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A PROPOSAL FOR IMPROVEMENT OF THE FIRST-LINE TREATMENT OF ADVANCED DIABETIC RETINOPATHY

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Abstract

Diabetic retinopathy (DR) can be resulted from high blood glucose levels that may damage the retinal pigment epithelium, located between the vascular choroids and the neurosensory retina, which functions as a barrier. The first-line treatment of DR comprises an anti-vascular endothelial growth factor (anti-VEGF) compound such as Avastin (bevacizumab), Lucentis (ranibizumab) and Eylea (aflibercept). Some patients suffering from static condition of advanced DR need a treatment that will lead to improvement of the DR condition, e.g., reduction of abnormal blood vessels on the optic disc and preventing further ischemic optic neuropathy. Thus, a combined simultaneous treatment of an anti-VEGF compound such as Avastin, or a biosimilar version, and oral administration of fucoxanthin that has a protective effect on the retina, optionally together with vitamin A, is proposed for treating advanced DR.

Keywords: Diabetic retinopathy, high blood glucose levels, first-line treatment, anti-vascular endothelial growth factor (anti-VEGF), chronic hyperglycemia, diabetes mellitus, optical coherence tomography (OCT), fluorescein angiography, antioxidant properties, anti-inflammatory activity, clinical trials.

Introduction

Chronic hyperglycemia can cause diabetic retinopathy (DR) because high blood glucose levels may damage the retinal pigment epithelium, located between the vascular choroids and the neurosensory retina, which functions as a barrier. The damage to the cells may cause accumulation of reactive oxidative species which further enhance lipid peroxidation. DR can cause vision loss and even blindness in people with severe un-treated diabetes mellitus. Nearly 40% of diabetes patients demonstrate different forms of DR, and diabetes is one of the top five causes for ophthalmic diseases in human population over 50 years old[1]. The retinal pigment epithelium, located between the vascular choroids and the neurosensory retina, forms the protected outer blood–retinal barrier, which maintains the normal structure and function of the retina. The present first-line treatment for DR is injecting medications into the eyes. These medications are injected into the vitreous of the eye in order to assist halting the growth of new blood vessels and decrease fluid buildup. These injections will need to be repeated typically in, e.g., one-month intervals and treatment may last several years. The first-line treatment comprises

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an anti-vascular endothelial growth factor (anti-VEGF) compound such as Avastin (bevacizumab), Lucentis (ranibizumab) and Eylea (aflibercept).

Avastin is a monoclonal antibody (mab) medication administered by injection into the eyes. It is preferred by eye specialists over using the other eye injections because it often comes at a lower cost for patients and insurance companies as a first-line treatment in addition to being safe and effective. However, medical research suggests that administering eye injections treatment for retinal diseases is not always effective. Some patients do not respond adequately to the treatment, leading to static condition and vision is not improved. Furthermore, the anti-VEGF injection is associated with a treatment burden because patients often report anxiety and inconvenience during the medical process and in addition there is an infrequent risk of intraocular inflammation.

Other DR treatments include Ozurdex injection, which comprises an intravitreal implant containing dexamethasone and Kenalog or Triesence containing triamcinolone acetonide (both dexamethasone and triamcinolone acetonide are steroids).

Progress in this treatment is usually monitored by optical coherence tomography (OCT), which is a non-invasive test used to visualize the structure of the eye, mainly the retina, allowing ophthalmologists to obtain high-resolution cross-sectional images of the eye tissues, which help monitoring the treatment's progress. In addition, fluorescein angiography is used employing a special dye (fluorescein) and a camera to examine the blood vessels in the retina and choroid helping to diagnose and monitor the condition of the eyes by visualizing blood flow and identifying the abnormalities. Thus, there is a need for those patients suffering from static condition of advanced DR for a treatment that will lead to improvement in the DR condition, e.g., reduction of abnormal blood vessels on the optic disc and preventing further ischemic optic neuropathy.

