

Individualized treatment with aflibercept in age-related macular degeneration patients with early persistent retinal fluid

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Age-related macular degeneration (AMD) is one of the leading causes of blindness among the elderly (1). Currently, there is no cure for the disease; however, intravitreal anti vascular endothelial growth factor (anti-VEGF) agents have significantly improved visual outcomes in patients with neovascular age-related macular degeneration (nAMD) (2-5). Ranibizumab was approved for the treatment of exudative AMD based on results from two phase III trials: ANCHOR (patients with predominantly classic choroidal neovascularisation) and MARINA (patients with minimally classic or occult choroidal neovascularisation) (2,3). Several subsequent studies showed that the best visual outcomes were achieved in these initial clinical trials, where monthly injections of anti-VEGF were applied (6). However, this regimen was not commonly followed outside clinical trials due to the high costs and level of care associated with a fixed treatment regimen, together with the possibility of administering unnecessary treatments to some patients (7). Consequently, the search for other drugs and/or treatment patterns that maintain efficiency by reducing the number of injections and visits has been the main objective of research in nAMD.

Aflibercept was the next approved anti-VEGF for nAMD treatment. This drug has a significantly higher affinity for VEGF-A compared with other monoclonal anti-VEGF antibodies. In addition to binding all VEGF-A isoforms, aflibercept also blocks other proangiogenic factors such as VEGF-B and placental growth factor (5,8). Two pivotal clinical trials, the VIEW 1 and 2, showed that aflibercept

achieves clinical results in patients with nAMD similar to those obtained with monthly ranibizumab, using a bimonthly treatment regimen after a loading dose of three intravitreal injections, which translates to less use of healthcare resources (5). It is possible that some patients could respond well beginning with bimonthly injections, but there are no data to confirm this and therefore this starting regimen is not recommended (8). Once the loading dose is complete, the patient can be controlled with bimonthly injections. Although changes in central retina thickness were observed in the group with aflibercept every 8 weeks in the VIEW studies, which suggests that the anatomical suppression is not continuous with this bimonthly dosing, the visual acuity (VA) results indicate that the large majority of patients can be treated effectively for 8 weeks since more than 90% of patients in this group did not lose vision (5). There is no evidence that these fluctuations in optical coherence tomography (OCT) negatively translate to VA (5). Therefore, the technical data sheet indicates that better results are not obtained when aflibercept is dosed every 4 weeks compared with every 8 weeks (9.3 *vs.* 8.4 ETDRS letters, in the VIEW studies) (5).

Using this process and given that the injection is done in a programmed manner, medical visits and complementary tests such as OCT can be avoided (7,8). A focused patient history allows the detection of worsening signs and can rule out a possible intraocular complication. Therefore, the fixed bimonthly patterns suppose a notable reduction

in the healthcare burden not only by lowering the number of injections and visits, but also by reducing supplementary tests (7). However, one must consider periodic testing with OCT not only in the affected eye but especially in the contralateral eye to detect the appearance of disease and to administer an early treatment before VA loss. The technical data sheet of aflibercept approved in the European Union allows switching to a personalized treatment regime in the second year, as can occur in the Treat and Extend protocol. In this way, the patients with a dry macula in the OCT after the first year of bimonthly injections could lengthen the period between injections to 3 months. In this second year, the VA, OCT, and fundus examinations are obligatory in all visits because the appearance of classic signs of reactivation make it necessary to shorten the injection interval. This causes an increased demand of healthcare resources but helps to reduce over-treatment during the second year.

In the primary analyses of these trials the effect on visual outcomes of persistent fluid as detected by OCT after the three loading doses were not explored. Jaffe and coworkers have recently showed that there is a subgroup of patients that present with persistent intra or subretinal fluid after the loading dose that could benefit from monthly injections (9). These authors have shown that monthly or bimonthly aflibercept and monthly ranibizumab therapy, had a similar effect on VA in eyes that did not have early persistent fluid, consistent with the overall results reported in the VIEW 1 and VIEW 2 studies. However, approximately 20% of eyes initially treated with aflibercept and 30% of eyes treated with ranibizumab had early persistent fluid after the initial 3 injections. These eyes may benefit from monthly aflibercept compared with the other regimens as demonstrated by a higher proportion of dry retinas, a greater improvement in VA, and a smaller proportion with VA loss (9).

Although it has been reported that eyes with persistent intraretinal fluid have worse VA outcomes than eyes with subretinal fluid (10), Jaffe and coworkers found that the type of fluid was not important in this regard and that eyes with early persistent intraretinal fluid benefited to the same degree with monthly aflibercept as those with subretinal fluid (9).

In order to detect the presence of persistent fluid on the OCT, it is necessary to perform an examination after finalizing the loading dose. If the OCT shows absence of fluid, the patient can continue with the fixed pattern of bimonthly injections, a situation that occurs in 80% of patients. On the contrary, if the OCT shows the presence of liquid (20% of the remaining cases), the patient will obtain

better visual results if maintained with monthly aflibercept injections until the macula is dry, followed thereafter by an individualized protocol as the Treat and Extend regime. Although this personalized treatment scheme from the onset results in a higher demand of healthcare resources, it has the potential advantage of improving visual results in 20% of patients (8,9). However, like all personalized regimens, it is more difficult and complex to perform (11). Jaffe and coworkers point out in their article that it would be useful to conduct a trial about the effect of a Treat-and-Extend, PRN, or PRN individualized dosing strategy and the consequence of switching to bimonthly aflibercept in eyes with persistent fluid after the loading doses with a different anti-VEGF agent. Individualized treatment regimens may reduce patient burden with satisfactory patient outcomes in nAMD (11-13). A PRN regimen requires monthly visits where the patient is treated in the presence of signs of lesion activity. Therefore, an early detection of reactivation of the disease with immediate retreatment is crucial to prevent VA loss (12). Several trials suggest that "Treat and Extend" and other proactive regimens provide a reasonable approach. The rationale of the proactive regimens is to perform treatment anticipating relapses or recurrences and therefore avoid drops in vision while individualizing patients' follow-up (12,13). Moreover, studies have shown that Treat and Extend results in significant direct medical cost savings from fewer treatments and office visits compared to monthly treatment (11).

Some studies also support the use of monthly aflibercept for treatment-resistant eyes (14-17). If after a loading dose the OCT shows little improvement with respect to the baseline, we can find ourselves dealing with a poor responder. In bimonthly visits, it is possible that the OCT shows some fluid but it is usually not associated with loss of VA with respect to the previous visit. The VIEW studies show that these slight increases in macular thickness are well tolerated during short periods without repercussions in VA, and thus a fixed bimonthly pattern will continue to be a good option despite the presence of a small quantity of intra or subretinal fluid on OCT (5).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest

to declare.

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