• Clinical Research •

One-year outcomes of resveratrol supplement with aflibercept versus aflibercept monotherapy in wet age-related macular degeneration

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Abstract

● **AIM:** To determine the one-year outcomes of resveratrol oral supplement in patients suffering from wet age-related macular degeneration (AMD).

● **METHODS:** Fifty naïve and previously untreated patients suffering from wet AMD, were randomly assigned in two subgroups of 25 patients each. All the participants were treated with 3 monthly intravitreal injections of 2.0 mg aflibercept (IAIs) followed by injections "according to need", while in one group the patients also received daily two tablets of resveratrol oral supplement. Prior to treatment initiation, a complete ophthalmological examination, including best corrected visual acuity (BCVA) and contrast sensitivity evaluation, optical coherence tomography (OCT) scans, fundus autofluorescence (FAF), fluorescein angiography, indocyanine green angiography, and OCT angiography (OCTA), was performed to every participant, while all of them completed the Hospital Anxiety and Depression Scale (HADS) questionnaire, in order to assess their quality of life (QoL) status. The patients were assessed monthly for 1y with FAF, and OCT or OCTA; the main endpoints were the number IAIs, the changes in BCVA, in contrast sensitivity, and in patients' QoL status.

● **RESULTS:** No significant differences were present between the groups regarding the baseline demographic and clinical data. Over the 12-month period, a similar number of IAIs was applied in both groups (4.52±1.00 *vs* 4.28±0.90, *P*=0.38), while the rest of the clinical data also did not differ significantly after the completion of the study period. However, for HADS Depression (11.88±2.51 *vs* 8.28±1.54, *P*<0.001) and HADS Anxiety (11.92±2.52 *vs* 7.76±1.51, *P*<0.001) questionnaires values, the score was significantly better in patients who received resveratrol supplements. Moreover, a statistically significant difference was detected in the mean change from baseline values of contrast sensitivity (0.17±0.19 *vs* 0.35±0.24, *P*=0.005), HADS Depression (0.08±1.38 *vs* -3.88±1.48, *P*<0.001), and HADS Anxiety (0.36±1.98 *vs* -5.12±2.70, *P*<0.001) scores, in favour of the patients treated with resveratrol supplements.

● **CONCLUSION:** The resveratrol oral supplement is a complementary treatment in cases of wet AMD, highlighting its effectiveness in improving patients' QoL status.

● **KEYWORDS:** wet age-related macular degeneration; resveratrol; aflibercept; Hospital Anxiety and Depression Scale; contrast sensitivity

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INTRODUCTION

Age-related macular degeneration (AMD), a progressive, degenerative, and multifactorial disease, is the leading cause of irreversible visual impairment among the elderly in the western world[1-2]. AMD is divided into two categories: non exudative or dry and exudative or wet AMD.

Wet AMD is characterized by the development of choroidal neovascularization. These new vessels tend to bleed and leak, resulting in the accumulation of subretinal and/or intraretinal fluid, and in the development of intra-retinal, sub-retinal, or sub-retinal pigment epithelium (RPE) hemorrhage[3]. If left untreated, irreversible damage occurs to the photoreceptors

and severe and rapid vision loss develops[4], having also as a consequence a detrimental effect in the patients' quality of life (QoL)[5-6].

Vascular endothelial growth factor (VEGF) plays a crucial role in the neovascularization, the development, and persistence of the exudative phenomena in wet AMD, by stimulating vascular endothelial growth and hypermeability of the new vessels[7-8]. The application of intravitreal injections of anti-VEGF agents was a hallmark in the treatment of wet AMD[9-10]. The anti-VEGF agents, including aflibercept, ranibizumab, and bevacizumab, exert their biological activity by blocking the binding of VEGF to its receptors, preventing thus its effect on neovascular endothelium[7-10]. However, a significant amount of the patients either do not experience significant beneficial results or suffer from adverse effects of the treatment[11], while anti-VEGF injections are yield of some contraindications making the optimal treatment for wet AMD even more questionable. Moreover, anti-VEGF treatment is frequently experienced by the patients with anxiety and fear, while at the same time the levels of depressive symptoms seem to be greater in them[12]. Therefore, the need for the development of new preventive and therapeutic approaches that would minimize morbidity and improve the patients' mental status, is highlighted[11].

