Title

Letter From the DSMC Regarding a Clinical Trial of Lutein in Patients With Retinitis Pigmentosa

Journal

JAMA Ophthalmology, 129(5)

ISSN

2168-6165

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Publication Date

2011-05-01

DOI

10.1001/archophthalmol.2011.76

Peer reviewed

prospective pathological study could better describe the incidence of this malformation and its clinical correlates.

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Financial Disclosure: None reported.

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Letter From the DSMC Regarding a Clinical Trial of Lutein in Patients With Retinitis Pigmentosa

We, the members of the Data Safety Monitoring Committee (DSMC) for Berson and colleague's clinical trial of lutein in patients with retinitis pigmentosa who are receiving vitamin A,[1] share many of the concerns Massof and Fishman[2] expressed in their editorial. We served as the DSMC from 2002 through 2009. We reviewed the protocol, the statistical analysis plan, and the emerging data. We were impressed by the conduct of the trial, especially the excellent patient retention and adherence to the protocol.

We reviewed and approved the manuscript before the authors submitted it for publication; however, we note some substantive changes made between the time of our review and the time of publication. For example, the article's new section on "Conclusions" is not consistent with our interpretation of the data, which emphasizes that the trial showed no effect of lutein on the primary outcome. We have carefully evaluated the data from the trial and view that the authors' conclusion and the section on "Application to Clinical Practice" overstate the strength of evidence for the use of lutein. We wish to remind the clinical community that the evidence adduced for benefit comes from one of several secondary outcomes in a trial in which the primary outcome showed no evidence of benefit (the *P* value for the effect on Humphrey field analyzer 30-2 field, dB/y was .66).

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Financial Disclosure: None reported.

1. Berson EL, Rosner B, Sandberg MA, et al. Clinical trial of lutein in patients with retinitis pigmentosa receiving vitamin A. *Arch Ophthalmol*. 2010;128(4):403-411.
2. Massof RW, Fishman GA. How strong is the evidence that nutritional supplements slow the progression of retinitis pigmentosa [editorial]? *Arch Ophthalmol*. 2010;128(4):493-495.

In reply

The DSMC acknowledges approval of our draft manuscript. The publication[1] contained what we regard as minor adjustments requested by the journal, including a "Conclusion" section in the "Abstract" that restated results. The "Application to Clinical Practice" section was in the draft manuscript approved by the DSMC. Throughout the publication we stated that the treatment effect of lutein was observed only on the secondary endpoint of midperipheral field sensitivity.

The DSMC suggests that if significant differences between the treatment groups are not seen with respect to the primary endpoint, then the results of the trial are negative and should have little or no affect on clinical practice. Precedent exists for modifying practice based on results seen with secondary endpoints and subgroup analyses.[2,3] In the Physicians' Health Study evaluating aspirin, the paucity of cardiovascular deaths led to revision of the primary endpoint to include nonfatal myocardial infarction; aspirin was then found effective in preventing primary heart attacks.[2] The Women's Health Study assessed aspirin's efficacy in preventing heart attack in women older than 45 years. Although results of the analysis of the entire study cohort were negative, subgroup analyses showed that aspirin reduced the risk of major cardiovascular events, ischemic stroke, and myocardial infarction in women older than 65 years.[3]

Similarly, results of the lutein trial should not be considered negative simply because the beneficial effect was based on a secondary endpoint. A significant benefit of lutein on preserving midperipheral field sensitivity was observed in randomized comparisons using both parametric (P=.05) and nonparametric analyses (P=.03). Furthermore, observational analyses showed that those with the highest serum lutein level and those with the highest increase in intraretinal macular pigment optical density (ie, a measure of intraretinal lutein) had the least decline in midperipheral field sensitivity (P=.01 and P=.006, respectively).[1]

Based on our results,[1,4,5] we reaffirm that most adults with typical retinitis pigmentosa should take 15 000 IU/d of vitamin A palmitate. They should avoid high-dose vitamin E supplementation.[4] Adults who start taking vitamin A for the first time should also take 1200 mg/d of docosahexaenoic acid (DHA) for 2 years; after 2 years, they should stop tak-

ing the DHA, continue taking vitamin A, and start to eat 1 to 2 three-ounce servings of omega-3 rich fish per week (eg, salmon or tuna, of which DHA is a major constituent).[5] The data also support the use of 12 mg/d of lutein to slow mid-peripheral field sensitivity decline in nonsmoking adults who are taking vitamin A.[1] We have observed no toxic effects of vitamin A, DHA, or lutein.[1,4-6] The benefit of this treatment regimen of up to 20 additional years of vision far outweighs any risks.

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Financial Disclosure: None reported.

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Ophthalmic Images

Limbal Juvenile Xanthogranuloma in an Adult

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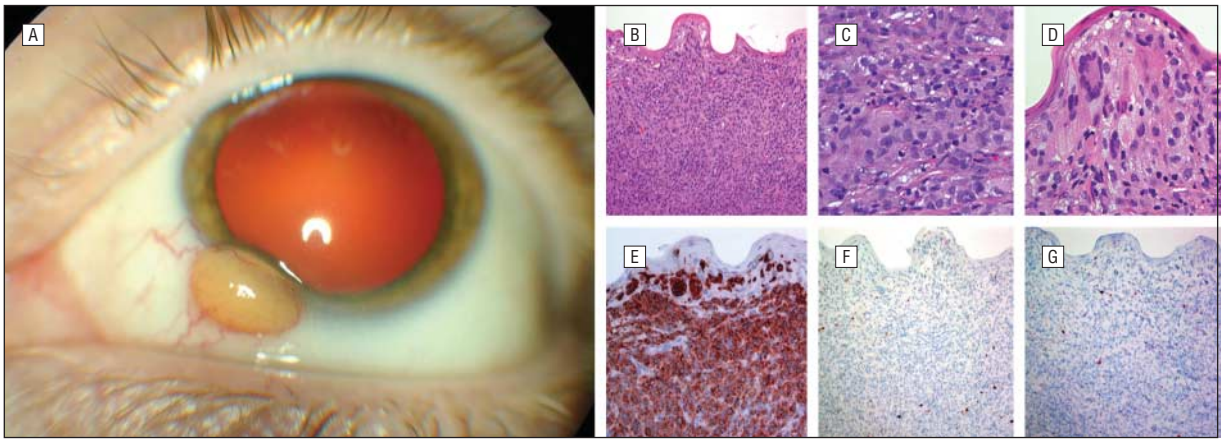

A 33-year-old man had a 2-week history of a yellowish painless limbal nodule (A). Histopathological examination shows infiltration of histiocytes, lymphocytes, plasma cells, and eosinophils (B and C) (hematoxylin-eosin, original magnification ×400) and Touton giant cells (D) (hematoxylin-eosin, original magnification ×1000). The lesion was positive for the macrophage marker CD68 (E) and negative for Langerin (F) and S-100 protein (G), confirming the diagnosis of juvenile xanthogranuloma (alkaline phosphatase antialkaline phosphatase, original magnification ×1000).