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Scientific article

Preferred treatment regimen of aflibercept after treatment interruption in patients with neovascular age-related macular degeneration

© Alexandr S. Kharakozov, Alexey N. Kulikov, Dmitrii S. Maltsev

S.M. Kirov Military Medical Academy, Saint Petersburg, Russia

BACKGROUND: The efficacy of antiangiogenic therapy in neovascular age-related macular degeneration depends on adherence to the intravitreal injection regimen and regular follow-up. In 2020, the COVID-19 pandemic and associated epidemiological restrictions in ophthalmological care delivery led to a massive lack of appropriate control and management of this condition.

AIM: To determine the preferred regimen of intravitreal anti-VEGF therapy in patients with neovascular age-related macular degeneration who experienced treatment interruption due to the COVID-19 pandemic.

MATERIAL AND METHODS: Thirty eyes of 26 patients (20 males and 6 females, mean age 73.7 ± 10.4 years) with neovascular age-related macular degeneration were included; all of them experienced treatment interruption due to the COVID-19 pandemic during the second year of aflibercept therapy. Re-starting therapy, all patients were divided in two groups and received treatment as per the fixed dosing (bimonthly), or as *pro re nata* (PRN) regimen. All patients underwent standard ophthalmological examination and optical coherence tomography before and after treatment interruption as well as six months after treatment re-start.

RESULTS: At six months after treatment re-start, best corrected visual acuity and central retinal thickness did not show statistically significant difference similar between the fixed dosing group and that of PRN dosing regimen ($p = 0.34$ and $p = 0.85$, respectively). However, patients of the fixed dosing group received for one more injection than those of the PRN group (median value – 2.0 injections, 95% confidence interval – 2.0-2.4; $p = 0.0001$). Preservation of the disease activity according to optical coherence tomography data, in the fixed regimen group was found in 10 eyes (71.4 %) versus 9 eyes (56.2 %) in the PRN group ($p = 0.63$).

CONCLUSIONS: For neovascular age-related macular degeneration patients at the second year of treatment, an adequate therapeutic strategy for re-starting anti-VEGF therapy after treatment interruption appears to be the PRN regimen. PRN regimen allows reducing one injection in comparison to fixed dosing regimen with comparable functional outcomes during first 6 month.

Keywords: neovascular age-related macular degeneration; anti-VEGF therapy; aflibercept; *pro re nata*; optical coherence tomography; COVID-19.

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Научная статья

Предпочтительный режим антиангиогенной терапии афлиберцептом после перерыва в лечении неоваскулярной возрастной макулярной дегенерации

© А.С. Харакозов, А.Н. Куликов, Д.С. Мальцев

Военно-медицинская академия им. С.М. Кирова, Санкт-Петербург, Россия

Актуальность. Эффективность антиангиогенной терапии неоваскулярной возрастной макулярной дегенерации зависит от строгого соблюдения режима интравитреальных инъекций и контроля активности заболевания. В 2020 г. пандемия COVID-19 и связанные с ней эпидемиологические ограничения в оказании офтальмологической помощи привели к массовому нарушению необходимого контроля и лечения этого заболевания.

Цель. Определить предпочтительный режим интравитреальной антиангиогенной терапии для пациентов с неоваскулярной возрастной макулярной дегенерацией, прервавших лечение в связи с пандемией COVID-19.

Материалы и методы. В исследование включили 30 глаз (26 пациентов, 20 мужчин и 6 женщин, средний возраст 73,7 ± 10,4 года) с неоваскулярной возрастной макулярной дегенерацией, прервавших лечение из-за пандемии COVID-19 на втором году терапии афлиберцептом. При возобновлении терапии пациенты были разделены на 2 группы и получали лечение по фиксированной схеме (1 раз в 2 мес.), или в режиме по потребности (*pro re nata* — PRN). Всем пациентам до и после перерыва, а также через 6 мес. после возобновления лечения проводили стандартное офтальмологическое обследование и оптическую когерентную томографию.

Результаты. Через 6 мес. после возобновления лечения показатели остроты зрения и центральной толщины сетчатки в группах фиксированного режима лечения и PRN не показали статистически значимых различий (p = 0,85 и p = 0,34 соответственно). Однако пациенты в группе фиксированного режима лечения получили на 1 инъекцию больше, чем пациенты группы PRN (медиана — 2,0 инъекции, 95 % доверительный интервал — 2,0–2,4; p = 0,0001). Сохранение активности по данным оптической когерентной томографии в группе с фиксированным режимом лечения наблюдалось на 10 глазах (71,4 %) против 9 глаз (56,2 %) в группе PRN (p = 0,63).

