Polskie Towarzystwo Okulistyczne
www.pto.com.pl

KLINIKA OCZNA 2023, 125, 4: 181-189
Received: 02.09.2023 **Accepted:** 4.09.2023

Access this article online

Website:
www.klinikaoczna.pl

DOI:
https://doi.org/10.5114/ko.2023.134018

Position Statement of the Polish Society of Ophthalmology establishing standards for the management of patients with exudative age-related macular degeneration

Marta Misiuk-Hojło[1], Alina Bakunowicz-Łazarczyk[2], Dariusz Dobrowolski[3], Iwona Grabska-Liberek[4], Jerzy Mackiewicz[5], Ewa Mrukwa-Kominek[6], Agnieszka Nowak[7], Weronika Pociej-Marciak[7], Bożena Romanowska-Dixon[7, 8], Marcin Stopa[9], Jacek Szaflik[10], Jakub Kałużny[11], Joanna Adamiec-Mroczek[1]

[1]Department of Ophthalmology, Wroclaw Medical University, Poland
[2]Pediatric Ophthalmology Department with Strabismus Treatment Center, Medical University of Bialystok, Poland
[3]Chair and Clinical Department of Ophthalmology, Medical University of Silesia in Katowice, Poland
[4]Department of Ophthalmology, Centre of Postgraduate Medical Education, Poland
[5]Department of Vitreoretinal Surgery, Medical University of Lublin, Poland
[6]Department of Ophthalmology, Medical University of Silesia in Katowice, Poland
[7]Department of Ophthalmology and Ocular Oncology, University Hospital in Krakow, Poland
[8]Department of Ophthalmology and Ocular Oncology, Jagiellonian University in Krakow, Poland
[9]Chair of Ophthalmology and Optometry, Poznan University of Medical Sciences, Poland
[10]Chair and Department of Ophthalmology, Medical University of Warsaw, Poland
[11]Department of Sensory Organs Examination, Nicolaus Copernicus University in Torun, Poland

ABSTRACT

Age-related macular degeneration (AMD) is a leading cause of impairment of vision in the population over 50 years of age in developed countries. The most important risk factors for the development of AMD include increasing age, living in northern regions of Europe, genetic factors and smoking. The recommendations support the use of supplements (antioxydants), intravitreal injection of anti-VEGF agents and photodynamic therapy (PDT). Anti-VEGF therapy (e.g., aflibercept, bevacizumab, ranibizumab, brolucizumab, faricimab) is the most effective way to manage neovascular AMD and represents the first line of treatment. In patients with neovascular AMD, early detection and prompt treatment improves the visual outcome. This paper presents the current treatment standards for neovascular AMD developed by a group of experts from the Polish Ophthalmological Society.

KEY WORDS: age-related macular degeneration, exudative AMD, standards of therapy, anti-VEGF agents.

CORRESPONDING AUTHOR
Joanna Adamiec-Mroczek, Department of Ophthalmology; Wroclaw Medical University, 213 Borowska St., 50-556 Wroclaw, Poland, e-mail: joanna.adamiec-mroczek@umw.edu.pl

INTRODUCTION

Age-related macular degeneration (AMD) is one of the leading causes of significant irreversible vision impairment in the population over 50 years of age in highly developed countries. In 2040, an estimated 288 million people worldwide will be affected AMD, which is due to steadily aging populations and increasing average life expectancy. Declining visual acuity in AMD patients continues to pose a major socioeconomic challenge. AMD is a disease entity with a complex multifactorial pathomechanism, leading to permanent damage to the area of the retina responsible for acute central vision and color vision. A range of heterogeneous factors leading to the development of the disease have been identified, of which particular emphasis is placed on the body's aging processes. Also highlighted is the significance of how environmental factors interact synergistically with specific genetic predispositions and inflammatory mechanisms. Over 50 gene *loci* have been identified as playing an important role in the development of AMD, with CFH and ARMS2 deserving a special focus. The primary modifiable risk factors for AMD are smoking and a diet lacking in antioxidants. The condition results in permanent damage to the outer layers of the retina and the adjacent choroid.

The pathological presentation of AMD depends on the severity of the disease and the nature of changes observed in the later stages of progression. The early stages of AMD are characterized by the build-up of protein and lipid deposits between the retinal pigment epithelium (RPE) and Bruch's membrane. These accumulations of pathological material are referred to as drusen. On ophthalmoscopic examination, drusen present as bright yellow foci of varying size. They are often accompanied by pathologies within the retinal pigment epithelium presenting as focal atrophy or hyperplasia of the RPE, visible on clinical examination as areas of hypo- and/or hyperpigmentation. Drusen and changes in RPE morphology are classified as benign lesions and usually do not cause central vision impairment. As the disease advances, anomalies within the photoreceptor cell layer and Bruch's membrane become apparent. Patients begin to report metamorphopsias and small scotomas.

