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EVALUATION BIOMARKERS ON OPTICAL COHERENCE TOMOGRAPHY IN PATIENTS WITH MACULAR EDEMA DUE TO CENTRAL RETINAL VEIN OCCLUSION WITH ANTIANGIOGENE TREATMENT

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Introduction

Retinal vein occlusions (RVO) are the second leading cause of vision loss from retinal vascular diseases in the adult population, right after diabetic retinopathy [1,2].

Depending on the location of the occlusion, it occurs as Central Retinal Vein Occlusion (*CRVO)* . and Branch Retinal Vein Occlusion (*BRVO*).

Epidemiological studies have analyzed the incidence and prevalence of macular edema secondary to branch occlusions and central retinal vein occlusion [3].

Recent data show that the overall prevalence of CRVO in the adult population is about 0.8/1000 inhabitants, and BRVO is about 5.2/1000 inhabitants [4].

Globally , CRVO affects approximately 2.5 million people. [4] Prevalence rates of CRVO do not differ significantly by race or gender.

Increasing age is the greatest risk factor for the development of CRVO, which is likely due to increased arteriosclerosis and other systemic and ocular risk factors , glaucoma, and other inflammatory and autoimmune conditions [3,4].

The prevalence of BRVO in Europe is three times higher than the prevalence of CRVO [4]. There is a difference in the risk factors for the development of CRVO and BRVO . Half of the patients with retinal occlusions also have systemic diseases. Increased risk for RVO occurs in patients with hypertension, diabetes, dyslipidemia, high body mass index and smokers [4].

Other risk factors include various forms of vasculitis, neoplasms, use of contraceptives and diuretics. etc. It often occurs in younger people, where it is usually correlated with cardiovascular disease and thrombophilia [4].

Retinal vein occlusion causes hypoxia, which activates signaling pathways, releasing inflammatory cytokines and increasing levels of growth factors, such as VEGF and PlGF , which affects the blood-retinal barrier, increasing vascular permeability, and as a result, fluid leakage occurs, causing edema in the macular area [5].

Ischemia is, in fact, a key, significant clinical feature of CRVO also leads to worse visual acuity compared to the non-ischemic form. In CRVO , 75% of patients initially have the non-ischemic form of the disease, but 34% progress to the ischemic form within 3 years, with the appearance of macular edema, vitreous hemorrhage, macular ischemia, and neovascular glaucoma, with irreversible vision loss. (5)

The use of anti-VEGF agents has revolutionized the treatment of this clinical entity in the last decade. Numerous randomized trials have shown good long-term efficacy and long-term effects of anti-VEGF treatment in patients with CRVO and BRVO [6].

Aflibercept's affinity for binding VEGF and PlGF, a specific multitargeting agent, results in reduced inflammation, vascular leakage, and pathological vascularization, and is much stronger than the binding of these growth factors to the native receptors VEGFR1 and VEGFR2, with a long-lasting VEGF suppression effect [6,7].

The effect of its application is based on qualitative and quantitative evaluation of changes, where relevant OCT biomarkers include : central retinal thickness (CRT), intraretinal cysts, integrity of the outer limiting membrane and ellipsoidal zone, disorganization of the inner retinal layers (DRIL), hyperreflective fossae, choroidal thickness, and signs of ischemia [8].

OCT angiography has the potential to quantitatively demonstrate retinal capillary density (VD) in the superficial and deep capillary layers and the foveal avascular zone (FAZ) area to better understand microvascular changes in patients with RVO [8].

The ability of OCTA to differentiate microvascular changes and ischemia in both the superficial and deep capillary plexuses is a great advantage because many vascular changes in RVO occur in the DCP , which is difficult to visualize with OCTA. angiography. O CTA scanning has a better resolution in detecting macular edema than F A or SD - OCT alone [8]

The aim of this paper is to present the antiangiogenic effect of aflibercept in macular edema resulting from central venous occlusion; to present the morpho-functional changes and evaluation of specific structural biomarkers monitored through OCT A ; the effect of the treatment on visual acuity and the correlation of the number of intravitreal applications with the therapeutic response.

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Material and methods

The study includes 24 patients with macular edema resulting from central retinal vein occlusion, who are treated with the antiangiogenic drug Aflibercept.

