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Research Article

The Choice of Method of Treatment for Macular Edema in Patients Following Retinal Vein Occlusion

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Abstract

A clinical efficacy assessment was performed for the therapy of post-occlusive cystoid macular edema (ME) after intravitreal ranibizumab injections in short and remote terms after the disease onset. It was shown that intravitreal injections of ranibizumab in patients with retinal vein occlusion allow to increase visual acuity and reduce retinal edema and, thus, rehabilitate patients in short terms. Intravitreal injections of vascular endothelial growth factor (VEGF) inhibitors in short terms from the disease onset allow to achieve stabilization of the pathological process with improvement of visual functions and reduction of number of repeated intravitreal injections.

Keywords: *Retinal Vein Occlusion; Macular Edema; VEGF Inhibitors; Ranibizumab*

Introduction

Retinal Vein Occlusion (RVO) is an acute circulatory disorder in the central retinal vein or in its branches that takes one of the leading places among causes of persistent vision loss [1,3]. Despite numerous studies, focused on this disease many questions still remain unclear up to date: its etiology and pathogenesis, diverse clinical course of retinal vein thrombosis. Various risk factors such as arterial hypertension, dyslipidemia and diabetes, make the doctor develop interdisciplinary individual approach to the therapy.

Rogers S., *et al.* conducted analysis based on population studies in the United States, in Europe, Asia and Australia. They found that about 16 million people worldwide suffer from RVO of at least one eye [14].

At present, RVO is divided into two types according to the clinical picture: non-ishemic and ischemic. Non-ischemic type of RVO occurs 4 times more often than ischemic one [14]. In non-ischemic type an incomplete venous obliteration of the vessel lumen occurs that can result in increase in intravascular pressure and transudation of blood components into retinal tissue according to Starling's law. This leads to interstitial edema of the focal tissue and increase in oncotic pressure, which makes adequate retinal blood supply difficult in capillaries and leads to ischemia in the end. Therefore, RVO classified as non-ischemic type, has varying degrees of retinal ischemia [7]. Patients with a non-ischemic type of RVO are more likely to have a recanalization of the vessel lumen with recovery of retinal perfusion. In ischemic

thrombosis total obstruction of the vein lumen occurs, as well as a complete cessation of retinal perfusion and a severe retinal ischemia develops. Moreover, in up to 70 - 90% of cases post-occlusion retinopathy develops with an increase of its symptoms. It should be mentioned that the main verifying method of non-ischemic occlusion from ischemic is fluorescent angiography (FAG).

The main reason of visual loss in central retinal vein thrombosis is macular edema (ME). Realizing of the pathogenesis of ME allows us to understand the mechanism of action of treatment that is being currently used nowadays in treatment of RVO and its complications. ME is an accumulation of the fluid and protein deposits in macular area. It can be focal or diffuse. Morphologically, fluid accumulates in outer and inner nuclear layers of the retina, and Mueller cells edema also occurs [3].

According to literature there are 2 types of post-thrombotic macular edema - vasogenic and cytotoxic [6]. In vasogenic ME the tissue is not necrotized, there is an increase in endothelial perfusion with transudation of the fluid into extracellular space. In cytotoxic ME the situation is opposite: firstly develops intracellular edema with tissue necrosis and after cells' membranes are destroyed, edema occurs in extracellular space. Cytotoxic or ischemic ME is able to be spontaneously resorbed.

ME is clearly diagnosed by means of optical coherent tomography (OCT), and in case of significant prominence it is visible during standard biomicroscopy [5]. Treatment of RVO and its consequences requires significant means and appears to be a serious social and economical problem. Conventionally, all methods of treatment of RVO can be subdivided into two groups: struggling with the main cause of clinical manifestations - vein occlusion and exposure directly on the main symptom - ME. The first group contains all variants of thrombolytic therapy, the second one - is treatment with angiogenesis inhibitors, steroids and retinal laser coagulation [3]. The "gold standard" for the treatment of post-occlusion retinopathy is laser coagulation in ischemic zones and closure of ischemic sites from pathological chain of VEGF hypersecretion.

Earlier ME developed after RVO was treated by laser coagulation of macular area performed by as a "horseshoe" or "grid". However, macula and especially fovea remain "restricted areas" for laser coagulation due to the danger of permanent central vision loss as directly from the coagulation of neuroepithelium, as due to the progression of retinal pigment epithelium atrophy around the burn area. Results of Multicenter Central Vein Occlusion Study published in 1995 showed that argon laser coagulation in central zone is not effective in the treatment of ME after RVO [8]. Greater effectiveness in the treatment of post thrombotic ME compared to laser-coagulation has topical administration of corticosteroids. But this method has a number of side effects such as development of cataract and secondary steroid glaucoma [4,9,10].

