, and she had a subsequent increase in serum zeaxanthin levels measured at 12 months. Of note, subjects did not have any dietary restrictions throughout the study, and there was a common trend for serum zeaxanthin levels to peak at 6–12 months, followed by declining serum zeaxanthin levels at the later time points.

Classification of Macular Pigment Optical Density in Patients with Idiopathic Macular Telangiectasia

As established by Zeimer et al⁶, the classification system for patterns of macular pigment distribution was used to categorize each patient. At baseline and study completion, all subjects were noted to be Class III, which corresponds to an oval effacement of macular pigment centrally with a surrounding halo of macular pigment at 5–7 degrees eccentricity. (Figure 2).

Macular Pigment Optical Density Response to Supplemental Zeaxanthin

All subjects had an initial increase in the maximum MPOD level with zeaxanthin supplementation (Figure 3). Although all subjects showed an increase in MPOD levels, this augmentation was solely in the oval-shaped perifoveal halo of macular pigment in 5 to 7 degrees eccentricity. (Figure 2A–C) There was no enhancement of macular pigment in the central fovea where pigment was absent.

One subject, Patient D, showed a sharp decrease in MPOD at 8 months as she had been asked to stop supplementation by the principal investigator two months earlier. When she restarted zeaxanthin supplementation at 10 months, her MPOD increased as measured at 12 months. (Patient D; Figure 3)

No Correlation Between MPOD Levels, OCT, and Visual Function

There was no discernable correlation between visual acuity, OCT thickness, and contrast sensitivity with MPOD (n = 8; Table 1). There was a general decline in visual acuity and contrast sensitivity with time. No trend could be established with macular thickness as measured by OCT.

Retinal Crystal Formation while on Zeaxanthin Supplementation

One patient (Patient D) developed yellowish retinal crystals in her macula while on oral zeaxanthin supplementation. They were first discovered with fundoscopic examination 6 months after starting 20 mg/day of oral zeaxanthin supplementation, and autofluorescence imaging confirmed that they had no intrinsic fluorescence and that they blocked underlying choroidal autofluorescence, consistent with the optical properties of the macular carotenoid pigments (Figure 4B). OCT imaging indicated that these crystals were in the inner retina (Figure 5), which differentiates these crystals from those typically seen in MacTel patients at the vitreoretinal interface which are neither hypo- nor hyperfluorescent. Upon observing these crystals, the patient was taken off of zeaxanthin supplementation. As expected, two months after stopping zeaxanthin, the patient's serum zeaxanthin levels declined (patient D; Figure 1), as well as her MPOD (patient D; Figure 3). The retinal crystals were no longer detectable at this time (Figure 4C), suggesting that these crystals were a direct result of oral zeaxanthin supplementation.

Discussion

Lutein, zeaxanthin, and *meso*-zeaxanthin are the three carotenoids that accumulate at the macula and are defined as macular pigment^{16,26–28}. Their redistribution appears to be a novel phenotypic characteristic specific to MacTel^{6,7,14,15}. Because of this unique feature, it is hypothesized that MP pattern changes may be part of the pathophysiology of this disease. The macular pigment is thought to offer protection against retinal damage via its short-wavelength light screening and antioxidant properties^{9,29}. Extensive knowledge regarding the molecular and storage mechanisms for macular pigments is lacking; however, the high concentrations of macular pigment in the retina compared to the blood indicate active transport and concentration mechanisms. Additionally, past studies have indicated that specialized carotenoid binding proteins and relative inactivity of carotenoid-specific cleavage enzymes in humans are involved in selective uptake and deposition in the macula^{30–32}.