The patients underwent a complete ophthalmological examination with additional examinations, OCT and OCT- angiography.

All patients received three consecutive monthly applications, recommended loading dose and then according to the degree of activity, patients were treated according to the treat and continue (T&E) regimen and the other group, patients who received anti- VEGF at the time of activity, treatment as needed (PRN) .

An analysis of the characteristics of SD -OCT /OCTA tomograms was performed at 3 time points (before treatment, at 3 months and 6 months) from the start of anti-VEGF treatment.

Biomarkers were analyzed: Central subfield thickness (CST), presence of vitreomacular adhesion or epiretinal membrane,

change in vascular density in the foveal zone before treatment and at the end of the 6th month of treatment, of course, evaluation of the effect on visual acuity and correlation with the number of intravitreal applications received.

Results

The evaluated 2 4 patients (2 4 eyes) were aged from 43 to 79 years (mean age 62.3± 18.7 years) of whom 14 (58 %) from the female gender and 10 (42 %) from the male gender . (Graph 1) The average number of intravitreal injections received was 4.7 for a follow-up period of 6 months.

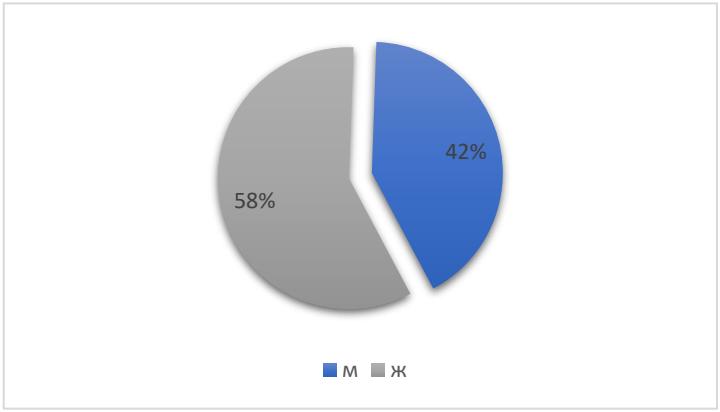

Figure 1. Gender representation display

The reduction in central retinal thickness was noted in all patients, after each application consecutively, and at the end of the follow-up there was no statistical significance in relation to the treatment regimen .

After treatment, the average central macular thickness (CST) significantly decreased from 556.67±163.3 to 274.75±56.25 (Figures 2, 3).

