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Review Article

Dietary supplements and drugs available in India along with the mechanism of action and clinical trial data for the medical management of age related macular degeneration (AMD)

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ABSTRACT

Age related macular degeneration (AMD) is one of the leading cause of blindness among elderly population which diminishes the visual quality. The main objective behind this review is to give the brief information about the dietary supplements and drugs which are available in India along with the mechanism of action and clinical trial data for the management for AMD. Also, we have commented, wherever any additional clinical trial data or regulatory approvals would be needed for using the pharmaceutical or nutraceutical product in Indian patients. The dietary supplements reviewed in this article includes Lutein and Zeaxanthin which are also referred as macular pigments and have important role in absorption of blue light prior reaching to the retina and have antioxidant functions, Zinc which has structural role in antioxidant enzymes, Copper which is cofactor for several ocular-enzymes, Astaxanthin, Vitamin C, Vitamin E, Resveratrol and Glutathione which are antioxidants. We have also reviewed Brimonidine for the management of non-neovascular AMD. Brimonidine is an alpha 2-adrenergic agonist but along with that it has neuroprotective as well as cytoprotective activities because of which it can be used for the management of non-neovascular AMD. In this review we have discussed many clinical trials for different combinations of above-mentioned dietary supplements and out of which AREDS 2 clinical trial was conducted on comparatively larger number of patients and for longer study duration.

1. Introduction

Age-related macular degeneration (AMD) is one of the foremost cause of blindness among the elderly population and also diminishes the vision related quality of life. A combination of genetic risk factors along with the hypertension, smoking, age above 60 years and environmental factors are recognized to contribute to the progression of AMD. [1–3]

A population-based study, named INDEYE study was conducted to estimate the age specific prevalence of early and late AMD in India. For age between 60 to 79 years old, the percent prevalence for late AMD was found 1.2% and for early AMD of grade 1 was 39.3%, of grade 2 was 6.7% and grade 3 was 0.2%. For people of age 80 years and older, the percent prevalence for late AMD was found 2.5% and for early AMD of grade 1 was 43.1%; of grade 2 was 8.1%; and of grade 3 was 0.5%. [4]

AMD mainly is of two types, dry AMD or non-exudative AMD and wet AMD or exudative AMD. Dry AMD and wet AMD are normally found in 90% and 10% patients, respectively out of total number of patients suffering from AMD. In the wet form of AMD the reason behind possible central loss of vision is a sub-choroidal neovascularization.

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In wet AMD pathological angiogenesis gets initiated by inflammatory reaction. Pathological neovascularization penetrates to the subretinal space through defects primarily present in Bruch membrane and secondarily in the retinal pigment epithelial (RPE) layer, where exudation and bleeding destroys photoreceptors. In dry AMD the slow death of cells of RPE layer happens which also may results into geographic atrophy and may further result into permanent central loss of vision.[5]

This review focuses on management of non-neovascular AMD by dietary supplements and drugs available in India, their mechanism of action and clinical trials conducted globally for the management of non-neovascular AMD.

Dry AMD is clinically defined by the presence of yellow sub-RPE deposits called drusen of diameter 63 μm or larger (intermediate size), RPE pigmentary abnormalities and reticular pseudo-drusen. Pigmentary abnormalities in AMD are clinical indication of RPE deterioration, which may ultimately result into death of RPE cells and of the covering photoreceptor cells.[6]

In dry AMD, there are two types of drusen including basilar laminar drusen and basilar linear drusen. Basilar laminar drusen gets deposited in membranous debris which is extracellular material between the RPE and its basement membrane whereas basilar linear drusen gets deposited between the RPE basement layer and the inner collagenous layer of Bruch's membrane. Drusen may lead to thickening of Bruch's membrane and degeneration of RPE. In AMD, vision loss is due to the degeneration of photoreceptor cells and the choriocapillaris, which rapidly results after RPE atrophy.[7]

There are few drusen characteristics which can be linked with the high risk of development of wet form of AMD which includes soft type of drusen, present in number more than 5, of size $\geq$ 63 μm, confluence and hyperpigmentation. The risk of developing wet AMD increases if there is history of choroidal neovascularization in the fellow eye or with a positive family history. Risk of eyes with bilateral drusen with good visual acuity (VA) to develop choroidal neovascularization normally lies between 0.2 to 18%. Confluence of drusen and focal hyperpigmentation were found to be associated with an higher risk of progression to wet or exudative AMD.[7]

Patients suffering from dry AMD normally develops geographic atrophy (GA) after the progression of confluent, large drusen to hyperpigmentation to finally regression of drusen.[5] GA of the RPE is the advanced form of non-neovascular AMD and also it is linked with the slow but progressive central vision loss. In patient dense scotomas frequently gets observed, corresponding to retinal areas affected by GA. These scotomas involve perifoveal and/ or parafoveal retinal areas in the early GA and may progress to foveal center in the late GA.[7]

2. Dietary Supplements for the Management of Non-neovascular AMD

Below we have given a brief review about the mechanism of action of dietary supplements which are available in India and can be used for the management of non-neovascular AMD.

