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ANTI-VEGF DRUGS IN THE TREATMENT OF DIABETIC MACULAR OEDEMA


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ДИАБЕТИК МАКУЛАР ШИШИНИ ДАВОЛАШДА АНТИ-VEGF ПРЕПАРАТЛАРИ

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АНТИ-VEGF ПРЕПАРАТЫ В ЛЕЧЕНИИ ДИАБЕТИЧЕСКОГО МАКУЛЯРНОГО ОТЕКА

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Резюме. *Диабетик макула шиши (ДМШ) диабет билан оғриган беморларда кўриш кескинлигининг пасайишининг асосий сабабларидан биридир. Қон томир эндотелиал ўсиш омили ингибиторларини интравитреал киритилиши (анти-VEGF терапияси) ДМШ учун янги даволаш усули сифатида таклиф қилинган. Ушбу шарҳда биз ДМШ билан оғриган беморларда VEGF ингибиторлари бўйича рандомизацияланган клиник тадқиқотлар натижаларини умумлаштирдик. Натижалар шуни кўрсатадики, ўрганилган барча ингибиторлар (ранибизумаб, бевасизумаб, пегаптаниб ва афлиберсепт) монотерапия сифатида ҳам, лазер билан даволаш билан биргаликда фойдаланилганда ДМШ билан оғриган беморларда ретинанинг қалинлигини камайтиради ва кўриш кескинлигини оширади. Келажакдаги тадқиқотлар VEGFга қарши терапиянинг оптимал давомийлигини ва унинг ДМШ самарадорлигини башорат қилувчиларни аниқлаши керак.*

Калит сўзлар: *диабетик макула шиши, қон томир эндотелиал ўсиш омили, ранибизумаб, бевасизумаб, пегаптаниб, афлибертсепт.*

Abstract. *Diabetic macular oedema (DMO) is one of the main causes of decreased visual acuity in diabetic patients. Intravitreal injection of vascular endothelial growth factor inhibitors (anti-VEGF therapy) has been proposed as a novel treatment for DMO. In this review, we summarised the results of randomised clinical trials of VEGF inhibitors in patients with DMO. The results indicate that all inhibitors studied (ranibizumab, bevacizumab, pegaptanib and aflibercept) reduce retinal thickness and improve visual acuity in patients with DMO when used both as monotherapy and in combination with laser treatment. Future studies should determine the optimal duration of anti-VEGF therapy and predictors of its efficacy in DMO.*

Keywords: *diabetic macular oedema, vascular endothelial growth factor, ranibizumab, bevacizumab, pegaptanib, aflibercept.*

Introduction. Diabetic macular oedema (DMO) is one of the main causes of reduced visual acuity in patients with diabetes mellitus (DM). According to generalised data, DME develops in 7% of DM patients [1, 2]. The main method of DMO treatment is laser photocoagulation of the retina (LPC). Conservative treatment includes intravitreal application of glucocorticoids in the form of injections or implants. Both methods are not without complications and not in all cases lead to resolution of AMD and improvement of visual acuity [3, 4]. In recent years, a new method of DME treatment based on local inhibition of vascular endothelium growth factor (VEGF: vascular endothelium growth factor) has entered clinical practice. In this review we have summa-

rised the results of clinical studies of intravitreal use of anti-VEGF drugs in patients with DMO.

Rationale for the use of anti-VEGF therapy in DMO. The UBOB family in humans includes the factors UBOB-L, -B, -C, -B, and placental growth factor (P1OB). Currently, the most studied is UBOB-L, which is expressed in many stromal and parenchymatous cells and circulates in the bloodstream. Increased levels of UBOB-A in blood plasma and urine have been recorded in patients with diabetes with different severity of angiopathies [5,8].