Заключение. Для пациентов с неоваскулярной возрастной макулярной дегенерацией второго года лечения адекватной терапевтической стратегией возобновления антиангиогенной терапии после длительного перерыва является режим PRN, который позволяет получить сравнимые с фиксированным режимом функциональные результаты, при выполнении на одну интравитреальную инъекцию меньше в течение первых 6 мес.

Ключевые слова: возрастная макулярная дегенерация; антиангиогенная терапия; афлиберцепт; *pro re nata*; оптическая когерентная томография; COVID-19.

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ЭКО•ВЕКТОР

BACKGROUND

A compliance with treatment regimen is critical to high anatomic and functional results of anti-VEGF therapy in neovascular age-related macular degeneration (nAMD). Although best results may be achieved using fixed frequency of injection regimen, such regimen is related to disproportional increase in load upon healthcare system and patient, and this is particularly remarkable when using medications with a short action period (bevacizumab and ranibizumab) [1]. This problem may be resolved in two ways: increasing the medication's duration of action, and elaborating personalized treatment regimen for each patient. However, there are external factors, which are able to influence the patient's compliance to the regimen, where organizational causes as well as human factor belong. As events of 2020 have shown, a substantial influence on the accessibility of specialized healthcare could exert the epidemic situation and the establishment of quarantine measures [2, 3]. A related discontinuation of anti-VEGF therapy leads to the worsening of anatomical and functional state of eyes with nAMD due to the increase in disease activity [4, 5]. Because the therapy discontinuation in such situation may be relatively long, it stays unclear which treatment regimen is to be used when restarting therapy. In particular, the patient may receive treatment following the fixed regimen with minimal recommended interval, or *pro re nata* regimen (PRN) depending on the disease activity.

The aim of the present investigation is to determine the preferred regimen of the intravitreal antiangiogenic therapy in nAMD patients, who discontinued the treatment due to the COVID19 pandemic. As far as within the anti-VEGF therapy outcome analysis among nAMD patients, it was established that patients of the second year of treatment have a higher risk of visual loss against the background of treatment discontinuation [6], in the present investigation, this particular subgroup of patients was studied.

MATERIALS AND METHODS

Prospective cohort study was performed on the basis of the Ophthalmology chair named after professor V.V. Volkov of the Military medical academy. Inclusion criteria were:

1) nAMD diagnosis based on optical coherence tomograpy (OCT) with/without OCT-angiography (OCT-A), with baseline best corrected visual acuity (BCVA) of not less than 0.05;

2) the patient receiving intravitreal anti-VEGF (aflibercept) therapy according to the regimen recommended by the manufacturer during no less than one year before the treatment discontinuation;

3) no visits to the center due to quarantine measures related to the COVID19 pandemic during at least 5 months;

4) presence of disease activity signs at the moment of first examination after the treatment discontinuation;

5) preservation of the chosen regimen of dosing during at least 6 months after the therapy re-start.

Exclusion criteria were: impairments of optical media transparency, which preclude the OCT performance, refractive errors of more than 3.0 diopters, concomitant to nAMD macular area condition (including diabetic retinopathy, macular hole, or epiretinal fibrosis), history of any surgeries for macular disease.

All patients underwent standard ophthalmologic examination and OCT. OCT results were received using RT-Vue100 tomograph (Optovue, USA) according to the MM6 protocol (12 radial scans of 6 mm length centered at the fovea). Into the OCT results evaluation, the central retinal thickness index (CRT) was included, which was determined as mean retinal thickness in the central sub-area of 1 mm diameter. The evaluation of the disease activity for patients receiving treatment in the PRN regimen was performed according to the presence of intra- or subretinal fluid, the appearance of new subretinal hemorrhages. The presence of intraretinal fluid was defined as hyporeflective round spots in the neurosensory retina in the foveal area in at least one cross-sectional scan. The presence of subretinal fluid was defined as a hyporeflective space between the neurosensory retina and the retinal pigment epithelium, also in the foveal area in at least one cross-sectional scan. OCT-angiography was used in order to verify the nAMD diagnosis, at that the evaluation of subretinal neovascular membrane over time was not carried out.

BCVA was tested using ETDRS charts and registered as number of signs read correctly by the patient.

