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THE VALUE OF ANTI-VEGF DRUGS IN THE TREATMENT OF VARIOUS STAGES OF DIABETIC RETINOPATHY (LITERATURE REVIEW)

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Abstract:

This article discusses treatments with angiogenesis inhibitors in the complex treatment of diabetic macular edema. A comparative analysis of all types of anti-VGEF drugs on macular edema is given. The use of brolucizumab is described in detail as the most optimal method among anti-VGEF drugs for the management of macular edema. It also provides the latest data with clinically confirmed data on the use of this drug.

Keywords: Angiogenesis Inhibitors, VGEF, DME, DM.

RELEVANCE.

The global incidence of diabetes mellitus (DM) is increasing and has now reached pandemic proportions. Over the past 10 years the number of people with diabetes has more than doubled, reaching 415 million people by the end of 2015. The International Diabetes Federation predicts that 642 million people will have diabetes by 2040 (I.I. Dedov, M.V. Shestakova, 2017).

According to the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR), the incidence of DR reaches almost 100% when type 1 diabetes (T1DM) has been present for more than 20 years [18], with one in 30 patients suffering a complete loss of vision [1]. In general, 20% of people with T2DM show signs of DR after 5 years, 60% after 10 years, and virtually all patients after 20-30 years.In type 2 diabetes (T2), approximately 2/3 of patients have DR 20 years after disease onset, with a fifth of patients showing the disease in its proliferative stage [2].

One of the serious complications of diabetes mellitus is diabetic maculopathy, which can be divided into exudative, ischaemic and tractional forms.

The exudative form is the most common: rings of solid exudates are formed and gradually increase towards the foveola. In general, solid exudates are deposition of lipids, lipoproteins in the retina due to their sweating from the vascular wall. They are more likely to come from retinal microaneurysms and capillaries. It has also been suggested that solid exudates are a product of degeneration of Müller cells containing yellow pigment. If left untreated, the process progresses with the formation of new solid exudates and the resorption of the old ones, leading to irreversible changes in the pigment epithelium. Ischaemic maculopathy is the worst prognosis for central vision. It is much less common than exudative MI. It is characterised by a lack of perfusion of the perifoveolar zone. On FAG the perifoveolar capillaries appear as if they are stumped and their terminal part is dilated.

Tractional MO usually occurs in posttraumatic and inflammatory retinal lesions, vitreoretinal masses are formed as a result of fibrous tissue overgrowth and contraction. The vitreous body then exerts a traction (pulling) effect on the retina causing macular edema and sometimes retinal detachment or rupture [3,4,5].

The primary mechanism of vision loss in patients with DR is the formation of diabetic macular edema (DME). In a population-based study, the prevalence of DME ranges from 4.2% to 7.9% in type 1 diabetic patients and from 1.4% to 12.8% in type 2 diabetic patients [19,20]. According to modern concepts, the pathogenesis of AMD is based on the disruption of the internal and external hematoretinal barrier (increased permeability of the capillary wall and inability of the pigment epithelium to reabsorb excess fluid), leading to edema and therefore to increased retinal thickness in the macular zone [1,4]. Proliferative DR is characterized by the growth of abnormal neovascular vessels, leading to decreased visual function up to complete loss due to wall failure (vitreal and preretinal hemorrhages), tractional effects (retinal detachment) or blockage of intraocular fluid

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flow (neovascular glaucoma) [2,5]. Recent work has shown that DM largely affects the neuronal component of the retina, causing what is essentially an isolated neuropathy, with inherent features due to the unique anatomy of the retinal structures [8,9]. This knowledge contributes to the identification of new targets for targeted therapies and a shift in strategic approaches to the prevention and treatment of pathological conditions such as retinal neuronal dysfunction, excessive vascular permeability, retinal ischaemia and neovascularisation.

The main therapeutic approaches for diabetic macular edema (DME) today are laser retinal photocoagulation (LCD) and intravitreal injection of angiogenesis inhibitors (IVIA). The efficacy of LCS in preventing blindness in diabetic patients has been proven by the largest DRS and ETDRS studies [6], and despite disadvantages such as low visual effect and increased risk of macular dystrophic changes, LCS remains the main method of DME treatment [7]. The most important advantage of IVIA over LKS is the increase in visual acuity proven in the RESTORE, DRCR.net studies [31]; however, the short-term effect of ranibizumab necessitates monthly repeated injections, which, considering the pharmacoeconomic aspect, makes the wide use of the drug in Russia difficult. Both LKS and antiangiogenic therapy affect the main pathogenetic mechanisms of DME development - hypoxia and increased vascular permeability. LKS is aimed at turning off zones of retinal ischaemia, suppressing neovascularisation, and obliterating vessels with increased permeability.

In recent years, the most important role of proangiogenic factors in the pathogenesis of these diseases, especially vascular endothelial growth factor (Vascular Endothelial Growth Factor, VEGF), which is a powerful inducer of angiogenesis, has been established. The action of VEGF is mediated through the tyrosine kinase receptors type 1 and 2, VEGFR-1 and VEGFR-2, on the surface of endothelial cells. The hypersecretion of VEGF results in two main biological effects: increased vascular permeability, which may be associated with the development of MI, and stimulation of growth of newly formed vessels. The human VEGF family includes VEGF-A, -B, -C, -D and placental growth factor (PlGF). Currently, VEGF-A, which is expressed in many stromal and parenchymatous cells and circulates in the bloodstream, is the most studied. Increased levels of VEGF-A in plasma and urine have been reported in DM patients with varying degrees of angiopathy [8].