Resveratrol is a polyphenol phytoalexin that belongs to stilbene class and can be found in many fruits and seeds, but mostly in grape skin, berries and peanuts[13-19]. Resveratrol is popular for its anti-diabetic and anti-cancer, and cardio-protective qualities, while through the activation of sirtuin-1 (SRT1), resveratrol exerts its anti-inflammatory, anti-oxidant, and anti-angiogenic properties[14-16,20]. Several studies have suggested that resveratrol and omega fatty acids may have a favourable effect in cases of wet AMD, through a cytoprotective effect in RPE cells[13-21]. More specifically, it has been proposed that in RPE cells they contribute to the inhibition of the oxidation and apoptosis, as well as to the suppression of VEGF expression[13-18]. Therefore, it could be hypothesized that oral supplements with resveratrol and omega fatty acids may help in reducing the neovascularization of patients suffering from wet AMD and thus in stabilizing and treating the disease more efficiently[18].

Resvega® (Laboratoires Thea/Clermont-Ferrand, France) is a new oral supplement, consisting of 30 mg of resveratrol, 665 mg of omega 3 fatty acids, 10 mg of lutein, 2 mg of zeaxanthin crystalline, vitamins C (120 mg), E (30 mg), and D (5 μg), 12.5 mg of zinc, and 1000 μg of copper. Recent reports have demonstrated that daily oral intake of Resvega® capsules alone, without any intravitreal injections of anti-VEGF agents, achieved improvement of retinal structure and visual acuity stabilization in patients suffering from wet AMD[22-23].

Taking into account the aforementioned points, we designed a study in order to evaluate the 1-year outcomes of the Resvega® supplement as a combined therapy with intravitreal injections of aflibercept (IAIs), compared to IAIs as monotherapy. To the best of our knowledge, no other study in literature has examined the long terms effects of Resvega in wet AMD cases.

SUBJECTS AND METHODS

Ethical Approval The study was performed according to the Helsinki Declaration and was approved by the ethical committee of Ophthalmological Institute OMMA (Protocol number: 58, Date: 25/01/2021). Benefits and risks were explained thoroughly to the participants and written informed consent was obtained by every participant.

This is an interventional, prospective, monocentric study designed and executed at Ophthalmological Institute OMMA, Athens, Greece. Fifty naïve and previously untreated patients suffering from wet AMD, were randomly assigned in two age- and gender- matched groups, each one comprising 25 subjects. In the first group, 3 monthly intravitreal injections of 2.0 mg aflibercept (Eylea, Bayer Healthcare, Germany), were applied, followed by reinjections according to need (Eylea group)[24-26]. The necessity of the injections was determined based on the emergence of subretinal, intraretinal fluid, or the increase in RPE detachment in spectral-domain optical coherence tomography (OCT)[24]. The second group followed the same treatment protocol, along with the daily consumption of two tablets of the oral supplement Resvega® (Eylea & Resvega® group). Intravitreal injections were performed under standard sterile conditions, while topical antibiotics were applied 4 times per day for 2d after the injection[27].

All the patients underwent a complete ophthalmological examination, including evaluation of best corrected visual acuity (BCVA), funduscopy, OCT (SPECTRALIS, Heidelberg Engineering, Heidelberg, Germany), fundus autofluorescence (FAF), fluorescein angiography (FA), indocyanine green angiography (ICGA), and OCT angiography (OCTA; Optovue, Inc., Freemont, CA, USA). Furthermore, contrast sensitivity was determined in every patient, using the Pelli-Robson chart, before the initiation and after the completion of the study[28-29]. Finally, all the participants, before and after the treatment, completed the Hospital Anxiety and Depression Scale (HADS) questionnaire[30], translated and validated in Greek, in order to assess their QoL and detect any possible alterations due to the applied treatment.