There is conflicting evidence in the literature about whether a relationship exists between MPOD levels and zeaxanthin dietary supplementation. Some studies suggest the absence of a clear relationship between carotenoid dietary supplementation or plasma carotenoid levels and MPOD levels.^{33,34} In other studies, lutein and zeaxanthin supplementation has been shown to increase MPOD in patients with age-related macular degeneration^{35–37}. A subsequent study determined that over a nine-month period, supplementation with a high concentration of lutein could increase MPOD in patients with MacTel; however, this occurred only in areas where macular pigment accumulation was still present at baseline⁷. Naturally, we asked if supplementation with high doses of zeaxanthin could normalize

macular pigment distribution in patients with MacTel, given that its distribution peaks more sharply at the fovea than lutein in normal eyes^{19,20}. Furthermore, one study determined that zeaxanthin was more reduced compared to lutein in the macula of patients with MacTel¹⁴. In an earlier pilot study, a continuum of changes in distribution of macular pigment was observed in patients with MacTel, and a classification system was developed⁶. At baseline, all subjects in our study met criteria for Class III, which is characterized by an oval effacement of macular pigment in the center of the fovea and a surrounding ring of macular pigment at 5° to 7°. After supplementation with high dose zeaxanthin, MPOD levels increased at an eccentricity of 5° to 7° only, with no increase detected between 0.5° and 2° eccentricity where macular pigment was not present at baseline.

The exact mechanisms governing macular pigment redistribution in MacTel have still not been elucidated. Previous studies suggest that it may be the result of progressive anatomical changes in the central retina⁶. Histologic analyses have shown that macular pigment is mainly localized in the outer plexiform layer. It is possible that the axons of photoreceptors and Müller glial cells may be structurally altered in MacTel, and prior reports provide evidence of Müller cell loss specifically in areas of depleted macular pigment^{38,39}. Furthermore, Degli Esposti et al⁴⁰ determined that the mean total amount of macular pigment within the central 21 degrees was greater for normal subject than for patients with an annular distribution of macular pigment, suggesting that there is a cumulative loss of macular pigment in MacTel.

The visual acuity and contrast sensitivity values progressively worsened for all subjects regardless of the elevation of macular pigment levels at 5° to 7° eccentricity. Robust statistical analyses could not be performed for these functional measurements of vision because of the small cohort of patients. Despite this limitation, we can conclude that increases in macular pigment at 5° to 7° eccentricity did not result in any functional improvement in vision as measured by visual acuity and contrast sensitivity in our cohort. Of note, there was no difference in OCT thickness between the beginning and end of the study.

Serum zeaxanthin levels initially increased in all subjects when started on supplementation. Over time, each subject had varying levels that tended to peak at about 12 months. This may be due to each subject's individual phenotype for various carotenoid-specific regulatory, binding, and transport proteins as has been described in the literature^{30,41–47}. The lack of obvious correlation between serum zeaxanthin and MPOD levels could be explained by each subject having varying levels of expression for carotenoid-specific binding proteins in the macula^{30,41,45}. No dietary restrictions were placed on the patients, which could also be responsible for variations in serum zeaxanthin levels. Lastly, compliance appeared high based on pill counts, however; whether the patients actually ingested the zeaxanthin pills is unknown, which could be another explanation as to the lack of correlation between serum zeaxanthin levels and MPOD.

Previous reports have described retinal crystalline formation from various medications or exogenous substances such as nitrofurantoin, tamoxifen, methoxyflurane, ethylene glycol, oxalic acid, and talc from IV drugs^{48–50}. Canthaxanthin, one of the 600 naturally occurring carotenoids, when ingested in sufficient amounts can also result in the formation of retinal

crystals^{51,52}. We describe the first case of crystalline retinopathy from oral zeaxanthin supplementation. These crystals were localized in the inner retina as determined by OCT, unlike those observed at the vitreoretinal interface seen in MacTel. Visual acuity was not affected by the crystals, and the patient did not experience any scotomas from them. Unlike canthaxanthin crystals, these crystals were rapidly reversible, as they dissolved within months of cessation of zeaxanthin supplementation. These crystals were very similar to our recently described crystalline maculopathy associated with high-dose lutein supplementation except the lutein crystals were located in the fovea⁵³.

Our study showed that patients with Class III MacTel on zeaxanthin supplementation increased MPOD in areas with preserved macular pigment at baseline, and there was no improvement in functional vision as measured by visual acuity or contrast sensitivity. Rather, these values appeared to worsen slightly over the course of the study, consistent with the natural history of the disease.

