The DA VINCI Study: Phase 2 Primary Results of VEGF Trap-Eye in Patients with Diabetic Macular Edema

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Purpose: To determine whether different doses and dosing regimens of intravitreal vascular endothelial growth factor (VEGF) Trap-Eye are superior to focal/grid photocoagulation in eyes with diabetic macular edema (DME).

Design: Multicenter, randomized, double-masked, phase 2 clinical trial.

Participants: A total of 221 diabetic patients with clinically significant macular edema involving the central macula.

Methods: Patients were assigned to 1 of 5 treatment regimens: 0.5 mg VEGF Trap-Eye every 4 weeks; 2 mg VEGF Trap-Eye every 4 weeks; 2 mg VEGF Trap-Eye for 3 initial monthly doses and then every 8 weeks; 2 mg VEGF Trap-Eye for 3 initial monthly doses and then on an as-needed (PRN) basis; or macular laser photocoagulation. Assessments were completed at baseline and every 4 weeks thereafter.

Main Outcome Measures: Mean change in visual acuity and central retinal thickness (CRT) at 24 weeks.

Results: Patients in the 4 VEGF Trap-Eye groups experienced mean visual acuity benefits ranging from +8.5 to +11.4 Early Treatment of Diabetic Retinopathy Study (ETDRS) letters versus only +2.5 letters in the laser group ($P \leq 0.0085$ for each VEGF Trap-Eye group vs. laser). Gains from baseline of 0+, 10+, and 15+ letters were seen in up to 93%, 64%, and 34% of VEGF Trap-Eye groups versus up to 68%, 32%, and 21% in the laser group, respectively. Mean reductions in CRT in the 4 VEGF Trap-Eye groups ranged from −127.3 to −194.5 μm compared with only −67.9 μm in the laser group ($P = 0.0066$ for each VEGF Trap-Eye group vs. laser). VEGF Trap-Eye was generally well tolerated. Ocular adverse events in patients treated with VEGF Trap-Eye were generally consistent with those seen with other intravitreal anti-VEGF agents.

Conclusions: Intravitreal VEGF Trap-Eye produced a statistically significant and clinically relevant improvement in visual acuity when compared with macular laser photocoagulation in patients with DME.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.
Ophthalmology 2011;118:1819–1826 © 2011 by the American Academy of Ophthalmology.

Diabetic macular edema (DME) is the most common vision-threatening manifestation of diabetic retinopathy. The population-based Wisconsin Epidemiologic Study of Diabetic Retinopathy reported 28% prevalence of DME 20 years after the diagnosis of type 1 or type 2 diabetes,[1] and the 10-year incidence of DME varies between 20% and 40% depending on age, diabetes type, and severity of diabetes.[2] The prevalence is projected to increase as the prevalence of diabetes mellitus increases from 180 million people worldwide to 300 million by the year 2025.[3]

Phosphorylation of tight junction proteins and disorganization of the blood–retina–barrier are the key events in the pathophysiology of DME,[4,5] to which hypoxia-triggered vascular endothelial growth factor (VEGF) release contributes significantly.[6] Intravitreal injection of VEGF has been shown to produce all findings of diabetic retinopathy, including microaneurysms, macular edema, and retinal neovascularization.[7,8] Correspondingly, intravitreal VEGF levels are elevated in patients with DME.[9] The importance of VEGF is underscored by the efficacy of anti-VEGF drugs in reducing swelling of the retina and improving vision in patients with DME. Recent prospective, randomized studies have demonstrated the efficacy of intravitreal injections of ranibizumab, a humanized monoclonal antibody that binds all isoforms of VEGF-A.[10,11] Comparable results were reported for bevacizumab, the complete antibody with almost identical binding sites to VEGF-A as ranibizumab, in interventional studies or case series.[12,13]

VEGF Trap-Eye (Regeneron Pharmaceuticals, Inc., Tarrytown, New York, NY, and Bayer Healthcare Pharmaceuticals, Berlin, Germany) is a 115-kDA recombinant fusion protein consisting of the VEGF binding domains of human VEGF receptors 1 and 2 fused to the Fc domain of human immunoglobulin-G1.[14] Animal studies have demonstrated