During RVO functional and structural changes in the retina, including a decreased blood flow in retinal capillaries, lead to hypoxia, which itself increases the activity of vascular endothelial growth factor (VEGF). VEGF expression is predominantly carried out by pigment epithelial cells, endothelial cells and Mueller cells [15]. VEGF breaks retinal vascular barrier, stimulates the growth of vascular endothelium and arises vascular permeability [11]. An increased concentration of this factor in the intraocular fluid was found in patients with RVO, and it was also noted a correlation between VEGF concentration and severity of ocular edema [12,13]. Because of the leading role of hyperproduction of VEGF in the development of ME and neovascularization in post-occlusal retinopathy, antiangiogenic therapy is a pathogenetically oriented method of treatment [1].

Anti-VEGF agent Ranibizumab (Lucentis®; Novartis Pharma) is currently widely used for the treatment of post-thrombotic cystic ME. Ranibizumab is approved for the treatment of neovascular (wet) forms of age-related macular degeneration and diabetic ME. It is a fragment of mouse monoclonal antibodies. Since 2007, two major randomized multicenter research works -BRAVO and CRUISE were devoted to the study of the effectiveness and safety of the application of ranibizumab in treatment of macular edema accompanying RVO. Research results show significant improvements in visual acuity in patients after ranibizumab intravitreal injection [2]. Ranibizumab was

registered in Russia in 2008 and since 2012 it is widely used in the treatment of post-thrombotic complications. However, despite existing schemes of treatment of patients with post occlusal cystic ME, it is not always possible to achieve a stable remission or high visual acuity. Moreover, it remains unclear when it is necessary to begin treatment with anti-VEGF drugs and is it worth using laser coagulation of the retina. Duration of required treatment with angiogenesis inhibitors, intervals between treatment and number of injections are needed to be studied.

Purpose of the Study

The purpose of following work is to evaluate the clinical effectiveness of treatment of post occlusal cystic macular edema using intravitreal administration of anti-VEGF drug ranibizumab in early and long-term periods after the disease onset.

Material and Methods

Characteristics of clinical material

A total of 80 patients with cystic ME developed after either central retinal vein occlusion (CRVO) or its branches (BRVO) were examined, including 36 men (45%) and 44 women (55%). Ischemic thrombosis with the calcification of zones of ischemia along venous branches and on the periphery was diagnosed in 20 patients (25%), 60 patients (75%) had non-ischemic type of RVO. All patients underwent standard ophthalmic examination and treatment in State Clinical Hospital named after S.P. Botkin Branch 1 in 2013 - 2015. The age of patients at the time of the study ranged from 46 to 85 years (average age was 67.9 ± 8.6 years). As for localization, CRVO was revealed in 29 patients (36.2%), thrombosis of the upper temporal branch - in 38 patients (47.5%), thrombosis of the inferior temporal branch - in 12 patients (15%) and one patient had a thrombosis of the macular branch of central retinal vein (1.3%). The most common concomitant diseases were: arterial hypertension (82.5%), atherosclerosis (67.5%) and ischemic heart disease (67.5%). Eight patients (10%) had second type of the diabetes. Depending on the received treatment all patients were divided into two groups.

The 1st group included 49 people (49 eyes), 20 of them were men (40.1%) and 29 women (59.1%). Group 1 underwent standard conservative treatment with dehydration drugs, steroids, vascular protectors, antiplatelet agents, antioxidants, thrombolytics. Terms of the moment of visual disorders onset and the time of admission to hospital ranged from 4 to 45 days (average time - 20.6 ± 12.5 days). Visual acuity before treatment ranged from 0.03 to 0.5 (an average of 0.17). Ischemic type of the thrombosis was diagnosed in 7 patients, non-ischemic one in 42 patients.

The 2nd group included 31 people (31 eyes), 16 of them were men (51.6%) and 15 women (48.4%). In addition to standard methods of treatment patients of this group had topical administration of an anti-VEGF drug ranibizumab ("Lucentis") in the vitreous body in an amount of 0.5 mg once in 1 or 2 months. Ranibizumab was injected through the flat part of the ciliary body in the operating room. Depending on start of treatment with VEGF inhibitors the 2nd group of patients was divided into 2 subgroups: 2a subgroup included 16 people (16 eyes) received ranibizumab injections in early terms from the disease onset (the first 3 - 4 weeks) and 2b subgroup with 15 people (15 eyes) received a later treatment with VEGF inhibitors (from 4 weeks up to 95 days), which was associated with late patients' visit to the ophthalmologist. Repeated treatment with anti-VEGF agent was held if persistence or amplification of edema in combination with a visual loss was diagnosed during dynamic observation. The duration of the disease from the appearing of disorders to the admission to hospital ranged from 2 to 95 days, averaging 22.5 ± 11.6 days. Visual acuity before treatment ranged from 0.01 to 0.3 (an average of 0.12). The 2nd group of patients with ischemic thrombosis was observed in 13 people, with non-ischemic type it was diagnosed in 18 people.

