Carotenoids in Age-related Maculopathy Italian Study (CARMIS): two-year results of a randomized study

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ORIGINAL ARTICLE

Carotenoids in Age-related Maculopathy Italian Study (CARMIS): two-year results of a randomized study

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Purpose. *The high concentration of carotenoids in the macula, plus evidence linking oxidative stress to age-related macular degeneration (AMD) and carotenoids to antioxidation, generated the hypothesis that higher antioxidant intakes can prevent AMD. The aim of this study was to determine whether nutritional supplementation with a targeted nutritional supplement improves visual acuity and visual function in AMD.*

Methods. *In this multicenter, prospective open-label randomized study, 145 patients were randomly assigned to 2 different treatment groups. Interventions were lutein (10 mg), zeaxanthin (1 mg), astaxanthin (4 mg; AZYR SIFI, Catania, Italy), and antioxidants/vitamins supplementation formula or no dietary supplementation for 2 years. Primary outcome was mean changes in visual acuity (VA) at 12 and 24 months. Other measures included contrast sensitivity (CS) and National Eye Institute visual function questionnaire (NEI VFQ-25) scores at 12 and 24 months.*

Results. *Patients in the treated group showed stabilization of VA with significantly (p=0.003) better VA scores (81.4±7.2) compared to the nontreated group (76.8±8.9) at 24-month follow-up. An improvement in CS (p=0.001) and final mean NEI VFQ-25 composite scores at 12 and 24 months higher in treated group compared to nontreated group were also shown (p<0.001).*

Conclusions. *Patients treated with lutein/zeaxanthin and astaxanthin together with other nutrients were more likely to report clinically meaningful stabilization/improvements in VA, CS, and visual function through 24 months compared with nontreated subjects. Further studies are needed with more patients and for longer periods of time.*

Key Words. *Age-related macular degeneration, Carotenoids, Lutein, Macular pigment, Zeaxanthin*

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INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss in the elderly population in the Western world (1). It is estimated that 1.6% of the population in the 50- to 65-year age group is affected, rising to 30% in the age group over 75 years (2-4). While the exact etiopathogenesis of AMD remains uncertain, there is a growing body of evidence that oxidative damage, which refers to tissue damage by reactive oxygen intermediates (ROIs), may play a causal role (5). The retina is thought to be highly susceptible to oxidative stress

given its high oxygen consumption, high concentration of polyunsaturated fatty acids and photosensitizers, and exposure to light. Although new treatments have emerged, they are suitable only for the small proportion of people with wet AMD (6-8). Recent findings have suggested that the antioxidant xanthophylls carotenoids lutein (L) and zeaxanthin (Z), which are naturally present in the retinal pigment epithelium, may protect against the development of AMD (9-13). Together these 2 carotenoids are referred to as macular pigment (MP). Macular pigment is purported to prevent or retard the development or progression of AMD because of its ability to absorb blue light at prereceptorial level, and its capacity to quench ROIs via its powerful antioxidant activity (14, 15). The relatively high concentration of MP in the inner retinal layers is very likely to indicate a photoreactive role, whereas the presence of MP in the rod outer segments is suggestive of a ROS-quenching function (L and Z have been found in higher concentration in the rod outer segments of the perifoveal retina than the peripheral retina, again lending support to their proposed protective role in age-related maculopathy and AMD) (16). Multiple studies have suggested that manipulation of nutritional factors can play a significant role in slowing the onset or limiting the effects of AMD (17-21). In the present study, we report the 2-year results of the Carotenoids in Age-Related Maculopathy Italian study (CARMIS), a multicenter prospective randomized study, designed with the objective of evaluating whether short-term supplementation with a fixed combination of selected antioxidants and carotenoids could influence psychophysical and psychometric parameters in patients with dry AMD by measuring visual acuity (VA), contrast sensitivity (CS), and vision-related quality of life by National Eye Institute Visual Function Questionnaire (NEI VFQ-25).

