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Morphology and Visual Acuity in Aflibercept and Ranibizumab Therapy for Neovascular Age-Related Macular Degeneration in the VIEW Trials

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Purpose: To compare the efficacy of intravitreal aflibercept and ranibizumab on the exudative activity of neovascular age-related macular degeneration (nAMD) using optical coherence tomography (OCT) and to correlate morphologic findings with visual acuity (VA) outcomes.

Design: Post hoc analysis of the prospective VIEW trials.

Participants: Data of 1815 patients randomized to 0.5 mg ranibizumab every 4 weeks (Q4wks), 2 mg aflibercept Q4wks, or 2 mg aflibercept every 8 weeks (Q8wks).

Methods: Standardized OCT evaluation was performed by masked reading centers for the presence of intraretinal cystoid fluid (IRC), subretinal fluid (SRF), and pigment epithelial detachment (PED). Rates of feature resolution were compared between drugs and regimen. Associations between morphologic features and VA were analyzed using multivariate modeling.

Main Outcome Measures: Resolution rates of IRC, SRF, and PED, and associations between morphology and VA.

Results: At baseline, the proportions of eyes with IRC, SRF, and PED were balanced between the aflibercept and ranibizumab groups. At week 12, IRC resolved in 50% of eyes with both agents. Subretinal fluid resolved in 70% of pooled aflibercept-treated eyes and in 59% of ranibizumab-treated eyes, and PED resolved in 29% and 24% of pooled aflibercept-treated eyes and ranibizumab-treated eyes, respectively. At week 52, IRC resolved in 57% (aflibercept Q4wks), 50% (aflibercept Q8wks), and 52% (ranibizumab) of patients; SRF resolved in 75% (both aflibercept Q4wks/Q8wks) and 66% (ranibizumab) of patients; and PED resolved in 40% (aflibercept Q4wks), 34% (aflibercept Q8wks), and 28% (ranibizumab) of patients. During fixed dosing (weeks 12−52) all exudative features showed synchronized fluctuations after treatment-free visits in the Q8wks aflibercept regimen. During pro re nata dosing (weeks 52−96), greater proportions of patients showed recurrent fluid in all treatment arms. Presence of IRC was generally associated with lower VA at baseline, which translated into poorer final VA outcomes.

Conclusions: Fluid resolution in all compartments was consistently greater for aflibercept Q4wks than for aflibercept Q8wks and ranibizumab. At week 52, Q8wks aflibercept−treated eyes were, on average, as dry as or drier than with ranibizumab despite the extended treatment interval. Independent of agent or regimen, preexisting morphologic features of the retina at baseline markedly influenced VA outcomes. *Ophthalmology 2016;■:1−9 © 2016 American Academy of Ophthalmology. Published by Elsevier Inc.*

Ranibizumab (Lucentis; Genentech, South San Francisco, CA) and aflibercept (Eylea; Regeneron, Tarrytown, NY) are the most widely used internationally approved treatments for choroidal neovascularization (CNV) in neovascular age-related macular degeneration (nAMD).[1−4] The visual acuity (VA) outcomes after 2 mg intravitreal aflibercept injection dosed every 4 weeks (Q4wks) or every 8 weeks (Q8wks) after 3 initial monthly injections were shown to be non-inferior and clinically equivalent to 0.5 mg ranibizumab Q4wks in the pivotal large-scale VIEW trials at week 52.[3,5] The VIEW studies provide a robust database for studying the effects of the approved agents, as well as fixed and flexible regimens, based on their randomized, prospective trial nature and population size.

As for anatomic efficacy, the VIEW studies found, in an integrated post hoc analysis at week 52, that numerically higher percentages of dry retinas (absent intraretinal cystoid fluid [IRC] and subretinal fluid [SRF]) were seen in the 2 mg aflibercept groups than in the ranibizumab group, with proportions of patients with dry retinas for ranibizumab and the 2 mg aflibercept Q4wks and Q8wks groups at 62.0%, 72.4%, and 67.7%, respectively.[3] However, the differences in antiexudative efficacy between ranibizumab and aflibercept based on morphologic analysis of optical

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coherence tomography (OCT) features have not been systematically investigated on a large scale. Furthermore, the impact of the characteristic morphologic features of nAMD on visual outcomes, with antiangiogenic therapy, is not yet fully understood. To investigate the antiexudative efficacy and its impact on distinct morphologic features, we performed a systematic post hoc analysis of the VIEW trials comparing the response of intraretinal, subretinal, and subpigment epithelial fluid between aflibercept- and ranibizumab-treated eyes using assessment of OCT images according to a standardized protocol. Morphologic features were correlated with VA outcomes to investigate the association between macular structure and function in nAMD treatment.