Examination methods included visometry, direct and indirect ophthalmoscopy, contactless tonometry of intraocular pressure, gonioscopy, Humphrey computer perimetry, optical coherent tomography (RTVue-100, version 4.0 "Optovue Inc.", USA), fundus photography and fluorescence angiography (FF 450 Plus (Carl Zeiss, Germany)). The following standard scanning protocols were fulfilled when mak-

ing OCT: Cross Line; 3D Macular and 3D Disc; E -MM5. Thickness and volume of outer and inner layers of the retina over all quadrants were evaluated. OCT scans in the first group were taken before and after treatment, 1 month, 2 months and six months after treatment. OCT scans in the second group were taken before intravitreal injection, 1 - 2 weeks after injection, 1 month later and then by necessity. We also evaluated follow-up scans six months later. If there were indications, such as retinal ischemic zones, leakage of dye in late phases and zones with detected retinal neovascularization by FAG, patients of both groups underwent laser coagulation of that segment of the peripheral retina, which corresponded to the area of the affected vein. If needed, further full pan-retinal laser coagulation combined with a "modified grid'' was performed. Statistical processing of obtained results were performed by using Microsoft Excel 2010 and software package of Statistic analysis - STATISTICA7.

Results and Discussion

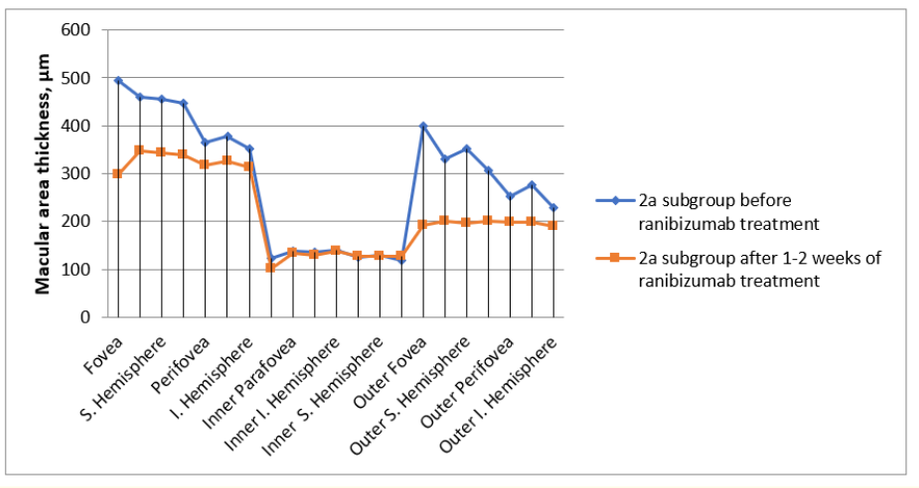
Data in table 1 show that patients with early injections of anti-VEGF agents (2a subgroup) had a significant increase in visual acuity - almost twice and after 1 - 2 weeks of ranibizumab injection it was 0,24 ± 0,05 (initial visual acuity was 0,13 ± 0,05; p = 0,003). The 2b subgroup also had an increase in visual acuity from 0,11 ± 0,07 before treatment to 0,15 ± 0,09 during first 2 weeks after injection of angiogenesis inhibitors, but this improvement was not statistically significant (p > 0,05). Patients with conservative treatment didn't have a significant increase in visual functions (p > 0,05).

Observation period	The 1st group of patients, Visus	The 2nd group of patients, Visus	
	Conservative treatment n = 49	2a subgroup (early intravitreal ranibizumab injections) n = 16	2b subgroup (late intravitreal ranibizumab injections) n = 15
Before treatment	0,08 ± 0,03	0,13 ± 0,05*	0,11 ± 0,07
After treatment (in 1 - 2 weeks)	0,09 ± 0,02	0,24 ± 0,05*	0,15 ± 0,09

Table 1: *Dynamics of changes in visual acuity during conservative treatment and intravitreal injections of ranibizumab depending on terms of treatment*

