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Efficacy and safety for the combination of lutein, vitamin C, zeaxanthin, zinc, copper, and vitamin E in Indian patients of age-related macular degeneration - Post marketing surveillance study

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ABSTRACT

Background: Age-related macular degeneration (AMD) is an ocular disease of complex nature which reduces the quality of life of the patient. Objectives behind the conduct of this study was to evaluate the efficacy as well as safety for the combination of Lutein, Vitamin C, Zeaxanthin, Zinc, Copper and Vitamin E in patients of AMD.

Materials and Methods: For the study 660 patients were recruited and 627 patients completed the study throughout India at 44 clinical trial sites. The study duration was of 90 days and efficacy and safety assessment was made on day 45 (visit 2) and day 90 (visit 3). Efficacy assessment was made by 2 efficacy assessment parameters including, "vision related quality of life (VRQOL)" and "vision Impairment score" obtained using "Vision Impairment Questionnaire". Safety assessment was made by adverse events reported by the patients.

Results: At baseline visit, the mean VRQOL score of all the patients completed the study was 5.733 which was increased to 6.682 on visit 2 and 7.476 on visit 3 where, percentage increase was of 16.550% and 30.403% respectively on visit 2 and 3 as compared to baseline. At baseline visit, the vision impairment score was 21.389 reduced to 17.352 on day 45 and further reduced to 14.135 on day 90.

Conclusion: Fixed dose combination of Vitamin C 250mg, Zinc 40mg, Lutein 5mg, Zeaxanthin 1mg, Copper 1mg and Vitamin E 200 IU per capsule was found efficacious and safe for the medical management of AMD in Indian patients.

1. Introduction

Age-related macular degeneration (AMD) is an ocular disease of complex nature which reduces the quality of life of the patient. In previous studies, the prevalence of the AMD was found to be increasing with the age. According to studies, more than 10% of people older than 80 years have late AMD. According to the World Health Organization (WHO), in western countries, AMD is the first cause of blindness.[1,2] According to WHO, by the year 2040, globally 288 million people would be suffering from AMD. AMD alone was responsible for 8.7% of the worldwide blindness and including India, its effect is at serious level is developing countries. According to three significant study reports including India Eye Study, Andhra Pradesh Eye Study and Aravind Comprehensive Eye Study, prevalence of AMD was ranging between 1.4% to 1.8% in India.[3]

AMD can also be considered as late-onset deterioration of retinal pigment epithelium (RPE) and photoreceptors

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present in the central retina which can be caused by various genetic factors and/ or environmental and/ or older age but not limited to it. There are two forms of AMD named as "dry AMD" and "wet AMD" form of AMD which is also called as "non-exudative" and "exudative" form of AMD respectively.[4] Dry or non-exudative AMD is a chronic ocular disease that usually causes vision impairment in the initial phase and sometimes may progresses to severe blindness. In contrast exudative form of AMD or wet form of AMD affects only 10–15% of the total patients suffering from the AMD. Exudative AMD emerges in a short duration and if left untreated then rapidly progresses to blindness.[2]

Risk factors for the development of AMD includes but not limited to gender (female are at the higher risk of developing AMD compared to male), age (people more than 65 years) and ocular factor (0.75 diopters or more Hyperopia are at the higher risk of developing wet form or exudative form of AMD).[5]

Although AMD is not curable but development of the disease can be prevented by the use of combinations of nutraceutical supplements.[5] This study was conducted to evaluate the efficacy for the medical management of AMD and safety for the combination of Lutein, Zeaxanthin, Vitamin C, Vitamin E, Zinc and Copper in the patients suffering from Age-Related Macular Degeneration (AMD). Below we have discussed the use or the protective mechanism of Lutein, Vitamin C, Zeaxanthin, Zinc, Copper and Vitamin E in the medical management of AMD.