Participants were evaluated monthly for one year. The examination protocol included BCVA measurement, FAF, and OCT or OCTA. Reinjections were performed according to need based on the aforementioned criteria. There was no significant difference in patients' visits intervals between the two groups. The primary endpoint outcome was BCVA change,

while the secondary endpoints included the number of applied anti-VEGF injections, as well as the changes in patients' QoL and in contrast sensitivity.

The Pelli-Robson test is a wall-mounted chart, 59-cm wide and 84-cm high, composed of 8 lines of 6 letters; 48 letters of different contrast in total. Each line has 6 letters divided in two triplets, and the first triplet (on the left) has more contrast than the second triplet (on the right). The contrast also decreases not only from left to right as the patients read the chart but also as the patients move downwards from line to line. Each triplet decreases in contrast sensitivity by 0.15 log units (each letter decreases by 0.05 log units), so that from 100% (top left corner) the contrast sensitivity reduces to 0.56% (bottom right corner). All patients sat at 1 m distance from the chart and the test ended when patients failed to identify 2 out of 3 letters in a single triplet[31-32].

HADS is a simple and brief self-rating questionnaire that consists of two scales, the Anxiety and the Depression scale, while the participants are graded separately for each one. Patients answer 14 questions regarding their emotional status in the last week (7 for each scale), while every question is graded depending on the answer from 0 to 3 points. Results vary between normal (score 0-7) and abnormal (score 11-21); a total subscale score >8 points denote considerable symptoms of anxiety or depression respectively[33-34]. Previous studies have already shown the significance of vision-related QoL, the direct association with visual function and the key role that these questionnaires play in the assessment of patients' mental state[35-38].

Statistical Analysis All variables were tested for normal distribution with Kolmogorov-Smirnov test. Normally distributed data were expressed as means±standard deviation. The comparisons of mean values between groups for continuous and normally distributed variables were performed with Student's *t*-test, while the non-parametric data were tested with Mann-Whitney *U* test. BCVA values, evaluated by Snellen charts (measured in decimals), were converted in a logarithm of the minimum angle of resolution (logMAR) scale for statistical purposes. The values of logarithmic contrast sensitivity (1/contrast) were calculated for statistical purposes. A paired sample *t*-test was used to test intra- and inter-group differences between the means of logMAR BCVA, contrast sensitivity, and HADS values. *P* values <0.05 were considered to indicate statistical significance. The statistical calculations were performed using SPSS software (version 20.0; SPSS, Chicago, IL, USA).

RESULTS

The participants' demographic and baseline clinical characteristics are shown in Table 1. No significant differences existed between the studied groups in mean age (74.88±7.58y *vs* 74.44±5.00y, *P*=0.81) and sex status (28% male *vs* 40% male, *P*=0.38). As well, we did not detect significant differences between the baseline values of BCVA (logMAR BCVA 0.66±0.25 *vs* 0.63±0.22, *P*=0.65), contrast sensitivity (0.87±0.45 *vs* 0.86±0.29, *P*=0.91), HADS Depression (11.80±3.11 *vs* 12.16±1.97, *P*=0.63), and HADS Anxiety (11.56±2.96 *vs* 12.68±2.06, *P*=0.13) questionnaires.

Table 1 Demographic and baseline clinical characteristics of the participants

Parameters	Eylea (*n*=25)	Eylea & Resvega® (*n*=25)	*P*
Age (y)	74.88±7.58	74.44±5.00	0.81
Male (%)	28	40	0.38
BCVA, logMAR	0.66±0.25	0.63±0.22	0.65
Contrast sensitivity	0.87±0.45	0.86±0.29	0.91
HADS Depression	11.80±3.11	12.16±1.97	0.63
HADS Anxiety	11.56±2.96	12.68±2.06	0.13

BCVA: Best corrected visual acuity; HADS: Hospital Anxiety and Depression Scale.