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ISSN 0161-6420/11/$–see front matter
doi:10.1016/j.ophtha.2011.02.018

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that intravitreal VEGF Trap-Eye has theoretic advantages over ranibizumab and bevacizumab, including a longer half-life in the eye and a higher binding affinity to VEGF-A.[15] In addition, the fusion protein binds placental growth factors 1 and 2, which have been shown to contribute to excessive vascular permeability and retinal neovascularization.[16] A phase 1 study showed that a single intravitreal injection of VEGF Trap-Eye had biologic activity by improving visual acuity and reducing excess retinal thickness in 5 eyes with DME.[17] On the basis of a sound biological rationale and encouraging phase 1 results, a phase 2 multicenter, randomized clinical trial was designed to compare intravitreal VEGF Trap-Eye with standard macular laser treatment after the modified Early Treatment of Diabetic Retinopathy Study (ETDRS) protocol.[18] The primary purpose of the DME and VEGF Trap-Eye: INvestigation of Clinical Impact (DA VINCI) Study was to determine whether different doses and dosing regimens of intravitreal VEGF Trap-Eye are superior to standard macular laser treatment over a 24-week study duration in eyes with DME.

Materials and Methods

The DA VINCI study was designed as a 52-week, multicenter, randomized, double-masked, active-controlled phase 2 clinical study, performed to assess safety and efficacy of VEGF Trap-Eye in comparison with laser photocoagulation. Patients were enrolled at 39 sites throughout the United States, Canada, and Austria in adherence to the tenets of the Declaration of Helsinki. The protocol was approved by the ethics committees at each site, and all participants provided written informed consent. Patients were enrolled between December 2008 and June 2009, and the last patient completed the 24-week primary end point visit in December 2009.

Participants

Consecutive qualifying patients presenting to each clinical site were considered for inclusion. Eligible participants were aged ≥18 years and diagnosed with type 1 or 2 diabetes mellitus, with DME involving the central macula defined as central retinal thickness (CRT) ≥250 μm in the central subfield based on Stratus optical coherence tomography (OCT). Participants were required to have a best-corrected visual acuity (BCVA) letter score at 4 m of 73 to 24 (Snellen equivalent: 20/40–20/320) measured by the ETDRS protocol.[19] Further, women of childbearing potential were included only if they were willing to not become pregnant and to use a reliable form of birth control during the study period.

Potential participants were excluded if any of the following criteria were met in the study eye: history of vitreoretinal surgery; panretinal or macular laser photocoagulation or use of intraocular or periocular corticosteroids or anti-angiogenic drugs within 3 months of screening; vision decrease due to causes other than DME; proliferative diabetic retinopathy (unless regressed and currently inactive); ocular inflammation; cataract or other intraocular surgery within 3 months of screening, laser capsulotomy within 2 months of screening; aphakia; spherical equivalent of >-8 diopters; or any concurrent disease that would compromise visual acuity or require medical or surgical intervention during the study period. In addition, patients were ineligible if any of the following criteria were met in either eye: active iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula; visually significant vitreomacular traction or epiretinal membrane evident biomicroscopically or on OCT; history of idiopathic or autoimmune uveitis; structural damage to the center of the macula that is likely to preclude improvement in visual acuity after the resolution of macular edema; uncontrolled glaucoma or previous filtration surgery; infectious blepharitis, keratitis, scleritis, or conjunctivitis; or current treatment for serious systemic infection. Further, the following systemic exclusion criteria were imposed: uncontrolled diabetes mellitus; uncontrolled hypertension; history of cerebral vascular accident or myocardial infarction within 6 months; renal failure requiring dialysis or renal transplant; pregnancy or lactation; history of allergy to fluorescein or povidone iodine; only 1 functional eye (even if the eye met all other entry criteria); or an ocular condition in the fellow eye with a poorer prognosis than the study eye.

