AREDS2 Supplementation in Patients with Wet Age-Related Macular Degeneration

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ABSTRACT **Background:** In recent years, major progress has been made in treating the wet form of age-related macular degeneration (AMD) with anti-vascular endothelial growth factors (VEGFs) which reportedly stabilize and improve vision.

Objectives: To examine the effect of dietary supplementation, as recommended by the Age-Related Eye Disease Study 2 (AREDS2), on the number of anti-VEGF injections administered to patients with wet AMD.

Methods: A retrospective study was conducted with 57 participants (27 participants in the study group and 30 in the control group) receiving injections of anti-VEGFs. The study group received dietary supplements for at least one year before the treatment was initiated, while the control group did not. Primary outcome was the number of injections a patient received over a 3-year period. Secondary outcomes were central macular thickness and visual acuity.

Results: The average number of injections per patient after 3 years was 21.89 ± 7.85 in the study group and 26.00 ± 5.62 in the control group (P = 0.083). Final visual acuities were 0.45 ± 0.45 and 0.8 ± 0.73 (P = 0.09), and final central macular thicknesses were 288.26 ± 55.38 and 313.12 ± 107.36 (P = 0.38) in the study and control groups, respectively.

Conclusions: The average number of injections after 3 years was lower in the study group, but this difference did not reach statistical significance. No statistically significant difference was found in final visual acuity or central macular thickness between the groups.

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KEY WORDS: age-related macular degeneration (AMD), anti-vascular endothelial growth factor (anti-VEGF), Age-Related Eye Disease Study 2 (AREDS2), choroidal neovascularization (CNV), visual acuity

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Age-related macular degeneration (AMD) is the leading cause of visual impairment and blindness in the elderly of the Western world [1,2] and its prevalence is expected to increase with longer life expectancies [3].

AMD is divided into two types: dry and wet. The dry type has three stages: an asymptomatic early stage, an intermediate stage characterized by mild to moderate vision loss, and a late atrophic stage [4] characterized by severe vision loss [5]. Wet AMD (also called advanced neovascular AMD) is a less common type of late AMD that usually causes rapid vision loss. A considerable number of patients with dry AMD will eventually develop wet AMD with choroidal neovascularization (CNV) [6].

Major progress has been made in treating the wet form of AMD with anti-vascular endothelial growth factors (VEGFs), which in most cases stabilize vision. In one-third of cases it even improves vision. Treatment is administered once every 1–3 months as an intravitreal injection (IVI), with an average of eight injections per year.

The main type of anti-VEGF drug blocks the action of the VEGF protein and includes both approved (e.g., ranibizumab, aflibercept) and off-label drugs (e.g., bevacizumab).

In contrast, there is no proven treatment for late dry AMD [7-11]. The current recommendation for patients with intermediate dry AMD is to use dietary supplements according to the AREDS2 study, which may halt or delay its progression into more advanced forms of AMD [12]. To the best of our knowledge, there are no reliable, published studies examining the effects of dietary supplements on patients with advanced AMD [13].

Over a 3-year period, we examined whether there was any benefit, in terms of macular thickness, visual acuity, and reduced number of anti-VEGF injections, by adding dietary AREDS supplements.

PATIENTS AND METHODS

In this retrospective study, data were collected from the medical records of patients diagnosed with wet AMD in at least one eye and treated with monthly IVIs of anti-VEGFs (bevacizumab, aflibercept, ranibizumab) in a treat-and-extend proto-

col. The injections were performed by ophthalmologists at the Wolfson Medical Center eye clinic for a period of 1–3 years.

The study was approved by the Wolfson Medical Center review board and was conducted according to the Declaration of Helsinki principles.

Fifty-seven participants were divided into two groups. The study group received dietary supplements according to the recommendations of AREDS2 formula (vitamin C 500 mg, vitamin E 400 IU, uutein 10 mg, zeaxanthin 2 mg, zinc 25 mg, and copper 2 mg [Eye-Vit Areds Free, Meditec, Israel]). This group received two tablets per day for at least one year before initiating treatment with anti-VEGF injections. The control group included patients who did not receive any dietary supplements, neither before nor after initiating treatment with anti-VEGF injections.

Patient data included the patient's name in acronym, state identification number, sex, age, background diseases, type of AMD in the randomly selected right or left eye, number of injections in the first 3 years, visual acuity (VA), central macular thickness (CMT) according to optical coherence tomography imaging (OCT) at baseline and after 1, 2, and 3 years, and whether the patient was treated with supplements according to AREDS2 study.