Table 2 Clinical outcomes of treatment regimens

Parameters	Eylea (*n*=25)	Eylea & Resvega® (*n*=25)	*P*
BCVA, logMAR	0.53±0.30	0.42±0.23	0.12
IAIs (*n*)	4.52±1.00	4.28±0.90	0.38
Contrast sensitivity	1.04±0.52	1.21±0.37	0.19
HADS Depression	11.88±2.51	8.28±1.54	<0.001
HADS Anxiety	11.92±2.52	7.76±1.51	<0.001

BCVA: Best corrected visual acuity; HADS: Hospital Anxiety and Depression Scale; IAIs: Intravitreal injections of aflibercept.

Table 2 summarizes the outcomes for both treatment regimens. After the completion of our study, between the studied groups no significant differences were detected in mean logMAR BCVA and mean contrast sensitivity (*P*>0.05). As for the number of applied IAIs, they were also similar between the "Eylea" and "Eylea & Resvega®" groups (4.52±1.00 *vs* 4.28±0.90, *P*=0.38). However, we found a significant difference in the values of both HADS Depression (Figure 1A) and HADS Anxiety (Figure 1B) questionnaires (*P*<0.001), in the favour of the patients of "Eylea & Resvega®" group.

It is worthy to note, that the patients in "Eylea & Resvega®" group experienced a significant improvement in logMAR BCVA and contrast sensitivity, as well as in QoL as it is evaluated by the HADS Depression and Anxiety questionnaires (*P*<0.001 for all). On the contrary, the patients in "Eylea" group experienced a significant improvement only in logMAR BCVA and contrast sensitivity values (*P*<0.001 for both).

We also demonstrated that between the studied groups, a statistically significant difference existed in the mean change from baseline values of contrast sensitivity (0.17±0.19 *vs* 0.35±0.24, *P*=0.005; Figure 2A), HADS Depression score (0.08±1.38 *vs* -3.88±1.48, *P*<0.001; Figure 2B), and HADS Anxiety score (0.36±1.98 *vs* -5.12±2.70, *P*<0.001; Figure 2C), in favour of "Eylea and Resvega®" group (Table 3).

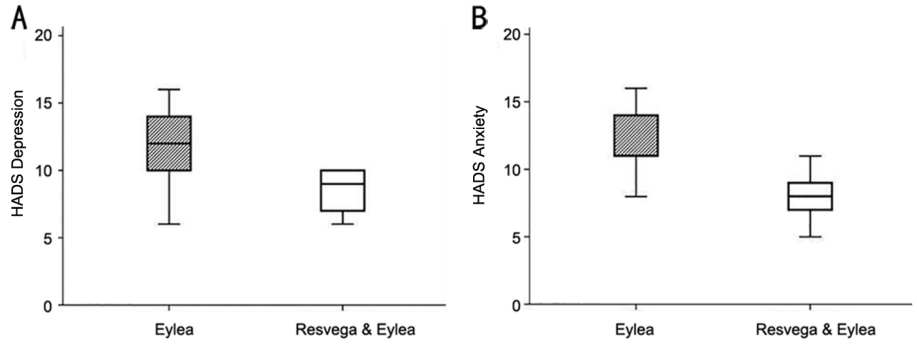

Figure 1 Box plots representing the differences in HADS Depression (A) and HADS Anxiety (B) values between the "Eylea" and "Eylea & Resvega®" group, after the completion of the study HADS: Hospital Anxiety and Depression Scale.