Treatment Groups

Patients were randomly assigned in a 1:1:1:1:1 ratio to 1 of 5 treatment regimens in 1 eye only: 0.5 mg VEGF Trap-Eye every 4 weeks (0.5q4); 2 mg VEGF Trap-Eye every 4 weeks (2q4); 2 mg VEGF Trap-Eye for 3 initial monthly doses and then every 8 weeks, (2q8); 2 mg VEGF Trap-Eye for 3 initial monthly doses and then on an as-needed (PRN) basis (2 PRN); or macular laser treatment by the modified ETDRS protocol.[19] Treatment groups were assigned on the basis of a predetermined randomization scheme. Patients in the laser arm received sham injections at each visit. In addition, patients in the 2q8 arm and 2 PRN arm received sham injections during visits in which an active dose was not given. VEGF Trap-Eye was administered by intravitreal injection via a prespecified protocol, using a 30-G needle. Post-treatment topical antibiotics were used at the discretion of individual investigators. Laser photocoagulation was applied using the modified ETDRS technique[19] with the baseline treatment applied at week 1. After topical anesthesia and placement of a contact lens, all areas of diffuse leakage associated with retinal thickening received grid therapy using laser wavelengths within the green to yellow spectrum, of 50 μm size and 0.05 to 0.1 second duration, spaced approximately 2 burn widths apart. Focal laser therapy to leaking microaneurysms within the areas of retinal thickening was similarly applied. All patients in the VEGF Trap-Eye groups received sham laser treatment at the week 1 visit, which was administered using the above procedure, with the laser remaining in the off position.

Retreatment Criteria

Patients in the VEGF Trap-Eye 2 PRN group were eligible for retreatment no more often than once every 4 weeks after the initial 3-month dosing phase if any of the following criteria were met: OCT CRT ≥250 μm; increase of >50 μm CRT compared with lowest previous measurement; loss of ≥5 letters from the previous BCVA measurement with any increase in CRT on OCT; or increase of ≥5 letters in BCVA between current and most recent visit. Patients in the laser photocoagulation group were eligible for laser retreatment no more often than once every 16 weeks beginning at week 16 if any of the following criteria were met: thickening of the retina at or within 500 μm of the center of the macula; hard exudates at or within 500 μm of the center of the macula, if associated with thickening of adjacent retina; or a zone or zones of retinal thickening ≥1 disc area, any part of which is within 1 disc diameter of the center of the macula. To maintain participant masking, sham injections were performed on visits when an active dose was not given, and a sham laser was given to the VEGF Trap-Eye groups at week 1. Study drug and sham injections and laser and sham laser treatments were performed by an unmasked physician who had no other role in the study except to assess adverse events (AEs) immediately posttreatment. Sham injections

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followed the active treatment protocol with the exception that no needle was attached to the syringe, and the syringe hub was gently applied to the sclera to mimic an injection. Sham laser consisted of placing a contact lens on the study eye and positioning the patient in front of the laser machine for the approximate duration of a laser treatment.

Evaluations

The schedule of study visits and interventions through the primary end point visit of 24 weeks is shown in Figure 1. After a screening visit to obtain informed consent and determine eligibility, participants attended a baseline visit during which they underwent a standardized refraction and determination of BCVA, examination of the anterior and posterior segments, determination of intraocular pressure (IOP), and OCT using the Stratus OCT with software version 3.0 or higher (Carl Zeiss Meditec, Jena, Germany); these evaluations were repeated at all postrandomization visits. Participants were then randomized to study treatment as described previously. Fundus photography and fluorescein angiography were performed according to clinic procedures at baseline, week 12, and week 24. Patients randomized to VEGF Trap-Eye received the first injection at this visit (and patients randomized to laser photocoagulation received a sham injection). One week later, patients randomized to laser photocoagulation received the first laser treatment (and patients randomized to VEGF Trap-Eye received sham laser treatment). At each subsequent visit, scheduled every 4 weeks for 24 weeks, patients received either active or sham VEGF Trap-Eye injection. Laser retreatment was administered to patients in the laser group no more often than every 16 weeks based on retreatment criteria, and patients who met retreatment criteria received an active laser retreatment 1 week after the scheduled visit at which the need for retreatment was identified. A safety assessment was conducted by telephone 3 days after every study drug or sham injection. In addition, AEs were solicited at each study visit. Laboratory samples for hematology and chemistry panel, and hemoglobin A1c were drawn at baseline and weeks 12 and 24.

