Invited Commentary

Of Age-Related Macular Degeneration and Vitamins

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The initial publication of results from the Age-Related Eye Disease Study (AREDS), nearly 20 years ago, showed that the progression of age-related macular degeneration (AMD), in its early stages, could be slowed by oral therapy with over-the-counter vitamins and zinc.[1] A much later report from the same group extended those results to 10 years' follow-up,[2] and still another publication from these investigators reported that the beneficial effect of this regimen applied even to those individuals with the high-risk complement factor H and age-related maculopathy susceptibility 2 genotypes.[3] The beneficial effect, although statistically highly significant, was relatively small: only 8% to 10% of the treatment group, considered either by progression from early- to high-risk AMD, or by loss of 15 letters best-corrected vision during the study interval. Even so, when universally applied to the entire at-risk population, this result can potentially benefit as many as 300 000 individuals in the United States,[4] a large number, but still a distinct minority of those who are in the highest category of risk. For this reason, attempts have continued to discover additional effective treatments to prevent progression of the early stages of AMD.

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The results of one such clinical trial are published in this issue of *JAMA Ophthalmology*.[5] This highly experienced clinical trial group has been exploring the use of supraphysiologic doses of vitamin D (2000 IU/d) and of 1 g per day of ω-3 fatty acids vs placebo in VITAL (the Vitamin D and Omega-3 Trial), a large (25 871 participants; median age, 67.1 years), controlled randomized clinical trial for prevention of cancer and heart disease,[6] but with several ancillary trials for a variety of disorders included as "add-ons" within this framework. The present study, titled VITAL-AMD, is one such. As with other components of VITAL, VITAL-AMD was conducted entirely remotely, via annual mailed questionnaires, which asked among other things, whether the participant had received a diagnosis of AMD within the last year. If so, the participant was asked to give permission for his or her ophthalmologist to provide details for documentation. Participants were also asked to give annual blood samples, which showed, among the much smaller number of participants who provided these, a mean rise of 40% in vitamin D level and 54.7% in ω-3 level. However, after a median follow-up of 5.3 years, there were no significant differences either in incident AMD or in progression of AMD existent at baseline, in participants randomized to receive either vitamin D_3 or ω-3 fatty acids supplementation, compared with placebo.[5]

These negative results of a large, well-designed, and well-conducted clinical trial, performed by highly experienced investigators, is discouraging. This is especially the case because the prior successes of AREDS and AREDS2 have led to considerable optimism that at least 1,[4] and possibly other,[7] common and highly disabling eye diseases can be substantially reduced in severity, or even prevented, by large but safe doses of commonly used and inexpensive vitamins and dietary supplements. That possibility has not been supported in the present instance, but, as in other of the several components of the VITAL trials, these investigators have shown that large-scale clinical trials in ophthalmology, as in other areas of medicine, can be successfully conducted remotely. And, although the present study yielded negative results, it has been abundantly clear over the last number of years that overall progress in other areas of research in the causes and treatment of AMD remains considerable.

ARTICLE INFORMATION

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