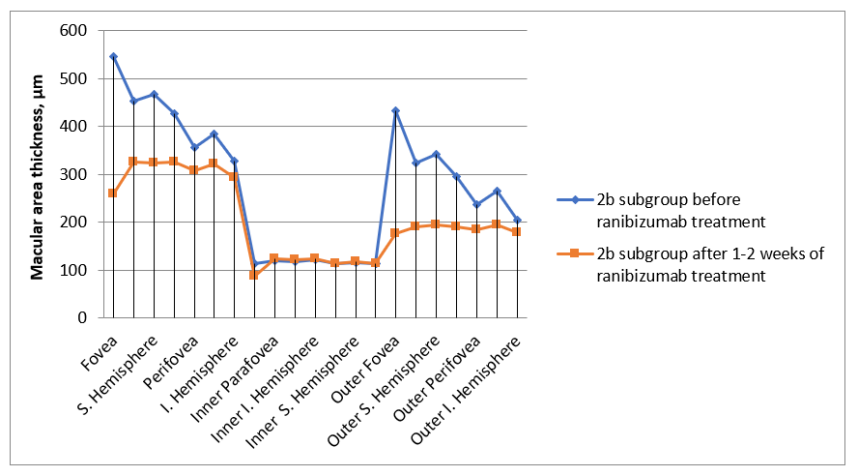
Comment: **: The difference between the data is statistically significant (p = 0,003).*

Graph 1 shows that early treatment with angiogenesis inhibitors from the onset of the disease improves a morphological state of macular area of the retina: edema reduction in all squares mainly due to a decrease in the thickness of outer layers of the retina.



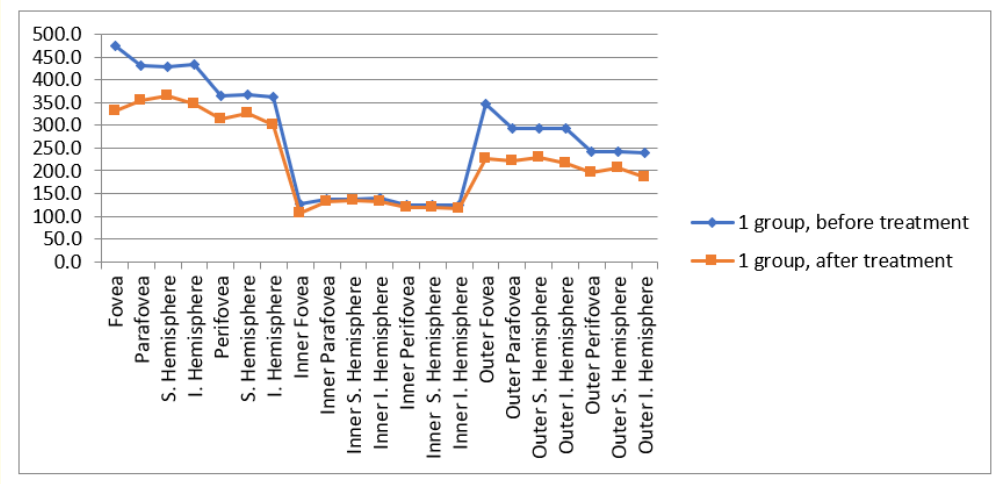
Graph 1: *Changes of thickness in macular area after 1 - 2 weeks of intravitreal ranibizumab injections in the 2a subgroup.*

It were also evaluated changes in the morphological state of the retina in patients of the 2b subgroup. As a result of treatment after 1 - 2 weeks, an improvement in the morphological state of macular area of the retina was also observed due to a decrease in the thickness of outer layers of the retina (Graph 2).



Graph 2: *Changes of thickness in macular area after 1 - 2 weeks of intravitreal ranibizumab injections in the 2b subgroup.*

A decrease in ME was also observed in patients of the 1st group, however, these changes were not so significant compared with patients of the 2nd group (Graph 3).



Graph 3: *Changes of thickness in macular area after 1 - 2 weeks of conservative treatment in the 1st group (µm).*

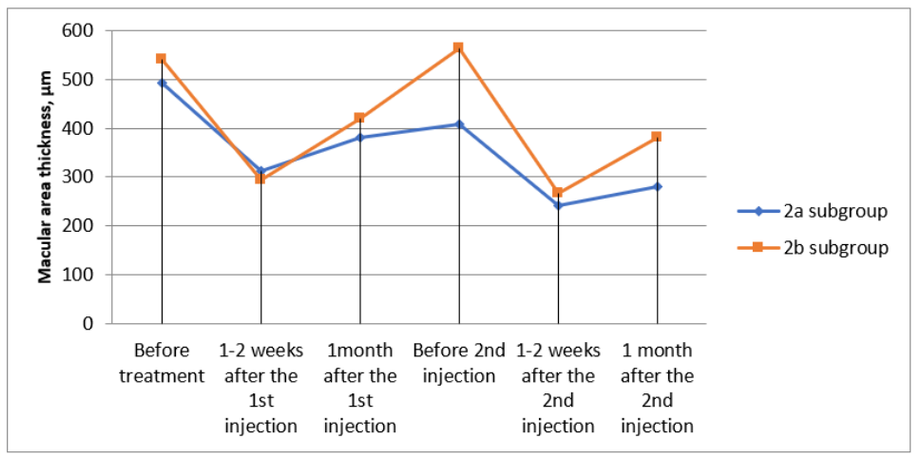
Data on the morphological state of the retina before and after treatment are presented in table 2.