In some individuals, early changes progress over time to geographic atrophy and/or exudative AMD, which lead to a significant deterioration of vision. Geographic atrophy (GA) is a sharply demarcated area of depigmentation associated with partial or complete atrophy of the RPE, followed by the outer layers of the sensory retina, with visible large choroidal vessels.

Lesions found on ophthalmoscopy of the macula form the basis of the classification based on the findings of the Age-related Eye Disease Study (AREDS) which allows estimation of the risk of disease progression (Table I).

Risk factors for progression to late AMD:

- presence of one or more large drusen (≥ 125 µm in diameter),
- pigmentary changes,
- if large drusen are absent, presence of bilateral intermediate drusen (63-124 µm in diameter),
- neovascular AMD (in the other eye).

Dry AMD presents with drusen and abnormalities within the RPE, manifesting as pigmentary changes often accompanied by focal areas of atrophy. Based on their ophthalmoscopic appearance, drusen can be divided into hard (small, with sharp borders), soft (with less defined borders), and confluent. Large confluent drusen may result in drusenoid pigment epithelial detachment (drusenoid PED). Reticular drusen (pseudodrusen), clearly visible on fundus autofluorescence, are deposits located on the inner surface of the RPE and associated with an increased risk of GA and neovascularization.

Advanced dry AMD is characterized by extensive geographic atrophy involving the central fovea, leading to progressive permanent loss of central vision. Atrophy detected on ophthalmoscopy may involve the RPE, the photoreceptor cell layer, Bruch's membrane, or the choriocapillaris. In 10-15% of cases, the lesions progress from dry to exudative AMD, with secondary neovascularization forming at the edge of atrophy.

At present, there are no effective treatments indicated specifically for AMD in Europe. In the initial stages of the condition, dietary supplementation with antioxidants is recommended (AREDS2 study). In the United States, in February 2023, the FDA approved the drug Syfovre (pegacetoplan) which is expected to slow the progression of geographic atrophy. For the time being, it is the sole drug approved for this indication.

Exudative AMD is also termed neovascular AMD. This type of age-related macular degeneration is characterized by proliferation of new vessels (MNV/CNV – macular neovascularization/choroidal neovascularization) originating from the choroid and localizing below the retinal pigment epithelium and/or in the subretinal space. This is how the most common forms of neovascularization arise: type 1 MNV (occult), type 2 MNV (classic) or their combination (predominantly

Table I. AMD classification based on AREDS criteria (modified)

AMD classification	Definition
No AMD	No drusen and pigmentary changes*
Normal aging processes (AREDS category 1)	A few small drusen (< 63 µm in size); no pigmentary changes
Early AMD (AREDS category 2)	Multiple small drusen, a few intermediate drusen (63-124 µm in diameter), no pigmentary changes
Intermediate AMD (AREDS category 3)	At least one large drusen (> 125 µm in diameter) and/or any pigmentary changes
Late AMD (AREDS category 4)	Neovascular AMD and/or geographic atrophy

**Pigmentary changes – any focal areas of hypo- or hyperpigmentation associated with the presence of intermediate or large drusen.*

or minimally classic type). Other, less commonly observed forms of neovascularization include type 3 MNV (retinal angiomatous proliferation, RAP) and PCV (polypoid choroidal vasculopathy). In type 3 MNV, neovascularization affects both the sensory retina and the choroid.

Two concepts have been proposed to explain the mechanisms underlying the development of this type of AMD. According to the first concept, the observed neovascularization originates in the retinal deep capillary plexus, and the progression of the condition leads to subretinal vascular proliferation towards the choroid. The second theory postulates the onset of neovascularization in the choroid (CNV), followed by vessel proliferation toward the sensory retina. Newly formed vessels have fenestrations through which blood and morphotic blood elements are able to penetrate the adjacent tissues, resulting in their separation, thickening, swelling, and the formation of cyst-like spaces.

Another variant of AMD is idiopathic polypoidal choroidal vasculopathy (PCV), with primary abnormalities including dilated small choroidal vessels progressing to secondary neovascularization under the pigment epithelium.

Ophthalmoscopic signs of exudative AMD:

- neovascularization under the RPE or under the sensory retina, visible as a focal lesion, gray-green in color,
- serous detachment of the neurosensory retina,
- detachment of the retinal pigment epithelium,
- sub-RPE, subretinal, intraretinal, preretinal, and (less commonly) intravitreal hemorrhages,
- hard exudates within the macular region,
- subretinal fibrous scar tissue representing the final stage of disease progression.

Additional examinations performed in the diagnostic work-up of exudative AMD are discussed below, in the section on anti-VEGF treatment.