Due to the haematoretinal barrier, the content of UBOB in the retina depends mainly on the local formation of the factor. UBOB producers in the retina are pigment epithelial cells, astrocytes, Müller cells, endotheliocytes, pericytes and ganglion cells [9]. Acting in an auto- and paracrine manner, UBOB selectively stimulates proliferation and migration of endothelial cells and their precursors, increases vascular permeability, and promotes vasodilation through increased production of nitric oxide (N0). In recent years it has been shown that UBOB ensures survival and structural integrity of retinal pigment epithelium [10], has anti-neurodegenerative effect and prevents apoptosis of retinal cells under conditions of ischaemia-reperfusion [11]. The molecular isoforms of UBOB (UBOB121, UBOB145, UBOB165, UBOB189, UBOB206) are products of a single gene formed as a result of alternative splicing of mRNA. The polymorphic positions -634, +936, -2578 have been identified in the UEOE gene; the correlations of nucleotide variants in these positions with the risk of developing diabetic retinopathy (DR) in different ethnic groups have been found. According to our data [6], combinations of homozygous variants of UEOE 2578SS, 936SS, genes of interleukins and matrix metalloproteinases: 1b4 590SS, 1b6 174OO, P10 592SS and 1082AA, GSA 238OO, 308OO and 863SS, MMP-2 1306SS and MMP-9 1562SS are characteristic for type 2 diabetes (DM2) patients. Genotype features determine an unstable balance of angiogenic and antiangiogenic factors and may be one of the causes of complex disorders of angiogenesis regulation in diabetes [8].

At present, hyperproduction of UBOB is attributed a leading role in the increase of retinal vascular permeability, development of macular oedema and retinal neovascularisation in DM. Hypoxia or retinal ischaemia is a powerful trigger for increased synthesis of UbOb and its receptors in DR. In addition, the production of UBOB in retinal cells is triggered by hyperglycaemia and associated biochemical abnormalities: accumulation of late glycation products, endoplasmic reticulum stress, and oxidative stress.

More than 10 years ago, it was shown in experimental models of DM that neutralisation of UBOB can block the increase in the permeability of the haematoretinal barrier. This prompted the development of UBOB inhibitors suitable for intraocular administration and clinical trials of their efficacy in the treatment of DMO. The differences between VEGF inhibitors concern the technology of production, structure and specificity against different isoforms of the regulator.

The mechanism of action of anti-VEGF drugs is realised through direct binding to the growth factor (ranibizumab, bevacizumab, pegaptanib), inhibition of VEGF gene expression (bevaciranib) or its receptor (aflibercept). Ranibizumab, bevacizumab, pegaptanib and aflibercept are currently in phase II-III clinical trials in DME.

Ranibizumab, a VEGF inhibitor, was specifically developed for use in ophthalmology. In 2006, the drug was approved by the Food and Drug Administration (FDA) for the treatment of non-ovascular (wet) age-related macular degeneration. Currently, it is the only anti-VEGF drug registered for the treatment of AMD in Russia. The efficacy of ranibizumab in the treatment of macular edema has been proven in a series of randomised multicentre studies performed according to GCP standards. The phase II RESOLVE (Safety and efficacy of ranibizumab in diabetic macular edema) study investigated the efficacy and safety of intravitreal injections of ranibizumab in 151 patients with AMD. The study protocol included monthly injections of ranibizumab at a starting dose of 0.3 or 0.5 mg or mock intravitreal injections (placebo). Treatment efficacy was assessed by changes in maximum corrected visual acuity and retinal thickness in the macular zone according to optical coherence tomography.

The study protocol included 3 monthly injections, after which the treatment could be stopped or continued depending on the achieved result. One month after the first injection, depending on the dynamics of retinal thickness, the dose could be increased to 0.6 or 1 mg. On average, 10.2 injections of ranibizumab and 8.9 placebo injections were performed. The study showed high

Aflibercept VEGF Trap-Eye Regeneron Pharmaceutical/ Sanofi-Aventis Recombinant antibody-like protein obtained by fusion of the supramembrane portion of the VEGF receptor (as antigen-binding fragment, Fab) and IgG (as Fc fragment) Binds VEGF-A, VEGF-B and PlGF

Bevasiranib - OPKO Small interfering RNA Inhibits transcription of UBOB genes Efficacy of ranibizumab in the treatment of DMO. Improvement of visual acuity on the background of the drug administration was noted one month after the first injection, the effect increased with the continuation of therapy. After 12 months of treatment in the group of ranibizumab visual acuity improved by 10.3 letters on average, in the placebo group deterioration of the index was observed (-1.4 letters, $p<0.0001$). Retinal thickness decreased by an average of 194 μm on the

background of active treatment and by 48 μm with simulated injections of the drug (p<0.0001). Improvement of visual acuity by 10 or more letters was observed in 60.8% of patients receiving ranibizumab and in 18.4% of patients in the placebo group (p<0.0001). The number of patients in whom therapy was discontinued early was similar in the ranibizumab and placebo groups (36.3 and 40.8%, respectively). Serious ocular side effects (retinal detachment, vitreous haemorrhage, retinal artery occlusion, endophthalmitis) were observed in 3% of patients in the ranibizumab group and in 2% of patients in the placebo group. The incidence of systemic serious adverse reactions (arterial hypertension, arterial thromboembolism, etc.) was 13.7% and 16.3%, respectively [2,6].

