MODERN MEDICINE AND PRACTICE
https://inovatus.es/index.php/ejmmp
EUROPEAN JOURNAL OF MODERN MEDICINE AND PRACTICE
Vol. 4 No. 12 (Dec - 2024) EJMMP ISSN: 2795-921X

VEGF INHIBITOR DRUGS IN THE TREATMENT OF DIABETIC RETINOPATHY: A REVIEW

Tadjiyeva Feruza Sultanbayevna
PhD, Associate Professor of the Department of "Medical sciences" of Urgench RANCH technology university

Abduraxmanova Iroda Ikram qizi
Urgench branch of the Tashkent Medical Academy "Department of Otorhinolaryngology and Ophthalmology", assistant of department

Xamroyev Farrux Muxtorovich
Urgench branch of the Tashkent Medical Academy "Department of Otorhinolaryngology and Ophthalmology", 2nd year clinical resident, specialty ophthalmology

Otaboyev Bobur Oybek o'g'li
Urgench branch of the Tashkent Medical Academy "Department of Otorhinolaryngology and Ophthalmology", 2nd year master's student, specialty ophthalmology

Abstract: Relevance: For the treatment of diabetic retinopathy (DRP) in the setting of diabetic macular edema (DME), the development of which is associated with the influence of vascular endothelial growth factor (VEGF), agents with anti-VEGF activity are used. The article provides an analytical review of these agents. Objective: to evaluate the comparative capabilities of anti-VEGF agents in the treatment of DRP. Material and methods: Eleven sources of literature on the above topic, identified using the PubMed search engine, were analyzed. Results: a comparative analysis of existing agents with anti-VEGF activity and used for intravitreal administration during DRP in DME conditions (bevacizumab, ranibizumab, aflibercept, brolucizumab) was carried out. Conclusion: Understanding the pathogenesis and molecular mechanisms underlying the development of DRP plays an important role in the development of innovative treatments for this condition. Research aimed at finding new therapeutic targets for DRP in the setting of DME may open up new opportunities to more effectively combat this complication of diabetes and prevent blindness and low vision.

Keyword: anti-VEGF drugs, diabetic retinopathy, diabetic macular edema.

For the therapy of diabetic retinopathy (DRP) in the context of diabetic macular edema (DME), the development of which is associated with the action of vascular endothelial growth factor (VEGF), drugs with anti-VEGF activity are used. This article presents an analytical review of these drugs.

Vascular endothelial growth factor (VEGF) is a protein (a key pro-inflammatory cytokine) produced by cells in our body both under normal conditions and during the development of ischemia due to various

causes (tumor growth, decompensated diabetes mellitus, neovascular age-related macular degeneration, post-thrombotic retinopathy, and complicated myopic chorioretinal degeneration) [1-5]. Excessive amounts of VEGF produced in patients with decompensated diabetes mellitus lead to the growth of abnormal blood vessels and an increase in vascular permeability in the retina, resulting in the development of pre-proliferative and proliferative diabetic retinopathy (DRP) with the formation of diabetic macular edema (DME) [1, 3, 12]. In turn, DRP and DME can be a cause of irreversible blindness and visual impairment [1, 5, 10]. The introduction of anti-VEGF agents for intravitreal injection into clinical practice has significantly improved the prognosis for preserving visual functions in patients with DRP and DME [1, 11, 15]. In our article, we present an analytical comparative review of the currently available anti-VEGF agents used in ophthalmological practice in various countries around the world.

Objective: To assess the comparative capabilities of anti-VEGF drugs in the treatment of diabetic retinopathy in the context of diabetic macular edema.

Materials and Methods. We analyzed eleven sources of literature on the above topic, identified using the PubMed search engine [1-15]. The article then provides an overview of existing drug formulations with anti-VEGF activity (bevacizumab, ranibizumab, aflibercept, brolucizumab), considering their application in the ophthalmological practice of the Republic of Uzbekistan as a "first-line" treatment for DME in patients with DRP.

