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Effectiveness of intravitreal bevacizumab in the treatment of macular edema secondary to retinal vein occlusions

Vesna Dimovska

University Eye Clinic
Medical Faculty, University "Saints Cyril and Methodius", Skopje, Macedonia

Keywords
retinal vein occlusion, macular edema, bevacizumab, optical coherence tomography

Abstract

Aim: The aim of the study was to evaluate anatomical and morphological changes after intravitreal bevacizumab (Avastin) in eyes with macular oedema secondary to branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO).
Material and methods: Twenty-two eyes (22 patients) with macular edema secondary to central retinal vein occlusion (10 eyes, 45%) and branch retinal vein occlusion (12 eyes, 55%) were enrolled in a prospective study conducted at the University Eye Clinic in Skopje. The patients were examined for best corrected visual acuity (BCVA), slit-lamp examination, tonometry, fundus examination on dilated pupil with 78/90 D Volk lenses and Spectral Domain Optical Coherence Tomography (SD-OCT Topcon 3D 2000). Eyes were treated with three initial intravitreal bevacizumab injections of 1.25 mg/0.05 ml at a monthly interval. Retreatment criteria were based on central retinal thickness (CRT) evaluated on optical coherence tomography and change in BCVA.
Results: Mean age in total group was 61.6 years; mean visual acuity gain obtained following treatment was 0.13 on Snellen's chart. Average injections number was 4.91, with more injections applied in the group with CRVO. Average CRT difference following treatment was assessed on 265.18 μm, with greater CRT decrease in the group of CRVO. Mean follow up was 1.4 years. No serious or sight threatening adverse effects were registered.
Conclusions: Bevacizumab has proven as safe, effective and beneficial for macular edema secondary to retinal vein occlusions as primary therapy in treatment-naive patients. Our experience suggests that more injections are associated with greater reduction of macular edema.

Corresponding address:
Vesna Dimovska, "Cedomir Minderovic" 30, 1000 Skopje, Macedonia, Phone: +38970370379,
E-mail address: vesnajdimovska@gmail.com

Introduction

"Research into CRVO is fraught with challenges, from accurate disease classification to its treatment; even the most prestigious trials have become controversial" (Canadian Journal of Ophthalmology, 2007).

Retinal vein occlusions (RVOs) remain second most common vision related vascular disorder following diabetic retinopathy. It has been identified as clinical entity since 1855, but many aspects of its pathogenesis and management remain uncertain.

Regarding to the site of occlusion it is classified as central retinal vein occlusion – CRVO (occlusion at the level of the optic disc), hemiretinal vein occlusion – HRVO (occlusion at the primary superior/inferior branch involving approximately half of the retina), and branch retinal vein occlusion – BRVO (obstruction of the distal branch of the retinal vein).

The location of the occlusion is greatly influencing the pathogenesis, clinical presentation and management of RVOs (1).

Retinal vein occlusion is further subdivided as ischemic and non-ischemic type, according to the amount of retinal capillary ischemia presented at fluorescein angiography (FA). Majority of patients (almost two thirds) with ischemic type develop severe complications, such as macular edema, macular ischemia and neovascularization, ultimately leading to blindness. The two subtypes cannot always be clearly and reliably distinguished based on physical evaluation alone.

Patients with ischemic CRVO are much more likely to have poor visual acuity, both at initial presentation and final visual acuity, compared to patients with non-ischemic type (1).

The incidence of CRVO is currently reported as 1.8% and 0.5% for BRVO (2). The prevalence of all types of RVOs increases with age. Most CRVOs are seen in patients over 65 years of age. BRVO is three times more common than CRVO.

In Beaver Dam Eye Study, the 15-year cumulative incidence of CRVO was found as 0.5%. Population based study in Australia, the Blue Mountains Eye Study, has reported 10-year cumulative incidence of CRVO in a population older than 48 years as 0.4%. And the Beijing Eye Study reported that prevalence of CRVO in a Chinese population over 40 years was 0.1% (2, 3). Similar prevalence of CRVO is found in different ethnic and racial groups.

