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Intravitreal Aflibercept for Diabetic Macular Edema

148-Week Results from the VISTA and VIVID Studies

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Purpose: To compare efficacy and safety of intravitreal aflibercept injection (IAI) with macular laser photocoagulation for diabetic macular edema (DME) over 3 years.

Design: Two similarly designed phase 3 trials: VISTA^{DME} and VIVID^{DME}.

Participants: Patients (eyes; n = 872) with central-involved DME.

Methods: Eyes received IAI 2 mg every 4 weeks (2q4), IAI 2 mg every 8 weeks after 5 monthly doses (2q8), or laser control. From week 24, if rescue treatment criteria were met, IAI patients received active laser, and laser control patients received IAI 2q8. From week 100, laser control patients who had not received IAI rescue treatment received IAI as needed per retreatment criteria.

Main Outcome Measures: The primary end point was the change from baseline in best-corrected visual acuity (BCVA) at week 52. We report the 148-week results.

Results: Mean BCVA gain from baseline to week 148 with IAI 2q4, IAI 2q8, and laser control was 10.4, 10.5, and 1.4 letters ($P < 0.0001$) in VISTA and 10.3, 11.7, and 1.6 letters ($P < 0.0001$) in VIVID, respectively. The proportion of eyes that gained ≥15 letters from baseline at week 148 was 42.9%, 35.8%, and 13.6% ($P < 0.0001$) in VISTA and 41.2%, 42.2%, and 18.9% ($P < 0.0001$) in VIVID, respectively. Greater proportions of eyes treated with IAI 2q4 and IAI 2q8 versus those treated with laser control had an improvement of ≥2 steps in the Diabetic Retinopathy Severity Scale (DRSS) score in both VISTA (29.9% and 34.4% vs. 20.1% [$P = 0.0350$, IAI 2q4; $P = 0.0052$, IAI 2q8]) and VIVID (44.3% and 47.8% vs. 17.4% [$P < 0.0001$ for both]). In an integrated safety analysis, the most frequent ocular serious adverse event was cataract (3.1%, 2.1%, 0.3% for 2q4, 2q8, and control).

Conclusions: Visual improvements observed with both IAI regimens (over laser control) at weeks 52 and 100 were maintained at week 148, with similar overall efficacy in the IAI 2q4 and IAI 2q8 groups. Treatment with IAI also had positive effects on the DRSS score. Over 148 weeks, the incidence of adverse events was consistent with the known safety profile of IAI. *Ophthalmology 2016;■:1–10 © 2016 by the American Academy of Ophthalmology*

Supplemental material is available at www.aaojournal.org.

The diabetes mellitus epidemic is growing. According to current predictions, by 2040, approximately 1 in every 10 adults (642 million) worldwide will have the disease.[1] Diabetic retinopathy and associated diabetic macular edema (DME) are serious diabetes mellitus complications and are the leading causes of blindness and visual disability in working-age adults.[2,3]

Current treatment options for DME include macular laser photocoagulation,[4] corticosteroids,[5] and anti-vascular endothelial growth factor (VEGF) agents (i.e., intravitreal aflibercept, ranibizumab, and off-label use of bevacizumab).[6–8] There is a large body of evidence to support anti-VEGF use. Because of superior anatomic and functional outcomes,[6–11] anti-VEGF agents have rapidly replaced macular laser photocoagulation as the standard of care to treat DME.

Aflibercept, a 115-kDA recombinant fusion protein, is composed of the key VEGF binding domains of human VEGF receptors 1 and 2 fused to the constant Fc domain of human immunoglobulin G1,[12] and it binds VEGF-A with high affinity.[13] Unlike ranibizumab and bevacizumab, aflibercept also binds to placental growth factor.[13] Intravitreal aflibercept injection (IAI), which is also known as "VEGF Trap Eye" or "IVT-AFL" in the scientific literature, is currently indicated to treat neovascular age-related macular degeneration (AMD), macular edema

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Table 1. Treatment Experience from Baseline to Week 148

	VISTA			VIVID		
	Laser Control (n = 154)	*IAI 2q4 (n = 155)*	*IAI 2q8 (n = 152)*	*Laser Control (n = 133)*	*IAI 2q4 (n = 136)*	*IAI 2q8 (n = 135)*
No. of scheduled treatments through week 148, mean (SD)						
Macular laser photocoagulation	3.8 (2.4)	–	–	2.6 (2.0)	–	–
Intravitreal aflibercept	–	29.6 (9.8)	18.1 (4.8)	–	32.0 (9.7)	18.1 (5.1)
Study eyes that received rescue treatment* from week 24 to week 148, n (%)	63 (40.9)*	7 (4.5)*	16 (10.5)*	47 (35.3)*	10 (7.4)*	16 (11.9)*
Mean (SD) No. of rescue treatment	13.5 (3.9)	1.4 (0.8)	1.4 (1.1)	13.5 (4.3)	2.3 (1.5)	1.9 (1.0)
Laser control eyes that received rescue or PRN† IAI treatment from week 24 to week 148, n (%)	134 (87.0)	–	–	109 (82.0)	–	–
Mean (SD) number of IAI injections	9.8 (5.0)	–	–	9.3 (5.2)	–	–