Differential diagnosis of exudative AMD:

- CNV associated with high myopia,
- CNV associated with inflammatory conditions, e.g. ocular histoplasmosis, punctate inner choroidopathy, post-inflammatory retinal scarring,
- CNV secondary to choroidal rupture and angioid streaks,
- chronic serous chorioretinopathy (CSR), especially complicated by CNV,
- parafoveal telangiectasias,
- pattern dystrophies,
- cystoid macular edema,
- diabetic macular edema associated with diabetic retinopathy,
- diabetic macular edema associated with retinal vein occlusion.

Aim of treatment of exudative age-related macular degeneration

The goal of treatment is to achieve long-term improvement or stabilization of the patient's visual acuity by limiting disease activity manifested as normalization of its anatomic parameters i.e. complete/partial absorption of intra-/subretinal fluid, reduction in PED, and resorption of sub- and/or intraretinal blood extravasations.

METHODS FOR TREATMENT OF EXUDATIVE AGE-RELATED MACULAR DEGENERATION

Anti-VEGF therapy

Intravitreal delivery of therapeutic agents reducing the intraocular level of VEGF, a pro-angiogenic factor that increases vascular permeability and plays a pivotal role in the development of abnormal neovascularization in patients with exudative AMD.

Anti-VEGF therapy is currently recognized as the gold standard in the treatment of exudative AMD and considered as the treatment of choice in patients with this condition. Prompt initiation of therapy (within 14 days of diagnosis) significantly improves treatment outcomes.

At present, based on a review of the results of registration clinical trials, the following therapeutic agents are used in the treatment of exudative AMD:

- **ranibizumab** (Lucentis) (used in Poland since 2007):
  - Ranibizumab is a humanized monoclonal antibody fragment produced in *Escherichia coli* cells by applying recombinant DNA technology.
  - One ml solution contains 10 mg ranibizumab. Each vial contains 2.3 mg ranibizumab in 0.23 ml solution. A single dose is 0.5 mg ranibizumab administered in 0.05 ml solution as an intravitreal injection.
  - Ranibizumab has an ability to bind VEGF-A.
- **aflibercept** (Eylea) (used in Poland since 2013):
  - Aflibercept is a fusion protein consisting of portions of human VEGF (vascular endothelial growth factor) receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 and produced in Chinese hamster ovary (CHO) K1 cells by applying recombinant DNA technology.
  - One ml solution for injection contains 40 mg aflibercept. One vial contains a volume of 0.1 ml, which is equivalent to 4 mg aflibercept. This provides a usable amount to deliver a single dose of 0.05 ml containing 2 mg aflibercept.
  - Aflibercept acts as a soluble decoy receptor that has the ability to inhibit VEGF-A and PlGF (placental growth factor) with higher affinity than their natural receptors.
- **brolucizumab** (Beovu) (used in Poland since 2020):
  - Brolucizumab is a humanized monoclonal single-chain Fv (scFv) antibody fragment produced in *Escherichia coli* cells by applying recombinant DNA technology.
  - One ml solution for injection contains 120 mg brolucizumab. Each pre-filled syringe contains 19.8 mg brolucizumab in 0.165 ml solution. This provides a usable amount to deliver a single dose of 0.05 ml solution containing 6 mg brolucizumab.
  - Brolucizumab binds with high affinity to VEGF-A isoforms, blocking their activity.

- **faricimab** (Vabysmo) (used in Poland since 2022):
  - Faricimab is a humanized bispecific immunoglobulin G1 (IgG1) antibody produced in Chinese hamster ovary (CHO) cell culture by recombinant DNA technology.
  - Each vial contains 28.8 mg faricimab in 0.24 ml solution. This provides a usable amount to deliver a single dose of 0.05 ml solution containing 6 mg faricimab.
  - Faricimab acts through the inhibition of two distinct pathways: by neutralization of both vascular endothelial growth factor A (VEGF-A) and angiopoietin-2 (Ang-2).
- **bevacizumab** (Avastin):
  - Bevacizumab is a recombinant humanized monoclonal antibody produced in Chinese hamster ovary (CHO) cells by applying DNA technology.
  - A single dose contains 1.25 mg active substance in 0.05 ml solution.
  - The approved indications of bevacizumab include advanced oncological diseases. In ophthalmology, bevacizumab is commonly used for similar indications and in comparable regimens as other anti-VEGF agents. However, it needs to be noted that it can only be prescribed as an off-label therapy.

As of yet, there are no published findings of randomized multicenter clinical trials directly comparing the efficacy of all available anti-VEGF agents, also with regard to various treatment regimens.

Alongside the original drugs described above, biosimilars of ranibizumab (Byooviz, Ranivisio, Ximluci) have also been approved for therapy.

