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APPROACHES TO THE TREATMENT OF DIABETIC RETINOPATHY

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INTRODUCTION

Year by year, the number of people with diabetes mellitus is increasing in the world, and according to WHO estimates, there are at least 130 million diabetics on the planet today. Moreover, according to the forecasts of this organization, by 2025, this figure will increase to 350 million. At least 2.5 million people live with diabetes in Russia alone. And these official statistics are actually 2-3 times lower than the actual picture of what is happening.

In ophthalmology, methods of treating diabetic retinopathy (DR) with modern conservative methods are being actively developed and widely implemented, the combination of which with standard therapy improves the long-term prognosis of the disease. Today, drugs that block vascular endothelial growth factor (VEGF), which is considered the main reason for triggering the mechanism of neovascularization, as well as vascular hyperfiltration into the retina, have become available in wide practice. A detailed study of the properties of VEGF provides an answer to the question of the appropriateness of their use in patients with diabetes mellitus, its effectiveness, as well as potential complications that can pose a serious threat to vision and health in general.

Keywords: Neovascular diseases, growth factor, intravitreal injections, diabetic retinopathy, PRP.

Pathogenesis of Diabetic Retinopathy

In the pathogenesis of DR, including DME, chronic hyperglycemia promotes biochemical alterations and consequent structural changes in the retinal blood vessels' wall. The latter include pericyte loss and endothelial cell damage leading to disruption of the blood–retina–barrier and consequent vascular hyperpermeability, while thickening of retinal capillaris' basement membrane ends up to vessel closure, capillary drop-out, and non-perfusion [1,2,3,4]. In both pathways, namely, vascular hyperpermeability and ischemia, vascular endothelial growth factor (VEGF) upregulation has been found to be the most prominent factor [5,6,7]. Specifically, VEGF-A is a key signaling glycoprotein, triggering endothelial cell proliferation, cell migration, vascular leakage and angiogenesis in oxygen-deprived tissues, being also the most potent angiogenic molecule among the other VEGF family members [8].

Norm and Pathology of Vascular Endothelial Growth Factor

In 1983, VEGF was first isolated as a factor that increases vascular fragility in tumors. It is a member of the family of homodimeric glycoproteins and is very similar in structure to platelet growth factor. VEGF is able to bind to five types of receptors with tyrosine kinase activity.

Pathological and physiological processes occurring in violations of the VEGF/VEGFR system include the regulation of female reproductive function, embryogenesis, pregnancy, wound healing, tumor growth, development of diabetic retinopathy and ischemic pathologies.

Currently, the most studied is VEGF-A with its various isoforms.

The most significant biological effect of VEGF is manifested when interacting with the VEGF-R2 receptor, a representative of transmembrane tyrosine kinases. A particularly frequently expressed isoform of VEGF is VEGF165. It has the best bioavailability parameters and the highest biological effect. With intravitreal administration of this form, there is a significant suppression of pathological neovascularization, although it practically does not affect physiological neovascularization.

In the processes of embryogenesis and early angiogenesis of newborns, VEGF is especially required. In adults, it works at different levels in the vascular wall as an effective vasodilator and factor that helps the survival of tissue endothelial cells. Under the strict control of VEGF, the functioning of the renal glomerular filter and glomerulogenesis itself are in the kidneys. Moreover, the glomerular filter has a direct effect on muscle cell regeneration, myocardial remodeling, and endochondral bone formation. Its action is similar to that of a chemoattractant, which mobilizes endothelial cells in the bone marrow.

Along with the physiological action, VEGF has other beneficial effects, although they are triggered by some pathogenic mechanisms. These include: the ability to form collateral circulation, which will allow cells to survive in conditions of oxygen starvation, and also improves trophism during wound healing.

VEGF is produced in the cells of the retinal pigment epithelium, which in diabetes mellitus is manifested by increased retinal edema and the appearance and growth of newly formed vessels. Proliferative diabetic retinopathy with neovascularization is most common in type 1 diabetes, while retinal edema usually occurs in type 2 diabetes, leading to loss of central vision if the macular area is involved.