Macular area thickness, µm	1st group Conservative treatment (M ± m)	2nd group				
		2a subgroup (early intravitreal ranibizumab injections) (M ± m)		2b subgroup (late intravitreal ranibizumab injections) (M ± m)		
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Fovea	474,2 ± 158,1*	332,9 ± 86,5* (p = 0,02)	494,8 ± 103*	313,8 ± 52* (p = 0,04)	542,3 ± 118,8*	295,7 ± 116,2* (p = 0,0008)
Paravofea	431,3 ± 110*	355,3 ± 52,7* (p = 0,005)	460,5 ± 87,5*	347,5 ± 19* (p = 0,027)	457,9 ± 73*	331,1 ± 50,2* (p = 0,0006)
Perifovea	365,2 ± 96,6*	314 ± 37,4* (p = 0,02)	365 ± 57*	319,5 ± 9,5* (p = 0,027)	365,8 ± 49,8*	306,1 ± 29,9* (p = 0,001)
Inner fovea	125,8 ± 23,3	105,7 ± 15,2 (p = 0,09)	123,5 ± 16,4*	101 ± 5* (p = 0,027)	117,3 ± 27,4*	86,8 ± 20* (p = 0,003)
Inner paravofea	138,2 ± 15,6	133,1 ± 18,3 (p = 0,23)	137,5 ± 12	135,8 ± 13,7 (p = 0,91)	121,5 ± 15,9	123,4 ± 15,8
Inner perifovea	124,2 ± 17,3	118,4 ± 12,7 (p = 0,21)	124,5 ± 7,7	124 ± 9 (p = 0,85)	115,1 ± 12,6	116,5 ± 8,8 (p = 0,95)
Outer fovea	348,2 ± 151,5*	227,1 ± 90,2* (p = 0,016)	399,16 ± 104*	213 ± 51* (p = 0,027)	424,9 ± 115*	208,9 ± 107* (p = 0,001)
Outer parafovea	293,1 ± 110,5*	222,2 ± 62,7* (p = 0,012)	329,8 ± 70*	211,6 ± 22,7* (p = 0,027)	336,2 ± 77,1*	207,8 ± 46,5* (p = 0,0006)
Outer perifovea	241 ± 88,5*	195,6 ± 39,6* (p = 0,009)	252,8 ± 56,7*	195,6 ± 8,5* (p = 0,027)	250,6 ± 52,7*	189,7 ± 28,4* (p = 0,001)

Table 2: *Changes of morphological state of macular area before and after treatment in patients of both groups.*

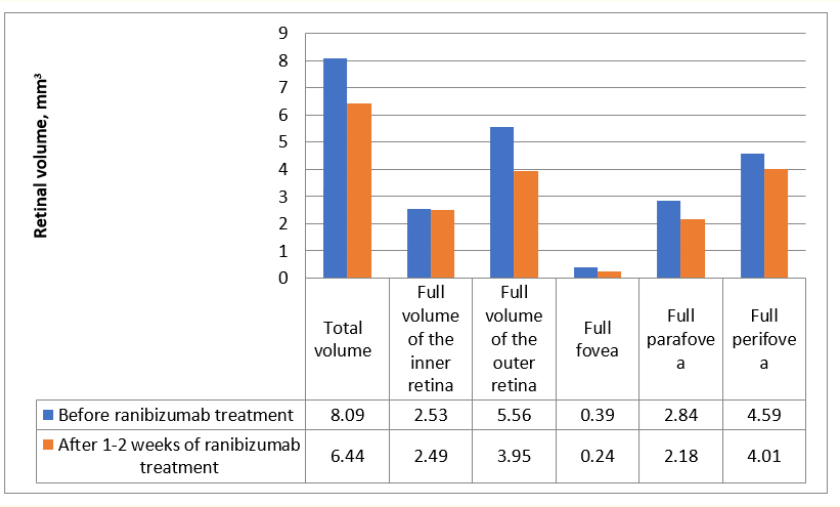
Comment: **: The difference between the data is statistically significant (p < 0,05).*

Data of table 2 show that treatment of post occlusive ME results in an improvement of morphological state of macular area predominantly by outer layers of the retina. Further observation revealed that macular thickness quickly returned to the initial state after treatment with ranibizumab in the 2b subgroup of patients over time, while in the 2a subgroup the effect remained longer and a slight increase in the macular thickness was observed a month after treatment. After 2 injections of ranibizumab in 10 (62.5%) patients of the 2a subgroup the normal macular thickness remained for a long time and these patients did not need re-injection with anti-VEGF drug. The dynamics of changes in foveal thickness in patients of the 2nd group is shown in graph 4.



