EXPERT CONSENSUS

Treatment approaches to patients with neovascular age-related macular degeneration who need frequent intravitreal injections of aflibercept

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On September 17, 2021, an Advisory Board was held in Kyiv to discuss treatment approaches to patients with neovascular age-related macular degeneration (nAMD) who need frequent intravitreal injections of aflibercept.

Nowadays anti-VEGF agents including aflibercept are routinely used worldwide as a first-line treatment in nAMD patients.[1] Yet visual acuity gains after initial injections are not always maintained in routine practice due to the use of reactive treatment regimens, such as PRN (pro re nata — as needed).[2] On the other hand proactive individualized treat-and-extend regimen (T&E), that implies a gradual extension of intervals between injections based on a stable visual and anatomical status, may be beneficial to achieve sustainable long-term treatment outcomes while reducing treatment burden to patients and ophthalmological clinics.[3]

Randomized phase 3b/4 study ARIES confirmed the similar outcomes with aflibercept early-T&E (after 3 initial monthly injections and the fourth injection after 8 weeks) and aflibercept late-T&E (after 1 year of a fixed 8-week injections). At the end of the study (week 104) ~50% patients achieved a treatment interval of ≥12 weeks and ~30% patients achieved a treatment interval of 16 weeks.[4] Currently the ability to achieve the treatment interval of 16 weeks in nAMD patients is the unique feature of aflibercept compared to other anti-VEGF agents licensed in Ukraine.

Although most nAMD patients in ARIES were able to significantly extend duration of the intervals between aflibercept injections, a small number of patients needed more intensive treatment. According to the protocol of the ARIES study the interval between aflibercept injections could be shorten <8 weeks in patients who need more intensive treatment, but in this case the study design did not specify clear criteria for shortening or further extending of the intervals between injections.[5]

Thus, the objective of the Advisory Board was to identify categories of patients with nAMD, who need frequent intravitreal injections of aflibercept after 3 initial monthly injections and to establish criteria for shortening or further extending of the intervals between injections in these patients.

According to the experts' practical experience, the number of nAMD patients who need an intensive therapy with aflibercept in routine practice is 5-10%. This finding is consistent with the data from the ARIES study, where the number of patients receiving aflibercept injections at <8 weeks intervals was 6-8% at the end of the 2nd year of the treatment.[4] According to the meeting participants, most of these cases are patients in late disease stages who were not timely initiated treatment. Some of them have already lost central vision in one eye due to the lack of adequate nAMD treatment. Sometimes these patients even insist on intensifying treatment because maintaining their visual acuity is critical for preserving quality of life.

The workgroup has emphasized that intensification of therapy by shortening intervals <8 weeks between injections at a certain point of the treatment is a temporary measure until signs of disease activity are completely resolved. Once visual and anatomical stability is achieved, the interval between injections can be extended to 8 weeks or more. The need for this approach may arise from the 4th injection, immediately after switching to bi-monthly injections, or at any subsequent patient's visit in the future. The interval between injections should not be less than 4 weeks.

The main discussion of the Advisory Board participants was focused on the criteria for shortening and extending intervals between injections in patients who need frequent intravitreal injections of aflibercept. A significant number of functional and anatomical parameters were suggested; however, to simplify and unify the algorithm for the management of such patients, the following criteria were approved by the experts:

Shortening the interval <8 weeks to the next injection should be planned when the disease dynamic is negative, as assessed by the presence of at least one of the following criteria from the time of the previous visit:

- New or persistent exudative intraretinal fluid (IRF)
- Vision loss of ≥5 ETDRS letters
- New neovascularization and/or new subretinal hemorrhage

Extending of the interval after its shortening should be planned in a case of positive dynamic of treatment, which is assessed by the presence of all the following:

- No sign of IRF; residual extrafoveal subretinal fluid (SRF) up to 50 μm is acceptable
- Vision acuity within 'stability corridor' (change <5 ETDRS letters)
- No new neovascularization

Although shortening and further extending of intervals <8 weeks between injections in the ARIES study was only at the investigators discretion and therefore the interval could be changed by 1, 2, 3, or even 4 weeks; the workgroup members advocate use of 2-week change as the basis. Other options of changing intervals between aflibercept injections should only be considered in specific cases.

The workgroup's recommended algorithm for shortening and extending intervals between aflibercept injections in nAMD patients who need an intensive treatment is provided at the end of the text.

In additional, a significant part of the expert discussion on the criteria for interval changes in nAMD patients was devoted to the tolerance of residual SRF when extending the intervals of aflibercept injections in T&E. According to the FLUID study, T&E approach that allows a certain amount of SRF is not inferior to an approach aimed at complete elimination of any fluid in the retina.[6] Considering these data as well as the design of the ARIES study, whereby the interval between aflibercept injections could be extended with residual amounts of SRF up to 50 μm, the workgroup recommends that residual amounts of SRF ≤50 μm with extrafoveal localization should not be considered as a sign of disease activity when deciding to extend the interval between aflibercept injections in T&E.

