



DOSING REGIMENS OF ANGIOGENESIS INHIBITORS IN THE TREATMENT OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION PATIENTS

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✧ The literature review compares the data on different dosing regimens of angiogenesis inhibitors in the treatment of neovascular age-related macular degeneration patients. Clinical approaches to the repeated intravitreal angiogenesis inhibitors dosing are described, the results of key clinical trials on the effectiveness of various drugs used in different dosing regimens are presented, positive and negative aspects of each of discussed treatment regimens are specified.

✧ **Keywords:** anti-VEGF therapy; angiogenesis inhibitors; neovascular AMD; treatment regimens; dosing regimens; intravitreal injections; fixed dosing; *pro re nata*; treat and extend; aflibercept; ranibizumab.

РЕЖИМЫ НАЗНАЧЕНИЯ ИНГИБИТОРОВ АНГИОГЕНЕЗА ПРИ ЛЕЧЕНИИ ПАЦИЕНТОВ С НЕОВАСКУЛЯРНОЙ ВОЗРАСТНОЙ МАКУЛЯРНОЙ ДЕГЕНЕРАЦИЕЙ

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✧ Данный обзор литературы посвящён сравнению различных режимов назначения ингибиторов ангиогенеза при лечении пациентов с неоваскулярной возрастной макулярной дегенерацией. Описаны подходы к назначению повторных интравитреальных инъекций ингибиторов ангиогенеза, представлены результаты исследований эффективности различных препаратов, применявшихся в разных режимах дозирования, а также перечислены сильные и слабые стороны каждого из рассматриваемых режимов лечения.

✧ **Ключевые слова:** антиангиогенная терапия; ингибиторы ангиогенеза; неоваскулярная ВМД; режимы лечения; режимы дозирования; интравитреальные инъекции; фиксированный режим; режим «по необходимости»; режим «лечить и увеличивать интервал»; афлиберцепт; ранибизумаб.

Age-related macular degeneration (AMD) is the primary cause of central vision loss and visual disability in older patients in developed countries. According to the global statistics, 8.7% of all cases of blindness (approximately 3 million individuals) are caused by AMD [1]. A “wet” (neovascular) AMD is characterized by an increased risk of rapid and irreversible loss of vision. This disease pathogenesis is based on an increase in the permeability of the

vascular wall and development of pathological retinal neovascularization, which is primarily induced by the vascular endothelial growth factor (VEGF). Contemporary treatment algorithms for “wet” AMD involve the intravitreal administration of angiogenesis inhibitors.

Currently, two angiogenesis inhibitors used in the treatment of “wet” AMD are registered in the Russian Federation. Ranibizumab (Lucentis®) is a Fab-fragment

of a monoclonal antibody that binds all VEGF-A isoforms. Aflibercept (Eylea®) is a fully human fusion protein consisting of extracellular domains of type 1 and 2 VEGF receptors connected by an IgG Fc-fragment. Aflibercept was specifically designed to expand and enhance antiangiogenic activity and, unlike other anti-VEGF drugs, block not only all VEGF-A isoforms but also placental growth factor, which is also involved in the development of pathological neovascularization [2].

Due to antiangiogenic therapy, it is possible to significantly improve the anatomical and functional parameters of patients with “wet” AMD. In view of the chronic nature of the disease and the need for long-term treatment, the selection of an optimal dosage regimen, which would reduce the number of necessary injections without losing the therapeutic effect, remains an urgent issue in the treatment of patients with “wet” AMD.

Monthly injections of anti-VEGF drugs provide the best overall result, but it can be difficult to

comply with such an intensive treatment regimen for both patients and overloaded clinics. In routine clinical practice, several arguments can be found in favor of rare injections, which include a reduction in the total number of invasive interventions fraught with potential complications and facilitating compliance with the injection regimen in patients who do not often visit the clinic (and often need help and support from relatives) and reduction in treatment costs. The following is the evidence base available to date on the efficiency of various regimens in anti-VEGF drug administration in patients with neovascular AMD.

It should be noted that, despite the differences in all regimens considered, supporters of any of these agree on the need to perform at least three monthly loading injections at the onset of therapy. A schematic comparison of injection regimens at the visits during the first year of treatment is presented in Figure 1.