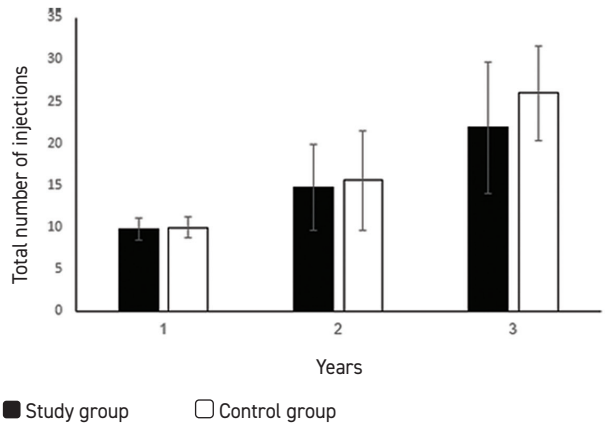
The chief investigator (N.S.) verified that each participant in the study group had taken the supplements during the study period.

We included participants who were over the age of 50 years, had been diagnosed with wet AMD (after ophthalmic examination and macular OCT imaging interpreted by a senior retina specialist), and were treated with anti-VEGF injections for at least 3 years with or without the additional supplements as recommended by the AREDS 2 study. We excluded participants younger than 50 years of age or those who had macular or retinal disease other than AMD, a history of eye surgeries other than cataracts, myopia greater than 6 diopters, or were incapable of signing an informed consent form.

STATISTICAL ANALYSIS

Based on the average number of administered IVIs per year for wet AMD, to achieve a power of 80% with $P = 0.05$, the minimum number of eyes needed for the study was calculated to be 32. Overall, 57 patients (27 participants in the study group and 30 in the control group) were included. Independent sample *t*-tests were used to compare baseline characteristics between the groups and differences the number of IVIs, CMT, and VA. All analyses were two-tailed, with an α of < 0.05 considered statistically significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 23 (SPSS, IBM Corp, Armonk, NY, USA).

Figure 1. Cumulative numbers of injections in the study group and the control group after 1, 2, and 3 years



RESULTS

Fifty-seven participants were included in the study. Of those, 27 were in the study group (9 females and 18 males) and 30 in the control group (15 females and 15 males). The number of males in the study group was higher in the control group (18 vs. 15 respectively, $P = 0.21$). The mean age of the participants was 81.37 ± 8.37 years in the study group and 83.5 ± 7.14 years in the control group ($P = 0.31$). There were no significant differences in the prevalence of hyperlipidemia, hypertension, diabetes mellitus, or smoking history between the two groups [Table 1].

Table 1. Demographic characteristics of the study and control groups

Characteristics	Study group (anti-VEGF + AREDS2) n=27	Control group (anti-VEGF) n=30	*P*-value
Age in years, mean ± SD (range)	81.37 ± 8.37 (65–98)	83.5 ± 7.14 (69–97)	0.31
Male sex, n (%)	18 (66.67%)	15 (50%)	0.21
Right eye, n (%)	12 (44.45%)	17 (56.67%)	0.37
Hyperlipidemia, n (%)	13 (48.15%)	17 (56.67%)	0.53
Hypertension, n (%)	17 (63%)	20 (66.67%)	0.78
Diabetes mellitus, n (%)	9 (33.33%)	10 (33.33%)	1
Smoking history, n (%)	4 (14.8%)	6 (20%)	0.62

AREDS2 = Age-Related Eye Disease Study 2, anti-VEGF = anti-vascular endothelial growth factor, SD = standard deviation

Table 2. CMT in the study and control groups at baseline and after 1, 2, and 3 years

	Study group (anti-VEGF + AREDS2) n=27	Control group (anti-VEGF) n=30	*P*-value
Initial CMT (μm) mean ± SD	416.85 ± 103.53	429.33 ± 149.12	0.72
CMT after 1 year (μm) mean ± SD	303.85 ± 64.13	303.67 ± 85.65	0.99
CMT after 2 years (μm) mean ± SD	297 ± 69.88	303.17 ± 92.97	0.8
CMT after 3 years (μm) mean ± SD	288.26 ± 55.38	313.12 ± 107.36	0.38

Anti-VEGF = anti-vascular endothelial growth factor, AREDS2 = Age-Related Eye Disease Study 2, CMT = central macular thickness, SD = standard deviation

Table 3. Visual acuity in the study and control groups at baseline and after 1, 2, and 3 years

	Study group (anti-VEGF + AREDS2) n=27	Control group (anti-VEGF) n=30	*P*-value
Initial visual acuity (LogMAR), mean ± SD	0.75 ± 1.31	0.6 ± 0.41	0.54
Visual acuity after 1 year (LogMAR), mean ± SD	0.47 ± 0.52	0.43 ± 0.36	0.75
Visual acuity after 2 years (LogMAR), mean ± SD	0.49 ± 0.42	0.48 ± 0.48	0.95
Visual acuity after 3 years (LogMAR), mean ± SD	0.45 ± 0.45	0.8 ± 0.73	0.09

Anti-VEGF = anti-vascular endothelial growth factor, AREDS2 = Age-Related Eye Disease Study 2, LogMAR = Logarithm of the Minimum Angle of Resolution, SD = standard deviation

The average number of injections after one year in the study group was9.78 ± 1.31 vs. 10.00 ± 1.31 in the control group ($P = 0.53$), after 2 years: study group: 14.75 ± 5.11, vs. 15.57 ± 5.99 in the control group ($P = 0.62$) and after 3 years: study group: 21.89 ± 7.85, vs. 26.00 ± 5.62 in the control group ($P = 0.083$) [Figure 1].