Pathophysiology of RVOs

The exact pathogenesis of the thrombotic occlusion of central retinal vein is not fully elucidated yet. Various local and systemic factors play a role in the pathological closure of the central retinal vein.

Intraluminal thrombus formation in RVO is associated with the venous stasis, endothelial injury and hypercoagulability of the Virchow triad. In CRVO, the vein is typically occluded by thrombus formation consisting of fibrin and platelets at or posterior to the level of the lamina cribrosa. The initiating factor in BRVO is most often compression of the adjacent vein by atherosclerotic retinal arteries at the site of AV-crossing, leading to turbulent flow and venous stasis (1, 4).

Vascular obstruction of the venous circulation leads to capillary non-perfusion, fluid/blood leakage, intraretinal hemorrhages, macular ischemia and macular edema. In ischemic types, final events result with neovascular complications, such as vitreous hemorrhage, neovascular glaucoma or tractional retinal detachment.

In both ischemic and non-ischemic CRVO, blockage of the retinal vein occurs, but the non-ischemic type is characterized with maintaining of better relative blood flow to the retina through the collateral vessels. The non-ischemic type of CRVO has milder clinical presentation with more favorable final prognosis and accounts for 75-80% of the cases. Neovascularization is rare, but unfortunately, conversion to the ischemic type is not excluded (1, 4, 5).

The risk factors for both CRVO/BRVO largely embrace vascular diseases in general, including increasing age, hypertension, diabetes mellitus, smoking, renal disease, obesity, oral contraceptive use, obstructive sleep apnea and hypercoagulable disorders. Glaucoma, which provokes stasis and decreased outflow, is also a significant independent risk factor.

Clotting can occur due to the number of systemic diseases, such as hypercholesterolemia, hyperhomocysteinemia, systemic lupus erythematosus (SLE), sarcoidosis, tuberculosis, multiple myeloma, leukemia, lymphoma (1, 4).

Increased physical activity, advantageous cholesterol profiles and alcohol consumption are considered protective by some physicians.

Clinical presentation of CRVO/BRVO

CRVOs usually present with acute sudden vision loss, and the site of occlusion is localized at the level of lamina cribrosa. About 75-80% of cases belong to

Abbreviations

RVO – Retinal vein occlusion; CRVO – Central retinal vein occlusion; BRVO – Branch retinal vein occlusion; BCVA – Best corrected visual acuity; CRT – Central retinal thickness; SD-OCT – Spectral Domain Optical Coherence Tomography; SS-OCT – Swept source Optical Coherence Tomography; VEGF – Vascular Endothelial Growth Factor; BVC – Bevacizumab; IVTA – Intravitreal triamcinolon acetonide; FDA – Food and Drug Agency

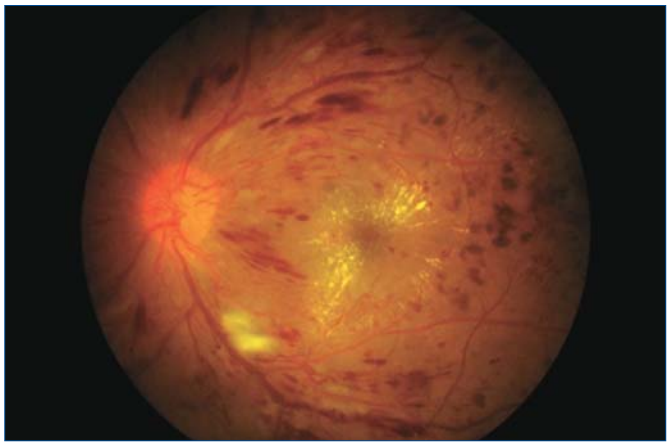

Figure 1. Central retinal vein occlusion (Source: www.shutterstock.com)