3. Lutein and Zeaxanthin

Lutein and zeaxanthin are stereoisomers of each other and belongs to the dietary carotenoid class and xanthophylls subclass. Lutein and Zeaxanthin are located at the center of the fovea, the area called macula lutea which is yellowish pigmented area which is the site for highest visual acuity. Lutein and Zeaxanthin are the most dense compounds located in the macula lutea because of which they are referred as macular pigments. It is considered that because the macula part of the retina is rich in Lutein and Zeaxanthin, it is yellow in colour. Lutein and Zeaxanthin mainly protects retina from damage caused by blue-light and oxidative damage. Light-induced damage caused to retina mainly depends on intensity, wavelength and time of exposure of light. The presence of Lutein and Zeaxanthin serves photoprotective function to the macula due to their property of high absorptivity to blue-light by absorbing the blue range wavelength.[8] Lutein and Zeaxanthin attenuates the blue-light before reaching to the delicate functional structures including RPE, photoreceptor cells and choriocapillaris. It is considered that the reduction in the intensity of blue light can be up to 90% on the higher side and normally it is about 40%. Specifically Lutein plays more specific role as compared to Zeaxanthin as a photoprotective agent.[9] Lutein and Zeaxanthin also have anti-oxidant properties and reduces the oxidative stress not only from retina but also from lens and choroid. Both are highly potent quenchers of free radicals and singlet oxygens.[8]

Natural synthesis of Lutein and Zeaxanthin in mammals is not possible and it must be obtained from the diet. Lutein and zeaxanthin can be obtained from fruits and vegetables (green leafy plants) and also from egg products. To reduce the risk of ocular diseases including AMD, the recommended daily dose of Lutein and Zeaxanthin for adults is 6 to 20 mg. Due to lipophilic nature of Lutein and Zeaxanthin it gets absorbed through fats and transport via high or low density lipoproteins but mostly via high density lipoproteins and gets accumulated in lipophilic tissues like liver tissues, adipose tissues etc. Other than AMD, Lutein and Zeaxanthin has several other benefits on human health including other ocular diseases, anti-carcinogenic effects, neuroprotective effects, cardioprotective effects, anti-diabetic effects and protective effects on skin damages. Lutein and Zeaxanthin supplementation in the required dose prevents the progression of AMD and may causes improved

visual performance.[10]

4. Zinc

In AMD, retina is prone to damage due to oxidative stress due to high oxygen consumption, constant exposure to visible light and presence of readily oxidizable polyunsaturated fatty acids in high concentration. Zinc is usually present in high concentration in areas of the retina that gets affected by AMD and along with the age it gets declined. Zinc present in the retina and RPE, interacts with Vitamin A and Taurine, modifies photoreceptor plasma membranes and orders the light-rhodopsin reaction and controls synaptic transmission. Zinc has its structural role in antioxidant enzymes.[11] For proper functioning of the antioxidant defence system zinc acts as a co-factor for the synthesis of important antioxidant enzymes. Zinc acts as a transcription factor which is important for the expression of genes which encodes antioxidant enzymes. Zinc protects cells against oxidative damage by enzyme inhibition of NADPH-Oxidase (nicotinamide adenine dinucleotide phosphate oxidase), induces metallothionein synthesis and also acts as a pro-oxidant. Zinc is a potent inducer of metallothionein. Under normal physiological conditions zinc bounds to metallothionein and under the stressed condition of oxidation, micronutrients gets released from the complex of zinc with metallothionein and exerts anti-oxidation actions. Also, studies have found that Zinc has an important role in the regulation of Gutathione peroxidase which is an antioxidant enzyme having antioxidant activities in retina as well as other parts of the body. Zinc acts as a co-factor for superoxide dismutase and also Zinc is one of its structural component. Superoxide dismutase is an antioxidant enzymes having antioxidant activities in retina.[12] Superoxide dismutase accelerates the conversion of superoxide radicals into oxygen and hydrogen peroxide, reduces the toxicity of reactive oxygen species by converting a highly reactive and harmful species to a less harmful one. Superoxide dismutase enzymes also reduces the levels of a reactive nitrogen species.[13]

Another antioxidant mechanism of action of Zinc is, it affects the expression of rate-limiting enzyme of glutathione de novo synthesis named glutamate-cysteine ligase. Administration of 100–150 mM of Zinc in the cultured human retinal pigment epithelial cell line ARPE-19 cells upregulates the mRNA levels of glutamate-cysteine ligase via an nuclear factor erythroid 2 (NFE2)-related factor 2 (Nrf2)-dependent pathway. In this way, zinc modulates the total cellular Glutathione concentration.[12]

