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Macular Supplements Containing Zinc and Vitamin A Should Be Replaced with Meso-Zeaxanthin, Lutein and Zeaxanthin: An Ophthalmic Need for Pharmacovigilance

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Abstract

Objective: The objective of this paper is to report the importance of ophthalmic pharmacovigilance in AREDS macular formulations due to the potential toxicity of these macular vitamins with minimal benefit for patients with advanced exudative macular degeneration.

Background: Age Related Eye Disease Studies macular formulations are currently treated as nutritional supplements and as such, do not undergo the required evaluation process for toxicity as pharmacologic agents. However, they more closely resemble a pharmacologic agent rather than a true nutritional supplement.

Results: Macular formations have minimal benefit for patients with advanced exudative age-related macular degeneration and contain unsafe doses of substances like beta-carotene and zinc, which have the potential to cause cancer, Alzheimer's disease, and worsen macular degeneration. This potential for toxicity necessitates pharmacovigilance for macular supplements to prevent exposure to harmful substances for negligible gain.

Conclusion: These supplements should be replaced with other compounds that have both macular protective properties and an excellent safety profile such as Meso-Zeaxanthin, lutein and zeaxanthin.

Keywords: AREDS; Toxicity; Macular degeneration

Introduction

Macular formulations to prevent development of age-related eye diseases, such as exudative macular degeneration, are not considered pharmacologic intervention by many regulatory bodies. Without regulation, many naturally occurring substances used in these supplements are dosed at unnaturally high levels and have potential pharmacologic-like toxicities.

When a new active pharmacologic agent undergoes evaluation by a regulatory body such as the Food and Drug Administration (FDA), dose-limiting toxicity evaluation by a clinical trial is required. Furthermore, pre-clinical toxicity studies are performed to understand the potential toxicities that could emerge in the clinical setting to guide the design of early phase safety studies.

The rigor and criteria for determining clinically acceptable toxicity are extremely stringent, and consequently, many pharmaceutical agents never reach clinical stage development or approval. The potential for toxicity can be a reason a pharmacologic agent does not progress to later stages of clinical trials. Furthermore, if a pharmacologic agent demonstrates the potential for adverse toxicity in the course of post-approval surveillance, black box warnings are usually placed to warn patients of the potential side effects.

On the other hand, supplements do not have to undergo this stringent evaluation or post-approval marketing surveillance. As a result, they represent the potential for undetected toxicities. Examples of substances not evaluated as pharmacologic agents that were found to result in severe disease include tobacco, high fructose corn syrup, and trans-fatty acids. Macular formulations using high-dose nutrients share more similarities to pharmacologic agents than nutritional supplements.

Macular formulations cause no acute toxicity so like these other products, they are generally considered to be acceptably safe. Chronic use of these products can lead to long-term health problems, a property shared with many macular formulations. Unlike food ingredients or consumer products like tobacco, the purpose of macular formulation is to prevent blindness. This is a pharmacologic and therapeutic purpose that is consistent with a pharmacologic agent.

Macular formulations also differ from true nutritional supplements. Supplements generally provide essential nutrients to address nutritional deficiencies or restore deficient levels of nutrients that are not absorbable due to the aging process.

This is in sharp contrast to the purpose of current macular formulations whose purpose is to prevent the development of exudative age-related macular degeneration (AMD). While these formulations may be called supplements, they are not restoring a nutritional deficiency; instead, these nutrients are being used in high doses in order to obtain a pharmacologic effect.

Pharmacovigilance is necessary for macular-directed supplements due to the use of high doses of naturally occurring nutrients to prevent progression of disease. The use of high-dose supplementation to prevent or treat disease resembles a pharmacologic agent with

potential for toxicities. These high-dose supplements should be evaluated as pharmacologic agents rather than nutritional supplements.

AREDS 1 and 2 Studies

Most ocular formulations are based on the Age Related Eye Disease Studies 1 and 2 (AREDS1 and 2). These studies were multicenter, multi-arm clinical trials designed in the early 1990's. The 3640 AREDS 1 study participants were randomly assigned to 4 arms.

