VEGF: A KEY PLAYER NOT ONLY IN MACULAR DEGENERATION. A REVIEW

Slíva J.

Institute of Pharmacology, 3rd Faculty of Medicine, Charles University, Ruská 87, 100 00 Prague 10

Received: 7. 3. 2020
Accepted: 6. 5. 2020
Available on-line: 30. 8. 2020

MUDr. Jiří Slíva, Ph.D.
Ústav farmakologie, 3. LF UK
Ruská 87
100 00 Praha 10
Jiri.Sliva@lf3.cuni.cz

SUMMARY

The issue of macular retinal degeneration is one of the key areas of ophthalmology. Recent advances in the targeted delivery of vascular endothelial growth factor (VEGF) suppressants have significantly impacted the patient's prognosis in the form of a significant deceleration in disease progression. Some of the drugs have gradually found their use in other indications (central retinal vein occlusion or diabetic macular edema). The following text gives a brief look at the physiology of VEGF, but not only in the eye, but throughout the human body, particularly in the context of adverse effects resulting from systemic inhibition of its effects.

Key words: VEGF, vascular endothelial growth factor, pharmacokinetics, adverse effects, ranibizumab, bevacizumab, aflibercept, pegaptanib

INTRODUCTION

Vascular endothelial growth factor (VEGF) is a strong angiogenic factor, which was first described as a fundamental growth factor for vascular endothelial cells. VEGF is up-regulated in several tumours, and its contribution to the angiogenesis of the tumour is well defined, inasmuch as its role in the pathophysiology of certain ocular pathologies is also well mapped. In addition to endothelial cells, VEGF receptors are exprimated also in a range of non-endothelial cells, including actual tumour cells.

VEGF is formed by several types of cells, including tumour-transformed cells, macrophages, thrombocytes, keratinocytes and renal mesangial cells. The action of VEGF is far from limited only to the vascular system; VEGF plays a role also in regular physiological functions such as bone formation, haematopoiesis or healing of wounds.

Advances in the field of pharmacotherapy have led to the establishment of targeted treatment of neovascular (wet) form of age-related macular degeneration. After approval on the level of the American Food and Drugs Administration (FDA) in 1999, photodynamic therapy with verteporfin became available, with the aim of slowing down the process of loss of sight, although no convincing stability or improvement of visual acuity was achieved. As a result, research turned to vascular endothelial growth factor, which plays a key role in macular angiogenesis and vascular permeability [1]. In 2004, the clinical use of pegaptanib sodium was commenced, an aptamer designed for targeting the isoform VEGF-A165, which brought about a new era in anti-VEGF therapy. It was followed by treatment using ranibizumab, bevacizumab (off-label in the Czech Republic) and aflibercept (note: brolucizumab is also available in the USA) [2].

A brief commentary on VEGF

The formation of the vascular system represents a fundamental structural pillar in the embryogenesis of vertebrates, in which it incorporates two basic processes: vasculogenesis, defined as a differentiation of progenitor endothelial cells and their configuration into the primary capillary plexus, and angiogenesis, the formation (sprouting) of new capillaries from already existing cells. In adulthood, angiogenesis is also essential during pregnancy and in the growth and repair of tissues. Unfortunately, however, it is also a key process in the pathogenesis of a series of pathologies, including oncological diseases or ocular pathologies (especially macular degeneration of the retina etc.).

The existence of substances stimulating the formation of new blood vessels was first noted in 1983 [3]. Subsequent research later demonstrated that in the given respect, the most significant factor was vascular

endothelial growth factor (VEGF-A). VEGF-A is a prototype of the family of related growth factors summarily referred to simply as VEGF. In addition to the aforementioned VEGF-A, this family includes also VEGF-B, VEGF-C, VEGF-D (syn. growth factor induced c-FOS; FIGF) and also placental growth factor (PLGF); in parapoxviruses a gene for VEGF-E has also been identified (in humans this triggers pustular dermatitis) and in fruit flies PVF1-3 (PDGF/VEGF-like factors) [4].