End Points

The primary end point of this trial was the mean change in BCVA from baseline to the week 24 visit. Secondary end points included the proportion of patients who gained at least 15 ETDRS letters in BCVA compared with baseline at week 24, the change from baseline in CRT (assessed by OCT) at week 24, and the number of focal laser treatments received.

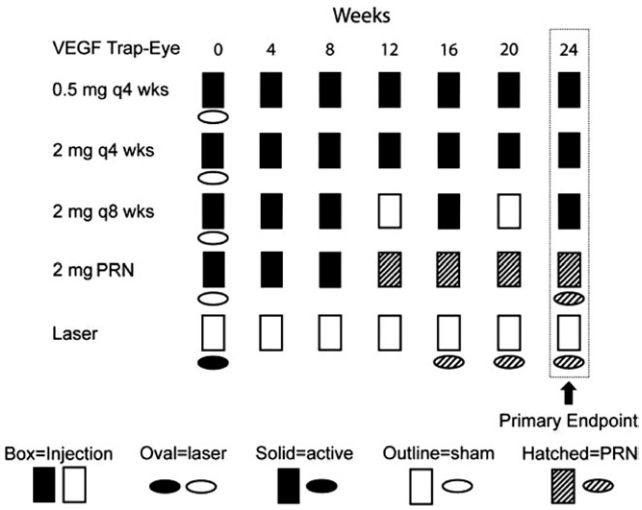

Figure 1. Study design showing schedule of visits and interventions through the primary end point visit of 24 weeks. PRN = as needed; q = every; VEGF = vascular endothelial growth factor.

Statistical Analysis

An analysis of covariance model was used for the evaluation of the primary end point, including baseline BCVA as a covariate and treatment effect as a fixed factor, and comparisons of each VEGF Trap-Eye group with the laser treatment group were performed using linear contrasts. Hochberg's method was used to adjust for multiple comparisons with an overall type 1 error rate (α) of 5%.[20] Changes from baseline to week 24 in CRT were evaluated using an analysis of covariance model with baseline retinal thickness as a covariate. Other secondary end points, as well as demographic, baseline, and safety data, were evaluated using summary statistics. Efficacy analysis was based on the full analysis data set, which included all randomized patients who received any study medication, had baseline assessments, and had at least 1 postbaseline assessment. Safety analysis was based on the safety data set, which included all patients receiving study treatment. Missing data were accounted for in the analyses using the last observation carried forward approach. A sample size of 200 patients (40 per group) was determined to provide 84% power to detect an 8-letter difference between each of the 4 VEGF Trap-Eye groups and the laser group, assuming a standard deviation of 10 letters per group, with a 2-sided t test at an α level 5%/4=0.0125.

Results

Subject Disposition and Demographics

Overall, 221 patients with DME were enrolled and randomized, and 200 completed the study (Table 1, available at http://aaojournal.org). Two randomized patients did not receive treatment and 19 patients discontinued the study after receiving at least 1 treatment for the following reasons: lost to follow-up (6 patients), withdrew consent (6 patients), death (3 patients), treatment failures (2 patients), AE (1 patient), and protocol deviation (1 patient). Discontinuations were evenly distributed among the 5 treatment groups. Demographic information and baseline characteristics are given in Table 2. The groups were generally similar, although the VEGF Trap-Eye 2q8 group had higher prevalences of type 1 diabetes and history of proliferative diabetic retinopathy (regressed at baseline) compared with the other groups. In addition, a history of any cardiac disease was twice as common in the VEGF Trap-Eye groups compared with the laser group.

Visual Acuity

Baseline values of mean visual acuity by treatment group are given in Table 2. Patients in the 4 VEGF Trap-Eye groups experienced mean visual acuity gains from baseline to week 24 ranging from 8.5 to 11.4 letters compared with only 2.5 letters in the laser photocoagulation group (Fig 2). The change in BCVA from baseline to week 24 was statistically significantly greater in each VEGF Trap-Eye group compared with the laser group (P = 0.0085). The study was not powered to detect differences among the VEGF Trap-Eye treatment groups, and no statistically significant differences were observed.

