Best Practices for Age-Related Macular Degeneration (AMD) Therapy

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SUMMARY

Age-related macular degeneration is one of the leading causes of severe loss of sight in developed countries. Diagnostic procedures have developed dramatically in recent years, and modern imaging methods have contributed to improved options for population screening, targeted diagnostics, and monitoring of the treatment process.
At the same time, new treatment options have also been developing rapidly.
The recommended procedures summarize the current knowledge with the aim of unifying procedures for the diagnosis, classification, and treatment of age-related macular degeneration (AMD).
Key words: age-related macular degeneration, anti-vascular endothelial growth factor, choroidal neovascular membrane, macular neovascularization, diagnostics, treatment, recommended procedures

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1. Introduction

Age-related macular degeneration (AMD) is one of the most common ocular pathologies occurring in persons aged over 50 years. This disease affects the central part of the retina and may cause severe deterioration or complete loss of sight [1–5].

The most recent epidemiological meta-analyses confirm a higher prevalence of this disease in the Europid (Caucasian) race than in Hispanics, Asians and Africans. The prevalence of AMD is stated at 12.33% in Europeans, 7.53% in Africans and 7.38% in Asians [6].

Worldwide AMD affects 196 million people (2020), with an increase to 288 million projected by 2040 [6].

The diagnosis of the disease is the outcome of a basic ophthalmological examination and a broad spectrum of imaging methods, which have undergone a dramatic development in recent years, and have thereby contributed to faster and improved diagnosis and aided therapeutic decision-making.

With regard to the classification that we present in further detail in the text below, it is estimated that 85% of patients have the "dry" form of the disease [6] (better characterized by the description "progressive degenerative form without neovascularization"). Approximately 15% of patients with AMD then progress to "wet" form, associated with the onset of choroidal neovascularization (CNV). It is the wet (neovascular) form that is responsible for approximately 90% of cases with the most severe affliction of visual functions – visual acuity (VA) lower than 6/60 [6].

Treatment of AMD is targeted at slowing or halting the progressive deterioration of visual functions and on minimizing the impact of the disease on patients' quality of life.

Prevention, genetic intervention and treatment of the dry form of the disease, in particular the terminal phase in the form of geographical atrophy, have recently been the focus of the greatest interest within the entire com-

plex of considerations concerning therapy. Intravitreal application of anti-VEGF preparations is now considered the standard treatment for neovascular form of AMD [7].

Most of the currently recommended procedures for the treatment of AMD [8–10] are targeted at timely diagnosis and adequate individualized therapeutic intervention. In the near future it will undoubtedly be necessary to incorporate programs with automated assessment into the process of timely identification of the disease, including the use of artificial intelligence.

2. Characteristics of AMD

Age-related macular degeneration is the chief cause of severe, often irreversible damage to sight in developed countries. The primary (non-influenceable) risk factors for the development of AMD include: increasing age, Europid race and genetic factors [11]. A series of clinical trials have demonstrated that the chief influenceable risk factor is smoking [12,13]. Other factors have also been considered – hypertension, cardiovascular health, Body Mass Index (BMI), diabetes mellitus (DM), intake of antioxidants and socio-economic status. Although we take these factors into account, no statistically significant dependency has been demonstrated [14-17]. With regard to both types of risk factors, today it is evident that the non-influenceable factors are decisive, and particularly that genetic predisposition is quite unambiguously the most decisive factor. Genetic influence contributes in as many as 55% of cases to the overall risk of development of the disease [18,19].

Age-related macular degeneration is characterized by one or more of the following symptoms [8]:

- presence of reticular pseudodrusen or small and medium-sized drusen (> 63 μm in diameter)
- presence of large drusen (> 125 μm in diameter) or drusenoid ablations of the retinal pigment epithelium
- abnormalities of the retinal pigment epithelium – weakening, irregularity (hypopigmentation, hyperpigmentation or fragmentation), atrophic defects of the retinal pigment epithelium (RPE)
- changes of the vascular complex – disorders and irregularities of the deep capillary plexus of the retinal circulation, changes (weakening and thinning) of the choriocapillaris
- presence of advanced pathologies: geographical atrophy (GA) of the RPE and outer layers of the retina
- choroidal neovascularization (CNV type I–III) with all associated manifestations (growth of neovascular membrane, presence of intraretinal and subretinal fluid, RPE ablation, hemorrhage, rupture of RPE, fibrosis or macular atrophy)

Normal, age-related changes in the central region of the retina as a consequence of ageing are a common manifestation of changes in the outer neuroretina, in the RPE, in the Bruch's membrane and in the choriocapillaris [20].