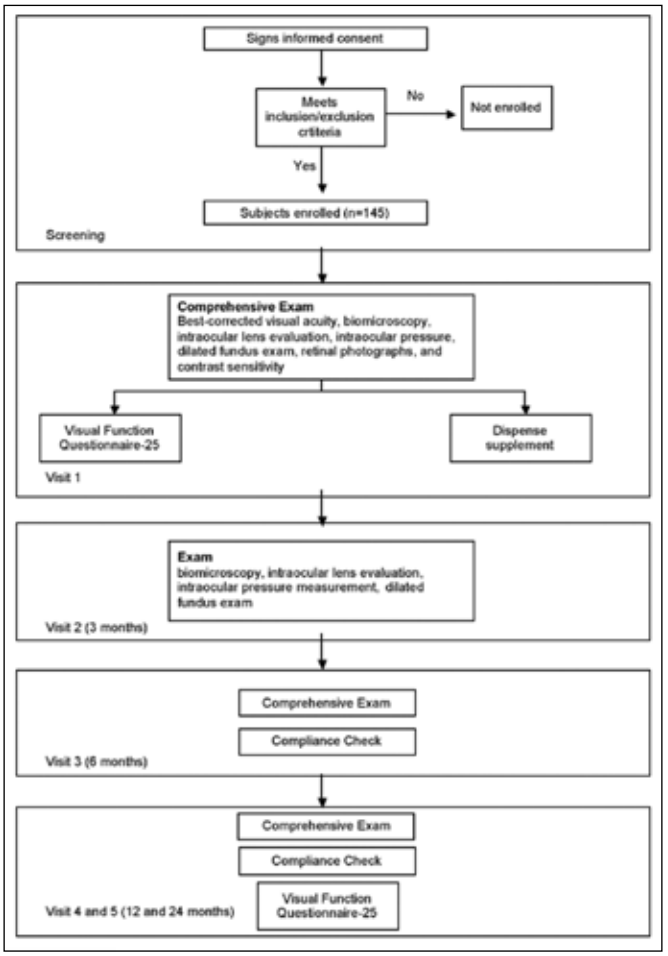

Fig. 1 - *Study design.*

METHODS

Study design

A 24-month prospective open-label randomized study took place between December 2003 and September 2006. A total of 145 eligible subjects (59 men and 86 women; mean age ± SD, 72.5±7 years; median 74 years) were recruited. Patients were randomized to receive a nutritional supplement based on carotenoids, oligoelements, and antioxidant vitamins (treated AMD [T-AMD] group), or no dietary supplementation (non-treated AMD [NT-AMD] group). Group T-AMD (41 men and 61 women; mean age 72.5±6.8 years) took oral daily supplementation of vitamin C (180 mg), vitamin E (30 mg), zinc (22.5 mg), copper (1 mg), lutein (10 mg), zeaxanthin (1 mg), and astaxanthin (4 mg [AZYR SIFI, Catania, Italy]) for 24 months; group NT-AMD (18 men and 25 women; mean age, 72.6±7.5 years) had no dietary supplementation during the same period. When patients fulfilled the inclusion criteria (Tab. I), the eye with the best VA was selected. When both eyes had the same VA, the right eye was chosen for final analysis. Study drug was administered by an unmasked physician who had no other role in the study. In order to allow for an unbiased assessment of VA and ancillary study measures, an independent physician was assigned the role of masked evaluator. The study coordinator allocated study numbers

TABLE I - INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria
Signed written consent
Between the ages of 55 and 80
Any race or gender
Diagnosis of nonexudative (dry) age-related macular degeneration (AMD) in at least one eye having extensive (as measured by drusen area) intermediate (≥63 mm, <125 mm) drusen; and at least one large (≥125 mm) drusen or geographic atrophy not involving the center of the macula
Best-corrected visual acuity in the trial eye ≥20/32 (0.2 logarithm of the minimum angle of resolution [logMAR]), 74 letters of Early Treatment Diabetic Retinopathy Study [ETDRS] chart)
Able to understand and comply with the requirements of the trial
Subjects must not have conditions that limit the view to the fundus (e.g., vitreous hemorrhage, cataracts, epiretinal membrane)
Subjects must be available for a minimum trial duration of approximately 6 months
Subjects must agree to take only the nutritional supplement that is provided during this study
Subjects or eyes must not meet any of the exclusion criteria
Exclusion criteria
Ocular
Visual acuity <20/32 (VA score <74 letters ETDRS chart)
Patients with advanced AMD in one or both eyes
Patients with ocular disease that causes irreversible reduction of visual acuity (amblyopia, uncontrolled glaucoma, anterior ischemic optic neuropathy, clinically significant macular edema)
Patients with significant opacity of the dioptrical media that prevents fundus examination; patients with evolved cataract; all patients with lens opacity and score 4+ (Lens Opacity Classification System II) will be excluded from the enrollment, while the possible surgery has to be performed at least 2 months before the enrollment in the study
Patients with insufficient pupil dilation
Patients already subjected to laser treatment of the posterior pole for any other reason
Patients with macular changes not attributable to AMD
General
Patients with carotenoids intolerance
Patients with major chronic disease
Life expectation lower than 6 months
Withdrawal of informed consent
Enrollment in another clinical study with experimental product within the last 4 weeks or during the current study
Patients unable and/or not willing

sequentially, as participants were enrolled. Participants were then randomly allocated to the treatment or no treatment group. A permuted blocks allocation scheme was used to perform this random allocation. The allocation list was stored at a remote site.

