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Evaluating the Impact of Intravitreal Aflibercept on Diabetic Retinopathy Progression in the VIVID-DME and VISTA-DME Studies

Paul Mitchell, MD, PhD,[1,2,3,4] *Ian McAllister, MBBS, DM,*[5] *Michael Larsen, MD, DMSc,*[6,7] *Giovanni Staurenghi, MD,*[8] *Jean-Francois Korobelnik, MD,*[9,10] *David S. Boyer, MD,*[11] *Diana V. Do, MD,*[12] *David M. Brown, MD,*[13] *Todd A. Katz, MD,*[14] *Alyson Berliner, MD, PhD,*[15] *Robert Vitti, MD,*[15] *Oliver Zeitz, MD,*[16,17,18] *Carola Metzig, MD,*[16] *Chengxing Lu, PhD,*[14] *Frank G. Holz, MD*[19]

Purpose: To evaluate the impact of intravitreal aflibercept (EYLEA, Regeneron Pharmaceuticals, Tarrytown, NY) versus laser on progression of diabetic retinopathy (DR) severity in Intravitreal Aflibercept Injection in Vision Impairment due to DME (VIVID-DME) and Study of Intravitreal Aflibercept Injection in Patients with Diabetic Macular Edema (VISTA-DME).

Design: Secondary and exploratory analyses of 2 phase 3, randomized, controlled studies.

Participants: All patients with a baseline Diabetic Retinopathy Severity Scale (DRSS) score based on fundus photograph (full analysis), patients who progressed to proliferative DR (PDR) (safety analysis) in VIVID-DME (n = 403) and VISTA-DME (n = 459), or both.

Methods: We randomized patients with diabetic macular edema (DME) to intravitreal aflibercept 2 mg every 4 weeks (2q4), intravitreal aflibercept 2 mg every 8 weeks after 5 initial monthly doses (2q8), or macular laser photocoagulation at baseline and sham injections at every visit.

Main Outcome Measures: Proportions of patients with 2-step or more and 3-step or more improvements from baseline in DRSS score, who progressed to PDR, and who underwent panretinal photocoagulation (PRP).

Results: Among patients with an assessable baseline DRSS score, most showed moderately severe or severe nonproliferative DR. The proportions of patients treated with 2q4, 2q8, and laser with a 2-step or more improvement in DRSS score at week 100 were 29.3%, 32.6%, and 8.2%, respectively, in VIVID-DME and 37.0%, 37.1%, and 15.6%, respectively, in VISTA-DME; the proportions with a 3-step or more improvement in DRSS score were 7.3%, 2.3%, and 0%, respectively, and 22.7%, 19.9%, and 5.2%, respectively. Fewer patients in the 2q4 and 2q8 groups versus the laser group progressed to PDR at week 100 in VISTA-DME (1.5% and 2.2% vs. 5.3%) and VIVID-DME (3.2% and 2.0% vs. 12.3%). The proportions of patients who underwent PRP were 2.9%, 0.7%, and 4.5%, respectively, in VIVID-DME and 1.9%, 0.7%, and 5.2%, respectively, in VISTA-DME. The most frequent serious ocular adverse event at week 100 was cataract (pooled intravitreal aflibercept, 1.7% of patients; laser, 3.5% of patients).

Conclusions: These analyses demonstrate the benefit of intravitreal aflibercept over laser with respect to DR progression, suggesting a benefit on DME, and on underlying DR. *Ophthalmology Retina 2018;■:1–9 © 2018 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Diabetic retinopathy (DR) is a progressive dysfunction of the retinal vasculature resulting from chronic hyperglycemia.[1] Diabetic retinopathy has been classified into 4 stages: mild nonproliferative DR (NPDR), moderate NPDR, severe NPDR, and proliferative DR (PDR). Typical management of mild and moderate NPDR involves observation and improved control of diabetes, whereas severe NPDR and PDR require referral to an ophthalmologist. Treatment options for DR in the absence of diabetic macular edema (DME) target only proliferative stages of DR.

Diabetic macular edema may occur at any point in the course of DR, although it is more frequent as the disease progresses. Most vision loss associated with DR is the result of DME.[2] The estimated global prevalence of DME currently is approximately 21 million,[3] and this is expected to increase with the rising diabetes prevalence; diabetes is projected to affect nearly 600 million people worldwide by 2035.[4]

Intravitreal anti–vascular endothelial growth factor (VEGF) agents (aflibercept [EYLEA, Regeneron Pharmaceuticals, Tarrytown, NY] and ranibizumab) are superior to laser for the treatment of center-involved DME.[5–9] Intravitreal aflibercept showed similar sustainable visual acuity (VA) gains with dosing every other month compared with

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ranibizumab given monthly. More recently, the National Institutes of Health–funded Protocol T study conducted by the Diabetic Retinopathy Clinical Research Network compared intravitreal aflibercept, ranibizumab, and non-licensed bevacizumab head to head.[10] At 12 months, VA gains achieved with intravitreal aflibercept, the study's primary end point, were statistically superior to those achieved with ranibizumab or bevacizumab, particularly in patients with baseline VA of 20/50 or worse.[10] After 2 years, the visual gains achieved with intravitreal aflibercept were statistically superior to those with bevacizumab, but not ranibizumab[11]; however, an area under the curve analysis showed that mean change in VA over 2 years was greater with intravitreal aflibercept than with bevacizumab or ranibizumab.[12]

