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SUB-RETINAL FLUID (SRF) AS A PROTECTIVE FACTOR AGAINST MACULAR ATROPHY AND POSITIVE RETINAL BIOMARKER OF VISUAL OUTCOME

Jana Nivichka Kjaeva[1], Natasa Trpevska Shekerinov[1], Igor Isjanovski[1],
Andrijana Petrushevka[1], Gazmend Mehmeti[1]
[1]University Clinic for Eye Diseases, Skopje, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia

Abstract

Age related macular degeneration is the leading cause of legal blindness in elderly people. Its prevalence increases significantly after the age of 50. Neovascular, exudative AMD accounts for less than 10% of cases, the wet form (nAMD) is responsible for the largest number of cases where severe central visual impairment occurs compared to the dry form of AMD. Neovascular AMD form is characterized by the growth of abnormal choroidal new blood vessels from pre-existing choriocapillaris vessels.

The exudation resulting from the immaturity of the blood vessels resulting in accumulation of fluids in different retinal compartments depending on the MVN (macular neovascular) extension and localization. Subretinal fluid is an exudation that is localized in the space between the neurosensory retina and the retinal pigment epithelium. VEGF-A plays a key role in the process of angiogenesis and vascular permeability. Anti-vascular endothelial growth factor (anti-VEGF) therapy currently plays a central role in the treatment of numerous retinal diseases, most notably exudative age-related macular degeneration (eAMD), diabetic retinopathy and retinal vein occlusions, offering significant functional and anatomic benefits in most of the patients.

Of all retinal biomarkers subretinal fluid (SRF) is the only imaging biomarker, that is, the only "pathological" morphological parameter that is consistently associated with a positive effect on visual acuity and has protective role against development of macular atrophy.

Key words*:* wet AMD, sub-retinal fluid, anti-VEGF treatment, macular atrophy.

Introduction

Age related macular degeneration, or age macular degeneration (AMD) was first described in the 1980s. These days it is the leading cause of legal blindness in elderly people. It is characterized by progressive loss of central vision which can strongly affect the vision quality of life [1].

Its prevalence increases significantly after the age of 50. By 2040 the AMD population is expected to be 288 million. The dry form of macular degeneration accounts for about 80% (8 out of 10) of patients with developed AMD have the dry form. It is characterised by the finding of drusen, abnormalities of the retinal pigment epithelium or geographic atrophy in the macula. Although neovascular, exudative AMD accounts for less than 10% of cases, the wet form (nAMD) is responsible for the largest number of cases where severe central visual impairment occurs [2].

In both forms of AMD, the degenerative process begins at the level of the choriocapillaris complex/Bruch's membrane and the cells of the retinal pigment epithelium/photoreceptor complex. Changes in any of these components result in the initiation of a so-called mechanism of mutual influence and activation of a series of complex reactions involved in the initiation of AMD. AMD is the result of a complex interaction between lipofuscinogenesis, drusenogenesis, and inflammation that can lead to choroidal neovascularization (CNV). Dysregulated angiogenesis begins when local inflammation and potential ischemia lead to a change in the balance between proangiogenic vascular endothelial growth factor (VEGF) and antiangiogenic pigment epithelium-derived growth factor (PEDF) [3].

Neovascular AMD is characterised by the growth of abnormal choroidal new blood vessels from pre-existing choriocapillaris vessels. They further proliferate and penetrate through Bruch's membrane into the space under the retinal pigment epithelium (RPE). Macular neovascularization or (MNV) can further proliferate in the subretinal space as well as in the intraretinal layers. The exudation resulting from the immaturity of the blood vessels results in the accumulation of fluid in different retinal compartments depending on the MVN extension and localization[4].