The biological effects of VEGF are mediated by a family of related receptors with tyrosine kinase activity (VEGFR). VEGF-A bonds to VEGFR2 (also termed KDR / Flk-1) and VEGFR1 (Flt-1); VEGF-C and VEGF-2 bond only to VEGFR1; and VEGF-E bonds to VEGFR2 [4]. In addition, certain isoforms of the VEGF family bond to non-tyrosine kinase receptors, which are termed neuropilins (NRP) with NP-1 receptors [5,6].

The VEGF group, similarly to PDGF (platelet-derived growth factor), is evolutionarily related to other groups including e.g. glycoprotein hormones, mucin-like proteins or more distantly also to the family of transforming growth factors (TGF-beta). Their current absence in single-cell eukaryotes (e.g. yeast fungi) indicates that they evolved relatively recently. This is attested to also by their function, consisting in the modulation of extracellular signal pathways in multicellular organisms, with organisation on the level of tissue. VEGFs have been found in all hitherto examined animal species of vertebrates, across which they are structurally mutually very close – e.g. VEGF-A of the blowfish (Fugu rubripes) manifests 68 % and 69.7 % amino-acid identity with human VEGF-A, or VEGF-A in mice (Mus musculus) [7].

Alternative splicing of the human VEGF-A gene is a source of at least six different transcripts defined by an amino-acid chain of various lengths: 121 (120 in mice), 145, 165 (164 in mice), 183, 189 and 206 [8].

Physiological significance of VEGF

All hitherto examined forms of VEGF in vertebrates with relevant receptors are capable of regulating angiogenesis, in which they participate in the development of vascular structures during embryogenesis, but also in adults. However, VEGF influences not only blood vessels.

Nonetheless, the cardiovascular system is mentioned in first place. VEGF expression is determined in cardiac myofibroblasts and in non-endothelial cells with morphological traits of fibroblasts. Myofibroblasts play the main role in the growth, development and reparation of normal tissue, and are not found in the place of myocardial infarction. Co-expression of VEGF and its receptors in myofibroblasts thus indicates that VEGF participates in an autocrine manner in the process of remodelling tissue in the place of myocardial infarction. VEGF may also play a role in the development of atherosclerosis. Since VEGF also increases vascular permeability, the formation of VEGF by foam cells and macrophages may worsen atherosclerosis by increasing the permeability of blood vessels for low density lipoproteins (LDL) [9].

On the level of the central nervous system, VEGF manifests a neurotrophic effect. It prolongs the length of survival of the Schwann cells, stimulates the growth of axonal projections [10] and protects hippocampal neurons against ischemic damage [11]. Worsened induction of VEGF in the spinal cord leads to the degeneration of motor neurons [12].

Although cartilage is essentially an avascular tissue, neovascularisation appears in the growth cartilage of developing bones. VEGF is formed by hypertrophied chondrocytes, and thereby significantly participates in the remodelling of intercellular matter, angiogenesis and new bone formation [13]. Among other factors, VEGF is also found in synovial fluid of patients with rheumatoid arthritis or osteoarthritis. It is also present in healthy cartilage, although only osteoarthritic cartilage exprimates receptors of VEGF, VEGFR-1, VEGFR-2 and NP-1 [14].

VEGF also plays an irreplaceable role in haematopoiesis [15]. VEGF is exprimated in bone marrow by haematopoietic stem cells, which it also stimulates – VEGF-1 and VEGF-2 receptors have been identified here [16].

Potential consequences ensuing from intravitreally applied anti-VEGF substances

Within the context of the outlined physiology of VEGF, it is undoubtedly rational to suppress the effects of VEGF only in the place of a pathological process. For this reason, anti-VEGF treatment is applied topically into the vitreous body with the aim of maximising the effect. However, even despite this there are concerns about potential systemic effects [17], primarily in relation to possible cardiotoxicity [18,19] or vascular toxicity [20], and generally from the perspective of development in small children.

It is possible to judge the risk of systemic adverse effect of intravitreally administered anti-VEGF preparations according to their systemic kinetics, i.e. how extensively they penetrate into the systemic circulation. Evidently the first team of authors to attempt to answer this question was that of Zehetner et al. [21], who compared bevacizumab, ranibizumab and pegaptanib in persons with diabetic macular edema or exudative form of age-related macular degeneration (n = 40), in relation to the concentration of VEGF in the peripheral vascular channel. In both groups of patients, the administration of bevacizumab led to a significant reduction of this concentration, whereas pegaptanib and ranibizumab did not have any significant influence [21]. Two years later, the same author also published a comparison of ranibizumab with aflibercept in subjects with macular degeneration (n = 38). Whereas ranibizumab did not generate any systemic changes, aflibercept significantly reduced the concentration of

VEGF in the peripheral channel [22].