At week 24, up to 34% of VEGF Trap-Eye–treated patients gained ≥15 letters from baseline, up to 64% gained ≥10 letters

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Table 2. Demographics and Baseline Characteristics

	Laser n=44	VEGF Trap-Eye Treatment Groups			
		0.5q4 (n=44)	2q4 (n=44)	2q8 (n=42)	2PRN (n=45)
Age (yrs), mean ± SD	64.0±8.1	62.3±10.7	62.1±10.5	62.5±11.5	60.7±8.7
Gender, n (%) female	17 (38.6%)	20 (45.5%)	17 (38.6%)	20 (47.6%)	16 (35.6%)
Ethnicity, n (%)					
White (non-Hispanic)	30 (68.2%)	28 (63.6%)	26 (59.1%)	33 (78.6%)	28 (62.2%)
White Hispanic	8 (18.2%)	13 (29.5%)	15 (34.1%)	3 (7.1%)	13 (28.9%)
Black	4 (9.1%)	3 (6.8%)	1 (2.3%)	2 (4.8%)	1 (2.2%)
Asian	1 (2.3%)	0	0	1 (2.4%)	2 (4.4%)
Other	1 (2.3%)	0	2 (4.5%)	1 (2.4%)	1 (2.2%)
Diabetes, n (%)					
Type 1	5 (13.6%)	1 (2.3%)	3 (6.8%)	4 (9.5%)	2 (4.4%)
Type 2	39 (88.6%)	43 (97.7%)	41 (93.2%)	38 (90.5%)	43 (95.6%)
HbA1c, mean ± SD	7.93±1.84	8.10±1.91	8.08±1.94	7.85±1.72	7.97±1.71
Baseline cardiac history, n (%)	8 (18.2%)	21 (47.7%)	15 (34.1%)	18 (42.9%)	15 (33.3%)
ETDRS BCVA, mean ± SD	57.6±12.5	59.3±11.2	59.9±10.1	58.8±12.2	59.6±11.1
CRT (μm), mean ± SD	440.6±145.4	426.1±128.3	456.6±135.0	434.8±111.8	426.6±152.4
Diabetic retinopathy Severity score (1–5), n (%)					
None (1)	1 (2.3%)	0	3 (6.8%)	0	0
Mild (2)	1 (2.3%)	2 (4.5%)	4 (9.1%)	3 (7.1%)	5 (11.1%)
Moderate (3)	29 (65.9%)	20 (45.5%)	25 (56.8%)	21 (50.0%)	25 (55.6%)
Severe (4)	12 (27.3%)	20 (45.5%)	11 (25.0%)	11 (26.2%)	14 (31.1%)
Proliferative (regressed) (5)	1 (2.3%)	2 (4.5%)	1 (2.3%)	7 (16.7%)	1 (2.2%)
Previous treatment, n (%)					
Laser (focal grid)	22 (50.0%)	21 (47.7%)	23 (52.3%)	28 (66.7%)	26 (57.8%)
Anti-VEGF (RBZ, BEV, PEG)	10 (22.7%)	5 (11.4%)	10 (22.7%)	6 (14.3%)	6 (13.3%)
Steroids (TRI, DEX)	12 (27.3%)	8 (18.2%)	7 (15.9%)	10 (23.8%)	9 (20.0%)

0.5q4 = 0.5 mg every 4 weeks; 2q4 = 2 mg every 4 weeks; 2q8 = 2 mg for 3 initial doses then every 8 weeks; 2 PRN = 2 mg for 3 initial doses then as needed; BCVA = best-corrected visual acuity; BEV = bevacizumab; CRT = central retinal thickness; DEX = dexamethasone; ETDRS = Early Treatment of Diabetic Retinopathy Study; HbA_{1c} = hemoglobin A_{1c}; PEG = pegaptanib; PRN = as needed; RBZ = ranibizumab; TRI = triamcinolone; SD = standard deviation; VEGF = vascular endothelial growth factor.