Macula lutea is placed in the posterior and central region of the retina and has the uppermost concentration of the photoreceptors, which is responsible for central vision and also the high resolution visual acuity and it is entirely made up of Lutein and Zeaxanthin. Lutein and Zeaxanthin also serves photoprotective function as they are capable of absorbing light of blue range wavelength and prevents excessive damage to the photoreceptors, the retinal pigment epithelium (RPE) and the underlying choriocapillaris. This reduction in the blue range wavelength that reaches to the photoreceptors, the retinal pigment epithelium (RPE), and the underlying choriocapillaris can be up to 90% and normally it is about 40% which can significantly reduce the oxidative stress of the retina and can also reduce the significant risk of developing AMD.[6–8] Also in clinical trial it was found that Lutein has good bioavailability due to its lipophilic nature. The maximum daily dose of Lutein can be up to 20 mg for the treatment of AMD.[7]

Zinc has structural role in antioxidant enzymes because of which it has a role in the prevention of AMD. In the regions of retina which are commonly found to be affected by AMD naturally found to be high in the concentration of Zinc and after AMD or old age, the Zinc content was commonly found to be decreased. Also, Zinc in the retina and RPE interacts with vitamin A and Taurine, modifies photoreceptor plasma membranes and regulates the light-rhodopsin reaction and modulates synaptic transmission.[9] Copper prevents degradation of glutathione peroxidase (GPx) and Superoxide dismutase (SOD). SOD and GPX enzymes are a primary defence system that protects biological macromolecules from oxidative damage. SOD and GPx are antioxidant enzymes that protects the retina from oxidative damage and are present in photoreceptors and the RPE. SOD is the main antioxidant enzyme involved in the metabolism of oxygen free radicals. As compared to the healthy people, SOD founds at the lower side in most of the AMD cases.[10]

Vitamin C is an effective water-soluble antioxidant present in the human blood which plays a vital role in the ocular antioxidant defence mechanism and also protects ocular tissues against photo-oxidative damage by acting as a free radical scavenger.[10] Vitamin E is an antioxidant which terminates the lipid peroxidation and also prevents free radical reactions with ocular cell membranes. Vitamin E reacts with unstable lipid radicals, produces stable lipids and a relatively more stable vitamin E radical and then reduces back to stable vitamin E by the reaction with Glutathione or Ascorbate.[11]

This post marketing surveillance study was conducted to test the efficacy for the medical management of AMD and safety for the fixed dose combination of Vitamin C 250 mg, Zinc 40 mg, Lutein 5 mg, Zeaxanthin 1 mg, Copper 1 mg and Vitamin E 200 IU per capsule in Indian patients for the indication of AMD.

2. Materials and Methods

Post marketing surveillance study was conducted at 44 clinical trial sites all across India. All investigators had minimum qualification of M.S. Ophthalmology. At 44 clinical trial sites, total 660 patients were recruited as per the below mentioned inclusion and exclusion criteria.

Patients of 50 years or more of either gender of male or female with confirmed diagnosis of AMD of best correction visual acuity no worse than 20/200 for each enrolled eye, who was ready to sign the informed consent form and can adhere to the study protocol for the study period of 90 days were recruited for the study. Also, for the study only those patients were recruited who could swallow capsule with the help of water. Also, during the study period, all the recruited patients were asked to stop taking the current supplements of Vitamin C, Vitamin E, Zinc, Lutein, Zeaxanthin and Copper.

As per the study exclusion criteria, patients with any retinal pathology other than AMD, patients took intravitreal injection, patients having seizure disorder and/ or cataract or patients with diabetic neuropathy or presence of vitreous haemorrhage or retinal detachment or macular hole were excluded. Also, patients with chronic requirement for any systemic or ocular medication administered for other disease and ocular medication known to be toxic to retina

or optic nerve, patients with intraocular pressure equal to or more than 26, patients with cataract surgery within last 3 months, patients with daily supplementation with 2 mg or more Lutein for the period of last 1 year or more prior to date of recruitment, patients with hemochromatosis or Wilsons disease, patients with recent diagnosis of oxalate kidney stones, patients hypersensitive to the investigational product and mentally ill patients who cannot adhere to the protocol were excluded from the study.

