# Early persistent retinal fluid during treatment of neovascular AMD with ranibizumab and aflibercept

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Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss in subjects aged >65 years living in economically developed countries (1,2). As birthrates drop and life expectancy rises, the prevalence of AMD is expected to increase, along with the social and economical burden associated with the disease and its treatment. Anti-vascular endothelial growth factor (VEGF) drugs have revolutionized the management of neovascular AMD (nAMD) and are now considered the mainstay of therapy (1,3). Although monthly injections seem to produce the best functional results according to clinical trials (4-7), the increasing patient numbers and exponentially growing costs made it clear that alternatives should be sought for a clinical practice setting. To this day, plentiful controversies still exist over the best available drug and treatment regimen for the management of nAMD. Variations in patient response to anti-VEGF therapy have been identified in clinical trials, regardless of the drug or regimen used. Understanding the reasons (epidemiological, genetic, functional, anatomical, etc.) behind these variations could help predict the injection requirements of individual patients, thus reducing unnecessary visits and preventing over- or undertreatment (8). Although most patients respond rapidly to anti-VEGF treatment, residual fluid on OCT persists in a subgroup of eyes across clinical trials of different drugs and regimens. Since treatment decisions are often driven by the presence of fluid on OCT, the quest for imaging biomarkers capable of predicting the functional and anatomical prognosis became the goal of several investigators.

The VIEW 1 and VIEW 2, two similarly designed, phase III trials, showed that intravitreal aflibercept dosed monthly or bimonthly after an initial 3-month loading dose, had similar efficacy and safety outcomes as monthly ranibizumab (9). The design of these studies allowed Jaffe *et al*. (10) to conduct a post hoc analysis aiming at comparing the effect of drug type (aflibercept or ranibizumab) and treatment regimen (monthly or bimonthly) on visual acuity (VA) outcomes in eyes with early persistent retinal fluid, defined as the presence of retinal fluid at baseline, week (w) 4, w8 and w12, i.e., during and 4w after the loading dose (3 monthly injections). Data about the retinal fluid characteristics was collected from independent masked graders at two central reading centers: Duke Reading Center (VIEW 1) and Vienna Reading Center (VIEW 2). The degree of retinal fluid fluctuation, the time to absence of retinal fluid, the fluid type (subretinal or intraretinal) and their influence on best-corrected VA (BCVA) were evaluated across treatment arms. From a total of 1,815 eyes (monthly 0.5 mg ranibizumab, n=595; monthly 2.0 mg aflibercept, n=613; and bimonthly 2.0 mg aflibercept, n=607), 413 met the criteria for early persistent retinal fluid (monthly 0.5 mg ranibizumab, n=175; monthly 2.0 mg aflibercept, n=115; and bimonthly 2.0 mg aflibercept, n=123). The authors did not include the monthly 0.5 mg aflibercept group of the VIEW studies in the post hoc analysis since this dose did not receive FDA approval and is not currently being used. When comparing the baseline characteristics of eyes with and without early persistent fluid, the authors found similar

VA, lesion sizes and lesion types across treatment groups. However, greater OCT baseline central subfield thickness was observed in the eyes with early persistent fluid. Among patients without early persistent fluid, no statistically significant differences were noted in BCVA variation from baseline to w52 across the three treatment arms. Conversely, when early persistent fluid was present, monthly aflibercept was found to be superior to the other treatment regimens, demonstrating a higher proportion of dry retinas, greater VA improvement and a smaller proportion of eyes with VA loss. Unlike the results of the first and second years of the Comparison of AMD Treatments Trials (CATT) (11,12), where the presence of foveal intraretinal fluid was associated with a poor functional prognosis and the presence of subretinal fluid correlated with better final VA, in this study the pattern of VA changes was similar regardless of whether the early persistent fluid was intra- or subretinal. Overall, the authors found that eyes treated with monthly aflibercept were more likely to sustain a dry retina and that in eyes with early persistent fluid, monthly aflibercept may provide additional clinical benefit over bimonthly aflibercept or monthly ranibizumab.

This study has several limitations. First, there were 91 eyes (34 eyes in the monthly ranibizumab group, 29 in the monthly aflibercept group and 28 in the bimonthly aflibercept group) with missing observations in at least one visit during baseline to w12 (the time-frame considered for the definition of early persistent fluid). These eyes were classified as wet if the preceding and the following visits were classified as wet. We believe that this might have introduced an important classification bias in the number of eyes considered to have early persistent fluid. Second, the VIEW 1 and VIEW 2 studies used low-resolution time-domain OCT equipments. This means that the definition of early persistent fluid was based on OCT images with uncertain quality and that results could have been different if higher-resolution, spectral-domain or swept-source systems had been used instead. Furthermore, by using time-domain OCT images, the graders could not precisely evaluate the effect of other microanatomical retinal changes, namely the integrity of the external limiting membrane or the ellipsoid zone. Several baseline characteristics have already been associated with poor functional results across nAMD clinical trials (8), including: epidemiological (older age); functional (worse VA) and anatomical features (larger lesion area; greater foveal thickness; subfoveal geographic atrophy or fibrosis; presence of intraretinal cysts; presence of pigment epithelial detachment and loss

of integrity of the external limiting membrane and of the ellipsoid zone). In fact, given the complexity of AMD, the most plausible scenario is that treatment outcomes are influenced by several baseline features and being able to define treatment response/outcomes based on a single culprit (e.g., early persistent retinal fluid) seems highly unlikely. Third, although an exhaustive and comprehensive statistical analysis was performed, the fact that this is a post hoc analysis constitutes another limitation, as the original study was not designed to answer what the ideal treatment should be for eyes with early persistent fluid. Fourth, the results are limited to w52 because in the VIEW studies (9), the dosing regimen changed to PRN from w52 to w96 in all treatment arms. Thus, we do not know how long it would have taken for eyes with early persistent fluid to achieve maximal visual gains, nor do the present results allow us to infer that patients with early persistent fluid would have benefitted from switching from monthly ranibizumab to monthly aflibercept after the loading dose. These questions remain to be answered and although this study is a relevant contribution for the current management of nAMD, further studies, ideally randomized controlled trials, are needed before extrapolating these findings to our everyday clinical practice.

## Footnote

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