Study follow-up

Each subject was scheduled for 5 visits (Fig. 1). During the first visit, those who met the inclusion and exclusion criteria underwent a comprehensive eye examination including medical and ophthalmic history, refraction, best-corrected visual acuity (BCVA) measured by Early Treatment Diabetic Retinopathy Study (ETDRS) logMAR charts at 4 m, biomicroscopy, intraocular lens evaluation, intraocular pressure, dilated fundus examination, and CS. Subjects were instructed to self-administer the oral supplements at 1 tablet a day, concurrent with food intake at the same time every day. During the second visit at 3 months, biomicroscopy, intraocular lens evaluation, intraocular pressure measurement, and dilated fundus examination were carried out. The third, fourth, and the final exit visits were carried out at months 6, 12, and 24, respectively, and were a repeat of the first visit in addition to a compliance assessment. The National Eye Institute Visual Function Questionnaire (NEI VFQ) Italian version (22) was conducted. The 25-item NEI VFQ was administered to all patients at baseline and at 12- and 24-month follow-up. Treatment compliance was assessed at each follow-up control, via a daily patient log. They were encouraged not to alter their diets or to change their current supplementation regimen. The number of capsules returned by participants during

the course of the study was documented as one measure of compliance. Participants were encouraged to report any adverse effects immediately and were asked specifically about adverse events and compliance during the follow-up examination. Adverse effects were investigated and periodically reported to the data monitoring and safety committee for review. The study adhered to the tenets of the Declaration of Helsinki for research involving human subjects and was approved by Ethics Committee. Each participant gave written consent prior to enrollment into the study.

Outcome measures

The primary outcome of the study was to measure changes in BCVA (the number of letters read on the logMAR chart) during the follow-up (6, 12, and 24 months). Secondary outcomes were changes in macular function by CS using a Pelli-Robson chart (Clement Clarke International, Harlow, Essex, UK) scored per lines and changes in visual function via the Italian-validated version of the 25-item test (22). The NEI VFQ-25 was administered prior to visual acuity measurements at baseline, 12, and 24 months by trained study-site personnel who were masked to treatment assignment.

Sample size calculation

Sample size was based on the expected outcome of the main endpoints of the study: VA and CS. A total number of 145 subjects was considered to be adequate to recognize as statistically significant a difference of at least 2.5 lines for VA, and 2.1 lines for CS between the mean values of the 2 groups at the 5% significance level and a power of 80%.

Statistical analysis

Analysis of variance with repeated measures (ANOVA-RM) was used to assess main outcome variables and NEI VFQ-25 scores. Main effects such as time and group as well as time–group interaction effect were tested. Additionally, follow-up analyses for significant group differences were done by pairwise comparisons between baseline and each time point (6, 12, and 24 months). Comparisons between the 2 groups were performed by means of Student *t* test or chi-square test when quantitative or qualitative variables were analyzed, respectively. A qualitative analysis of changes over time has been conducted. Changes of the main parameters at 24 months from the beginning of study were classified for VA as follows: 1) worsened if the subject lost more than one line; 2) improved if the subject gained more than one line; and 3) stable otherwise. For CS: 1) worsened if the subject lost 3 or more letters; 2) improved if the subject gained 3 or more letters; and 3) stable otherwise. NEI VFQ-total score: 1) worsened if the subject lost 10 or more points; 2) improved if the subject gained 10 or more points; and 3) stable otherwise. A joint criterion to classify subjects in terms of VA, CS, and VFQ-total score changes has been introduced as well. Subjects were classified as 1) worsened if they appeared to be worsened in at least one parameter; 2) improved if at least one of their parameters did so; 3) stable otherwise. Subjects who, according to this classification, appeared worsened in one parameter and improved in one other were considered incoherently classifiable and hence excluded from the analysis. Relative risks (RR), and their 95% confidence interval (CI), were computed in order to evaluate the capability of preventive treatment of a subject's worsening in terms of parameter changes. Data analysis was adjusted for age, gender, and cataract progression. A separate analysis evaluated the effect of lens opacity progression when it occurred in the eye with better VA at the first administration in persons with at least a 5-letter difference in VA between eyes. In all statistical analyses, $p<0.05$ was considered as statistically significant. All analyses were performed by SAS® 9.1.3 statistical package on personal computer (SAS Institute Inc. SAS/STAT®. Cary, NC: SAS Institute Inc.; 2007).

