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REVIEW ARTICLE

Anti-vascular endothelial growth factor (anti-VEGF): its function in proliferative diabetic retinopathy management

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ABSTRACT

Introduction. Among working-age adults, diabetes is a primary cause of visual impairment. Pan-retinal photocoagulation, the standard treatment for proliferative diabetic retinopathy, is effective but comes with well-established adverse effects, including limitations on the peripheral visual field. The mechanism of vascular proliferation is thought to be triggered by vascular endothelial growth factor (anti-VEGF). Anti-VEGF medications have been studied extensively in the treatment of diabetic macular edema, and the results suggest that treatment with anti-VEGF medications causes a decrease in diabetic retinopathy. Anti-VEGF therapies can be used to treat underlying proliferative diabetic retinopathy in cases of vitreous bleeding when platelet-rich plasma cannot be used, delaying, or reducing the necessity for a vitrectomy. However, the limitations of anti-VEGF therapy require careful patient selection and constant observation. Recent clinical trials and recommendations for the use of anti-VEGF in proliferative diabetic retinopathy are presented in this review.

Material and methods. The effectiveness of anti-VEGF medicines in the treatment of diabetic retinopathy was the subject of a comprehensive review of the scientific and medical literature. A structured search was performed in the PubMed, Scopus, and HINARI databases, considering relevant articles published in the last 10 years. The search terms used (in English) were: "angiogenesis inhibitors", "anti-VEGF", "pan-retinal photocoagulation", "intravitreal injection", "diabetic retinopathy". Accurate diagnosis, side effects, quality of life, and patient satisfaction were analyzed and compared for each treatment option.

Results. Anti-VEGF treatments have been demonstrated to be beneficial in reducing macular edema, enhancing visual acuity, and slowing the advancement of diabetic retinopathy. While generally safe, different anti-VEGF medicines have varied side effects profiles.

Conclusion. When choosing an anti-VEGF treatment for diabetic retinopathy, factors such as patient satisfaction, quality of life, side effects, and correct diagnosis should be taken into account. While anti-VEGF treatments show promise, further study is required to fully understand their advantages and disadvantages and to optimize their application.

Keywords: angiogenesis inhibitors, anti-VEGF, pan-retinal photocoagulation, intravitreal injection, diabetic retinopathy.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

Anti-VEGF therapy has been shown to be more effective than laser photocoagulation in treating mild to severe vision impairment related to diabetic macular edema.

The research hypothesis

Although anti-VEGF therapy has been demonstrated to have better results, laser photocoagulation has been the conventional treatment for diabetic macular edema.

The novelty added by manuscript to the already published scientific literature
In high-risk proliferative diabetic retinopathy patients, the combination of anti-VEGF therapy and panretinal photocoagulation has shown significant improvements in visual acuity, central foveal thickness, and microaneurysms.

Introduction

Diabetes affects 425 million people worldwide today and is expected to affect over 690 million by the year 2045. It is a major public health concern. The Republic of Moldova's Statistical Yearbook provides data on the overall population with diabetes and those receiving insulin treatments. However, for a thorough evaluation of the effects of diabetes on the healthcare system, this data is insufficient. A survey was conducted among family physicians to gather more information about individuals with diabetes, including age, type, duration, BMI, HbA1c, total cholesterol, presence of amputations, and presence of cardiovascular pathologies. According to information submitted by 57.3% of family physicians in the Republic of Moldova, there were 60.000 patients with diabetes mellitus registered in 2019 [1]. There is no diabetes registry in the Republic of Moldova. To report diabetic patients, unified guidelines are required for determining target values, treatment features, and the presence and stage of chronic complications. The establishment of a diabetes registry will benefit healthcare providers and the overall system by enabling the collection of information needed for more effective time and resource management [1]. Among patients with diabetes, 4.4% had vision-threatening retinopathy, and 28.5% showed signs of diabetic retinopathy. Proliferative diabetic retinopathy (PDR) is characterized by the growth of neovessels, which are prone to tractional retinal detachment, hemorrhage, and the formation of vitreoretinal membranes. These vessels may also invade the anterior segment, leading to ischemia or neovascular glaucoma. PDR carries a significantly higher risk of vision loss than nonproliferative diabetic retinopathy (NPDR), and it is more common in patients with type 1 diabetes, who are typically younger [2, 3]. For many years, panretinal photocoagulation has been the standard treatment for PDR. Recent results, however, show that PDR can be treated with intravitreal injections of anti-VEGF without leading to photocoagulation of the peripheral retina. This review aims to highlight the limitations of anti-VEGF treatment, which call for prudent patient selection and monitoring, as well as to explain the positive outcomes of anti-VEGF use in PDR [4].

