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Therapy for neovascular age-related macular degeneration: updated review

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Abstract
Age-related macular degeneration (AMD) constitutes a prevalent, chronic, and progressive retinal degenerative disease of the macula that affects elderly people and cause central vision impairment Neovascular ("wet") form of age-related macular degeneration (nAMD) is the leading cause of irreversible visual impairment in people over the age of 60 in economically advanced countries. Until recent time, the diagnosis of nAMD was actually a verdict for the patient in terms of visual prognosis - it was clear to both doctors and patients that a decrease in central vision was inevitable, the only question was the timing of maintaining functionally useful vision of the affected eye, as well as the timing of damage to the fellow eye and disability of the patient.

Introduction

The discovery of the role of vascular endothelial growth factor (VEGF) in the pathogenesis of nAMD and other vasoproliferative diseases, followed by the creation and launch of anti-VEGF drugs on the market, led to the appearance of angiogenesis inhibitors in the arsenal of ophthalmologists, which made it possible to radically change the situation [1]. Randomized clinical trials (RCTs), which studied the effect of new drugs, showed that they can not only avoid a decrease in visual acuity (VA), but also achieve its increase [2-4].

However, with the beginning of a wider use of anti-VEGF drugs in real clinical practice, it turned out that not in all cases the results obtained correspond to RCT data and justify the expectations from therapy, the success of which can be assessed differently by patients and doctors.

It has been found that the response to anti-VEGF treatment depends on many factors, including the characteristics of the lesion, the duration of the disease, the initial VA, the regularity of treatment, etc. Moreover, morphological and functional responses to anti-vasoproliferative therapy do not necessarily correlate . From the patient's point of view, the success of treatment is most determined by the improvement in vision, but additional important criteria are the duration of the course of treatment, the subsequent frequency of visits to the clinic, the frequency of injections, etc. [5–7].

Currently, the important tasks of ophthalmologists are to determine the parameters of the effectiveness of response to anti-VEGF therapy in patients with nAMD, their interpretation, recommendations on the tactics of further treatment, especially in patients demonstrating an insufficient initial morphofunctional response.

Neovascular form of age-related macular degeneration (AMD):

- Main risk factors for the disease

1. Age (>50 years)
2. genetic predisposition
3. Smoking
4. Hypertension and cardiovascular disease
5. Gender (often female)

-Aggressive disease

1. Rapid disease progression leading to permanent vision loss (within a year)
2. The therapeutic window for starting treatment is no more than 12 months from the onset of the disease.

-The economic impact of neovascular AMD is significant for patients, their families and the healthcare system (loss of independence, disability)

Symptoms of neovascular AMD

- Decreased visual acuity
- Reduced contrast sensitivity

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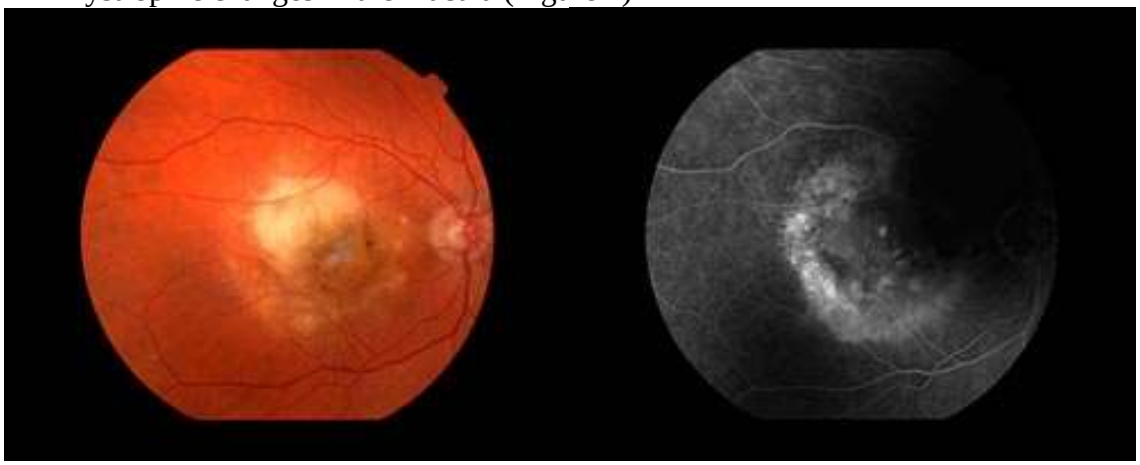
- Presence of central scotoma
- Metamorphopsia - the perception of objects in a distorted form
- Dystrophic changes in the macula (Figure 1)



- **Fig.1** Dystrophic changes in the macula

Approaches to evaluate response to anti-VEGF therapy

W.M. Amoaku et al. (2015) [7] proposed a unified classification of the success rate of response to anti-VEGF therapy based on two groups of parameters: VA and macular morphology according to optical coherence tomography (OCT) data (Table 1).