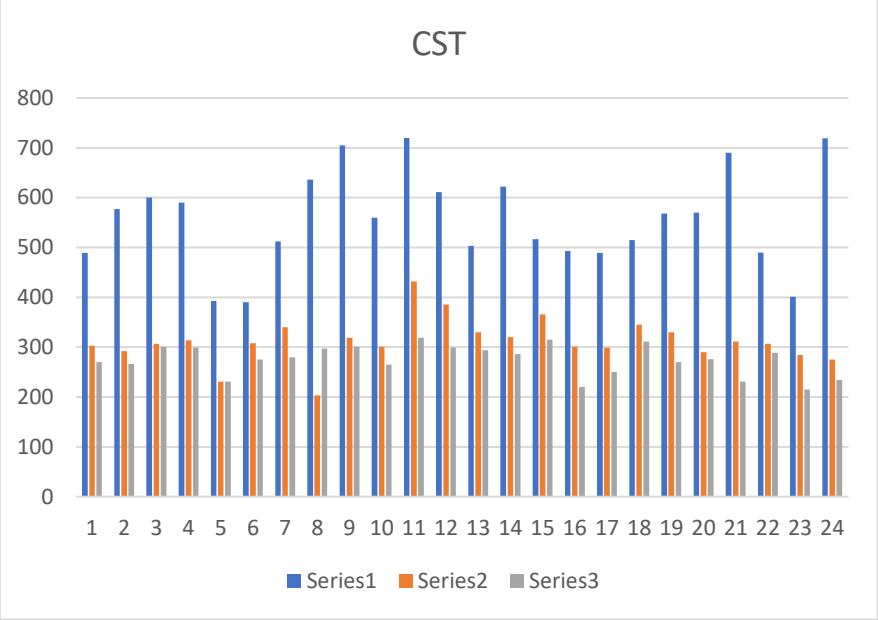

Figure 2. Graphic representation of central subfoveal thickness – CST

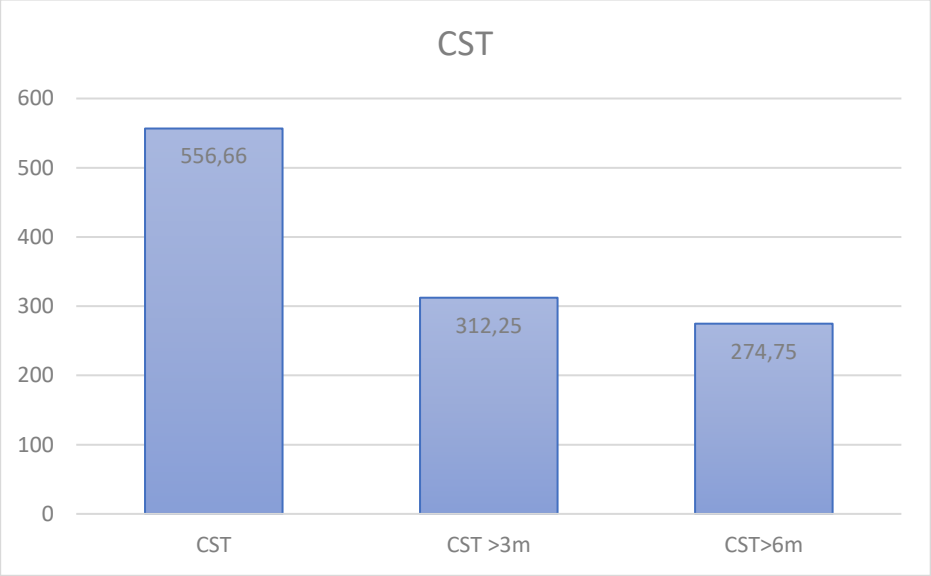

Figure 3. Graphical representation of central subfoveal thickness before and after treatment

In terms of average visual acuity, it changed two lines in line with the Snellen optotype.(Graph 4)

A qualitative analysis of the tomograms was performed at the end of the evaluated period for the presence of vitreomacular adhesion disorder, with the formation of an epiretinal membrane, and it was observed in 42% of the patients.

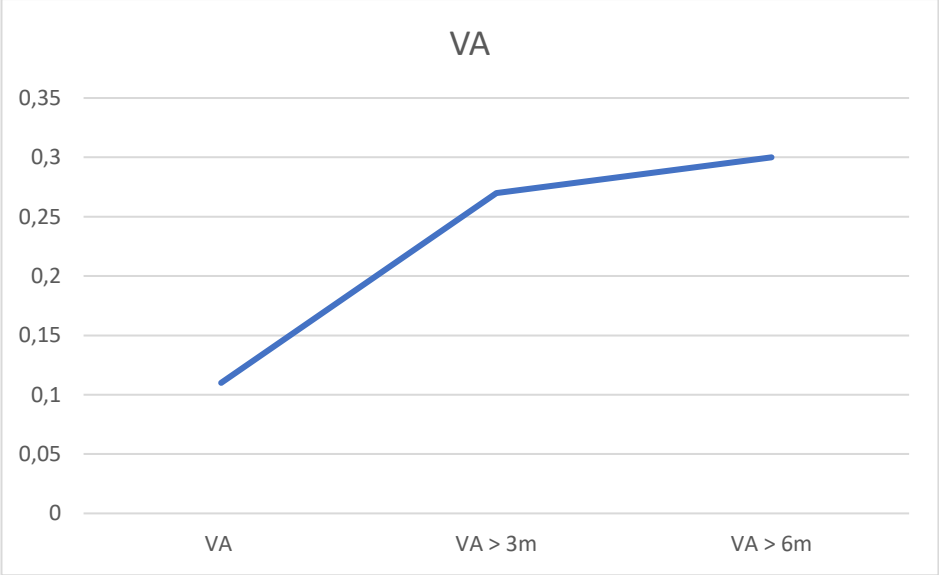

Figure 4. Graphical representation of the change in visual acuity

During the treatment, angiograms (OCTA) were performed and vascular density (VD) was evaluated . Namely, vascular density before starting treatment was on average 31.73% ± 11.13 compared to 20.58% ± 7.26 at the end of the 6th month follow-up.

anti -VEGF treatment were observed and correlated with improvement in visual acuity. Visual acuity had the greatest increase after the three bolus applications and was then maintained throughout the follow-up.