No significant difference in CMT was observed between the study group and the control group as measured by OCT. The initial mean CMT in the study group was 416.85 ± 103.53 microns and 429.33 ± 149.1 in the control group ($P = 0.72$). After 1 year, the CMTs were 303.85 ± 64.13 and 303.67 ± 85.65, respectively ($P = 0.99$). After 2 years, they were 297 ± 69.88 and 303.17 ± 92.97, respectively ($P = 0.8$), and after 3 years, 288.26 ± 55.38 and 313.12 ± 107.36, respectively ($P = 0.38$) [Table 2].

No statistically significant difference was found between the study and control groups in LogMAR units for the initial and final VA. Initial VA was 0.75 ± 1.31 for the study group compared to 0.6 ± 0.41 for the control ($P = 0.54$). Final VA for the study group was 0.45 ± 0.45 compared with 0.79 ± 0.73 (control) ($P = 0.09$) [Table 3].

A VA improvement of at least one line was observed among 55.6% (15 of 27) of participants in the study group and 50% (15 of 30) of the control group. An improvement of two or more lines was observed in 40.7% (11 of 27 patients) in the study group after 1 year of follow-up, 29.2% (7 of 24) after 2 years, and 36.8% (7 of 19) after 3 years. In the control group, an improvement of two or more lines was observed in 43.3% (13 of 30) of patients after 1 year of follow-up, 17.4% (4 of 23) after 2 years, and 5.9% (1 of 17) after 3 years. The study group showed a total increase of three lines in VA compared to a decrease of two lines in the control group [Table 3].

DISCUSSION

AMD is the chief cause of blindness in older people in the Western world, and its incidence is increasing dramatically as the elderly population grows [14].

The management of wet AMD has been positively transformed by the introduction of anti-VEGF, which stabilizes vision in most cases and even improves it in some [10]. There are many risks and complications associated with IVIs, such as endophthalmitis, intraocular inflammation, retinal detachment, increased intraocular pressure, choroidal bleeding, and conjunctival hemorrhage [9]. Therefore, we should reduce the number of injections administered per patient.

AREDS2 modified the original AREDS supplement, replacing beta-carotene with luthein and zeaxanthin. In the AREDS study, patients with intermediate or advanced AMD who took antioxidant vitamins had a 25% reduced risk of progression to more-advanced stages of AMD [15].

The AREDS2 study also showed that similar supplements did not prevent early AMD from developing into intermediate AMD. However, for patients with late AMD in only 1 eye, the AREDS2 formulation may slow down the progression of AMD in the other eye [12].

We hoped to find that the AREDS2 supplementation would have a favorable effect in lowering the number of anti-VEGF

IVIs. The average number of injections after 3 years was lower in the study group, but this difference did not reach statistical significance (P = 0.083) [Figure 1]. No statistically significant differences in CMT [Table 2] and final VA [Table 3] were found between the groups. However, there was a trend for better VA after 3 years in the study group compared with the control group. Further studies with a larger cohort are needed to validate the favorable trends we found.

STRENGTHS AND WEAKNESSES

A strength of this study is the similarity between the study and control groups in terms of demographic characteristics and baseline CMT and VA.

Weaknesses

Our retrospective study was based on a relatively small cohort. Participants received different types of anti-VEGFs, which might have affected the results, although with regard to AMD treatment protocols, the superiority of one drug over another is inconclusive. The monitoring of supplemental consumption relied solely on participant self-reports. A lower number of IVIs administered did not necessarily reflect treatment success.

CONCLUSIONS

The average number of injections after 3 years was lower in the study group, but this difference did not reach statistical significance. No statistically significant difference was found in final visual acuity or central macular thickness between the groups.

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Capsule

How do neurons die in Alzheimer's disease?

Neurons are one of the longest-living and enduring cell types of the human body. **Balusu** and associates xenografted human neurons into mouse brains containing amyloid plaques. The human neurons, but not the mouse neurons, displayed severe Alzheimer's pathology, including tangles and necroptosis. Human neurons up-regulated the neuron-specific maternally expressed gene 3 (MEG3) in response to amyloid plaques. Down-regulation of MEG3 protected the neurons from dying in the xenograft model of Alzheimer's disease. Downstream of MEG3, genetic or pharmacological manipulation of signaling kinases in the necroptosis pathway also protected neurons, suggesting a potential lead toward therapeutic approaches for Alzheimer's disease.

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