5. Copper

Decreased anti-oxidant capacity and increased oxidative stress are main reasons behind progression of AMD. Copper and Zinc functions as a cofactor in several ocular enzymes which includes copper-zinc-superoxide dismutase which is one of the first-line anti-oxidant enzyme present in retina.[14] During the clinical trial superoxide dismutase was found to be lowered in AMD patients as compared to normal people. It is present in retina and protects RPE and photoreceptors (rods and cones) from oxidative stress.[15] Also Copper has an important role in the synthesis of melanin which is a storage protein for copper, iron and zinc in melanocytes and RPE. The cellular homeostasis of copper, iron and zinc is highly interlinked. If one of these metals becomes deficient, another metal may accumulate.[16] Also it is proven by the clinical trial that homeostasis plays a role in the retinal health and AMD.[14]

6. Vitamin E

Vitamin E is an lipid soluble antioxidant present in retinal membrane and its deficiency can cause retinal degeneration. Along with the antioxidant activities, it also increase the bioavailability of Lutein.[17,18] Retinal membrane has high quantity of polyunsaturated fatty acids due to which reactive oxygen species initiates chain reactions of lipid peroxidation which injures the retina, especially that part of the retinal membrane which has important roles in visual functions.[19] Vitamin E has antioxidant roles in ocular cell membranes by preventing free radical reactions and terminating lipid peroxidation.[18] Lipid peroxidation which is a chain reaction proceeds in three stages including initiation then propagation and finally termination. In the first step initiation, from a polyunsaturated fatty acid moiety by the abstraction, a carbon-centered lipid radical (an alkyl radical) gets produced. This step can be catalysed by transition metals, heat or light. In the second step named propagation, produces alkyl radicle which rapidly reacts with molecular oxygen and gives peroxyl radical. The peroxyl radical (a chain carrying radical) is capable of attacking another polyunsaturated lipid molecule. The peroxyl radical gets converted into a hydroperoxide and this produces a new alkyl radical, which rapidly gets converted into another peroxyl radical. The chain type of reaction does not stops until the chain carrying peroxyl radical meets and combines with another radical to form inactive products which is the termination step of lipid peroxidation. Vitamin E works as an antioxidant by breaking the chain in the propagation step of lipid peroxidation by converting peroxyl radicle into hydroperoxide by donating its phenolic hydrogen atom to a peroxyl radical and converts it to a hydroperoxide. By donating a phenolic hydrogen atom to a peroxyl radical it gets converted into tocophenroxyl radicle that is sufficiently stable to be unable to continue the chain rection so it gets removed from the cycle by reaction with another peroxyl radical to form an inactive, non-radical product.[20]

7. Vitamin C

Vitamin C is one of the most efficacious water soluble antioxidant found in retina. Vitamin C plays important role in the eye (ocular muscles including retina) in antioxidant defence mechanism by protecting against photooxidative damage due to its property as a free radical scavenger.[15] Vitamin C exerts its antioxidant activity by donating its electron. Vitamin C gets oxidized and prevents other compounds from being oxidized. By various species (molecules or free radicles), vitamin C gets oxidized and species receives electron and gets reduced which had potential involvement in human diseases including AMD. The species which receives electron and gets reduced by vitamin C can be divided into classes as mentioned below.[21]

1. Compounds having unpaired electrons (radicals) such as nitrogen-oxygen radicals, sulphur radicals and oxygen related radicals (hydroxyl radical superoxide and peroxyl radicals). With the exception of the sulphur radicals, these compounds are sometimes termed as reactive oxygen species and reactive nitrogen species.[21]
2. Compounds that are not radicals but reactive including nitrosamines or other nitrosating compounds, hypochlorous acid, ozone and nitrous acid related compounds.[21]
3. Compounds formed in any reaction with either of the first two classes and then have ability to react with vitamin C.[21]
4. Transition metal-mediated reactions involving iron and copper.[21]

8. Astaxanthin

Astaxanthin is an antioxidant and its antioxidant activities are exerted by scavenging radicals or quenching singlet oxygen to terminate chain reactions. The intensity of antioxidant activities of Astaxanthin is higher compared to other carotenoids such as β-carotene, Lycopene, Lutein and α-Carotene. Astaxanthin has 10 times greater antioxidant activities as compared to antioxidant activities of β-carotene, Canthaxanthin, Lutein and Zeaxanthin whereas it has 100 times greater antioxidant activities than vitamin E. Along with acting as an antioxidant it also enhances the activity of superoxide dismutase which is an antioxidant enzyme. Astaxanthin inhibits the enzyme thioredoxin reductase. Due to unique molecular structure of Astaxanthin, it shows anti-lipid peroxidation activities both inside and outside the cell membrane. It shows better protection against lipid peroxides as compared to vitamin C and β-carotene.[22]

9. Glutathione

Glutathione has antioxidant functions and shows antioxidation activities by direct elimination of aldehydes and peroxides. Also it maintains Vitamin C and Vitamin E in their reduced and functional forms. Role of vitamin C and Vitamin E in the management of AMD in reviewed above.[23]

There is no clinical trial data for Glutathione saying that it is efficacious for the management of AMD but Glutathione is available in India along with the combination of Lutein, Zeaxanthin and Astaxanthin for the management of AMD.