non-ischemic type but conversion of non-ischemic to ischemic type occurs in 30% of the cases.
Ischemic CRVO is characterized with poor baseline and final visual acuity. There is massive capillary non-perfusion that ranges from 10-30 DD that increases considerably the risk of neovascularization. The afferent papillary defect has diagnostic value (1, 5).
Fluorescein angiography (FA) is one of the standard diagnostic methods used in the classification of CRVOs but during the early stage of the disease, due to the extensive hemorrhages, it provides little information regarding the retinal perfusion. The method obtains valuable information after the hemorrhage resolution.
Pathophysiology of CRVO is related to the vein compression and hemodynamic disturbances, as well as changes in the blood and vessel wall. Central retinal vein obstruction has been associated with various systemic pathological conditions, although the exact relationship has not been proven (1).
The prognosis of CRVO depends upon the reestablishment of patency of the venous system by recanalization, dissolution of clot, or formation of optociliary shunt vessels.
The Central Venous Occlusion Study (CVOS, 1995) has greatly contributed to defining the visual loss morbidity in CRVO. Visual recovery in the study was found to vary, with the presenting visual acuity as best predictor of final visual acuity (6). Vision loss is mostly related to macular edema, macular ischemia, retinal hemorrhage and development of neovascular glaucoma. The assumed mechanism of vision loss is associated with photoreceptor cell death (3).
The location of BRVOs is usually at the arterio-venous crossing site. It is presented with sectorial retinal hemorrhage, retinal ischemia and macular edema. The extent of vision loss is closely related to the amount of macular edema. Some studies are suggesting strong correlation of BRVO and retinal arteriolar changes (7).
Management of RVOs should be aimed towards: identification and resolving of modifiable risk factors and recognition and management of sight-threatening complications.
Broad diagnostic procedures should be performed in order to complete diagnosis and distinguish the types of RVOs: fundus biomicroscopy (Volk lenses of 90/78 D), fundus photography, fluorescein angiography (FA), optical coherence tomography (SD-OCT/SS-OCT/OCT-Angiography), color-Doppler imaging, electroretinography and histological findings.
Regarding contemporary treatment approaches, the main treatment targets should be macular edema management and prevention of neovascularization (8).
Actual treatment approach recommends two general options, applied alone or in a manner of combination therapy: laser photocoagulation and intraocular pharmacology (like anti-VEGF treatment, corticosteroids, PKC inhibitors).

Macular edema

Macular edema is one of the significant, but treatable causes of decreased visual acuity in patients with CRVO and BRVO. The exact pathophysiological mechanism of macular edema occurrence is unclear, but multiple factors are involved including increased venous pressure, elevated levels of vascular endothelial growth factor (VEGF) and deregulation of multiple inflammatory mediators leading to increased capillary permeability and leakage.
The postulated mechanism for macular edema is up-regulation of VEGF in response to retinal ischemia secondary to increased resistance to venous blood flow. The reported intravitreal levels of VEGF-A are higher in CRVO than in any other ischemic retinal vascular disease. VEGF increases vascular permeability, leading to macular edema and development of neovascularization (1, 4, 5, 8).
Various treatment modalities have been used and a lot of randomized clinical studies are currently going on, in efforts to further elucidate pathogenesis of macular edema, as well as most favorable treatment modalities.

Intraocular pharmacology for treatment of RVOs

Having in mind that main subject of the article is anti-VEGF treatment for RVOs other treatment options would be only briefly overviewed.
Laser photocoagulation is accepted treatment of choice for various complications associated with retinal vascular diseases (diabetic retinopathy, branch retinal vein occlusion). Panretinal photocoagulation has been used for a long time in the treatment of neovascular complications of central retinal vein occlusion. In 1995 National Eye Institute (NEI) has sponsored

multicenter prospective study, the Central Vein Occlusion Study (CVOS) that provided guidelines for the treatment and follow up care of patients with CRVO. CVOS evaluated the efficacy of macular grid photocoagulation in preserving or improving central visual acuity in eyes with macular edema due to central retinal vein occlusion. The study demonstrated that grid laser treatment of macular edema was not beneficial for eyes with CRVO, but recommended to be performed in macular edema induced by BRVO. Also, CVOS concluded that prophylactic panretinal photocoagulation in CRVO is ineffective in prevention of iris neovascularization. Therefore, the standard of care in this study for CRVO was recommendation of waiting for early iris neovascularization and performing panretinal photocoagulation afterwards (6, 8, 9).