VEGF-A plays a key role in the process of angiogenesis and vascular permeability. The VEGF-A gene is organised in 8 exons on the 6p21 chromosome. The most prevalent of all 9 isoforms is VEGF 165. VEGF, or most commonly known as VEGF is a dimeric glycoprotein that interacts with the two tyrosine kinase receptors, VEGFR-1 and VEGFR-2 located on endothelial cells [5]. Anti-vascular endothelial growth factor (anti-VEGF) therapy is a new treatment option and currently plays a central role in the treatment of numerous retinal diseases, most notably exudative age-related macular degeneration (eAMD), diabetic retinopathy and retinal vein occlusions resulting in better BCVA as well as preservation of the visual acuity in these patients.

Progression from early stage and intermediate AMD to late AMD stage is more frequent in patients with bilateral AMD [6]. Both can progress to macular atrophy (MA), some forms of which are called geographic atrophy.

Macular atrophy (MA) is characterized by the death of the cells of the photoreceptor layer and loss of vision. The change is correlated with progressive atrophy and thinning of the RPE and the choriocapillary layer [7].

The staining of Henle's layer of nerve fibers comprising photoreceptor axons can be used to identify photoreceptor loss [8].

The change or loss of photoreceptors can be defined by changes in the retinal layers that are visible using the OCT method. OCT criteria for the loss of photoreceptor cells are loss of the ellipsoidal layer and the outer limiting membrane [9], as well as thinning of the outer nuclear layer, which together with Henle's bundle and photoreceptor on OCT is shown as a single hypo-reflective band.

Optical coherence tomography is a non-invasive, high-resolution, fast and comparative imaging technique of the structures of the posterior eye segment. The method is an optical analog of the ultrasound recording technique that uses coherent interferometry, with the help of which cross-sections of the retinal tissue are obtained. It provides a complete quantitative and qualitative morphological analysis of the degenerative and exudative form of AMD. A novelty in non-invasive imaging methods is optical coherence angiography with 3D (SD-OCT) imaging of the retinal and choroidal vasculature. Its application makes a particular contribution to determining the presence and localization of newly formed vascular complexes in wet forms of AMD. With this technique, the changes are shown much more precisely due to the absence of the masking effect that is obtained with contrast angiograms.

Through the ability to perform multiple B-scans on a given volume of tissue, optical coherence angiography provides 3D detailed insight into the layers of the choriocapillaris, RPE, and neuro-retinal structures in wet macular degenerations with the possibility of following them in vivo.

Subretinal fluid is an exudation that is localized in the space between the neurosensory retina and the retinal pigment epithelium. It is most often correlated with a finding of type 1 MNV, although it can also occur in type 2 MNV. In type 3 neovascular complexes, the finding of subretinal fluid is followed by the finding of intraretinal fluid (IRF) as well as fluid under the retinal pigment epithelium (PED) [10].

Sub-retinal fluid (SRF) has been discussed as a protective factor against macular atrophy in eyes with neovascular age-related macular degeneration (nAMD). Subretinal fluid (SRF) is the only imaging biomarker, that is, the only "pathological" morphological parameter that is consistently associated with a positive effect on visual acuity. There is also evidence for that, which has been presented and supported by several post-hoc analyses. According to the analyzes of [11] as an initial finding SRF is present in 70%-85% of patients. SRF occurs as a possible finding in all CNV types and is typically the first sign of an exudative type-1 CNV lesion [12].

When it comes to visual acuity numerous studies show a positive effect of SRF with VA (Jaffe et al., 2013; Schmidt-Erfurth et al., 2015). There are also analyzes i.e. studies demonstrating the positive outcome of SRF treatment with anti-VEGF preparations as well as the absence of development of RPE atrophy in intensive and monthly applications during treatment (Sadda et al., 2014; Sato et al., 2015). The hypothesis of the positive effect of SRF is associated with the presence of CNV and the perfusion of nutrients at the level of the RPE/photoreceptor layer layers in hypoxic conditions in nAMD forms. CNV is defined as the survival factor of the outer layers of the retina. SRF presence, unlike IRF presence, is a sign of non-aggressiveness of the disease, and this is supported by a recent study by [13].

