ARTYKUŁ POGLĄDOWY / REVIEW PAPER
Otrzymano/Submitted: 05.02.2025 • Zaakceptowano/Accepted: 06.05.2025

Monoclonal antibodies – application in ophthalmology

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Abstract

The introduction of monoclonal antibody therapy in treating ophthalmic diseases has contributed to a significant improvement in the prognosis for many patients. Modern biological drugs are particularly important in the treatment of diseases, controlling pathological angiogenesis in the eye or intraocular inflammation. Main indications include: age-related macular degeneration (AMD), diabetic macular edema (DME), proliferative diabetic retinopathy (PDR), retinopathy of prematurity (ROP), uveitis, and ocular tumors. These diseases often lead to significant impairment or even complete loss of vision. The occurrence of such ailments is a serious problem because it limits the independence of patients. Thanks to the use of biological drug therapy, it is possible to stop the progression of retinal diseases and even improve visual acuity. *(Farm Współ 2025; 18: 241-254) doi: 10.53139/FW.20251839*

Keywords: monoclonal antibodies, age-related macular degeneration, proliferative diabetic retinopathy, diabetic macular edema, Ranibizumab, Aflibercept

This work aims to fully discuss the use of biological drugs in modern ophthalmology and present the pathomechanisms of diseases. This method of presentation will allow for a more detailed understanding of the action of these drugs. The effectiveness of these substances has been assessed in numerous clinical studies, some of which we will cite below. In this article, we want to emphasize how modern therapies have changed the treatment of many diseases and improved the prognosis for patients previously at risk of rapid vision loss. This has a very significant impact on the life of society because blindness is associated with the exclusion of patients from certain areas of life, such as work, and makes them partially dependent on the support of other people. Currently, thanks to the use of these therapies, patients have a chance to stop the development of diseases such as age-related macular degeneration (AMD) and many others.

Monoclonal antibodies are used in ophthalmology, particularly in treating diseases related to abnormal blood vessel growth in the retina. An example is the treatment of wet age-related macular degeneration (AMD), where drugs such as ranibizumab (Lucentis), aflibercept (Eylea), and bevacizumab (Avastin) are used. These drugs block vascular endothelial growth factor (VEGF), inhibiting pathological new blood vessel formation and fluid leakage into the retina. Their mechanism of action includes neutralization of the target, inhibition of disease processes, and modulation of the immune system, ultimately leading to inhibition of disease progression.

These medications are also used in the treatment of proliferative diabetic retinopathy (PDR), diabetic macular edema (DME), certain forms of glaucoma, and other vascular eye diseases. Additionally, they are employed in less common conditions such as retinopathy of prematurity (ROP), ocular tumors, and complications arising from central retinal vein occlusion (CRVO). Often, these drugs are the only way to prevent progressive vision loss, especially in cases where traditional treatments such as laser therapy are no longer sufficient [1-3].

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Vascular endothelial growth factor (VEGF)-A is recognized as the most potent stimulator of neoangiogenesis. It exerts its effects by binding various isoforms of the factor with receptors on endothelial cells–VEGFR-1 and VEGFR-2. The VEGFR-2 receptor exhibits strong tyrosine kinase activity and stimulates the initiation of a signaling cascade leading to angiogenesis. This involves the phospholipase-Cgamma-protein kinase-C signaling pathway, which activates MAPKs (mitogen-activated protein kinases), ultimately resulting in DNA synthesis activation. Inhibition of this signaling pathway is critical in treating many retinal diseases and malignant tumors, as it directly leads to pathological angiogenesis [4,5].

The VEGFR-1 receptor, in addition to being present on endothelial cells, is also found on the surface of macrophages. It transmits signals that promote the migration and production of biologically active factors, such as pro-inflammatory cytokines, by these cells. VEGFR-1 also plays a significant role in developing malignant tumors and forming metastases by stimulating angiogenesis and lymphangiogenesis. Its activity promotes endothelial cell proliferation and migration, the induction of proteinases modeling the extracellular matrix, increased vascular permeability, and stabilization of newly formed microvessels [6].

Age-related macular degeneration (AMD)

Age-related macular degeneration (AMD) is one of the most common causes of irreversible vision loss in developed countries. Two forms of this condition are recognized: dry (geographic atrophy) and wet (neovascular). In the wet form of AMD, pathological neovascularization occurs in the subretinal space, leading to intraretinal fluid leakage, bleeding, and retinal and subretinal scarring [2,7]. As a result of the process, vessel growth is promoted and inhibited by the action of cytokines, especially endothelial growth factor (VEGF). VEGF promotes vessel proliferation, which tends to leak and rupture. This process results in macular neovascularization (MNV). If appropriate treatment for MNV is not initiated, the prognosis is unfavorable; complete loss of vision may occur within a short period. First symptoms noticed by patients include visual disturbances, such as blurriness and metamorphopsia.

