TREATMENT REGIMENS OF NEOVASCULAR FORM OF AGE-RELATED MACULAR DEGENERATION. A REVIEW

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SUMMARY

This article presents an overview of treatment regimens of drugs containing antivascular endothelial growth factor for the treatment of neovascular form of age-related macular degeneration. Currently, drugs containing antivascular endothelial growth factor are the only effective treatment for this chronic and progressive disease. The treatment regimens for this disease in the last two decades have seen a shift from a simple endeavor to stabilize the disease to achieving maximum improvement of visual acuity and its maintenance, with improvement of the patient's quality of life and a minimal treatment burden on patients and their families. Other goals of the alternative dosing regimens that have replaced the original fixed regimens were greater individualization of the dosing regimen, better patient cooperation, saving financial costs and reducing the burden on application centers. Age-related macular degeneration, whether dry form or wet form, represents a serious health and socioeconomic problem, as the disease is one of the most common causes of severe and irreversible central visual acuity disorders up to the degree of practical blindness of one or both eyes in people over 50 years of age in developed industrialized countries. The most important issue is to ensure early diagnosis of this disease, followed by prompt and continuous treatment with an individualized proactive treatment regimen, with the aim of stabilizing and improving anatomical and functional results.

Key words: treatment regimens, vascular endothelial growth factor, antivascular endothelial growth factors, neovascular age-related macular degeneration

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INTRODUCTION

At present, the drugs of first choice in the treatment of neovascular (wet) form of age-related macular degeneration (ARMD) are pharmaceuticals containing antivascular endothelial growth factor (anti-VEGF), which are applied into the intravitreal space providing that there are no contraindications for intravitreal administration of this therapy. These are antibodies acting against vascular endothelial growth factor (VEGF), the main mediator of angiogenesis, which prevent the growth of newly formed blood vessels and reduce excessive vascular permeability [1]. The fundamental pathophysiological unit of wet form ARMD is choroidal neovascularization (CNV). CNV is defined as the growth of newly formed blood vessels in the region of the choroid, beneath the retinal pigment epithelium (sub-RPE) or into the subretinal space. Although the name and basic definition refers only to the vascular component, CNV is more precisely defined as a growth of aberrant tissue composed of endothelial and immune cells, which is contributed to by angiogenesis and inflammation [2]. Of the numerous identified activators of angiogenesis, the most relevant above all is the aforementioned VEGF. VEGF is a homodimeric glycoprotein with monomers in an antiparallel structure. To date, six subtypes of VEGF are known, namely VEGF-A, B, C, D, E and placental growth factor – PlGF. In humans, VEGF-A occurs in 5 isoforms: VEGF-A121, VEGF-A145, VEGF-A165, VEGF-A189 and VEGF-A206. The isoforms most commonly occurring in the human eye are VEGFA121 and VEGFA165 [3]. VEGF-A binds to the surface of the endothelial cells via the VEGF-R1 and VEGF-R2 receptors. VEGF-A plays a role in the development and maintenance of the function of the vascular channel. Increased binding of VEGF to the endothelial cells leads to angioge-