These are:

- reduction of density and changes of distribution of the photoreceptors
- depletion of melanin granules, accumulation of lipofuscin and other residual bodies in the RPE cells
- changes in the basal membrane of the RPE – accumulation of deposits between the membrane of the RPE cell and its basal membrane (basal laminar deposits)
- accumulation of lipoprotein deposits between the basal membrane of the RPE and the Bruch's membrane, with subsequent formation of drusen
- progressive involution changes in the choriocapillaris

These phenomena are physiologically linked with age and do not come within the designation of the pathological unit of AMD, though they are typically present in the pre-stage of its development.

3. Classification of AMD

The modern classification of AMD is derived from the classic texts by Gass [21] and Ryan [22], taking into account the classification according to the AREDS study [23]. This synthesis of previous classifications contains material compiled by a group of leading vitreoretinal specialists from 2013 [20].

In these Best Practices we use the classification of AMD according to the unified panel of specialists [20] and according to the AREDS study [23].

3.1 No AMD changes (AREDS category 1): macula without drusen whatsoever or with a few small extrafoveal drusen (drusen smaller than 63 μm).

3.2 Early AMD (AREDS category 2): presence of small drusen (< 63 μm), small number of medium-sized drusen (63–125 μm) or minimal changes of the retinal pigment epithelium. The risk of progression within a 10-year time frame is relatively low [20]. According to the AREDS study (observation 10 years), the risk of progression towards large drusen is approximately 15% [23].

3.3 Intermediate AMD (AREDS category 3): numerous medium-sized drusen or at least one large druse (≥ 125 μm) in one or both eyes, confluent soft drusen or geographic atrophy of the RPE and outer retinal layers not affecting the fovea. The average risk of progression within a 5-year time frame is 18% [20]. However, there may be large variability of the findings within this category.

3.4 Advanced VPMD (AREDS category 4): geographic atrophy affecting the fovea (terminal dry form of AMD), neovascular maculopathy – presence of CNV (of any type) or fibrosis of the foveal region. In this phase the visual functions of at least one of the patient's eyes are always affected. The risk of progression of the other eye to this late phase within a 5-year time frame is stated by various studies within the range of 22–50% (AREDS 35–50% [23,24], Beaver Dam Eye Study 22% [25,26], Submacular Surgery Trial 30–50% [27]). The deterioration of visual functions is slower in the case of geographic atrophy than in the case of progression of neovascular AMD.

3.4.1 Advanced AMD – atrophic macular degeneration, (geographic atrophy, GA)

Atrophic macular degeneration is a manifestation of progressive atrophy of the choroid (especially the choriocapillaris), retinal pigment epithelium and the structures of the outer retinal layers located above them.

In terms of AMD, geographic atrophy is responsible in total for approximately 10% of afflictions with a deterioration of VA to a level of 6/60 or lower [28]. Extrafoveal localization of GA does not diminish VA in either distance or near vision. Patients with borderline affliction of the foveola may have relatively good distance VA, although near visual functions are generally diminished. In the more advanced phases with full affliction of the fovea, there is a pronounced deterioration of VA in both near and distance vision. The speed of development of GA and the risk factors of progression which we pay particular attention to are size of the lesion, its localization, the number of deposits of atrophy, the character of the finding on autofluorescence and symmetry in both eyes [29–32].

3.4.2 Advanced AMD – neovascular/wet form AMD

Neovascular AMD is characterized by the presence of choroidal or chorioretinal neovascularization, which is accompanied by typical signs: RPE elevation (serous, vascular, fibrovascular or hemorrhagic) RPE defects, degradation of the outer retinal layers, intraretinal or subretinal accumulation of fluid, hemorrhage and fibrotic remodeling of the macula.