Table 1. Classification of the response to anti-VEGF therapy [7]

Response	Structural abnormalities	Changes in VA
Good	No signs of CNV activity (no fluid on OCT or reduced fluid amount or a 75% reduction in CMT at the end of loading phase)	VA gain ≥5 letters ETDRS
Partial (suboptimal)	CMT reduction by 25–75% and/or persistent IRF, SRF, IRC or new IRF, SRF, IRC in regular therapy	VA gain 1–5 letters ETDRS
Poor	CMT reduction by 0–25% and/or persistent IRF, SRF, IRC or new IRF, SRF, IRC in regular therapy	VA gain 0–4 letters ETDRS
No	No changes or increase in CMT, IRF, SRF, IRC in regular therapy	VA loss compared to baseline 1 month after the 3rd loading injection

Note. VA, visual acuity; CNV, choroidal neovascularization; IRF, intraretinal fluid; SRF, subretinal fluid; IRC, intraretinal cysts; CMT, central macular thickness.

Choice of optimal tactics of patient management

When evaluating the degree of response to ongoing anti-VEGF therapy, it is necessary to take into account issues related to the correctness of the treatment, including early initiation of therapy, its regularity, choice of dosing regimen for intravitreal injections, etc. It is impossible to obtain the maximum increase for this patient OZ with its maintenance in the long term, as well as to adequately assess the response to therapy in case of chaotic and untimely treatment.

The Vision Academy Steering Committee [8] formulated 4 key principles that an ideal anti-VEGF therapy regimen for retinal diseases should comply with. The authors believe that the ideal treatment regimen should be effective, proactive, individualized and convenient. Let us dwell on these principles in more detail, since they quite accurately summarize the data of clinical studies accumulated to date and recommendations for their practical application.

1. Maximize and maintain HP gain for all patients.

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Achieving and maintaining achieved VA gains should be the goal of anti-VEGF therapy for all patients, not just those who respond well to therapy. Early initiation of treatment and a sufficient frequency of injections are equally necessary to achieve and maintain maximum VA gains.

2. Plan when to give your next injection, rather than deciding whether to inject now.

The success of anti-VEGF therapy depends not only on the treatment of active disease, but also on the prevention of relapse and deterioration of the condition. Planning for the next injection helps minimize the chance of late treatment, gives you time to prepare for the injection, and streamlines the workflow in the clinic. The patient also benefits from knowing the time of the injection in advance and being able to plan ahead. A proactive regimen, such as T&E, allows doctors to stay ahead of the disease and, by minimizing the need for interim diagnostic visits, helps reduce the burden of treatment for both the clinic and the patient.

3. Choose the interval between injections according to the needs of the patient.

The duration of VEGF suppression varies between patients and differs between different anti-VEGF drugs. Anti-VEGF drugs with a longer duration of action allow longer intervals between injections to be achieved than drugs with a shorter duration of action. An individual approach to determining treatment intervals eliminates the need for intermediate monitoring, while at the same time providing an optimal result for the patient.

4. Inject at every follow-up visit.

Monitoring and treatment during the same visit eliminates the possibility of disease activation that can occur between separate diagnostic and treatment visits. The number of visits required for each patient is reduced, which reduces the burden on the patient and the clinic, and reduces the stress experienced by the patient.

If all 4 principles are put into practice, then both the patient and the doctor will benefit. A personalized approach and a reduction in the burden of therapy can also increase patient adherence to treatment. The authors, recommending adherence to these principles, expect to improve patient routing, reduce the burden on the clinic, optimize outcomes for each patient while minimizing treatment delays and the risk of vision loss.

Conclusion

Thus, in summary, we can say that today both the doctor and the patient have the right to expect good functional and anatomical results from the antivasoproliferative therapy of nAMD, provided that a number of necessary conditions are met: with a clear assessment of the individual characteristics of the patient (initial level of VA, type of CNV, concomitant diseases, condition retinal fluid and its differentiation); timely (as early as possible) initiation of treatment after diagnosis and determination of relevant indications; strict adherence to a proactive personalized T&E regimen with the required number of injections at an individually selected interval; the use of aflibercept, which has the longest duration of VEGF suppression among currently available anti-VEGF drugs, which makes it possible to achieve a maximum interval between injections of up to 16 weeks. [9, 10,11] and thereby reduce the burden of treatment and improve the quality of life of patients with this serious, potentially disabling disease.

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