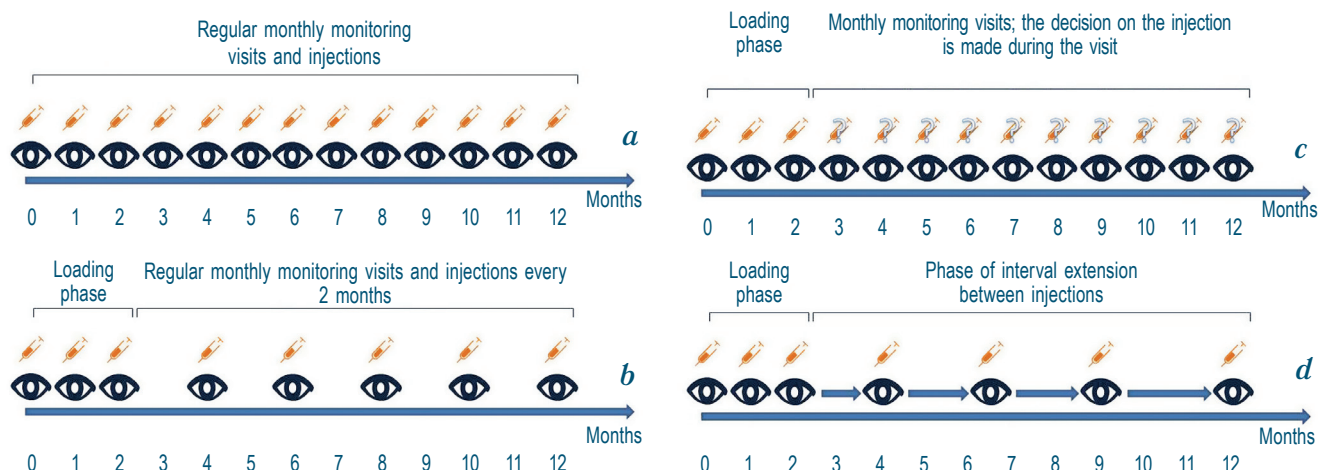


Fig. 1. Regimens of anti-VEGF therapy: *a* – the fixed regimen includes monthly monitoring visits, on each of which patient is being injected; *b* – fixed mode with a frequency of injections of 1 every 2 months. After 3 monthly loading injections, the interval between visits, on which the injection is made increases to 2 months; *c* – PRN (*Pro re Nata*) involves the injection of necessity. After the end of the loading phase, the frequency of monitoring visits continues on a monthly basis, with decision making about inject or not on each of them; *d* – Treat & Extend therapy regimen (T & E) is based on an individual approach to disease activity. After the loading phase, the intervals between exams, each of which is accompanied with injection, increase for a certain period, for example 2 weeks. After determining the maximum possible interval between injections, the patient continues therapy in this mode. If the patient shows a return of the disease activity, the intervals between injections should be shortened accordingly. The image reflects the treatment regimen scheme with the stepwise interval extension

Рис. 1. Режимы анти-VEGF-терапии: *a* — фиксированный режим подразумевает ежемесячные мониторинговые визиты, на каждом из которых производится инъекция; *b* — фиксированный режим с частотой инъекций один раз в 2 месяца. После проведения трёх ежемесячных загрузочных инъекций интервал между визитами, на которых выполняется инъекция, увеличивается до 2 месяцев; *c* — режим PRN (*pro re nata*) подразумевает проведение инъекций по необходимости. После завершения загрузочной фазы сохраняется ежемесячная частота мониторинговых визитов, на каждом из них принимается решение о выполнении инъекции; *d* — режим терапии Treat & Extend (Т & Е, «лечить и увеличивать») основан на индивидуальном подходе к активности заболевания. После загрузочной фазы интервалы между осмотрами, на каждом из которых производится инъекция, увеличиваются на определённый период, например 2 недели. После решения вопроса о максимально возможном интервале между инъекциями пациент продолжает терапию в этом режиме. Если у пациента наблюдается возврат активности заболевания, интервалы между инъекциями сокращают. На рисунке представлен вариант проведения инъекций с увеличением интервала между инъекциями

FIXED TREATMENT REGIMEN

The fixed regimen (fixed dosing [FiDo]) of dosing of angiogenesis inhibitors implies the injection of the drug in a fixed period. Depending on the interval between injections, the fixed regimen options are different, such as injections every month and every two months. The latter option involves loading injections (in patients with AMD, three injections with an interval of 1 month) at the beginning of therapy.