nesis, lymphangiogenesis and the production of proteases and cytokines. Similarly, it increases vascular permeability and has a pro-inflammatory effect. PlGF may act in synergy with VEGF-A in activating the VEGF-R1. With regard to the key role of VEGF in the pathogenesis of CNV, the VEGF molecule has been identified as a suitable candidate for targeted biological therapy [4]. The use of pharmaceuticals with an anti-VEGF content in clinical practice has been supported by several randomized clinical trials, in which their efficacy, safety profile and low incidence of adverse side effects has been demonstrated. Another of their advantages is their short biological half-life, which leads to a quick breakdown of the substance from the organism. Pharmaceuticals with an anti-VEGF content block binding and activation of the receptors for VEGF molecules and the proliferation of endothelial cells of choroidal neovascularizations and retinal vessels, thereby inhibiting the growth of abnormal new vessels and reducing excessive vascular permeability. A key factor for the stabilization of the pathology, and in many cases also for achieving an improvement of visual acuity (VA) is its timely diagnosis and immediate commencement of treatment [5]. The most beneficial diagnostic tests for the detection of newly occurring or recurring pathological neovascularization, as well as for the monitoring of treatment, are new diagnostic modalities, namely optical coherence tomography (OCT), OCT angiography (A-OCT), as well as the older fluorescence angiography (FAG) and indocyanine green angiography (ICGA). OCT examination has made a significant contribution to the evaluation of the disease and the course of treatment. It is a non-invasive, non-contact, transpupillary examination of the retina with a high-resolution capacity employing optical reflectivity, which displays the retina and the surrounding structures of the posterior pole of the eye in a transverse cross-section, pinpoints the localization of the changes and objectivizes their thickness. Invasive FAG or ICGA differentiates the neovascularizations beneath the retina, and if applicable beneath the retinal pigment epithelium (RPE), with the aid of contrast substances administered into the cubital vein [6,7]. A-OCT is the latest non-invasive imaging method of examination, which enables the display of the blood flow in the retinal vessels and choroid with high resolution, and in addition it differentiates neovascularizations and serves for diagnosis and monitoring. We also produce color images of the ocular fundus with the aid of a digital fundus camera. In the examination scans are obtained of a direct, enlarged image of the ocular fundus. The scans are then evaluated by computer [8,9].

Diagnosis of ARMD

The diagnosis of ARMD is determined on the basis of a complete ophthalmological examination, with an emphasis on determining the patient's subjective complaints, as well as their family and personal medical history and general physical condition. Distance VA with optimal correction is determined on an ETDRS (Early Treatment Diabetic Retinopathy Study) chart, i.e. best corrected visual acuity (BCVA). Intraocular pressure (IOP) is measured. The morphological examination incorporates biomicroscopy of the anterior segment of the eye with the aid of a slit lamp and examination of the finding on the ocular fundus by special lenses in mydriasis. Using the latest imaging method, namely OCT, we visualize the structures of the macula from profile, such as retinal swelling, pathological neovascularizations and detachment of the neuroretina [10].

Types of pharmaceuticals with anti-VEGF content (brief overview)

At present we have 4 types of anti-VEGF preparations (ranibizumab, aflibercept, brolucizumab and faricimab) and three biosimilars (ranibizumab) approved for on-label treatment by the European Medicines Agency (EMA). Bevacizumab is used for intravitreal treatment of ocular pathological vascular diseases in an "off-label" regimen, because its use in ophthalmology is not approved by the FDA (Food and Drug Administration – the federal US government agency responsible for the monitoring and regulation of foodstuffs, food supplements, pharmaceuticals, cosmetic preparations, medical instruments, biopharmaceutical and blood products in this country) [11–14].

The first effective preparation for the treatment of ARMD was pegaptanib sodium (Macugen, Pfizer), a modified RNA oligonucleotide that selectively and with high affinity binds specifically only to the isoform VEGF-A165 and blocks its binding to the receptor. It is no longer used in Slovakia due to its lower effectiveness in comparison with other anti-VEGF preparations [15,16].

The second anti-VEGF preparation to be introduced onto the market is ranibizumab (Lucentis, Novartis Pharma GmbH) (Figure 1 A). This is a fragment of a humanized recombinant antibody with a size of 48 kDa (kiloDalton), which does not have an Fc fragment and which was created in *Escherichia coli* cells by recombinant DNA technology. The target of the effect of ranibizumab is all isotopes of VEGF-A, thereby preventing the binding of VEGF-A to its receptors VEGF-R1 and VEGF-R2 on the endothelial cells of the CNV, which prevents the growth and enlargement of these CNV membranes. The small size of its molecule enables easy permeability via the retina to the target CNV membrane following intravitreal application. Another advantage is its short plasmatic half-life, which leads to a quick breakdown of the substance within the organism. The efficacy, safety and methods of dosing of ranibizumab have been verified by several years of research. The fundamental clinical trials for determining efficacy and safety were the MARINA and ANCHOR trials, which unequivocally demonstrated the positive effect of this therapy. Studies which verified efficacy in different methods of dosing were PIER, EXCITE, SUSTAIN, SAILOR and PrONTO. One ml of injection solution contains 10 mg of ranibizumab. One full injection syringe contains 0.165 ml, corresponding to 1.65 mg of ranibizumab. The volume that can be obtained from one full syringe is 0.1 ml. This provides a usable quantity for the administration of a single dose of 0.05 ml, which contains 0.5 mg of ranibizumab [17].

