Reviewer’s report

Title: The TOZAL study: multi-site trial of taurine, omega-3 fatty acids, zinc, antioxidants, and lutein in the treatment of atrophic age-related macular degeneration

Version: Date: 18 December 2006

Reviewer: Stuart Richer

Reviewer’s report:

General

TOZAL STUDY – AN OPEN CASE CONTROL STUDY OF AN ORAL ANTIOXIDANT AND OMEGA III SUPPLEMENT FOR DRY AMD---suggested new title

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

ABSTRACT-conclusion section --- The results of TOZAL agree with the LAST and CARMIS studies, and are predictive for positive outcomes with the AREDS II trial.

2nd paragraph is not accurate, and needs to be rewritten and be historically accurate as follows:

In 1996, Richer et al found that a broad-spectrum antioxidant and mineral supplement was effective in delaying AMD related vision loss, but was unable to reverse vision loss.


In 2004, The Lutein Antioxidant Supplementation Trial (LAST) demonstrated that nutritional supplementation with lutein or lutein together with antioxidants, vitamins and minerals, improved visual function and symptoms in atrophic

REF---- your reference #13

4th paragraph-- The HOPE study involving a selective meta-analysis of 400 IU vitamin E….has been highly criticized by the scientific community including researchers at the National Eye Institute who issued a press release on the subject matter. As well, there was no increased mortality from the dose of Beta Carotene used in AREDS. It would be helpful to present a more balanced picture with respect to the potential for unbalanced high doses of any nutrient to have the potential for side effects.

4th paragraph - Reduce or eliminate the risk of side effects from vitamins and supplements

Vitamin and mineral formulations are many orders of magnitude less non toxic than aspirin or Tylenol. Am J Emergency Med 20: 391-452, 2002 Please don’t give the reader a case of nutriphobia.

STUDY DESIGN—provide references on micro-current stimulation Some studies have found this to be useful….. How many patients at each of the 5 centers? This is really an open case control study and not a double blind study. Likely not enough Taurine to have a physiological effect.

Statistical analysis – Present all outcome measures—is visual acuity still positive post Bonferroni correction?
RESULTS—where are the CSF, VFQ-25 and central 10 degree field results, retinal photographs and FANG

DISCUSSION SECTION – rewrite this section... AREDS formulations are for patients with high risk findings such as multiple small retinal drusen, large drusen, parafoveal geographic atrophy and sudden loss of vision in one eye. By design—it is a formula to be taken to prevent catastrophic vision loss in high risk AMD patients. It does not address the vast majority of patients who want to improve visual function, while also preventing advanced AMD. Again, in medicine, the “dose is the poison” and the authors do not provide scientific rational for reducing beta carotene while maintaining vitamin A at 10,000 IU which has been equally criticized and leaving zinc at a high dose—which has been criticized and modified to only 25mg in the new AREDS II trial

Conclusion Section, reflect back on the LAST, LUXEA & CARMIS studies to see that the present study is confirmation of the direction and magnitude of the increase in visual acuity, in dry AMD, published previously.

LAST STUDY

(Snellen equivalent visual acuity improved in both intervention groups: mean eye improvements of 5.4 letters for group 1 L (95% confidence interval [CI] 2.7 – 8.0, P=.01) and 3.5 letters for group 2 L/A (95% CI 0.8 – 6.1, P=.04)... an entire range of other factors were evaluated as well including contrast sensitivity, glare recovery and defects of the Amsler Grid—in atrophic AMD patients.


The results of this 6 month study show that supplementation can improve mesopic contrast acuity thresholds and hence visual performance at low illumination.

CARMIS STUDY M Sartore et al, Short term supplementation with Carotenoids & Antioxidants Padova, Italy- ARVO 2006 #2139

? N= 153 w AMD (AREDS category 3, 4) & VA greater than 20/32 (0.3 LogMAR)

? Treated with: Lutein 10mg, Zeaxanthin 1 mg, Astaxanthin 4 mg, vit C 180mg, vit E (30mg), ZN (22.5mg ) CU(1mg) known as (AZYR SIF®, Sifi Italy)

? Baseline , 6 month and 1 year follow-up w EDTRS and 39-item NEI-VFQ)

“After 1 year, treated AMD patients showed stabilization of visual acuity and significantly better EDTRS scores (87+/− 6) compared to controls (80 +/- 7) p=0.02. VFQ 39 scores significantly increased in the treatment group (p=0.001).

Additional comments

This is a limited study with 30 something patients at 5 centers.

This is a limited time frame study.

Cannot predict that patients taking this study will have any less or more chance of developing catastrophic vision loss as the original dose of the AREDS nutrients were modified. Would have to have a larger n and study the patients for a long period of time.....

This is an open case control study, and the patients in the MIRA 1 control also had improved vision, which is one reason that there was not a statistically significant improvement against rheo-therapy when the final results with 150 individuals were released to the scientific community.
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)

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What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare no competing interests; I am a consultant to multiple supplement manufacturers