10. Resveratrol

Resveratrol is a nonflavonoid polyphenol which is an antioxidant, it scavenges free radicles and inhibits lipid peroxidation. Compared to Vitamin C and Vitamin E, Resveratrol has better free radical scavenging activities and similar to flavonoids Quercetin and Epicatechin.[24]

11. Clinical Trials Conducted for Dietary Supplements for the Management of Non-neovascular AMD

11.1. AREDS clinical trial

A Randomized, placebo-controlled, double blind clinical trial was conducted at 11-centers on 3,640 subjects suffering from AMD of age between 55-80 years old and average follow-up was taken for 6.3 years. Out of the recruited subjects 2.4% subjects were lost to follow up. Clinical trial was sponsored by National eye institute (NEI), one of the federal government's National Institutes of Health and named as AREDS clinical trial. Recruited subjects were randomized to either the combination of Vitamin C (500 mg), Vitamin E (400 IU), Beta-carotene (15 mg), Zinc (80 mg) as Zinc oxide and Copper (2 mg) as Cupric oxide; or combination of Zinc (80 mg) as Zinc oxide and Copper (2 mg) as Cupric oxide; or combination of Beta-carotene (15 mg), Vitamin C (500 mg) and Vitamin E (400 IU) or placebo. There was found 25% reduction in the risk of developing the advanced AMD which was statistically significant with odds ratio 0.72, 99% confidence interval and 19% reduction in the risk of vision loss in the group of subjects taken combination of Vitamin C, Vitamin E, Beta-carotene, Copper and Zinc as compared to the placebo. Subjects taken combination of Zinc and Copper were found with the 21% reduced risk of developing advanced AMD with odds ratio 0.75, 99% confidence interval and 11% of reduced risk of vision loss as compared to placebo. Subjects taken combination of Vitamin C, Vitamin E and beta carotene were found with 17% reduced risk of advanced AMD with odds ratio 0.80, 99% confidence interval and 10% of reduced risk of vision loss as compared to the placebo. According to results it was concluded that

nutritional supplement which is also called as AREDS formula as per NEI which is combination of Vitamin C (500 mg), Vitamin E (400 IU), Beta-carotene (15 mg) and Zinc (80 mg) and Copper (2 mg) can reduce the risk of developing advanced AMD.[25–27]

11.2. AREDS 2 clinical trial

After successful completion of AREDS clinical trial, AREDS 2 clinical trial was conducted by NEI (the same research group) to improve the AREDS formula. The main objective behind this clinical trial was to evaluate whether adding Zeaxanthin and Lutein or EPA and DHA or both to the AREDS formulation decreases the risk of developing advanced AMD or not; to evaluate the efficacy of reduced dose of Zinc which was 80 mg in the AREDS formulation to 25 mg; to evaluate the effect of eliminating the Beta-carotene on efficacy of AREDS formulation as Beta-carotene was found to be associated with increased risk of lung cancer among smokers, as per National Cancer Institute and also to evaluate the efficacy and safety for replacement of Beta-carotene with Lutein and Zeaxanthin.

It was a double blind, multicentric, placebo-controlled, randomized phase III clinical trial. It was conducted on human subjects of age between 50 to 85 years old which were considered to be at high risk of progression to advanced AMD. The study duration was kept 5 years. Recruited subjects were randomized to receive either the combination of Lutein (10 mg) + Zeaxanthin (2 mg) or DHA (350 mg) + EPA (650 mg) or Lutein+ Zeaxanthin and DHA (350 mg) + EPA (650 mg) or placebo by keeping Copper (2 mg), Vitamin E (400 IU) and Vitamins C (500 mg) unchanged in all the subjects while varying beta-carotene and Zinc by either keeping Zinc at the original level (80 mg) as AREDS formula or lowered amount of Zinc to 25 mg or eliminated only Beta-carotene or lowered amount of Zinc 25 mg.