Patients in arm 1 received daily oral tablets containing vitamin C, 500 mg; vitamin E, 400 IU; and beta carotene, 15 mg. Patients in arm 2 received daily oral tablets 80 mg zinc oxide and 2 mg of cupric oxide. Patients in arm 3 received combination of vitamins and zinc. Patients in arm 4 received placebo [1].

The results of the AREDS I study demonstrated a statistically significant odds reduction for the development of advanced AMD with an odds ratio for antioxidants plus zinc compared to placebo of 0.72. The odds ratio for zinc alone compared to placebo was 0.75 and antioxidant alone compared to placebo was 0.80.

Interestingly, a subgroup of patients was responsible for the majority of the effect. If 1064/3640 patients with extensive small drusen, non-extensive intermediate size drusen, or pigment abnormalities were excluded, the odds reduction for antioxidants plus zinc was 0.66, for zinc alone was 0.71, and for antioxidants was 0.76.

These results demonstrate that a subgroup corresponding to two-thirds of the study participants drove the majority of the effect. In essence, only patients with intermediate to advanced AMD had a reduction in the conversion of non-exudative AMD to exudative AMD. These results were published in 2001 and were implemented without regulatory oversight.

Without regulatory oversight, the AREDS 1 formulation has been recommended to anyone with any form of macular degeneration, including those who had already developed exudative macular degeneration. The AREDS 1 formulation is not uniformly beneficial to all patients with macular degeneration.

The AREDS formulation does not improve vision, attenuate non-exudative macular degeneration, or restore normal levels in patients with deficiency states. On the other hand, the AREDS formulation may be potentially harmful.

Vitamin A

Supplementing Vitamin A at recommended daily doses is important in those with inadequate dietary intake. Vitamin A deficiencies cause a myriad of problems such as night blindness and keratosis.

Patients who are taking macular formulations do not have a deficiency in zinc, Vitamin A, Vitamin E or Vitamin C. Yet these formulations contain several times the recommended levels of these vitamins and nutrients. These formulations do not represent supplements but are pharmacologic formulations and as such, carry potential pharmacologic toxicities.

The doses in this formulation are several times higher than the recommended daily allowance of these nutrients, especially for beta-carotene and zinc. The AREDS 1 study demonstrated a mild decline in the risk of developing exudative AMD in patients who had intermediate non-exudative AMD.

This subgroup of the overall study population was statistically responsible for the mild efficacy signal. If the AREDS study had been an FDA registration trial, approval for the formulation would be only for this subgroup and not for the general population, especially in light of the known toxicity profile of high dose beta-carotene.

The increase in lung cancer risk with high-dose beta-carotene, which demonstrated the carcinogenic potential of vitamin A in the smoking population, was known before the release of the AREDS 1 study results [2,3]. In the AREDS II study, the increase in lung cancer risk was also shown in patients who had previously quit smoking.

This further demonstrates the carcinogenicity of macular formulation containing excessive Vitamin A [4]. Macular formulations should warn patients of this potential toxicity, and high-dose beta-carotene should be removed as a component of these macular formulations. Pharmacovigilance mandates removal of these components from macular formulations.

Zinc

The potential toxicities of high-dose zinc in the urinary tract should raise the concern of patients and physicians alike. The prostate contains high levels of zinc and has been shown to have an imbalance in zinc homeostasis in conditions such as prostate cancer and benign prostatic hypertrophy. While studies are conflicting in regards to the role of zinc in these conditions, it is clear that there is potential toxicity to consuming supplemental zinc.

Epidemiological studies have shown a potential correlation between high dietary zinc and prostatic hypertrophy [5]. High-dose zinc has also been associated with an increased risk of developing prostate cancer [6-9]. An analysis of the AREDS I cohort also demonstrated an increase in genitourinary-caused hospitalizations [10]. While these studies are not definitive, they do demonstrate considerable potential long-term and short-term toxicities.

Recent studies on the mechanism of Alzheimer's disease (AD) implicate the potential of zinc to increase Amyloid Precursor Protein (APP). In a transgenic mouse model of AD, feeding transgenic mice high-dose zinc resulted in increased APP production and deposition of amyloid [11].