The limitations of our study include the lack of a placebo control and a small sample size which makes it difficult to determine statistically significant outcomes, especially with regard to whether or not zeaxanthin supplementation could improve functional vision, halt progression of the disease, or delay remodeling of macular pigment. Zeimer and colleagues determined in a 5-year follow up study that in patients with MacTel without any carotenoid supplementation there was a small increase in the MPOD at the 4.53° to 6.21° eccentricity⁸. Based on this study, the level of MPOD accumulation at the 5° to 7° eccentricity we determined appears to be larger than would be expected for unsupplemented MacTel patients; however, a larger study with appropriate controls is necessary to determine this with statistical significance. Another shortcoming was the use of single-wavelength instead of dual-wavelength autofluorescence imaging because digitally subtracting an autofluorescence image taken at a wavelength (~550 nm) with minimal macular pigment absorption improves image quality and reliability of assessing distribution of macular pigment⁵⁴, but unfortunately, this feature was not available on the Spectralis in the United States at the time of this study.

Future studies should look into the effect of *meso*-zeaxanthin supplementation on macular pigment distribution in MacTel patients, as one study has shown that carotenoid formulations including *meso*-zeaxanthin showed an increase in MPOD at all eccentricities and visual performance in normal subjects compared to those on carotenoid formulations without *meso*-zeaxanthin⁵⁵. Other studies have shown a statistically significant augmentation of the macular pigment spatial profile in age-related macular degeneration patients on a carotenoid formulation containing *meso*-zeaxanthin versus one without it^{56, 57}. Future studies comprised of larger intervention groups will be necessary to answer these questions with clinical significance.

Although we showed no beneficial effect of zeaxanthin supplementation, many of the subjects felt that they were seeing better, and the majority of our subjects have continued taking zeaxanthin supplements on their own after the completing the study. Until further studies are done, we conclude that zeaxanthin supplementation in MacTel patients at 10 mg

per day is generally safe and might increase MPOD in the ring surrounding the fovea, but it does not increase foveal pigment density and results in no objective visual benefit.

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Summary Statement

High-dose zeaxanthin supplementation does not normalize aberrant macular pigment distribution and does not provide any visual benefit in patients with macular telangiectasia type 2 (MacTel). Also, we report the first case of retinal crystal formation with zeaxanthin supplementation.

Fig. 1.

Quantitative analysis of serum zeaxanthin levels for each patient while on oral zeaxanthin supplementation. Measurements were obtained at baseline, then every 6 months until the end of the study at 24 months. Generally, most patients had an initial increase in serum zeaxanthin levels, which had subsequent varying profiles. Values at baseline and 24 months were not obtained for patient B. Patient F did not have values obtained at 18 and 24 months. Patients A and D did not have measurements at 24 months. Patient D was taken off of supplementation at 6 months due to the development of retinal crystals, which explains the sharp decrease in levels at 8 months. She restarted supplementation at 10 months once the crystals disappeared.

Fig. 2.

Autofluorescence images with 488-nm excitation of subject E showing (A) an oval area of reduced macular pigment in the center fovea with a surrounding ring of macular pigment (arrows; A) at baseline. While on zeaxanthin supplementation, there is a gradual enhancement of the surrounding ring of macular pigment with time (arrows; B & C). Corresponding serum zeaxanthin levels (Z) at each time point are listed at the top right of each panel.

Fig. 3.

Quantitative analysis of MPOD for each patient while on oral zeaxanthin supplementation. Peak MPOD values at the ring were obtained at baseline, then every 6 months, until study completion at 24 months. Overall, there was an initial increase in MPOD levels from baseline for all subjects. Thereafter, the trending values varied for all subjects. Patient D showed significant decline in MPOD at 8 months due to being taken off of supplementation because of the development of retinal crystals. She was placed back on reduced-dose supplementation at 10 months once the crystals dissolved. MPOD levels were not obtained for patient A at 6 months, patient E at 18 months, patient G at 12 months, and patients D and F at 24 months.

Fig. 4.