VEGF Inhibitors

VEGF inhibitors differ in some aspects related to their production, as well as in the details of the structure of the substances and specificity in relation to various isoforms of the regulator. The action of anti-VEGF drugs (ranibizumab, bevacizumab, pegaptanib) is due to direct binding to the growth factor, suppression of the expression of the VEGF gene or its receptor. To date, phase II-III clinical trials for AMD therapy have been completed: bevacizumab, pegaptanib, ranibizumab, aflibercept. Most of them are already officially approved as treatments for age-related macular degeneration.

Ranibizumab (Lucentis, Lucentis)

The substance contained in Lucentis was specifically addressed to ophthalmologists. This VEGF inhibitor has been approved by the Food and Drug Administration (FDA) for use in the United States in the treatment of age-related wet macular degeneration. Today, this is the only

drug with anti-VEGF activity officially registered in Russia. Its effectiveness in the treatment of macular edema has been proven by a series of randomized trials conducted in many ophthalmological centers.

Bevacizumab (Avastin)

This anti-VEGF drug is mainly used in oncology for the treatment of malignant tumors; in ophthalmology, its use has no official status ("off-label"). The efficacy of bevacizumab in the treatment of wet AMD has been the subject of more than 40 clinical trials to date. Moreover, the last of them were aimed at comparing the effect of bevacizumab and corticoids (triamcinol, dexamethasone) in the treatment of neovascular macular degeneration.

Pegaptanib (Makugen, Macugen)

This anti-VEGF drug is approved for the treatment of neovascular AMD in the US and European countries. Its effect has been confirmed by a number of studies. Pegaptanib, administered at a dose of 0.3 mg, has been shown to significantly improve visual acuity, with results lasting 6 weeks post-injection. A long-term effect is achieved by introducing at least three injections within six months.

Aflibercept (Eylea, Eylea, Eylea)

This drug has the broadest anti-VEGF activity. It is able to act on VEGF-A, VEGF-B and PlGF. In the US, it is approved for use in the treatment of wet neovascular macular degeneration as well as metastatic rectal tumors. Studies of aflibercept as a treatment for AMD came later than other anti-VEGF drugs.

Among the latest generation of anti-VEGF agents, which are only undergoing the necessary studies for subsequent use as a therapy for macular edema, it is worth noting bevasiranib. This drug, which is based on RNA, suppresses the gene that synthesizes VEGF. It is also administered intravitreally.

The drug "VEGF Trap-Eye" is already quite well known. Initially, it was developed to fight tumors, but it has become a real "trap" for VEGF, because its molecular structure is similar in shape to the VEGF receptor. When administered intravitreally, the agent neutralizes all VEGF-A and PlGF12 isoforms.

Ophthalmic Complications of Anti-VEGF Therapy

The use of anti-VEGF drugs in the treatment of ophthalmic diseases can lead to a number of pathological conditions: retinal detachment, increased intraocular pressure, endophthalmitis, lens damage. According to available research data, the frequency of such complications is no more than 1-1.5% of all cases of therapy. Systemic side effects are also rare. Sometimes there are: increased blood pressure, myocardial infarction, stroke, proteinuria.

Experts associate such reactions with the ingress of a certain amount of the drug into the bloodstream. There is evidence that after intravitreal administration of bevacizumab, its level in the bloodstream gradually decreases over the course of a month, and after the administration of ranibizumab and pegaptanib, it remains unchanged.

Another study initiated at the present time aims to assess the degree of penetration of VEGF inhibitors into the bloodstream during intravitreal injections. In addition, the task of the study will be to assess the safety of such drugs in patients with severe diseases: diabetes mellitus, macrovascular pathologies, high levels of arterial hypertension, and nephropathy. Subsequent

studies will determine the optimal duration of anti-VEGF therapy, the advisability of combining with other AMD treatment options.