Fixed dose combination of Vitamin C 250 mg, Zinc 40 mg, Lutein 5 mg, Zeaxanthin 1 mg, Copper 1 mg and Vitamin E 200 IU per capsule was the investigational product. Patients were advised to take investigational product in the dose of 1 capsule twice a day; 1 in the morning and 1 in the evening with food for the study duration of 90 days.

This study was conducted at 44 clinical trial sites and at all clinical trial sites, all the investigators were of minimum qualification MS Ophthalmology. Before recruiting the patient for the study, patients were completely informed about the study and if they had doubt about the same then it was also resolved by the investigator. Before recruiting the patient for the study, a medical history was recorded by asking the recruited patients and/ or guardian of the patient and physical examination conducted and recorded by the investigators on the case record form. The study duration was of 90 days and during the same the patients were asked to visit the clinical trial site on day 45 (visit 2) and day 90 (visit 3) considering the baseline visit as day 0 (visit 1). Patients were given free physician samples of investigational products and advised to take in the dose of 1 capsule twice a day from day 1 for a study period of 90 days as 1 in the morning and 1 in the evening with food. Baseline efficacy assessment was made on visit 1 (day 0) and efficacy as well as safety assessment was made on visit 2 and visit 3. The method or procedure for the efficacy and safety assessment is briefly described below in the section "efficacy assessment" and "safety assessment".

Efficacy assessment was made by using 2 parameters including "vision related quality of life (VRQOL)" and "vision Impairment score" obtained using "vision Impairment Questionnaire". For the first efficacy assessment parameter, "vision related quality of life", patients were asked to rate the overall vision related quality of life on a scale of 1-10, where 1, 2 was considered as very poor VRQOL; 3, 4 was considered as poor VRQOL; 5, 6 was considered as average VRQOL; 7, 8 was considered as good VRQOL and 9, 10 was considered as very good VRQOL on visit 1, 2 and 3. Secondary efficacy assessment was made by asking ''vision Impairment Questionnaire" which is mentioned in Table 1 to the patient on visit 1, 2 and 3 and patients were asked to choose the given answers as mentioned in Table 2 for the questions mentioned in Table 1. The options given to the patient for the questions asked in the Table 1 were common for all the questions and for each answer the score was provided which is also mentioned in Table 2. Vision impairment score was calculated by addition of score obtained from all 10 questions.

After recruited patients the reported adverse events, the adverse events were classified into either serious or non-serious adverse events. Also, for all the adverse events, causality assessment was made to check the causal relationship of investigational products with the adverse events using the WHO- UMC scale.

No concomitant therapy including any medicinal or nutraceutical supplement containing Vitamin C, Zinc, Lutein, Zeaxanthin, Copper or Vitamin E was allowed to take during the study period of 90 days to the patients recruited in the study.

The investigational product was approved for manufacturing and marketing in India and also it was available under various brands in India. Before recruiting patient for the study, all the patients were briefly informed about the study procedures and the investigational product in their understandable language and all their doubts were resolved.

3. Results

For the study, total 660 patients were recruited at 44 clinical trial sites out of which 627 patients completed the study. All the patients recruited were of confirmed diagnosis of AMD as per the study inclusion and exclusion criteria as mentioned in the section study procedure above. Results for the efficacy and safety assessment are mentioned below in the section efficacy assessment and safety assessment respectively.

Efficacy assessment was made by 2 efficacy assessment parameters including vision related quality of life and vision impairment questionnaire, detailed procedure for the efficacy assessment is mentioned in the section study procedure above. In 1^{st} efficacy assessment parameter, which was vision related quality of life (VRQOL), at baseline the mean VRQOL score was 5.733 which was increased to 6.682 on visit 2 and further increased to 7.476 on visit 3 which is graphically presented in Figure 1. On visit 2 and 3, the percentage increase in VRQOL was 16.550% and 30.403% respectively as compared to visit 1.

