

Evidence for Including Lutein and Zeaxanthin in Oral Supplements for Age-Related Macular Degeneration

David C. Musch, PhD, MPH

In a **National Eye Institute** press release¹ issued on May 5, 2013, with simultaneous online publication in *JAMA*,² the results from the second phase of the Age-Related Eye Disease Study 2 (AREDS2) were announced.



Related article

This press release was titled “NIH study provides clarity on supplements for protection against blinding eye disease,” and indeed in its first paragraph, the primary outcome was clearly stated: “The plant-derived antioxidants lutein and zeaxanthin also had no overall effect on [age-related macular degeneration (AMD)] when added to the combination; however, they were safer than the related antioxidant beta-carotene.” This study provided us with a striking example of a major clinical trial in which the primary outcome was negative, but yet its broader findings prompted substantial changes in the formulation of so-called eye vitamins that constitute a major market presence and are likely recommended by most eye care practitioners for a patient they determine to be at risk for developing neovascular AMD. The ability of companies to market their eye vitamins as providing an exact match to the AREDS2 formula is evidently important because we encounter such statements in venues ranging from our professional journals to television commercials. While some might say that the train has long since left the station, the purpose of this editorial is to critically evaluate the evidence underlying formulation changes that are under way or have already taken place.

In this issue’s article,³ the AREDS2 investigators provided us with a detailed look at additional analyses that led them to support adding lutein and zeaxanthin to, and deleting beta carotene from, the previously recommended oral formulation for eye health, termed the *AREDS formula*. Like the analyses presented in their initial report, some of these analyses were termed *exploratory* in nature and relied on results from inspecting subgroups that were not prespecified and thus were post hoc in nature. Subgroup analyses have been viewed as a 2-edged sword by Wittes,⁴ who wrote: “If reporting on subgroups is tempting but treacherous, failing to report on them seems unscientific and incurious.” As Fleming and Watelet⁵ pointed out, the results of such analyses should usually be viewed as hypothesis generating rather than definitive in nature. They advised that definitive conclusions from such analyses occur only in rare situations: when very strong associations are found that are biologically plausible and supported by results from other sources. Even so, claims of treatment efficacy that result from such findings are not uncommon. The subgroup analysis finding from the Steroids for Corneal Ul-

cers Trial that corticosteroids may be beneficial for treatment of bacterial keratitis when baseline visual acuity is count fingers or worse, or when the ulcer was completely centrally located, was advised to be viewed with caution in a letter to the editor.⁶ In their reply, the trial’s investigators fully agreed that their findings, while based on prespecified subgroup analyses, should be subject to further confirmation.⁷ When pivotal phase 3 trials of proposed treatments yield negative or equivocal results, a commonly encountered directive from the sponsor is to revisit the data in an attempt to identify subgroups that show efficacy; thus the derogatory term *data dredging* and the humorous, but sometimes real, claim that if you torture your data long enough, they will confess.

A critical look at the evidence from AREDS2 for an efficacious effect of lutein/zeaxanthin supplementation starts with the authors’ *JAMA* article,² in which a prespecified comparison of those receiving lutein/zeaxanthin vs those who did not receive lutein/zeaxanthin revealed a 10% reduction in the risk for progression to late AMD. A second prespecified analysis showed that those in the lowest quintile of dietary intake of lutein/zeaxanthin who received lutein/zeaxanthin along with the original AREDS formulation had a 26% reduced risk for progression to late AMD relative to participants receiving the original AREDS formulation without lutein/zeaxanthin. Finally, an exploratory look at the group given lutein/zeaxanthin in its supplement showed an 11% reduced risk for developing neovascular AMD vs those who received only beta carotene in their supplement.

The further analyses presented herein include an exploratory analysis of the 1114 participants who received lutein/zeaxanthin added to an AREDS formulation without beta carotene vs the 1117 participants who received only beta carotene in the AREDS formulation. This revealed that those receiving lutein/zeaxanthin without beta carotene supplement had an 18% reduction in the risk for late AMD and a 22% reduction in the risk for neovascular AMD (both which met the $P < .05$ criterion), as well as a 6% reduction in the risk for geographic AMD (which yielded a P value of .67). A prespecified analysis of progression on the AREDS severity scale for AMD⁸ did not reveal a beneficial effect of lutein/zeaxanthin supplementation (with or without beta carotene) on reducing the risk for a 2 or more step progression. However, in an exploratory look at the subset who only received lutein/zeaxanthin (without beta carotene) vs the subset who received only beta carotene, lutein/zeaxanthin supplementation reduced the risk for a 2 or more step progression by 13%. The results were compelling for the subset of 1748 subjects who had bilateral large drusen and were evaluated for progression to neovascular AMD, which developed in 11.5% (99

of 862) of those who received lutein/zeaxanthin with a beta carotene-free version of the AREDS formulation and in 17.2% (152 of 886) of those who received the AREDS formulation with beta carotene but no lutein/zeaxanthin. This direct comparison yielded a risk reduction of 35%.