Currently, monoclonal antibodies, primarily anti-VEGF agents, are used to treat the wet form of AMD. The medication is administered via intravitreal injections. The indication for monoclonal antibody treatment in AMD is active macular neovascularization, which significantly improves prognosis. The best results are achieved when therapy is initiated within 2–3 weeks of the onset of symptoms. The most commonly used

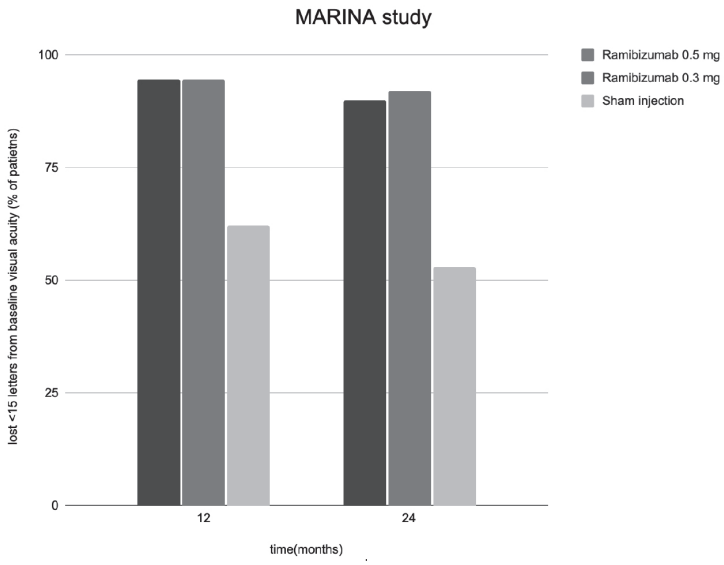

Figure 1. Percentage of patients with lost fewer than 15 letters of visual acuity at 12 months and 24 months from baseline in the MARINA study

monoclonal antibodies are ranibizumab (Lucentis), bevacizumab (Avastin), and aflibercept (Eylea).

Ranibizumab (Lucentis) is a humanized monoclonal antibody fragment used in ophthalmology. Its mechanism of action is based on blocking VEGF-A. Studies on the efficacy and safety of ranibizumab have shown that intravitreal injections significantly reduce the risk of vision loss in subretinal neovascularization (CNV) and macular edema (ME). One of the first multicenter clinical trials on the efficacy of ranibizumab was the MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration) study, with results published in 2006. The study was conducted over 24 months and included 716 patients with neovascular age-related macular degeneration. The majority of study participants had early-stage neovascularization or the latent form. Patients received intravitreal injections of ranibizumab at doses of 0.3 mg, 0.5 mg, or placebo over 24 months. After 12 months of treatment, 94.5% (0.3 mg dose) and 94.6% (0.5 mg dose) of patients had a loss of visual acuity that was 15 letters less than the control group. After 24 months, mean visual acuity in the ranibizumab groups improved by 6.5 letters (0.3 mg) and 7.2 letters (0.5 mg) compared to the placebo group, which experienced a mean loss of 10.4 letters. During follow-up, there was a low risk (<2%) of serious complications such as endophthalmitis. Over the 2-year study period, the drug effectively prevented vision loss and improved visual acuity in patients with active macular neovascularization in AMD and is now widely used [8].

In 2009, the results of the multicenter phase III ANCHOR study were published. The study compared the effects of intravitreal injections of ranibizumab (Lucentis) versus verteporfin photodynamic therapy (PDT) in patients with CNV suffering from AMD. The follow-up period was 24 months and included a total of 423 patients, of whom approximately 77% completed the entire study. Patients were randomized to 3 groups: ranibizumab 0.3 mg or 0.5 mg, PDT, or sham injections. After 12 months of treatment, the first results were evaluated, which showed an advantage of treatment with Lucentis over PDT. At 24 months of follow-up, the results were as follows: 89.9% to 90.0% of ranibizumab-treated patients lost < 15 letters from baseline compared with 65.7% of PDT patients. In contrast, 34% to 41% gained ≥ 15 letters in the ranibizumab group compared with 6.3% in the PDT group. At 12 months, the Lucentis group had a significant change in total CNV area of 0.1-0.3 DA compared with 2.3-2.6 DA in the control groups. The incidence of severe complications with ranibizumab injections was low. The study's final analysis showed that biological therapy (Lucentis) provided superior clinical outcomes for patients compared with PDT [9].

Bevacizumab (Avastin) is a humanized monoclonal antibody against VEGF-A that leads to inhibition of the signaling pathway activating the angiogenesis process. The drug is primarily used in oncology, treating cervical, pancreatic, rectal, breast, and ovarian cancers [10]. Although it lacks registered indications for ophthalmic use, it is widely employed off-label, and its efficacy is well-documented in numerous scientific publications. It has a long half-life, persists in the eye for a long time, and affects the systemic pool of VEGF [11].

Aflibercept (Eylea) is a human recombinant fusion protein that acts as a receptor for vascular endothelial growth factors, including VEGF-A, VEGF-B, and placental growth factor (PlGF). It has a much higher affinity for the VEGF-A isoform than ranibizumab or bevacizumab and is considered the strongest of the three anti-VEGF drugs [12].

In 2012, the results of the multicenter phase III VIEW1 and VIEW2 studies were published, evaluating the efficacy of Eylea administered via intravitreal injections in patients with the neovascular form of AMD compared to treatment with ranibizumab. The observation period lasted 96 weeks and included 2,412 patients, of whom 1,817 were treated with Eylea. The patients' ages ranged from 49 to 99 years, with an average age of 76. The participants were randomized into four groups; three received Eylea, and the last received ranibizumab at the standard dose.

An assessment conducted after 52 weeks of treatment revealed that vision was maintained in 95.1% and 95.6% of patients in the Eylea groups in the VIEW1 and VIEW2 studies, compared to 94.4% in the ranibizumab group. Visual acuity improved in 30.97% of patients treated with Eylea, compared to 32.44% in those treated with ranibizumab.