The second parameter for the efficacy assessment was vision impairment score obtained from vision impairment questionnaire. At baseline visit the vision impairment score was 21.389 which was decreased to 17.352 on visit 2 and further decreased to 14.135 on visit 3 which is graphically presented in Figure 2. At visit 2 and 3, the percentage reduction in vision impairment score was 18.872% and 33.912% respectively as compared to the baseline.

In the total population of patients recruited for the post marketing surveillance study, 6 adverse drug reactions were

Table 1: Vision impairment questionnaire

Question no.	Question asked to the patient
1	How much difficulty do you have reading ordinary print in newspapers?
2	How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools?
3	How much difficulty do you have finding something on a crowded shelf?
4	How much difficulty do you have reading street signs or the names of stores/shops?
5	How much difficulty do you have going down steps, stairs, or curbs in dim light or at night?
6	How much difficulty do you have noticing objects off to the side while you are walking?
7	How much difficulty do you have viewing movies, plays, or sports events?
8	How much difficulty do you have doing things like shaving, styling your hair, or putting on makeup?
9	How much difficulty do you have seeing TV/Computer/Laptops?
10	How much difficulty do you experience while reading messages or dialling number on your mobile phone?

Table 2: Options given to the patient for the vision impairment questionnaire mentioned in Table 1 along with the score allotted for each answer

Options given to the patient for answering all the questions asked in Table 1	Score allotted to the answer
No difficulty at all	0
A little difficulty	1
Moderate difficulty	2
Extreme difficulty	3
Stopped doing this due to insufficient vision	4

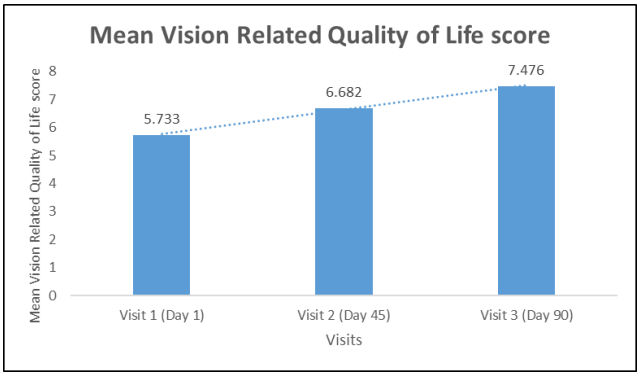

Fig. 1: Mean vision related quality of life score on visit 1, 2 and 3

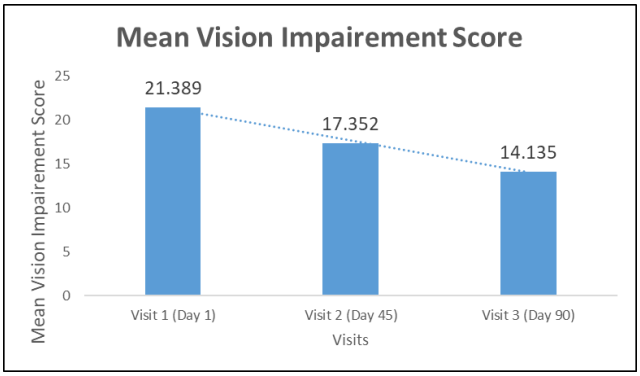

Fig. 2: Mean vision impairment score at visit 1, 2 and 3

reported and all episodes were of hyperacidity which was non-serious in nature.