Materials and methods

The effectiveness of anti-VEGF medicines in the treatment of diabetic retinopathy (DR) was the subject of a comprehensive review of the scientific and medical literature. A structured search was performed in the PubMed, Scopus, and HINARI databases, considering relevant articles published in the last 10 years. The search terms used (in English) were: "angiogenesis inhibitors", "anti-VEGF", "pan-retinal photocoagulation", "intravitreal injection", "diabetic retinopathy". Accurate diagnosis, side effects, quality of life, and patient satisfaction were analyzed and compared for each treatment option. Original articles, meta-analyzes and systematic reviews were selected.

Results and discussion

After processing the information from the PubMed, Scopus and HINARI databases, according to the search criteria, 189 articles on anti-VEGF factor in diabetic retinopathy management were selected. The final bibliography contains 26 relevant sources, which were considered representative of the material published on the topic of this synthesis article. Publications that did not reflect the research topic, as well as articles that were not accessible through the HINARI database, were excluded.

Anti-VEGF treatments have been demonstrated to be beneficial in reducing macular edema, enhancing visual acuity, and slowing the advancement of diabetic retinopathy. While being generally safe, there were variations in the negative side effect profiles of the various anti-VEGF medicines.

Relative retinal ischemia creates a proangiogenic setting in proliferative diabetic retinopathy, a microvascular disease.

The pathophysiology of diabetic retinopathy (DR) involves several mediators, one of which is vascular endothelial growth factor (VEGF). Increased vascular permeability and proliferation of vascular endothelial cells are caused by aberrant VEGF synthesis and release. VEGF also plays a crucial role in the pathophysiology of diabetic macular edema (DME). Additionally, it is a key mediator in the development of retinal neovascularization, which can lead to vitreous bleeding and tractional retinal detachment.

VEGF is a major mediator of angiogenesis. Several isoforms of the VEGF family are necessary for the proper growth of the lymphatic and blood vessels. Research on molecules has demonstrated that VEGF-A stimulated angiogenesis and vascular permeability by interacting with VEGF receptor 2 on vascular endothelial cells. This interaction leads to weakening of blood arteries due to the breakdown of capillary endothelial tight-junction and the formation of endothelial cell fenestration. Additionally, VEGF-A induces the migration and proliferation of endothelial cells, which are modifications associated with early angiogenesis. Pathologic revascularization in the retina of the eye has been linked to the VEGF-A165 splice variant of VEGF-A. VEGF injections into animal eyes resulted in a feature set that includes retinal edema, intrareticular vascular proliferations, vessel tortuosity, and intrareticular bleeding, similar to those observed in diabetic or ischemic retinopathy [4].

On the other hand, VEGF suppression stopped the neovascularization of the iris. Research on humans revealed

that compared to normal eyes, eyes with PDR exhibited greater amounts of VEGF in the vitreous or fibrovascular tissues [4].

VEGF refers to a group of factors that include VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and VEGF-FPGF.

The first isoform is considered one of the main pathogenic factors associated with DR. Intravitreous anti-VEGF medications became available, and they had an important impact on the course of DR and the prognosis of patients, including a notable decrease in the prevalence of legal blindness. Anti-VEGF molecules now commonly affect several VEGF isoforms and metabolic pathways. While using anti-VEGF as a first line treatment helped manage DME, there is significant disagreement regarding how to treat the proliferative type [5-7].

The use of laser techniques, delivered through various strategies (immediate, delayed, etc.), in the anti-VEGF era is still the subject of much debate in the literature. We provided a general overview of VEGF-targeting medications and their mechanisms of action to prevent the growth of retinal neovascularization in diabetic retinal disease.

Using the terms "proliferative diabetic retinopathy" and "anti-VEGF" a PubMed literature search was conducted to find studies published up until January 2024. The articles from the Retinopathy Clinical Research Network (DRCRnet) were also examined.

Vascular endothelial growth factor: methods of action and biochemical characteristics in diabetic retinopathy.

Over 100 million people worldwide suffer from diabetic retinopathy (DR), the most prevalent microangiopathic consequence of diabetes mellitus [2, 3]. In developed countries, DR is a leading cause of blindness [7]. The two traditional classifications of DR are proliferative (PDR) and non-proliferative (NPDR). NDPR is characterized by retinal hemorrhages, cotton-wool exudates, microaneurysms, intraretinal microvascular abnormalities (IRMA), peripheral and macular capillary low-perfusion, and is further divided into different stages. The onset of neovascularization marks the progression to PDR. In 5% cases, blindness is associated with neovascular glaucoma, while the majority of blindness cases result from posterior PDR problems such vitreous hemorrhage and retinal detachment [5, 6, 7].