The READ-2 (Primary end point (six months) results of the ranibizumab for edema of the mAcula in diabetes) and RESTORE (Ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema) studies showed the advantages of ranibizumab therapy and its combination with laser versus traditional laser therapy. The READ-2 phase II study included 126 patients with DME. Patients in group 1 received 0.5 mg of ranibizumab at the beginning of the study and after 1, 3 and 5 months, group 2 received focal LCS at the beginning of the study and (if indicated) after 3 months, group 3 used a combination of 0.5 mg ranibizumab and focal LCS. The improvement in visual acuity and reduction in retinal thickness at 6 and 24 months after the start of treatment was greatest in the ranibizumab group [7]. Some patients who participated in READ-2 continued treatment with ranibizumab (0.5 mg monthly) for another year if the retinal thickness in the central fossa was 250 μm or more. Further improvement in visual acuity (+10.3 letters at the end of year 3 compared to +7.2 letters at the end of year 2, p=0.009) and reduction of retinal thickness in the macular zone (282 μm at the end of year 3, 352 μm at the end of year 2, p=0.006) were observed [9]. The READ-3 trial is currently underway to study the safety and efficacy of two doses of ranibizumab (0.5 and 2 mg) in DMO.

The phase III RESTORE study enrolled 345 patients with DM1 and DM2 who were randomised into three groups: 1) ranibizumab and mock LCS; 2) ranibizumab and LCS; and 3) mock injections of ranibizumab and LCS. By the end of the study in the groups of patients receiving ranibizumab, there was an increase in visual acuity (group 1: +6.1 letters, group 2: +5.9 letters), in the LCS group visual acuity did not change significantly (+0.8 letters). When analysing individual parameters, a significant improvement in visual acuity (>15 letters) was found in 22.6% of patients treated with ranibizumab and in 8.2% of patients after LCS. The reduction in retinal thickness in the macular zone was more pronounced with ranibizumab compared to LCS as the sole treatment (p<0.001). The study showed no increased risk of cardiovascular and cerebrovascular complications, cases of endophthalmitis; increased intraocular pressure was noted in two patients treated with ranibizumab [3,10].

The largest project that confirmed the efficacy of ranibizumab in the treatment of DMO was a multicentre study of the Diabetic Retinopathy Clinical Research Network (DRCR.net). The study included 691 patients (854 eyes). During randomisation, patients were divided into 4 groups:

1) placebo injection + urgent LCS (3-10 days after injection);

2) ranibizumab 0.5 mg + urgent LCS;

3) ranibizumab 0.5 mg + delayed LCS for 24 weeks or more;

4) triamcinolone 4 mg + urgent LCS.

Ranibizumab was administered monthly (injections could be skipped in case of positive dynamics of visual acuity and retinal thickness), triamcinolone - once in 16 weeks. One year later, the best results in terms of visual acuity change were achieved in the groups of patients receiving ranibizumab (+9 letters) compared to Group 1 (+3 letters, p<0.001). The gain in visual acuity on the background of tri-amcinolone did not significantly differ from LCS (+4 letters, p=0.31). By the end of the second year of follow-up, the positive dynamics of visual acuity was maintained in the ranibizumab groups (+7 letters when combined with immediate LCS, p=0.01; + 10 letters when combined with delayed LCS, p<0.001). The study recorded 3 cases of endophthalmitis in the groups of patients receiving ranibizumab (0.8%). Increase of intraocular pressure was recorded in 11% of cases in the group of ranibizumab, in 7% in control (LCS) and in 50% of cases on triamcinolone background. Cataract surgery was required more often in the triamcinolone group than in other patient groups (59% and 14%) [11].