RESULTS

Demographics and baseline characteristics of the 145 patients receiving the nutritional supplement are outlined in Table II. Eighty-four patients and 26 in group T-AMD vs group NT-AMD, respectively, have been considered for the final statistical analysis of psychophysical and psychometric tests. Nineteen people in the group T-AMD, and 16 subjects from the group NT-AMD, were excluded from final data analysis. Thirteen (12.7%) subjects in the T-AMD group developed CNV, and 4 (9.3%) in the group NT-AMD. There were no statistically significant differences in the development of CNV between the 2 groups (chi-square test, p=0.760). The patients who failed to complete the final

TABLE II - DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Variable	T-AMD group (n=103)	NT-AMD group (n=42)	p value
Gender, n (%)			
Female	62 (60.1)	25 (59.2)	—
Male	41 (39.8)	17 (40.7)	—
Age, y			
Mean ± SD	72.5 ± 6.8	72.6 ± 7.5	0.30
Range	54 to 84	57 to 90	
55–69 y	34	14	
70–79 y	55	25	
80–90 y	15	3	
Current smoker, no, n (%)	17 (16.5)	7 (16.6)	0.71
Former smoker, n (%)			
No	42 (40.7)	23 (54.7)	0.4
Yes	44 (42.7)	12 (28.5)	0.34
Body mass index			
Underweight	2 (1.9)	1 (2.3)	0.78
Normal range	47 (45.6)	12 (28.5)	0.56
Overweight	47 (45.6)	24 (57.4)	0.80
Obese	7 (6.7)	5 (11.9)	0.45
Blue iris color	21 (20.3)	11 (26.1)	0.63
Diabetes	4 (3.8)	—	0.23
Hypertension	16 (15.5)	—	0.1
Heart disease	13 (12.6)	1 (2.3)	0.15
Other	31 (30)	—	0.06
Cataract surgery	31 (30)	—	0.07
Cataract (R LOCS-III rating)	2.73 (1.0)	2.78 (1.12)	0.58
Nuclear opalescence (SD)			
Cortical	1.80 (1.05)	1.75 (1.05)	0.67
Posterior subcapsular	1.02 (0.15)	1.25 (0.80)	0.23
Cataract (L LOCS-III rating)	3.12 (0.94)	3.00 (1.31)	0.56
Nuclear opalescence (SD)			
Cortical	1.70 (0.84)	1.75 (1.07)	0.13
Posterior subcapsular	1.04 (0.25)	1.16 (0.75)	0.78
Glaucoma	8 (7.7)	—	0.2
Diabetic retinopathy	—	—	—
Mean ± SD baseline BCVA (ETDRS letter score)	82 ± 5.7	81.5 ± 5.9	0.67
Mean ± SD baseline CS (letter score)	32.1 ± 4.4	31.8 ± 4.8	0.34
Mean ± SD baseline NEI VFQ-25	81.6 ± 13.6	82.9 ± 13.3	0.56

BCVA = best-corrected visual acuity; CS = contrast sensitivity; ETDRS = Early Treatment Diabetic Retinopathy Study; LOCS = Lens Opacity Classification System; NEI VFQ-25 = National Eye Institute Visual Function Questionnaire; NT-AMD = nontreated age-related macular degeneration; T-AMD = treated age-related macular degeneration.

