Pro Index | Journal of Science in Medicine and Life

Volume: 1 Issue: 4 Year: 2023

http://journals.proindex.uz

The Role of Antiangiogenic Drugs in the Treatment of Diabetic Macular Edema

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Abstarct: The article presents the characteristics of the first antiangiogenic drug registered for the treatment of diabetic macular edema, ranibizumab, as well as the new long-acting drug brolucizumab.

Key points: diabetic macular edema, antiangiogenic therapy, ranibizumab, brolucizumab, neovascularization, diabetic retinopathy.

The article presents the characteristics of the first antiangiogenic drug registered for the treatment of diabetic macular edema, ranibizumab, as well as the new long-acting drug brolucizumab.

Introduction. The number of patients with diabetes mellitus (DM) increases every year in the world. According to forecasts, by 2035 this figure will reach 592 million. Diabetic retinopathy (DR) and diabetic macular edema (DME) are serious complications leading to vision loss in patients with diabetes [2]. DME can develop at any stage of DR. This pathology leads to disability of the working population and is considered one of the pressing problems of modern healthcare due to the increase in economic costs for treatment and rehabilitation of patients. In addition, screening for DR and DME is currently of particular importance in ophthalmology for the correct choice of tactics for managing patients with diabetes.

VEGF is a vascular endothelial growth factor that is produced in the early stages of DR. Hypoxia and hyperglycemia cause increased synthesis of VEGF and its receptors, and hyperproduction of VEGF, in turn, contributes to increased permeability of retinal vessels, the development of macular edema and neovascularization. Determination of the role of VEGF in the pathogenesis of DR and DME initiated studies of the interaction of pro- and antiangiogenic growth factors, proinflammatory cytokines, adhesion molecules, chemokines and proteases [3]. As a result of the study of VEGF, inhibitors of angiogenesis (anti-angiogenic drugs, or anti-VEGF drugs) were developed. A breakthrough in the treatment of patients with DME is associated with these drugs. However, despite the proven effectiveness of antiangiogenic drugs in modern ophthalmology, the search for new drugs to reduce the number of injections and the burden on patients and doctors continues. In clinical studies, new anti-VEGF drugs demonstrate safety and effectiveness. Meanwhile, while in studies the use of these drugs is associated with maintaining or improving visual acuity in almost 90% of cases, in real clinical practice such results are not observed [4]. Ophthalmologists often encounter patients violating injection intervals due to exacerbation of other concomitant diseases; not all patients are suitable for new drugs. The approach to the choice of therapy for each patient with diabetes should be purely individual. Clinicians should not forget about well-known drugs that have already proven themselves.

Let us consider the characteristics of the first antiangiogenic drug registered for the treatment of DME, ranibizumab, as well as the new long-acting drug brolucizumab.

Ranibizmub is an antiangiogenic drug specially created for use in ophthalmology. In 2006, the drug was approved by the US Food and Drug Administration (FDA) for the treatment of neovascular age-related macular degeneration (AMD), in 2010 - for the treatment of macular edema after occlusion of the central retinal vein and its branches, and in 2012 – for the treatment of DME. Ranibizumab was the first intraocular drug for DME. In 2015, an additional FDA license was obtained for the treatment of DR in patients with DME, which in 2017 extended to all patients with DR, including patients without DME. Since 2019, a license has been in effect for the use of ranibizumab for retinopathy of prematurity [2].

Ranibizumab is a fragment of a humanized antibody to vascular endothelial growth factor A (VEGF-A), which selectively binds to VEGF-A (VEGF110, VEGF121, VEGF165) and prevents its interaction with receptors on the surface of endothelial cells (VEGFR1 and VEGFR2), which leads to suppression of neovascularization and proliferation of endothelial cells [5].

When visual acuity (VA) decreases due to DME, the recommended dose of ranibizumab in adults is 0.5 mg, which corresponds to 0.05 ml of solution, as an intravitreal injection. An interval of at least four weeks should be observed between injections of the drug in one eye. To achieve disease stabilization, three or more consecutive monthly injections of the drug may initially be required. After stabilization of the disease is achieved, the time interval between injections is set by the doctor depending on the activity of the disease, assessed based on the maximum correctable visual acuity and/or anatomical parameters. There are two modes of drug administration - treat and extend (T&E) and treatment as needed (pro re nata, PRN). When using the T&E regimen, upon reaching maximum VA and/or in the absence of signs of disease activity, a gradual increase in the intervals between intravitreal injections is possible. With DME, each subsequent interval between injections is increased by no more than one month [5].

The effectiveness of ranibizumab in DME has been proven in a number of randomized multicenter studies performed according to GCP standards, and is also confirmed by many years of experience in using the drug in real clinical conditions [6].

The READ-2 and RESTORE studies show the advantages of ranibizumab therapy and its combination with retinal laser coagulation (LRCC) over traditional laser treatment.

The READ-2 study (Primary end point (six months) results of the ranibizumab for edema of the macula in diabetes) involved 126 patients with DME, who were divided into three groups. Patients in the first group received 0.5 mg of ranibizumab at the beginning of the study and after one, three and five months. Patients in the second group underwent focal LCS at the beginning of the study and (if indicated) three months later. In the third group, a combination of 0.5 mg ranibizumab and focal LCS was used.

The best results (improved VA and reduced retinal thickness) after six and 24 months from the start of treatment were obtained in the ranibizumab group [7].

The randomized, double-blind, multicenter, phase III RESTORE (Ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema) study assessed the efficacy and safety of ranibizumab in patients with visual impairment caused by DME. 345 patients with type 1 and type 2 diabetes were divided into three groups:

- ranibizumab 0.5 mg in combination with simulated laser coagulation;
- ranibizumab in combination with laser coagulation;
- imitation injection in combination with laser coagulation.

