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EFFECTIVENESS OF ANTI-VEGF AGENTS IN PATIENTS WITH RETINAL VEIN OCCLUSION

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ЭФФЕКТИВНОСТЬ АНТИ-VEGF ТЕРАПИИ У ПАЦИЕНТОВ С ОККЛЮЗИЕЙ ВЕН СЕТЧАТКИ

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Retinal vein occlusion is a significant medical problem that requires urgent correction. We conducted a prospective observational study (n=124 patients) to investigate the efficacy of anti-vascular endothelial growth factor therapy (intravitreal injections of aflibercept 2 mg in 0.05 mL) compared with standard treatment in patients with retinal vein occlusion. When post-thrombotic neovascular glaucoma occurred, the concentrations of transforming growth factor α and β in the lacrimal fluid in both groups (with and without aflibercept) increased by 1.7-fold and 28-fold, respectively. When aflibercept was administered, the blood flow rates in ophthalmic and central retinal arteries, as well as the maximum velocity in the superior ophthalmic and central retinal veins, were improved compared with patients who received standard therapy. Thus, aflibercept therapy for retinal vein occlusion leads to the normalization of blood flow in retinal vasculature, preventing neovascularization and providing a better clinical outcome for patients.

Keywords: central retinal vein occlusion, anti-angiogenic therapy, optical coherence tomography, angiography

В современной офтальмологии окклюзия вен сетчатки является одной из наиболее важных медицинских проблем, требующей поиска оптимальных методов коррекции. Нами выполнено проспективное наблюдательное исследование (n=124) по изучению эффективности антиангиогенной терапии (интравитреальные инъекции афлиберцепта 2 мг в 0,05 мл) по сравнению со стандартной терапией у пациентов с окклюзией вен сетчатки. Установлено, что при развитии посттромботической неоваскулярной глаукомы концентрации трансформирующих факторов роста α и β в слезной жидкости в обеих группах (с применением афлиберцепта и без) увеличивались в 1,7 и 28 раз соответственно. При введении афлиберцепта скорость кровотока в центральной артерии сетчатки и максимальная скорость в центральной вене сетчатки улучшались по сравнению с пациентами, получавшими стандартную терапию. Таким об-

разом, афлиберцепт-терапия при окклюзии вен сетчатки способствует нормализации кровотока в сосудах глаза, предотвращая неоваскуляризацию и обеспечивая лучший клинический результат для пациента.

Ключевые слова: окклюзия центральной вены сетчатки, антиангиогенная терапия, оптическая когерентная томография, ангиография

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CRVO – central retinal vein occlusion
TGF – transforming growth factor

VEGF – vascular endothelial growth factor

Disturbances of venous outflow are the second most common vascular pathology of the fundus after diabetic retinopathy. According to S. Rogers, 16.4 million people worldwide are reportedly diagnosed with central retinal vein occlusion (CRVO) and branch retinal vein occlusion; CRVO affects 0.8 per 1000 people [1]. If the thrombus remains in the vein without subsequent treatment, retinal ischemia occurs, which is the source of neovascularization; hemophthalmia and secondary neovascular glaucoma may follow [2]. Macular edema due to occlusion of the branches of the central retinal vein is the one of the most common causes of vision loss [3, 4, 5]. Currently, there is no consensus regarding the management of retinal vein occlusion; however, a number of clinicians have recommended intravitreal corticosteroids (e.g., triamcinolone acetonide) and anti-vascular endothelial growth factor (VEGF) agents (e.g., bevacizumab and ranibizumab) as suitable treatment methods. Several surgical techniques, such as radial optic neurotomy and arteriovenous sheathotomy, have not proven to be clinically effective and are not currently used in the management of retinal vein occlusion; these techniques are mainly of historical interest [6, 7, 8].