From a safety perspective, the authors concluded that removing beta carotene from the original AREDS formulation seems warranted. They based this on previous reports of increased lung cancer risk among cigarette smokers who took beta carotene in supplements to their diet,^{9,10} as well as on more frequent incident lung cancer in AREDS participants who were assigned beta carotene. Nonsmokers who were randomized to receive beta carotene developed more lung cancer than those in the no-beta carotene group (2% [23] vs 0.9% [11]; nominal $P = .04$).² Of the 34 who developed lung cancer, 31 (91%) were ex-smokers. In addition, the National Cancer Institute has judged that the evidence base is solid for an increased lung cancer incidence and mortality among high-intensity smokers who take pharmacologic doses of beta carotene.¹¹ Such concerns, along with the fact that smokers and ex-smokers are prevalent in older populations who might benefit from taking the AREDS-type formulation, suggest that removing beta carotene from over-the-counter supplements is advised.

The authors concluded in their *JAMA* article that lutein/zeaxanthin “could be an appropriate carotenoid substitute in the AREDS formulation.”² They now concluded that “the totality of evidence on beneficial and adverse effects from AREDS2 and other studies suggests that lutein/zeaxanthin could be more appropriate than beta carotene in the AREDS-type supplements.”³ Is the addition of the AREDS2 evidence to that previously reported sufficient to support this conclusion? If this were a clinical guideline, one might turn to the GRADE system to rate the quality and strength of the evidence.¹² Given that this evidence is based on subgroup analyses from a clinical trial within a highly educated and well-nourished population, the quality could plausibly be rated as moderate in nature—wherein further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. And so, the conclusions the authors made contain phrases such as “could be an appropriate carotenoid” and “suggests that lutein/zeaxanthin could be more appropriate than beta carotene” to include in AREDS-type supplements. This cautious wording lends about as much strength as can legitimately be applied to the evidence at hand.

The Hill criteria for causation could also be applied.¹³ A temporal relationship is supported by the findings—exposure to lutein/zeaxanthin did precede measurement of progression to neovascular AMD. The strength of the association, as measured by the hazard ratios and their statistical significance, is not indicative of a very strong effect, but rather a moderate effect. A dose-response relationship remains to be evaluated because only 1 dose of lutein/zeaxanthin was used. The consistency of the impact that lutein/zeaxanthin supplementation may have on re-

ducing progression to neovascular AMD can only be assessed in a limited manner. Several observational studies¹⁴⁻¹⁷ support a possible role for lutein/zeaxanthin supplementation in reducing the risk for developing neovascular AMD, as do the current study's results. And then there are the related concepts of plausibility and coherence. Including lutein/zeaxanthin in the AREDS2 formulation has some biological rationale. Lutein and zeaxanthin are the primary constituents of pigments in the macula and are present in surrounding retinal tissue. They may serve to prevent tissue damage from products of oxidation and/or to shield the macula from harmful wavelengths of light.

While based mostly on exploratory analyses of subsets, the evidence from AREDS2 presents a consistent picture of a beneficial effect for reducing the risk for the neovascular form of advanced AMD and serves to enhance a small body of other supportive evidence for why lutein/zeaxanthin would reduce the risk for progression to neovascular AMD. However, many questions remain unanswered. The clinician who advises patients regarding taking dietary supplements for preventing progression of AMD must recognize that neither AREDS nor AREDS2 results provide support for these supplements having a beneficial impact on the risk for developing geographic atrophy nor on reducing the risk for developing large drusen in an individual who presents with lesser signs of macular degeneration. Also, clinicians must weigh the potential improved safety of lutein/zeaxanthin over beta carotene with the lack of long-term information on the safety of lutein/zeaxanthin supplementation. Are there subtle but undue safety concerns related to lutein/zeaxanthin supplementation? The best advice is *caveat emptor* (“let the buyer beware”) and *primum non nocere* (“first, do no harm”). Unlike drugs, the manufacturer is responsible for ensuring that its dietary supplement products are safe before they are marketed because dietary supplements fall under the Dietary Supplement Health and Education Act of 1994 and do not need approval from the Food and Drug Administration before they are marketed unless the manufacturer or distributor (not the Food and Drug Administration) determines a dietary ingredient is new. Are lutein and zeaxanthin the optimal carotenoids for use in supplementation? Are the doses of lutein (10 mg) and zeaxanthin (2 mg) used in AREDS2 optimal for producing the most beneficial effect? Will the reduction in the risk for progression to neovascular AMD reported in AREDS2 participants prove true in general use?