The third anti-VEGF preparation is aflibercept (Eylea,

Bayer AG) (Figure 1 B). This is a recombinant fusion protein with a size of 115 kDa, which combines an Fc part of a full monoclonal antibody and the two highest affinity binding domains of the VEGF receptors type VEGF-R1 and VEGF-R2. After intravitreal administration it acts through its receptors as bait for VEGF-A, VEGF-B and PlGF, thereby preventing their binding to the receptors of the endothelial cells of the retinal and choroidal membranes and thus preventing the growth and enlargement of these CNV membranes. The efficacy and safety of aflibercept has been verified by the clinical trials VIEW 1 and VIEW 2. In addition to these two large clinical trials, there are various publications evaluating the effect of aflibercept in regular clinical practice. These are predominantly publications comparing the efficacy of aflibercept treatment with other anti-VEGF preparations, in some cases evaluating its effect in patients following prior treatment with a different anti-VEGF preparation. 1 ml of injection solution contains 40 mg of aflibercept. Each full injection syringe contains 0.09 ml, which corresponds to 3.6 mg of aflibercept. This provides a usable quantity for the administration of a single dose of 0.05 ml, which contains 2 mg of aflibercept [18].

The newly available, fourth anti-VEGF preparation is brolucizumab (Beovu, RTH 258, formerly ESBA 1008, Novartis Pharma GmbH) (Fig. 1 C). The EMA approved brolucizumab for use in the European Union on 17 February 2020. Brolucizumab has been available in Slovakia since 1 August 2021. It is a single-chain variable fragment of a humanized single-chain Fv monoclonal antibody (scFv) created in *Escherichia coli* cells by recombinant DNA (deoxyribonucleic acid) technology. Brolucizumab inhibits all isoforms of VEGF-A from binding to the receptors VEGF-R1 and VEGF-R2. Its molecular density is 26 kDa, in comparison with 115 kDa in the case of aflibercept and 48 kDa in the case of ranibizumab. The small size of the molecule enables the creation of an injection solution with a high concentration of brolucizumab of up to 120 mg/ml. Each full injection syringe contains 19.8 mg of brolucizumab in 0.165 ml of solution. It provides a usable quantity for the administration of a single dose of 0.05 ml of solution, which contains as much as 6 mg of brolucizumab. Data from the 3rd phase of the registration clinical trials HAWK and HARRIER demonstrated that brolucizumab administered as 3 initial intravitreal injections and subsequently administered in 8- and 12-weekly intervals was not inferior in comparison with aflibercept in terms of change of VA, and at the same time, in comparison with aflibercept demonstrated better reduction of fluid in the retina (intraretinal and/or subretinal, sub-RPE). However, during treatment with brolucizumab a higher development of adverse side effects was recorded worldwide in the form of intraocular inflammation, including retinal vasculitis and/or retinal occlusion, which occurred already after the first intravitreal application and/or at any time during treatment, with a subsequent decrease of BCVA. Although in most cases the decrease of BCVA proved to be reversible after the commencement of anti-inflammatory treatment with corticosteroids, application centers are approaching the indication of brolucizumab more cautiously and stringently [19,20].