Gianniou et al., 2015 present a cohort of patients where SRF is refractory to treatment but is not associated with poor visual acuity outcome. Certain studies have also investigated the density of

SRF lesions using optical coherence tomography. Increased SRF reflectivity has been found to correlate with worse BCVA as well as worse response to anti-VEGF treatment [14].

Since its inception (Huang et al., 1991) and introduction into ophthalmology (Fercher et al., 1993), OCT has become the leading diagnostic tool in modern ophthalmology.

Material and methods

The study conducted is a prospective cohort study. The study included 80 eyes with established, diagnosed wet form of age-related macular degeneration. All patients are previously untreated, newly diagnosed (n-AMD) patients with present, developed choroidal neovascularization (CNV) and reduced visual acuity. Inclusion criteria for entering the study were: best-corrected visual acuity >20/200 per (Snellen), age (patients over 60 years old), determined wet form of senile macular degeneration, hyperlipidemia, hypercholesterolemia, hypertension.

We analyzed and monitored patients with sub-retinal retinal fluid findings, their response to treatment, fluid fluctuations, and the number of patients who developed macular atrophy at the end of treatment as well as the total number of injections during the first year of the treatment.

All patients underwent the standard eye examination that included best corrected visual acuity (BCVA), air puff non- contact tonometry and fundus examination with dilated eye pupils. Imaging and monitoring of fundus changes was performed exclusively on the DRI OCT Triton, Swept Source Optical Coherence Tomography (OCT) device.

OCT images and non-contrast angiography were performed in both eyes in the macula lutea zone. The resulting tomogram confirmed: exudation and its localisation (intra-retinal, sub-retinal and below the RPE, the finding, activity and the localisation of the neo-vascular complex. Patients were treated with the drug aflibercept, which is an inhibitor of vascular endothelial and placental growth factor. The drug aflibercept is given according to the so-called "treat and extend treatment" or T&E regime. All patients initially received 3 monthly doses of anti-VEGF and the 4^{th} on the 4^{th} month after what dose interval continued according to the morphologic and functional criteria.

Results

78 of 80 eyes were assessed in the study. In the studied groups, 47 (60.3%) were women, while 31 (39.7%) were men. Hyperlipidemia was present in 43 (56%) subjects. 45 (57.7%) of the respondents had hypercholesterolemia.

Elevated triglyceride values were observed in 41 (53%) of the subjects. Elevated blood pressure values were observed in 50 (64.1%) of the subjects. At the beginning all patients had a certain volume of sub-retinal fluid (SRF).

After initiation of treatment, 3 monthly loading doses of anti-VEGF at 3 months, SRF was present in 70/78 or 89% of subjects as it is shown in table I.

At week 16, SRF was present in 70 (89%) of the patients. SRF was present in 69 (89%) of patients at 6 months (table II).

At 9 months of the study, SRF was present in 22 (28%) of the patients. SRF was present in 16 (20%) subjects at the end of the study on month 12 (table III).

Table 1. 3 monthly loading doses of anti-VEGF at 3 months, SRF was present in 70/78 or 89% of subjects

Cross table				
Number				
			SRF0 present	
			negative	Positive finding
Improved 12		No	3	28
		Yes	5	42
Total number			8	70

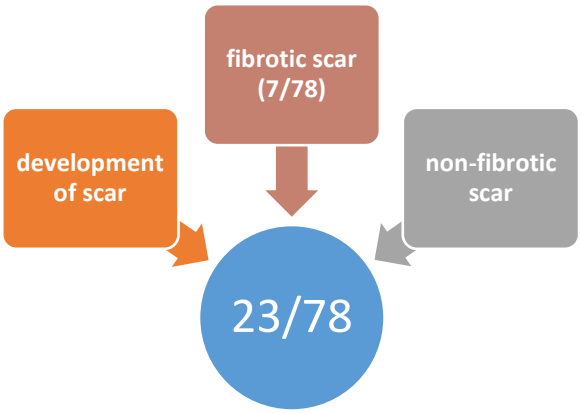
Table 2. At week 16, SRF was present in 70 (89%) of the patients. SRF was present in 69 (89%) of patients at 6 months