An important topic for the discussion during the meeting was the safety of intensive treatment in nAMD patients. Comparing the results of the ARIES study, that allowed aflibercept administration at a frequency of <8 weeks, and the ALTAIR study, where the minimum interval between injections was 8 weeks, the number of adverse events in two studies was comparable. Moreover, in ARIES were not reported any adverse events not previously observed in other aflibercept studies.[4]

A good overall safety profile in the aflibercept group was also demonstrated in the MERLIN study; however, due to increased rates of retinal vasculitis and retinal vascular occlusions in the brolucizumab group, the MERLIN study was prematurely terminated.[7] In this study nAMD patients in both the aflibercept and brolucizumab groups received an intensive treatment with injections every 4 weeks. In the light of brolucizumab safety concerns and the manufacturer's prohibition of brolucizumab use frequently than every 8 weeks after the first three injections, experts do not recommend switching to brolucizumab in nAMD patients who need an intensive treatment.[8]

As a conclusion of the Advisory Board discussion, participants agreed that shortening the interval <8 weeks between aflibercept injections in nAMD patients who need an intensive treatment is an effective and safe therapeutic option to achieve complete resolution of disease activity and thereafter return to a treatment with extended intervals.

The results of the ARIES study were included in the latest version of aflibercept summary of product characteristics in Ukraine, so that the interval between aflibercept injections after 3 initial monthly injections no longer needs to be limited to a minimum of 8 weeks in nAMD patients who need an intensive treatment. Thus, to date the use of aflibercept T&E in nAMD patients allows individual adjustment of treatment intervals in the widest range among anti-VEGF agents: from 4 to 16 weeks.

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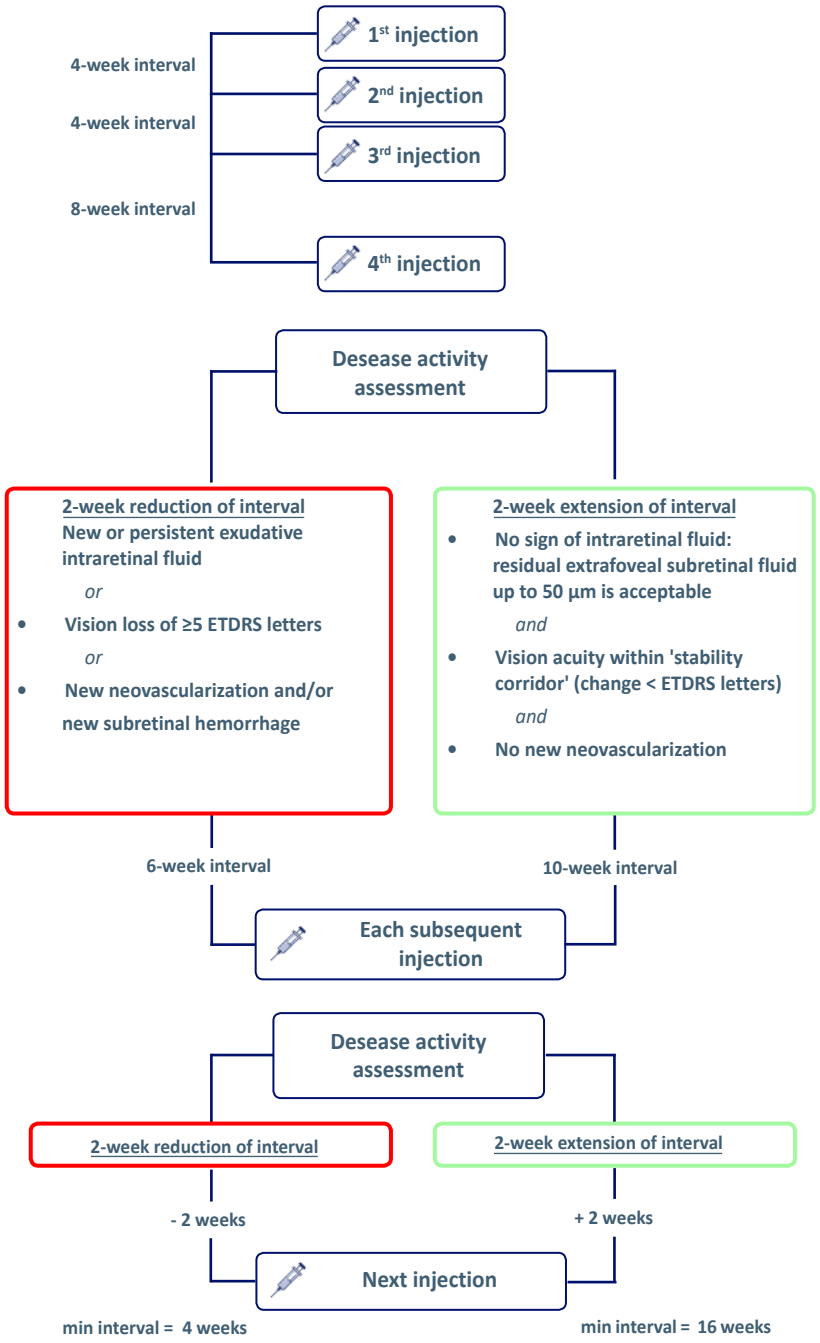

Algorithm of treatment approach to nAMD patients who need frequent intravitreal aflibercept injections