Vascular endothelial growth factor inhibition has been shown not only to influence the course of DME positively, but also to have a positive impact on overall DR severity.[6,13,14] Herein we report on an unplanned retrospective analysis of the impact of intravitreal aflibercept treatment on changes in Diabetic Retinopathy Severity Scale (DRSS) scores, progression of DR to PDR in patients with DME, and use of panretinal photocoagulation (PRP) in the Intravitreal Aflibercept Injection in Vision Impairment due to DME (VIVID-DME) and Study of Intravitreal Aflibercept Injection in Patients with Diabetic Macular Edema (VISTA-DME) studies.

Methods

Design

Study design and methods have been published previously.[8,9] Key details are summarized here. Both VIVID-DME (clinicaltrials.gov identifier, NCT01331681) and VISTA-DME (clinicaltrials.gov identifier, NCT01363440) were phase 3, randomized, double-masked, active-controlled, 148-week trials comparing 2 dosing regimens of intravitreal aflibercept with laser for the treatment of DME. The studies were conducted at 127 sites in the Unites States, Europe, Japan, and Australia and in accordance with the principles of the Declaration of Helsinki and International Conference on Harmonisation. All information presented in this study complies with the Health Insurance Portability and Accountability Act for United States sites. Institutional review board or ethics committee approval was obtained at each site before the studies commenced, and all patients provided written consent.

Participants

Adult patients with diabetes mellitus with central DME involvement (defined as retinal thickening involving the 1-mm central OCT subfield [central subfield thickness]) were included if best-corrected VA (BCVA) was between 73 and 24 letters (Snellen equivalent, 20/40–20/320) in the study eye. Only 1 eye per patient was included.

Randomization and Treatment

We randomized patients 1:1:1 to treatment with intravitreal aflibercept 2.0 mg every 4 weeks (2q4), intravitreal aflibercept 2.0 mg every 8 weeks after 5 initial monthly doses (2q8), or macular laser photocoagulation at baseline and sham injections at every visit. Eyes in the 2q8 group received sham injections on nontreatment visits. From week 24 onward, additional active treatment (laser in the intravitreal aflibercept groups or intravitreal aflibercept in the laser group) was allowed if BCVA decreased because of disease reoccurrence or worsening based on prespecified criteria. Panretinal photocoagulation was allowed at any time at the investigator's discretion for PDR.

Outcomes

The primary efficacy end point in VIVID-DME and VISTA-DME was the BCVA change from baseline in Early Treatment Diabetic Retinopathy Study (ETDRS) letter scores at week 52. Results for the primary end point of these studies are reported elsewhere.[8] Herein, we report the proportion of eyes with 2-step or more and 3-step or more improvement in DRSS score at weeks 52 and 100, the proportion of eyes in which PDR developed at weeks 52 and 100, and the proportion of eyes that underwent PRP at weeks 52 and 100. The 2-step or more improvement in DRSS score was a prespecified secondary end point at week 52 and an exploratory end point at week 100 for these studies.

We assessed central subfield thickening using spectral-domain OCT every 4 weeks, and performed fluorescein angiography and color fundus photography at baseline and weeks 24, 52, and 100. Masked graders evaluated images at independent reading centers. For VIVID-DME, readers at the Vienna Reading Center (Vienna, Austria) evaluated OCT images and fundus images. For VISTA-DME, clinicians at the Duke Reading Center (Durham, NC) assessed OCT images and clinicians at the Digital Angiography Reading Center (Great Neck, NY) evaluated fundus images. Although the 2 reading centers used similar methods, the differences in the proportions of ungradable images at baseline were the result of slightly different algorithms used by each center.

Patients were considered to have PDR if their baseline DRSS score was less than 61 and there was at least 1 postbaseline DRSS score of 61 or more. Laser photocoagulation (panretinal or macular) in the study eye within 90 days of day 1 and active PDR in the study eye were exclusion criteria for VIVID-DME and VISTA-DME. Approximately 5% of patients demonstrated PDR at baseline. It was agreed by the reading centers that DRSS level 60 (which indicates prior PRP) would not be used in the study, and therefore patients with prior PRP could still improve on the DRSS scale.

Statistical Analysis

Patients included in the efficacy analyses are those from the full analysis set (FAS) in both studies (VIVID-DME and VISTA-DME). This includes all randomized patients who received any study medication and underwent at least 1 baseline and 1 post-baseline assessment. We analyzed the FAS as randomized. In calculating the percentage of patients with a 2-step or more and 3-step or more improvement in DRSS score, the denominator for VIVID-DME was all patients in the FAS who had a baseline evaluable measurement of DRSS score and at least 1 postbaseline evaluable assessment of DRSS score; the denominator for VISTA-DME was all patients in the FAS. For patients missing a DRSS score at weeks 52 and 100, we imputed missing values using the last observation carried forward method, in which we used the last value before additional treatment for eyes that received additional treatment. The use of these different denominators is consistent with the health authority submission packages for the 2 studies. For the end point of PDR development, we excluded missing and ungradable entries for DRSS score from both studies.