The development of what is so far the fifth anti-VEGF treatment, despite the important clinical successes of anti-VEGF drugs, started out on the basis of certain limitations of anti-VEGF drugs which still remain, such as the large therapeutic burden, the presence of unsatisfactory results in a certain percentage of patients and long-term decrease of VA as a consequence of complications such as macular atrophy and fibrosis. Targeting of the angiopoietin/Tie (Ang/Tie) pathway, outside of the VEGF pathways, may be a potential therapeutic strategy that could have the potential to resolve certain of the above-stated problems [21,22].

The fifth anti-VEGF preparation, faricimab (Vabysmo™, Genentech, San Francisco, CA) (Fig. 1 D) is a drug with a combined mechanism, with simultaneous and independent binding to VEGF-A and angiopoietin-2 (Ang-2). It is a humanized bispecific IgG antibody produced by recombinant DNA technology in a mammalian cell culture of a Chinese Hamster Ovary (CHO). Faricimab has a total size of 150 kDa and its structure is formed by 2 antigen-binding fragments (Fab), more precisely speaking binding to Ang-2 and VEGF-A, and a modified fragment crystallizable region (Fc region). Faricimab was developed using CrossMAB technology. This technology is based on crossing of the antibody domain within one Fab region of a bispecific IgG antibody in order to enable correct connection of the chain, thus facilitating the heterodimerization of 2 different antigen-binding domains in a single molecule, and as a result this "cross-over" process is associated with the high affinity of faricimab to Ang-2 and VEGF-A, and

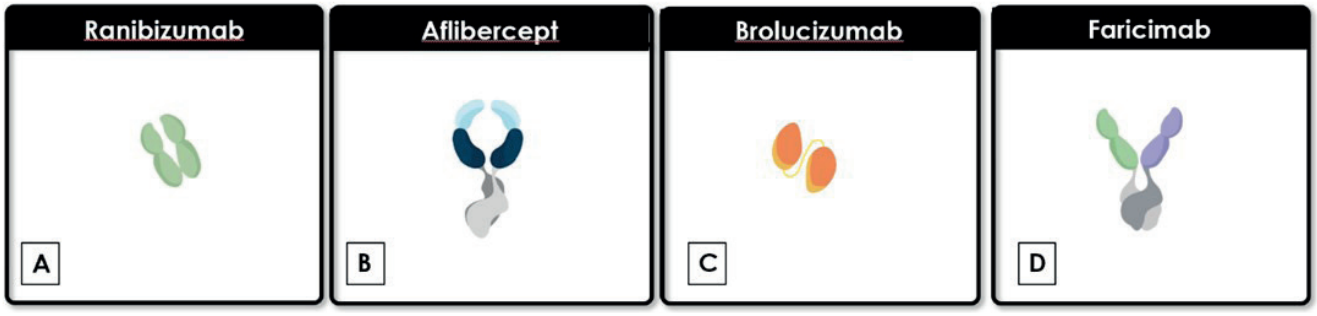

Figure 1. Molecules of anti-VEGF drugs

despite this also with a better stability profile in comparison with natural antibodies. However, further studies are required in order to provide further evidence on the role of the Ang/Tie pathway in the prevention of fibrosis in retinal pathologies. Faricimab was approved by the FDA in January 2022, and by the EMA in September 2022. The results of the studies of phase III TENAYA and LUCERNE in the case of wet form VPDM demonstrated the potential of faricimab to maintain clinical effectiveness in longer therapeutic regimens in comparison with aflibercept (12 or 16 weeks), with a good safety profile [21,22].

Bevacizumab is a fully humanized recombinant monoclonal IgG1 antibody acting against VEGF-A with a size of 148 kDa, which has been approved for intravenous treatment of adult patients with tumoral pathologies (metastasizing carcinoma of the large intestine or rectum, breast carcinoma, lung carcinoma). This drug is also widely used in intravitreal treatment in an "off-label" regimen, because it does not have FDA approval for its use in ophthalmology [17,23].