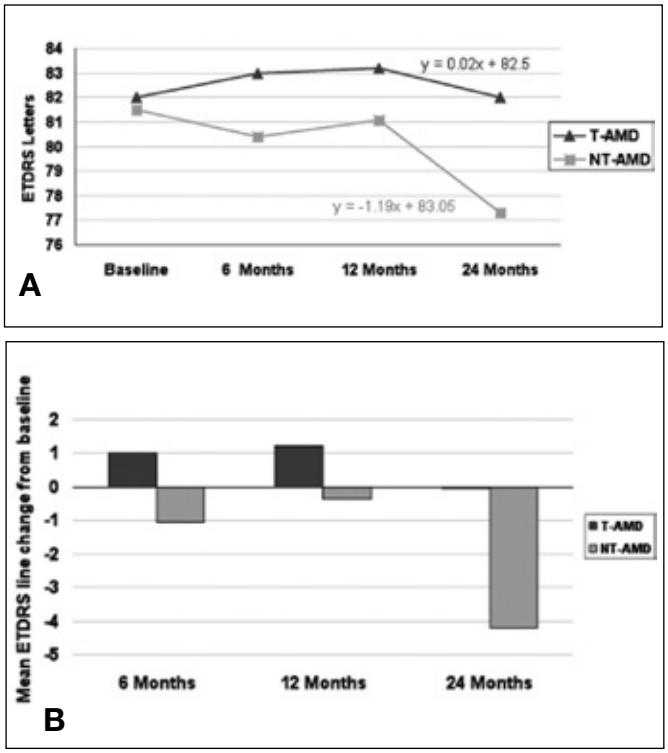

Fig. 2 - (A) *The repeated-measures analysis of variance on visual acuity (VA) showed a significant group by time of measurement interaction (F[3,273]=4.66, p=0.0034). After 2-year supplementation treated age-related macular degeneration (T-AMD) patients showed a positive trend of VA Early Treatment Diabetic Retinopathy Study (ETDRS) score (slope 0.02x) compared to the nontreated age-related macular degeneration (NT-AMD) group (slope –1.19x).* **(B)** *Mean ETDRS line change from baseline to 6, 12, and 24 months. A significant mean ETDRS line gain was observed at each time point in group T-AMD vs group NT-AMD (+1.01 vs –1.04) (p=0.03); +1.21 (95% confidence interval [CI] 0.22 to 2.19) vs –0.36 (95% CI –1.58 to 0.85) (p=0.04); –0.02 (95% CI –1.42 to 1.36) vs – 4.18 (95% CI –7.34 to –1.01) (p=0.008) in group T-AMD compared to group NT-AMD at 6, 12, and 24 months, respectively; Student t test).*

evaluation did not differ statistically on demographics, VA, CS, or VFQ from those patients who completed it. During the 1-year study, 95% of the subjects took approximately 92% of their assigned tablets. The rate of compliance with the study protocol for treatment and examinations was high and similar for both groups. There was no difference in compliance between the 2 groups (χ^2=4.61, *df*=1, p=0.57). There were no significant systemic or ocular adverse events related to the nutritional supplementation. There was no difference in nutritional supplementation habits between the 2 groups (Tab. III).

Visual acuity

The ANOVA-RM on VA showed a significant group by time of measurement interaction (F[3,273]=4.66, p=0.0034) (Fig. 2A). At 6 and 12 months, 80.2% of patients in T-AMD group showed stabilization/improvement of VA and significantly better ETDRS letters scores compared to group NT-AMD. A significant mean ETDRS line gain was observed at each time point in group T-AMD vs group NT-AMD (Fig. 2B). The ANOVA-RM analysis on VA indicated significant within-group differences over time. Within group T-AMD tests comparing baseline to final study visit showed significant VA improvement in group T-AMD (p=0.03; p=0.01; p=0.05, at 6, 12, and 24 months). At 24 months, of those subjects in group T-AMD, 59.1% experienced improved BCVA, 21.1% maintained their BCVA, and 19.7% experienced worsened BCVA. The VA increased in group T-AMD not depending on the severity of disease. Data analysis showed that fewer patients treated with nutritional supplementation lost 5 or more letters at 24-month follow-up. The ratio of

TABLE III - REASONS FOR WITHDRAWAL OR DISCONTINUED INTERVENTION

	Withdrawn		Discontinued intervention	
	Carotenoids	Control	Carotenoids	Control
Died	0	0	0	0
Adverse reaction	0	0	0	0
After cataract extraction	2	1	2	2
Health-related	1	0	4	2
Personal	2	1	7	8
Compliance	3	0	0	1
Adverse event (choroidal neovascularization)	6	1	7	4
Total	14	3	20	17