At present we use the following division of types of CNV according to Gass [33] and Yanuzzi [34,35]:

3.4.2.1 Choroidal neovascularization CNV type I (previously occult CNV)

CNV I (occult neovascular membrane) is neovascularization dominantly localized beneath the RPE. The process undergoes a typical development and diagnostically can be identified in the following phases: RPE elevation without breach of the RPE and without changes of the retinal structure, more pronounced RPE elevation with combined content (serous – hemorrhagic – angioproliferative), weakening and defects of the RPE with infiltration beneath the sensory epithelium, defects of the retinal layers (disorders of outer layers, formation of edemas), in some cases progression of neovascularization to the retinal layers (mixed types of CNV), degradative microcysts in the receptor line (ONL) and microcysts in the zone of bipolar cells, inactive soft fibrosis of original CNV (scarring with atrophy of the outer retinal layers) [36].

3.4.2.1.1 Choroidal neovascularization CNV type I – non-exudative type of occult CNV

In this case CNV is not manifested in the usual signs of activity (hemorrhage, infiltration), and is clinically quiescent. The usual manifestation on a classic OCT scan is a "double layer sign" (flat, thin RPE ablation), on OCT angiography there is a finding of inactive CNV. Within one year a development of activity takes place in approximately 21% of cases. Inactive CNV type I (quiescent CNV) is also generally associated with a potentially protective effect against the development of geographic atrophy [37].

3.4.2.2 Choroidal neovascularization CNV type II (previously classic CNV)

The source of this neovascularization is again primarily choroidal, but the basic strain of neovascularization passes through the defective RPE and the branching of CNV itself is dominant over the RPE (sub and intraretinally). A loosening of the retinal structures occurs in the surrounding area of CNV type II, with varying degrees of serous or serous-hemorrhagic infiltration. In the late phases fibrosis again occurs, with atrophy of the outer retinal layers and more pronounced breach of the adjacent structures [36].

3.4.2.3 Chorioretinal neovascularization – CNV type III (retinal angiomatous proliferation – RAP)

RAP is typically manifested in primary proliferation of the retinal blood vessels (region of the superficial and deep capillary plexus of the retinal circulation), and it is only later that CNV penetrates through further layers of the retina and anastomoses with secondary choroidal neovascularization. According to the degree of development of the finding, we observe only retinal thickening (edema, cysts and infiltration in all layers with potential serious ablation of the RPE), or later also RPE ablation with signs of choroidal CNV [36].

4. Diagnosis of AMD

Diagnosis of AMD is founded on the following basic points: medical history, classic ophthalmological examination and imaging methods.

4.1 Medical history

In connection with AMD it is of fundamental importance to record subjective symptoms (metamorphopsia, development of deterioration of central VA, data on disorders of color sense and contrast sensitivity), overview of systemic medication, ocular anamnesis (operations, refractive procedures, inflammations), family medical history with focus on AMD and social history (occupation, smoking).

4.2 Ophthalmological examination

Determination of best corrected visual acuity (BCVA) in distance vision (it is of fundamental importance that these patients are tested on an ETDRS chart by a trained person under standard conditions) and in near vision, referential examination on Amsler grid, examination on slit lamp (anterior segment and possible context of deterioration of visual functions) and fundus biomicroscopy.

4.3 Imaging methods

a) Optical coherence tomography (OCT) is the basic and fundamental diagnostic imaging method for primary diagnosis and monitoring of the development of the pathology during treatment.
b) Optical coherence tomography – angiography (angioOCT, OCTA) is a noninvasive method of imaging the vascular channel of the central retina for detection of any applicable presence of choroidal neovascularization.
c) Color fundus photography.
d) Autofluorescence of fundus (especially for detection of pathological and atrophic areas of RPE).
e) Fluorescein angiography (FAG) – invasive method of imaging blood vessels of the retinal circulation using an intravenously applied contrast substance. In the era of OCTA it is now used only on a small number of patients with AMD in the case of diagnostic ambiguities.
f) Indocyanine green (ICG) angiography – invasive method of imaging blood vessels of the choroidal

and retinal circulation using an intravenously applied contrast substance. Today it is used only on a minimal number of patients with AMD, again in the case of diagnostically ambiguous findings.