– = not applicable; IAI = intravitreal aflibercept injection; PRN = pro re nata; SD = standard deviation; 2q4 = 2 mg IAI every 4 weeks; 2q8 = 2 mg IAI every 8 weeks after 5 initial monthly doses.
Safety analysis set.
*Rescue treatment was 2 mg IAI every 4 weeks for 5 initial doses followed by dosing every 8 weeks in the laser control group, and active laser for the IAI 2q4 and 2q8 groups.
†Laser control patients who did not meet criteria for rescue treatment during weeks 24 to 96 received IAI 2 mg PRN per the prespecified retreatment criteria from week 100 to week 144. In VISTA and VIVID, respectively, 71 and 64 laser control patients received a mean (SD) of 6.5±3.2 and 6.0±3.3 PRN IAI injections from week 100 to week 148.

secondary to retinal vein occlusion, myopic choroidal neovascularization, and DME. Intravitreal aflibercept injection is approved for the treatment of DME in the United States, the European Union, Australia, and Japan.

The efficacy and safety of IAI in DME have been demonstrated over 2 years in the VISTA^{DME} and VIVID^{DME} studies.[7,14] Both trials showed that, after 52 and 100 weeks of treatment, IAI provides significantly greater improvements in both functional and anatomic outcomes when compared with macular laser photocoagulation.[7,14] In addition, the proportion of eyes with ≥2-step improvement in the Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (DRSS) score was significantly greater with IAI than with laser control, suggesting a beneficial effect on the underlying diabetic retinopathy.[7,14] We report the 148-week results of the VISTA and VIVID studies.

Methods

Study Design

VISTA and VIVID were 2 similarly designed, double-masked, randomized, active-controlled, 148-week, phase 3 trials. VISTA (registered at www.clinicaltrials.gov; NCT01363440) was conducted across 54 sites in the United States, and VIVID (registered at www.clinicaltrials.gov; NCT01331681) was conducted in 73 sites across Europe, Japan, and Australia.[7,14] Each clinical site's respective institutional review board or ethics committee approved the study. All patients provided written informed consent. Both VISTA and VIVID were conducted in compliance with the International Conference on Harmonization guidelines and the Health Insurance Portability and Accountability Act of 1996.[15,16] Data for this report, which present the 148-week results, were collected between May 2011 and March 2015.

Patient eligibility for the VISTA and VIVID studies has been described.[14] Briefly, adult patients with type 1 or 2 diabetes mellitus who presented with central-involved DME (defined as retinal thickening involving the central 1-mm subfield [central subfield thickness {CST}] as determined by spectral domain optical coherence tomography [SD OCT]) were eligible for enrollment if best-corrected visual acuity (BCVA) was between 73 and 24 letters (20/40 to 20/320 Snellen equivalent) in the study eye. Only 1 eye per patient was enrolled in the study. Eyes were randomized in a 1:1:1 ratio to 3 groups to receive 1 of the following treatments (a) 2 mg IAI every 4 weeks (2q4), (b) 2 mg IAI every 8 weeks after 5 initial monthly doses (2q8), and (c) macular laser photocoagulation at baseline. Treatments continued through week 148.

Beginning at week 12, study eyes in all treatment groups were assessed for laser retreatment. If any ETDRS-defined, clinically significant macular edema was present (defined as thickening of the retina or hard exudates at ≤500 μm of center of the macula, or at least 1 zone of retinal thickening 1 disc area or larger, any part of which was within 1 disc diameter of center of the macula), study eyes in the IAI 2q4 and IAI 2q8 groups received sham laser and those in the laser group received active laser, but no more frequently than every 12 weeks.

Beginning at week 24, study eyes in all treatment groups also could receive additional (rescue) treatment if DME worsened, as defined by a ≥10-letter loss at 2 consecutive visits or ≥15-letter loss at 1 visit from the best previous measurement, when BCVA was not better than baseline. When these criteria were met, study eyes in the IAI 2q4 and IAI 2q8 groups could receive active laser (rather than sham laser) from week 24 onward and continued with the existing IAI regimen; study eyes in the laser control group received 5 doses of 2 mg IAI every 4 weeks followed by dosing every 8 weeks until the end of the study (rather than sham injections), in addition to laser, when the laser retreatment criteria were met. Patients could receive both laser and IAI, when applicable, at the same visit.

Beginning at week 100, patients in the laser control group who did not meet criteria for rescue treatment during weeks 24 to 96