A biosimilar is a biologically similar drug. This means that a biosimilar pharmaceutical is very similar to a biological drug (biological – originating from a biological source – from live cells or organisms), i.e. to a referential pharmaceutical which is already permitted within the European Union. The EMA has progressively approved three biosimilars, namely Byooviz (Samsung Bioepis NL B.V, Netherlands) in August 2021, Ranivisio (Midas Pharma GmbH, Germany) in August 2022 and Ximluci (STADA Arzneimittel AG, Germany) in November 2022. The referential pharmaceutical for the pharmaceuticals Byooviz, Ranivisio and Ximluci is Lucentis. The drug in the pharmaceuticals Byooviz, Ranivisio and Ximluci is ranibizumab. In laboratory studies in which the pharmaceuticals Byooviz, Ranivisio and Ximluci were compared with Lucentis, it was demonstrated that the drug in the pharmaceuticals Byooviz, Ranivisio and Ximluci is very similar to that of the pharmaceutical Lucentis in terms of its structure, purity and biological effect. Since Byooviz, Ranivisio and Ximluci are biologically similar to the pharmaceutical Lucentis, the studies on the efficacy and safety of ranibizumab that were performed in the case of Lucentis need not be repeated in the case of Byooviz, Ranivisio and Ximluci. The EMA, in accordance with the EU requirements for biologically similar drugs, decided that a very similar structure, purity and biological effect was demonstrated in the case of the pharmaceuticals Byooviz, Ranivisio and Ximluci as in the case of the pharmaceutical Lucentis, and that they were distributed in the same manner within the body. As a result, the EMA decided that as in the case of the pharmaceutical Lucentis, the benefit of the pharmaceuticals Byooviz, Ranivisio and Ximluci is greater than the identified risks, and that the drugs may therefore be permitted for use within the EU [14].

Therapeutic regimens

The strategy in the process of treatment of wet form ARMD is an algorithm of deciding on the choice of the most appropriate manner of therapy. The target of treatment is to achieve and sustain over the long term the maximum response to treatment, with the best possible functional and anatomical result. The question therefore concerns determining the criterion of success of the treatment. It is important to set realistic establish, when the improvement of VA becomes clinically significant. In its natural course, neovascular form of ARMD leads to a loss of 2.7 rows of the ETDRS chart over one year, and 4 rows of the ETDRS chart over 2 years. As a result, a gain of 5 letters in vision, i.e. a gain of 1 row, proved to be a significant and clinically important result for the patient, with an improvement in quality of life. A fundamental prerequisite for successful treatment is timely diagnosis, and especially timely commencement of safe and effective treatment. In the opposite case the treatment has minimal success or is entirely unsuccessful, and in many cases its commencement is not even indicated. However, if treatment is indicated, it continues for several years for a large number of patients, often for the patient's entire life, which ensues from the etiopathogenesis of wet form ARMD. In lifelong therapy it is essential to ensure long-term monitoring and an individual approach. As a result, the development of new pharmaceuticals and therapeutic regimens is directed towards prolonging the time of effect of the drug, to reducing the frequency of dosing of drugs, and towards new mechanisms of effect of the drugs. Several therapeutic regimens have been investigated and published for the administration of drugs with an anti-VEGF content [24,25]. The aim of developing therapeutic regimens was to create the simplest and at the same time most effective therapeutic schema. The original reactive therapeutic regimens have been surpassed over the course of the years and replaced by proactive regimens. The dosing scheme of the original reactive regimens is followed, in the "treat-to-target" regimen, with regular monthly dosing of the pharmaceutical unless the pathology was stable (monitoring of response and treatment was administered on the basis of predefined criteria of VA and/or anatomical criteria), or a pro re-nata (PRN) regimen, i.e. administration in the case of need, which required regular monitoring and treatment on the basis of predefined criteria of VA and/or anatomical criteria, which was often associated with undertreatment of the patient, when applications of the drug were applied as a response to worsening of the pathology. As a result, proactive treatment brings substantial advantages in comparison with reactive treatment. Although the original proactive fixed regular dosing of the pharmaceutical at planned monthly or 2-monthly intervals independently of the visual or anatomical results may have prevented worsening of the pathology, it may have been associated with an increased therapeutic burden. Over the course of time, with the increasing burden placed on application centers in connection with the growing number of patients in the centers, as well as with the heterogeneity of this disease and the variable response to treatment, with the prolonging of the length of life, as well as with the personnel capacity of the application centers, it became necessary to evaluate and optimize the effectiveness of treatment and the length of the application intervals between the individual intravitreal applications, and to strategically determine the most