Results and Discussion. Currently, scientific literature presents information on four anti-VEGF agents and some substances that may potentially be used for anti-VEGF therapy [1-11]. ***Bevacizumab*** was first approved by the FDA for the treatment of various types of cancer. Its use for treating eye diseases is considered "off-label." It is a fully humanized immunoglobulin G1 (IgG1) molecule weighing 148 kDa, which specifically binds to isomers of vascular endothelial growth factor VEGF-A (the use of which is prohibited in ophthalmology by the Ministry of Health of Uzbekistan, Order No. 29/08-20305).

Aflibercept is a dimeric glycoprotein weighing 115 kDa, also known as a VEGF trap. It is formed by the fusion of the first three Ig VEGFR-1 domains and the Fc region of human IgG1 [11]. These biochemical properties ensure a high affinity for VEGF-A and PGF isomers, as well as a relative affinity for VEGF-B. Another variant of the molecule, differing from aflibercept only in excipients and higher osmolarity, which demonstrates an almost identical biochemical profile, is ziv-aflibercept [2]. Although this molecule has been associated with promising effects in macular diseases, the use of ziv-aflibercept is still not approved [3]. The main studies assessing the efficacy and safety of aflibercept in DRP were VIVID-VISTA (aflibercept versus laser in DME) (Korobelinik Yu.F., Do D.V., Schmidt-Erfurth U. et al.), ENDURANCE (extension of VIVID-VISTA studies) [4], APOLLON - data on aflibercept in DME, and PANORAMA studies (aflibercept in NPDR) [5,6]. In addition, the DRCR network studied the impact of aflibercept on the progression of DR, the occurrence and outcomes of complications: Protocol V (aflibercept versus laser versus observation in DME) (Baker K.V., Glassman A.R., Boley V.T.), and Protocol W (aflibercept versus sham in preventing vision-threatening complications in non-proliferative DRP) without DME [6].

Ranibizumab is a recombinant humanized fragment of a monoclonal antibody (Fab) of the immunoglobulin G1κ isotype, weighing 48 kDa, which binds various isoforms of VEGF-A and prevents interaction with VEGF receptors 1 and 2. The absence of a crystallizable fragment (Fc) and the small size of the molecule may allow for an increased affinity to a greater number of VEGF-A isoforms (VEGF165, VEGF121, and VEGF110), enhancing the molecule's penetration into the retina and choroid [7]. Ranibizumab is characterized by only one type of VEGF binding; for this reason, two molecules of ranibizumab bind to one dimer of VEGF (Vaidyanathan U, Moshirfar M.). This unique configuration allows the ranibizumab/VEGF-A complex to have higher stability energy than bevacizumab (Platania CB, Di Paola L, Leggio GM et al.) and greater molecular affinity for VEGF compared to both bevacizumab and aflibercept (Yan J., Wan H., Fuh J. et al.).

The Diabetic Retinopathy Clinical Research Network (DRCR) has conducted several multicenter clinical studies, including Protocol S, to investigate the similarities and differences in the effectiveness of ranibizumab compared to other approaches in the treatment of diabetic retinopathy (DR). Protocol S compared the efficacy of ranibizumab with laser therapy in the treatment of proliferative diabetic retinopathy (PDR) (Table 1).

The results of the study helped to determine the best approach to treating this condition and to assess the advantages and disadvantages of using ranibizumab compared to laser therapy. They also contributed to the development of treatment recommendations and standards for patients with diabetic retinopathy (Gross J.G., Glassman A.R., Jampol L.M. et al.), including Protocol T (ranibizumab vs aflibercept vs bevacizumab in DME) (Wells J.A., Glassman A.R., Ayala A.R.) and Protocol I (fluocinolone acetonide vs ranibizumab plus deferred laser in DME) (Singer M.A., Miller D.M., Gross J.G. et al.). TREX-DME became an important study for modern clinical practice and helped improve the approach to treating patients with diabetic macular edema (Payne J.F., Waikov K.S., Clark V.L.), ROTATE (ranibizumab for persistent DME after bevacizumab treatment), RELATION (ranibizumab plus laser vs using only laser in DR), and REFINE studies (ranibizumab vs laser in DME) (Li X, Dai H, Li X et al.) [3,5,10].