Formation of intraretinal crystals in patient D while on zeaxanthin supplementation. Prior to the start of supplementation there are no crystals on color fundus images (A) or autofluorescence 488-nm images (B). After six-months on zeaxanthin supplementation, retinal crystals formed (arrow; C), also appreciated as a hypoautofluorescent lesion (arrow; D) on autofluorescence imaging. Two months after stopping zeaxanthin supplementation, the retinal crystals resolved (E & F). Corresponding serum zeaxanthin levels at each time point are listed at the top right of each panel.

Fig. 5. Infrared image (A), corresponding optical coherence tomography image (B) and color fundus photograph (C) for patient D after 6 months on zeaxanthin supplementation showing the crystals to be in the inner retina.

Table 1

Study Results at Baseline (BL) and End-of-Study (EOS).

Subject	Sex	Age	Zeaxanthin Dose (mg/day)	Study Eye	MPOD	Serum Zeaxanthin (ng/mL)	CS	BCVA (Log MAR)	OCT thickness (μm)
A (BL) (EOS)	Female	38	20	OD	0.45	26	A 0.8, B 0.8, C 1.0, D 0.85	20/100 (0.7)	257*
					0.56	106*	A 0.6, B 0.65	20/250 (1.1)	242
B (BL) (EOS)	Female	79	20	OD	0.11	319*	A 1.0, B 0.9, C 0.9, D 0.4	20/80 (0.6)	285
					0.2	57*	A 1.0, B 0.8, C 0.8, D 0.95	20/100 (0.7)	281
C (BL) (EOS)	Male	68	20	OD	0.14	70	A 1.15, B 1.1, C 1.25, D 1.35	20/16 (−0.1)	273
					0.3	230	A 1.1, B 1.1, C 1.25, D 1.35	20/20 (0)	289
D (BL) (EOS)	Female	57	20	OD	0.38	59	A 0.7, B 0.8, C 0.7, D 0.55	20/160 (0.9)	235
					0.42	686*	A 0.6, B 0.65, C 0.7, D 0.55	20/320 (1.2)	247
E (BL) (EOS)	Female	66	20	OS	0.37	49	A 1.0, B 0.95, C 0.9, D 0.85	20/32 (0.2)	326
					0.58	748	A 0.7, B 0.8, C 0.7, D 0.7	20/40 (0.3)	340
F (BL) (EOS)	Female	59	10	OD	0.28	50	A 0.9, B 0.95, C 1.0, D 0.95	20/50 (0.4)	246
					0.42*	246*	A 1.1, B 0.95, C 0.8, D 0.95	20/50 (0.4)	241
G (BL) (EOS)	Female	51	10	OS	0.15	40	A 1.0, B 0.95, C 1.25, D 1.35	20/20 (0)	225
					0.16	75*	A 1.25, B 1.1, C 1.25, D 1.35	20/16 (−0.1)	221
H (BL) (EOS)	Female	55	10	OD	0.38	211	A 1.1, B 1.1, C 1.25, D 1.35	20/16 (−0.1)	284
					0.37	512	A 1.0, B 1.1, C 1.25, D 1.35	20/16 (−0.1)	295

Subject	Sex	Age	Zeaxanthin Dose (mg/day)	Study Eye	MPOD	Serum Zeaxanthin (ng/mL)	CS	BCVA (Log MAR)	OCT thickness (µm)
Mean (BL) (EOS)					0.28 ± 0.13	103 ± 104	A(0.96 ± 0.15) B(0.94 ± 0.11) C(1.04 ± 0.20) D(0.97 ± 0.37)	0.33 ± 0.38	266 ± 33
P					0.38 ± 0.15	333 ± 278	A(0.91 ± 0.25) B(0.89 ± 0.20) C(0.96 ± 0.27) D(1.03 ± 0.33)	0.44 ± 0.52	270 ± 39
					0.21	0.05	A(0.72), B(0.54), C(0.6), D(0.78)	0.63	0.86

* Baseline and end-of-study results were not obtained. The closest beginning and end point results were used instead.

A = 3 cycles/degree, B = 6 cycles/degree, C = 12 cycles/degree, D = 18 cycles/degree

BCVA = best corrected visual acuity

MPOD = macular pigment optical density

CS = contrast sensitivity

OCT = optical coherence tomography

STD = standard deviation

P = p-value