WEB OF SCIENTIST: INTERNATIONAL SCIENTIFIC RESEARCH JOURNAL
ISSN: 2776-0979, Volume 3, Issue 10, Oct., 2022

USE OF ANTI-VEGF DRUGS IN DIABETIC RETINOPATHY (LITERATURE REVIEW)

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Abstract
The treatment of diabetic retinopathy (DR) with modern conservative methods, the combination of which with standard therapy improves the long-term prognosis of the disease, is being actively developed and widely implemented. Today, tools that block vascular endothelial growth factor (VEGF), which is considered to be the main cause of the mechanism of neovascularization, as well as vascular hyperfiltration into the retina, have become widely available in practice. A detailed study of the properties of VEGF answers the question of the appropriateness of its use in patients with diabetes, its effectiveness, and the potential complications that could pose a serious threat to vision and health in general

Keywords: anti-VEGF drugs, diabetic retinopathy, endothelial cells, ophthalmology

Introduction

The primary cause of disease onset and progression is chronic hyperglycemia, which triggers a variety of biochemical, pathophysiological as well as molecular genetic mechanisms that result in pathological changes in the retina. High glucose levels in the retina initiate vascular endothelial cell damage (oxidative stress, deposition of glycation end products and lipid disorders, activation of the polyol shunt), causing the activation of certain mechanisms that stimulate the production of cytokines, growth factors and extracellular matrix lipids, resulting in cell dysfunction and death or cell disintegration (apoptosis). These changes cause vascular desquamation, pericyte death, leakage of plasma through the vascular wall and hemorrhage causing retinal hypoxia (oxygen deprivation). Hypoxic damage in the retinal tissue leads to an increased intracellular concentration of a specific protein controlling gene transcription, HIF-1. Increased intracellular concentration of HIF-1 leads to increased

transcription of the VEGF gene. The latter is released into the intercellular structure and acts specifically on the epithelium, activating proliferation, stimulating regeneration and growth of new blood vessels.

Norm and pathology of vascular endothelial growth factor

In 1983, VEGF was first isolated as a factor that increases vascular fragility in tumours. It is a member of the homodimeric glycoprotein family and is very similar in structure to platelet-derived growth factor. VEGF is able to bind to five types of receptors with tyrosine kinase activity. Pathological and physiological processes occurring in the VEGF/VEGFR system include the regulation of female reproduction, embryogenesis, pregnancy, wound healing, tumour growth, development of diabetic retinopathy and ischaemic pathologies. Currently, the most studied is VEGF-A with its different isoforms. The most significant biological effect of VEGF is manifested through its interaction with the receptor VEGF-R2, a representative of the transmembrane tyrosine kinases. A particularly frequently expressed isoform of VEGF is VEGF165. It has the best bioavailability parameters and the highest biological effect. Intravitreal administration of this form significantly suppresses pathological neovascularization, although it has little effect on physiological neovascularization. In the processes of embryogenesis and early neonatal angiogenesis, VEGF is particularly essential. In adults, it functions at different levels in the vascular wall as an effective vasodilator and as a factor that helps the survival of endothelial tissue cells. Under the strict control of VEGF in the kidneys is the work of the renal glomerular filter and glomerulogenesis itself. Moreover, the glomerular filter has a direct effect on muscle cell regeneration, myocardial remodeling, as well as endochondral bone formation. Its action is similar to that of a chemoattractant, which mobilises endothelial cells in the bone marrow. In addition to its physiological effects, VEGF has other beneficial effects, although they are triggered by several pathogenetic mechanisms. These include the ability to form a collateral circulation, which allows cells to survive in conditions of oxygen starvation, as well as improving trophics during wound healing. VEGF is produced in the cells of the retinal pigment epithelium, which in diabetes is manifested by an increase in retinal edema and the emergence as well as the growth of newly formed vessels. Proliferative diabetic retinopathy with neovascularization is the most common in type 1 diabetes, while in type 2 diabetes, retinal edema tends to occur, leading to loss of central vision if macular zone is involved.