It is necessary to perform all the above examinations within the course of a single patient visit. The precise composition and use of the above methods is determined by the attending physician. In the case of monitoring and treatment of patients in the advanced phase of AMD, an OCT examination should be performed at every visit. Today angioOCT is also an important component of diagnosis in AMD. It is a highly suitable noninvasive method of detecting the complex of CNV before the commencement of therapy, after the conclusion of the loading phase of anti-VEGF treatment and subsequently at any time during treatment and during subsequent monitoring of the patient. The other two methods mentioned above – FAG and ICG – are now performed only minimally in the case of AMD.

4.4 Genetic diagnosis

Methods of genetic diagnosis are now coming to the forefront of interest – in particular of the two main genes CFH and ARMS2/HTRA [18,38]. However, at present the American Academy of Ophthalmology (AAO) recommends proceeding with restraint in genetic diagnosis until the significance for the prognosis and therapeutic response is confirmed [8].

5. Treatment of AMD

Treatment of AMD is targeted at slowing and stabilizing the deterioration of visual functions, and on mini-

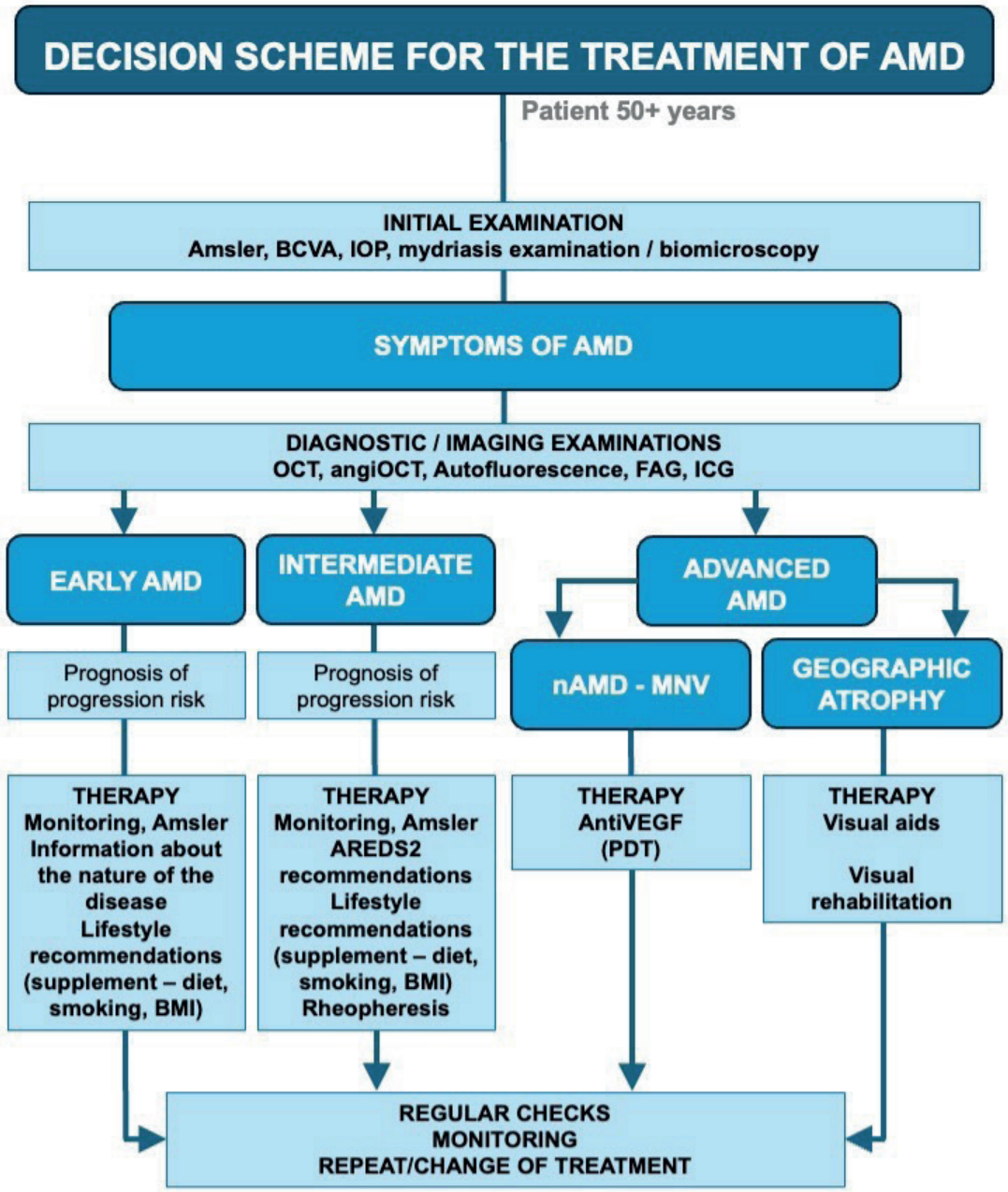

Figure 1. Decision-making framework for the treatment of AMD

AMD – age-related macular degeneration, BCVA – best-corrected visual acuity, IOP – intraocular pressure, OCT – optical coherence tomography, FAG – fluorescence angiography, ICG – angiography with indocyanine green, nAMD – neovascular AMD, MNV – macular neovascular membrane, BMI – body mass index, AREDS – study, VEGF – vascular endothelial growth factor, PDT – photodynamic therapy

mizing the impact of the disease on patients' quality of life (Figure 1).

5.1. Early AMD

In this phase we educate the patient about the disease and can provide basic information about the prognosis based on the individual finding. We recommend quitting smoking (strong level of evidence), reducing obesity and excess weight (BMI), stabilizing blood pressure (control of arterial hypertension – medium level of evidence). The influence of cataract surgery, UV radiation and blue light emission from