The long-term safety and efficacy of intravitreal triamcinolone acetonide was investigated in a multicenter clinical trial named Standard Care versus Corticosteroids for Retinal Vein Occlusion Study in 2009 – the SCORE Study.

The SCORE Study has recommended observation in cases of CRVO and laser treatment in patients with BRVO. Intravitreal triamcinolone acetonide (IVTA) has been shown effective in improving vision and reducing macular edema secondary to BRVO, but its use is often associated with cataract formation and increased intraocular pressure (8, 10).

New pharmacologic agents have changed the treatment paradigm of macular edema secondary to RVOs. Pharmacologic treatment with intravitreal antivascular endothelial growth factor (anti-VEGF) agents is currently first-line therapy for macular edema (1, 4, 8, 9, 11).

Dexamethazone intravitreal implants, ranibizumab and aflibercept have FDA approval for the treatment of macular edema secondary to BRVO. Aflibercept has been approved for the treatment of macular edema secondary to CRVO also.

Apart from those treatment options, intravitreal injections of bevacizumab (Avastin, Genentech) have been extensively used off label for treating both CRVO and BRVO.

Pathophysiological mechanism of anti-VEGF agents Pegaptanib (Macugen, Eytech/Pfeizer 2004) (bevacizumab)

Since 2004, there are following available options for intravitreal anti-VEGF treatment: bevacizumab (Avastin, Genentech/Roche, 2005), ranibizumab (Lucentis, Novartis, 2006) and Aflibercept (Eylea, Regeneron/Bayer 2011).

The following text will mostly deal with the efficacy and safety of intravitreal bevacizumab in the treatment of retinal vein occlusions.

Vascular endothelial growth factor (VEGF) when triggered by hypoxia, has been shown to increase in pathological ischemic conditions, thus implicating as the major factor responsible for increased vascular permeability and macular edema in CRVO. In those cases there is evidence of intraretinal up-regulated expression of mRNA. Increased concentration of VEGF in the vitreous body of patients with ischemic CRVO has been reported and furthermore, it is postulated to play a role in the increased vascular permeability that triggers development of macular edema. So, the injection of anti-VEGF agent in the vitreous body has been accepted as favorable treatment for macular edema secondary to CRVO. Following intravitreal bevacizumab injections, VEGF levels have shown considerable decrease, even to concentration lower than physiologic levels (4, 9, 10).

In May 2005 at the Bascom Palmer Eye Institute, bevacizumab was first injected into the vitreous of an eye with macular edema due to CRVO. Bevacizumab is a full-length recombinant, humanized monoclonal antibody that binds all isoforms of VEGF-A and since the initial report, intravitreal bevacizumab has been widely used and accepted as the primary pharmacotherapy for macular edema secondary to CRVO/BRVO, diabetic macular edema and wet age related macular degeneration. Bevacizumab has FDA approval for the treatment of metastatic colon-rectal cancer and its ophthalmic use is still conducted off label.