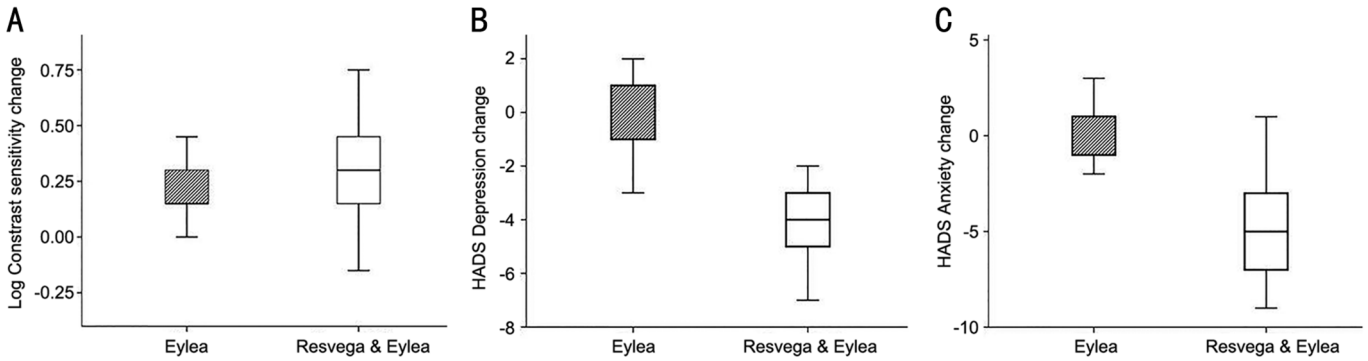

Figure 2 Box plots representing the differences in mean change from baseline values in contrast sensitivity (A), HADS Depression (B), and HADS Anxiety (C) values between the "Eylea" and "Eylea & Resvega®" group HADS: Hospital Anxiety and Depression Scale.

Table 3 Changes before and after the applied treatment

Parameters	Eylea (*n*=25)	Eylea & Resvega® (*n*=25)	*P*
BCVA, logMAR	-0.13±0.16	-0.22±0.19	0.09
Contrast sensitivity	0.17±0.19	0.35±0.24	0.005
HADS Depression	0.08±1.38	-3.88±1.48	<0.001
HADS Anxiety	0.36±1.98	-5.12±2.70	<0.001

BCVA: Best corrected visual acuity; HADS: Hospital Anxiety and Depression Scale.

DISCUSSION

Wet AMD, as a major cause of severe visual disturbances[1], is associated with loss of independence among the patients and as a consequence with a decline in their QoL[39-43]. The rates of mental disturbances, including anxiety and depression, are substantially elevated compared to the general population of the elderly[44]. In this upsetting condition contribute both the presence of the disease itself, but also the nature of the applied treatment, consisting of intravitreal injections of anti-VEGF agents, which is accompanied by an exacerbation of mental and emotional stress[45].

The findings of our study suggested that the daily oral consumption of Resvega® in patients suffering from wet AMD could be identified as a useful supplementary aid to the established treatment. We demonstrated that Resvega® intake was accompanied by a significant improvement in patients' mental status, as it is expressed by the values of HADS Depression and HADS Anxiety scores. As well, the patients that took this supplement, experienced important gains in contrast sensitivity, which resulted in an improvement of their visual function. However, we did not detect a noteworthy beneficial long-term impact regarding the BCVA or the frequency of the applied IAIs; it could be attributed to the fact that the 12-month studied period is possibly too short in order to draw safe conclusions concerning the influence of Resvega® intake on the aforementioned parameters.

