AREDS Formulation: What We Know Now

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AREDS

The Age-Related Eye Disease Study (AREDS) was a major clinical trial sponsored by the National Eye Institute in late 2001. In two separate trials, AREDS was designed to understand the natural history and risk factors of age-related macular degeneration (AMD) and cataracts; AREDS also evaluated the effect of high doses of vitamin C, vitamin E, beta-carotene, and zinc on the progression of AMD and cataracts.¹

When the AREDS formulation was developed in the 1990s, I was very supportive because wet macular degeneration was invariably blinding; we did not understand its pathogenesis, and we did not have a sight preserving treatment. At that time the overarching goal was to stop pathologic new blood vessels from arising from the choroid (choroidal neovascularization or CNV). We hypothesized that using excessive amounts of zinc, vitamin A, and vitamin E could stop the angiogenic pathway. From this hypothesis the AREDS trial was developed and executed.

OBSOLESCENCE AND SIDE EFFECTS OF AREDS FORMULATION

Historically, the demonstration that AREDS supplements statistically reduced the development of CNV was of great importance, but due to the rapid progress in basic research, the AREDS formulation is now obsolete. Furthermore, potential side effects of the AREDS formulation create an unacceptable risk benefit ratio. During the prolonged course of the AREDS trial, the role of VEGF in wet AMD was elucidated, and intravitreal anti-VEGF injections were found to be an effective sight restoring therapy for patients with wet macular degeneration.¹ Coincidentally, nonophthalmic studies discovered serious side effects from individual components of the AREDS formulation, including increased risk of cancer, mortality, and memory loss.

High-dose vitamin A found in the AREDS formula when given to a previous smoker or current smoker increased their rate of lung cancer. This relationship was found to be significant in this small cohort of patients on analysis of the AREDS data.¹ This finding confirmed other nonophthalmic studies dating back decades that examined the development rate of lung cancer.²

High-dose vitamin E in a nonophthalmic study demonstrated a potential increase of mortality for patients taking a level of 400 IU or more.³ The AREDS formulation utilizes that dose. Vitamin E theoretically has a positive effect, but if there is a suggestion and biologic plausibility of increased mortality using high-dose vitamin E, patients need to be warned of this potential toxicity.

High-dose zinc has a myriad of positive and negative effects; it likely powered the positive statistical benefit of the AREDS formulation. However, it has well-known dose-dependent toxicities. The US FDA already has warnings on the use of zinc in high doses.⁴ The use of zinc as a nasal spray has caused permanent anosmia highlighting the direct neurotoxicity of zinc to olfactory nerves.⁴ The toxicity of zinc to retinal ganglion cells, photoreceptors, and retinal pigment epithelium cells can explain zinc’s modest ability to inhibit CNV.⁴ In the presence of high-energy visible blue light, zinc can induce retinal photoreceptors, muller cells, and retinal pigment epithelium cell death in cell culture and in animals.⁴ By killing retinal cells that produce VEGF you can reduce the development of CNV.

High-dose zinc found in AREDS has also been associated with the development of prostate cancer and memory loss. Epidemiological data demonstrates that taking chronic high-dose zinc supplements can increase the risk of prostate cancer by more than 200%.⁵,⁷ In rats, high-dose zinc supplementation results in depletion of intracellular zinc in the hippocampal area of the brain and results in impairment of hippocampal mediated memory tasks. The intracellular depletion of zinc caused by
excessive dietary zinc supports a role of high-dose zinc supplementation in memory loss.

Zinc’s dose-dependent retinal and neuronal toxicity combined with its potential carcinogenesis outweighs the modest benefit of inhibiting CNV considering that anti-VEGF injections are a safe and effective treatment for this previously devastating complication of AMD. If AREDS supplements were considered a drug and regulated by the US FDA, just one of these side effects would have potentially blocked its approval. Historically, drugs have been removed from the market for lesser reasons. As physicians, our highest credo is to do no harm. As physicians, we cannot, in good conscience, recommend AREDS formulation to any of our patients.

CAROTENOID THERAPY

In contrast to the development of the AREDS formulation, the oral supplement that should be recommended, MacuHealth (MacuHealth), was discovered and developed to address the underlying pathology of macular degeneration (Figure 1). MacuHealth contains three carotenoids, including meso-zeaxanthin, lutein, and zeaxanthin. It’s the answer to several basic, clinical, and therapeutic questions in retinology:

1. What is the natural macular protectant, antioxidant, anti-inflammatory, and internal high-energy visible light filter?  
2. What is depleted that permits macular degeneration to develop as we age?  
3. What strategy halts the progression of macular degeneration and potentially reverses it?  

Retinal researchers have hypothesized that macular pigment is the answer to all these questions. Macular pigment is localized to the fovea and parafoveal region; it has been shown clinically to filter high-energy visible blue light. Foveal macular pigment is clinically depleted in older patients, smokers, and macular degeneration patients.

Initially, zeaxanthin and lutein were thought to be the only molecules that made up macular pigment. More recent research identified meso-zeaxanthin as the most potent antioxidant and predominant isoform found in the fovea. When all three carotenoids are tested for antioxidative capacity, the combination of all three provides greater antioxidative capacity than any single carotenoid. These three carotenoids also can inhibit the complement pathway and the innate immune system which has been implicated in the pathogenesis of AMD.

The natural way to upregulate macular pigment is through dietary consumption of foods containing the three carotenoids, such as spinach, kale, and collard greens. Because of the devolution of these vegetables in terms of carotenoid content, to get adequate dosage of these carotenoids, bushels of vegetables must be eaten daily to upregulate foveal macular pigment.

Adhering to carotenoid therapy is the most efficient method for upregulating foveal macular pigment. Studies have shown that all three carotenoids in a ratio of 10 mg of meso-zeaxanthin, 10 mg of lutein, and 2 mg of zeaxanthin (MacuHealth), compared to 20 mg of lutein and 2 mg of zeaxanthin, are required to produce significant foveal macular pigment upregulation.

CONCLUSION

AMD is a leading cause of vision loss and blindness affecting millions of people around the world. It affects a person’s central vision, which is needed for reading, driving, and identifying people and surroundings. If left untreated, the disease may eventually lead to loss of independence and complete blindness. For many aging patients, addressing the oxidative stress that your eyes endure through the years is vital for living a healthy, active lifestyle. Unlike the AREDS formulation, which has an unacceptable risk-benefit ratio, MacuHealth has no known clinical or theoretical toxicity and demonstrates a significant clinical benefit making MacuHealth the only macular nutritional supplement that physicians should recommend to all their patients.

Figure 1. MacuHealth carotenoid dietary supplement.

 Clinically, carotenoid therapy has been demonstrated to improve visual function in patients who have intermediate macular degeneration. Several cases have also been presented that demonstrate a potential to enhance the efficacy of anti-VEGF therapies in patients not responding optimally to anti-VEGF injections alone.

Lastly, these three carotenoids localize predominantly in the eye and brain. Toxicity studies demonstrate a maximum tolerable dose of approximately 5,000 pills per day. Furthermore, the carotenoids are derived from organically grown marigold flowers allowing its use to be classified as holistic and natural. Thankfully, we do not need to use unnatural doses to obtain the desired clinical effect.

Disclaimer: Pregnant and lactating women should consult a doctor before using. A food supplement should not be used as a substitute for a varied diet or healthy lifestyle. These statements have not been evaluated by the US FDA. The product is not intended to diagnose, treat, cure, or prevent any disease.
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