Graph 4: *Dynamics of changes of an average thickness in macular area in patients of the 2nd group.*

The total volume of macula in the 2a subgroup (Graph 5) decreased on average from 8.09 ± 1.06 mm^3 before using ranibizumab to 6.44 ± 0.17 mm^3 1 - 2 weeks after treatment.



Graph 5: *Retinal volume change before and after treatment in subgroup 2a.*

The change in retinal volume in all groups before and after treatment is presented in table 3.

Retinal volume, mm^3	1st group (M ± m)		2nd group			
		2a subgroup (M ± m)		2b subgroup (M ± m)		
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Total V	7,87 ± 1,96	6,79 ± 1,83 p = 0,007	8,09 ± 1,06	6,44 ± 0,17 *	7,90 ± 1,12	6,16 ± 0,67 **
Full V of the inner retina	2,6 ± 0,34	2,49 ± 0,22 p = 0,5	2,53 ± 0,16	2,49 ± 0,16 *	2,30 ± 0,26	2,31 ± 0,20 p = 0,17
Full V of the outer retina	5,26 ± 1,87	4,3 ± 1,73 **	5,56 ± 1,14	3,95 ± 0,25 *	5,60 ± 1,18	3,85 ± 0,63 **
Full fovea	0,37 ± 0,12	0,26 ± 0,06 p = 0,02	0,39 ± 0,08	0,25 ± 0,04 *	0,43 ± 0,09	0,23 ± 0,09 **
Full parafovea	2,71 ± 0,69	2,23 ± 0,33 **	2,84 ± 0,47	2,18 ± 0,12 *	2,88 ± 0,46	2,08 ± 0,32 **
Full perifovea	4,78 ± 1,25	4,29 ± 1,46 p = 0,11	4,59 ± 0,72	4,01 ± 0,12 *	4,60 ± 0,62	3,85 ± 0,38 **

Table 3: *Retinal volume changes before and after treatment in all groups.*

Comment: **p = 0.027; **p = 0.005.*

The data in table 3 show that early treatment with angiogenesis inhibitors (subgroup 2a) results in a significant decrease in all areas of the macular volume. After the treatment a decrease in the retinal volume was also registered in patients of groups 1 and 2b, however, the treatment does not affect the volume of the inner retinal layers ($p > 0.05$).

With further monthly follow-up, 4 patients out of 16 from subgroup 2a showed stabilization of the process and no additional injections of ranibizumab were required. The remaining 12 patients of subgroup 2a required additional injections of angiogenesis inhibitors to stabilize the process. Half of patients of subgroup 2a (8 patients) underwent laser retinal coagulation because of the presence of ischemic zones according to the FAG. On average, these patients had from 1 to 3 injections with ranibizumab, averaging 2 injections. It was noted that treatment with angiogenesis inhibitors of severe ischemic thrombosis with initially low visual acuity does not improve the condition and further injections of ranibizumab should not be carried out. The management of such patients includes one intravitreal injection and further course of laser treatment to prevent the neovascularization development.

Long-term results were taken into account 6 months after the treatment. Stabilization of the thickness and volume of the retina in the macular area was noted in 10 (62.5%) patients of subgroup 2a, which made it possible to transfer them to dynamic observation.

Despite the reduction of edema, 10 patients of subgroup 2b had the same visual acuity which remained low that can be explained by significant degenerative changes in the retinal tissue and duration of the disease. According to OCT in such patients, cystic maculopathy is already determined, which is difficult to treat. Anti-VEGF therapy ranged from 1 to 5 injections, averaging 3 injections. Almost all patients of subgroup 2b (14 out of 15 people) required laser retinal coagulation to stabilize the process. One patient needed 5 injections of ranibizumab and 2 laser treatments for stabilization.

Group 1 in addition to conservative drug treatment, also underwent laser coagulation of the retina in case of presence of ischemic zones, dyeing of the walls of veins in late phases, and leakage of the dye determined by the FAG. A total of 42 patients of the 1st group underwent laser coagulation. 7 patients of the 1st group showed a regression of ME after the conservative treatment and did not require additional treatment. This was due to the presence of non-ischemic thrombosis of the branch of central retinal vein in these patients with low ME, which is easily amenable to drug therapy, as well as, early treatment at the hospital.

Long-term results are presented in table 4.