At the same time, both CST and ERM are correlated with the final visual outcome, i.e. the reduction in central retinal thickness is directly proportional to the improvement in VA , while in those in whom the occurrence of ERM was noted , visual acuity did not show improvement, which is in close correlation with the ischemic form of CRVO.

Discussion

It has been shown that 58% of patients with CRVO who are younger than 50 years of age also have certain risk factors, such as systemic disease, blood hypercoagulability, use of hormone therapy, systemic diseases (in SLE there is a 3.5-fold higher risk), etc. Although men and women are equally affected, the incidence of RVO increases with age, so that > 50% occurs over the age of 65. Systemic factors that protect against the development of RVO are increased levels of lipoproteins (HDL), moderate alcohol consumption and physical activity.

Most are typically unilateral, but 5-6% of branch vein occlusions and 10% of central vein occlusions have bilateral involvement [8].

Vascular endothelial growth factor (VEGF) is a signaling protein that initiates angiogenesis and vascularization in response to ischemic conditions, and plays a major role in the pathophysiology of CRVO [9].

Recommendations from European and world protocols emphasize the use of anti-VEGF agents as standard first-line treatment for patients with RVO , a therapy that specifically inhibits VEGF and thus targets the pathophysiological mechanisms for the occurrence of RVO . Early initiation of treatment is extremely important [10].

The development of SD-OCT allowed quantitative analysis of impaired photoreceptor integrity in the fovea in retinal diseases.

And if central retinal thickness is an important criterion for assessing treatment, certain structural biomarkers that can indicate anatomical and functional outcomes also have predictive value and are increasingly the focus of recent studies.

Indicators such as disorganization of the inner layers (DRIL), changes in the outer limiting membrane (ELM) and disruption of the elliptical zone (EZ), the presence of serous macular edema

(SMD), hyperreflective foci (HRF) , epiretinal membrane (ERM) have been proposed as potential OCT biomarkers for the degree of retinal vein occlusion and the effect of anti-VEGF treatment (8, 1 1 -1 3).

Chan et al. (1 3) analyzed OCT t omograms indicating that regression of DRIL correlated with improvement in BCVA after three months of application. Similarly, the study by Mimouni et al [1,2] showed that improvement in DRIL at 4 months was associated with improvement in BCVA.

The outer limiting membrane (ELM) functions as a barrier within the retinal tissue to large macromolecules, such as lipids and proteins, from the damaged retinal vasculature [1,4], [1,5]. Therefore, greater disruption of the ELM will cause refractory macular edema as a result of migration of macromolecules into the inner retinal layers, which will correlate with more intravitreal injections.

PLATON study highlights that certain biomarkers can and should guide the choice of treatment regimen. Thus, older age, better initial VA, and less improvement in visual acuity according to the degree of DRIL severity after the initial 3-monthly applications might make it reasonable to consider an early switch to a fixed monthly treatment regimen.

In younger patients, photoreceptors may be less affected by vascular damage and have an increased functional and anatomical capacity for recovery. Paradoxically, patients with better initial BCVA, who would be expected to have less anatomical or functional damage, have a greater limitation of visual gain after injection treatment [16].

Improvement in DRIL in the first 3 months was correlated with improvement in vision, independent of age and initial VA , while the study by Sirakaya et al. [17] showed that in the short-term response after 3 - monthly injections of aflibercept, improvement in BCVA and age were negatively correlated.

In the presented study, there was an improvement in visual acuity by 0.2 lines according to Snellen optotype, with the greatest improvement in visual acuity after subsequent recommended loading doses correlating with ultimate maintenance of vision.

The average value of intravitreal applications applied was 4.7 . In the series, there was no significant difference in effect depending on the treatment regimen, which at the same time cannot be taken into account due to the short evaluation period. However, the improvement in vision was correlated with the reduction in CST and was greater in those who did not have ischemia or the appearance of an epiretinal membrane.

And in follow-up studies, from the integrated data of the COPERNICUS (USA) and GALILEO (Asia, Europe) studies, it is seen that intravitreal administration of Aflibercept is well tolerated and an effective treatment for macular edema secondary to CRVO [18].