from baseline, and up to 93% of patients gained ≥0 letters from baseline, compared with only 21%, 32%, and 68% in the laser group, respectively (Fig 3). Conversely, 9.1% of patients in the laser group and 4.5% of patients treated with 0.5 mg VEGF Trap-Eye lost ≥15 letters at week 24, whereas no patients in any of the 2 mg VEGF Trap-Eye groups experienced such vision loss at this time point. Figure 4 (available at http://aaojournal.org) illustrates BCVA changes for each individual patient in each treatment group. Few patients in the VEGF Trap-Eye groups,

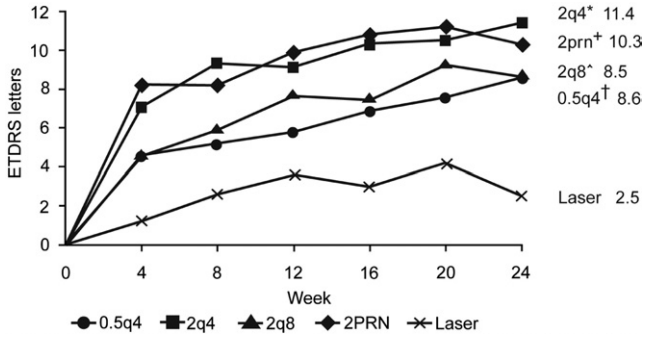

Figure 2. Mean changes in BCVA by treatment groups (laser and VEGF Trap-Eye). Last observation carried forward analysis; n=44 (laser; VEGF Trap-Eye 0.5q4, 2q4); n=42 (VEGF Trap-Eye 2q8); n=45 (VEGF Trap-Eye 2PRN). Difference between each treatment versus laser analysis of covariance: *$P < 0.0001$; +$P=0.0004$; ^$P=0.0085$; †$P=0.0054$. Differences among the VEGF-Trap-Eye treatment arms were not significant. Treatment groups are defined as follows: 0.5q4 = 0.5 mg every 4 weeks; 2q4 = 2 mg every 4 weeks; 2q8 = 2 mg for 3 initial doses then every 8 weeks; 2PRN = 2 mg for 3 initial doses then as needed. ETDRS = Early Treatment of Diabetic Retinopathy Study; 2 PRN = as needed; q = every; VEGF = vascular endothelial growth factor.

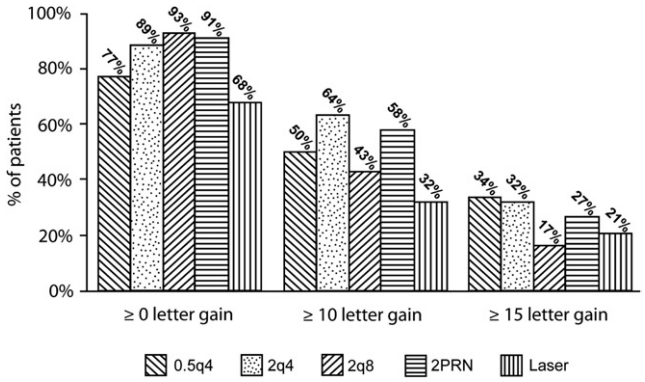

Figure 3. Percentage of patients with changes in BCVA at 6 months by treatment groups (laser and VEGF-Trap-Eye). Last observation carried forward analysis; n=44 (laser; VEGF Trap-Eye 0.5q4, 2q4); n=42 (VEGF Trap-Eye 2q8); n=45 (VEGF Trap-Eye 2PRN). Treatment groups are defined as follows: 0.5q4 = 0.5 mg every 4 weeks; 2q4 = 2 mg every 4 weeks; 2q8 = 2 mg for 3 initial doses then every 8 weeks; 2 PRN = 2 mg for 3 initial doses then as needed. BCVA = best-corrected visual acuity; PRN = as needed; q = every.