electronic devices is not conclusive (weak level of evidence). Similarly, no fundamental influence of kinetic activity has been demonstrated [11–17]. The current knowledge also does not support the influence of systemic use of a combination of antioxidants, vitamins and minerals for reducing or slowing progression from the early to the intermediate form of AMD [39].

5.2 Intermediate AMD and advanced AMD without CNV

The randomized, multicentric, double-blind and placebo-controlled trial AREDS2 demonstrated the effectiveness of systemic therapy in slowing the progression of the disease from intermediate to advanced AMD [40,41]. Effective supportive therapy according to the AREDS2 trial contains (daily doses): vitamin C (500 mg), vitamin E (400 IU), zinc (25 mg), copper (2 mg), lutein (10 mg) and zeaxanthin (2 mg).

No positive effect of adding further supportive preparations, specifically beta-carotene and omega-3 supplements, was confirmed [41]. This supportive therapy is not recommended for patients with a finding of bilateral fibrosis in the macula or central geographic atrophy.

Further alternative therapies for intermediate and advanced forms of AMD without CNV are: photobiomodulation and rheopheresis. Rheopheresis of blood plasma is reserved for the treatment of AMD with an accumulation of soft drusen and drusenoid ablation of the retinal pigment epithelium. Rheopheresis may retard or alleviate the development of the aforementioned changes by influencing microcirculation, thus by improving the perfusion of the choroid and retina while reducing the viscosity of blood plasma [42–44].

An important subject of interest in recent years is intravitreal pharmacotherapy of the advanced phase of AMD with geographic atrophy. This frequently (monthly) applied intravitreal therapy acts by inhibition on various levels, slowing the progression of geographic atrophy in the macula. Some studies have not been successful [45], others have demonstrated partial effectiveness (on average approximately 20% slowing of progression of GA) and have obtained FDA approval in the USA. These are the molecules pegcetacoplan and avacincaptad pegol [46,47]. However, this treatment for GA has not yet been approved by the European Medicines Agency (EMA).