Evaluation of treatment success in RVOs is most often based upon the assessment of functional efficacy (best corrected visual acuity) and anatomical/morphological outcome represented by central retinal (macular) thickness measurement obtained by optical coherence tomography. On the other hand, the treatment response is closely related to the degree of macular ischemia, amount of retinal hemorrhages, extent of irreversible photoreceptor damage, and finally, the progression that occurs over time (depending on the type of perfused/non-perfused RVOs)

Materials and Methods

In the University Eye Clinic in Skopje, interventional, non-randomized prospective study was conducted that included 22 eyes of 22 patients with RVO. The patients were subdivided in CRVO group (10 eyes) and BRVO (12 eyes). All patients were examined for BCVA by Snellen's chart, slit-lamp biomicroscopy, tonometry, fundus examination on dilated pupil with Volk lenses 90/78 D. Treatment was performed with three monthly intravitreal injections of bevacizumab (Avastin, Genentech Inc, San Francisco, CA) with standard dosing regimen of 1.25 mg/0.05 ml. The anatomical result of the treatment was assessed with evaluation of central retinal (macular) thickness measurement (CRT) conducted at baseline, following the third injection and after re-injections. PRN protocol was applied in pa-

Table 1. Results of the conducted study at the University Eye Clinic, Skopje

	Total number	CRVO (%)	BRVO (%)
Patients number	22	10 (45)	12 (55)
Mean age	61.6	62.9	60.4
Mean VA gain	0.13	0.06	0.19
Mean number of injections	4.9	5.3	4.6
Average CRT before BVC	560.5	698.6	445.4
Average CRT following BVC	295.3	281.3	307.0
Mean CRT difference (μm)	265.2	417.3	138.4
Mean follow up (years)	1.4	1.6	1.3

tients that needed re-injections. The measurements were provided with spectral domain OCT (SD-OCT) Topcon 3D 2000. The re-injection criteria were based on the changes of BCVA, CRT and the appearance of fluid collection on OCT. The procedure was performed by standard protocol in operating room with fully aseptic conditions, after obtained signed patients inform consent. The follow up interval varied in range of 6-33 months.

Results and Discussion

The mean age of the participants was 61.6 years. The mean follow up was 1.4 year. The average visual acuity (BCVA) improvement in both groups was 0.13 on Snellen's chart, with better improvement in the group with BRVO (0.19). Mean injections number was 4.9 (5.3 injections in CRVO vs 4.6 in BRVO group).

The average CRT at baseline was 560.5 μm (698.6 μm in CRVO vs 445.4 μm in BRVO). The average CRT following intravitreal bevacizumab was 295.3 μm (281.3 μm for CRVO and 307.0 μm for BRVO group). The average CRT decrease post treatment was 265.2 μm (417.3 μm in CRVO vs 138.4 μm in BRVO group).

The results are presented in Table 1. and Figure 2.

The results in our study did not show significant improvement of BCVA following bevacizumab injections. An average improvement was 0.13 on Snellen's chart, with greater improvement in the group with BRVO (0.19). It is expected, due to the smaller extent of macular edema in this group, compared to CRVO.

On the other hand, SD-OCT has confirmed that greater post treatment decrease of CRT was achieved in the group with CRVO, although there was not substantial visual acuity gain. These findings are consistent with the work of Bodia (12). They examined 43 patients with RVOs treated with intravitreal bevacizumab. The study concluded that in the CRVO group bevacizumab failed to show any significant improvement in terms of increase of visual acuity despite of clinically significant reduction in macular thickness (12).

In a study conducted in the UK, although significant decrease of CMT was found after 1 year, no significant improve¬ment of BCVA was registered after 12 months of follow-up (13, 14).

In relation to this finding, the study of Pikkel (9) emphasizes that "bevacizumab intravitreal injections applied up to 3 months following CRVO improve visual acuity. While both early first injection and multiple injections were found to have positive effect on final visual acuity, treatment timing had a greater effect than the number of injections administered". It has been demonstrated that, the patients who are going to have good treatment response, would typically