A subsequent assessment at week 96, based on a pooled data analysis, showed vision maintenance in 92.42% of patients treated with Eylea, compared to 91.60% in the ranibizumab group. The studies also demonstrated improved visual acuity in the Eylea group, with a rate of 33.44% versus 31.60% in the ranibizumab group. Moreover, the studies indicated a

significantly lower number of required injections when using aflibercept (Eylea) compared to ranibizumab. The mean number of injections in the Eylea group was 7.6 at week 52 and 11.2 at week 96, while for ranibizumab it was 12.3 at week 52 and 16.5 at week 96.

Both VIEW1 and VIEW2 studies also showed a mean reduction in the size of choroidal neovascularization (CNV), as assessed by OCT (optical coherence tomography), in both the Eylea and ranibizumab groups. The final analysis demonstrated that Eylea provided better clinical outcomes with significantly fewer intravitreal injections [13].

One of the newer biological drugs gaining increasing interest is faricimab (Vabysmo). It is the first dual-acting monoclonal antibody used in ophthalmology. It works by inhibiting VEGF and angiopoietin-2 (Ang-2). The mechanism of inhibition of endothelial growth factors (VEGF) is commonly used in retinal diseases. The inhibition of angiopetin-2 is something that distinguishes this drug. This factor also has angiogenic effects, and its level is increased in hypoxia conditions and active inflammatory processes. Both of these factors act synergistically, leading to vascular leakage, macular edema, and the development of pathological blood vessels. Studies have shown that this drug, by inhibiting Ang-2, also supports the stability of vessel walls and limits the effect of VEGF on them. Multicenter clinical trials have shown that patients with wet AMD receiving Faricimab intravitreal injections for 48 weeks improved visual acuity and reduced macular edema comparable to those receiving Aflibercept 2 mg injections. Additionally, faricimab has a low risk of severe complications, such as retinal detachment or vitreous hemorrhage (<1% complications). It is currently used in patients with wet AMD and DME [14,15].

Another drug with proven efficacy in treating the neovascular form of AMD is brolucizumab (Beovu), a humanized single-chain Fv fragment of a monoclonal antibody. The drug exhibits high affinity for the VEGF-A isoform and prevents its binding to VEGF receptors 1 and 2. As a result, it limits the growth of pathological blood vessels and their permeability, thereby inhibiting the development of macular edema [16].

Its molecular structure allows it to remain in the vitreous body longer, resulting in extended intervals between injections. Its production is cheaper and easier than other biologic drugs, as it can be manufactured using genetically modified bacterial strains [17,18].

Brolucizumab is administered via intravitreal injection [16].

The results of two similar phase III clinical trials, HAWK and HARRIER, demonstrate the efficacy of brolucizumab compared to aflibercept in treating macular edema in the neovascular form of AMD. These randomized, double-masked studies were conducted over two years across 408 centers and included 1,817 patients with active macular choroidal neovascularization (CNV). Eligible participants were over 50 years old and had previously untreated macular edema due to exudative AMD.

In the HAWK trial, participants received either brolucizumab at 3 or 6 mg or aflibercept at 2 mg. In the HARRIER trial, patients were given brolucizumab at 6 mg or aflibercept at 2 mg. Initially, Beovu was administered every 4 weeks for the first three doses in both studies, followed by dosing every 12 weeks or at intervals adjusted according to disease activity.

The primary endpoint for assessing treatment efficacy was the change in best corrected visual acuity (BCVA) from baseline to week 48. Final results showed that brolucizumab 6 mg, administered every 8 or 12 weeks, produced non-inferior therapeutic outcomes compared to aflibercept 2 mg administered every 8 weeks. After 48 weeks, patients receiving 6 mg of Beovu gained an average of 6.6 letters on the ETDRS (Early Treatment Diabetic Retinopathy Study) chart, compared to 6.8 letters in patients treated with aflibercept.

When evaluating anatomical changes (such as retinal thickness and the presence of intraretinal fluid), brolucizumab showed better outcomes at both weeks 16 and 48 compared to the aflibercept group. The safety profile of brolucizumab was found to be noninferior to aflibercept. Thus, it represents an attractive alternative to other biologic drugs, offering longer intervals between injections and allowing dosing to be tailored to disease activity and the individual needs of each patient [19].

Diabetic macular edema (DME)

Diabetic maculopathy refers to swelling or exudation in the macula observed in patients with diabetes. It is caused by disruption of the blood-retina barrier, which consists of inner and outer parts. The cascade leading to the damage of this barrier involves numerous substances such as angiotensin II, advanced glycation end products, diacylglycerol, endothelin, lipoxygenase,

nitric oxide, protein kinase C, and vascular endothelial growth factor (VEGF) [20]. One of the most significant risk factors is poor diabetes control with high blood glucose levels. The edema can occur in a diffuse form due to intense capillary leakage or in a focal form due to leakage from microaneurysms [21]. As a result of this process, the retina thickness and central vision deteriorate. This is one of the most common causes of vision loss in diabetic patients [22].

In recent years, intravitreal administration of monoclonal antibodies–vascular endothelial growth factor inhibitors–has gained importance in treating diabetic maculopathy. The results of studies comparing the use of laser photocoagulation with biological drugs show that they can provide better therapeutic results [3].

The treatment of this condition most commonly involves two biological drugs that inhibit VEGF: Ranibizumab and Aflibercept [23]. Brolucizumab and Faricimab are also registered in DME therapy.