Discussion

Angiogenesis is the formation of new blood capillaries from preexisting blood vessels. VEGF is one of the most important pro-angiogenic factors involved in angiogenesis of several diseases. Anti-VEGF strategies to treat cancers were designed to target the pro-angiogenic function of VEGF and thereby inhibit neovascularization. Anti-VEGF therapies may target both the pro-angiogenic activity of VEGF and the anti-apoptotic/pro-survival functions of VEGF. Combination drug therapies using an anti-VEGF medication with chemotherapy are effective against several types of tumors, because in addition to angiogenic inhibition, VEGF blocking renders tumor cells more susceptible to conventional treatment.

Avastin is a monoclonal antibody (mab) anti-VGEF medication traditionally used to treat a number of types of cancers such as colon cancer, lung cancer, ovarian cancer, glioblastoma, hepatocellular carcinoma, and renal-cell carcinoma.

VEGF protein promotes the growth of abnormal blood vessels in the retina, a key factor in DR. The anti-VEGF injections that are used for treating DR, e.g., Avastin, Lucentis and Eylea target the VEGF protein and by blocking VEGF these medications help to reduce macular edema, slow down the progression of the disease, and improve vision.

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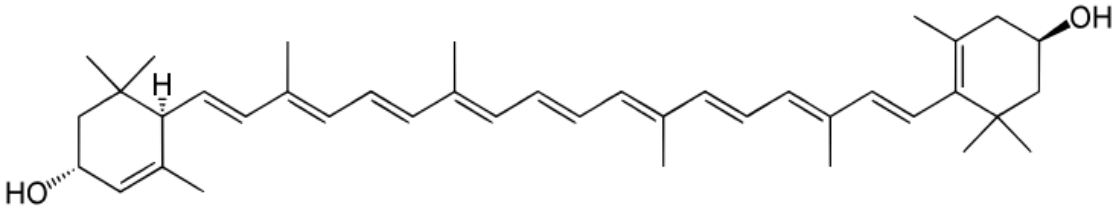
There is a continuous global effort by pharmaceutical companies and health institutes to develop new treatments for DR. The following are few notable examples of clinical trials concerning drugs or drug combinations for the treatment or prophylaxis of DR as per the reports of the US National Library of Medicine (an official website of the United States government). Clinical trial NCT03863535 tested Conbercept, a drug used as an ophthalmic injection, to treat conditions caused by abnormal blood vessel growth in the retina. Clinical trial NCT05310916 tests dapagliflozin, used to treat diabetes mellitus as a competitive sodium/glucose cotransporter 2 inhibitor, on DR in Type 2 diabetes mellitus patients. Clinical trial NCT05310916 tests sleep and circadian regulation in DR: the role of intrinsically photosensitive retinal ganglion cells and melatonin supplementation. Clinical trial NCT04885153 tested the effects of oral fenofibrate on retinal thickness and macular volume. Clinical trial NCT00846716 tests whether the oral anti-diabetic drug thiazolidine is effective in suppression of onset or progression of diabetic nephropathy in Japanese Type 2 diabetic patients. Clinical trial NCT04265261 tested the efficacy and safety of RG7774 (vicasinabin) in patients with diabetes mellitus Type 1 or 2 with treatment-naive DR patients. The study's main purpose was to assess the safety, tolerability, and effect of oral administration of RG7774 on the severity of DR in participants with moderately severe to severe non-proliferative DR and good vision. Clinical trial NCT03811561 tests semaglutide in comparison to placebo in its effect on diabetic eye disease in patients with Type 2 diabetes. Clinical trial NCT01208948 tested alpha lipoic acid in the treatment of DR. Clinical trial NCT02587741 tests the comparison of DR among Type 2 diabetic patients treated with different regimens of metformin, Lantus (long-acting insulin) and Novomix30 (a biphasic suspension of an insulin analogue) in a multi-center randomized parallel-group clinical trial. Clinical trial NCT00406991 tested the retinal blood flow and microthrombi (small blood clots) administering aspirin and clopidogrel in Type 1 diabetes. Clinical trial NCT02985242 compares empagliflozin to glimepiride in patients with Type 2 diabetes mellitus in addition to standard of care treatment to verify whether empagliflozin slows down DR progression rate and thus causes a lower microaneurysm formation rate compared to subjects treated with glimepiride by substantially decreased cellular glucotoxicity.