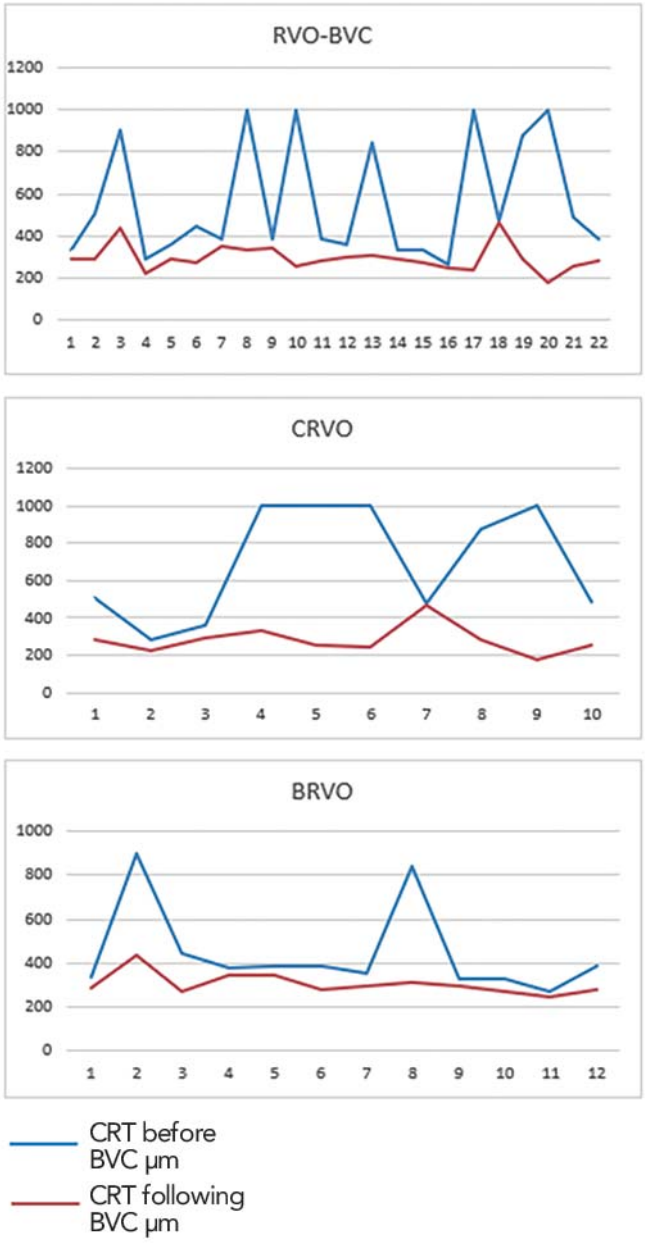

Figure 2. CRT in both groups prior and following BVC treatment

achieve that within the three first injections. The longer presence of the edema is associated with worse visual outcome (8, 15).

One of the possible explanations for such finding in our study is the fact that in the group with CRVO were recruited patients with chronic/persistent macular edema. This explanation is further supported when the number of applied injections is considered. Mean injections number in our group was 4.9, with more injections applied in the CRVO group (5.3 vs 4.6 in the BRVO group). This parameter should be interpreted in relation to the type of edema in CRVO group, the higher CMT and the longer the treatment and follow up period in our study. In the study conducted by Mehany and coworkers (11), the mean number of injections was 2.7 on 6-8 weeks intervals and follow up of 12 months. Older study by Iturralde and al (16) has reported mean injections number of 2.8 with short follow up.

Study of Praeger (17) reports mean 8 injections of bevacizumab for treatment of persistent chronic macular edema in 29 consecutive eyes with CRVO and BRVO. The study has also short follow up (12 months), and raises the question of changes in the regimen dosing during the treatment. Eyes were treated with three initial intravitreal bevacizumab injections of 1 mg at a monthly interval. If continuous injections were indicated up to month 6, the dose was increased to 2.5 mg.

The higher number of applied injections in our study necessarily implicates the need for re-injections in order to achieve macular edema decrease. The re-injections were applied on PRN basis following the initial treatment of three monthly bevacizumab injections. The re-injection criteria were set on the changes/worsening of BCVA, and/or assessment of central macular thickness >250 μm or appearance of intraretinal fluid obtained on SD-OCT.