The phase III CRUISE (CRVO - Ranibizumab for Macular Edema following Central Retinal Vein Occlusion) study investigated the efficacy and safety of intravitreal injections of ranibizumab in 392 patients with macular edema and central retinal vein occlusion. The study protocol involved monthly intravitreal injections of 0.3 or 0.5 mg of ranibizumab or mock injections (placebo group) for six months. By the end of the study, a significant improvement in visual acuity was observed in patients receiving 0.3 mg (+12.7 letters) and 0.5 mg (+14.9 letters) ranibizumab, but not in the placebo group (+0.8 letters; differences between groups: p < 0.0001). Visual acuity improved by 15 or more letters in 46.2% and in 47.7% of patients receiving ranibizumab at doses of 0.3 and 0.5 mg, and in 16.9% of the placebo group. Retinal thickness in the macular zone decreased by 434 μm on the background of 0.3 mg ranibizumab

administration, by 452 μm on 0.5 mg ranibizumab administration and by 168 μm on mock injections (ranibizumab vs. placebo groups: p<0.0001) [12].

Bevacizumab - this drug is registered for use in metastatic colorectal cancer, breast cancer and some other malignant tumours, and is used 'off-label' in ophthalmology. More than 40 studies have investigated beva-cizumab in the treatment of DMO.

In a retrospective multicentre study PACORES (Pan-American Collaborative Retina Study) the efficacy of two doses of bevacizumab (1.25 mg or 2.5 mg) was compared in 82 patients with DMO (101 eyes). On average, 3 injections were performed each. The improvement in visual acuity observed by the end of the first month after drug administration (p=0.0001) was maintained throughout the 12-month follow-up. The dynamics of visual acuity and retinal thickness were similar for both doses. Side effects included transient increase in blood pressure (1 case), intraocular pressure (1 eye), and traction retinal detachment (1 case) [4].

A multicentre phase II study by the DRCR.net group evaluated the efficacy of bevacizumab in 109 patients with DMO. Patients received five treatment regimens: 1) focal LCS at baseline; 2) 1.25 mg bevacizumab at baseline and after 6 weeks; 3) 2.5 mg bevacizumab at baseline and after 6 weeks; 4) 1.25 mg bevacizumab at baseline and mock injections after 6 weeks; 5) 1.25 mg bevacizumab at baseline and after 6 weeks with focal LCS after 3 weeks. At week 12 of the study, the reduction in retinal thickness was 21% in group 1, 33% in groups 2 and 3, 14% in group 4, and 25% in group 5, respectively. At week 12, visual acuity in the bevacizumab groups was higher on average by 1 line than after LCS. Side effects of bevacizumab included endophthalmitis (1 case) and transient increase in intraocular pressure (6 cases), and 2 cases of myocardial infarction and one episode of congestive heart failure were reported in patients with an aggravated cardiovascular history [5].

The two-year British phase III study BOLT (A prospective randomised trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema) included 80 patients with clinically significant AMD who had already undergone at least one LCS session. Patients were randomised to bevacizumab therapy (1.25 mg once every 6 weeks, 3 to 9 injections in the first 12 months, n=42) and the LCS group (once every 4 months, one to three sessions in 12 months, n=38). By the end of the first year of the study, the median gain in maximum corrected visual acuity in the bevacizumab group was 8 ETDRS letters, while in the LCS group the index decreased by 0.5 letters (p=0.0002). A gain of 10 or more letters was observed 5.1 times more often with bevacizumab compared to LCS (p=0.02). The reduction in retinal thickness was also more convincing on anti-VEGF therapy (129 and 68 μm, p=0.02). By the end of the second year of the study, patients had received an average of 13 bevacizumab injections and 4 laser photocoagulation sessions. The median visual acuity gain was 9 letters in the bevacizumab group and 2.5 letters in the LCS group (p=0.005). Visual acuity gains of 10 or more letters were observed in 49% and 7% of patients, respectively (p=0.001). Retinal thickness decreased by 146 μm on average with bevacizumab, while in the laser coagulation group - by 118 μm [8].