appropriate therapeutic regimen enabling adaptation of treatment to the patient's condition, as well as patient cooperation, with respect to the continuity and organization of work at the center. Correspondingly, at present, thanks to new clinical experiences, a proactive treatment regimen referred to as treat and extend (TAE) has been introduced, consisting in the administration of the drug at the planned visit regardless of the condition of VA and/or anatomical condition, with progressive extension of the treatment intervals between the individual applications after the first year of treatment, and most recently administration of the drug with a progressive prolonging of the treatment intervals between the individual administrations beginning after the 4th application in the first year of treatment. The proactive TAE regimen maximally respects the individual requirements of the patient, with the aim of preventing undertreatment or overtreatment of the patient, and provides us with the individualized treatment of the patient we expect. At the same time, the proactive TAE application regimen is the most preferred treatment regimen worldwide. The drug is administered at a planned visit regardless of the condition of VA and/or the anatomical condition, and adjustment of the injection intervals takes place on the basis of VA and/or the anatomical results in order to achieve a balance between the therapeutic burden and its benefit [26,27].

The treatment is commenced by three consecutive intravitreal applications of an anti-VEGF preparation at four-weekly intervals (i.e. once per month), which represents the loading phase of the treatment. Until recently, within the proactive TAE application regimen this was continued up to the end of the 1st year of treatment at eight-weekly intervals, and it was only after the first year of treatment that it became possible to individualize the therapeutic intervals on the basis of the activity of the pathology, determined by means of VA and/or anatomical parameters. The subsequent application interval was then adjusted adequately, either extended by 2 weeks until maintenance of the maximum response to treatment had been achieved, or in the case of recurrence of signs of activity of the pathology ensuing from deteriorated functional and/or anatomical parameters, the interval was shortened by 2 weeks until stabilization of the pathology, or alternatively the therapeutic interval was left unchanged. Most recently, within the proactive TAE application regimen it has become possible to individualize the therapeutic intervals at each planned visit based on the activity of the pathology determined by means of VA and/or anatomical parameters already after the 4th injection. The subsequent application interval is then adjusted adequately, either extended by 2 or up to 4 weeks until the maximum response to treatment has been achieved, or upon recurrence of signs of activity of CNV ensuing from deteriorated functional and/or anatomical parameters the therapeutic interval is shortened by 2 or up to 4 weeks (according to which week of treatment the patient is in), or alternatively the therapeutic interval is left unchanged [28,29].

In Slovakia, standard procedures have been compiled for the treatment of wet form ARMD by anti-VEGF drugs by means of the treat and extend regimen, and published by the Ministry of Health, effective as of July 1, 2022 [30].

Monitoring of treatment and the possibility of criteria for adjustment of the application intervals

At each visit it is necessary to determine BCVA on an ETDRS chart, to measure IOP, examine the anterior segment under a slit lamp, examine the posterior segment stereoscopically, and to perform OCT and/or A-OCT.

Definition of maximum response to treatment and

Table 1. Treat and extend treatment regimen for the treatment of neovascular ARMD with anti-VEGF, based on specific criteria

Maintaining injection interval	**Extending injection interval** (by 2 to 4 weeks max. for a period of 12–16 weeks according to the SPC of the antiVEGF drugs)	Shortening the interval (by 2 to 4 weeks)	**Interruption of treatment**	**End of treatment**
• Resorption IRF and/or SRF • IRF and/or SRF is not reduced for 2 consecutive visits according to OCT • BCVA does not change by +/-5 letters ETDRS optotype during two consecutive treatment visits • No new CNV • No new macular hemorrhage	• No IRF and/or SRF • BCVA does not change by +/- 5 letters ETDRS optotype during two consecutive treatment visits • With long-term stabilization (three consecutive application visits) • No new CNV • No new macular hemorrhage	• New IRF and/or SRF • An increase in RPE ablation associated with worsening of BCVA during two consecutive treatment visits • New CNV • New macular hemorrhage	• Maximal response on three consecutive applications at 12 to 16 week intervals according to BCVA or OCT	• Loss BCVA below 20/200 or • Below 20/320 with monocular vision