In treatment, aflibercept (Eylea, Bayer, Germany) was used; 2.0 mg dose was injected intravitreally following the scheme recommended by the manufacturer: first 3 injections were performed with 1 month interval, following 4 – with 2 months interval. During the second year of treatment, all patients included in the study received treatment according to the PRN regimen. At every visit to the clinic, in all patients, ophthalmologic examination and OCT were performed. In case the disease activity was revealed after the treatment discontinuation, the patient was randomly included in one of the treatment groups: fixed dosing group (1 injection every 8 weeks), and PRN group.

After 6 months from the follow-up re-start, patients were also examined following the above-mentioned algorithm with BCVA testing and OCT. The BCVA dynamics from the treatment start was estimated, as well as CRT dynamics and activity preservation according to ophthalmoscopy and OCT results (according to ophthalmoscopy

data: the appearance of new subretinal hemorrhages; according to OCT data: incomplete resorption / appearance of free retinal fluid).

For statistical data processing, the software package MedCalc 18.4.1 (MedCalc Software, Belgium) was used. Data were presented as mean value ± standard deviation, or as median value and 95% confidence interval. Data were checked for distribution normality using the Kolmogorov-Smirnov test. Paired *t*-test was used to estimate the statistical significance of CRT and BCVA changes at different study stages. The single-factor analysis of variance was used to evaluate the statistical significance of age, baseline and endpoint visual acuity and CRT. To compare the gender composition and the number of injections received before the treatment discontinuation, the chi-square test was used. Differences were considered to be statistically significant at $p < 0.05$.

RESULTS

In total, 30 eyes with nAMD were included in the study (26 patients, 20 men and 6 women, mean age was 73.7 ± 10.4 years). After randomization, 14 eyes (12 patients) were included into the fixed dosing regimen group, 16 eyes (14 patients) – into the PRN group.

The age in the fixed dosing regimen group did not have any statistically significant differences from that in the PRN group: 69.4 ± 10.7 and 77.4 ± 8.9 years, respectively ($p = 0.1$). Studied groups did not have statistically significant differences in gender (ratio of men and women was 4/8 and 2/12 in fixed regimen and PRN groups, respectively, $p = 0.51$).

The index of retinal thickness ($p = 0.39$) and that of visual acuity ($p = 0.72$) did not have statistically significant differences between the studied groups before the anti-VEGF therapy start. Duration of treatment discontinuation ($p = 0.11$), follow-up duration ($p = 0.34$), and number of aflibercept injections carried out before it ($p = 0.36$) also did not significantly differ between the studied groups.

No statistically significant differences were found in fixed dosing regimen and PRN groups in BCVA indices before the treatment discontinuation ($p = 0.65$) and after it ($p = 0.97$), in the dynamics of BCVA change during the treatment discontinuation period ($p = 0.82$), in CRT values after the treatment discontinuation ($p = 0.22$), and in the dynamics of CRT change ($p = 0.87$).

After 6 months from the anti-VEGF therapy re-start, patients on fixed dosing regimen got 3 intravitreal aflibercept injections versus median 2.0 injections in patients on PRN regimen ($p = 0.0001$). At that, BCVA indices ($p = 0.85$) and BCVA change dynamics ($p = 0.48$), CRT values ($p = 0.34$), and CRT change dynamics ($p = 0.39$) did not also differ significantly in the fixed dosing regimen and the PRN groups.

Patients in the fixed dosing regimen group received in average 1 injection more than those in the PRN group during the first 6 months after the treatment re-start. Detailed data of fixed dosing and PRN regimen groups comparison are presented in the table (see table).

Among all patients, the activity preservation after 6 months according to the OCT results was found in 19 eyes (63.3%), at following distribution between groups: in the group with fixed dosing regimen, the activity remained in 10 eyes (71.4%), against 9 eyes (56.2%) in the PRN group ($p = 0.63$).