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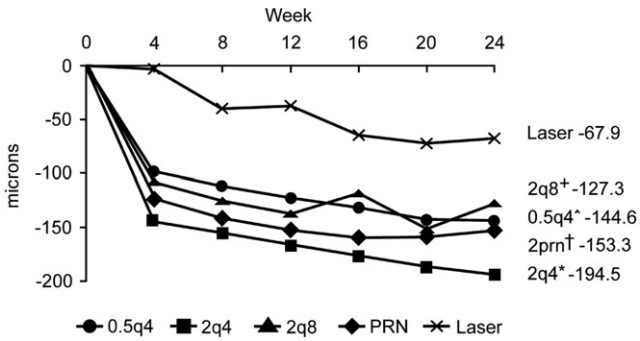

Figure 5. Mean change in CRT by treatment groups (laser and VEGF-Trap-Eye). Last observation carried forward analysis; n=44 (laser; VEGF-Trap-Eye 0.5q4, 2q4); n=42 (VEGF-Trap-Eye 2q8); n=45 (VEGF-Trap-Eye 2PRN). Difference between each treatment versus laser analysis of covariance: *$P < 0.0001$; +$P=0.0066$; ^$P=0.0002$; †$P < 0.0001$. Differences among the VEGF-Trap-Eye treatment arms were not significant. PRN = as needed; q = every.

particularly the groups receiving 2 mg doses, experienced any loss of vision.

Central Retinal Thickness

Baseline values of mean CRT by group are given in Table 2. Reductions in CRT in each group were consistent with the observed improvements in visual acuity. Patients in the 4 VEGF Trap-Eye groups experienced mean reductions in CRT ranging from 127.3 to 194.5 μm by week 24 compared with only 67.9 μm in the laser photocoagulation group (Fig 5). The reduction in CRT in each VEGF Trap-Eye group was statistically significant when compared with the laser group ($P = 0.0066$).

Treatment Exposure

Patients in the VEGF Trap-Eye 0.5q4 and 2q4 treatment groups were scheduled to receive a total of 6 monthly injections by week 24, and received a mean of 5.6 (range 1–6) and 5.5 (range 1–6) injections, respectively. Patients in the VEGF Trap-Eye 2q8 group received a mean of 3.8 (range 1–4) of 4 planned injections. Patients in the VEGF Trap-Eye 2 PRN group were scheduled to receive 3 monthly injections followed by up to 3 PRN injections based on prespecified retreatment criteria. Patients in this group received a mean of 1.5 (range 0–3) of the 3 possible PRN injections, for a mean total of 4.4 (range 1–6) of up to 6 possible injections by week 24. Patients in the laser group received laser treatment at baseline and were eligible for up to 1 additional laser treatment by week 24; patients in this group received a mean of 1.7 (range 1–3) laser treatments by week 24. According to the protocol, only 2 laser treatments were allowed for patients in the laser arm during the first 6 months of the study. However, 1 patient received 3 laser treatments during this period.

Safety

Ocular AEs in patients treated with VEGF Trap-Eye were generally consistent with those seen with other intravitreal anti-VEGF agents and typical of those seen with intravitreal injections. The most frequent ocular AEs are listed in Table 3. Conjunctival hemorrhage was the most common, occurring in 18.9% of VEGF Trap-Eye–treated eyes and 18.2% of laser-treated eyes. Other common AEs included eye pain, ocular hyperemia, and vitreous floaters, all of which were seen at approximately equal rates in both the VEGF Trap-Eye and laser groups. Two patients had endophthalmitis in the study eye, 1 each in the 2q4 and 2 PRN arms. One case was culture negative, and the other was positive for *Staphylococcus epidermidis*. One patient in the 0.5q4 arm had a diagnosis of uveitis, which was treated as endophthalmitis. Seventeen patients (9.7%) in the VEGF Trap-Eye groups had AEs of increased IOP, none of which were reported as serious. All of these events occurred immediately after intravitreal injection, and IOP normalized within 1 hour. Topical IOP-lowering medications were administered in all but 1 case. One patient in the laser arm had an AE of increased IOP that did not require treatment.