Recently, the literature has focused on the role of VEGF in multiple diseases, where it plays an essential role in triggering neovascularization. VEGF has been shown to contribute to the pathogenesis of retinal vein occlusion and its consequences (e.g., vascular leakage and retinal edema). Some intravitreal injections of anti-VEGF agents, such as ranibizumab and aflibercept, have been approved by the Food and Drug Administration for the treatment of CRVO [9, 10, 11]. Anti-VEGF therapy seems to be a clinically sound and effective method of treatment for CRVO. Many treatment regimens have been suggested based on clinical trials with these drugs, in the form of monthly or as-needed injections [12, 13, 14, 15]. However, an optimal treatment regimen has not yet been established.

The aim of our study was to investigate the effectiveness and optimal regimen of anti-VEGF therapy in the treatment of CRVO.

Material and Methods. This prospective observational clinical trial recruited patients who were treated for CRVO in our clinic between 2010 and 2015. The clinical characteristics of the study and control groups are summarized in Table 1. In total, 124 patients with CRVO (mean age: 54.3±8.9 years) and 20 healthy control subjects (mean age: 54.6±9.1 years) were included in this prospective study. The mean ages of the groups did not significantly differ ($p=0.96$).

Table 1
Clinical characteristics of the study groups

Characteristics	Group 1 n=66	Group 2 n=58	Control group n=20
Age (years), mean±SD*	54.4±8.5	54.1±10.3	54.6±9.1
Comorbidities:			
Dyslipoproteinemia	6	5	2
Arterial hypertension	5	4	2
Diabetes mellitus	2	2	1

* SD – standard deviation.

The trial adhered to the tenets of the Declaration of Helsinki. The study protocol and informed consent documentation were approved by centralized institutional review board and ethics committee (Protocol № 17, 10.05.2010, Institute of Emergency and Reconstructive Surgery named after V. C. Gusak, Donetsk, Ukraine). The study protocol was explained in detail to all participants, and written informed consent was obtained from each participant before they were enrolled in the study. We examined patients who were admitted within the first ten days after the onset of the disease (i.e. in the stage of acute ischemic CRVO). The patients' previous clinical histories included acute cerebral circulatory disorder, myocardial infarction, and thrombophlebitis of deep and superficial veins of the lower extremities. During the examination of our patients, we closely monitored arterial hypertension, hyperglycemia, and hypercholesterolemia. We formed two groups: group 1 consisted of 66 patients who received standard therapy in the form of local anticoagulant therapy (dexamethasone with heparin) or plasminogen 5000 U 2 times per day № 5, as well as antiplatelet agents (e.g., pentoxifylline or emoxypine). Treatments also included intravenous rheopolyglukin 200–400 mL with intramuscular dexamethasone 4–8 mg and actovegin. Treatments for macula edema and neovascularization included laser coagulation and intravitreal triamcinolone. Group 2 consisted of 58 patients who were treated with intravitreal aflibercept (Bayer Pharma, Leverkusen, Germany) 2 mg in 0.05 mL, in addition to standard therapy. Treatment with intravitreal aflibercept began with one injection once per month for five consecutive months; it was subsequently reduced to one injection every two months without monitoring between injections.

Twelve months after the start of treatment, the interval between injections was increased based on the patient's visual acuity and anatomical parameters. Optical coherence tomography (RTVue XR Avanti with AngioVue, Optovue Inc, Fremont, CA, USA) was performed at the start of anti-VEGF treatment, as well as one week and one month after the start of treatment. The concentrations of transforming

growth factor (TGF)- α and TGF- β in the lacrimal fluid were measured in the basic research laboratory of the Institute of Emergency and Reconstructive Surgery named after V. C. Gusak (Donetsk, Ukraine) by using an enzyme-linked immunosorbent assay with a multiplate reader (Versamax; Molecular Devices, Sunnyvale, CA, USA). A Doppler ultrasound (multipurpose Doppler system Sequoia 512; Acuson Corporation, Siemens Medical Solutions USA Inc., Mountain View, CA, USA) was used to investigate blood flow in the eye; a 10-MHz sensor was used. Blood flow parameters were evaluated in color Doppler mapping and spectral Doppler modes. Velocities (systolic and diastolic) and peripheral blood flow resistance indices (pulsation index and resistance index) were measured in the ophthalmic artery, central retinal artery, superior ophthalmic vein, and central retinal vein. Healthy patients without any ocular disease were used as the control group.