Lutein and zeaxanthin are key ingredients in a commercial nutritional supplement used for, e.g., improving visual acuity and reducing the risk of cataract. Lutin, which is named (1*R*)-4-[(1*E*,3*E*,5*E*,7*E*,9*E*,11*E*,13*E*,15*E*,17*E*)-18-[(1*R*,4*R*)-4-hydroxy-2,6,6-trimethylcyclohex-2-en-1-yl]-3,7,12,16-tetramethy-loctadeca-1,3,5,7,9,11,13,15,17- nonaenyl]-3,5,5-trimethylcyclohex-3-en-1-ol, is one of the widespread carotenoid alcohols in nature typically found, e.g., in egg yolk, algae and yellow flowers. The molecule of this xanthophyll includes 10 conjugated double bonds including 9 conjugated double bonds in the aliphatic chain and one in the 6-membered ring. The double bond in the other 6-membered ring is not conjugated to the aliphatic chain. Lutein has the following structure:



Lutein

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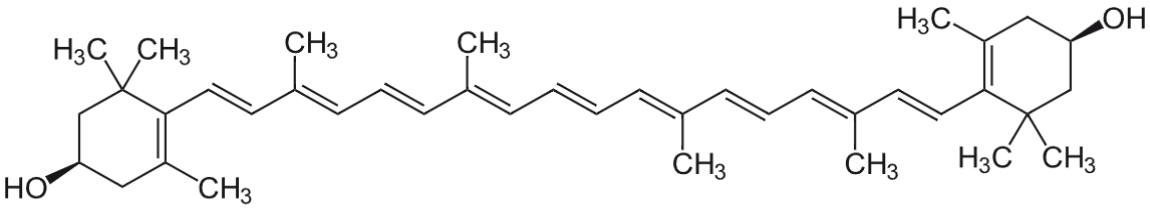
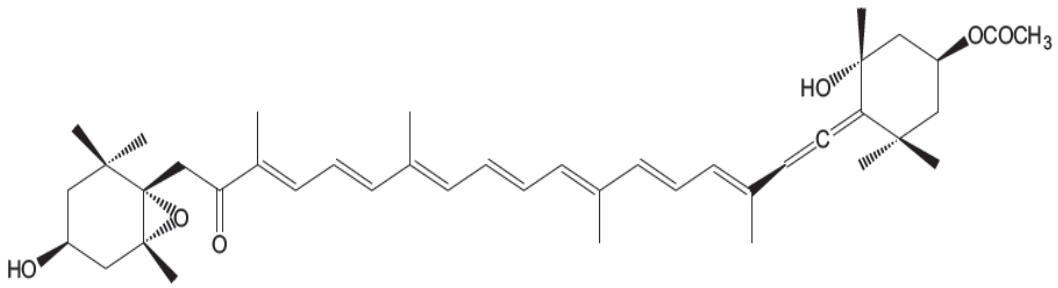
Zeaxanthin is named (1*R*)-4-[(1*E*,3*E*,5*E*,7*E*,9*E*,11*E*,13*E*,15*E*,17*E*)-18-[(4*R*)-4-hydroxy-2,6,6-trimethylcyclohexen-1-yl]-3,7,12,16-tetramethyloctadeca-1,3,5,7,9,11,13,15,17-nonaenyl]-3,5,5-trimethylcyclohex-3-en-1-ol. The molecule of zeaxanthin includes 11 conjugated double bonds including 9 conjugated double bonds in the aliphatic chain and one in each of the two 6-membered rings. Zeaxanthin has the following structure:



Zeaxanthin

Fucoxanthin is yet another xanthophyll typically found, e.g., in brown seaweeds and diatoms. Fucoxanthin contributes more than 10% of the estimated total production of carotenoids in nature. Fucoxanthin is involved in photosynthesis as part of the photochemical system II. Being a xanthophyll, it renders brown color to the brown algae and thus is the characteristic pigment in brown algae. Fucoxanthin is typically used commercially as an active nutraceutical ingredient in dietary supplements. The chemical name of fucoxanthin is (1*S*,3*R*,4*M*)-3-hydroxy-4-{(3*E*,5*E*,7*E*,9*E*,11*E*,13*E*,15*E*,17*E*)-18-[(1*S*,4*S*,6*R*)-4-hydroxy-2,2,6-trimethyl-7-oxabicyclo[4.1.0]heptan-1-yl]-3,7,12,16-tetramethyl-17-oxooctadeca-1,3,5,7,9,11,13,15,17-nonaen-1-ylidene}3,5,5-trimethyl-cyclohexyl acetate and it has the following chemical structure:



Fucoxanthin

The molecule of fucoxanthin is unique in comparison to other xanthophylls because it has an allene bond in addition to 7 conjugated double bonds, epoxy, hydroxyl, ketonic carbonyl and carboxyl ester moieties that contribute to its structure. According to some recent studies, important pharmacological activities can be attributed to said allene bond of fucoxanthin.

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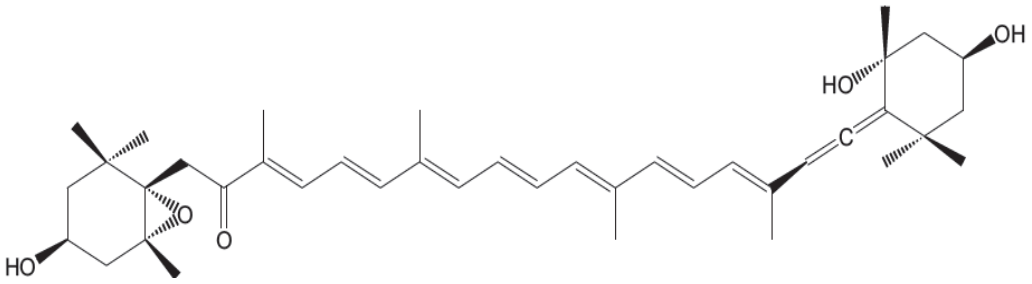
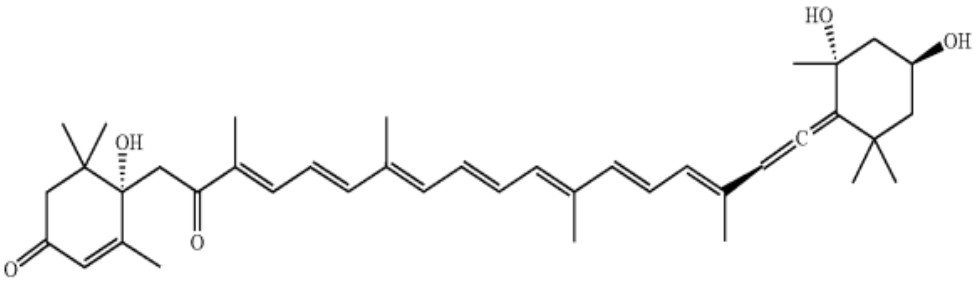
There exist in the art several clinical studies which have demonstrated the pharmacological functions of fucoxanthin sourced from macroalgae (seaweeds) and also from the microalga *Phaeodactylum tricornutum*. Maeda H, and Miyashita K. J , et al. showed that fucoxanthin regulated high expression of the uncoupling protein (UCP1) gene in the animal white adipose tissue (WAT), causing decrease in fat contents in the entrails. In addition, fucoxanthin reduced the amount of WAT in rats and fat in KK-Ay mouse. The researchers concluded that mediated by fucoxanthin, the expression of UCP1 in the WAT expedited the oxidation of fatty acids[2,3].