In the case of DME treatment, it is worth focusing on faricimumab because it is a monoclonal antibody with bispecific action. By inhibiting Ang-2 and VEGF-A, it not only halts pathological angiogenesis but also suppresses inflammatory processes [24]. The results of the FARETINA-DME study from 2024 show that faricizumab has high efficacy in the treatment of DME resulting from this dual action of the drug. An essential aspect of this study was the inclusion of patients previously treated with another VEGF inhibitor. Both previously untreated and previously treated patients achieved improvement in visual acuity and improvement in anatomical parameters [reduction in the thickness of the central subfield of vision (CST)] [25].

The results of a study (Early Response to Anti-Vascular Endothelial Growth Factor and Two-Year Outcomes Among Eyes with Diabetic Macular Edema in Protocol T) published in 2018 in JAMA presented a comparison of changes in visual acuity and anatomical outcomes over a two-year period following treatment with anti-VEGF biologic agents–aflibercept, bevacizumab, and ranibizumab–in patients with diabetic macular edema (DME). The initial treatment effects were assessed at 12 weeks, with a follow-up evaluation after two years.

At the first follow-up point, the mean change in visual acuity (VA) from baseline was greater with aflibercept than with bevacizumab (adjusted difference of 2.9 letters; 95% confidence interval [CI]: 1.1–4.7 letters; $P < 0.001$) or ranibizumab (adjusted difference of 2.6 letters; 95% CI: 0.8–4.3 letters; $P = 0.002$). There was no significant difference between bevacizumab and ranibizumab (adjusted difference of -0.4 letters; 95% CI: -1.9 to 1.1 letters; $P = 0.63$).

These findings were compared with the results after two years of observation. It was found that eyes gaining fewer than five letters at the 12-week mark showed less improvement in visual acuity from baseline after two years than eyes that had gained 10 or more letters at the first assessment.

The second parameter evaluated in the study was Central Subfield Thickness (CST). The mean relative change in CST from baseline at 12 weeks was greater with aflibercept than with bevacizumab (adjusted difference of -9.6%; 95% CI: -13.3% to -5.9%; $P < 0.001$). However, there was no statistically significant difference between aflibercept and ranibizumab (adjusted difference of -1.9%; 95% CI: -5.0% to 1.2%; $P = 0.22$). The mean relative change was also greater with ranibizumab than with bevacizumab (adjusted difference of -7.7%; 95% CI: -11.2% to -4.2%; $P < 0.001$).

After the 24-month follow-up, it was found that 42% of patients treated with aflibercept, 31% of those treated with bevacizumab, and 47% of those treated with ranibizumab had gained 10 or more letters. This indicates a lack of long-term correlation between early minimal improvement in visual acuity (gaining fewer than five letters) and long-term outcomes [26].

Retinopathy of prematurity (ROP)

Retinopathy of prematurity (ROP) is the leading cause of blindness and significant vision impairment in young children worldwide. It primarily affects premature infants with low gestational age and very low birth weight. This disease results from an abnormal process of blood vessels and connective tissue development in the retina. The multicenter Cryotherapy for Retinopathy of Prematurity study showed that the most important risk factors include: low gestational age, low birth weight, white race, multiple birth, and delivery outside a referral center. Long-term oxygen therapy with high oxygen concentrations and infectious factors in intrauterine infections also play a significant role in pathogenesis. The latter plays a key role in developing the severe form of ROP. These factors contribute to increased vascular endothelial growth factor (VEGF) expression, which stimulates abnormal proliferation

of blood vessels along the retina and into the vitreous body.

The goal of treatment is to inhibit neovascularization, stimulate the formation of normal blood vessels, and support the proper development of retinal neuroreceptors. Currently, two primary methods are used in therapy: laser photocoagulation and biological anti-VEGF drugs, either as monotherapy or combined. Monoclonal antibodies are administered via intravitreal injections. Anti-VEGF therapy (bevacizumab) was first used in the treatment of ROP in 2007 - it was a single injection and was successful. Currently, it is believed that VEGF therapy has similar efficacy to laser therapy, while at the same time it has a lower risk of developing myopia and side effects. The first drug approved for use in retinopathy of prematurity is ranibizumab [27].

A phase III clinical trial, RAINBOW, conducted on premature infants weighing less than 1500 g and meeting the criteria for ROP, compared the therapeutic effects among three groups. The first group was treated with laser therapy, the second received intravitreal ranibizumab injections at 0.1 mg, and the third received ranibizumab at 0.2 mg. The final results showed that a 0.2 mg dose of ranibizumab could provide better therapeutic outcomes and fewer complications than laser therapy [28]. Another drug approved for ROP treatment is aflibercept (Eylea). Retrospective studies on premature infants treated with ranibizumab and aflibercept between 2015 and 2017 showed that both drugs were effective in ROP therapy. Still, patients receiving aflibercept had a longer relapse-free period. The average recurrence times were 8.2 ± 0.92 weeks for ranibizumab and 14.2 ± 1.03 weeks for aflibercept [29].

The FIREFLEYE study (JAMA) aimed to compare the efficacy and safety of intravitreal aflibercept injections (0.4mg) with laser photocoagulation in preterm infants with severe retinopathy of prematurity (ROP). Laser photocoagulation is the standard treatment but is associated with complications such as narrowing the visual field. Previous studies suggested that anti-VEGF therapy (including aflibercept) might be an alternative. The study was a randomized, open-label phase 3 clinical trial lasting 24 weeks. It was conducted in 64 centers across 27 countries. The patients were preterm infants (gestational age <32 weeks or birth weight 1500 g) with severe ROP (in Zone IL stages 1+ to 3+; Zone II: stages 2+ to 3+ or aggressive posterior ROP [AP-ROP]). Infants with stage 4 or 5 ROP, active ocular infections, or severe neurological disorders were excluded.