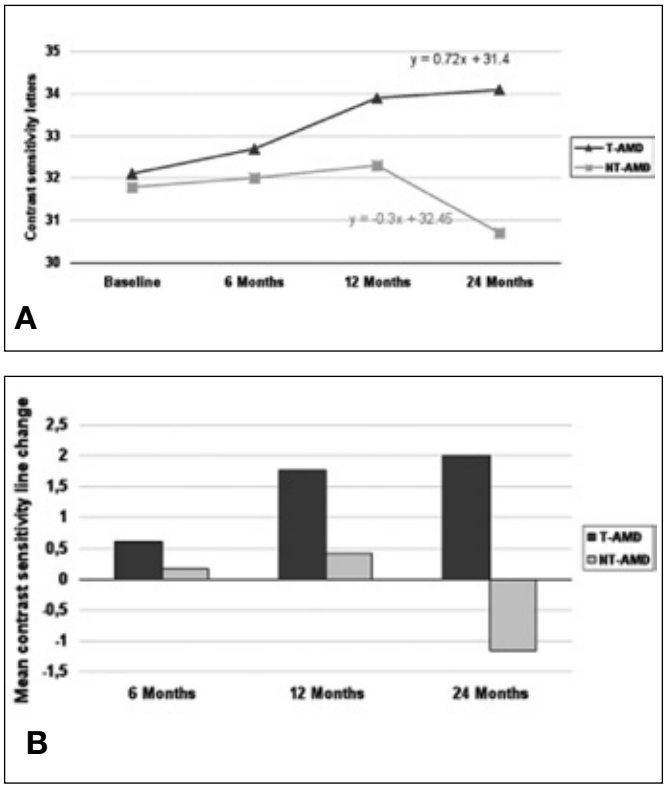

Fig. 3 - (A) *The repeated-measures analysis of variance showed a significant group by time of measurement interaction (F [3,258]=5.11, p=0.0019). The treated age-related macular degeneration (T-AMD) group showed a positive trend of contrast sensitivity (CS) letters score (slope 0.72x) compared to the nontreated age-related macular degeneration (NT-AMD) group (slope –0.3x).* **(B)** *Mean CS line change from baseline to 6, 12, and 24 months. At 6, 12, and 24 months follow-up the mean CS line change increased by 0.6 (95% confidence interval [CI] 0.04 to 1.17), 1.76 (95% CI 1.09 to 2.44), and 2 (95% CI 0.80 to 3.19) in group T-AMD, and decreased by 0.15 (95% CI –0.74 to 1.05), 0.42 (95% CI –1.25 to 2.09), and 1.15 (95% CI –2.86 to 0.54) in group NT-AMD (p=0.4; p=0.08; p=0.01 at 6, 12, and 24 months, respectively; Student t test).*

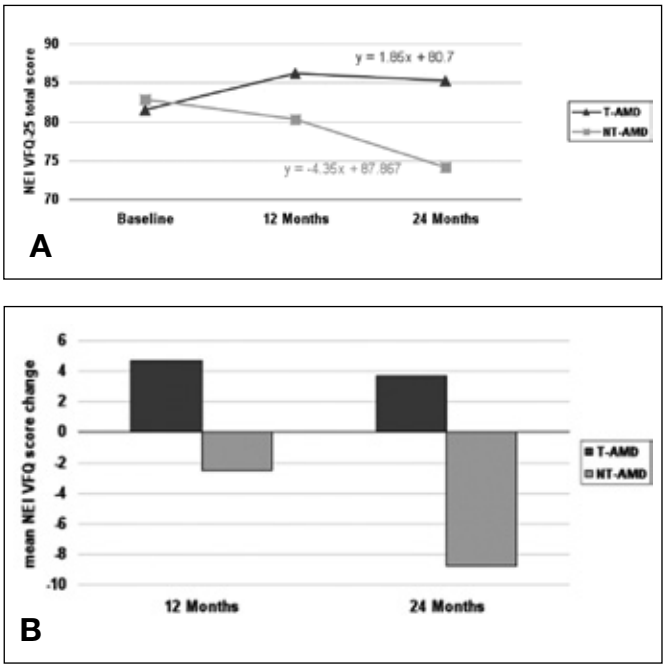

Fig. 4 - (A) *Mean National Eye Institute Visual Function Questionnaire (NEI VFQ-25) score from baseline to 12 and 24 months. Treated age-related macular degeneration (T-AMD) patients showed a positive trend of overall NEI VFQ score (slope 1.85x) compared to the nontreated age-related macular degeneration (NT-AMD) group (slope –4.35x).* **(B)** *Mean change from baseline through 24 months in NEI VFQ-25 subscale scores by treatment and control group. The mean change in overall composite NEI VFQ-25 score was 4.6 (95% confidence interval [CI] 2.79 to 6.57) in group T-AMD and –2.5 (95% CI –10.12 to 5.10) in the controls, at 12- and at 24-month follow-up 3.6 (95% CI 0.50 to 6.81) and –8.7 (95% CI –16.54 to –0.97) in T-AMD and NT-AMD, respectively.*

the proportions of cases with a positive outcome (loss ≤5 letters) was significantly different in group T-AMD with the overall RR of VA loss of 0.46 (95% confidence interval [lsqb]CI[rsqb] 0.23 to 0.90).