5.3 Therapy of advanced AMD with CNV

(neovascular AMD)

We try to commence therapy of choroidal neovascular membrane in the macular localization as soon as possible after clinical activity of the disease has been confirmed. Timely therapeutic intervention produces better functional and anatomical results, with a smaller number of follow-up examinations and interventions.

a) **Observation**. In the case of clinically inactive CNV (quiescent CNV) we do not indicate treatment, only regular monitoring is recommended within a range of 3–6 until the time of clinical development of affliction [37].
b) **Anti-VEGF therapy**. Injected intravitreal anti-VEGF pharmacotherapy is the method of choice for neovascular AMD [48]. Anti-VEGF therapy is currently provided in instituted application centers ("care centers") in the Czech Republic, which are bound by the conditions of payment set by the State Institute for Drug Control, and treatment is covered financially under these conditions from the resources of public health insurance.
c) **Surgical treatment**. Pars plana vitrectomy (PPV) is indicated in two basic situations associated with neovascular form of AMD. These are findings of vitreomacular adhesion, traction of the separating vitreous or presence of an epimacular membrane, which may significantly reduce the effect of anti-VEGF therapy. A second indication for PPV is the onset of acute subretinal hemorrhage in connection with the activity of CNV. In this case timely indication of PPV with subretinal instillation of a recombinant tissue plasminogen activator (rTPA) and tamponade with expansive gas can substantially improve the prognosis for preservation of useful central vision [49]. Upon subsequent fulfilment of the indication criteria the patient may be placed within the regimen of center treatment.
d) **Photodynamic therapy (PDT) with verteporfin.** This is not recommended for subfoveal CNV after the commencement of anti-VEGF therapy. In most cases this technique does not effectively avert severe losses of sight [50], and as a consequence it is currently recommended in other indications, e.g. for pachychoroid spectrum disorders.
e) **Destructive methods.** It is theoretically possible also to use photothermic destruction by direct laser photocoagulation in the treatment of extrafoveal CNV. However, in as many as 50% of cases this technique produces complications in the sense of persistence or recurrence of neovascularization, and therefore cannot be recommended in the era of anti-VEGF therapy [51]. Other techniques of direct destruction of CNV such as transpupillary thermotherapy (TTT), radiation methods or surgical extraction of neovascular tissue are also not recommended. In the great majority of cases they lead to permanent damage to the macular landscape, with a deterioration of visual functions.

5.3.1 Fundamental principles and phases of application of anti-VEGF preparations

Commencement of therapy – loading phase. Therapy is commenced intensively in a fixed regimen. The effect of treatment during the loading phase has a decisive influence on the future development of the disease and the frequency of subsequent therapy.

Continuation of therapy – in continued therapy fo-

llowing the initial intensive phase we use various dosing regimens, which we divided into reactive and proactive regimens.

The least effective used regimen is the reactive pro re nata (PRN – according to requirement) regimen, in which the pharmaceutical is applied at irregular intervals, always only upon demonstrated activity of the disease. Today it is rarely used due to problematic planning, the required higher frequency of follow-up examinations and the low effectiveness of this reactive therapy.

A regimen at the opposite end of the spectrum of therapeutic approaches is the fixed regimen (FIX). This is a highly proactive regimen, in which the patient is treated at regular, fixed intervals. From the perspective of both the patient and the application center, the management of therapy is considerably simplified by this regimen, though it may lead to overtreatment of the patient.

In between these two application models is a loose proactive regimen – treat and extend (TaE), which is unequivocally the preferred and most widely used dosing regimen used today. After the loading phase, the interval of further applications is progressively extended or shortened based on the current individual finding, until the ideal interval of treatment for the patient is determined using this method.

Change of therapy – switch. In a situation in which the treatment used hitherto is not anatomically or functionally successful, or in cases where it is necessary to apply an anti-VEGF preparation extremely frequently in order to maintain control over the disease, it is possible to consider a change of medication. This procedure is referred to as a switch (this term is also commonly used within the Czech environment). Discussions are ongoing worldwide concerning the conditions for switch of therapy and its timing [52]. In our opinion the following constitute reasons for switch of therapy:

a) Non-response – worsening of finding or zero response to treatment in the first 4 months.
b) Suboptimal response – limited, insufficient anatomical and functional response even upon shortening of the intervals of treatment, in which there is a danger of irreversible changes of tissue.
c) Impossibility of further shortening of intervals of applications – this reason ensues from the SPC of the used medications, which are defined by the minimum interval of treatment in the period following the loading phase.
d) Tachyphylaxis – decrease of effectiveness of therapy following an initial beneficial effect. Mostly associated with long-term application of a specific preparation.
e) Intolerance of medication – incidence of adverse effects in connection with a specific type of preparation. In particular this concerns immune – inflammatory reactions to the pharmaceutical in question.
f) Patient compliance with therapy – when the patient has limited possibilities to attend very frequent therapy it is possible to consider a switch to a preparation with an expected greater effect and longer intervals between applications.