Total 1608 clinical trial subjects (1940 study eyes) completed the clinical trial. It was found that addition of Lutein and Zeaxanthin or DHA and EPA or both to the AREDS formula had no statistically significant reduction in progression to advanced AMD. Elimination of Beta-carotene or lowering the amount of Zinc from 80 mg to 25 mg did not show any statistically significant effect in lowering the progression to advanced AMD. Adverse events of lung cancer were found among smokers who were randomized to take formulation containing Beta-carotene. So it was concluded that Lutein and Zeaxanthin can be used as an replacement of Beta-carotene to improve the safety and reduce the risk of lung cancer among smokers. It was also concluded that the combination of Vitamin C (500 mg), Zinc (80 mg), Lutein (10 mg), Zeaxanthin (2 mg), Copper (2 mg) and Vitamin E (400 IU) per day can be used for the management of AMD.[28,29]

11.3. Lutein 10 mg vs Lutein 20 mg vs combination of Lutein 10 mg and Zeaxanthin 10 mg

Huang Y M et al conducted a randomized, placebo controlled, double blind clinical trial on 112 subjects of AMD in China for the study duration of 2 years. During the clinical trial, 4 subjects were lost to follow-up. Subjects were either randomized to receive Lutein 10 mg (n=26) or Lutein 20 mg (n=27) or combination of Lutein 10 mg and Zeaxanthin 10 mg (n=27) or placebo (n=28). All subjects recruited for the study were of age older than 50 years, suffering from early AMD. Early AMD was defines by the presence of soft drusen with retinal pigmentary abnormalities. Study evaluation parameters were macular pigment optical density, serum concentration of Lutein/ Zeaxanthin, best-spectacle corrected visual acuity, flash recovery time, contrast sensitivity and vision-related quality of life by VFQ25.

Serum and macular concentration of Lutein/ Zeaxanthin was found to be increased in all the group of subjects randomized to active but there was no increase found in the placebo group of subjects. Among the active group of subjects highest increase in the concentration of Lutein/ Zeaxanthin was found in the group of subjects randomized to Lutein 20 mg (6.75 fold) compared to Lutein 10 mg (4.30 fold) or Lutein and Zeaxanthin (5.57 fold). Macular pigment optical density was found to be most significantly increased at 24 weeks in group of subjects randomized to Lutein 20 mg and to the same level it was found to be increased by 2 years in the group of subjects randomized to Lutein 10 mg. VFQ 25 score was found to be negatively grown and there was no significant effect on flash recovery time and best-spectacle corrected visual acuity in the group of subjects randomized to either of the active group. Statistically significant increase in the contrast sensitivity was found in group of subjects randomized to Lutein and Zeaxanthin in 48 weeks and comparatively more statistically significant increase was found by 2 years in group of subjects randomized to Lutein 20 mg and Lutein 10 mg. It was concluded from the clinical trial that long term supplementation of Lutein can improve macular pigment optical density, serum Lutein/Zeaxanthin concentration and contrast sensitivities in patients suffering from early AMD.[30]

11.4. Lutein 10 mg vs Lutein 20 mg vs combination of Lutein 10 mg and Zeaxanthin 10 mg

Huang Y M et al conducted a randomized clinical trial on 112 subjects for the study duration of 2 years. The objectives behind the clinical trial was to study changes in macular pigment optical density and functional changes in patients having early AMD after multiple supplementation of Lutein and Zeaxanthin. Subjects were equally divided into 4 groups and randomized to receive either Lutein 10

mg or Lutein 20 mg or combination of Lutein 10 mg and Zeaxanthin 10 mg or placebo. Efficacy assessment was done by macular pigment optical density at baseline, week 48 and at the end of the clinical trial which was by 2 years. Macular pigment optical density was found to be increased the most by 48 weeks in group of subjects randomized to Lutein 20 mg and to the same level it was found to be increased by 2 years in the group of subjects randomized to Lutein 10 mg. Also mean retinal sensitivity was found to be statically significantly increased in the group of subjects randomized to 10 mg or 20 mg of Lutein and there was no increase in the group of subjects randomized to placebo. So it was concluded that supplementation of Lutein alone or in combination with Zeaxanthin can significantly increase the macular pigment optical density and only supplementation of Lutein can enhance retinal sensitivity in patients with early AMD.[31]

11.5. Effect of Omega-3 fatty acids on the combination of Lutein, Zeaxanthin, Copper, Zinc, Vitamin C, E and B3 for the management of AMD

Wolf-Schnurrbusch UE at al conducted an open label, randomized clinical trial for the study duration of 12 months. Total 79 subjects were recruited for the clinical trial out of which 40 subjects were randomized to the combination of Lutein 10 mg, Vitamin C 60 mg, Vitamin E 20 mg, Vitamin B3 10 mg, Copper 0.25 mg, Zinc 10 mg, Zeaxanthin 1 mg and Omega-3 fatty acids (DHA/EPA) 160 mg whereas 39 subjects were randomized same combination of dietary supplements excluding Omega-3 fatty acids for the study duration of 6 months. All recruited subjects were investigated at month 1, 3, 6, 7, 8, 9 and 12. At each visit subjects were investigated for macular pigment optical density and contrast sensitivity. It was found that serum Lutein and Zeaxanthin were significantly increased in the first month and maintained for 6 months for the group of subjects randomized to the combination of Lutein 10 mg, Vitamin C 60 mg, Vitamin E 20 mg, Vitamin B3 10 mg, Copper 0.25 mg, Zinc 10 mg, Zeaxanthin 1 mg but not in the same combination with Omega-3 fatty acids (DHA/EPA) 160 mg. Also it was found that contrast sensitivity and macular pigment optical density were increased in the group of subjects randomized to the combination of Lutein 10 mg, Vitamin C 60 mg, Vitamin E 20 mg, Vitamin B3 10 mg, Copper 0.25 mg, Zinc 10 mg and Zeaxanthin 1 mg but not in the group of subjects randomized to the same combination with Omega-3 fatty acids (DHA/EPA) 160 mg as compared to their respective baseline readings. Visual acuity was found to be unchanged in both group of subjects. So it was concluded that addition of Omega-3 fatty acids to the combination of Lutein 10 mg, Vitamin C 60 mg, Vitamin E 20 mg, Vitamin B3 10 mg, Copper 0.25 mg, Zinc 10 mg and Zeaxanthin 1 mg reduces the bioavailability of Lutein and deceases its beneficiary effects on macular pigments and contrast sensitivity.[32]