The pathophysiology of diabetic retinal disease (DR) is primarily defined by the co-occurrence of neurovascular unit dysfunction, neoangiogenesis, inflammation, penetration of the blood retinal barrier, and capillary non-perfusion [7, 8]. Angiogenous and inflammatory mediators are produced in greater amounts because of all these abnormalities. In this case, VEGF is definitely a significant pathogenic component that describes DR and its complications. When ischemic or hypoxic stimuli are present in DR, VEGF synthesis is stimulated, leading to a number of changes at various levels. In fact, VEGF raises the phosphorylation of proteins involved in tight junctions, which in turn improves the permeability of retinal capillaries [9]. Induced changes of many intercellular molecules, including occludin, catenins, and cadherins, enhanced transcytosis, and activated NOS-mediated processes, can also lead to VEGF-related hyperpermeability [10].

The initiation and progression of a typical DR-related complication, DME, involve a complex cascade of additional processes and mediators beyond the VEGF-related phenomena, which are primarily regulated by VEGF-A isoforms [11]. Additionally, despite the paucity of research, there is mounting evidence that VEGF-B and PGF play significant roles in the pathophysiology of DR. Strong survival cues on vascular and nonvascular cells can be promoted by VEGF-B, which can also induce neovascular phenomena towards non-inflammatory mechanisms. Similarly, PGF acts as a potent pro-angiogenic mediator, with a strong correlation between the severity of DR and the likelihood that it will advance in both serum and ocular concentrations. Therefore, it is widely agreed that VEGF inhibition plays a crucial role in the therapy of DR [12].

In relation to the neovascular problem, neoangiogenesis is promoted by endothelial cell migration and proliferation, triggered by enhanced VEGF synthesis and release. In fact, VEGF molecules stimulate proliferation of endothelium by activating receptors of tyrosine kinase, VEGFR-1 and VEGFR-2, which facilitates in the progression to PDR. VEGF contributes significantly to the neovascular process associated with DR, however it is only one element in a more intricate pathogenic cascade. It has been shown that the angiopoietin system can actually stimulate and amplify the effects of VEGF neovascular stimuli in addition to regulating vascular integrity. Moreover, neuropilin-1 (NRP1) functions as a co-receptor for VEGF receptor 2 and VEGF165 receptor, further influencing the neovascular process. [7, 13].

Another system involved in DR pathogenesis and in enhancing the neovascular stimulus provided by VEGF is the renin-angiotensin system. The severity of DR, measured by the progression rate of NPDR or the transition to PDR, is closely linked to the activity of the renin-angiotensin system. Given this context, the main therapeutic target of anti-VEGF medications is the VEGF-A isoforms. [7]. It is important to note that endogenous anti-VEGF systems already exist, however they are weakened in conditions affecting the retina, such DR. The physiologic anti-VEGF mechanisms are a subject that has not yet received much attention. Limited data was derived from animal models, which reported, for instance, VEGF165b isoform's anti-VEGF action. More specifically, VEGF165b appears to impede the migration and proliferation of endothelial cells as well as angiogenic stimulation brought on by hypoxia and VEGF overexpression [7, 14].

The following molecules are currently available as anti-VEGF drugs: Bevacizumab (Avastin®, Hoffmann-La Roche); Pegaptanib (Macugen, Eyetech/Pfizer); Ranibizumab (Lucentis®, Novartis Pharmaceuticals Canada Inc.); Aflibercept (Eylea®, BAYER Pharma AG, Germany); and Brolucizumab (Beovu®, Novartis Pharmaceuticals Canada Inc.) [7].

Aflibercept. VEGF Trap, or Aflibercept (Eylea®, BAYER Pharma AG, Germany), is a 115 kDa dimeric glycoprotein. These biochemical characteristics offer relative affinity for VEGF-B and high affinity for PGF and VEGF-A isoforms. Another form of the molecule is Ziv-aflibercept (Zaltrap; Sanofi-Aventis and Regeneron Pharmaceuticals, USA), and it differs from aflibercept mainly in that it has a higher osmolarity and different excipients, but otherwise shows nearly the same biochemical profile. Despite aflibercept's potential benefits in treating macular disorders, its use is still off-label [7, 12].

Bevacizumab. The 148 kDa completely humanized immunoglobulin G1 molecule bevacizumab (Avastin®, Hoffmann-La Roche) binds to VEGF-A isoforms. The intravitreal use of this antibody for retinal illnesses is still regarded as "off-label" treatment as it was initially created for cancer treatment. The basic mechanism of action of bevacizumab is to prevent the neovascular stimulation and VEGF-induced enhanced vascular permeability. It functions as a pure anti-VEGF antibody. Moreover, bevacizumab may interact with HIF-1, obstructing its ability to stimulate the synthesis of VEGF. Bevacizumab is a cost-effective and effective treatment for retinal disorders, according to multiple studies, but its off-label designation limits its use [14-16].