Number of studies are reporting favorable, but short-lasting effect of intravitreal bevacizumab, most often from 3-6 weeks after multiple injections (4, 8). The peak in visual acuity improvement is considered to be reached between 3-6 weeks following injections. Having in mind that visual acuity decrease is most often related to macular thickness increase, some researchers are suggesting OCT evaluation to be performed between weeks 3 and 6 in order to estimate the proper time for re-injection (8, 18).

Persistent macular edema at month 3 as measured by SD-OCT indicates a worse prognosis and probable need for more injections and continuous monitoring (3). Results from previous studies indicate that progression of retinal non-perfusion continues in eyes that did not gain resolution of macular edema and whereas anti-VEGF agents were given sporadically. The authors are emphasizing that in eyes with macular edema secondary to RVOs, the resolution of macular edema should not be the only treatment objective, but also the prevention of worsening retinal non-perfusion (3).

The data obtained from randomized clinical trials are suggesting that some eyes with macular edema secondary to RVOs stabilize after a few consecutive monthly injections and require a few injections afterwards, but the vast majority require frequent follow up and multiple injections to control macular edema. Findings from SD-OCT, Swept source OCT (SS-OCT) or OCT-Angiography may be of extreme importance to predict the functional and anatomical outcome.

Regarding to the safety of bevacizumab, in our study no any serious ocular or systemic adverse event has been reported. Most common side effects were conjunctival hyperemia and subconjunctival hemorrhage at the injection site. Moreover, there was substantially long-term treatment and follow up interval in range of