A total of 118 infants were randomly assigned in a 2:1 ratio to the aflibercept group (75 infants) or the laser photocoagulation group (43 infants), with evaluation using Bayesian statistical methods. Non-inferiority to standard therapy was defined as a difference of ≥ -5%. Of the 118 infants, 113 received treatment (mean gestational age: 26.3 weeks, 53 female infants). Of these, 16.8% had aggressive posterior ROP, 19.5% had Zone I ROP, and 63.7% had Zone II ROP. A total of 104 infants completed the study. Treatment was mainly bilateral (92.9%), and 82.2% of eyes in the intravitreal aflibercept group received one injection per eye. Therapeutic success (defined as no active ROP and no unfavorable structural outcomes, such as retinal detachment, macular traction, macular folding, or lens opacity, at 24 weeks) was achieved in 85.5% of the intravitreal aflibercept group and 82.1% of the laser photocoagulation group, with a difference of 3.4%. Aflibercept did not meet the non-inferiority criterion as the lower limit (-8.0%) was below -5%. In subgroup analyses, the efficacy of aflibercept was 70.8% in Zone I (vs 64.4% for laser). 92.0% in Zone II (vs 84.9%), and 73.3% in aggressive posterior ROP (vs 72.2%). Notably, ROP recurrences were more frequent after aflibercept treatment (21.9% vs. 8.3% after laser photocoagulation), although fewer eyes required additional treatment (4.8% vs. 11.1%). Regarding safety, severe ocular adverse events occurred in 13.3% of the aflibercept group compared to 7.9% in the laser photocoagulation group, while systemic adverse events were reported in 24.0% and 36.8%, respectively. Between weeks 4 and 9 post-treatment, three deaths occurred in the aflibercept group, but these were deemed unrelated to therapy. The study also provided data on the practical aspects of both therapies. The procedure time was significantly shorter for aflibercept injections (average of 3.7 minutes per patient) than laser therapy (average of 121.5 minutes). Moreover, while most laser procedures (83.7% vs 54.1% for injections) required general anesthesia, local anesthesia was often sufficient for injections (34.2%).

The study results indicate that intravitreal aflibercept injections did not meet the non-inferiority criterion compared to laser photocoagulation in terms of therapeutic success at 24 weeks. In summary, although aflibercept did not demonstrate non-inferiority to laser photocoagulation, the findings suggest that both methods are effective but differ in safety profiles and

recurrence rates. The high efficacy of laser photocoagulation in this study (82.1%) was notably higher than in previous studies (~72% in the RAINBOW and BEAT-ROP trials), which may have influenced the conclusions. Differences in ROP recurrence rates, the need for additional treatment, and adverse events indicate the need for further research, particularly regarding long-term effects. Currently, long-term ophthalmological and general clinical outcomes up to the age of five are being investigated in the FIREFLEYE Next study, with final results expected in 2026 [30].

Bevacizumab is used in the treatment of ROP despite the lack of registration indications. A randomized phase III study conducted in 2008-2010 comparing the therapeutic effect of bevacizumab injection with laser photocoagulation in patients with aggressive ROP showed that bevacizumab injections produced better treatment outcomes than laser therapy. The study group included 150 premature infants with ROP; the follow-up period was 2 years. The results were as follows: in the case of treatment with a biological drug, the risk of recurrence was significantly lower (by 18 percentage points) than in the case of laser treatment. This benefit was only observed in zone I; there was no significant difference in zone II. Peripheral angiogenesis continued after treatment with intravitreal bevacizumab, whereas in patients after laser therapy, permanent destruction of the peripheral retina was observed [31].

Central retinal vein occlusion (CRVO)

This is one type of retinal vein occlusion, occurring less frequently than branch retinal vein occlusion (BRVO). This group of diseases is the second most common cause of blindness related to retinal diseases. Central retinal vein occlusion (CRVO) refers to the anatomical site of its occlusion, which occurs within the optic disc or just behind it. In the fundus examination, we observe such a clot as retinal petechiae, venous dilation, and retinal telangiectasia in all four quadrants [32,33].

Risk factors primarily include advanced age and systemic conditions such as atherosclerosis, hypertension, diabetes, hypercholesterolemia, and heart disease. Individuals with coagulation disorders, such as thrombophilia, or those with a history of ischemic stroke, are also at higher risk [34,35]. Studies indicate long-term open-angle glaucoma is a significant ophthalmic risk factor for developing CRVO [36].

A complication of retinal vein occlusion is progressive retinal hypoxia, which leads to secondary macular edema and, consequently, partial or complete vision loss. This occurs due to alterations in the blood-retinal barrier function and excessive release of cytokines and growth factors such as VEGF. These substances contribute to active transcellular protein transport through the blood-retinal barrier and increased interstitial osmotic pressure, directly causing macular edema [37]. VEGF activity also frequently leads to late complications such as neovascular glaucoma [38].

