Author's response to reviews

Title: TOZAL Study: An open case control study of an oral antioxidant and omega-3 supplement for dry AMD

Authors:

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Author's response to reviews: see over
Dear Dr. Edmunds,

I want to thank you for your continued consideration of my manuscript.

I have addressed the reviewers’ comments by giving a point-by-point response to their concerns and I have revised the manuscript accordingly.

Reviewer 1 (Dr. Eperjesi)

**Snellen verses ETDRS (logMAR)**

Both the control group and the treatment group were evaluated using the EDTRS chart (logMAR) and all line changes were measured as EDTRS line changes. The reviewer astutely noticed my error in using the term “Snellen” and revisions have been made to the manuscript to reflect this correction.

With respect to the mention of Snellen BCVA in the inclusion/exclusion criteria (Table 1), I reported the inclusion BCVA as 20/32 to 20/125 in an effort to be consistent with other peer-reviewed publications (i.e., MIRA-1) which also lists inclusion criteria as Snellen BCVA.

**AREDS affect on patients with intermediate or advanced AMD (standard of care)?**

I have revised the manuscript per the reviewer’s suggestion.

**Forms of Zinc and Lutein**

I have revised Table 2 to include a description of zinc as “zinc oxide” and lutein as “free, not esterified.”

**Increased visual function in the LAST study**

I have revised the second paragraph to properly acknowledge that the LAST study improved visual function.

**Clinical significance of the study**

Clinical significance, unlike statistical significance, is somewhat subjective. I have purposefully not addressed clinical significance in the manuscript so the reader can come to his/her own conclusion. The logMAR line difference between the treatment group and placebo-control group was 2.03 lines. As Dr. Eperjesi points out, most clinicians would consider two lines of improvement clinically significant. The data from this project was
reviewed by Dr. Jerome Sherman, Distinguished Teaching Professor at State University of New York College of Optometry, who has rendered a written opinion that the results are indeed clinically significant.

**Microcurrent Stimulation (MCS)**

I have revised the manuscript and added additional data on previous research regarding MCS and described, in detail, both the treatment and sham MCS devices.

**Intervention at Visit 1 verses Visit 2**

The mean age of the elderly patients in this study was 76.6 years. The length of Visit 1 was on average over two (2) hours. The investigators did not feel that a one (1) hour instruction period (the time needed to explain and initiate the intervention) was prudent following the initial visit. Subsequently, the decision was made to initiate intervention when the patient was mentally and physically fresh on Visit 2.

Regarding VA and Contrast Sensitivity being measured on Visit 2, it was considered standard protocol to measure both VA and Contrast Sensitivity on each and every visit.

**Supplement with food**

I have revised the manuscript and clarified this issue per the reviewer’s suggestion.

**Reviewer 2 (Dr. Richer)**

**New Title**
I have revised the name of the manuscript per the reviewer’s suggestion

**Abstract**
I have revised the Conclusion section of the manuscript per the reviewer’s suggestion

**2nd Paragraph**
I have revised the 2nd paragraph of the manuscript per the reviewer’s suggestions

**4th Paragraph**
I have revised the 4th paragraph of the manuscript per the reviewer’s suggestions. I agree with the reviewer regarding the need to present a more balanced picture and have removed those sentences that may cause nutriphobia in the reader.
Study Design

I have revised the manuscript and added additional data on Allen’s research regarding MCS and described, in detail, both the treatment and sham MCS devices.

I have revised the manuscript to list the number of patients at each of the 5 centers.

I agree with Dr. Richer that it is unlikely that the taurine had a physiological effect. However we are unable to comment further on this issue since we don’t completely understand the synergies and interactions between each nutrient.

Statistical analysis and results of all measure outcomes

I have revised the manuscript and noted that there were no changes in CSF, VFQ-25, Central 10 Fields, Retinal Photos, and FANG.

The primary objective of this trial, as defined by the trial protocol, was to measure the change from baseline in visual acuity at 6 months in patients with dry AMD. I feel the change from baseline in visual acuity (the primary objective of this trial) should be considered on its individual merit and I respectfully disagree with the reviewer’s suggestion of Bonferroni correction.

The Bonferroni adjustment is an issue about which there is much, and ongoing, debate. Perneger states that “Bonferroni adjustments are, at best, unnecessary and, at worst, deleterious to sound statistical inference.” Adjusting statistical significance for the number of tests that have been performed on study data – the Bonferroni method – creates more problems than it solves. The main weakness is that the interpretation of a finding depends on the number of other tests performed.


Discussion Section / Conclusion Section

I have rewritten these sections and included the reviewer’s suggestion and references (LAST, LUXEA, CARMIS).

In the revision I have addressed the reviewer’s question regarding the scientific rationale for reducing beta-carotene while maintaining vitamin A.

With respect to zinc and the new AREDS II trial, participants in AREDS II will be offered treatment with the original AREDS formulation (now considered standard of care) and variations of this formula with lower amounts of zinc. Until such time that the results of AREDS II are published, the author feels zinc at a higher dose remains the standard of care.
I appreciate this opportunity to present a revised manuscript and thank the reviewers and editors for their continued consideration.

Respectfully,

Francis E Cangemi, MD