Brolucizumab (Beovu® Novartis Pharmaceuticals Canada Inc.) is a new single-chain antibody fragment weighing 26 kDa, characterized by the absence of the Fc portion and designed to reduce the size of the molecule and improve affinity for VEGF-A isoforms compared to other molecules (Yannuzzi N.A., Freund K.B., Schmidt-Erfurth U., Garcia-Arumi J., Bandello F., Sharma A., Kumar N., et al.). Brolucizumab was recently approved for the treatment of neovascular age-related macular degeneration, demonstrating comparable efficacy and higher penetration in the retina and choroid compared to other anti-VEGF molecules (Nguyen K.D., Das A., Do D.V. et al.). Regarding DRP and DME, current clinical studies KITE and KESTREL reported preliminary positive results for brolucizumab in DME compared to aflibercept [2], suggesting it may soon be approved for DRP treatment.

Conclusion. Understanding the pathogenesis and molecular mechanisms underlying the development of diabetic retinopathy and diabetic macular edema plays a crucial role in developing new innovative treatment and prevention methods for this condition. Research aimed at finding new therapeutic targets for diabetic retinopathy and diabetic macular edema may open new possibilities for more effective management of these complications of diabetes, thereby preventing vision loss and visual impairment in this complex patient population. Continuous research in this area is key to improving the methods of diagnosing, treating, and predicting diabetic retinopathy.

References

1. Baker K.V., Glassman A.R., Boley V.T., DRCR Retina Network et al. The effect of initial treatment with aflibercept versus laser photocoagulation and observation on vision loss in patients with diabetic macular edema involving the center of the macula and good visual acuity: a randomized clinical trial. JAMA. 2019; 321(19): 1880–1894.
2. Garweg J.G. A randomized double-masked phase III multicenter study to evaluate the efficacy and safety of brolucizumab compared to aflibercept in patients with vision impairment due to diabetic macular edema (KITE). Klin Monbl Augenheilkd. 2020; 237(4): 450–453.
3. Lang G.E., Liakopoulos S., Fögeler J. et al. RELATION Study: Efficacy and safety of ranibizumab in combination with laser photocoagulation compared to laser monotherapy in patients with NPDR and PDR with diabetic macular edema. Acta Ophthalmol. 2018; 96(3): e377–e385.
4. Ferrara N., Damico L., Shams N. et al. Development of ranibizumab, an anti-VEGF antigen-binding fragment for the treatment of neovascular age-related macular degeneration. Retina. 2006; 26(8): 859–

870. Low J., Araujo J., Yan J. et al. Ranibizumab inhibits multiple forms of biologically active vascular endothelial growth factor in vitro and in vivo. Exp Eye Res. 2007; 85(4): 425–430.