The first convincing evidence on the efficiency of a fixed dose regimen with anti-VEGF drugs was obtained in randomized clinical trials MARINA and ANCHOR aimed at assessing the efficacy and safety of ranibizumab in doses of 0.5 and 0.3 mg when injected every month. Monthly injections of ranibizumab provided a significantly more pronounced improvement in functional and anatomical parameters compared to those noted in the control group (sham injections/photodynamic therapy with verteporfin) [3, 4]. Despite the good results of such treatment, a fixed regimen with injections every month is difficult to comply under conditions of routine clinical practice due to the serious load on the patient and medical institution.

Subsequently, the results of numerous retrospective studies have shown that, in clinical practice, it is not possible to achieve the same good results that ranibizumab provided in prospective clinical trials (e. g., the AURA, LUMINOUS, and COMPASS trials) [5–7]. First, these failures are associated with noncompliance with a fixed injection regimen and, generally, with the insufficient number of injections that patients receive in ordinary life circumstances.

Attempts to reduce the number of injections were made in the PIER study. In this study, the efficacy and safety of ranibizumab in doses of 0.3 and 0.5 mg were analyzed for injections every 3 months after three monthly loading injections compared to sham injection. The study noted a gradual decrease in vision below the baseline by month 12 of therapy when switching to quarterly dosing after loading injections [8]. Comparable results were obtained from the EXCITE study, comparing the efficacy and safety of ranibizumab (0.3 and 0.5 mg) administered every 3 months and monthly injections of ranibizumab (0.3 mg). This study confirmed less efficiency with ranibizumab injections every 3 months compared to monthly dosing. A noticeable difference between the groups according to the change in the best corrected visual acuity (BCVA) was noted 2 months after the last loading injection [9].

A fixed regimen with 2 mg aflibercept injections every 2 months (after three monthly injections) was analyzed in the VIEW1 and VIEW2 studies. It was revealed that the efficiency of aflibercept therapy in the every 2 months regimen is comparable to that in the monthly administration of ranibizumab [10]. Additionally, the efficiency of aflibercept injections every 2 months (after three monthly injections) had been confirmed by the results of numerous studies in routine clinical practice (Talks et al., 2016; study at the Moorfields clinic, 2017; PERSEUS, 2018; Epstein et al., 2016; Almuhtaseb et al., 2017) [11–15].

The primary advantage of a fixed injection regimen is that its implementation does not depend on changes in the BCVA or retinal anatomical parameters and is easily planned. Moreover, subject to the injection regimen based on the instructions for the use of the drug, one can achieve the maximum possible results.

The negative aspects of fixed regimens include the possible risk of insufficient or excessive treatment, depending on the interval between injections. The disadvantages of the fixed monthly injection regimen also include the difficulty in compliance in real practice (this, obviously, applies to a lesser extent to the fixed injection regimen with an interval of 2 months).

“AS NEEDED” INJECTION REGIMEN

To optimize the management of patients with neovascular AMD and reduce the number of necessary injections of anti-VEGF drugs, attempts were made to personalize the treatment in accordance with the individual needs of the patients. Pro re nata (PRN) regimen (from Latin *pro re nata*, “as needed”) implies monthly monitoring of the condition and injection in response to the resumption of clinical manifestations of the disease due to activation of choroidal neovascularization (CNV). The results of the studies that aimed to determine the efficiency of the use of anti-VEGF drugs in PRN regimen are contradictory. Generally, there is a tendency toward a decrease in the BCVA after converting to “as needed” injection regimen.

In a prospective, open-label, single-center, non-comparative study PRONTO, the efficacy of ranibizumab 0.5 mg in PRN regimen was evaluated after three monthly injections. By the end of the first year of the study, visual acuity (VA) increased by an average of 9.3 letters when 5.6 injections are performed annually. A special aspect of the study

was the fact that monitoring visits were performed monthly, and in determining the criteria for the resumption of the disease activity and indications for repeated injections, the authors focused not only on visual acuity results but also on indicators of optical coherence tomography (OCT) and ophthalmoscopy [16]. Perhaps, the results obtained are accurately explained by the thoroughness and regularity of monitoring the patient's condition. However, this single-center study had a small sample size (only 40 patients).

