Expert Consensus

Optimization of the anti-VEGF treatment regimens with aflibercept in patients with neovascular age-related macular degeneration and visual impairment as a result of diabetic macular edema

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On May 22, 2019, an Advisory Board was held in Odessa on optimizing the regimens of intravitreal anti-VEGF therapy* with aflibercept (Eylea®) in patients with neovascular (wet) age-related macular degeneration (nAMD) and visual impairment due to diabetic macular edema (DME), including the prospects for the application of a proactive dosing regimen with aflibercept "Treat-and-Extend" (T&E) in patients with nAMD during the first year of therapy.

Intravitreal anti-VEGF therapy is now considered the standard for the treatment of various retinal conditions (Lanzetta P., Loewenstein A.; Vision Academy Steering Committee, 2017). According to the American Academy of Ophthalmology guideline, intravitreal injection therapy using anti-VEGF agents is the most effective way to manage nAMD and represents the first line of treatment (American Academy of Ophthalmology Retina/Vitreous Panel, 2015). Since 2012 intravitreal anti-VEGF injections are considered the new gold standard of therapy for eyes with centre-involving macular oedema and reduced vision (The Royal College of Ophthalmologists, 2012).

To date, a series of principles are formulated that are fundamental for anti-VEGF management of retinal diseases and aimed to achieve optimal results in everyday practice. These principles were developed with consideration of chronic retinal diseases that require regular therapy, in particular nAMD and DME (Lanzetta P., Loewenstein A.; Vision Academy Steering Committee, 2017).

Aflibercept — is a decoy receptor with multitargeted mechanism of action (MoA), inhibiting all isoforms of VEGF-A, as well as Placental Growth Factor (PGF), unlike other anti-VEGFs that binds only VEGF-A (Papadopoulos N. et al., 2012).

MoA of aflibercept is characterized by strong binding affinity – binds VEGF tighter than its native receptors and other anti-VEGFs (Papadopoulos N. et al., 2012). Aflibercept is characterized by extended durability – the duration of intraocular VEGF suppression during aflibercept treatment was 71±18 days (Fauser S. et al., 2014).

The features of the molecule and the MoA of aflibercept serve as a basis for the effective anti-VEGF treatment with gradual extending of intervals between injections.

In randomized clinical trials, good results regarding the improvement of visual acuity and anatomical parameters at the end of the 1st year of treatment with aflibercept were obtained using the proactive fixed regimen:

- in nAMD — 1 injection per month for 3 consecutive doses, followed by 1 injection every 2 months in VIEW 1 & 2 trials (Heier J.S. et al., 2012);
- in DME — 1 injection per month for 5 consecutive doses, followed by 1 injection every 2 months in VIVID & VISTA trials (Korobelnik J.F. et al., 2014).

These data are reflected in the Eylea® label.

In real-life settings, the 1st year results comparable to those in clinical trials can be reproduced by following the aflibercept proactive fixed regimens according to the label recommendations in patients with nAMD (Framme C. et al., 2018) and DME (Campos Polo R. et al., 2018).

Vision gains achieved during the 1st year of treatment with aflibercept can be maintained on the high levels in the long term with fewer injections (Heier J.S. et al., 2016, Kaiser P. et al., 2017, Eleftheriadou M. et al., 2018).

The results of the ALTAIR study (Wai K.M., Singh R.P., 2018) demonstrated the possibility to obtaining high functional results when using aflibercept in T&E regimen during the 1st year of treatment in nAMD patients.

In the ALTAIR study 3 initial monthly loading injections of aflibercept were administered, followed by one injection after a further 2 months, and then continued with a T&E regimen with extension the intervals between injections by 2 (group 1) or 4 (group 2) weeks.

By the end of the 1st year of treatment, a significant increase in visual acuity was achieved in both groups. Moreover, at the last visit up to week 52, more than half of patients in both groups (57%) had their next injection scheduled at an interval of 12 weeks or beyond.

Thus, the use of aflibercept in T&E regimen during the 1st year of treatment provides an opportunity to individualize the treatment, matching the interval between injections according the need for each patient, reducing the number of injections in later years.

Based on the results of the ALTAIR study, the relevant recommendations for the use of aflibercept in the T&E regimen during the 1st year of treatment in patients with nAMD were included in the Eylea® label in Europe (August 2018) and in Ukraine (September 2019).

The experts also discussed the questions on planning the long-term treatment and increasing the compliance of patients with nAMD and DME.

Experts have reached consensus on optimization of the anti-VEGF treatment regimens with aflibercept in patients with retinal pathology that require long-term monitoring and treatment — nAMD and DME:

1. The primary goal of anti-VEGF therapy is to achieve the maximum possible visual acuity in each individual patient and to maintain it (not only improving anatomical parameters). Maximal improvement of visual functions is an important factor in improving the quality of life and functional independence of the patient.

2. For maximizing and maintaining gains in visual acuity early initiation of anti-VEGF therapy and a sufficient frequency of injections are necessary. Delay with anti-VEGF treatment in nAMD and DME may lead to irreversible vision loss.

3. It is recommended that patients with nAMD or suspected nAMD, as well as patients with DME of any severity be referred urgently to a retinologist.

* Intravitreal injections of Vascular Endothelial Growth Factor (VEGF)

4. Intravitreal anti-VEGFs is the first-line therapy in nAMD. Treatment with additional agents should not lead to any delay in the initiation of pathogenetic therapy with anti-VEGFs.

5. In patients with visual impairment due to DME, for which antiangiogenic treatment is indicated, anti-VEGF therapy should be initiated as soon as possible to achieve optimal results.

6. Systemic disorders requiring control (hyperglycemia, arterial hypertension, dyslipidemia) are of great importance in DME patients. However, the early initiation of intravitreal anti-VEGF therapy is very important, therefore, correction of systemic disorders can be carried out in parallel with anti-VEGF treatment.

7. Timely initial treatment with recommended monthly loading injections of aflibercept (3 – in nAMD and 5 – in DME) allows to achieve the maximum possible improvement in vision, as well as the normalization of anatomical parameters.

8. Vision gain achieved with loading injections can be maintained with proactive regimens of aflibercept to the end of the 1st year (fixed every 2 month in nAMD and DME, T&E — in nAMD) and beyond (T&E) with fewer injections.

9. In nAMD patients, after 3 initial monthly loading injections and an additional injection after 2 months, it is possible to increase the time between injections with the obligatory injection at each visit, i.e. using the T&E regimen. With this regimen, it seems advisable to extend the intervals between injections by 2 weeks.

10. The natural course of nAMD and DME requires long-term anti-VEGF therapy, which necessitates the development and discussion of long-term monitoring and treatment plans with the patient (relatives, caregivers).

11. Of great importance is the formation of the patient's realistic expectations from treatment from the very beginning and their adjustment during therapy. It is recommended to actively find out from the patient (relatives, caregivers) his/their expectations from therapy, for example, to return the ability to self-care, the ability to watch TV, read, drive a car.

12. When prescribing intravitreal anti-VEGF therapy, one should pay attention to the following key points and make sure that patients (relatives, caregivers) understand:

- the importance of early treatment (late or inadequate treatment may lead to irreversible vision loss);
- the goals of treatment: 1) achieving the maximal possible improvement in visual functions during the phase of loading injections, and 2) their maintenance for a long time, which is possible with a sufficient number of injections;
- the possibility of reducing the frequency of injections after the 1st year of adequate treatment.

Active involvement of patients (relatives, caregivers) in discussions about their treatment is the key to its success.

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