AREDS2 RESULTS

Carotenoid substitution will provide a better formulation as it can be taken by patients regardless of their smoking history

by Cheryl Guttman Krader

In October 2001, results from the Age-Related Eye Disease Study (AREDS) were published and found that progression to advanced age-related macular degeneration (AMD) was reduced by about 25 per cent in high-risk individuals receiving high doses of antioxidant vitamins (C and E), beta-carotene and zinc. A follow-up study published in April 2013 showed the protective effect of the “AREDS formulation” persisted at 10 years. However, new findings released from AREDS2 at the 2013 annual meeting of the Association for Research in Vision and Ophthalmology (ARVO) suggest the AREDS formulation may be improved by including lutein 10mg plus zeaxanthin 2mg (L/Z) and removing beta-carotene, said Emily Y Chew, MD, who reported the AREDS2 results. Dr Chew is chair of AREDS2 and deputy director, Division of Epidemiology and Clinical Applications at the National Eye Institute, sponsor of AREDS & AREDS2. She told EuroTimes. “We feel this carotenoid substitution is prudent and will provide a better formulation because it can be taken by patients regardless of their smoking history.”

Several lines of evidence provided a rationale for investigating various modifications to improve the efficacy and safety of the AREDS formulation. As its primary goal, AREDS2 evaluated the effects of adding high supplemental doses of L/Z and/or the omega-3 fatty acids docosahexaenoic acid (350mg) + eicosapentaenoic acid (650mg) (DHA/EPA) on the risk of progression to AMD.

Thus, in a primary randomisation, 4,203 patients ages 50 to 85 with intermediate AMD bilaterally or intermediate AMD in one eye and advanced AMD in the fellow eye were randomised 1:1:1:1 to receive the original AREDS formulation alone (control) or supplemented with L/Z, DHA/EPA, or L/Z and DHA/EPA.

Based on concerns about the safety of beta-carotene and high dose zinc, a secondary randomisation allocated consenting participants into four groups to receive the original AREDS formulation or modifications with no beta-carotene, lowering the zinc dose, or removing beta-carotene.

The primary analysis showed the five-year probability of progression to AMD ranged from 29 per cent to 31 per cent across all four study groups, and hazard ratio calculations showed none of the nutrient additions to the AREDS formulation significantly affected progression to AMD. However, a main effects analysis found treatment with L/Z reduced the risk for progression to AMD by 10 per cent compared with no L/Z (P=.04). The benefit was mostly for reducing the risk of progression to neovascular AMD (11 per cent risk reduction). There was no significant impact on progression to central geographic atrophy.

“In trying to evaluate an additive effect of L/Z and the omega-3s, it makes more sense to use the main effects analysis that compares the population half randomised to the additional nutrient versus the half that was not. Here we found a benefit with L/Z,” Dr Chew told EuroTimes.

Pre-specified subgroup analyses stratifying patients by baseline dietary history found participants in the lowest quintile of L/Z dietary intake had a 26 per cent lower risk of AMD progression if they were treated with L/Z than if they were not (P=.01). Additionally, post hoc subgroup analyses found reductions of 18 per cent in AMD progression risk (P=.02) and of 22 per cent for neovascular AMD (P=.01) favouring participants receiving L/Z and the AREDS formulation without beta-carotene versus those treated with the original AREDS formulation and no L/Z (P=.02).

“Beta-carotene significantly suppressed the absorption of concomitantly administered L/Z, and that interaction may have confounded the ability of AREDS2 to accurately determine the effects of adding L/Z,” noted Dr Chew.

Otherwise, the main effects and other exploratory analyses found no treatment effects for adding DHA/EPA, lowering the zinc dose, or removing beta-carotene.

A safety analysis including only non- and former smokers found an increased incidence of lung cancer development in the beta-carotene versus no beta-carotene group (two per cent vs. 0.9 per cent; P=.04), with >90 per cent of the cases occurring in former smokers.

“These are important findings as data from our studies and others show that former smokers represent about half of the AMD population,” Dr Chew said.

Whereas in AREDS, zinc versus no zinc was associated with increased rates of GI disorders and hospitalisations for genitourinary disorders, the frequency of these events was similar in AREDS2 in the low and high dose zinc groups. There were no statistically significant differences between the primary randomisation study groups in rates of mortality or serious adverse events.

The AREDS formulation had no effect on the progression of lens opacities, but observational data suggested treatment with L/Z might be beneficial. With about 75 per cent of AREDS2 participants evaluable for cataract progression, L/Z supplementation had no statistically significant effect on the primary endpoint of progression to cataract surgery or in any of the secondary outcomes that looked at development of any cataract, development of any severe cataract, or a 15-letter visual acuity loss.