In a much larger, multicenter, open-label, non-comparative study SUSTAIN, which aimed to assess the safety and efficacy of ranibizumab, less significant results were achieved, despite the same frequent monitoring visits. The study included 513 patients. Three monthly loading injections of ranibizumab 0.3 mg were performed in patients, after which further injections were performed in the PRN regimen. Some patients were converted to ranibizumab therapy with a dose of 0.5 mg after registration of the drug in Europe. Monitoring visits were conducted at least once a month. By the end of the first year of therapy, VA of the patients on average increased by +3.6 letters on the ETDRS scale. The annual average number of injections was 5.6. The most pronounced increase in vision was noted a month after the loading injection phase, so the average increase in VA was 5.8 letters, after which the VA decreased on average by 2.2 letters by month 12. Additionally, it should be considered that, in cases where patients resumed anti-VEGF therapy after the decrease in vision, the treatment did not allow the return to the level of lost indices. Thus, in patients with a decrease in vision by 10 letters on the ETDRS scale after treatment, vision increased on average by only five letters [17].

An attempt to monitor patients less than monthly was made in a multicenter study SAILOR, which aimed to assess the safety and efficacy of ranibizumab in the treatment of patients with neovascular AMD. The study protocol involved monitoring two cohorts of patients. In cohort 1, patients were randomized at a ratio of 1:1 to receive ranibizumab injections in doses of 0.5 or 0.3 mg. Initially, three monthly loading injections were performed, and then the injections were resumed based on the predetermined criteria according to the OCT or BCVA index. Mandatory monitoring visits occurred on months 3, 6, 9, and 12 of the study. In cohort 2, patients received 0.5 mg of ranibizumab, and the resumption of injections was decided by the attending physician.

The results from cohort 1, treated with ranibizumab 0.5 mg therapy, are noteworthy. Particularly, it was found that, in patients who had not previously undergone treatment, one month after the loading injection phase, the BCVA increased by an average of 7.0 letters. Then, there was a gradual decrease in this indicator to 2.3 letters on the ETDRS scale by month 12 of therapy. Similar results were noted in the group of patients who previously received the therapy [18].

It is interesting that such a gradual loss of the initially achieved increase in VA is noted not only when the treatment in the PRN regimen starts immediately after the loading phase but also when patients are converted to treatment "as needed" after a preliminary long course of monthly injections (HORIZON study [19]).

As shown, even with careful and regular monitoring of the retinal condition, the PRN regimen cannot provide the same good results as regular injections in most patients. Moreover, the need for monthly monitoring visits to the clinic nullifies attempts to reduce the burden on both the patient and clinic.

The failure of the PRN regimen to maintain a steady increase in vision has also been confirmed in routine clinical practice. Thus, Muether et al. (2013) conducted a prospective study to assess the efficacy of ranibizumab 0.5 mg in PRN regimen in real clinical practice. In the course of this study, an increase in patients' vision by an average of five letters was noted at the end of the loading injection phase, after which there was a gradual decrease in the BCVA indicators below the initial level by month 12 of therapy. The average change in BCVA in month 12 of therapy was -0.66 letters. Meanwhile, the average number of injections administered annually was 6.9. The authors of the study associated the results obtained with a time delay between the identification of indications for resumption of the anti-VEGF therapy and the direct administration of the injection, which cannot always be immediately performed in routine clinical practice. The average delay in administration of the injection in case of the need in resumption of treatment was 23.5 days. It is noteworthy that the decrease in VA caused by the delay between the prescription and conduct of anti-VEGF therapy was significantly more pronounced than its increase during subsequent treatment. Thus, during this delay, the BCVA decreased on average by 2.16 letters, while its increase after resuming the treatment was 0.34 letters [20].