Table. Difference between fixed dosing and *pro re nata* regimens at different stages of follow-up

Таблица. Различие групп фиксированного режима лечения и лечения в режиме PRN на различных этапах наблюдения

Indices	Fixed dosing regimen	PRN regimen	*p*
Baseline CRT, μm	354.1 ± 105.4	323.1 ± 90.5	0.39
Baseline BCVA, signs (95% confidence interval)	39.0 (25.0–44.6)	37.5 (29.6–41.4)	0.72
CRT before treatment discontinuation, μm	287.6 ± 63.5	251.6 ± 38.3	0.07
BCVA before treatment discontinuation, signs	39.9 ± 13.3	40.4 ± 9.8	0.65
CRT after treatment discontinuation, μm	318.5 ± 63.4	286.0 ± 76.6	0.22
BCVA after treatment discontinuation, signs	34.7 ± 14.7	34.5 ± 14.0	0.97
BCVA dynamics during treatment discontinuation period, signs (95% confidence interval)	–3.5 (–6.4... –0.9)	–4.0 (–10.7... –0.4)	0.82
CRT dynamics during treatment discontinuation period	30.9 ± 43.6	34.4 ± 66.3	0.87
CRT after treatment re-start, μm	252.1 ± 41.1	238.4 ± 35.6	0.34
BCVA after treatment re-start, signs	36.2 ± 13.5	37.2 ± 14.3	0.85
CRT dynamics after treatment re-start, μm	–66.4 ± 62.8	–47.6 ± 54.3	0.39
BCVA dynamics after treatment re-start, signs (95% confidence interval)	0.0 (–2.3–5.3)	3.5 (–0.72–5.0)	0.48
Number of injections during 6 months after treatment re-start, median value (95% confidence interval)	3.0 (3.0–3.0)	2.0 (2.0–2.4)	0.0001

Note. BCVA – best-corrected visual acuity, CRT – central retinal thickness.

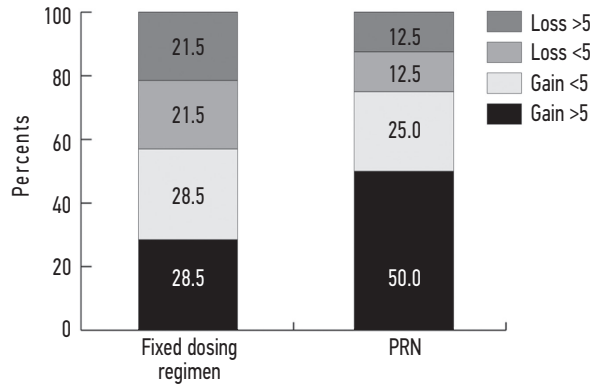

Figure. Change in best corrected visual acuity after treatment
Рисунок. Изменение максимальной корригированной остроты зрения после лечения

BCVA distribution at the end of the follow-up period in groups (increase or preservation / decrease in ETDRS signs) in the fixed dosing regimen group was: 8 (57%) / 6 (43%) eyes; in the group of PRN regimen: 12 (75%) / 4 (25%) eyes (p = 0.52) (see the picture).

DISCUSSION

In the present study, we showed that for nAMD patients of the second year of therapy an adequate treatment strategy of anti-VEGF therapy re-start after a long discontinuation period is the PRN regimen. The PRN regimen use in this cohort of patients allows to obtain functional results that are not worse in comparison with fixed dosing regimen with injections once in 8 weeks, at that the number of intravitreal injections was one fewer (about 2 injections in 6 months in the PRN group against 3 injections in the fixed dosing regimen group).

In spite of a long previous therapy, nAMD patients, who experienced a treatment discontinuation period, demonstrate an overall negative dynamics during the discontinuation period of 6 months. This is evidenced by the decrease in BCVA and increase in CRT. This is foremost characteristic for patients preserving the disease activity immediately before the discontinuation, but the absence of activity does not guarantee the safety of anatomical and functional status after the treatment discontinuation. Thus, at the elimination of obstacles to the care delivery, the treatment has to be continued.

The recommended aflibercept injection frequency is one injection every 8 weeks. However, some studies show an additional benefit of higher injection frequency than that in the manufacturer's instruction [7]. Nevertheless, the ratio of visit to the center frequency, the load on the specialist and on the patient, and the potential benefit from higher injection frequency not always favors the last one or even the fixed dosing regimen. Personalized regimens "treat and extend" (T&E) and PRN, notable for their ease and convenience of practical use, serve as an alternative. At that T&E regimen is considered as proactive and devoid from insufficient treatment risk [8], but according to some data demands more injections than PRN [9]. In our study, all patients at the moment of discontinuation received treatment in the PRN regimen and therefore it was unclear whether this regimen could be used at treatment re-start, or patients had to follow maximally intensive recommended therapy – once every 2 months. In our study, during first 6 months after therapy re-start, patients in the PRN group received 30% less injections at comparable anatomical and functional results. This may have a certain social and economic significance, taking into consideration the high cost of anti-VEGF medications for intravitreal use. Reasons why the PRN regimen demonstrates non inferior results versus the fixed dosing regimen may lay in the special aspects of the chosen category, because second year of treatment patients more often demonstrate low disease activity. In spite in our study participated only patients who discontinued their treatment due to COVID19 pandemic, the results of present investigation may be extrapolated on different situations, in terms of which nAMD patients have a 6 months discontinuation in treatment. For example, this may be due to domicile change, severe concomitant diseases, economic problems, or non-compliance. Moreover, we cannot exclude the probability of quarantine measures renewal due to the ongoing pandemic.

