

Dietary Supplements as Adjuncts in Combination Therapy for AMD

A new study suggests that nutritional supplements may have the potential to enhance the effect of anti-VEGF agents plus photodynamic therapy or laser.

BY R. JOSEPH OLK, MD

The deterioration of the retinal pigment epithelium (RPE) has been linked to a variety of genetic and lifestyle risks, and there is evidence suggesting that nutrition may play an important role in the prevention of AMD.

PUBLISHED EVIDENCE

The Age-Related Eye Disease Study (AREDS) has been the only large-scale randomized controlled clinical trial to evaluate the impact of a combination of antioxidant vitamins plus zinc (vitamin C, vitamin E, beta-carotene, and zinc, plus copper) on AMD.¹ This study of more than 3000 patients found that individuals at high risk for developing advanced AMD (categories 3 or 4) reduced their risk of developing advanced stages of AMD by about 25% when treated with a combination of antioxidants and zinc. The AREDS formula of antioxidants and zinc also reduced the risk of visual acuity loss in categories 3 and 4 AMD compared with placebo. However, no statistically significant evidence was shown of a beneficial delay in progression for category 2 patients. A newer study, AREDS-2, looking for additional benefits of lutein, zeaxanthin, and omega-3 fish oil in AMD, should be completed in late 2013.

A systematic review of published studies pertaining to

The AREDS formula of antioxidants and zinc reduced the risk of visual acuity loss in categories 3 and 4 AMD compared with placebo.

lifestyle modification, dietary, nutritional, and vitamin supplements for preventing occurrence or halting progression of AMD concluded that high dietary intakes of omega-3 fatty acids and macular xanthophylls, including zeaxanthin, have been associated with a lower risk prevalence and incidence of AMD.²

Zeaxanthin is one of 3 carotenoids found in the macula, and it is also found in certain fruits and vegetables. The other 2 carotenoids are lutein and the metabolite, meso-zeaxanthin, which is converted from lutein in the absence of dietary zeaxanthin. Lutein seems to be consumed in greater amounts in a normal daily diet; daily zeaxanthin intake is most likely less than 0.5 mg/day.

The Rotterdam Study evaluated 2167 individuals at risk of AMD and found that a high dietary intake of lutein and zeaxanthin reduced the risk of early AMD in those at

high genetic risk from a risk ratio of 2.63 to 1.72.³ The study authors concluded that clinicians should provide dietary intake advice to young susceptible individuals in order to postpone or prevent the vision-disabling consequences of AMD.

A collaborative study between Tufts University and researchers in China has shown that lower levels of serum carotenoids, in particular zeaxanthin and lycopene, are associated with an increased likelihood of having exudative AMD.⁴ The significant risk reduction seen in that study was similar to an earlier study in Southern France, the POLA Study, which concluded that xanthophylls, in particular zeaxanthin, play a strong role in protection against AMD.⁵

EXPANDED ROLE FOR NUTRITIONAL SUPPLEMENTS?

The results of these numerous studies have convinced me that there are benefits to repopulating the pigment concentration of zeaxanthin in the macula. In general, I recommend nutritional supplements, including zeaxanthin, to my patients who are in the early stages of AMD.

Due to the numerous studies showing the favorable impact of zeaxanthin in the prevention of AMD, I have also begun investigating its effect on my patients being treated for choroidal neovascularization (CNV) in exudative AMD.⁶ My colleagues and I conducted a pilot study of 157 eyes of 140 previously untreated patients with predominantly classic or occult subfoveal CNV. Patients were placed on 20 mg/day of oral zeaxanthin (EyePromise, ZeaVision) and sequentially treated with intravitreal bevacizumab 1.5 mg (Avastin, Genentech), dexamethasone 4 mg, and either full-fluence photodynamic therapy with verteporfin (Visudyne, QLT) (classic CNV) or large-spot diode 810 nm laser (occult CNV) and followed for at least 12 months. Patients were examined every 6 weeks on a typical treat-and-extend cycle until no residual cystoid macular edema on OCT examination, no leakage on fluorescein angiography, no plaque lesions on indocyanine green angiography, and no sub-retinal fluid on clinical examination were seen.

The results at 1 year showed that 83% of eyes had stable or improved vision and that, overall, the mean number of treatment cycles was 1.42 at 1 year. Four out of 99 patients (4%) developed CNV in the second eye at 12 months. The stability of the mean visual acuity in combination with a low number of treatment cycles represents a significant advantage for these patients. The results suggest that the addition of 20 mg/day of zeaxanthin to patients undergoing triple therapy for exudative AMD may reduce the number of treatment cycles required to achieve anatomic stabilization with

Scientific advances regarding preventing AMD or halting its progression would be of great benefit to the large at-risk population.

comparable visual results. A randomized clinical trial is now under way to further investigate these preliminary findings and validate the results.

SUMMARY

Patients in the early stages of AMD are in a watch-and-wait period, as there is no current medical treatment for that stage of the disease. Although the AREDS study results showed a benefit from a specific formulation of antioxidants and zinc only in categories 3 and 4 of the disease, many other clinical trials are testing to see if something can be done to halt or substantially slow the progression of earlier categories of AMD. The Rotterdam, China, and POLA studies are parts of a growing excitement nowadays that nutritional supplements may not only be effective in patients with AMD, but could possibly also play a critical role in diabetic retinopathy.⁷

Scientific advances regarding preventing AMD or halting its progression would be of great benefit to the large at-risk population.

I look forward to the results of additional trials that will shed greater light on the role of zeaxanthin in the management of patients with AMD. ■

R. Joseph Olk, MD, is a retinal specialist in private practice in Saint Louis, MO. Dr. Olk can be reached via email at rjoretina@aol.com.

1. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss. *Arch Ophthalmol*. 2001;119:1417-1436.
2. Sin HP, Liu DT, Lam DS. Lifestyle modification, nutritional and vitamins supplements for age-related macular degeneration [published online ahead of print January 23, 2012]. *Acta Ophthalmol*. doi:10.1111/j.1755-3768.2011.02357.x.
3. Ho L, van Leeuwen R, Witterman JC, et al. Reducing the genetic risk of age-related macular degeneration with dietary antioxidants, zinc, and ω -3 fatty acids: the Rotterdam study. *Arch Ophthalmol*. 2011;129(6):758-766.
4. Zhou H, Zhao X, Johnson EJ, Lim A, Sun E, Yu J, Zhang Y, Liu X, Snellings T, Shang F, Liu N. Serum carotenoids and risk of age-related macular degeneration in a Chinese population sample. *Invest Ophthalmol Vis Sci*. 2011;52(7):4338-4344.
5. Delcourt C, Carrier I, Delage M, et al. Plasma Lutein and Zeaxanthin and Other Carotenoids as Modifiable Risk Factors for Age-Related Maculopathy and Cataract: The POLA Study. *Invest Ophthalmol Vis Sci*. 2006;47:2329-2335.
6. Peralta E, Olk RJ, Sayegh SI, Gierhart D. Oral zeaxanthin improves anatomic and visual outcome of triple therapy for subfoveal CNV in age-related macular degeneration (ARMD). Presented at the Retinal Society Meeting; September 21-25, 2011; Rome.
7. Kowluru R, Zhong Q. Beyond AREDS: Is there a place for antioxidant therapy in the prevention/treatment of eye disease? *Invest Ophthalmol Vis Sci*. 2011;52(12):8665-8671.