Methods

The VIEW program consisted of 2 parallel randomized, double-masked, active-controlled, multicenter, phase III trials conducted in the United States and Canada (VIEW 1), and South America, Europe, Asia, and Australia (VIEW 2). The study protocol, inclusion and exclusion criteria, treatment regimen, and main outcomes of the VIEW trials have been presented in detail.[3,5] Thus, only procedures immediately relevant to the current post hoc analysis are described in this article. The ethics committees/institutional review boards at the international study sites approved the study protocol applicable to the respective study site. The trials were registered with ClinicalTrials.gov (identifiers NCT00509795 and NCT00637377), and all patients signed a written consent form before initiation of the study-specific procedures. The study was conducted in compliance with the principles of the Declaration of Helsinki.

Treatment Regimens

Patients were randomized to receive intravitreal injections of 0.5 mg ranibizumab Q4wks, 0.5 mg or 2 mg aflibercept Q4wks, or 2 mg aflibercept every month for 3 months followed by dosing Q8wks until week 52. From weeks 52 to 96, patients received a "capped" pro re nata (PRN) regimen with re-treatment based on monthly evaluations with mandatory dosing at least every 12 weeks. Because the 0.5 mg aflibercept dose is not licensed anywhere in the world, data of patients receiving 0.5 mg aflibercept were not included in this analysis.

Functional and Anatomic Assessments

Patients were examined monthly for 96 weeks, including assessment of best-corrected visual acuity (BCVA) with Early Treatment Diabetic Retinopathy Study charts by examiners who were masked to the treatment and certified for the task. Stratus OCT (Carl Zeiss Meditec, Dublin, CA) scans were acquired monthly (by protocol in VIEW 2 and by common practice in VIEW 1) by masked, certified operators.

The Duke Reading Center (for VIEW 1) and the Vienna Reading Center (for VIEW 2) evaluated OCT images to provide a uniform, standardized assessment of defined retinal morphology for each visit of all patients. In VIEW 1, OCT was analyzed by protocol on a quarterly basis. In VIEW 2, the central reading center analyzed all monthly OCT data. All OCT images underwent a standardized, comprehensive grading in a validated, cross-reading center–consistent fashion.[6] The 6-mm cross-hair scan was used for morphologic analysis. In terms of macular morphology, the presence or absence of IRC fluid and SRF was assessed using a prespecified grading protocol including quality-control procedures previously described in detail.[7] Assessments for pigment epithelial detachment (PED) were performed differently in VIEW 1 and VIEW 2. The Vienna Reading Center graded PED as present if a retinal pigment epithelium elevation was measured more than 400 μm in width and 75 μm in height, or more than 200 μm in height. The Duke Reading Center measured the width and height of any retinal pigment epithelium elevation at each visit. The described width and height cutoffs were applied post hoc to the VIEW 1 data to dichotomize and harmonize the PED grading for this analysis.

Statistical Analysis

The main outcomes of the VIEW trials (VA-based noninferiority of 2 mg aflibercept Q4wks or Q8wks to 0.5 mg ranibizumab Q4wks) have been reported.[3] Our study was an exploratory study of a comprehensive clinical trial database. Thus, no formal hypotheses were formulated, no sample size calculations were performed, and no multiplicity adjustments were made. Reported *P* values are to be viewed as hypothesis generating. All analyses were performed using the statistical software package SAS version 9 (SAS Institute Inc., Cary NC).

Morphologic Efficacy of Aflibercept and Ranibizumab

To determine whether the treatments imposed the same impact on the morphologic parameters from baseline to week 12 and week 52, patients in the respective treatment arms were categorized into groups of fluid "resolving" (fluid present at baseline/absent at week 12/52) or "not resolving" (all possibilities other than "resolving," including fluid absent at baseline/present at week 12/52, or fluid present or absent at both baseline and week 12/52). Patients receiving aflibercept Q4wks and Q8wks were pooled for analysis of the 12-week time point because treatment in these 2 groups was identical through the first 3 months. Adjusted differences and 95% confidence intervals (CIs) were calculated using Cochran–Mantel–Haenszel weights, adjusted for study (VIEW 1/2).

Change in Morphologic Features on a Monthly Basis

To assess the change in morphologic features on a monthly basis, only the VIEW 2 population was included because monthly OCT readings were not mandated per protocol in the VIEW 1 trial.

Association between Retinal Morphology and Visual Function

Multivariable analyses were performed to analyze the impact of retinal morphology on contemporaneous visual function at baseline, week 12, and week 52 in all 3 treatment arms pooled together. Analysis of covariance (ANCOVA) models were fit for BCVA at those end points, with all the morphology compartments (IRC/SRF/PED) in the model, as well as treatment assignment and studies (VIEW 1/2) as fixed effects. Baseline BCVA also was included in the model for postbaseline end points (week 12 and week 52). Least-squares mean BCVA scores with 95% CIs are reported.