Photodynamic therapy with verteporfin

Photodynamic therapy (PDT) with verteporfin (Visudyne) is approved for the treatment of adult patients with exudative age-related macular degeneration, but only with predominantly classic CNV. Follow-up examinations (with fluorescein angiography performed at each visit to precisely determine CNV boundaries) and treatments, if needed, are scheduled at three-month intervals, based on the assessment of disease activity. In the treatment of exudative AMD, photodynamic therapy may be an alternative to anti-VEGF treatment in patients who have various contraindications to a therapy based on intravitreal injections. PDT can also be prescribed to patients with idiopathic polypoidal choroidal vasculopathy either as monotherapy or in combination treatment. Access to PDT is currently limited, as multiple medical centers have ceased to provide this therapy because of considerably wider applications of anti-VEGF treatment.

Surgical procedures

Surgical procedures are not routinely used in daily clinical practice because of their limited indications.

Exceptions include vitrectomy procedures in patients with extensive massive subretinal or premacular hemorrhage involving the fovea, for the purpose of administering a tissue plasminogen activator subretinally or intravitreally (on an off-label basis), often in combination with an anti-VEGF agent. The procedure is completed by gas injection (20% SF6, 14% C3F8) into the vitreous chamber. Another available treatment modality involves the removal of hemorrhage from the subretinal space combined with autologous translocation of the choroid and RPE.

The following part of the guidelines addresses only the commonly used anti-VEGF therapy.

DIAGNOSTIC WORK-UP FOR EXUDATIVE AMD BEFORE AND DURING ANTI-VEGF THERAPY

1. General and ophthalmic history.
2. Best-corrected visual acuity (BCVA) determined using either the Snellen or ETDRS charts.
3. Dilated stereoscopic ophthalmoscopy.
4. Optical coherence tomography (OCT) – to be performed directly before the start of treatment and as part of the patient's ongoing follow-up during therapy.
5. OCT-angiography (OCTA) – visualizes pathological blood vessels; since the technique does not conclusively prove CNV activity, findings should be considered in conjunction with the patient's history and results of other examinations.
6. Fluorescein angiography (FA) – to determine the extent, type, size and location of CNV; FA is indicated in atypical cases (e.g. in patients with PCV) or diagnostically uncertain situations.
7. Indocyanine green angiography (ICGA) – performed optionally in selected doubtful cases such as suspected PCV, massive serous PED or other abnormalities yielding inconclusive FA and OCT findings.

CRITERIA OF PATIENT ELIGIBILITY FOR ANTI-VEGF THERAPY

1. Age over 45 years.
2. BCVA of 0.05-0.9, provided that impaired visual acuity is due to active CNV secondary to exudative AMD (under the publicly-funded drug program, the National Health Fund reimburses treatment for patients with best-corrected visual acuity between 0.2 and 0.8).
3. All types of CNV lesions associated with exudative AMD are suitable for treatment, provided that the lesions are active. Typical indicators of lesion activity include petechial hemorrhage on fundus ophthalmoscopy; intraretinal, subretinal or sub-RPE fluid on OCT; and pigment leakage detected by fluorescein angiography.
4. Lesion location:
   - subfoveal,
   - parafoveal – if the lesion is active and carries the risk of foveal involvement and impairment of visual acuity,
   - extrafoveal – where there is a risk of vision loss.
5. Disease duration until the initiation of treatment is not relevant, as long as the lesion is active.
6. If there are indications for the treatment of both eyes, the preferred option is to start therapy from the eye with the better prognosis. Injections can be administered to both

eyes during a single day, but with strict adherence to aseptic protocols and use of separate surgery drapes for each eye.

CRITERIA OF PATIENT INELIGIBILITY FOR ANTI-VEGF THERAPY

A. Absolute

1. Hypersensitivity to the active substance or to any of the excipients.
2. Active inflammatory changes within the globe and ocular adnexa.
3. History of recurrent uveitis.
4. Cataract preventing correct diagnosis.
5. Uncontrolled glaucoma or advanced glaucomatous neuropathy with the risk of significant progression due to temporary increases in intraocular pressure after intravitreal injections.
6. Dominant scarring involving the center of the macula.
7. Dominant geographic atrophy involving the center of the macula.

B. Relative

1. Ischemic stroke within the last 6 months.
2. Myocardial infarction within the last 6 months.
3. Other thromboembolic events within the last 6 months.
4. Treatment with anticoagulants if the INR exceeds 1.5. Patients taking anticoagulants should be informed about the risk of complications: usually mild (typically subconjunctival hemorrhage) and in some cases severe (such as intravitreal hemorrhage). Patients should also be informed that treatment with anticoagulants in the presence of CNV carries a risk of disease complications regardless of anti-VEGF therapy. However, since systemic therapy takes priority over ophthalmic treatment, interruptions in anticoagulant therapy are not recommended.
5. Ophthalmic procedure (cataract surgery or vitrectomy) performed during the preceding month. In patients with advanced cataract and aggressive CNV, anti-VEGF treatment should not be discontinued in view of the risk of significant progression of lesions. The optimal approach seems to be the administration of an anti-VEGF agent 0-7 days before and four weeks after cataract surgery.
6. Dominant massive subretinal hemorrhage involving the entire macular field. In this patient group, the crucial factor is the timeframe between blood extravasation and the initiation of therapy (optimally up to 7 days). Anti-VEGF therapy combined with intravitreal administration of tissue plasminogen activator (tPA), often in conjunction with SF6 gas, may lead to some improvement in visual acuity. Another option is surgical intervention (vitrectomy with subretinal tPA delivery or autologous translocation of the choroid).