A meta-analysis of 8 studies investigating the effect of a single intravitreal injection of bevacizumab (1.25 or 1.5 mg) versus triamcinolone (4 mg) in patients with DME (434 eyes) showed that triamcinolone restored visual acuity to a greater extent at the 4th, 8th, 12th and 24th week after injection (p<0.02). No significant differences were found in the effect of the drugs on retinal thickness after 8, 12 and 24 weeks [38]. New studies comparing the effects of bevacizumab and glucocorticoids: triamcinolone, dexa-metasone (NCT01572350, NCT01571232, NCT01787669), bevacizumab and ranibizumab (NCT01635790, NCT01627249) in the treatment of DMO are in progress.

Pegaptanib-a selective inhibitor of VEGF165-pegaptanib is approved for the treatment of the neovascular form of age-related macular degeneration in the USA and in European countries. Several studies evaluated the effect of the drug in AMD. Analysis of retrospective data showed the ability of pegaptanib at a dose of 0.3 mg to improve visual acuity in the first 6 weeks after injection. At least three injections were required to obtain a significant effect within 6 months [9]. In the multicentre phase II Macugen Diabetic Retinopathy Study, 172 patients with DMO received pegaptanib at a dose of 0.3, 1 or 3 mg or placebo injections. The drug was administered at the beginning of the study, at weeks 6 and 12, and at the investigator's discretion at weeks 18, 24, and 30. Starting at week 13, LCS could be performed as indicated. The results were evaluated at week 36. The best dynamics of visual acuity and retinal thickness was observed with pegaptanib at a dose of 0.3 mg. In this group improvement of visual acuity by 10 and more letters was observed in 34% of patients (in control - in 10%, p=0.003), retinal thickness decreased by 68 μm (in control - increased by 4 μm, p=0.02). The need for LCS on the background of treatment with pegaptanib at a dose of 0.3 mg occurred 2 times less often than in the placebo group (25% and 48%, p=0.04). One case of endophthalmitis per 652 injections (0.15%) was recorded in the study, no systemic complications were observed [10]. In a multicentre two-year blinded controlled phase II-III study conducted by Macugen 2013 Study Group, the efficacy of pegaptanib 0.3 mg was evaluated in 260 patients with DME and visual impairment. The drug or place-

bo was injected once every 6 weeks (9 injections in the first year, in the second year - according to the protocol conditions, depending on visual acuity, retinal thickness and other signs). Starting from the 18th week, LCS could be performed if necessary. By the end of the first year of the study, visual acuity improvement of 10 or more letters was observed in 37% of patients receiving pegaptanib and in 20% of patients receiving placebo (p=0.005). By the end of the second year, visual acuity improved by an average of 6.1 letters in the pegaptanib group and by 1.3 letters in the placebo group (p<0.01). The need for LCS occurred in 23% of patients receiving the active drug and 42% of patients receiving placebo (p=0.002). The incidence of side effects was similar between pegaptanib and placebo [11].

Aflibercept-the drug has the broadest spectrum of anti-VEGF activity, binding VEGF-A, VEGF-B and PlGF. It is approved in the USA for the treatment of wet age-related macular degeneration and metastatic colorectal cancer. Studies of aflibercept (VEGF Trap-Eye) in DMO started later than other anti-VEGF drugs.

The DA VINCI (Study ofVEGF Trap-Eye in eyes with diabetic macular edema) phase II study compared different doses of aflibercept with laser therapy. Patients were randomised into the following groups: 1) 0.5 mg aflibercept monthly; 2) 2 mg aflibercept monthly; 3) 3 monthly injections of 2 mg, then once every 2 months; 4) 3 monthly injections of 2 mg, then as needed; 5) LCS. After 24 weeks, visual acuity improved by 8.6, 11.4, 8.5, and 10.3 letters in the aflibercept treatment groups, respectively. The LCS group showed a more modest result (2.5 letters, differences with all groups were significant: p<0.009). At week 52, positive dynamics of visual acuity remained in the aflibercept treatment groups: an increase of 11, 13.1, 9.7 and 12 letters, in the LCS group - by 1-3 letters (p<0.0001). Improvement of visual acuity by 15 and more letters according to ETDRS table was observed in 40.9, 45.5, 23.8 and 42.2% of patients in aflibercept treatment groups and in 11.4% of patients who received LCS (p=0.003, p=0.0007, p=0.16, p=0.002 in comparison with laser therapy). Retinal thickness in the macular zone decreased by 165.4, 227.4, 187.8 and 180.3 μm in the aflibercept treatment groups, and by 58.4 μm in the LCS group (p<0.0001). Thus, the DA VINCI study demonstrated that aflibercept restores visual acuity and reduces retinal thickness in DMO to a greater extent than LCS [12].