	1st group (M ± m)	2nd group	
		2a subgroup (M ± m)	2b subgroup (M ± m)
Visual acuity	0,1 ± 0,05*	0,3 ± 0,05* p = 0,03	0,15 ± 0,09
Retinal thickness in fovea, μm	341,7 ± 74,5*	280,8 ± 47,2* p = 0,001	292,4 ± 80,4* p = 0,01
Full volume of fovea	0,27 ± 0,07	0,24 ± 0,05	0,25 ± 0,09

Table 4: *Long-term treatment results (after six months) in patients of all groups.*
Comment*: *: Differences between groups are statistically significant (p < 0.05).*

Clinical Case

Patient A., 66 years old, complained of a sharp decrease in vision of the left eye after the episode of high blood pressure. He was hospitalized for urgent reasons to a hospital with a diagnosis of thrombosis of the upper temporal branch of central retinal vein. Best cor-

rected visual acuity (BCVA) at admission was 0.2. In the hospital he was administered the standard medication including thrombolytic, angioprotective, antiplatelet therapy, vitamin therapy, physiotherapy, as well as, retrobulbarly injection of the drug "Diprospan". BCVA at discharge was 0.3. BCVA of the left eye was 0.3 one month after discharge, but OCT showed cystic ME (up to 537 μm) (Figure 1). Ophthalmoscopy revealed plethora and tortuosity of veins, hemorrhage along upper branches of the central retinal vein, hemorrhage and signs of ME (Figure 2).

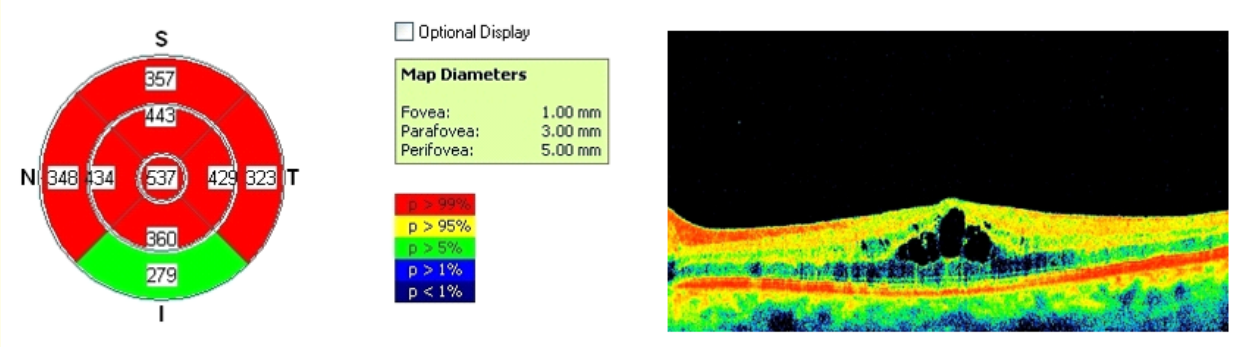


Figure 1: *Cystic macular edema.*

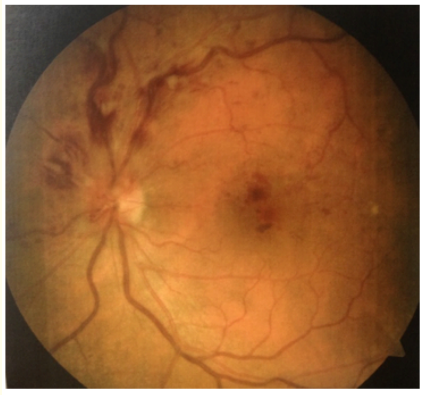


Figure 2: *Picture of the eye fundus of the patient before treatment with angiogenesis inhibitors.*

FAG showed narrowed arteries and wide veins with uneven caliber, hypofluorescent zones, hemorrhages along upper branches of the central retinal vein. The capillary network above fovea was enlarged and it was noted a leakage of fluorescein from altered vessels into the late phases.

The patient was recommended intravitreal administration of the drug ranibizumab. One month after the injection, visual acuity increased by 0.1 and BCVA reached 0.4. An ophthalmoscopic improvement in venous blood flow and a decrease in hemorrhage were noted (Figure 3).

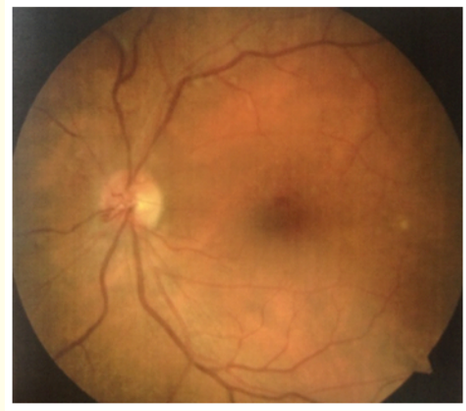


Figure 3: *Picture of the eye fundus one month after ranibizumab administration.*

According to OCT data (Figure 4), a decrease in retinal thickness in the fovea before and after treatment was noted (from 537 μm to 251 μm). The decrease in peripapillary retinal thickness was also determined (Figure 5).