To prevent progressive vision loss and subsequent complications, anti-VEGF agents have been employed. Monoclonal antibodies used in this disease include ranibizumab (Lucentis) since 2011, aflibercept (Eylea) since 2013, and bevacizumab. Numerous studies comparing the efficacy of these drugs have shown that in selected cases of macular edema in the course of CRVO with recurrent symptoms or non-reducing retinal edema in patients treated with ranibizumab or bevacizumab, switching to aflibercept may be beneficial. Unfortunately, no functional improvement was achieved despite the reduction of retinal edema. This is most likely the result of changes already made to the macula in the case of recurrent macular edema [39].

Its efficacy in treating macular edema, secondary to retinal vein occlusion, has been confirmed in multicenter studies such as GALILEO and COPERNICUS. The GALILEO study results show that patients receiving monthly intravitreal aflibercept injections experienced significant improvements after 24 weeks of treatment, with sustained effects after switching to a different treatment schedule at 52 weeks. Patients achieved a visual acuity improvement of 15 letters or more and a reduction in macular edema. The drug was well-tolerated, with the most common side effects including eye pain, transient increase in intraocular pressure, and subconjunctival hemorrhages. The second COPERNICUS study, conducted in the United States, similarly demonstrated improved visual outcomes for patients with macular edema. These studies indicate that earlier treatment initiation leads to better outcomes [40,41].

One of the new biological drugs is conbercept (Lumitin), which has high binding affinity for VEGF, a long half-life in the vitreous body, and blocks all isoforms of VEGF-A, VEGF-B, VEGF-C, and PlGF [42]. Its efficacy was demonstrated in a randomized

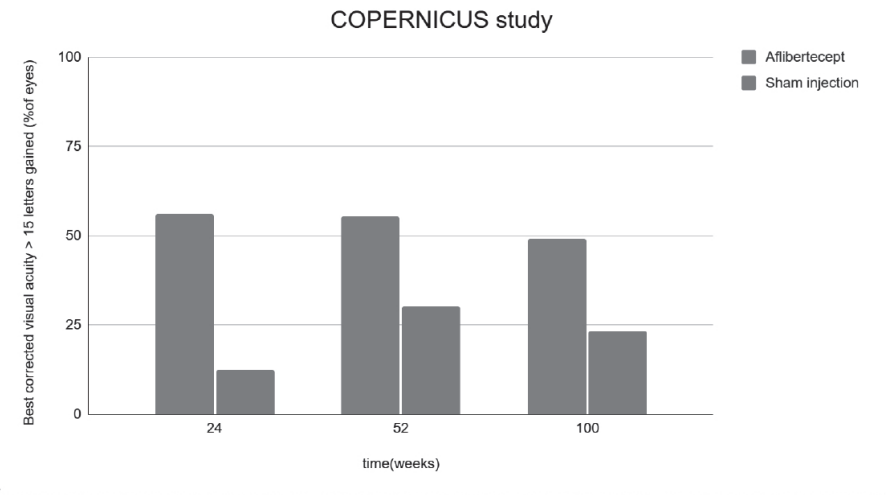

Figure 2. Visual acuity test results of patients treated with Aflibercept (Eylea) after 24, 52, and 100 weeks of follow-up. COPERNICUS study

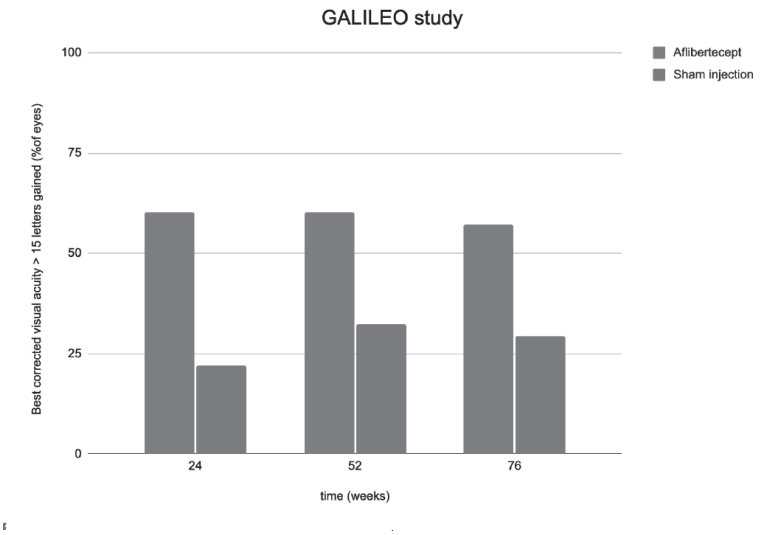

Figure 3. Visual acuity test results of patients treated with Aflibercept (Eylea) after 24, 52, and 76 weeks of follow-up. GALILEO study

trial conducted by the Shandong University Medical School Institute of Ophthalmology in China.

Patients in groups receiving intravitreal injections of conbercept (0.5 mg) and conbercept (0.5 mg) combined with dexamethasone (0.2 mg) showed an improvement in visual acuity of approximately 14 letters and a reduction in retinal thickness in the macular area after 12 months of treatment. During the study, 328 intravitreal injections were administered, with the most common adverse effects being subconjunctival hemorrhages, conjunctival irritation, or transient increases in intraocular pressure, which normalized after the administration of antihypertensive drugs. One patient experienced a vitreous hemorrhage, which fully resolved within the subsequent 12 months. No systemic complications were observed throughout the study.

The results showed that this drug, as monotherapy or combined with dexamethasone, significantly improves visual acuity and reduces macular edema without causing severe complications [43].