Contrast sensitivity

The baseline CS scores were 32.1±4.4 vs 31.8±4.8 letters for group NT-AMD vs group T-AMD. The ANOVA-RM showed a significant group by time of measurement interaction (F[3,258]=5.11, p=0.0019) (Fig. 3A). At 6, 12, and 24 months follow-up, the mean CS line change increased by 0.6 (95% CI 0.04 to 1.17), 1.76 (95% CI 1.09 to 2.44), and 2 (95% CI 0.80 to 3.19) in group T-AMD, and decreased by 0.15 (95% CI –0.74 to 1.05), 0.42 (95% CI –1.25 to 2.09), and 1.15 (95% CI –2.86 to 0.54) in group NT-AMD (p=0.4; p=0.08; p=0.01 at 6, 12, and 24 months, respectively; Student *t* test). The ANOVA-RM analysis on CS indicated significant within-group differences over time. Within-group T-AMD tests comparing baseline to final study visit showed that CS improved significantly in group T-AMD (p=0.03; p≤0.01; p=0.0014 at 6, 12, and 24 months) (Fig. 3B). At 24 months, in group T-AMD, 88.7% of patients improved or maintained their CS score (39.4% experienced improved CS, 49.3% maintained their CS, and 11.2% experienced worsened CS). The CS also improved at baseline and after 12 and 24 months of supplementation within group T-AMD. We observed CS worsening in 11.2% in group T-AMD and

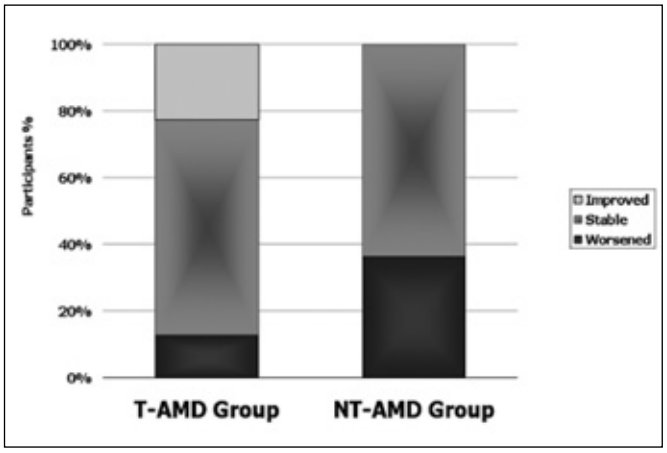

Fig. 5 - *Percentage of patients with improvement of 10 or more points or loss of 10 or more points from baseline to 12 or 24 months in National Eye Institute Visual Function Questionnaire-25 subscale scores by treatment and control group (chi-square distribution: p=0.006). NT-AMD = nontreated age-related macular degeneration; T-AMD = treated age-related macular degeneration.*

40.9% in the controls. The RR of 3 or more letter visual loss was 0.26 (95% CI 0.11 to 0.59) in group T-AMD.

Vision-related quality of life

The 25-item National Eye Institute visual function questionnaire subscale scores ANOVA-RM analysis showed a significant group by time of measurement interaction ($F[2,178]=7.53$, $p=0.0007$) (Fig. 4A). Over baseline, 12- and 24-month measurements, group T-AMD showed a significant increase of mean overall composite score (83.9±12.1; p=0.06 at 12 months; 82.1±15.9; p=0.0008 at 24 months; Student *t* test). The mean change in overall composite NEI VFQ-25 score was 4.6 (95% CI 2.79 to 6.57) in group T-AMD and –2.5 (95% CI –10.12 to 5.10) in the controls, at 12- and at 24-month follow-up 3.6 (95% CI 0.50 to 6.81) and 8.7 (95% CI –16.54 to –0.97) in T-AMD and NT-AMD, respectively (Fig. 4B). Few patients treated with supplementation had NEI VFQ overall composite and most subscale scores decreased by at least of 10 points at the end of 2 years follow-up (the RR was 0.16 [95% CI 0.38 to 0.89]), compared with scores in the NT-AMD Group (Fig. 5).