The present study is not devoid of limitations. To begin with, the study traces only a limited period of time after the therapy re-start, and further anatomical and functional dynamics stays unknown. In our study, at the 6th month of anti-VEGF therapy continuation, the activity preservation was found in more than 50% of patients (71.4% – in the fixed regimen group, and 56.2% – in the PRN group; p = 0.63). The BCVA decrease ranged from 25% in the PRN regimen group to 43% in the fixed dosing regimen group (p = 0.52). Thus, a significant part of patients demands a prolongation of an active treatment. At that, differences between regimens may appear later. From this point of view, it is important to remember that in the conditions of normal therapy continuation without any break, the

efficacy of different regimens is comparable. However even in a short timeframe a certain treatment regimen has to be chosen and, in such case, PRN regimen has advantages of less injections. On the second hand, it stays unknown whether the PRN regimen is suitable as a prolongation of treatment in patients, who discontinued their treatment for a longer period of time than that investigated in the present study. Moreover, the study results cannot be directly extrapolated on patients of the first year of treatment, although the analysis of the treatment discontinuation consequences shows that they are at lower risk of anatomical and functional indices deterioration in comparison with patients of the second year of treatment [6]. Because of limited number of cases, we included in the study contralateral eyes of 4 patients, 2 in each group, and this may have influence statistical analysis results. However due to a small number of paired eyes and their inclusion in equal proportion into both groups, the impact of this limitation has to be considered as non-significant.

CONCLUSION

In the present study, we showed that patients receiving anti-VEGF therapy in the pro re nata regimen in case of up to 6 months treatment discontinuation, could at treatment re-start receive injections of an anti-VEGF medication following the same regimen without any harm for functional result, and this also allows decreasing the number of injections during first 6 months after the therapy re-start.

ADDITIONAL INFORMATION

The input of the authors. All authors certify the conformance of their authorship to the international ICMJE criteria (all authors played an important role in elaborating of the conception, conducting of the study, and preparing the article, read and approved the final version before publishing). A.S. Kharakozov – acquisition and processing of materials, analysis of obtained data, writing of the text, review of literature; A.N. Kulikov – conception and design of the study, final text revision; D.S. Maltsev – analysis of obtained data, text revision.

Conflict of interests. The authors declare the absence of obvious and potential conflict of interests related to the publication of the present article.

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AUTHORS' INFO

***Alexandr S. Kharakozov,** ophthalmologist;
address: 21, Botkinskaya str., Saint Petersburg, 194044, Russia;
ORCID: https://orcid.org/0000-0003-4598-0826;
eLibrary SPIN: 1208-5237; e-mail: kharakozoff@mail.ru

Alexey N. Kulikov, MD, Dr. Sci. (Med.), assistant professor;
ORCID: https://orcid.org/0000-0002-5274-6993;
eLibrary SPIN: 6440-7706; Scopus: 57001225300;
e-mail: alexey.kulikov@mail.ru

Dmitrii S. Maltsev, MD, Dr. Sci. (Med.);
ORCID: https://orcid.org/0000-0001-6598-3982;
e-mail: glaz.med@yandex.ru

ОБ АВТОРАХ

***Александр Сергеевич Харакозов,** врач-офтальмолог;
адрес: Россия, 194044, Санкт-Петербург, ул. Боткинская, д. 21;
ORCID: https://orcid.org/0000-0003-4598-0826;
eLibrary SPIN: 1208-5237; e-mail: kharakozoff@mail.ru

Алексей Николаевич Куликов, д-р мед. наук, доцент;
ORCID: https://orcid.org/0000-0002-5274-6993;
eLibrary SPIN: 6440-7706; Scopus: 57001225300;
e-mail: alexey.kulikov@mail.ru

Дмитрий Сергеевич Мальцев, д-р мед. наук;
ORCID: https://orcid.org/0000-0001-6598-3982;
e-mail: glaz.med@yandex.ru

* Corresponding author / Автор, ответственный за переписку