11.6. Carotenoids in age-related maculopathy Italian study (CARMIS)

Stefano Piermarocchi et al. conducted a prospective, unblinded, open label, multicentric, randomized clinical trial to test the efficacy for the combination of Vitamin E (30 mg), Vitamin C (180 mg), Zinc (22.5 mg), Copper (1 mg), Astaxanthin (4 mg), Lutein (1 mg) and Zeaxanthin (1 mg) against no dietary supplement in the management of AMD. The clinical trial was conducted on 145 subjects, out of which 102 subjects were randomized to above mentioned dietary supplement whereas 43 subjects were randomized to no dietary supplement. All subjects were investigated for the clinical trial duration of 2 years. Primary objective of the efficacy assessment was to evaluate the changes in visual acuity at 12 and 24 months. Secondary efficacy assessment was done by investigating National Eye Institute visual function questionnaire (NEI VFQ-25) scores and contrast sensitivity at month 12 and 24. Subjects treated with the above mentioned combination of dietary supplements shown stabilization of visual acuity with comparatively better visual acuity scores (81.4 ± 7.2) to subjects with no dietary supplements (76.8 ± 8.9) at month 24. Also in the group of subjects treated with the study combination of dietary supplements, contrast sensitivity and the final mean NEI VFQ-25 composite score obtained at month 12 and 24 was higher as compared to the non-treated group and there was improvement in it as compared to the baseline. So it was concluded that subjects treated with the combination of Vitamin E (30 mg), Vitamin C (180 mg), Zinc (22.5 mg), Copper (1 mg), Astaxanthin (4 mg), Lutein (1 mg) and Zeaxanthin (1 mg) showed statistically significant stabilization or improvement in visual acuity, visual functions and contrast sensitivity composite score and the same combination can be used for the management of AMD.[33]

11.7. Clinical trial for resveratrol and its analogs

Jung-Hwan Kang et al conducted a cell line study to evaluate the protective effects of Resveratrol, Piceatannol and Resveratrol glycones on blue light- induced RPE cell death caused by A2E photooxidation. It was observed that human RPE cells (ARPE-19) gets significantly damaged if treated with A2E treatment followed by blue light exposure. But damages were reduced by pre- and post-treatment of Resveratrol and Piceatannol during in vitro models. The results of FAB-MS analysis and cell free system showed that reduction of A2E by blue light exposure was significantly rescued, and that oxidized forms of A2E were significantly reduced by Resveratrol or Piceatannol treatment. It was also found during the study that Resveratrol and Piceatannol inhibits the accumulation of A2E intracellularly. Along

with the Resveratrol and Piceatannol also Resveratrol glycones showed protection of ARPE-19 cells against blue-light-induced photodamage along with A2E. These results confirmed that Resveratrol and its analogs have protective action against ARPE-19 cell death because of blue light and A2E through A2E accumulation and photooxidation of A2E. Thus, it was concluded from the study that Resveratrol and its analogs can have beneficial action for the management of AMD.[34]

But the above study was conducted on cell lines and not on human subjects suffering from AMD. Resveratrol and its analogues are approved under food category and available in India. So there is need of a phase IV clinical trial on Indian patients suffering from AMD to prove its efficacy so that it can be used by ophthalmologists for the treatment of AMD.