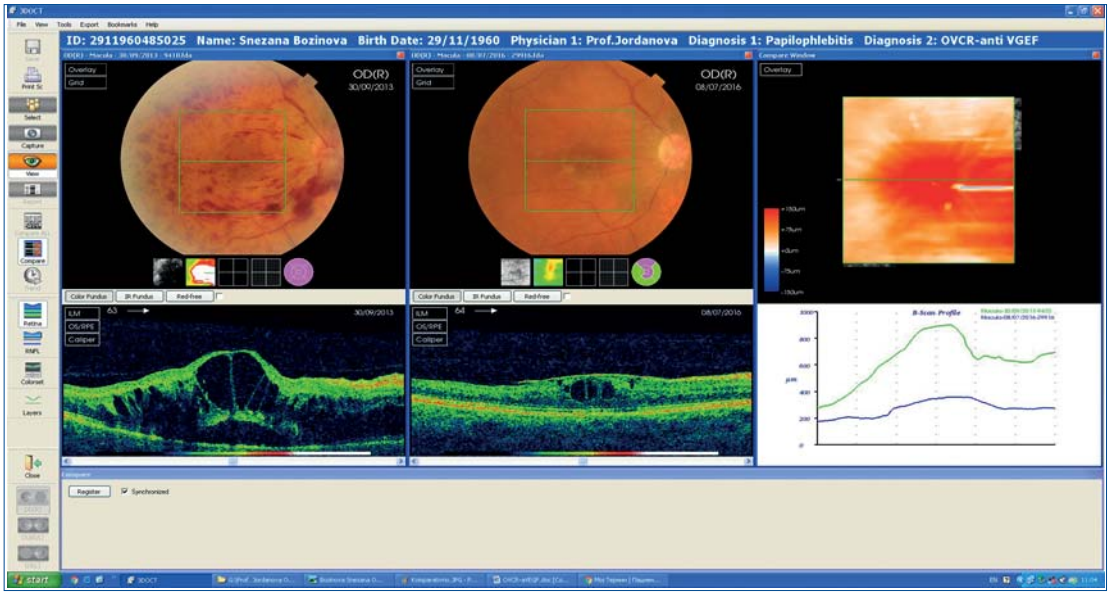

Figure 3. Comparative OCT scan of CRVO prior and following BVC treatment

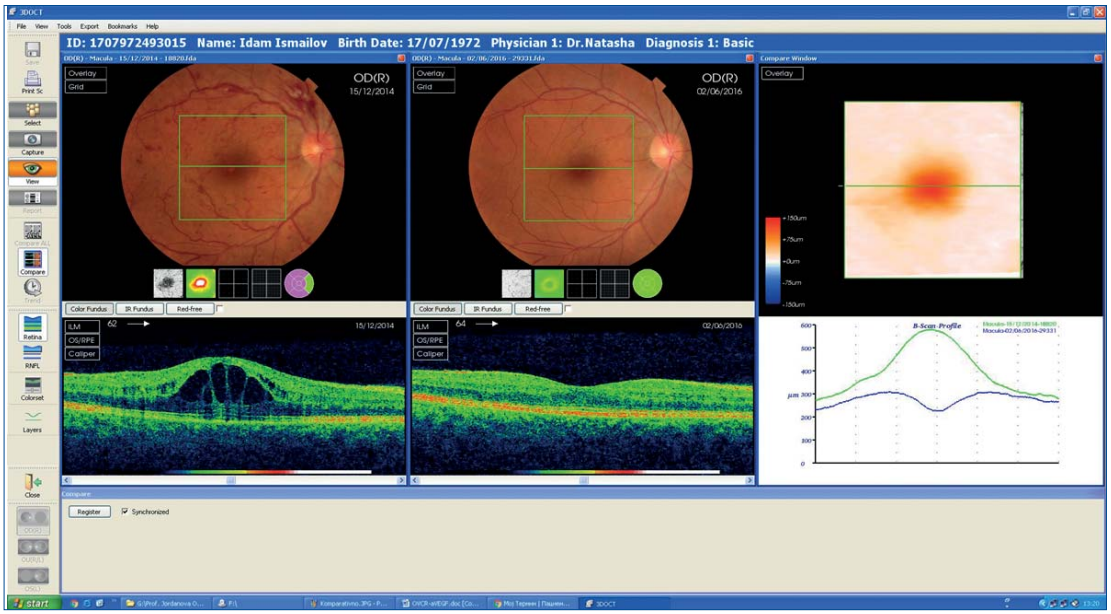

Figure 4. Comparative OCT scan of BRVO prior and following BVC treatment

6-33 months. This is consistent with the majority of conducted studies, reporting evidence on the safety of intravitreal injections of bevacizumab (4, 11, 14, 16, 19, 20).

Besides, number of studies designed and conducted to compare the safety of bevacizumab relative to FDA approved anti-VEGF agents (ranibizumab, aflibercept), did not demonstrate increased adverse events in patients treated with off label bevacizumab (21, 22).

Objective limitations of our study include small sample and the use of Snellen's decimal chart for visual acuity determination. The patients underwent the treatment after their referral to the clinic, which was at different time-periods following the retinal vein occlusion.

Having in mind the limited results (mostly beneficial in short-term) of available monotherapies regarding visual acuity improvement and resolving of macular edema, this has lead to rationale of considering combination approach to target several mechanisms of edema and angiogenesis simultaneously. Number of current studies are reporting results of combined laser/intravitreal triamcinolone/anti-VEGF treatment. Combination therapy is especially referring to the non-responders to monotherapy.

Conclusions

The anti-VEGF treatment for macular edema secondary to retinal vein occlusions has imposed nowadays as first-line therapy. Our study has confirmed the beneficial effect of bevacizumab mostly in reducing of macular thickness in both groups, although visual acuity improvement as second end point did not show statistically significant gain in patients with CRVO. Undoubtedly, multiple injections are needed to achieve favorable, and so far, short-term outcome.

However, there is still missing unified treatment protocol and recommended clinical guidelines. Future long-term randomized controlled clinical trials should facilitate clarification of unresolved issues, mainly regarding number and timing of injections, long-term efficacy and indications for treatment cessation.

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