The research results, the purpose of which was to compare the efficiency criteria of anti-VEGF therapy during injections in fixed and PRN regimens, demonstrate the advantages of the fixed regimen in terms of achieving a more pronounced and sustained increase in BCVA. Within the framework of a prospective intervention study, Mori et al. (2017), who analyzed the results of the first year of aflibercept therapy with injections every two months and PRN regimen after three monthly injections, showed that, when injecting 2 mg of aflibercept in the PRN regimen, there was a less pronounced increase in BCVA by month 12 of therapy compared to the group in which treatment was performed every 2 months after three monthly loading injections, namely, +3.4 letters versus +7.1 letters on the ETDRS scale, respectively. The annual average number of injections was 5.8 and 7.0, respectively [21].

Comparable results were obtained in studies on routine practice. PERSEUS is a prospective observational cohort study that aimed to assess the efficiency criteria of the drug aflibercept in the treatment of “wet” AMD in real clinical practice in Germany. The follow-up period was 24 months, and the number of patients with neovascular AMD was 848. With regular treatment with aflibercept (treatment was considered regular when performing an injection of aflibercept once a month [with an error margin of -1 to $+2$ weeks] for the first three months, followed by injections once every 2 months [an interval of 6 to 12 weeks was acceptable]), BCVA on average increased by 6.1 letters on the ETDRS scale. With irregular injections, the BCVA increased by an average of only 1.5 letters. The annual average number of injections was 7.5 and 5.2, respectively [13].

Eletheriadou et al. (2017) conducted a retrospective nonrandomized intervention study on a series of clinical cases of patients with neovascular AMD, who had not previously received treatment (94 eyes, 88 patients), to assess the efficiency of aflibercept in routine clinical practice in the Moorfields Eye Hospital in the UK. By the end of the second year of aflibercept therapy, according to the instructions (in the first year of therapy, every 2 months after three monthly loading injections, and in the second year, the “treat and extend” [T & E] regimen), the average increase in BCVA was 7.1 letters, which is significantly higher than the indicator in the group in which patients received treatment “when necessary,” namely, +3.1 letters on the ETDRS scale. The average number of injections was 13.5 and 8.7, respectively, in 2 years [12].

The main advantage of the PRN regimen, which was the first attempt to implement a personalized approach to the treatment of neovascular AMD, is the ability to reduce the necessary number of injections. However, to achieve this purpose, it is almost always required to sacrifice the efficiency of the treatment. In none of the publications known to us, the PRN regimen showed advantages in the average increase in VA than any of the previously studied anti-VEGF therapy regimens.

The disadvantage of the PRN regimen primarily includes the fact that the next injection is performed only in response to the resumption of CNV activity that has already occurred, which can lead to deterioration in the functional results of treatment and a gradual irreversible loss of vision due to progression of subretinal fibrosis. To timely detect the signs of recurrence of CNV activity, monthly monitoring of the patient's condition is required, which deprives the PRN regimen of one of its most attractive aspects, which is the possibility of less frequent patient visits to the clinic. Additionally, the timeliness of the next injection is based on the criteria that are used in the clinic to assess the CNV activity, which in turn depends on the available diagnostic equipment and subjectivity of the physician in assessing the need to repeat the injection.

Thus, we can conclude that the PRN regimen does not meet all the requirements for anti-VEGF therapy. However, there is still the need to implement a personalized approach to the treatment of neovascular AMD globally. The expediency of research in this direction is confirmed by two aspects. First, there are individual but regular intervals, after which the CNV activity is resumed, as shown by Mantel et al. (2013) in a prospective study of the patterns and predictability of the need for intravitreal injection of ranibizumab in patients with neovascular AMD [22]. Second, the duration of VEGF suppression in the eye in patients with neovascular AMD along with anti-VEGF therapy varies in different patients but is constant for each patient, as shown by Muether et al. (2013) in a prospective, nonrandomized clinical study that aimed to assess the stability of the individual duration of intraocular VEGF suppression in patients with neovascular AMD, who were treated with ranibizumab [23].

The response to this need for personalized treatment of neovascular AMD was the development of another approach to injections, the T & E regimen.