ARMD – age-related macular degeneration, anti-VEGF – anti-vascular endothelial growth factors, max. – maximum, SPC – Summary of product characteristics, IRF – intraretinal fluid, SRF – subretinal fluid, BCVA – best corrected visual acuity, CNV – choroidal neovascularization, RPE – retinal pigment epithelium, OCT – optical coherence tomography

criteria for maintenance of application interval (Table 1)

According to OCT examination, resorption of the intraretinal and/or subretinal fluid, intraretinal and/or subretinal fluid that no longer reduces after two consecutive visits based on OCT examination, absence of new hemorrhage, absence of new neovascularization, BCVA no longer changed by ±5 letters on ETDRS chart during two consecutive visits with administration of treatment.

Criteria for extension of application intervals (Table 1)

Attained maximum response to treatment, i.e. no intraretinal and/or subretinal fluid according to OCT examination, BCVA no longer changes by ±5 letters on ETDRS chart in comparison with the previous two consecutive visits with administration of treatment and/or in long-term stabilization (three consecutive application follow-ups), absence of new neovascularization, absence of new macular hemorrhage. In this case it is possible to extend the application interval by 2 to 4 weeks, up to a maximum length of 12–16 weeks, in the sense of the summary of product characteristics (SPC) of the anti-VEGF drug in question.

Criteria for shortening of application intervals (Table 1)

Presence of new fluid or increased volume of intraretinal and/or subretinal fluid according to OCT examination, mainly if in association with deterioration of BCVA, new neo-vascularization, any new macular hemorrhage, increase in RPE ablation in association with deterioration of BCVA during two consecutive visits with administration of treatment.

Criteria enabling suspension of treatment (Table 1)

Treatment may be suspended if the maximum response to treatment is achieved and maintained at three consecutive applications within 12- to 16-weekly intervals according to the SPC (summary product characteristics) of the anti-VEGF drug in question, evaluated according to OCT examination or based on BCVA. The patient is subsequently monitored at 4- to 12-weekly intervals according to the decision of the attending physician. In the case of reactivation of the pathology, treatment is recommenced in three consecutive injections at four-weekly intervals and subsequently the treatment proceeds according to the above-stated instructions.

Criteria for termination of treatment (Table 1)

Treatment is terminated upon a deterioration of BCVA below 20/200, or below 20/320 in the case of vision in only one eye.

CONCLUSION

No consensus exists on which treatment regimen of dosing optimizes the visual and anatomical results. However, at present the most preferred treatment regimen worldwide for the administration of drugs with an anti-VEGF content in the treatment of wet form ARMD, which is used for the majority of patients, is the proactive TAE treatment regimen. In contrast with reactive regimens, with dosing once per month, the main advantage of the proactive TAE treatment regimen is the possibility of identifying patients who do not require fixed treatment. After the initial three-month loading phase, the minimum treatment interval is 8 weeks, and the maximum treatment interval 16 weeks. Extension of the interval by 2 to 4 weeks may be adequate for the treated group of patients. The main benefit of the proactive TAE treatment regimen in regular clinical practice is its individualized approach based on the functional and anatomical findings, depending on the progression of the pathology, and minimizing of the incidence of progression of the pathology, with concurrent maximizing of the long-term visual results. At the same time, this treatment regimen eliminates the possibility of the overtreatment or undertreatment of patients. It also means that a lesser burden is placed on patients, centers, and brings lower financial costs. It enables us to achieve and maintain of the long term very good gains of visual acuity with a relatively small number of applications, without the necessity of routine monitoring.

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