VEGF Inhibitors

Today there are anti-VEGF drugs that are used in the treatment of cancer patients with metastatic tumours. VEGF inhibitors are monoclonal antibodies that selectively

bind and block VEGF. Their action is to inhibit neoangiogenesis in tumours, which deprives the tumours of growth. Research findings on the role of VEGF in diabetic retinopathy have provided an opportunity to offer anti-VEGF drugs for its treatment. To date, several drugs are available in ophthalmology that block VEGF. These include: Macugen (Eyetech Pharmaceuticals/Pfizer) with the active ingredient pegaptanib, which affects VEGF165; Lucentis (Genentech/ Roche) with the active ingredient ranibizumab and Avastin (Genentech/Roche) with the active ingredient bevacizumab, which can suppress all VEGF isoforms.

Pegaptanib (the active ingredient in Macugen) is a neutralising RNA aptamer that binds to polyethylene glycol, which has the highest affinity to VEGF165. In rodent experiments, it was found that intravitreal injections of pegaptanib significantly inhibited leukostasis, retinal neovascularisation and cellular hyperfiltration provided by VEGF. The use of pegaptanib was approved by the FDA (Food and Drug Administration, USA) in 2004 as a therapy for age-related macular dystrophy (edema wet form).

Ranibizumab (active ingredient in Lucentis) is a substance developed specifically to prevent neovascularisation in age-related macular dystrophy through specific changes in the structure of rat long-chain monoclonal antibodies. Ranibizumab is able to bind and inhibit the action of all human VEGF isoforms, in contrast to pegaptanib. In experiments with non-human monkeys, when creating choroidal neovascularisation in primates by laser irradiation, intravitreal injections of ranibizumab showed high suppression of new vessel formation as well as a significant reduction in the permeability of existing vessels. In 2006 this drug was also approved by the FDA in the treatment of moist forms of age-related macular dystrophy.

Bevacizumab (the active ingredient of Avastin) is a drug based on antibodies to VEGF in laboratory mice. Like ranibizumab described above, it is able to bind all VEGF isoforms. Intravitreal injections of bevacizumab are also used in the therapy of age-related macular dystrophy to stop the process of neovascularisation. However, the use of this drug has not yet been approved by the authorities due to the insufficient number of randomised trials conducted.

Results of studies on the use of anti-VEGF drugs

Intravenous administration. Only one study examined the systemic intravenous administration of bevacizumab in ophthalmic pathology. Eighteen patients with age-related macular dystrophy with neovascularisation participated in the trial. The study was uncontrolled and the drug dose was 5 mg/kg. The injections were given 1, 2 and 3 times every 2 weeks. The result of treatment was an increase in visual acuity as early

as 2 weeks from the start of therapy, with the effect persisting even after 5-6 months of follow-up. By the end of the study, a significant reduction in retinal thickness was noted. During the follow-up period, only 6 of the treated patients received additional therapy. However, despite these positive results, the study did not identify any potential side effects of the therapy or its complications.

Intravitreal injection. A therapy regimen with pegaptanib and ranibizumab was chosen for large-scale clinical trials in subjects with age-related macular degeneration. It was found that pegaptanib is slightly less effective than ranibizumab, but has significantly fewer adverse effects. For example, there is a risk of cardiovascular events, including stroke (found in three studies), and bleeding when using ranibizumab, although this complication was not statistically significant.

Several studies have concluded that the treatment is effective in patients with diabetes mellitus. For example, one study involved 172 people with diabetic macular edema. The therapy lasted 36 weeks and by the end of the study, participants administered pegaptanib showed better visual results and had a smaller thickness in the central zone of the retina. In addition, fewer of the people in this group required laser treatment at a later date. Many ophthalmologists now use Bevacizumab as a preoperative therapy preceding vitrectomy surgery for proliferative diabetic retinopathy.

Risks and complications of treatment with VEGF inhibitors

Anti-VEGF drugs are injected by puncturing the sclera inside the vitreous body. However, this does not guarantee their penetration into the systemic bloodstream and can in turn cause undesirable systemic effects. The systemic effects of anti-VEGF drugs can be observed in hypertension and proteinuria, which are particularly frequent during the treatment of oncological diseases. At the same time, the increase of blood pressure level is explained by the increased resistance of peripheral vascular blood flow due to the blocked synthesis of nitric oxide by endothelial cells, which is generated by VEGF by activating NO synthase. In addition, hypertension may be an additional factor of impaired renal function

Other possible complications of anti-VEGF therapy often include infertility, gastrointestinal bleeding as well as the inability to regenerate muscle tissue, myocardial recovery, wound healing and the recreation of collateral circulation. Moreover, all these disorders are a consequence of VEGF-suppressing drugs, especially dangerous for people with diabetes mellitus. The most frequent ophthalmological consequences of anti-VEGF therapy are retinal detachment, endophthalmitis and damage of the crystalline lens. Serious complications are rare

with intraocular injections of the above mentioned drugs, but there is a cumulative risk in diabetics, as they require regular treatment courses over many years.