INTRAVITREAL INJECTION PROCEDURE

1. Intravitreal injection procedures should be performed by a qualified ophthalmologist with appropriate experience in administering intravitreal injections or by a resident under the supervision of a specialist.
2. Appropriate local anesthesia should be used (instillation of anesthetic drops into the conjunctival sac).
3. The procedure should be done under aseptic conditions, including topical administration of bactericidal substances with a broad spectrum of activity on the skin around the eye and the eyelid, and the ocular surface. Antibiotic prophylaxis in the form of eye drops is not recommended either before or after the procedure because of the risk of developing antibiotic resistance to saprophytic strains in the human conjunctival sac.
4. Surgical hand disinfection, and the use of sterile gloves, sterile surgical drapes and sterile eyelid speculum are recommended, along with rinsing the conjunctival sac with 5% povidone iodine solution (60 s) after washing the skin of the eyelids with 10% povidone iodine solution.
5. The injection needle (30 G) should be inserted into the central part of the vitreous chamber, at a distance of approximately 3.5-4.00 mm behind the corneal limbus (avoiding the horizontal meridian and aiming toward the center of the globe). Subsequent injections should be administered in other scleral locations, if possible.
6. After the intravitreal injection, the vascular perfusion status of the optic nerve disc and sense of light should be evaluated. Intraocular pressure can be measured, particularly in patients with glaucoma (approximately 30 minutes after injection). In cases where symptoms of central retinal artery occlusion arise, anterior chamber paracentesis should be performed immediately.
7. After the intravitreal injection procedure patients should be instructed to report immediately any symptoms that might be suggestive of endophthalmitis (such as pain, red eye, photophobia, blurred vision).

INITIAL PHASE OF TREATMENT

1. Ranibizumab, aflibercept, brolucizumab, bevacizumab:
   - three monthly injections at intervals of not less than 4 weeks.

   Faricimab:
   - four monthly injections at intervals of not less than 4 weeks.
2. Before each injection, the following should be performed:
   - assessment of BCVA,
   - evaluation of intraocular pressure,
   - slit-lamp examination of the anterior segment of the eye,
   - dilated indirect ophthalmoscopy,
   - OCT.
3. Fluorescein angiography is optionally recommended in patients with an unexplained significant decrease in BCVA.

CONTINUATION OF THERAPY AND PATIENT MONITORING AFTER THE INITIAL PHASE OF TREATMENT

At each follow-up visit, the following examinations should be done:

- assessment of BCVA,
- measurement of intraocular pressure,
- slit-lamp examination of the anterior segment of the eye,
- dilated indirect ophthalmoscopy,
- OCT,
- optionally fluorescein angiography in patients with an unexplained significant decrease in BCVA.

After the initial phase of treatment, the schedule for continued therapy depends on the patient's outcomes and the agent used.

Ranibizumab (Lucentis)

After the initial phase of treatment, therapy should be continued until maximum visual acuity is achieved and/or there are no signs of disease activity, i.e. no changes in visual acuity or other physical symptoms associated with exudative AMD. Afterwards, treatment intervals and follow-up examinations should be determined by the physician depending on disease activity, as assessed by visual acuity and/or anatomic parameters.

In some patients, a "treat-and-extend" regimen may be adopted. In this approach, once maximum visual acuity has been achieved and/or there are no signs of disease activity, the intervals between doses can be gradually extended until the recurrence of disease activity or visual decline is observed. In patients with AMD, the intervals between doses should be extended by no more than two weeks at a time. If disease activity recurs sooner than expected, the intervals between doses should be shortened accordingly.

Where, based on the evaluated visual acuity and anatomic parameters, the physician concludes that continued therapy does not improve the patient's condition, discontinuing treatment with Lucentis or switching the medication should be considered.

Aflibercept (Eylea)

After treatment initiation with one injection per month for three consecutive doses, the interval between doses is extended to two months. Based on the physician's judgement of the patient's visual and/or anatomic parameters, the interval between doses may be either maintained at two months or further extended according to the treat-and-extend dosing regimen. In this therapeutic approach, injection intervals are increased in two- or four-weekly increments with a view to maintaining the therapeutic response in terms of visual and/or anatomic parameters. If the patient's visual and/or anatomic outcomes deteriorate, the interval between consecutive doses should be reduced accordingly. There is no requirement for monitoring between injections. Based on the physician's judgement, the schedule of monitoring visits may be more frequent than the schedule of injection visits. Injection intervals longer than four months or shorter than four weeks have not been studied.