Currently, this drug is not approved for use in European countries, and clinical trials are still being conducted on its effectiveness and safety [42].

Vabysmo has shown promising results, making it a potential future option for CRVO treatment. Vabysmo may offer extended treatment intervals, but its use is still being evaluated in clinical trials [44].

Proliferative diabetic retinopathy (PDR)

One of the complications experienced by patients with diabetes is diabetic retinopathy. This condition involves pathological changes in the retina and its blood vessels, which can lead to vision loss [45]. The main risk factors for its development include the lack of metabolic control of diabetes, long duration of the disease, a positive history of cardiovascular diseases, hypertension, lipid disorders, and the presence of other diabetes-related complications, such as nephropathy [46].

The most common treatment method for this condition is retinal laser photocoagulation, which is intended to limit blood vessel leakage and inhibit macular edema formation. Combined therapies, involving laser treatment and intravitreal injections, are less commonly used [47].

Neovascular glaucoma (NVG)

Neovascular glaucoma (NVG) most commonly develops as a result of prolonged retinal ischemia. Due to hypoxia, the retina produces large amounts of pro-neovascularization factors, such as VEGF. This leads to the formation of new, abnormally structured blood vessels, which also involve the choroid and gradually close the anterior chamber angle in the eye. A complication of this process is increased intraocular pressure, which causes gradual damage to the optic nerve and significant pain for the patient. This condition most frequently occurs as a complication of retinal vascular occlusion, diabetes, and other vascular diseases [48].

The most commonly used treatment is retinal laser panretinal photocoagulation, which, if performed early enough, significantly limits the development of pathological blood vessels. VEGF inhibitors such as bevacizumab (Avastin), Ranibizumab (Lucentis), and Aflibercept (Eylea) have been used as adjuvant therapy [49]. One study evaluating the efficacy of ranibizumab (Lucentis) 0.5 mg over 12 months showed that patients receiving the treatment rapidly achieved reductions in intraocular pressure, reduced iris neovascularization, and improved visual acuity. Patients with neovascular glaucoma received an average of 2.3 injections during the observation period. Changes in mean intraocular pressure were as follows: baseline pressure of 41.4 ± 13.4 mmHg, which quickly dropped (18.2 ± 12.3 mmHg on day 14, $p = 0.005$) and stabilized during the observation period (15.6 ± 2.0 mmHg, $p < 0.05$) [50].

A randomized study published in 2009 on the use of bevacizumab injection in patients with neovascular glaucoma showed that after approximately 6 months of follow-up, patients had a decrease in intraocular pressure and a reduction in the process of iris neovascularization compared to the control group. The study included 26 participants, of whom 14 received three bevacizumab injections of 2.5 mg each, while the remaining received saline injections. The treatment group demonstrated a reduction in intraocular pressure from a baseline of 33.4 ± 14.5 mmHg to 21.8 ± 13.7 mmHg after one month, 25.1 ± 20 mmHg after two months, and 23.9 ± 18.7 mmHg six months after the start of treatment. Iris neovascularization decreased from an initial extent of 347 ± 48 degrees to 180 ± 180 degrees six months after the intervention [51].

Uveitis

Uveitis can be classified into anterior, intermediate, posterior, and pan-uveitis (inflammation of the entire uveal membrane). It can be caused by infectious diseases, non-infectious conditions, or as a paraneoplastic syndrome in the course of cancer. Non-infectious uveitis may be associated with systemic diseases such as sarcoidosis, multiple sclerosis, or the presence of the HLA-B27 antigen (accounting for approximately 20% of all anterior uveitis cases) or may occur without an identifiable cause. The primary goal of treatment is to control the inflammatory process, which can lead to further ocular damage and permanent visual impairment [52]. First-line treatment typically involves corticosteroids and subconjunctival injections.

Currently, an alternative in the case of a lack of response to standard treatment is the administration of biological drugs, including monoclonal antibodies. Numerous biological factors, such as interleukins (IL-1, IL-2, IL-6, IL-8), tumor necrosis factor (TNF),

and transforming growth factor (TGF)-β, regulate the inflammatory process and the breakdown of the blood-retinal barrier [53]. Modern biological drugs are designed to inhibit the effects of these substances on tissues. They reduce the intensity of the inflammatory process by binding to molecules that trigger the inflammatory response. Most commonly, TNF (tumor necrosis factor) inhibitors are used, such as infliximab, adalimumab, etanercept, golimumab, and certolizumab. They are particularly useful in treating resistant inflammation of the uvea, e.g., in the course of Behçet's disease [54,55]. Tumor necrosis factors include two proinflammatory cytokines: TNF-α and TNF-β. They bind to the same cell surface receptors and have similar effects. They are produced by leukocytes at sites of inflammation [56].

Adalimumab (Humira) is a recombinant human monoclonal antibody produced through expression in Chinese hamster ovary cells. It specifically binds to human tumor necrosis factor (TNF) and inhibits its activity by binding to the TNF receptors p55 and p75 on the cell surface [57]. A retrospective cohort study was conducted in two hospitals in Turkey to evaluate the efficacy and safety of adalimumab therapy in chronic non-infectious uveitis (NIU). The study included 51 patients and assessed parameters such as anterior chamber reaction, vitreous haze, visual acuity, central macular thickness (CMT), prednisone use, and uveitis flare-up frequency. Injections were administered at weekly intervals. During treatment, a reduced number of uveitis flare-ups was observed in patients. The therapy was evaluated as safe and effective [58].