Statistical data were processed using the Statistic 6.0 software package (StatSoft, Inc., Tulsa, OK, USA). The Shapiro – Wilk test was used to assess whether the data exhibited a normal distribution across groups. The paired Student’s t-test for independent samples was used to determine significant differences between the groups. Differences were regarded as statistically significant when $p < 0.05$.

Results and Discussion. Although small numbers of patients in both study groups were admitted to the hospital in the first week with early stages of CRVO, the level of TGF- α did not change, whereas TGF- β increased by more than 10-fold. When post-thrombotic neovascular glaucoma occurred, the concentration of TGF- α in lacrimal fluid increased by 1.7-fold, whereas the concentration of TGF- β increased by 28-fold (Table 2). Notably, the degree of scarring in the subretinal neovascular membrane directly depends on the interactions of cytokines affecting neoangiogenesis, including TGF- α and TGF- β .

Table 2

Concentrations of transforming growth factors in the lacrimal fluid in patients with central retinal vein occlusion, pg/ml

Group	TGF- α	TGF- β
Normal value	18.4 \pm 2.1	23.4 \pm 3.3
Retinal vein occlusion	28.7 \pm 4.9*	646 \pm 112*
Group 1 after 4 weeks of treatment	24.9 \pm 2.4*	422 \pm 85*
Group 2 after 4 weeks of treatment	19.8 \pm 3.1	284 \pm 38*

* Significant difference between normal values and the values observed for each transforming growth factor in each category group. The study group is reliable ($p < 0.05$).

At four weeks after treatment, patients in group 1 exhibited reductions in both TGF- α and TGF- β concentrations. However, patients in group 2 exhibited a decrease in TGF- α concentration that did not significantly differ from the level of control patients. Patients in group 2 also exhibited a TGF- β concentration that was 2.3-fold lower than the level before treatment; however, this remained significantly greater than the concentration in the control group.

In ischemic branch retinal vein occlusion (Table 3), there are reductions in systolic and diastolic blood flow velocities in the ophthalmic artery and central retinal artery, as well as in the maximum velocities in the superior ophthalmic vein and central retinal vein. In this study, the systolic velocities in the ophthalmic artery were 32.8 \pm 3.2 cm/s (in controls) and 29.6 \pm 0.6 cm/s (in group 1), while the diastolic velocities in the ophthalmic artery were 9.2 \pm 1.8 (in controls) and 6.7 \pm 0.2 cm/s (in group 1) ($p < 0.05$). The resistance indices did not significantly differ between controls and

group 1, whereas pulsation indices were 1.3 \pm 0.05 (in controls) and 2.3 \pm 0.4 (in group 1). Systolic velocities in the central retinal artery were 10.7 \pm 0.9 cm/s (in controls) and 7.9 \pm 0.2 cm/s (in group 2), while diastolic velocities in the ophthalmic artery were 3.1 \pm 1.6 (in controls) and 2.1 \pm 0.3 cm/s (in group 2) ($p < 0.05$). The resistance indices did not significantly differ between controls and group 2, whereas pulsation indices were 1.4 \pm 0.07 (in controls) and 3.2 \pm 0.05 (in group 2). In addition, the maximum velocities in the superior ophthalmic vein were 8.4 \pm 1.6 (in controls) and 5.1 \pm 1.5 cm/s (in group 2), whereas the maximum velocities in the central retinal vein were 4.4 \pm 0.68 (in controls) and 2.8 \pm 0.04 cm/s (in group 2) ($p < 0.05$). When anti-VEGF therapy was administered, all parameters were significantly improved in group 2, compared with those in group 1.