In the phase III study GALILEO (VEGF Trap-Eye for macular oedema secondary to central retinal vein occlusion) aflibercept was administered at a dose of 2 mg monthly, while the comparison group received mock injections. The study included 177 patients and the duration of follow-up was 24 weeks. By the end of the study, visual acuity improved by an average of 18 letters in patients receiving aflibercept, and by 3.3 letters in the comparison group (p<0.0001). Improvement of visual acuity by 15 or more letters was observed in 60.2% of patients in the aflibercept group and in 22.1% of patients in the comparison group (p<0.0001). The reduction in retinal thickness was also more pronounced on aflibercept (448.6 and 169.3 μm, p<0.0001). The most frequent side effects in the active treatment group included ocular pain (11.5%), increased intraocular pressure (9.6%) and conjunctival bleeding (8.7%) [14].

The presented results suggest that UBOB inhibitors may be an alternative or an adjunct to conventional laser treatment and triamcinolone use in patients with DMO.

Conclusions: The development and introduction into practice of UBOB inhibitors for intravitreal administration have opened new perspectives in the treatment of AMD. The use of anti-UBOB therapy, both as a single treatment method and in combination with LCS, reduces the severity of macular oedema and increases visual acuity. Ranibizumab (Lucentis, Oepen1esb/Koua1) is currently registered in Russia for the treatment of DMO. The indication for prescribing this drug is macular oedema with decreased vision and retinal thickness in the macular zone of more than 300 μm [5]. However, positive results in randomised clinical trials have been obtained with bevacizumab, pegaptanib and aflibercept. Current studies are planned to compare the efficacy of these drugs in the treatment of DMO (N0101610557, N0101627249). The effects of intravitreal application of bevasiranib, an inhibitor of UEOE gene transcription, are being studied [1, 6].

Ophthalmological complications of anti-UBO therapy include endophthalmitis, increased intraocular pressure, lens damage and retinal detachment. The incidence of these complications, according to most studies, does not exceed 1-1.5 cases per patient per year. Systemic adverse reactions are also rarely observed and include increased blood pressure, stroke, myocardial infarction, proteinuria. These reactions may be associated with the penetration of small amounts of the drug into the bloodstream. It has been reported that the level of UBOB in the bloodstream remains reduced for a month after intravitreal administration of bevacizumab and does not decrease after administration of ranibizumab and pegaptanib [4, 7]. A study designed to assess the extent of 'leakage' of UBOB inhibitors into the circulation during intravitreal administration has now been initiated (N0X01661946). It is required to specifically evaluate the safety of UBOB inhibitors in 'problem' categories of DM patients with macrovascular complications, severe arterial hypertension and nephropathy.

Future studies will determine the optimal duration of anti-UBOb therapy, predictors of its efficacy,

and the appropriateness of combining it with other DMD therapies.

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АНТИ-VEGF ПРЕПАРАТЫ В ЛЕЧЕНИИ ДИАБЕТИЧЕСКОГО МАКУЛЯРНОГО ОТЕКА

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Резюме. *Диабетический макулярный отек (ДМО) является одной из основных причин снижения остроты зрения у больных сахарным диабетом. Интравитреальное введение ингибиторов фактора роста эндотелия сосудов (анти-VEGF терапия) предложено в качестве нового метода лечения ДМО. В данном обзоре мы обобщили результаты рандомизированных клинических исследований ингибиторов VEGF у больных с ДМО. Результаты свидетельствуют, что все изученные ингибиторы (ранибизумаб, бевацизумаб, пегаптаниб и афлиберцепт) уменьшают толщину сетчатки и повышают остроту зрения у пациентов с ДМО при использовании как в виде монотерапии, так и в комбинации с лазерным лечением. В будущих исследованиях необходимо определить оптимальную длительность анти-VEGF терапии и предикторы ее эффективности при ДМО.*

Ключевые слова: *диабетический макулярный отек, фактор роста сосудистого эндотелия, ранибизумаб, бевацизумаб, пегаптаниб, афлиберцепт.*