12. Drugs for the Treatment of Non-neovascular AMD

12.1. Brimonidine

Brimonidine is an alpha 2-adrenergic agonist, also shows neuroprotective and cytoprotective activities in cultured cells as well as variety of animal models for optic nerve and retinal diseases.[35–37]

Claudio Ramírez et al. conducted an in vitro experiment to investigate the cyto-protective effects of Brimonidine pre-treatment on human retinal pigment epithelium cells (ARPE-19) and human retinal Müller cells (MIO-M1) that had been treated with hydroquinone which is a toxicant present in cigarette smoke and other sources. It was found that Brimonidine prevents oxidative stress and mitochondrial damaging effects. Brimonidine was also found to be having some blocking effects on hydroquinone necrotic components.[35]

Arturo Ortín-Martínez et al. conducted an animal study on adult albino rats to analyse the protective effects of Brimonidine on cone-photoreceptors from blue light phototoxicity and concluded that Brimonidine has neuroprotective effects on L- or S-cone cells present in retina.[36]

In multiple rodent models of optic nerve injury, including injury produced by elevated intraocular pressure, retinal ischemia or optic nerve crush, topical or systemic administration of Brimonidine demonstrates to promote the survival of retinal ganglion cells.[37]

Baruch D. Kuppermann et al. conducted a phase II, randomized, multicentric (25 clinical trial sites in 7 countries), double-masked, parallel-group, sham-controlled clinical trial to evaluate the safety and efficacy of Brimonidine drug delivery system, a biodegradable intravitreal implant containing dose of 132 μg or 264 μg Brimonidine, for the treatment of GA secondary to AMD. Study was conducted on patients of age above 50 years with GA in both eyes. Patients were either treated with Brimonidine drug delivery system, 132 μg (n= 49) or 264 μg (n= 41) or sham procedure (n = 23) at day 1 and retreated at month 6. The implant was administered intravitreally through the pars plana using standard sterile technique and a single-use 22-gauge applicator system and a proprietary applicator system. The implant was designed in such a way that Brimonidine would diffuse out of the implant as the polymer matrix degrades to the vitreous humour and would take several months. For the sham procedure, a needleless applicator was pressed against the temporal bulbar conjunctiva of the eye. Topical and subconjunctival anaesthetics were used before the Brimonidine drug delivery system and sham procedures, and a broad-spectrum topical antibiotic was administered before and for 3 days after the procedures. Efficacy evaluation was done by measuring the change in the GA lesion area, based on stereoscopic fundus photography. Stereoscopic fundus photography and fluorescein angiography were performed at screening (baseline assessment) and months 3, 6, 9, 12, 15, 18 and 24. The primary endpoint was the change in GA lesion area from baseline to Month 12. GA lesion growth was significantly reduced in both group of subjects treated with Brimonidine drug delivery system groups compared with sham. At Month 12 (primary endpoint), GA lesion growth was reduced by 19% and 28% compared with sham in the Brimonidine drug delivery system 132 μg and 264 μg groups, respectively. So it was concluded that Brimonidine drug delivery system was well tolerated and have an ability to reduce the GA growth in patients with GA secondary to AMD.[38]

Brimonidine ophthalmic solution or gel is currently approved in India for lowering of IOP in patients with open angle glaucoma, ocular hypertension but not for AMD so there is need of phase II and phase III clinical trial to be conducted on Indian patients in India to get the marketing authorization and product can be used by ophthalmologists for the treatment of geographic atrophy secondary to age related macular degeneration.[39]

13. Discussion

Age-related macular degeneration (AMD) is one of the foremost cause of blindness among the elderly population which diminishes the quality of life. A combination of genetic risk factors along with the hypertension, smoking, age above 60 years and environmental factors are recognized to contribute to the progression of AMD.[1–3] Above we have reviewed dietary supplements as well as drugs which can be used for the management non-neovascular AMD along with their mechanism of action and studies conducted for the same and shortly discussed below.

Under dietary supplements we have reviewed Lutein and Zeaxanthin which are macular pigments and have important role in the absorption of blue light prior reaching to the retina and also have antioxidant action,[8–10] Zinc has important structural role in antioxidant

enzymes.[12,13] Copper works as an a co-factor in several ocular enzymes.[14–16] Astaxanthin, Vitamin C, vitamin E, Resveratrol and Glutathione have antioxidant functions.[15–24]

First we will discuss AREDS clinical trials which were sponsored by National Eye Institute which includes AREDS and AREDS2 clinical trials.[27] AREDS was a randomized, placebo controlled, double blind clinical trial conducted on 3640 subjects for the average study duration of 6.3 years and concluded that the combination of Vitamin C (500 mg), Vitamin E (400 IU), Beta-carotene (15 mg), Zinc (80 mg) and Copper (2 mg) can reduce the risk of developing advanced AMD.[25–27] Further it was suggested by the National Cancer Institute that Beta-carotene is associated with the increased risk of lung cancer among smokers. So the AREDS 2 clinical trial was conducted to evaluate the effect of elimination of Beta-carotene; efficacy of Lutein and Zeaxanthin instead of Beta-carotene; lower dose of Zinc (25 mg) and effect of adding Lutein and Zeaxanthin or DHA and EPA or both for the management of AMD. The study was conducted on 1608 subjects and 1940 eyes for the study duration of 5 years. And it was concluded that lowering the amount of Zinc from 80 mg to 25 mg will not have any significant effect on efficacy of the formulation, Lutein and Zeaxanthin can be used to replace Beta-carotene to improve safety without lowering efficacy of the formulation. The new formulation, AREDS 2 formula was suggested for the management of AMD which was the combination of Lutein (10 mg), Zeaxanthin (2 mg), Vitamin C (500 mg), Vitamin E (400 IU), Zinc (80 mg) and Copper (2 mg). Along with the AREDS 2 clinical trial, other clinical trials were conducted for the management of non-neovascular AMD whose conclusions were found to be supporting for the conclusion of AREDS2 clinical trial are shortly discussed below.[28,29]