In cases where, at any time during therapy, based on the assessment of visual acuity and anatomic parameters, the physician concludes that continued therapy does not improve the patient's clinical condition, discontinuation of Eylea or switching the medication should be considered.

Brolucizumab (Beovu)

After three loading doses, the physician may individually adjust the intervals between doses depending on the patient's disease activity determined on the basis of visual acuity and/or anatomic parameters. An assessment of disease activity is suggested at 16 weeks (4 months) after treatment initiation. In patients without disease activity, treatment every 12 weeks (3 months) should be considered, and in patients with detectable disease activity, treatment every 8 weeks (2 months) should be taken into consideration. In the clinical trials in subjects selected for the two-month regimen or in whom the three-month regimen was reduced to two months during the period of follow-up, the option of introducing or returning to the three-month intervals was not considered. Based on real-life outcomes, the decision on the frequency of reinjection is made by the attending physician based on the anatomic and functional improvement. After the initial phase of treatment, the drug should not be administered more frequently than every two months. In view of reported cases of sterile endophthalmitis, including occlusive vasculitis, patients receiving brolucizumab therapy should be closely monitored.

Faricimab (Vabysmo)

At the start of therapy, the drug is administered monthly for the first four doses. Then, an assessment of disease activity based on anatomic parameters and/or visual acuity is recommended 20 and/or 24 weeks after treatment initiation. Depending on the patient's therapeutic response, treatment is continued at regular intervals. In patients without disease activity, administration of faricimab every 16 weeks (4 months) should be considered. In patients with disease activity, treatment every 8 weeks (2 months) or 12 weeks (3 months) should be taken into consideration. Visits to monitor the patient's status between dose administrations should be scheduled based on the treatment outcomes and at the physician's discretion. If the patient's anatomic and/or visual parameters deteriorate, the interval between consecutive doses should be reduced accordingly. There is currently limited available data regarding the safety of treatment intervals shorter than eight weeks between injections. If visual and/or anatomic parameters indicate that the patient gains no benefit from continued treatment, therapy should be discontinued.

THERAPEUTIC REGIMENS

The current practice is proactive treatment which allows maximization and sustained improvement of vision over the long term.

In the PRN (*pro re nata*, i.e., as needed) treatment approach, the decision to perform reinjections relies on the results of follow-up assessment comprising anatomic parameters (OCT, dilated fundus ophthalmoscopy) and functional outcomes (visual acuity). The presence of disease activity is an indication for ther-

apy. For PRN treatment to be effective, it is important to schedule frequent ophthalmological check-ups and administer injections promptly upon detecting signs of MNV activity. In routine daily practice, the PRN regimen is frequently linked to inadequately intensive anti-VEGF therapy, leading to inferior treatment outcomes compared to clinical trial results.

In the T&E regimen, each follow-up examination involves intravitreal drug administration.

Depending on the results of the follow-up examination, the interval until the next injection should:

- remain unchanged if an attempt to extend the interval resulted in a recurrence of disease activity and/or a decline in visual acuity,
- be reduced by two to four weeks – if signs of MNV activity/deterioration in visual acuity are observed,
- be extended by 2 to 4 weeks – if there are no signs of MNV activity; presence of a stable volume of subretinal fluid with intensive therapy.

This treatment approach allows for a considerable decrease in visit frequency while maintaining the optimal number of drug administrations to sustain the achieved anatomic and functional improvement.

DISEASE ACTIVITY CRITERIA WARRANTING CONTINUATION/RESUMPTION OF THERAPY

1. Presence of subretinal fluid after the initial phase of treatment – continued therapy is indicated until maximum fluid withdrawal is achieved (OCT findings).
2. Appearance of new or increase in the volume of preexisting subretinal fluid.
3. Increase in central retinal thickness on OCT, secondary to diffuse edema.
4. Formation/increase of intraretinal fluid spaces unrelated to degenerative changes (e.g. intraretinal fluid accompanying atrophy/scarring processes).
5. Appearance/increase in the amount of fluid under the pigment epithelium (PED).
6. Progressive decrease in visual acuity, which is not due to retinal atrophy/scarring processes.
7. Blood extravasations – injections are recommended on a monthly basis until the blood is absorbed.

CRITERIA FOR THERAPY SWITCH

Therapy switching should be considered if no improvement or deterioration in anatomic parameters and a decrease in visual acuity are noted despite appropriate therapy. Evaluation should be performed no earlier than 3-6 months of the treatment (as per the drug program, after seven intravitreal injections). Some patients may have a delayed response to therapy. In this group, after the initial phase of treatment, despite a weak response, continuation of injections results in further improvement. Hence, it is recommended to assess the effects of therapy even after a 12-month period.

Following therapy switch, it is possible to revert to the previous treatment if it yielded superior results compared to other available medications.