High-dose zinc diets in transgenic and wild type mice also developed behavioral deficits that mimicked AD [12]. An imbalance in zinc homeostasis has been implicated in development of AD [13], with high levels potentially exacerbating the pathological process leading to AD [14] Combined zinc and copper imbalances have been implicated in neuro-degenerative diseases such as AD and Parkinson's disease [13].

While the AREDS study group tested for changes in cognitive function in a subpopulation of patients in the AREDS 2 study, it lacked the statistical power and duration to detect clinical manifestations of early AD.

The cognitive tests used to evaluate the AREDS patients can only detect clinical manifestations. The study did not use any of the biomarkers often used in studying AD such as positron emission tomography. Studies have shown that a clinically measurable cognitive decline occurs only after extensive deposition of cortical amyloid [15,16].

Utilization of zinc supplementation in humans was not preceded by pre-clinical toxicity studies. Having been performed only recently,

these studies demonstrate that zinc is actually detrimental to retinal physiology. In a mouse model of light-induced retinal degeneration that mimics geographic atrophy, zinc appeared to be involved in the potentiation of light-induced damage.

When zinc was diet-restricted or zinc transport was inhibited, it proved effective in reducing light-induced retinal degeneration [17]. In this same experimental model, reduction in zinc with chelation was beneficial in protecting retinas from light-induced degeneration [18]. This in vivo data reflects what is seen in vitro where zinc is considered a cytotoxic element to neuronal and retinal cells [19,20].

In vivo and in vitro safety studies should be done prior to testing in humans but in this case, these experiments were performed afterwards. Did any of these potential toxicities manifest clinically? The answer is yes.

While the AREDS I study was able to demonstrate a subtle efficacy, the study lacked the statistical power and duration to detect toxicity. The ten-year results did demonstrate a potential toxicity of worsening center involving geographic atrophy.

In AREDS Report 35 on long-term follow-up of patients on zinc, there was an increased odds ratio for the development of center involving geographic atrophy [21]. While not statistically significant, the increased development of geographic atrophy only in patients on anti-oxidation and zinc should have raised toxicity concerns.

This report was followed with genetic analysis that demonstrated potential macular toxicities of zinc. When analyzing the AREDS 1 dataset, subgroups of patients who received zinc supplementation appeared to have worse outcome if they had a certain genetic polymorphisms [22,23].

In combination with the pre-clinical data, this finding is biologically consistent. If pharmacovigilance had played a role in the development of this supplementation, this potential toxicity signal would have been grounds for delay of approval or black box warnings on the use of zinc supplementation for macular degeneration.

If components of the AREDS1 were not potentially carcinogenic or retinotoxic, then the risk benefit ratio could have proven acceptable. With these potential toxicities, the risk benefit ratio is unacceptable. Currently, the conversion of non-exudative AMD to exudative AMD is no longer an invariably blinding situation.

In the last decade, exudative AMD has been effectively treated with intravitreal injections of anti-VEGF therapy. This therapeutic breakthrough has reduced the clinical benefit of AREDS at the same time more toxicities have been discovered.

The reduction in conversion to exudative AMD no longer outweighs the potential carcinogenicity, amyloidogenicity, and geographic atrophy-forming potential of the AREDS-based formulation. Without mandated pharmacovigilance and label warnings, many patients may be exposing themselves to untoward toxicities with only minimal benefit.

In light of the minimal benefit and the considerable potential toxicities, these formulations should warn patients of their potential dangers. This lack of pharmacovigilance needs to be corrected.

Meso-Zeaxanthin, Lutein and Zeaxanthin

Another supplement exists that demonstrates both benefit and an excellent theoretical and clinical safety profile. This supplement contains the three macular carotenoids: Meso-Zeaxanthin, Lutein and Zeaxanthin (MLZ). Unlike the AREDS formulation, MLZ truly restores a deficiency state in the macula. Representing the retinal area responsible for central vision, the macula contains a pigment which serves to protect the macula from oxidative and photo-oxidative stress [24].