4. Discussion

AMD can be considered as late-onset deterioration of retinal pigment epithelium (RPE) and photoreceptors present in the central retina which can be caused by various genetic factors and/ or environmental and/ or older age but not limited to it. Risk factors for AMD includes but not limited to gender (female are at the higher risk of AMD compared to male), age (people more than 65 years) and ocular factor (0.75 diopters or more Hyperopia are at the higher risk of developing wet form or exudative form of AMD).[5] Although AMD is not curable but development of the disease can be prevented by the use of combinations of nutraceutical supplements.[5] This study was conducted to test the efficacy in medical management of AMD and safety for the combination of Vitamin C 250 mg, Zinc 40 mg, Lutein 5 mg, Zeaxanthin 1 mg, Copper 1 mg, Vitamin E 200 IU per capsule in the Indian patients for the indication of AMD. Efficacy assessment was made by two efficacy assessment parameters including vision related quality of life and vision impairment score obtained using vision impairment questionnaire. At baseline visit, the mean vision related quality of life score of all the patients completed the study was 5.733 which was increased to 6.682 on visit 2, which was the percentage increase of 16.550% as compared to the baseline. At visit 3, the mean vision related quality of life score was increased to 7.476 which was increase of 30.403% as compared to the baseline. At baseline visit, the vision impairment score was 21.389 which was decreased

to 17.352 at visit 2 and further decreased to 14.135 on visit 3. At visit 2 and 3, the percentage reduction in the vision impairment score as compared to baseline was 18.872% and 14.135% respectively. The above-mentioned results for both the parameters of efficacy assessment shows that there was overall improvement in visual functions of AMD patients who took the investigational product and also no serious adverse event was reported during the post marketing surveillance study. Below we have discussed some of the studies which we could found out from the literature where similar kind of studies were conducted.

A randomized, placebo-controlled, double-blind clinical trial was conducted at 11-centers on 3,640 human subjects suffering from AMD of age between 55-80 years old which was sponsored by National eye institute, one of the federal government's National Institutes of Health and named the study as ARED clinical trial. Out of the recruited subjects 2.4% subjects were lost to follow up. Subjects in the clinical trial were recruited having extensively small or intermediate or large drusen, noncentral geographic atrophy, pigment abnormalities in 1 or both eyes or advanced AMD or vision loss due to AMD in one eye and at least 1 eye had best correlated visual acuity equal to or better than 20/32. Out of 3640 subjects, 888 subjects were randomized to take Vitamin C (500 mg), vitamin E (400 IU), beta-carotene (15 mg) and Zinc (80 mg) as zinc oxide and Copper (2 mg) as Cupric oxide; 904 subjects were randomized to take Zinc (80 mg) as Zinc oxide and Copper (2 mg) as Cupric oxide; 945 subjects were randomised to take beta-carotene (15 mg) and 903 subjects were randomised to take placebo. It was found that there was 25% reduction in the risk of developing the advanced AMD (OR 0.72, 99% CI, 0.52- 0.98) and 19% reduction in the risk of vision loss in the group of subjects taken Vitamin C, vitamin E, beta-carotene, Copper and Zinc as compared to the placebo. Subjects taken Zinc and Copper were found with the 21% of reduced risk of developing advanced AMD and 11% (OR 0.75, 99% CI, 0.99- 1.03) of reduced risk of vision loss as compared to placebo. Subjects taken Vitamin C, Vitamin E and beta carotene were found to be 17% (OR 0.80, 99% CI, 0.59- 1.09) of reduced risk of advanced AMD and 10% of reduced risk of vision loss as compared to the placebo. It was concluded that nutritional supplement combination (also called as AREDS formulation as per NEI) of Vitamin C (500 mg), vitamin E (400 IU), beta-carotene (15 mg) and Zinc (80 mg) as zinc oxide and Copper (2 mg) as Cupric oxide can reduce the risk of developing advanced AMD.[12–14]