Due to the hematoretinal barrier, the VEGF content in the retina depends mainly on the local formation of the factor. Pigment epithelial cells, astrocytes, Müller cells, endotheliocytes, pericytes and ganglion cells are all producers of VEGF in the retina [35]. Acting in autocrine and paracrine ways, VEGF selectively stimulates the proliferation and migration of endothelial cells and their precursors, increases vascular permeability, and promotes vasodilation by enhancing nitric oxide (NO) production. In recent years, it was shown that VEGF ensures the survival and structural integrity of retinal pigment epithelium [6], has anti-neurodegenerative effect and prevents apoptosis of retinal cells under ischemia-reperfusion conditions [3, 7]. Molecular isoforms of VEGF (VEGF 121, VEGF 145, VEGF 165, VEGF 189, VEGF 206) are the products of one gene resulting from alternative mRNA splicing. Polymorphic positions -634, +936, -2578 have been identified in the VEGF gene; relationships of nucleotide variants at these positions with the risk of developing diabetic retinopathy (DR) in different ethnic groups were found [15]. According to our data [9, 10], combinations of homozygous variants of VEGF 2578CC, 936CC, IL4 590CC, IL6 174GG,IL10 592C and 1082AA, TNFA 238GG, 308GG and 863C, MMP-2 1306CC and MMP-9 1562CC are typical for type 2 DM patients (DM2). The specific genotype defines an unstable balance of angiogenic and anti-angiogenic factors and may be one of the causes of the complex dysregulation of angiogenesis in DM [11]. VEGF hyperproduction is now thought to play a leading role in increasing retinal vascular permeability, macular edema and retinal neovascularisation in DM [12]. A powerful trigger for increased synthesis of VEGF and its receptors in DR is hypoxia or retinal ischemia. In addition, hyperglycemia and related biochemical abnormalities such as accumulation of late glycation products [14], endoplasmic reticulum stress [4,5], and oxidative stress [4, 6] trigger VEGF production in retinal cells. Differences between VEGF inhibitors relate to production technology, structure and specificity to different regulator isoforms.

The current development of anti-VEGF therapy is directed towards the synthesis of drugs that allow the inhibition of an increasing number of angiogenesis factors. The first anti-VEGF drug was pegaptanib, a pegylated oligonucleotide specific to VEGF165. Due to its low efficacy it was never registered in most countries. More recently, bevacizumab (a monoclonal humanised mouse antibody, not registered for ophthalmic use) and ranibizumab (a fragment of the above antibody) have appeared. Both drugs bind all isoforms of VEGF-A [3, 4, 10]. Aflibercept ('VEGF trap') is a recombinant human hybrid protein composed of fragments of the extracellular domains of human VEGF

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receptor 1 (VEGF-R1) and 2 (VEGF-R2) coupled with an Fc-fragment of human immunoglobulin G (IgG1). Aflibercept, unlike other anti-VEGF drugs, binds not only all isoforms of VEGF-A, but also PlGF and VEGF-B [13, 14, 16, 17]. In the treatment of DME to date, retinal laser photocoagulation has only been regarded as the historical standard for the treatment of DME. Unlike laser photocoagulation, the use of VEGF inhibitors has proven effective not only in improving anatomical parameters, but also in restoring vision. Thus, VEGF inhibitors are the treatment of choice for most patients [15].

A new drug, brolucizumab (NovartisPharma, Wiskyou) is approved for use in the United States in 2019 and was also registered with the Russian Ministry of Health in 2020.Brolucizumab (RTH258) was developed by ESBATech (ES-BATech AG - Schlieren ZH, Switzerland) originally as ESBA1008, an inhibitor of humanized single-stranded fragment antibody (scFv) of all isoforms of vascular endothelial growth factor-A (VEGF-A). Compared to the full antibody fragment, brolucizumab is a single-stranded antibody fragment, the smallest functional subunit of the antibody, which still retains full binding capacity to the intended target. Brolucizumab has a molecular weight of 26 kDa, which is much lower than that of bevacizumab (149 kDa), aflibercept (115 kDa) or ranibizumab (48 kDa) [20]. The smaller molecular weight made it possible to accommodate a higher molar concentration of the drug in a 50 µl lentravitreal injection with a drug dosage of 6 mg. The smaller size of the brolucizumab molecule permits more efficient permeation through retinal and choroidal layers compared to other anti-VEGF molecules.

CONCLUSIONS:

Thus, in a rabbit experiment, brolucizumab was shown to have a 2.2-fold higher effect on the retina and a 1.7-fold higher effect on RPE and vasculature compared to ranibizumab. Broflucizumab is characterised by higher affinity to VEGF-A isoforms compared to the cancer drug bevacizumab. Clinical studies have shown that brolucizumab has numerically higher affinity to all VEGF-A isoforms compared to aflibercept and ranibizumab. The efficacy and safety of different doses of brolucizumab compared to aflibercept was studied in randomised multicentre double-masking trials with HAWK and HARRIER.

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