TREAT AND EXTEND REGIMEN

The “treat and extend” the interval regimen (T & E) involves injecting anti-VEGF drugs once a month until the signs of the disease activity disappear. If signs of the disease activity are not revealed (stable functional indicators, primarily BCVA, the absence of sub- and/or intraretinal fluid on OCT¹, absence of new hemorrhages, etc.), the interval between injections is sequentially increased, usually by 2 weeks, until the maximum interval of 12 or 16 weeks is reached. In case of resumption of the disease activity, the interval between injections is decreased. It is important to note that anti-VEGF drug injections are performed at each planned visit of the patient to the clinic. Ophthalmologists show increasing interest in this treatment regimen. In 2015, more than 60% of vitreoretinal specialists in the USA recognized that they prescribed injections of anti-VEGF drugs in the “T & E” regimen [24].

Clinical studies have shown that the use of anti-VEGF drugs in the “T & E” regimen can significantly improve the functional parameters of patients with neovascular AMD with a decrease in the required number of injections. A multicenter randomized study LUCAS that aimed to compare the efficacy and safety of 1.25 mg bevacizumab and 0.5 mg ranibizumab in patients with neovascular AMD in the T & E regimen included 441 patients. By the end of the first year of therapy with ranibizumab 0.5 mg, the average increase in BCVA was 8.2. Moreover, an average of 8.0 injections was performed. It is noteworthy that, despite the possibility of increasing the interval between injections in a number of patients, approximately a third of them (32.9%) still needed monthly injections of ranibizumab [25]. An analysis of the therapy results in the second year showed the preservation of the indices achieved. The average increase in BCVA was 6.6 letters in the ranibizumab treatment group. The number of injections necessary for the second year also did not change and was 8.0. Moreover, the total number of injections in 2 years was 16.0 [26].

Similar results were obtained in a randomized study, TREX-AMD, which compared the efficacy of ranibizumab with monthly injections and T & E regimen for the treatment of neovascular AMD. The average change in BCVA by the end of the year 1 was +10.5 letters with the number of necessary injections of 10.1. However, 22% of patients required monthly ranibizumab injections [27].

Thus, despite the fact that the “T & E” regimen slightly reduced the number of necessary injections of ranibizumab or bevacizumab² and achieved sufficiently high functional indices, many patients still need monthly injections of these drugs. The results obtained are probably due to the duration of suppression of intraocular VEGF after ranibizumab injection, which has an average of 36.4 days in patients with neovascular AMD [20].

The use of aflibercept in the “T & E” regimen was analyzed in an open-label randomized clinical study ALTAIR, which aimed to assess the efficacy and safety of the drug with various approaches to the “T & E” regimen. The study included 246 patients with neovascular AMD. All patients received three monthly loading injections and another injection after 2 months. Then, the patients were randomized into two groups: in group 1, the patients received injections in the “T & E” regimen with a change in the interval between injections by 2 weeks, and in the group 2, they received injections with a change in the interval by 4 weeks. By the end of the first year of therapy, patients in the group with a change in the interval by 2 weeks had an increase in VA by an average of 9.0 letters, while, in the group with a change in the interval by 4 weeks, the BCVA increased by an average of 8.4 letters. The average number of injections was 7.2 and 6.9, respectively. It was also revealed that 42.3% and 49.6% of patients in the groups 1 and 2, respectively, achieved an interval of ≥ 12 weeks between injections. Moreover, in the group with an interval change of 4 weeks, 40.7% achieved the interval of 16 weeks between injections by the end of the first year of therapy [28, 29].

Additionally, the results of studies on the use of aflibercept in the regimen “T & E” are available in year 2 of the therapy. Epstein et al. (2016) conducted a retrospective study of VA and BCVA in patients with neovascular AMD, who received aflibercept injections every 2 months (after three monthly injections) in the first year with subsequent transition to the “T & E” regimen starting from the second year. By the end of the first year of therapy, the BCVA of patients increased on average by 7.2 letters with an average of 7.7 injections. In the next 6 months of treatment of the “T & E” regimen, an average of 2.2 injections was required. Moreover, the average increase in the BCVA by month 18 was 8.7 letters [15].

¹ The study of the need to achieve an absolutely “dry” retina is ongoing.

² In the Russian Federation, bevacizumab is used off label to treat neovascular AMD (not according to registered indications).