Both of the aforementioned studies are fully in accordance with other studies, this time comparing bevacizumab against ranibizumab and aflibercept in 56 patients with macular degeneration. Although all three substances were transferred into the bloodstream, ranibizumab was quickly broken down and excreted, whereas bevacizumab and aflibercept persisted for longer, which corresponded also with more pronounced peripheral suppression of VEGF [23]. This finding corresponds also with the conclusions of the author's latest study covering patients with macular degeneration, diabetic macular edema or central retinal vein occlusion (n = 151). The least expressed was the peripheral effect of ranibizumab, while in contrast VEGF was blocked most pronouncedly by aflibercept [24]. Practically identical results were also produced by Japanese authors on a cohort of 72 patients with diabetic macular edema, i.e. ranibizumab did not influence peripheral concentration of VEGF, whereas aflibercept and bevacizumab significantly reduced it [25].

CONCLUSION

In contemporary medicine, vascular endothelial growth factor is a very frequent therapeutic target of a range of pharmaceutical substances in all kinds of pathological conditions. In ophthalmology this concerns wet form of macular degeneration of the retina, central retinal vein occlusion and diabetic macular edema. Intravitreally administered substances act with a similar though not identical mechanism of effect. Within the context of clinical experiences to date, and taking into account the pharmacokinetics of individual representatives, it is evident that upon their use it is possible to expect not only partial difference in terms of effect, but also differences with regard to the potential risks of adverse systemic side effects due to extraocular blockade of VEGF.