In the beginning, during hospital admission, both groups had significant macular edema. Table 4 shows that, after one month of treatment, patients in group 1 had slight reductions in retinal edema in some fields; after two months of treatment, group 1 exhibited further reduction of retinal edema. In contrast, group 2 exhibited a significant decrease in retinal edema in all the parts of the retina after one month of anti-VEGF therapy; this trend was maintained after two months of treatment.

One week after the start of treatment, vascular loops, microaneurysms, vessel crimping, and newly formed vessels were visualized in the outer layers of the retina in both study groups (i.e., in the angio outer retina, the segment between the outer plexiform layer and Bruch’s membrane) (Figure). All layers were adhered, and a single parafoveal cyst was located in the middle layers of the retina, which violated the differentiation of the inner segment/outer segment layer in the fovea. Moreover, edema in the central fovea decreased by 105 μ m, whereas parafoveal edema from the nasal side decreased by 234 μ m. There was a significant improvement in the studied parameters in group 2 between 1 and 2 months after the start of treatment (Table 4); this was reflected by improvement in visual acuity. After 2–3 weeks of anti-VEGF therapy, optical coherence tomography angiography showed a significant reduction in the number of newly formed vessels. Thus, the main effect of anti-VEGF treatment was to prevent neoangiogenesis, which led to reduction of retinal edema and improved quality of life in patients with CRVO.

A key factor in the induction of neoangiogenesis is the presence of excess VEGF in retinal tissue. Common aspects in all types of intraocular neovascularization include the formation of newly formed blood vessels without endothelial basement membrane, as well as the presence of multiple fenestras in the vascular wall leading to transudation, exudation, and hemorrhage. Similar changes are characteristic of any wound or inflammatory process when the integrity of the vessel wall is violated. Shortly after this violation of integrity, an exudative reaction occurs, and the stage of scarring begins; this represents another universal process in the body, which aims to restore the integrity of the tissue structure by intensive proliferation of connective tissue accompanied by partial or complete loss of a specific tissue function [16, 17]. Scarring on and under the retinal surface, as well as in the retina itself, is inevitably accompanied by a loss of visual function. Thus, the mechanism of intraocular neovascularization, which is designed to combat ischemia, is futile [18]. In the literature, many multicenter studies have been published regarding the effectiveness of anti-VEGF therapy for treatment of macular edema caused by CRVO; in particular, there is considerable usage of intravitreal ranibizumab [19, 20, 21, 22]. However, several issues remain unresolved, such as the proper dose of the drug and the effects of various

comorbid diseases on the outcomes of anti-VEGF therapy. It has been established that hypertensive angiosclerosis increases intravascular pressure, leading to changes in the microcirculatory bed and damage to the blood-retinal

barrier, which is accompanied by increased vascular permeability [23]. Long periods of untreated hypertension lead to disturbances in the microcirculatory bed [24]. These factors should be considered in future studies.

Table 3

Data from ultrasound study

Characteristics	Vmax			Vmin		
	Control	Group 1	Group 2	Control	Group 1	Group 2
OA	32.8±3.2	29.6±0.6	27.4±0.5*	9.2±1.8	6.7±0.2	8.2±0.15*
CRA	10.7±7.9	7.9±0.2	6.1±1.87*	9.1±0.6	7.2±0.4	7.5±0.21
CRV	7.60±0.57	11.5±0.88	10.97±0.32*	3.9±0.15	3.6±0.2	2.9±0.8*

Note: * – significant difference between areas of the macula between the start of treatment and 1 month after starting treatment for both groups 1 and 2; OA – ophthalmic artery; CRA – central retinal artery; CRV – central retinal vein.