We have already mentioned a retrospective non-randomized intervention study of a series of clinical cases of patients with neovascular AMD who have not previously received treatment (94 eyes, 88 patients), which aimed to assess the efficiency of aflibercept therapy in routine clinical practice at the Moorfields Eye Hospital in the UK [12]. By the end of the first year of treatment, the BCVA of patients increased by an average of 7.3 letters with an average of 8.0 injections. In the subsequent year of treatment, in the “T & E” regimen, the required number of injections decreased to 5.5. Meanwhile, the average increase in BCVA by the end of the second year of therapy was 7.1 letters [12].

All these data indicate that the use of aflibercept in the “T & E” regimen can significantly reduce the number of necessary injections in the first and second year of treatment, without sacrificing functional outcomes of the therapy. The ability to increase the intervals between injections without loss of clinical efficacy may be related to the structural aspects of the aflibercept molecule and the long period of suppression of intraocular VEGF, which is noted after injection of this drug. According to various clinical studies, the average duration of suppression of intra-

ocular VEGF after aflibercept injection ranges from 69 to 71 days [30, 31].

The main advantage of the “T & E” regimen is the compliance with the principle of proactive personalized treatment, which prevents relapse of neovascularization activity in accordance with the individual characteristics of the patient and reduces the number of necessary injections without the need for additional monitoring of the patient's condition. Moreover, the likelihood of both excessive and insufficient treatment is significantly reduced.

The only difficulty associated with the use of this regimen in practice is a variable treatment schedule, which requires planning. However, this can hardly be considered a disadvantage, because, unlike the PRN regimen, the dates of visits are known in advance. Furthermore, it is psychologically easier for the patient to set his mind on the injection when he knows in advance that it will be performed during the visit and does not perceive the prescription of the injection as a sign of deterioration of his own condition (which often occurs when injections are performed in the “as needed” regimen). The strengths and weaknesses of the compared injection regimens discussed above are summarized in Table 1.

Table 1 / Таблица 1

The comparison of different dosing regimens of anti-VEGF drugs
Сравнение различных режимов инъекций анти-VEGF-препаратов

Comparison indicators	FiDo	PRN	T&E
Provides the best functional results	+	—	+
Enables performing fewer injections	— ¹	+	+
Personalized approach to treatment of a patient	—	+	+
Risk of excessive treatment	+	—	—
Risk of insufficient treatment	— ²	+	—
Proactive approach to disease control	+	—	+
Needs frequent thorough examinations of the patient	—	+	—
Simple and convenient for practical use	—	+	+

Примечание. FiDo — fixed dosing, фиксированный ежемесячный режим; PRN — *pro re nata*, режим по необходимости; T & E — treat and extend, «лечить и увеличивать интервал». «+» — свойственно для данного режима; «—» — не свойственно данному режиму; красным выделены негативные характеристики, зелёным — положительные. ¹ за исключением режимов с проведением инъекций один раз в 2 и один раз в 3 месяца. ² при фиксированном режиме существует риск недостаточного лечения в том случае, если речь идёт о режимах с проведением инъекций один раз в 2 и один раз в 3 месяца.

Note. FiDo, fixed dosing, fixed monthly regimen; PRN, *pro re nata*, “as needed” regimen; T & E, treat and extend, “treat and extend” the interval. “+,” typical for this regimen; “—,” not typical for this regimen; negative characteristics are highlighted in red, positive characteristics are highlighted in green. ¹Except for regimens with injections once every 2 months and once every 3 months. ²With a fixed regimen, there is a risk of insufficient treatment in the case of regimens with injections once every 2 months and once every 3 months.

Therefore, the “T & E” regimen is to date the best choice between the most effective regimens of regular and usually quite frequent injections (which, as practice has shown, cannot be implemented in real conditions, outside the protocols of clinical studies, in most patients) and quite simple for use in routine practice. However, the “as needed” regimen is obviously an insufficiently effective regimen, in which the disease is always one step ahead of the therapy (which leads to a gradual decline in visual function). The development of modern diagnostic methods, such as angio-OCT, will probably allow for a more individualized approach to planning the treatment regimen, at least in some cases with some subtypes of neovascular AMD. Nevertheless, presently, using anti-VEGF in the “T & E” regimen, it is possible to individually select such a frequency of injections so that their minimum amount can be used without losing efficiency. The data of numerous studies presented above convincingly demonstrate in the example of aflibercept the possibilities for implementation of all advantages of this treatment regimen.

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