The side effects of the injection itself are not the only negative reaction of the body to the administration of anti-VEGF drugs. There are other potential adverse effects that are due to the suppression of VEGF. After all, VEGF promotes the formation of retinal pigment cells, so it is responsible for the vitality of the choriocapillaries and provides neuroprotective effects in case of retinal ischemia. When pegaptanib, which cannot bind to VEGF120, is used as an anti-VEGF drug, the number of retinal ganglion cells is not reduced. In other studies, when bevacizumab, which blocks all VEGF isoforms, was used for intravitreal injection, there was no toxic effect on retinal ganglion cells. However, it is worth noting that although a negative effect on the retina, detected by side-light microscopy, has not yet been proven, intravitreal injection of bevacizumab in rat tests showed mitochondrial destruction in the inner layer of photoreceptors (by electron microscopy) and increased apoptosis. The development of VEGF-blocker drugs that would suppress the pathological effects of VEGF but retain its neuroprotective effect is still in progress.

Conclusion

Intravitreal injection of anti-VEGF drugs is an effective method of delivering the drug solution directly to the retina. This has been proven in the clinical treatment of patients with age-related macular dystrophy and proliferative diabetic retinopathy. However, this injection is an invasive procedure, with the risk of possible bleeding, endophthalmitis, and retinal detachment.

To date, Macugen (pegaptanib), Lucentis (ranibizumab) and Avastin (bevacizumab) are available as clinically proven anti-VEGF drugs in ophthalmology. So far, their use is only a complementary therapy to the main conventional treatment. The use of anti-VEGF drugs allows for a significantly better long-term prognosis, a reduced need for retinal laser photocoagulation in patients, and preoperative preparation before surgical interventions such as vitrectomy and anti-glaucomatous surgery. In addition, anti-VEGF drugs significantly reduce the risk of postoperative complications.

At the same time the use of anti-VEGF drugs can activate the cardiovascular disease process. Therefore, their use in ophthalmology requires additional studies, which will be directed along with revealing of potential positive effects, on determining of possible risk of systemic complications that is especially important for diabetic patients.

Literature

1. Kirilyuk M.L. Drug treatment and prevention of diabetic retinopathy in type 1 diabetes mellitus Literature review and clinical studies // International Endocrinological Journal. – 2012. – Vol. 8. – No. 5 – pp. 70-75.
2. Shchuko A.G., Volkova N.V., Samsonova Yu.S. Ocular manifestations of diabetes mellitus: a textbook. – Irkutsk: IGMU; 2015.
3. Bezdetko P.A. Drug therapy of diabetic retinopathy at the stages of its development (problems, doubts, solutions). Ophthalmology Eastern Europe. Professional publications (Minsk). 2016; 1 (28): 109–23.
4. Velichko P.B., Osmanov E.M. Modern methodological approaches to the treatment of diabetic retinopathy. Bulletin of the Tambov University. 2013; 6 (18): 3248-9.
5. Shchulkin A.V., Kolesnikov A.V., Barenina O.I., Nikiforov A.A. Genetic markers of diabetic retinopathy development. Fundamental research. 2014; 4 (2): 411-4.
6. Balashevich L. I. Ocular manifestations of diabetes. St. Petersburg: Publishing House SPbMAPO, 2004. 453 p.
7. Shadrichev F. E. Diabetic retinopathy // Modern optometry. 2008. No. 4. pp. 36-42.
8. Bondar IA, Klimontov BB. Excretion of insulin-like growth factor 1 and vascular endothelial growth factor in urine in patients with type 1 diabetes mellitus with nephropathy. Problems of endocrinology. 2007;53(6):3–7.