5. Fechter S., Fraser H., Marcus W.B. et al. Ranibizumab 0.3 mg for persistent diabetic macular edema after recent, frequent, and chronic bevacizumab: the ROTATE study. Ophthalmic Surg Lasers Imaging Retina. 2016; 47(11): 1–18.
6. Mansur A.M., Al-Ghadban S.I., Younis M.H. et al. Ziv-aflibercept in macular disease. Br J Ophthalmol. 2015; 99(8): 1055–1059.
7. Maturi R.K., Glassman A.R., Yosik K., DRCR Retina Network et al. Effect of intravitreal anti-vascular endothelial growth factor compared with sham treatment for the prevention of vision-threatening complications of diabetic retinopathy: Protocol W of a randomized clinical trial. JAMA Ophthalmol. 2021; 139(7): 701–712.
8. Michaelides M., Keynes A., Hamilton R.D. et al. Prospective randomized study of intravitreal bevacizumab versus laser therapy for diabetic macular edema (BOLT study). Twelve-month data: report 2. Ophthalmology. 2010; 117(6): 1078–1086.e2.
9. Cheng Y.D., Yan H., Chen G.K. et al. Molecularly targeted drugs for the treatment of metastatic colorectal cancer. Drug Des Devel Ther. 2013; 7: 1315–1322.
10. Yuldasheva N.M., Tadjieva F.S., Yuldasheva M. M. Diabetic Vitreopathy in Patients with Type 1 Diabetes Mellitus, Relationship with Local and Systemic Factors - «Teikyo Medical Journal», ISSN: 03875547 Volume 45, Issue 01, February, 2022.
11. Yuldasheva N.M., Tadjiyeva F.S., Ilyasov Sh.Sh., Ishanxadjaeva F.Sh., Yuldashev Sh.M- Усиления тракции при антиVEGF- терапии диабетической макулопатии (случай из практики). «XXI asr qand kasalligi. Global muammolar, local yechim» ilmiy-amaliy konferensiyaga bag'ishlangan Toshkent tibbiyot akademiyasi axborotnomasining maxsus soni. 2019 - yil. 123-125 б. ISSN 2181-7812. O'zbekiston. Toshkent
12. Yuldasheva N.M., Tadjieva F.S Ранняя оценка стекловидного тела у молодых людей при сахарном диабете 1 типа. Russian ophthalmological journal. 2022; 15(3): 80-84
13. Yuldasheva N.M., Tadjieva F.S., Sultanova F. A Оценка состояния стекловидного тела у условно здоровых лиц по данным МСКТ. Новый день в медицине. 2023; 3 (53); С. 225-229
14. Yuldasheva N.M., Tadjieva F.S., Sultanova F. A. Роль стекловидного тела в развитии и прогрессировании диабетической ретинопатии. Специальный выпуск журнала "Инфекция, иммунитет и фармакология" посвящённый международной научно-практической конференция «Проблемы и этапы развития иммунофизиологии в новом Узбекистане». Узбекистан, Ташкент 2023; С. 173-180
15. Wykoff CC, Le RT, Khurana RN, исследовательская группа ENDURANCE и др. Результаты применения афлиберцепта и макулярного лазера по мере необходимости после III фазы исследования VISTA DME: 12-месячное продленное исследование ENDURANCE. Am J Офтальмол. 2017 год; 173 :56–63.

Table 1. Comparative Characteristics of Anti-Angiogenic Drugs

Anti-VEGF Active Drug	Mechanism of Action	Доза и частота введения	Increase in Visual Acuity (Letter Gain)	Changes in Patients with DME and DR
Bevacizumab	Humanized full-length mouse monoclonal antibody; binds only to VEGF-A	1.25 mg	1 year (20/32–20/40): +7.5 1 year (20/50–20/320): +11.8 2 years (20/32–20/40): +6.8 2 years (20/50–20/320): +13.3	2 years: 30% improvement *
Ranibizumab	Fragment of humanized mouse mAb, binds VEGF-A, with higher affinity	0.3-0.5 mg, once a month, 3 doses for loading; then frequency based on clinical situation – “as needed” (PRN)	1 year (20/32–20/40): +8.3 1 year (20/50–20/320): +14.2 2 years (20/32–20/40): +8.6 2 years (20/50–20/320): +16.1	2 years: 38% improvement Less loss of visual field over 5 years compared to panretinal laser photocoagulation
Aflibercept	Human fusion protein of the Fc region of IgG; binds VEGF-A, VEGF-B, PlGF-1, and PlGF-2	0.5 mg, once a month, 5 doses for loading; then, once every 2 months; may extend intervals based on clinical situation – “treat and extend”	1 year (20/32–20/40): +8.0 1 year (20/50–20/320): +18.9 2 years (20/32–20/40): +7.8 2 years (20/50–20/320): +18.1	2 years: 70% improvement 3 years: 62% improvement, 33% indication for vitrectomy
Brolucizumab	Single-chain antibody fragment (scFv) with high affinity for VEGF	0.5 mg, once a month for AMD - 3 doses for loading; then, once every 3 months; may extend intervals based on clinical situation – “treat and extend,” for DME – under investigation	1 year: +9.2 and +10.6	1 year: 29.6% improvement

Notes: VEGF – Vascular Endothelial Growth Factor; PlGF – Placental Growth Factor; scFv – Single-Chain Antibody Fragment.