CRITERIA FOR SUSPENSION OF THERAPY

1. No recurrence of disease activity in patients treated in the PRN regimen for six months is regarded as inactive MNV – follow-up visits every three months are recommended.
2. In the event of recurrence of activity or CNV membrane formation in a new location, treatment should be resumed, with the therapeutic regimen adjusted individually to the patient's clinical condition and experience of the treating physician.
3. No MNV activity for 12 months (inactive MNV) in the T&E treatment regimen – recommended follow-up every three to four months without continued therapy.
4. If signs of disease activity are detected, treatment should be resumed.

In Poland, the treatment guidelines for exudative AMD are primarily governed by the regulations outlined in the retinal disease treatment program.

CRITERIA FOR DISCONTINUATION OF THERAPY

1. Lack of patient's consent to continue treatment.
2. Severe adverse reaction associated with drug administration.
   Note: Disruption of the retinal pigment epithelium is not an indication for discontinuation of therapy.
3. Permanent damage to the retinal structure within the central foveal region with no potential for visual acuity improvement.

COMPLICATIONS

1. Endophthalmitis:
- risk of occurrence: 0.02–0.09%/injection,
- prevention:
  - use of 5% povidone iodine solution before injection,
  - surgical hand washing,
  - use of sterile gloves and sterile eyelid speculum,
  - administering the injection while preventing the needle from coming into contact with the edges of the eyelids.

2. Iatrogenic cataract secondary to damage to lens structure by the injection needle.
   Among patients receiving intravitreal injections, a decrease in ligament tension in the lens is commonly observed.
3. Glaucoma – the risk increases with each subsequent intravitreal injection. Patients should have their intraocular pressure monitored.

DISCLOSURE

The authors declare no conflict of interest.