After successful completion of AREDS clinical trial, AREDS 2 clinical trial was conducted by National eye institute (the same research group) to improve the AREDS formula. In the improved combination, 15 mg Beta-Carotene was replaced by 10 mg Lutein and 2 mg zeaxanthin as antioxidants as Beta-Carotene increases the risk of lung cancer among people who smoke as per National Cancer Institute and Lutein and Zeaxanthin belongs to the same family of nutraceuticals as Beta-Carotene and have important functions in the retina. Omega-3 fatty acids were added is associated with a lower risk of developing advanced AMD and dose of Zinc was reduced to 25 mg from 80 mg. Oral supplementation with the AREDS formulation had positive results towards reduction of the risk of progression to advanced age-related macular degeneration (AMD). Observational data suggested that increased dietary intake of Lutein and Zeaxanthin (carotenoids), omega-3 long-chain polyunsaturated fatty acids (Docosahexaenoic acid [DHA] and Eicosapentaenoic acid [EPA]), or both might further reduce this risk. The main objective behind this clinical trial was to determine whether adding DHA and EPA, Lutein and Zeaxanthin or both to the AREDS formulation decreases the risk of developing advanced AMD and to evaluate the effect of lowering zinc doses, eliminating beta carotene or both in the AREDS formulation. Participants were randomized to receive Lutein (10 mg) + Zeaxanthin (2 mg), DHA (350 mg) + EPA (650 mg), Lutein+ Zeaxanthin + DHA+ EPA or placebo. All participants were also asked to take the original AREDS formulation or accept a secondary randomization to 4 variations of the AREDS formulation, including elimination of beta carotene, lowering of zinc dose, or both. It was a phase 3, multicentered, double blind, randomized, placebo-controlled study conducted on 4203 human subjects aged 50 to 85 years at risk for progression to advanced AMD with bilateral large drusen or large drusen in 1 eye and advanced AMD in the fellow eye. Investigational follow-up was taken for 5 years, with 1940 study eyes with 1608 participants progressing to advanced AMD. Kaplan-Meier probabilities of progression to advanced AMD by 5 years were 31% (493 eyes [406 participants]) for placebo, 29% (468 eyes [399 participants]) for Lutein and zeaxanthin, 31% (507 eyes [416 participants]) for Omega 3 fatty acids, and 30% (472 eyes [387 participants]) for Lutein and Zeaxanthin and Omega 3 fatty acids. Comparison with placebo in the primary analyses demonstrated no statistically significant reduction in progression to advanced AMD (hazard ratio [HR], 0.90 [98.7% CI, 0.76- 1.07]; P=.12 for Lutein and Zeaxanthin; 0.97 [98.7% CI, 0.82-1.16]; P=.70 for Omega 3 fatty acids; 0.89 [98.7% CI, 0.75-1.06]; P=.10 for Lutein and Zeaxanthin and Omega 3 fatty acid). There was no apparent effect of beta carotene elimination or lower-dose Zinc on progression to advanced AMD. More lung cancers were noted in the Beta-Carotene vs no Beta Carotene group (23 [2.0%] vs 11 [0.9%], nominal P=.04), mostly in former smokers. So, from the clinical trial it was concluded that addition of Lutein and Zeaxanthin, DHA and EPA or both to the AREDS formulation in primary analyses did not further reduced the risk of progression to advanced AMD. But to reduce the incidences of lung cancer in smokers, Lutein and Zeaxanthin was concluded as a better carotenoid substitute

in the AREDS formulation.[15–17]

5. Conclusion

The fixed dose combination of Vitamin C 250 mg, Zinc 40 mg, Lutein 5 mg, Zeaxanthin 1 mg, Copper 1 mg and Vitamin E 200 IU per capsule was found to be efficacious as well as safe in the Indian patients of AMD.

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6.1. Disclosure

This post marketing surveillance study was conducted as a part of pharmacovigilance activity for the fixed dose combination of Vitamin C 250 mg, Zinc 40 mg, Lutein 5 mg, Zeaxanthin 1 mg, Copper 1 mg and Vitamin E 200 IU per capsule which is available in India under the brand name Ocubless Capsules which is marketed by Centaur Pharmaceuticals Pvt Ltd.