To evaluate the efficacy of Lutein 10 mg vs Lutein 20 mg vs the combination of Lutein 10 mg and Zeaxanthin 10 mg, Huang Y M et al conducted a randomized clinical trial on 108 subjects of early AMD. And it was concluded that Lutein alone or in combination with Zeaxanthin can increase the macular pigment optical density.[31]

Another clinical trial was conducted in the same way as above clinical trial by Huang Y M at al and it was found that daily supplementation of Lutein 10 mg can increase serum Lutein concentration and visual sensitivity in early AMD.[30]

Another clinical trial was conducted by Wolf-Schnurrbusch et al which was an open-label, randomized, clinical trial to find out the effect of Omega-3-fatty acids on the efficacy for the combination of Lutein, Zeaxanthin, Vitamin C, Vitamin E, Vitamin B3, Copper and Zinc conducted for the study duration of 12 months. It was found in the clinical trial that Omega-3-fatty acids have negative effects on serum Lutein and Zeaxanthin concentration. Also it was found that Omega-3- fatty acid decreases the beneficial effects of the combination of Lutein, zeaxanthin, Vitamin C, Vitamin E, Vitamin B3, Copper and Zinc.[32]

Anther clinical trial was conducted by Stefano Piermarocchiet et al which was a prospective, unblinded, open label, multicentric, randomized clinical trial to test the efficacy for the combination of Vitamin E (30 mg), Vitamin C (180 mg), Zinc (22.5 mg), Copper (1mg), Astaxanthin (4 mg), Lutein (1 mg) and Zeaxanthin (1 mg) against no supplementation. Study conducted on 145 subjects for the management of AMD for the study duration of 2 years. It was found that study combination was efficacious for stabilization of visual acuity with comparatively better scores and for contrast sensitivity also NEI VFQ-25 composite score found to be increased.[33]

Above studies, we found to be supporting with the AREDS 2 clinical trial during our review. Below we have also discussed about Resveratrol and Glutathione which can be used for the management of AMD.

A cell line study was conducted by Jung-Hwan in which Resveratrol and its analogs, shown protective action against ARPE-19 cell death because of blue light and it was concluded that Resveratrol and its analogs can have beneficial action for the management of AMD. But as per our literature review there is no clinical trial conducted on human subjects for Resveratrol for the management of AMD. So before using Resveratrol for the management of AMD, it would be better to have clinical trial data for its efficacy in the management of AMD.[34]

Samiel P S et al. mentioned in the article that Glutathione has antioxidant properties and it maintains Vitamin C and E in their reduced and functional form and because of which it can be used for the management of AMD but, same as Resveratrol some additional clinical trial data would be needed for Glutathione.[23]

Along with dietary supplements we have also reviewed Brimonidine for the management of non-neovascular AMD. In drugs we have not discussed any other clinical trial for any other drug for the management of AMD, as only Brimonidine was found to have positive results for the management of non-neovascular AMD as per the our literature search. Brimonidine is an alpha-2-adrenergic agonist which also has neuroprotective and cytoprotective activities. Bruch D Kappermann et al. conducted a phase II, randomized, global, multicentric, double masked, parallel-group, sham-controlled clinical trial to evaluate the safety and efficacy of Brimonidine 132 μg and 264 μg biodegradable intravitreal implant for the management of GA on 113 subjects. From the study Brimonidine was concluded to be safe as well as efficacious for reduction in the growth of GA.[38]

Brimonidine ophthalmic solution or gel is currently approved in India for lowering of IOP in patients with open angle glaucoma and ocular hypertension but not for AMD so there is need of phase II and phase III clinical trial to be

conducted on Indian patients in India to get the marketing authorization and product can be used by ophthalmologists for the treatment of GA secondary to age related macular degeneration.[39]

So, from the above reviewed dietary supplements and drugs for the management of non-neovascular AMD and their studies, AREDS 2 clinical trial was conducted on more number of subjects and for the larger study duration as compared to other trials conducted. Also, AREDS 2 clinical trial provided positive and statistically significant results for the AREDS 2 formula for the management of AMD. Also, other clinical trials supports the conclusion of AREDS 2 clinical trial as discussed above. So, looking at all the above factors AREDS 2 formula can be used for management of AMD in Indian patients and it is also commercially available at PAN India level.

14. Source of Funding

None.

15. Conflict of Interest

None.

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