Selected references

1. Lahita R, Kluger J, Drayer DE, et al. Antibodies to nuclear antigens in patients treated with procainamide or acetylprocainamide. N Engl J Med 1979; 301: 1382-1385.
2. Ferris FL 3rd, Wilkinson CP, Bird A, et al. Clinical classification of age-related macular degeneration. Ophthalmology 2013; 120: 844-851.
3. Spaide RF, Jaffe GJ, Sarraf D, et al. Consensus Nomenclature for Reporting Neovascular Age-Related Macular Degeneration Data: Consensus on Neovascular Age-Related Macular Degeneration Nomenclature Study Group. Ophthalmology 2020; 127: 616-636.
4. National Institute for Health and Care Excellence. Age-related macular degeneration. NICE guideline [NG82]. 2018. National Institute for Health and Care Excellence. Serious eye disorders 2019.
5. Gualino V, Tadayoni R, Cohen SY, et al. Optical coherence tomography, fluorescein angiography, and diagnosis of choroidal neovascularization in age-related macular degeneration. Retin 2019; 39: 1664-1671.
6.. Perrott-Reynolds R, Cann R, Cronbach N, et al. The diagnostic accuracy of OCT angiography in naive and treated neovascular agerelated macular degeneration: a review. Eye (Lond) 2019; 33: 274-282.
7. Charakterystyka produktu leczniczego ranibizumab.
8. Charakterystyka produktu leczniczego aflibercept.
9. Charakterystyka produktu leczniczego brolucizumab.
10. Charakterystyka produktu leczniczego farycymab.
11. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular agerelated macular degeneration. N Engl J Med 2006; 355: 1432-1444.
12. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006; 355: 1419-1431.
13. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology 2012; 119: 2537-2548.
14. Schmidt-Erfurth U, Chong V, Loewenstein A, et al. Guidelines for the management of neovascular age-related macular degeneration by the European Society of Retina Specialists (EURETINA). Br J Ophthalmol 2014; 98: 1144-1167.
15. National Institute for Health and Care Excellence. Age-related macular degeneration: diagnosis and management. NICE Guideline NG82. 2022.
16. Gale RP, Mahmood S, Devonport H, et al. Action on neovascular age-related macular degeneration (nAMD): recommendations for management and service provision in the UK hospital eye service. Eye (Lond) 2019; 33 (Suppl 1): 1-21.
17. Chong V. Ranibizumab for the treatment of wet AMD: a summary of real-world studies. Eye (Lond) 2016; 30: 1526.
18. Lanzetta P, Loewenstein A, Vision Academy Steering Committee. Fundamental principles of an anti-VEGF treatment regimen: optimal application of intravitreal anti-vascular endothelial growth factor therapy of macular diseases. Graefes Arch Clin Exp Ophthalmol 2017; 255: 1259-1273.
19. Kim LN, Mehta H, Barthelmes D, Nguyen V, Gillies MC. Metaanalysis of real-world outcomes of intravitreal ranibizumab for the treatment of neovascular age-related macular degeneration. Retina 2016; 36: 1418-1431.
20. Holz FG, Tadayoni R, Beatty S, et al. Multi-country real-life experience of anti-vascular endothelial growth factor therapy for wet age-related macular degeneration. Br J Ophthalmol 2015; 99: 220-226.
21. Rufai SR, Almuhtaseb H, Paul RM, et al. A systematic review to assess the ‚treat-and-extend' dosing regimen for neovascular agerelated macular degeneration using ranibizumab. Eye (Lond) 2017; 31: 1337-1344.
22. Silva R, Berta A, Larsen M, et al. Treat-and-extend versus monthly regimen in neovascular age-related macular degeneration: results with ranibizumab from the TREND study. Ophthalmology 2018; 125: 57-65.
23. Real JP, Granero GE, De Santis MO, et al. Rate of vision loss in neovascular age-related macular degeneration explored. Graefes Arch Clin Exp Ophthalmol 2015; 253: 1859-1865.
24. Muether PS, Hermann MM, Koch K, Fauser S. Delay between medical indication to anti-VEGF treatment in age-related macular degeneration can result in a loss of visual acuity. Graefes Arch Clin Exp Ophthalmol 2011; 249: 633-637.
25. Foot B, MacEwen C. Surveillance of sight loss due to delay in ophthalmic treatment or review: frequency, cause and outcome. Eye (Lond) 2017; 31: 771-775.
26. Patel PJ, Devonport H, Sivaprasad S, et al. Aflibercept treatment for neovascular AMD beyond the first year: consensus recommendations by a UK expert roundtable panel, 2017 update. Clin Ophthalmol 2017; 11: 1957-1966.
27. The Royal College of Ophthalmologists. The Way Forward. Age-Related Macular Degeneration and Diabetic Retinopathy. Report 2017. Available at: https://www.rcophth.ac.uk/wp-content/uploads/2015/10/RC Ophth-The-Way-Forward-AMD-300117.pdf.
28. Yadav S, Parry DG, Beare NAV, Pearce IA. Polypoidal choroidal vasculopathy: a common type of neovascular age-related macular degeneration in Caucasians. Br J Ophthalmol 2017; 101: 1377-1380.
29. The Royal College of Ophthalmologists. Age-related macular degeneration: guidelines for management. The Royal College of Ophthalmologists 2013.
30. Koh AHC, Parikh S. Efficacy and safety of ranibizumab with or without verteporfin photodynamic therapy for polypoidal choroidal vasculopathy: 24-month results from the EVEREST II study. Clin Ophthalmol 2018; 13: 1789-1799.
31. Almuhtaseb H, Kanavati S, Rufai SR, Lotery AJ. One-year real-world outcomes in patients receiving fixed-dosing aflibercept for neovascular age-related macular degeneration. Eye (Lond) 2017; 31: 878-883.
32. Amoaku WM, Chakravarthy U, Gale R, et al. Defining response to anti-VEGF therapies in neovascular AMD. Eye (Lond) 2015; 29: 1397-1398.
33. Ferris FL 3rd, Maguire MG, Glassman AR, et al. Evaluating effects of switching anti-vascular endothelial growth factor drugs for age-related macular degeneration and diabetic macular edema. JAMA Ophthalmol 2017; 135: 145-149.
34. Kim JH, Kim CG, Lee DW, et al. Intravitreal aflibercept for submacular hemorrhage secondary to neovascular age-related macular degeneration and polypoidal choroidal vasculopathy. Graefes Arch Clin Exp Ophthalmol 2020; 258: 107-116.
35. Maggio E, Deiro AP, Mete M, et al. Intravitreal recombinant tissue plasminogen activator and sulphur hexafluoride gas for submacular hemorrhage displacement in age-related macular degeneration: looking behind the blood. Ophthalmologica 2020; 243: 224-235.

36. Kimura S, Morizane Y, Hosokawa MM, et al. Outcomes of vitrectomy combined with subretinal tissue plasminogen activator injection for submacular hemorrhage associated with polypoidal choroidal vasculopathy. Jpn J Ophthalmol 2019; 63: 382-388.
37. The Royal College of Ophthalmologists. Ophthalmic Service Guidance. Intravitreal injection therapy. The Royal College of Ophthalmologists 2018.
38. Wingard JB, Delzell DA, Houlihan NV, et al. Incidence of glaucoma or ocular hypertension after repeated anti-vascular endothelial growth factor injections for macular degeneration. Clin Ophthalmol 2019; 13: 2563-2572.
39. Stellungnahme der Deutschen Ophthalmologischen Gesellschaft, der Retinologischen Gesellschaft und des Berufsverbandes der Augenärzte Deutschlands. Anti-VEGF-Therapie bei der neovaskulären altersabhängigen Makuladegeneration. Stand 15.10.2022.
40. Parolini B, Di Salvatore A, Pinackatt SJ, et al. Long-term results of autologous retinal pigment epithelium and choroid transplantation for the treatment of exudative and atrophic maculopathies. Retina 2020; 40: 507-520.