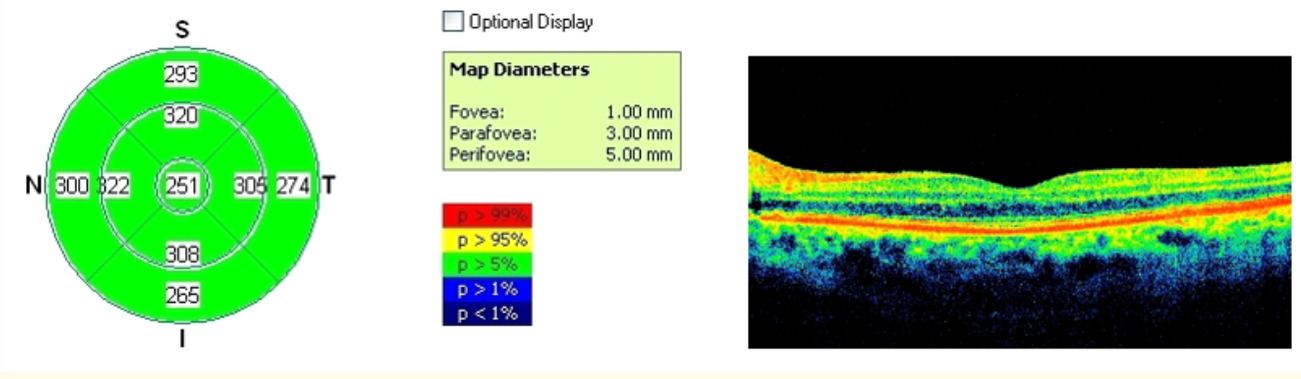


Figure 4: *OCT scans: reduction of ME one month after ranibizumab administration.*

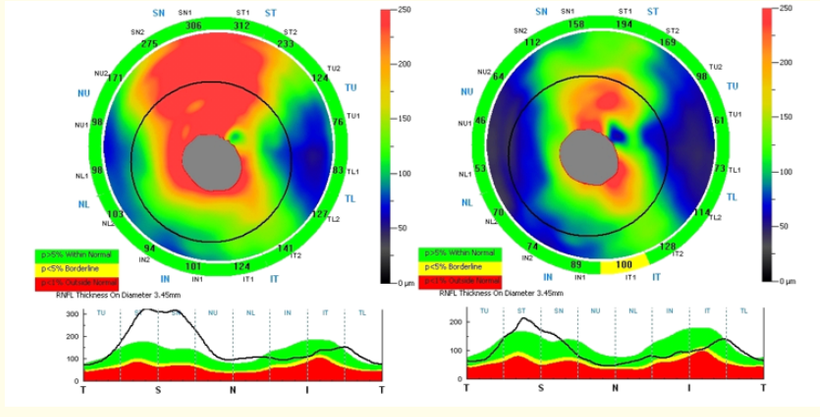


Figure 5: *OCT scans: peripapillary retinal thickness before treatment (left) and one month after ranibizumab administration (right).*

Further observation (2 months after the treatment) showed that BCVA reached 0,5. Long-term results were taken into account 6 and 12 months after the treatment. According to OCT ME did not increase and the patient did not need additional injections of anti-VEGF drugs (Figure 6).

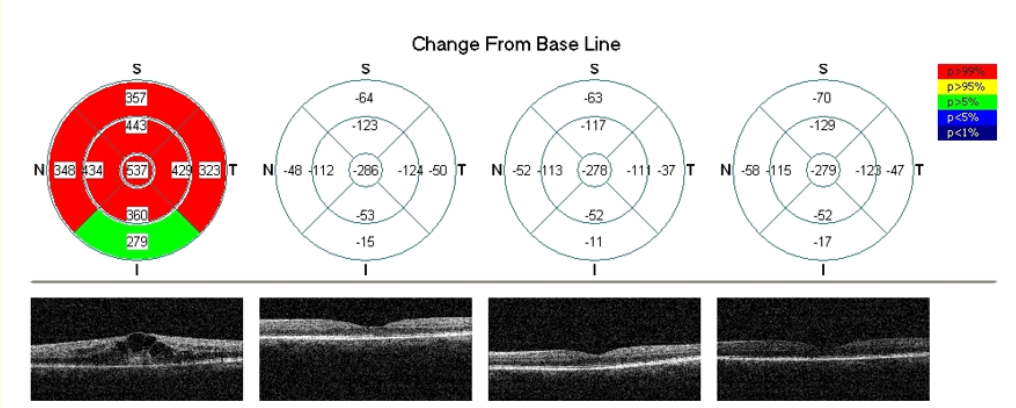


Figure 6: *OCT scans: long-term results of treatment with angiogenesis inhibitors.*

Conclusion

Thus, the intravitreal ranibizumab administration in patients with RVO allows to increase visual acuity and reduce retinal edema, and, thereby rehabilitate patients as soon as possible. The introduction of drugs that inhibit the vascular endothelial growth factor in early stages of the disease onset allows to stabilize the pathological process with maintaining or improving visual functions and reducing the frequency of repeated intravitreal injections.

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