Combination of Intravitreal Anti-VEGF Agents and Panretinal Photocoagulation in the Treatment of Proliferative Diabetic Retinopathy

Several studies pointed out to the combination of intravitreal anti-VEGF agents with PRP for the treatment of PDR. Filho et al. compared intravitreal 0.5 mg ranibizumab with PRP versus PRP alone for the treatment of high-risk PDR in 40 patients [9]. They found significant reduction in fluorescein angiography leakage in both groups through week 48, but the reduction was significantly greater in the combination group, along with significant improvement in visual acuity and central retinal thickness [9].

Similar results were reported in the prospective, randomized PROTEUS study ("Prospective, Randomized, Multicenter, Open-label, Phase II/III Study to Assess Efficacy and Safety of Ranibizumab 0.5 mg Intravitreal Injections Plus Panretinal Photocoagulation (PRP) Versus PRP in Monotherapy in the Treatment of Subjects With High Risk Proliferative Diabetic Retinopathy"), in which intravitreal 0.5 mg ranibizumab plus PRP was compared to PRP alone in the regression of neovascularization area in patients with high-risk PDR without DME over a period of 12 months. The PROTEUS study showed that at month 12, 92.7% of participants in the combination group presented total reduction of neovascularization versus 70.5% of the PRP monotherapy participants, which differed significantly in favor of the combination group. Complete regression of neovascularization was observed in 43.9% in the combination group versus 25.0% in the PRP monotherapy group, which also differed in favor of combination group, although there was no difference in visual acuity change at month 12 between the two groups [10].

Furthermore, the PRIDE study ("Multicenter 12 Months Clinical Study to Evaluate Efficacy and Safety of Ranibizumab Alone or in Combination With Laser Photocoagulation vs. Laser Photocoagulation Alone in Proliferative Diabetic Retinopathy") compared intravitreal 0.5 mg ranibizumab alone, PRP alone, and combination of them in 106 patients with PDR and no DME, showing that at month 12, there was a statistically significant greater improvement in visual acuity in the combination group, which was consistent with the stronger effect of the ranibizumab either alone or in combination with PRP on neovascularization leakage and area reduction [11]. This was in line with Chatziralli et al., who demonstrated that both intravitreal ranibizumab 0.5 mg alone and in combination with PRP could be used effectively for the treatment of PDR and co-existent DME, although the combination group presented greater regression of neovascularization with less injections [12]. Accordingly, Ferraz et al. concluded that the combination of intravitreal ranibizumab and PRP can be an effective treatment in eyes with non-high-risk PDR and DME [13]. Note that in cases where combination of anti-VEGF and PRP is used, Cao et al. have observed that the sequence of intravitreal ranibizumab before PRP showed clear advantages over that in PRP before intravitreal injection, not only in the use of lower energy for PRP, but also in the more rapid regression of neovascularization and less need of additional treatment [14]. In the long-term follow-up, however, the two-year results of the above-mentioned PRIDE study showed that discontinuation of ranibizumab treatment in PDR patients may results in an increase of neovascularization area and visual loss, suggesting

that tight monitoring of disease activity and continued treatment beyond the first year are needed to maintain disease control [15].

CONCLUSION

Intravitreal anti-VEGF therapy is the standard-of-care for DME, providing improvement which seems to maintain over time with limited adverse events. Moreover, it has been shown that anti-VEGF agents may improve DR severity, although there is no general consensus and no specific protocol for anti-VEGF use in patients with DR. In fact, there is lack of evidence to help physicians determine when to discontinue injection and when to retreat in patients with NPDR. Regarding PDR, based on the existing literature, both PRP and anti-VEGF agents are viable treatment options, while specific factors, such as cost and compliance, should be considered when choosing a treatment in patients with PDR. Given the chronic nature of PDR and the pharmacokinetics of intravitreal anti-VEGF agents, one of the disadvantages of anti-VEGF monotherapy for PDR is that these drugs have to be administered periodically for some time, while interruption of treatment could be devastating and lead to irreversible visual loss. Therefore, the high "loss to follow-up" rate in patients with PDR should be taken into account in the decision of treatment, based on an individualized approach. Combination treatment of intravitreal anti-VEGF agents and PRP may be a reasonable alternative for PDR.

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