Termination of therapy – there is a professional consensus on the definition of the conditions for terminating therapy, which is reflected by the current valid wording of the indication restrictions for financial coverage for all preparations used today. According to this definition, therapy is terminated if it is not possible to expect any further effect of therapy on the basis of the clinical finding.

5.3.2. Anti-VEGF preparations for the treatment of neovascular form of AMD – in alphabetical order:

1. **Aflibercept (2 mg, therapeutic dose 0.05 ml)**
   Trap antibody molecule targeted at receptors for VEGF-A, VEGF-B and PlGF. In the VIEW 1 and VIEW 2 trials, aflibercept was applied after loading in a fixed interval of once every two months [53]. The trials demonstrated that aflibercept was not inferior in comparison with ranibizumab, which was applied in a dosage of once per month. In actual clinical practice it is used in the continuation phase of therapy in a fixed regimen every two months, or in an individualized Treat and Extend regimen with an interval of individual applications of up to four months.
2. **Aflibercept (8 mg, therapeutic dose 0.07 ml)**
   Trap receptor for VEGF-A, VEGF-B and PlGF. In the PULSAR trial, aflibercept 8mg was applied after loading in a fixed interval of once every three or four months [54]. The trial demonstrated that aflibercept was not inferior in a comparison of both branches, in which aflibercept 2 mg was applied after loading in a fixed regimen of once every two months. Based on the results of the second year of the trial, it is possible to apply aflibercept 8 mg in an interval of four to six months while maintaining similar effectiveness as with the original variant of the pharmaceutical (2 mg).
3. **Brolucizumab (6 mg, therapeutic dose 0.05 ml)**
   Small fragment of anti-VEGF-A antibody with high affinity to receptors and large degree of penetration into tissue. In the HAWK and HARRIER trials brolucizumab was compared against aflibercept 2 mg in a dosage of once very two months [55]. Brolucizumab was demonstrated not to be inferior in both dosing branches of continuation therapy – every two and every three months. Nevertheless, brolucizumab is associated with a higher risk (in up to 4% of patients) of incidence of immune-inflammatory ocular complications (sterile uveitis, vitritis, vasculitis, occlusive vasculitis).
4. **Faricimab (6 mg, therapeutic dose 0.05 ml)**
   Fragment of antibody acting against VEGF-A and simultaneously against Angiopoietin 2 (Ang-2). In the TENAYA and LUCERNE trials it was compared against aflibercept 2 mg in a dosage of once every two months [56]. Faricimab was demonstrated not to be inferior in all three dosing branches (application once every two, three or four months), with the possibility of extension according to the development of the disease. The majority of the patients in this trial had an application interval of longer than three months in the second year of treatment.
5. **Ranibizumab (0.5 mg, therapeutic dose 0.05 ml)**
   Fragment of antibody acting against VEGF-A. In the ANCHOR and MARINA trials ranibizumab was demonstrated to be clearly superior in a comparison against sham and

PDT [57,58]. In actual clinical practice, an individualized application Treat and Extend regimen is most frequently applied for ranibizumab. In comparison with other anti-VEGF molecules it has the lowest effectiveness, and for a comparable result of treatment it must be used in a higher frequency of applications. At present it is now possible also to use biosimilar products of ranibizumab.

5.3.3. Technique of intravitreal application of anti-VEGF preparations

a. Application venue

Worldwide intravitreal applications are performed under the following conditions: application in surgery, in special application room (clean room) or operating theater. With regard to safety, above all with regard to evaluating the incidence of post-application endophthalmitis, there is no difference between these venues. This is confirmed by numerous studies from actual clinical practice [59–62].