LITERATURE

1. Miller JW, Le Couter J, Strauss EC, Ferrara N. Vascular endothelial growth factor a in intraocular vascular disease. Ophthalmology. 2013 Jan;120(1):106–114.
2. Campa C, Alivernini G, Bolletta E, Parodi MB, Perri P. Anti-VEGF Therapy for Retinal Vein Occlusions. Curr Drug Targets. 2016;17(3):328–336.
3. Senger DR, Galli SJ, Dvorak AM, Perruzzi CA, Harvey VS, Dvorak HF. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. Science. 1983 Feb 25;219(4587):983–985.
4. Holmes DI, Zachary I. The vascular endothelial growth factor (VEGF) family: angiogenic factors in health and disease. Genome Biol. 2005;6(2):209.
5. Soker S, Takashima S, Miao HQ, Neufeld G, Klagsbrun M. Neuropilin-1 is expressed by endothelial and tumor cells as an isoform-specific receptor for vascular endothelial growth factor. Cell. 1998 Mar 20;92(6):735–745.
6. Gluzman-Poltorak Z, Cohen T, Herzog Y, Neufeld G. Neuropilin-2 is a receptor for the vascular endothelial growth factor (VEGF) forms VEGF-145 and VEGF-165 [corrected]. J Biol Chem. 2000 Jun 16;275(24):18040–18045.
7. Gong B, Liang D, Chew TG, Ge R. Characterization of the zebrafish vascular endothelial growth factor A gene: comparison with vegf-A genes in mammals and Fugu. Biochim Biophys Acta. 2004 Jan 5;1676(1):33–40.
8. Robinson CJ, Stringer SE. The splice variants of vascular endothelial growth factor (VEGF) and their receptors. J Cell Sci. 2001 Mar;114(Pt 5):853–865.
9. Yang PY, Rui YC, Jin YX, Li TJ, Qiu Y, Zhang L et al. Antisense oligodeoxynucleotide inhibits vascular endothelial growth factor expression in U937 foam cells. Acta Pharmacol Sin. 2003 Jun;24(6):610–614.
10. Sondell M, Lundborg G, Kanje M. Vascular endothelial growth factor has neurotrophic activity and stimulates axonal outgrowth, enhancing cell survival and Schwann cell proliferation in the peripheral nervous system. J Neurosci. 1999 Jul 15;19(14):5731–5740.
11. Jin KL, Mao XO, Greenberg DA. Vascular endothelial growth factor: direct neuroprotective effect in in vitro ischemia. Proc Natl Acad Sci U S A. 2000 Aug 29;97(18):10242–10247.
12. Oosthuyse B, Moons L, Storkebaum E, Beck H, Nuyens D, Brusselmans K et al. Deletion of the hypoxia-response element in the vascular endothelial growth factor promoter causes motor neuron degeneration. Nat Genet. 2001 Jun;28(2):131–138.
13. Gerber HP, Vu TH, Ryan AM, Kowalski J, Werb Z, Ferrara N. VEGF couples hypertrophic cartilage remodeling, ossification and angiogenesis during endochondral bone formation. Nat Med. 1999 Jun;5(6):623–628.
14. Enomoto H, Inoki I, Komiya K, Shiomi T, Ikeda E, Obata K et al. Vascular endothelial growth factor isoforms and their receptors are expressed in human osteoarthritic cartilage. Am J Pathol. 2003 Jan;162(1):171–181.
15. Ferrara N, Chen H, Davis-Smyth T, Gerber HP, Nguyen TN, Peers D et al. Vascular endothelial growth factor is essential for corpus luteum angiogenesis. Nat Med. 1998 Mar;4(3):336–340.
16. Ziegler BL, Valtieri M, Porada GA, De Maria R, Müller R, Masella B et al. KDR receptor: a key marker defining hematopoietic stem cells. Science. 1999 Sep 3;285(5433):1553–1558.
17. Semeraro F, Morescalchi F, Duse S, Gambicorti E, Cancarini A, Costagliola C. Pharmacokinetic and Pharmacodynamic Properties of Anti-VEGF Drugs After Intravitreal Injection. Curr Drug Metab. 2015;16(7):572–584.
18. Touyz RM, Herrmann J. Cardiotoxicity with vascular endothelial growth factor inhibitor therapy. NPJ Precis Oncol. 2018 May 8;2:13.
19. Neves KB, Rios FJ, van der Mey L, Alves-Lopes R, Cameron AC, Volpe M et al. VEGFR (Vascular Endothelial Growth Factor Receptor) Inhibition Induces Cardiovascular Damage via Redox-Sensitive Processes. Hypertension. 2018 Apr;71(4):638–647.
20. Touyz RM, Herrmann SMS, Herrmann J. Vascular toxicities with VEGF inhibitor therapies-focus on hypertension and arterial thrombotic events. J Am Soc Hypertens. 2018 Jun;12(6):409–425.
21. Zehetner C, Kirchmair R, Huber S, Kralinger MT, Kieselbach GF. Plasma levels of vascular endothelial growth factor before and after intravitreal injection of bevacizumab, ranibizumab and pegaptanib in patients with age-related macular degeneration, and in patients with diabetic macular oedema. Br J Ophthalmol. 2013 Apr;97(4):454–459.
22. Zehetner C, Kralinger MT, Modi YS, Waltl I, Ulmer H et al. Systemic levels of vascular endothelial growth factor before and after intravitreal injection of aflibercept or ranibizumab in patients with age-related macular degeneration: a randomised, prospective trial. Acta Ophthalmol. 2015 Mar;93(2):e154–159.
23. Avery RL, Castellarin AA, Steinle NC, Dhoot DS, Pieramici DJ, See R et al. Systemic pharmacokinetics following intravitreal injections of ranibizumab, bevacizumab or aflibercept in patients with neovascular AMD. Br J Ophthalmol. 2014 Dec;98(12):1636–1641.
24. Avery RL, Castellarin AA, Steinle NC, Dhoot DS, Pieramici DJ, See R et al. Systemic pharmacokinetics and pharmacodynamics of intravitreal aflibercept, bevacizumab, and ranibizumab. Retina. 2017 Oct;37(10):1847–1858.
25. Hirano T, Toriyama Y, Iesato Y, Imai A, Murata T. Changes in plasma vascular endothelial growth factor level after intravitreal injection of bevacizumab, aflibercept, or ranibizumab for diabetic macular edema. Retina. 2018 Sep;38(9):1801–1808.