Such questions cannot be answered by AREDS2. In the absence of evidence from follow-up studies to AREDS2, the onus is placed on informed clinicians to educate patients about the knowns and unknowns of available information on the safety and efficacy of AREDS-type supplements. The AREDS2 results certainly warrant our attention, but perhaps most importantly point out that even in this era of evidence-based medicine, there remains an important need for clinicians to provide sound and balanced counsel to their patients.

ARTICLE INFORMATION

Author Affiliation: Departments of Ophthalmology and Visual Sciences and Epidemiology, University of Michigan, Ann Arbor.

Corresponding Author: David C. Musch, PhD, MPH, Department of Ophthalmology and Visual Sciences, and Department of Epidemiology,

University of Michigan, Kellogg Eye Center, 1000 Wall St, Ann Arbor, MI 48105-1912 (dmusch@umich.edu).

Published Online: December 5, 2013.
doi:10.1001/jamaophthalmol.2013.7443.

Conflict of Interest Disclosures: None reported.

REFERENCES

1. NIH study provides clarity on supplements for protection against blinding eye disease [press release]. Bethesda, MD: National Eye Institute; May 5, 2013. <http://www.nei.nih.gov/news/pressreleases/050513.asp>.
2. Age-Related Eye Disease Study 2 (AREDS2) Research Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial [published correction appears in *JAMA*. 2013;310(2):208]. *JAMA*. 2013;309(19):2005-2015.
3. The Age-Related Eye Disease Study 2 (AREDS2) Research Group. Secondary analyses of the effects of lutein/zeaxanthin on age-related macular degeneration progression: AREDS2 report no. 3 [published online December 5, 2013]. *JAMA Ophthalmol*. doi:10.1001/jamaophthalmol.2013.7376.
4. Wittes J. On looking at subgroups. *Circulation*. 2009;119(7):912-915.
5. Fleming TR, Watelet LF. Approaches to monitoring clinical trials. *J Natl Cancer Inst*. 1989;81(3):188-193.
6. Dulku S. Subgroup analysis in the Steroids for Corneal Ulcers Trial. *Arch Ophthalmol*. 2012;130(6):807-808; author reply 808.
7. Srinivasan M, Mascarenhas J, Rajaraman R, et al. Subgroup analysis in the Steroids for Corneal Ulcers Trial: reply. *Arch Ophthalmol*. 2012;130(6):807-808.
8. Davis MD, Gangnon RE, Lee LY, et al; Age-Related Eye Disease Study Group. The Age-Related Eye Disease Study severity scale for age-related macular degeneration: AREDS report no. 17. *Arch Ophthalmol*. 2005;123(11):1484-1498.
9. Albanes D, Heinonen OP, Huttunen JK, et al. Effects of alpha-tocopherol and beta-carotene supplements on cancer incidence in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study. *Am J Clin Nutr*. 1995;62(6)(suppl):1427S-1430S.
10. Omenn GS, Goodman GE, Thornquist MD, et al. Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial. *J Natl Cancer Inst*. 1996;88(21):1550-1559.
11. National Cancer Institute. Lung cancer prevention (PDQ). http://www.cancer.gov/cancertopics/pdq/prevention/lung/HealthProfessional/page1#Section_206. Accessed October 30, 2013.
12. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.
13. Hill AB. The environment and disease: association or causation? *Proc R Soc Med*. 1965;58(5):295-300.
14. Seddon JM, Ajani UA, Sperduto RD, et al; Eye Disease Case-Control Study Group. Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. *JAMA*. 1994;272(18):1413-1420.
15. SanGiovanni JP, Chew EY, Clemons TE, et al; Age-Related Eye Disease Study Research Group. The relationship of dietary carotenoid and vitamin A, E, and C intake with age-related macular degeneration in a case-control study: AREDS report no. 22. *Arch Ophthalmol*. 2007;125(9):1225-1232.
16. Augood C, Chakravarthy U, Young I, et al. Oily fish consumption, dietary docosahexaenoic acid and eicosapentaenoic acid intakes, and associations with neovascular age-related macular degeneration. *Am J Clin Nutr*. 2008;88(2):398-406.
17. Sangiovanni JP, Agrón E, Meleth AD, et al; Age-Related Eye Disease Study Research Group. omega-3 Long-chain polyunsaturated fatty acid intake and 12-y incidence of neovascular age-related macular degeneration and central geographic atrophy: AREDS report 30, a prospective cohort study from the Age-Related Eye Disease Study. *Am J Clin Nutr*. 2009;90(6):1601-1607.