The absorption and metabolism of fucoxanthin are closely related to its bioavailability. According to Asai A., et al.[4], fucoxanthin was rapidly hydrolyzed to fucoxanthinol, retaining the allene bond, in the gastrointestinal tract within 2 hours after the administration and no unchanged fucoxanthin was detected in the plasma or liver in mice. Fucoxanthinol has the following structure:



Fucoxanthinol

The researchers studied the biotransformation of fucoxanthinol into amarouciaxanthin A in mice and in HepG2 cells. Fucoxanthinol was converted into amarouciaxanthin A, which was predominantly shown in liver microsomes of mice and in HepG2 cells. Hashimoto T., et al.[5] demonstrated that dietary fucoxanthin accumulated in the heart and liver of mice as fucoxanthinol and in adipose tissue as amarouciaxanthin A, which has the following structure:



Amarouciaxanthin A

Fucoxanthin exists in either trans or cis configuration. The trans-isomer is a potent antioxidant and relatively stable compared to the cis-isomer. Due to its unique structure, fucoxanthin is able to quench reactive oxygen and nitrogen species, which contribute to its lipophilicity and antioxidant activities.

Komba S. et al[6]., recited decomposing fucoxanthin under mild conditions of ozonolysis comprising using the following reaction conditions: O_3/CH_2Cl_2-MeOH/0°C. The two compounds obtained by said

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decomposition had the same structures as degraded fucoxanthin compounds found in nature, i.e., apo-9'-fucoxanthinone, which retained the allene bond structure, and apo-13-fucoxanthinone.
According to an article published by Chiang Y.F et al.[7], fucoxanthin has strong antioxidant properties, due to its unique biologically active structure, as mentioned above. According to the authors, fucoxanthin reduced lipid peroxidation and hence DNA damage in addition to its anti-inflammatory activity.
The authors described the protective effect of fucoxanthin on the retina using human retinal epithelial cells (ARPE-19) in cell viability test to investigate the protective effect of fucoxanthin on high glucose stress-(glucose 75 mM) and high lipid peroxidation stress (4-hydroxynonenal, 30 μM))-induced DR. The cell viability tests showed that fucoxanthin recovered the cell damage, and Western blotting showed that fucoxanthin reduced the inflammation response and maintained the integrity of the blood–retinal barrier by reducing its apoptosis and cell adhesion factor protein expression. Using an antioxidant enzyme assay kit, the authors stated that the protective effect of fucoxanthin may be related to its antioxidant properties, which increases catalase and reduces oxidative stress to produce a protective effect on the retina. Therefore, it may be assumed that the combined action of an anti-VEGF compound such as Avastin, or a biosimilar version, and the antioxidant property of fucoxanthin is synergistic. Furthermore, since fucoxanthin can be given orally, it may allow greater treatment uptake, improve compliance, and, since DR is frequently bilateral, it may benefit both eyes simultaneously.
Thus, it is proposed herein that improving the first-line treatment of advanced DR may be achieved by employing a combined simultaneous treatment of an anti-VEGF compound such as Avastin, or a biosimilar version, and oral administration of fucoxanthin (that has a protective effect of on the retina) optionally together with vitamin A.

Legal status

Biosimilar versions of Avastin (bevacizumab) are available since 2019 in the US, following the expiration of Avastin's patents, which led to the approval of biosimilars. There are currently several FDA-approved biosimilars to Avastin including, for example, Mvasi (bevacizumab-awwb), Zirabev (bevacizumab-bvzr), Alymsys (bevacizumab-maly) and Vegzelma (bevacizumab-adcd).

The FDA has allowed the use of fucoxanthin as a dietary ingredient. The approved daily dose has been 3 mg daily for an indefinite time or 5 mg for up to 90 days. Fucoxanthinol may be the primary active metabolite of fucoxanthin in humans. The recommended daily amount of vitamin A is 900 micrograms (mcg) for men and 700 mcg for women.

Conclusion

A combined simultaneous treatment of an anti-VEGF compound such as Avastin, or a biosimilar version, and oral administration of fucoxanthin that has a protective effect on the retina, optionally together with vitamin A, is proposed for treating advanced DR. Clinical trials of the proposed combination can serve as a suitable candidate for fast-track clinical trials in order to get this drug and the dietary ingredient combination to the patients as early as possible.

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General Remak

The author has served for many years as a patent attorney and information specialist in a global pharmaceutical company, drafting patent applications and opinions relating to drugs and drug combinations for treating diseases such as diabetes mellitus and cancer. As such, the information included herein should be regarded as a general opinion on the proposed treatment discussed in the present article.

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