The macular pigment serves as a protective barrier against photo-oxidative blue light and acts as a free radical sink. The amount of pigment declines with age and smoking, which are the main risk factors for AMD. The macular pigment is composed exclusively of MLZ [25].

MLZ represent carotenoid isomers, both structural and enantiomers. Lutein and Zeaxanthin are structural isomers and Meso-Zeaxanthin and Zeaxanthin are enantiomers. Alone each is an excellent anti-oxidant. Together, they act as a more potent anti-oxidant than any individual isomer [26]. In combination, they provide the most potent anti-oxidants that can localize to the macula and represent the natural oxidative protectant.

The macular pigment is produced solely through dietary intake. Initially, breast milk is the source of these nutrients, and the carotenoids derived from breast milk allow for the maturation of the retina and macula [27]. Afterwards, dietary intake dictates the levels of macular pigment. Dietary intake of green leafy vegetables, eggs, and fish can serve as sources of these carotenoids [28].

Because typical diets contain little carotenoids, supplementation with physiological levels of MLZ has proven to be a useful strategy to elevate the macular pigment as measured by macular pigment densitometry especially in elderly patients who have early stages of dry macular degeneration. As would be expected, pre-clinical toxicity studies have demonstrated an excellent safety profile [29].

MLZ supplementation can produce a definitive upregulation in macular pigment especially in the perifoveal lesion that has the steepest decline in disease [30]. A study using MLZ in patients with AMD and in the elderly demonstrated a statistically significant improvement in contrast sensitivity.

Furthermore, patients followed for 5 years demonstrated no progression of disease while on MLZ. No patients in this study suffered from exudative macular degeneration and no patient on MLZ developed exudative AMD in the 5-year time span of the study [31].

Patients seen in our practice have been able to reverse signs of exudative macular degeneration by starting on MLZ. Patient GD came in with symptoms of metamorphopsia and a decline in vision. On presentation, her vision in her right eye was 20/40. Optical coherence tomography (OCT) and angiography demonstrated evidence of exudative macular degeneration (Figure 1A).

After taking MLZ for 8 weeks, the patient improved her vision. OCT demonstrated elimination of sub-retinal fluid (Figure 1B). The patient decided after the visit to stop taking MLZ resulting in a recurrence of the exudation in 8 weeks (Figure 1C).

She then restarted on twice the dose of MLZ which eventually resulted in the resolution of sub-retinal fluid (Figure 1D). These anecdotal cases support further need for clinical studies using MLZ as a therapeutic agent for both exudative and non-exudative AMD.

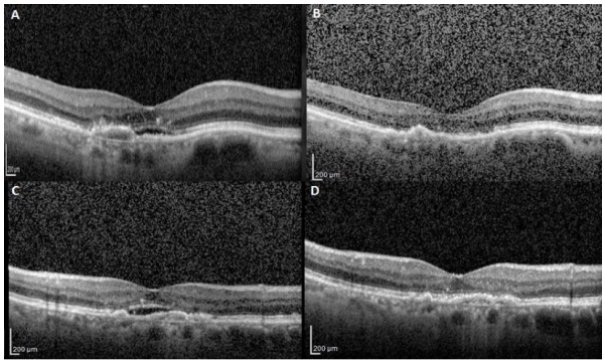

Figure 1: A. Optical coherence tomography (OCT) demonstrating evidence of exudative macular degeneration with a baseline visual acuity of 20/40 in the right eye. Patient was started on MLZ supplementation. B. After taking MLZ for 8 weeks, her visual acuity improved to 20/30 and OCT demonstrated elimination of sub-retinal fluid. C. Discontinuation of MLZ resulted in a recurrence of the exudation in 8 weeks. D. Restarting on twice the dose of MLZ eventually resulted in the resolution of sub-retinal fluid after 8 weeks.

Conclusion

In summary, currently recommended supplementation based on the AREDS formulation poses much potential toxicity and has only a mild therapeutic effect. From a pharmacovigilance perspective, the carotenoids MLZ should be recommended over the AREDS based formulations. MLZ represents the native macular protectant and supplementation restores this protective barrier in a physiological and not pharmacologic fashion.

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