Notably, approximately 55% of eyes in the aflibercept-treated group gained >15 letters with a mean VA gain of +16.2 letters. In comparison, only 30% of eyes in the placebo group gained >15 letters with a mean VA change of +3.8 letters. The authors also concluded that BCVA can be maintained with anti- VEGF treatment according to a PRN regimen, but with careful monitoring and less frequent dosing [18].

CENTERA study also highlights the advantages of applying the T&E regimen in patients with CRVO, noting clinically significant improvements in functional and anatomical outcomes and with an application interval of ≥ 8 weeks [19].

In the VIBRANT study , the primary objective was to assess the improvement in visual acuity after treatment compared with baseline visual acuity, with the improvement being greatest at the start of treatment, with maximal improvement at month 3 or after the 3rd application of treatment, and this effect was maintained through month 12 [20].

Many real-world clinical studies have so far demonstrated the efficacy of aflibercept in the treatment of macular edema secondary to BRVO and CRVO .

To date, several studies have reported macular vascular density (VD) and perfusion and changes in the focal avascular zone (FAZ) before and after therapy. [21,23].

Vascular perfusion density is another important factor associated with photoreceptor integrity and visual acuity [22].

OCTA can assess the microvascular structures of the retina and choriocapillaris in patients with CRVO and quantify the severity of the occlusion. The results of certain studies refer to a significant correlation between vascular density and visual acuity, noting that the more affected the choriocapillaris is associated with lower visual acuity [24].

On the other hand, Mastropasqua et al. [25] found that the functional parameter visual acuity was not correlated with vascular density on OCTA.

Regarding the parameters examined with OCTA in our series, although a correlation was established, an objective disadvantage is the small sample of evaluated cases. Therefore, it is technically not possible to make a distinction between deep and superficial capillary plexus.

The decrease in parafoveal vascular density in the superficial and deep capillary plexuses in eyes with CRVO is explained by the increase in intravascular pressure from occlusion and hydrostatic pressure leading to a decrease in flow [26].

The subsequent decrease in flow results in a decrease in vascular density on OCTA.

And the temporary decrease in flow in the choriocapillaris may be due to pronounced severe retinal edema and the presence of various inflammatory mediators or as a masking effect and artifacts in the evaluation.

The authors (Shimura M. Chan EW, Campa C,)showed a decrease in macular flow in both the superficial and deep capillary plexuses and parafoveal vascular density in the deep plexus of the contralateral eye, revealing a decrease in vascular perfusion in both 53% and 25% of the other eye in patients with CRVO and BRVO respectively, or an increased risk of vein occlusion in the other eye in the same patients compared to the general population [26].

On the other hand, the degree of vascular density may be related to the severity of retinal ischemia. Koskas et al. reported a correlation between parafoveal capillary disruption in OC TA and peripheral ischemia in FA [27].

S eknazi et al. in a retrospective study found that vascular density less than 46% in DCP in eyes with CRVO threshold below which peripheral retinal nonperfusion is evident is an indication for the proposal to perform fluorescein angiography.

Suzuki et al. reported that the FAZ was larger in eyes with CRVO than in BRVO. In fact, the size of the FAZ was a result of the level of V EGF intraocularly, the FAZ was also larger in D CP, SCP in eyes that had fewer applications [21].

Aflibercept has a well-established ocular and systemic safety profile across numerous randomized clinical trials conducted in various indications for the drug. In our series, there were no major complications or side effects, with the exception of subconjunctival hemorrhages as minor, transient, mild complications and a feeling of discomfort in patients shortly after drug administration.

Conclusion

The analysis of the results from the examined sample confirms that ANTI-angiogenic treatment is the first line of treatment for retinal vein occlusions.

Timely and correctly indicated use of these agents to inhibit growth factors acts on vascular leakage, which is crucial for a better outcome in visual acuity, and OCTA has prognostic value in visual outcome.

Modern diagnostic modalities SD-OCT/ OCTA have made it possible to quantitatively and qualitatively evaluate the impaired integrity of retinal tissue in the macular region and to identify the risk of possible late complications.

Given that retinal occlusion is a chronic vascular disease, long-term monitoring is required, which, together with therapy, should be individualized and personalized in accordance with the recommendations and protocols of leading European and world associations.

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