The Resvega® supplement consists of various components, such as zeaxanthin, lutein, and omega 3 fatty acids. AREDS/2 and NAT-2 studies have already proven the beneficial role of these substances in slowing the progression of AMD, especially in stages 3 and 4[46-47]. Resveratrol is the substance that differentiates Resvega® from the rest of oral supplements that are administered in cases of AMD. As we previously mentioned, resveratrol suppresses VEGF-A and VEGF-C in cultures of human RPE cells, as well as it inhibits the inflammatory pathway that is believed to be a major pathophysiological component in the AMD pathology, having thus a beneficial effect on retina remodeling[13-21]. The aforementioned attributes classify resveratrol as a promising component in the battle against the disease. As for the safety profile of resveratrol, it has been suggested that it is well tolerated even in high daily doses and no significant toxic effects have been reported following its long term

consumption[48]. However, it has been reported that occasionally the oral consumption of resveratrol was accompanied by episodes of diarrhea, stomach pain, nausea, loss of appetite, flu-like symptoms, and acne outbursts[49]. Finally, it is worthy to note that a recent study has compared the secretion of VEGF-A in human RPE cells between resveratrol alone and Resvega® (omega-3/resveratrol combination), highlighting the superiority of the latter[50].

Taking into account the visual function, in our study the consumption of Resvega® did not result in a significant improvement of BCVA in the patients of "Eylea & Resvega®" group compared to the patients that were treated only with IAIs. However, the addition of Resvega® was followed by a significant improvement in contrast sensitivity. Contrast sensitivity is a measure of an individual's ability to perceive low contrast images and to identify differences between dark and light, being a key parameter in the overall assessment of vision[51]. Several ocular diseases have been accompanied by a deterioration of contrast sensitivity, including among others AMD, diabetic retinopathy, cataract, and glaucoma[51-53]. Enhancement in contrast sensitivity has been associated with elevated vision related QoL, since it allows a person to perform vision-related tasks and activities, including among others driving and reading[51,54]. In accordance to our findings, a previous study has also demonstrated that resveratrol improves contrast sensitivity in AMD patients[23]. It has been suggested that the underlying mechanism connecting the improvement of contrast sensitivity with resveratrol consumption is possibly the ability of the latter to re-establish retinal architecture, decrease lipofuscin accumulation, increase choroidal perfusion, and increase macular pigment volume[23].

Finally, the results of HADS questionnaire were very promising. Although the number of applied IAIs and the BCVA values were similar between the studied groups, it is notable that the consumption of Resvega® was followed by a significant improvement of patients' mental status and QoL, as they are assessed by the HADS Depression and Anxiety scores. This finding should not be depreciated, since it has been suggested that AMD effects may be exacerbated by depression; thus any measures that ameliorate this distressing situation are steps in the right direction[33,55]. A plausible explanation for our observation is the aforementioned improvement of contrast sensitivity, which is accompanied by an improvement of vision related QoL. Furthermore, previous studies in rat models suggested that resveratrol manifests antidepressant and anxiolytic effects, through the downregulation of the hyperactivity of the hypothalamic-pituitary-adrenal axis and by the regulation of both the hypothalamic-pituitary-thyroid (HPT) axis and the Wnt/β-catenin pathway[56-58]. Recent studies in humans were in accordance with the aforementioned hypothesis[59-60].

Despite the interesting findings of this study, there are some inherent limitations. The 12-month study period may be too short to accurately assess the effectiveness of Resvega® in wet AMD cases, and studies with longer follow-up period are needed in order to efficiently determine the impact of the aforementioned oral supplement in wet AMD. Moreover, the relatively small sample size limits the generalizability of our conclusions; thus further studies with more participants are required in order to validate our results. Lastly, our patients were treated with IAIs; it would be of great interest to examine whether our findings are replicated in cases treated with other anti-VEGF agents.

In conclusion, our study highlighted the superiority of a treatment modality consisting of IAIs and daily oral consumption of Resvega® in cases of wet AMD, since this treatment regimen yielded better outcomes regarding the participants' contrast sensitivity and QoL. Our findings strengthen the theory according to which in devastating long-term ophthalmic conditions, such as wet AMD, the ophthalmologists apart from evaluating the visual/functional outcomes of the applied treatment, they should also pay attention to their patients' psychological and mental state. Therefore, our study underlines the need for future treatment strategies that would also focus on their impact on patients' QoL.

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