7. Source of Funding

None.

8. Conflict of Interest

None.

References

1. Carneiro A, Andrade JP. Nutritional and Lifestyle Interventions for Age-Related Macular Degeneration: A Review. *Oxid Med Cell Longev*. 2017;2017:6469138. doi:10.1155/2017/6469138.
2. Kolar P. Classification and clinical features of AMD. In: Giudice GL, editor. Age-Related Macular Degeneration - Etiology, Diagnosis and Management - A Glance at the Future. IntechOpen; 2013. p. 105–32. doi:10.5772/56745.
3. Sharma R, Mehta K, Bhatti JS, Mastana S, Singh M, Singh P. Prevalence and Predictors of Age Related Macular Degeneration in the Population of Punjab: North Indian Age Related Macular Degeneration Epidemiology and Molecular Genetic Study (NIARMEMS). *Int J Health Sci Res*. 2018;8(10):1–8.
4. Maurya RP, Gupta S. Gene therapy in age-related macular degeneration. *Indian J Clin Exp Ophthalmol*. 2023;9(1):1–2.
5. Optometric clinical practice guideline care of the patient with visual impairment. St. Louis: American Optometric Association; 1997. Available from: https://www.aoa.org/AOA/Documents/Practice%20Management/Clinical%20Guidelines/Consensus-based%20guidelines/Care%20of%20Patient%20with%20Visual%20Impairment%20%28Low%20Vision%20Rehab%29.pdf.
6. Koushan K, Rusovici R, Li W, Ferguson LR, Chalam KV. The role of lutein in eye-related disease. *Nutrients*. 2013;5(5):1823–39.
7. Juturu V, Bowman JP, Stringham NT, Stringhan JM. Bioavailability of lutein/zeaxanthin isomers and macular pigment optical density response to macular carotenoid supplementation: A randomized double blind placebo controlled study. *New Front Ophthalmol*. 2016;2(4):140–5.
8. Widomska J, Subczynski WK. Why has nature chosen lutein and zeaxanthin to protect the retina? *J Clin Exp Ophthalmol*. 2014;5(1):326. doi:10.4172/2155-9570.1000326.
9. Vishwanathan R, Chung M, Johnson EJ. A systematic review on zinc for the prevention and treatment of age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2013;54(6):3985–98.
10. Yildirim Z, Ucgun NI, Yildirim F. The role of oxidative stress and antioxidants in the pathogenesis of age-related macular degeneration. *Clinics (Sao Paulo)*. 1807;66(5):743–6.
11. Yamauchi R. Vitamin E: mechanism of its antioxidant activity. 1997;3(4):301–9.
12. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol*. 2001;119(10):1417–36.
13. Age-Related Eye Disease Study Research Group. The age-related eye disease study (AREDS): design implications AREDS report no. 1. Controlled clinical trials. *Control Clin Trials*. 1999;20(6):573–600.
14. Age-Related Eye Disease Studies (AREDS/AREDS2): major findings. Last reviewed on 20 Jan 2022. Available from: https://www.nei.nih.gov/research/clinical-trials/age-related-eye-disease-study-areds/areds-background-and-results.
15. Chew EY, Clemons T, Sangiovanni JP, Danis R, Domalpally A, Mcbee W, et al. The Age-Related Eye Disease Study 2 (AREDS2): study design and baseline characteristics (AREDS2 report number 1). *Ophthalmology*. 2012;119(11):2282–9.
16. Aronow ME, Chew EY. AREDS2: Perspectives, recommendations, and unanswered questions. *Curr Opin Ophthalmol*. 2014;25(3):186.
17. Chew EY, Clemons TE, Sangiovanni JP, Danis R, Ferris FL, Elman M, et al. Lutein+ zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. *JAMA*. 2013;309(19):2005–15.

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