By the end of the study, an increase in VA was observed in the ranibizumab groups (first group +6.1 letters, second +5.9 letters). In the LKS group, VA did not change significantly (+0.8 letters). With

the use of ranibizumab, the decrease in retinal thickness in the macular zone was more pronounced [8].

The randomized, controlled, double-blind, multicenter, phase II RESOLVE (Safety and efficacy of ranibizumab in diabetic macular edema) trial assessed the safety and efficacy of ranibizumab as a treatment for DME at 12 months in 151 patients with DME. Study participants were divided into three groups:

- administration of ranibizumab at an initial dose of 0.3 mg;
- administration of ranibizumab at an initial dose of 0.5 mg;
- imitation of intravitreal injections (placebo).

The study protocol included three monthly administrations of ranibizumab at an initial dose of 0.3 or 0.5 mg or sham intravitreal injections. Improvement in VA during the administration of the drug was noted a month after the first injection, the effect intensified with continued therapy. After 12 months of treatment, VA improved by an average of 10.3 letters in the ranibizumab group. The placebo group experienced a deterioration in the score (-1.4 letters). Retinal thickness decreased by an average of 194 μm during active treatment and by 48 μm when simulating injections of the drug [9].

The largest study confirming the effectiveness of ranibizumab is DRCR.net (Diabetic Retinopathy Clinical Research network). In 2010, the results of this key project were published. DRCR.net was a multicenter study that included 691 patients (854 eyes). The patients were divided into four groups:

- placebo injections + urgent LCS (3–10 days after injection);
- ranibizumab 0.5 mg + urgent LCS;
- ranibizumab 0.5 mg + LCS delayed 24 weeks or more;
- triamcinolone 4 mg + urgent LCS.

Ranibizumab injections were given monthly, and triamcinolone was administered once every 16 weeks. After a year, patients who received ranibizumab (+9 letters) showed better results in terms of changes in VA compared to patients who were prescribed placebo injections and urgent LCS (+3 letters). There were no significant differences in the increase in VA when using triamcinolone and LCS. By the end of the second year of observation, the positive dynamics of VA remained in the ranibizumab groups (+7 letters when combined with immediate LCS, +10 letters when combined with delayed LCS) [3].

The safety of ranibizumab has been confirmed by many years of experience in its use. Most of the adverse reactions that occur during the use of ranibizumab are associated specifically with the intravitreal injection procedure, and not with the effect of the drug. Adverse reactions include eye pain, increased intraocular pressure, redness of the eye, conjunctival hemorrhage, dry eye syndrome, blepharitis, retinal hemorrhage, inflammation and opacification of the vitreous, and vitreous detachment. More serious, but less common complications are retinal detachment, endophthalmitis, and iatrogenic traumatic cataract [5].

It should be noted that most initial clinical trials of anti-VEGF agent therapy for DME used ranibizumab, which is specifically designed for intraocular use. Bevacizumab has not been approved by the FDA for intraocular use.

Brolucizumab. In 2019, the FDA approved the drug brolucizumab. Brolucizumab is a single chain Fv (scFv) fragment of a humanized monoclonal antibody that binds with high affinity to various isoforms of VEGF-A (particularly VEGF110, VEGF121 and VEGF165), interfering with the binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2 . Brolucizumab inhibits VEGF-A binding, thereby inhibiting endothelial cell proliferation, reducing pathological neovascularization and vascular permeability [10]. Brolucizumab is one of the modern antiangiogenic drugs used in ophthalmology. The advantage of brolucizumab is its low molecular weight (26 kDa) compared to

other anti-VEGF molecules, which allows a larger amount of the drug to be administered in one dose. Consequently, its duration of action and tissue penetration are higher [11].

KITE and KESTREL were randomized, two-year, multicenter, double-blind, phase III studies evaluating the safety and efficacy of brolucizumab in DME. In these studies, brolucizumab showed positive results [12]. In both studies, after the first five doses were given every six weeks (loading dose), patients were switched to dosing every 12 or eight weeks (depending on disease activity). The effectiveness of brolucizumab was not inferior to that of the comparator drug aflibercept 2 mg [13].

Speaking about the safety of brolucizumab, it should be emphasized that its use is associated with such an undesirable reaction as conjunctival hemorrhage. The most serious complications include endophthalmitis, retinal vasculitis, and/or retinal vascular occlusion. Complications are observed in patients with antibodies that appeared during treatment. These immune-mediated phenomena can develop both after the first intravitreal injection and at any time during treatment, most often at the beginning. Patients should be informed that in the event of a sharp decrease in vision, they should immediately consult an ophthalmologist [10].

A new indication for brolucizumab was registered in 2022: the treatment of vision loss associated with DME. In 2023, brolucizumab was included in the new clinical guidelines “Diabetes mellitus: diabetic retinopathy, diabetic macular edema” [14].

Comparative characteristics of ranibizumab and brolucizumab are presented in the table.

Conclusion. In domestic practice, various antiangiogenic drugs are used to treat patients with DME. However, modern ophthalmology continues to search for new drugs, the use of which is associated with fewer injections and, consequently, less burden on the patient and the healthcare system. The choice of a specific drug in patients with DME should be purely individual and take into account the characteristics of the medical history, the course of diabetes, as well as the presence of other somatic pathologies. Despite the success of new drugs demonstrated in clinical trials, it takes time to evaluate their effectiveness in real clinical practice. When choosing patient management tactics, ophthalmologists should not forget about already known drugs, the safety of which has been confirmed by many years of experience in their use.

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