Cross table				
Number				
			SRF0 present	
			negative	Positive finding
Improved 28		No	1	18
		Yes	7	52
Total number			8	70

Table 3. At 9 months of the study, SRF was present in 22 (28%) of the patients. SRF was present in 16 (20%) subjects at the end of the study at month 12

Cross table				
Number				
			SRF52 present	
			negative	Positive finding
Improved 52		No	11	5
		Yes	51	11
Total number			62	16

Graphic 1. Presenting the number of patients which developed scar at year one from the beginning of treatment)



Discussion

SRF volume at baseline in our study cohort ranged within mean values of 2044.00 µm in height and 3685.00 µm in width, or a mean of 1278355.00 µm. BCVA was 3.95 according to Snellen's optotype. At week 12 privisection, after three monthly applications of 2 mg aflibercept, SRF had values of 762.00 µm and 2541.00 µm, with a mean value of 485507.00 µm. BCVA at week 12 was 6.90. At this section we obtained volume values that were 792.848 µm lower than the value before starting treatment and we obtained an increase in visual acuity of 2.95. In our study, at 16 weeks or 4 months of treatment there was a decrease in SRF height of 300.00 µm and residual lesion width of 2751.00 µm, with a mean value of 690.501 µm. There was also a decline in BCVA of 4.90. On this section, we obtained a small increase in the volume of the fluid and a decrease in visual acuity, which may be due to the localisation of the fluid or, on the other hand, to the accompanying morphological changes of the retina that affect its central thickness. At week 28 in SRF eyes, height and width values ranged from 576.00 µm to 1954.00 µm, with a mean of 361490.00 µm. BCVA was 1.00. At the third cut at week 28 there was a drop in SRF values and an increase in VA by 3.90. At the 4th cut at 38 weeks we obtained height and width values of 186.00 µm and 2700.00 µm for this parameter, with a mean value of 294300.00 µm and a drop in VA to 6.90. Given the increase in the width of the fluid stretch in the macula, even though there was a drop in height, there was a drop in visual acuity due to the larger volume of the region. At week 52 at study exit, the SRF values in our subjects were 186.00 µm and 1061.00 µm in height and width, with a mean of 143235.00 µm and a BCVA of 0.90. These results show a persistently unchanged height value from 38 to 52 weeks, but a decreased fluid width value and a significant rebound after the final best-corrected visual acuity.

According to the number of applied doses, most of the respondents 20 (25.6%) received 6, i.e. 8 doses, while 7 doses received 13 (16.7%), 10 doses received 10 (12.8%), 6 (8.3%) received 9 doses, while the least respondents were 2 (2.6%) with 11 doses and with 5 doses were 1 (1.3%) of the respondents. In the treated patients out of 78, 23 patients developed scar, of which fibrotic 7, and non-fibrotic 16.

Conclusion

In our study the fluctuation of subretinal fluid is shown to be in correlation with BCVA, and the response to the anti-VEGF injections. The larger volume of fluids is correlated with increased central retinal thickness and therefore declined visual acuity. In the study anti-VEGF gave the best response at the beginning after the tree loading monthly doses after what the activity of the disease was controlled with certain number of anti-VEGF injections. The activity of the disease was monitored by the fluids volume fluctuation on B-scan OCT, changes in central retinal thickness, BCVA, and OCT angiogram. Sub-retinal fluid gave positive response to the treatment and preservation of stable visual acuity. As retinal biomarker sub-retinal fluid is shown to be positive and protective for scar development in treated patients.

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