Table 4

Data from optical coherence tomography scans of the patients' eyes at different times in the study

Measurement area of the different regions of the macula	Normal area in μm	Admission to the hospital before the start of treatment	Group 1		Group 2	
			After 1 month	After 2 months	After 1 month	After 2 months
Fovea minimum	135–215	687±34	612±29	513±31**	440±25*	390±26**
Fovea	168–239	396±27	640±35*	582±24	452±31*	387±24
Temporal Inner Macula	240–294	586±24	507±41*	445±22	371±27*	334±19
Superior Inner Macula	243–296	320±23	588±33*	473±28**	401±29*	370±23**
Nasal inner Macula	240–297	587±31	547±25	412±19	396±15*	376±24
Inferior Inner macula	246–297	429±22	378±24	301±27	426±22*	384±27**
Temporal outer Macula	199–276	479±31	438±25	343±29	138±17*	136±18
Superior Outer Macula	207–256	529±12	475±29	362±32	346±12*	316±19**
Nasal Outer Macula	198–274	536±24	474±22*	325±37	324±35*	329±28
Inferior Outer Macula	207–256	438±28	378±18	301±26	290±21*	256±22**

Note: * – significant difference between areas of the macula between the start of treatment and 1 month after starting treatment for both groups 1 and 2; ** – significant difference between areas of the macula between 1 and 2 months after starting treatment for both groups 1 and 2.

AngioVue Retina Multi Scans View

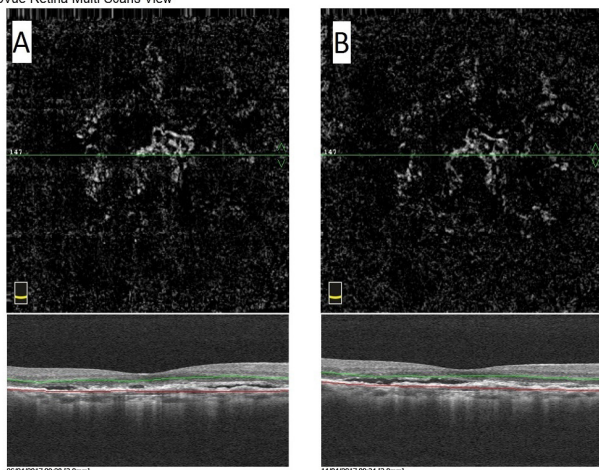


Fig. Optical coherence tomography angiography in a patient with central retinal vein occlusion on day 0 of anti-vascular endothelial growth factor treatment (A) and 8 days after starting anti-vascular endothelial growth factor therapy (B). Note the reduction and destruction of newly formed vessels

Although modern intravitreal injection therapy is invasive, it is currently the only method for safe and effective delivery angiogenesis inhibitors. There are a small number

of ophthalmologic complications and side effects of anti-VEGF therapy; notably, the majority of these are due to the injection of anti-VEGF drugs directly into the eye. This problem may be resolved by using alternative methods for introduction of anti-VEGF agents. Despite its clinical effectiveness, anti-VEGF therapy is not a definitive cure for CRVO; moreover, repetitive intravitreal administration of anti-VEGF agents increases the risk of rare complications, which may have severe negative effects [25].

Conclusions. The use of anti-VEGF therapy significantly reduced retinal edema in the fovea within one month after the start of treatment, compared with edema in the group that did not receive anti-VEGF therapy. This difference persisted during the second month of treatment. These outcomes of anti-VEGF therapy were accompanied by normalization of the hemodynamics of the eye and restoration of the cytokine balances of TGF- α and TGF- β in the lacrimal fluid. Thus, our findings demonstrated the pathophysiological effectiveness of anti-VEGF therapy in patients with CRVO. Combination therapy with an anti-VEGF drug (therapeutic regimen: intravitreal injections of 2 mg aflibercept in 0.05 mL, once per month for five consecutive months, with subsequent reduction to one injection every two months), in addition to standard therapy, may increase treatment efficacy and improve therapeutic outcomes among patients with CRVO.

Disclosures:

The authors declare no conflict of interest.

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