DISCUSSION

The results of the CARMIS study suggest that supplementation with a formulation containing vitamin C (180 mg), vitamin E (30 mg), zinc (22.5 mg), copper (1 mg), lutein (10 mg), zeaxanthin (1 mg), and astaxanthin (4 mg) for 24 months may have an effect on psychophysical and psychometric tests in patients with AMD, with a significant trend toward stabilization/improvement of VA, CS, and vision-related function compared to control eyes. The positive effects observed in the present study suggest that carotenoids, along with a broad spectrum of antioxidants, and vitamins not only help to delay progression to advanced stages of AMD (21), but they may also improve some visual performances.

Left untreated, patients with AMD are at risk for substantial vision loss. A growing body of evidence from epidemiologic and experimental studies has implicated a role for MP in protection against AMD (17-20). The long-term, large-population National Eye Institute Age-related Eye Disease Study showed that in people with intermediate or moderately advanced AMD in one eye, the combination of vitamins C, E, beta-carotene, zinc, and copper reduced 5-year risk of severe visual loss by 25% (21). In the CARMIS study, subjects receiving L/Z and other antioxidants did better in overall visual function (VA, CS, and NEI VFQ) than controls whose did not receive any supplementation. Consistent with these results, patients treated with oral supplementation were 50%–75% less likely to lose one or more lines of VA and 3 or more letters of CS. At 24 months, 59.1% of those subjects in group T-AMD experienced improved BCVA, 21.1% maintained their BCVA, and 19.7% experienced worsened BCVA. Overall 80.2% of patients improved or maintained their BCVA with the nutritional supplementation. In group T-AMD at 24 months, 88.7% of patients improved or maintained their CS (39.4% experienced improved CS, 49.3% maintained their CS, and 11.2% experienced worsened CS). The CARMIS trial also reported clinically relevant improvements in patient-reported vision-related function with carotenoids treatment compared with nontreatment for the overall and across most of the subscales (10-point change from baseline). More patients treated with carotenoid supplementation experienced improvements than those nontreated at most points. These gains were maintained in most patients at 12 and 24 months. The largest

improvements in NEI VFQ-25 were seen in patients with the largest improvement in visual function. This confirms a previous report demonstrating that the NEI VFQ is sensitive to changes in VA over a 1-year period in the better eye of patients with AMD.

The supplement formulation prescribed in the CARMIS study (180 mg vitamin C, 30 mg vitamin E, 22.5 mg zinc, 1 mg copper, 10 mg lutein, 1 mg zeaxanthin, and 4 mg astaxanthin) was designed to address the effect of carotenoids intake on MP. In addition to the other ingredients, in the CARMIS trial 4 mg of astaxanthin (AX) has been added. Astaxanthin (a red-orange carotenoid pigment) is a powerful biological antioxidant which is found naturally in a wide variety of living organisms. One of the most important characteristics of AX is its antioxidant property, which is reportedly more than 10 times higher than zeaxanthin and lutein (100 times more than α-tocopherol) (23, 24). The use of a mixed antioxidant-mineral formulation, however, does not permit the assessment of the effect of specific nutrients on visual function. The rationale for using a mixed formulation is that nutrients are thought to work synergistically together.

There are some obvious limitations to our study. The study followed up over 24 months, and included a relatively small number of patients (75%) for the statistical analysis. However, the number of patients dropping out did not represent an important negative factor for the final statistical results. Indeed, patients who failed to complete the final evaluation did not differ statistically on demographics, VA, CS, or VFQ from the patients who completed it. As most significant results regard intrapatient modification during the 2-year follow-up, we chose not to apply the Rasch analysis to our data.

In conclusion, this study demonstrates that lutein/zeaxanthin combined with additional carotenoids (astaxanthin) and antioxidants/minerals (including zinc) significantly improved some psychophysical (VA and CS) and psychometric (VFQ) parameters. These findings on the role of L/Z in the retina, together with our observations on the improvement of VA as well as the quality of vision, raise the expectancy that antioxidant supplementation may be useful to preserve visual function. Further studies are needed to evaluate the long-term effect of antioxidants, vitamins, and minerals on patients with atrophic AMD.

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S.T., S.S., M.V., M.Z., G.V., and G.L.G. conceived of the study, participated in its design, coordination, and recruitment, and drafted and revised the manuscript. I.F. was involved in training, coordination, and recruitment. F.C. performed statistical analyses. All authors read and approved the manuscript

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