For intravitreal therapy centers in the Czech Republic we recommend a special application room (clean room), which is the most widely used overall in Europe.

b. Antibiotic prophylaxis

At present the benefit of using local antibiotics (ATB) preoperatively, perioperatively and postoperatively has not been sufficiently confirmed. We do not consider an ATB preparation in any form to be essential [63–65].

c. Disinfection of area of eye, eyelids and conjunctival sac

Povidone-iodine is used for disinfection of the eye and the surrounding area and for rinsing the conjunctival sac, for disinfection of the eyelids in a 10% concentration and for disinfection of the conjunctival sac in a 5% concentration. In the case of disinfection of the eyelids and the surrounding area of the eye no greater safety was demonstrated, and it is therefore not essentially necessary [66,67].

However, rinsing of the conjunctival sac is absolutely essential and demonstrably increases the safety of the procedure. Povidone-iodine should be left to act for at least 30 seconds [68–70].

For patients hypersensitive to povidone-iodine it is possible to use chlorhexidine as an alternative disinfecting agent.

d. Mouthpiece and speaking during application

During the course of the procedure it is recommended to minimize speaking between the patient and the attending physician, and to use a surgical mask. Aerosol dispersion from the oral or nasal cavity may lead to contamination of the operating field and is generally the most frequent source of infection [68].

e. Eye speculum

This is not a necessary condition for correct application. An alternative is manual fixation of the eyelid or use of a cotton-wool bud [71–73].

f. Intravitreal injection

A 30G syringe is most often used. According to the literature, the length of the needle is not of fundamental significance for the safety of the application [74]. The localization of the injection should be between the direct vertical and horizontal muscle, approx. 3.5–4.0 mm from the limbus. The choice of precise quadrant is based on the patient's individual requirements and the discretion of the attending physician. The injection is most frequently applied in a direction towards the center of the eye, with a small shift of the conjunctiva. In the case of repeated multiple applications it is appropriate to alternate the place of injection. A fundamental factor for limiting the risk of infection is to prevent contamination of the needle from the edge of the eyelid (margin, eyelashes etc.) [75].

g. Surgical gloves and mask

The WHO guidelines on hand hygiene in healthcare state that hand hygiene and surgical gloves are required as standard for surgical procedures [76].

There are no prospective randomized data on the use of sterile or non-sterile gloves and surgical masks for intravitreal applications. Concordantly with the opinion of the panel of experts, we recommend the use of sterile gloves, while we consider the use of a surgical mask optional [77].

h. Covering the eye after intraocular application

At present this is no longer used as standard. Application of a protective cover on the eye after application depends on the preference of the attending physician and the customs/guidelines of the center [78].

i. Bilateral injection

From the data presented in the current literature, bilateral intravitreal application on the same day is considered a regular procedure [79]. However, bilateral application should always be carefully considered, and each eye should be treated as a separate procedure – preparation of the operating field, change of gloves, new single-use instruments.

6. Management of treatment of AMD

The aim of AMD treatment is to attain the optimal therapeutic response with a minimal number of injections with regard to the burden placed on the patients, as well as the providers and payers of healthcare. The most recent preparations (aflibercept 8 mg and faricimab) attain the therapeutic targets (improvement of visual acuity and the clinical finding) within registration and comparative studies, with a smaller number of injections overall than ranibizumab. At the same time they have a significantly higher proportion of patients treated at intervals of longer than 8 weeks, and in a significant proportion of patients reach even longer intervals (16 to 24 weeks) without the need for monitoring visits in the interim period [54,56].

The total costs for care are therefore significantly lower, even despite the higher price/more expensive coverage of modern pharmaceuticals [80–82], also in the case of treatment of similar diagnoses (DME, RVO) [83–86]. At a hypothetically same price/coverage of pharmaceutical preparations, it is possible to expect an unequivocal benefit for all subjects involved (patients, healthcare facilities, payers of healthcare) upon the use of these modern pharmaceuticals with longer therapeutic intervals.

Treatment (and monitoring) in longer intervals also fully corresponds to the goal of attaining full physical, mental and social well-being according to the WHO definition of health. Last but not least it brings a significant saving not only on the direct costs of these visits, but also on

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