Infliximab (IFX) is a chimeric monoclonal antibody targeting TNF-α [59].

Tocilizumab is a humanized monoclonal antibody directed against interleukin-6 (IL-6), a cytokine that plays a key role in developing severe, treatment-resistant uveitis. Studies conducted in animal models have shown that blocking IL-6 with tocilizumab limited the development of severe uveitis by inhibiting the immune response of Th17 lymphocytes. Observational data indicate that tocilizumab is also effective in treating uveitis resistant to immunosuppressive therapy and TNF inhibitors in the course of rheumatoid diseases [60,61]. The results of a multicenter, retrospective observational study involving 204 participants showed that the use of tocilizumab doubled the chances of patients experiencing complete regression of macular edema compared to the group receiving infliximab. However, no significant difference was recorded in the frequency of disease relapses and improvement in visual acuity in both groups. The drug is assessed as safe - the risk of serious adverse events is low. The most frequently observed complaints included: increased levels of aminotransaminases, symptoms of respiratory tract infection, increased blood pressure, pain, and dizziness [60,61]. Infliximab and Tocilizumab are recommended for intravenous injection. They are currently not registered in Poland for the treatment of uveitis [62,63].

Treatment programs

In Poland, treatment of individual retinal and uveal diseases is available as part of treatment programs. In diseases such as neovascular AMD, DME, and chronic or recurrent uveitis, treatment is financed by the state. Patients for therapy under the program are qualified by a team of coordinators appointed by the President of the National Health Fund (NFZ) based on tests performed by the attending physicians.

The drug program in the treatment of CNV in the course of AMD uses aflibercept in a dose of 2 mg and 8 mg, brolucizumab 6 mg, faricimab 6 mg, and ranibizumab 0.5 mg in intravitreal injections. The most important criteria for qualification include the presence of active choroidal neovascularization (CNV) confirmed by OCT, age over 45 years, lesion size greater than 12 DA, and best corrected visual acuity (BCVA) in the treated eye of 0.2-0.8 (Snellen chart).

In the case of diabetic macular edema (DME), patients must meet the following criteria: presence of diffuse, clinically significant macular edema with foveal involvement in the course of diabetes, be at least 18 years old, BCVA in the treated eye of 0.2-0.8 (Snellen chart), meet the HbA1c value criterion and the absence of a dominant preretinal membrane. In this program, we use aflibercept 2 mg and 8 mg, bevacizumab 2 mg, brolucizumab, faricimab, and ranibizumab. The treatment is monitored by assessing visual acuity, performing fundus examinations, and monitoring blood glucose levels. OCT or angio-OCT tests may also be performed.

In patients with retinal vein occlusion (RVO), the drug program finances treatment with bevacizumab. Patients qualified for the program must have: macular edema secondary to RVO diagnosed within 9 months of RVO diagnosis, at least 18 years of age, mean thickness of the central retinal subfield >250 μm in OCT exami-

Table I. The table presents monoclonal antibodies and their registered indications in Poland. The table is prepared on the basis of data from the summary of product characteristics. [16,24,62,63,65-71]

	Ranibizumab (Lucentis)	Bewacyzumab	Aflibercept	Faricimab-Vabysmo™)	Tocilizumab	Infliximab	Brolucyzumab	Adalimumab	Golimumab	Certolizumab	Etanercept
Age-related macular degeneration (AMD)	+	–	+	+	–	–	+	–	–	–	–
Diabetic macular edema (DME)	+	–	+	+	–	–	+	–	–	–	–
Proliferative diabetic retinopathy (PDR)	+	–	–	–	–	–	–	–	–	–	–
Central retinal vein occlusion (CRVO) Branch retinal vein occlusion(BRVO)	+	–	+	+	–	–	–	–	–	–	–
Neovascular glaucoma (NVG) - treatment of visual disturbances caused by choroidal neovascularization (CNV)	+	–	+	–	–	–	–	–	–	–	–
Retinopathy of prematurity (ROP)	+	–	+	–	–	–	–	–	–	–	–
Uveitis	–	–	–	–	–	–	–	+	–	–	–

nation, and BCVA within the range of 0.05-0.8 (Snellen chart). Patients receive 1.25 mg of bevacizumab by intravitreal injection. Each time, the attending physician qualifies for the next drug dose.

The last disease whose treatment is financed under the treatment program by the National Health Fund (NFZ) is non-infectious uveitis. The two most important criteria for qualification include: confirmation of non-infectious chronic, persistent uveitis based on SUN criteria, and age of at least 18 years. The treatment is based on adalimumab at an initial dose of 80 mg administered subcutaneously. [64]

Summary

The above article presents in detail the positions of modern treatment methods, such as the use of monoclonal antibodies in eye diseases. The research method consisted of discussing the pathomechanisms of diseases, presenting the mechanism of action of drugs, and analyzing the results of clinical trials cited in the above text. Analyzing all this data, it can be concluded that monoclonal antibodies not only allow for effective treatment and stopping the progression of diseases that previously led to loss of vision, such as neovascular AMD, but also inhibit the development of complications after retinal vein occlusion (RVO). Many of these drugs are also considered as an alternative to standard treatment techniques due to the lower number of complications. Such substances include aflibercept as an alternative method of treatment for ROP. However, biological treatment is a relatively new topic in medicine, and most clinical trials conducted so far include observations of patients for up to 24 months. It is necessary to continue research on the health status of patients, their vision, and the complications that occur over many years.

Conflict of interest
Brak/None

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