Ranibizumab. Ranibizumab, also known as Lucentis® by Novartis Pharmaceuticals Canada Inc., is a 48 kDa monoclonal antibody fragment (Fab) of humanized immunoglobulin G1κ isotype that binds to various VEGF-A isoforms and blocks their interaction with VEGF receptors 1 and 2. Its affinity for other VEGF-A isoforms (VEGF165, VEGF121, and VEGF110) may have been expanded due to the absence of a fragment crystallizable (Fc) domain and its short molecule size, which may have increased the molecule's penetration into the retina and choroid [7 -11]. Because ranibizumab has a single VEGF binding site, two molecules of the antibody bind to a single VEGF dimer. This unique arrangement enables the ranibizumab/VEGF-A complex to have a higher molecular affinity for VEGF than bevacizumab and aflibercept and a higher stability energy than bevacizumab. Numerous clinical trials, such as READ-2, RESOLVE, RESTORE, RISE and RIDE, LUCIDATE, REVEAL, RELIGHT, RETAIN, and READ-3, explored the use of ranibizumab in various modalities and concentrations, as well as alone or in combination with laser. In order to compare ranibizumab to other methods of managing DR, such as corticosteroids, lasers, or other anti-VEGF molecules, the DRCR network conducted several multicenter clinical trials. These trials included Protocol S (ranibizumab vs. laser in PDR), Protocol T (ranibizumab vs. aflibercept vs. bevacizumab in DME), and Protocol I (fluocinolone acetonide vs. ranibizumab plus deferred laser).

Other notable ranibizumab clinical trials included ROTATE (ranibizumab in persistent DME after bevacizumab treatment), RELATION (ranibizumab plus laser vs. laser alone in DR), REFINE (ranibizumab vs. laser in DME), and TREX-DME (ranibizumab "treat and extend" regimen with or without laser in DME) [7, 17-22].

Brolucizumab. The purpose of brolucizumab (Beovu®, Novartis Pharmaceuticals Canada Inc.) is to reduce molecule size and improve affinity for VEGF-A isoforms in comparison to other molecules. A novel 26 kDa single-chain antibody fragment lacks the Fc portion. In comparison to other anti-VEGF molecules, brolucizumab has demonstrated non-inferiority and better penetrance inside the retina and choroid, leading to its recent approval for the treatment of neovascular age-related macular degeneration. Regarding DR, the ongoing KITE and KESTREL clinical studies have shown promising initial outcomes when it comes to the use of brolucizumab in DME when compared to aflibercept, indicating that it will soon be approved for the management of DR [7,22].

Two novel anti-VEGF compounds that are presently being researched in this area. A new generation antibody biopolymer conjugate called KSI-301 (KODIAK sciences, Palo Alto, CA) is being studied in two trials: a DAZZLE phase 2 trial (NCT04049266) and a phase 1b trial (NCT03790852). It is made up of a phosphorylcholine-based polymer that is specifically designed to prolong anti-VEGF activity and a humanized anti-VEGF monoclonal antibody. A clinical trial, Phase 2b (NCT0334582) is examining a VEGF-C/D inhibitor - OPT-302, for exudative macular degeneration. Moreover, a clinical trial, Phase 3 (NCT03610646) contrasting aflibercept with intravitreal MYL-1701P, a biosimilar recombinant fusion protein to aflibercept, is presently being conducted [7, 22-25].

PDR is a very challenging and potentially severe stage of DR. The use of panretinal photocoagulation has been the primary treatment for this complex form of DR. While it has a significant effect on the visual field, the irreversible destruction of peripheral ischemic retina is associated with a decrease in VEGF production and stabilization of the central retina. Most of the research mentioned earlier attempted to evaluate how anti-VEGF therapies affected peripheral ischemia and neovascularization regression. The key concern is whether anti-VEGF injections alone might replace panretinal photocoagulation. According to a 2014 Cochrane meta-analysis, the safety and effectiveness of anti-VEGF in PDR were found to have low levels of evidence, despite the fact that intravitreal injection use was associated with a moderate risk reduction. The viability and sustainability of DR patient care for hospitals and public health systems will be significantly impacted by the development of longer-lasting anti-VEGF treatments. This advancement is expected to shift current treatment indications away from laser approaches. Anti-VEGF molecules are the preferred treatment for the majority of DR patients, according to the EURETINA guidelines, due to their high efficacy, safety profiles, and manageability. Patients with significant cardiovascular risk may not be suitable candidates for this treatment; in these cases, alternative strategies, such as corticosteroids, should be used instead. For diabetic eyes with a very severe type of DR and for patients who are not able to comply with intravitreal therapy protocols, laser techniques remain useful [25, 26].

Conclusions

When choosing an anti-VEGF treatment for diabetic retinopathy, factors such as patient satisfaction, quality of life, side effects, and correct diagnosis should be taken into account. While anti-VEGF treatments show promise, further study is required to fully understand their advantages and disadvantages and to optimize their application.

Competing interests

None declared.

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Ethics approval

Not needed for this study.

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