Systemic AEs are given in Table 4. Four patients had serious AEs of hypertension (1 in the VEGF Trap-Eye 0.5q4 group and 3 in the VEGF Trap-Eye 2q4 group), all of whom had a medical history of hypertension. Three patients had arterial thromboem-

Table 3. Ocular Adverse Events Occurring in More Than 5% of Subjects and All Serious Ocular Adverse Events by Treatment Group, n (%)

	Laser n=44	VEGF Trap-Eye Treatment Groups				All VEGF Trap-Eye n=175
		0.5q4 (n=44)	*2q4 (n=44)*	*2q8 (n=42)*	*2PRN (n=45)*	
Adverse events						
Conjunctival hemorrhage	8 (18.2%)	8 (18.2%)	5 (11.4%)	11 (26.2%)	9 (20.0%)	33 (18.9%)
IOP increased	1 (2.3%)	5 (11.4%)	6 (13.6%)	4 (9.5%)	2 (4.4%)	17 (9.7%)
Eye pain	2 (4.5%)	3 (6.8%)	4 (9.1%)	3 (7.1%)	5 (11.1%)	15 (8.6%)
Ocular hyperemia	2 (4.5%)	4 (9.1%)	1 (2.3%)	3 (7.1%)	3 (6.7%)	11 (6.3%)
Vitreous floaters	2 (4.5%)	4 (9.1%)	2 (4.5%)	2 (4.8%)	1 (2.2%)	9 (5.1%)
Serious AEs						
Endophthalmitis	0	0	1 (2.3%)	0	1 (2.2%)	2 (1.1%)
Uveitis	0	1 (2.3%)	0	0	0	1 (0.6%)
Diabetic retinal edema	1 (2.3%)	0	0	0	0	0
Visual acuity reduced	1 (2.3%)	0	0	0	0	0
Vitreous hemorrhage	1 (2.3%)	0	0	0	0	0
Corneal abrasion	0	0	0	1 (2.4%)	0	1 (0.6%)
Retinal tear	0	0	0	1 (2.4%)	0	1 (0.6%)

0.5q4 = 0.5 mg every 4 weeks; 2q4 = 2 mg every 4 weeks; 2q8 = 2 mg for 3 initial doses then every 8 weeks; 2 PRN = 2 mg for 3 initial doses then as needed; AEs = adverse events; IOP = intraocular pressure; PRN = as needed; VEGF = vascular endothelial growth factor.

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Table 4. Key Systemic Adverse Events and Deaths by Treatment Group, n (%)

	Laser n=44	VEGF Trap-Eye treatment groups				All VEGF Trap-Eye n=175
		0.5q4 (n=44)	*2q4 (n=44)*	*2q8 (n=42)*	*2PRN (n=45)*	
Hypertension	3 (6.8%)	4 (9.1%)	7 (15.9%)	2 (4.8%)	4 (8.9%)	17 (9.7%)
Myocardial infarction	0	1 (2.3%)	1 (2.3%)	0	0	2 (1.1%)
Cerebrovascular accident	0	1 (2.3%)	1 (2.3%)	0	0	2 (1.1%)
Death	0	1 (2.3%)	1 (2.3%)	1 (2.4%)	0	3 (1.7%)

Treatment groups are defined as follows: 0.5q4 = 0.5 mg every 4 weeks; 2q4 = 2 mg every 4 weeks; 2q8 = 2 mg for 3 initial doses then every 8 weeks; 2 PRN = 2 mg for 3 initial doses then as needed. PRN = as needed; VEGF = vascular endothelial growth factor.

bolic events. One patient had a cerebral vascular accident in the VEGF Trap-Eye 0.5q4 group. One patient had a myocardial infarction in the VEGF Trap-Eye 0.5q4 group. Although the infarction was not fatal, it was immediately followed by surgical intervention, and the patient died of multiorgan failure; in addition to diabetes, this patient had a history of coronary artery disease, hypertension, and hypercholesterolemia. One patient experienced a cerebrovascular event and a silent myocardial infarction on the same day in the VEGF Trap-Eye 2q4 group; in addition to diabetes, this patient had a history of hypertension and hypercholesterolemia.

In this study of diabetic patients, there were 3 deaths over the first 24 weeks. One patient in the VEGF Trap-Eye 2q8 group, with a history of hypertension, seizures, and evidence of impaired renal function on baseline laboratory examinations, died of renal failure. One patient (described above) in the VEGF Trap-Eye 0.5q4 group, with a history of cardiac disease, died of multiorgan failure a few days after experiencing a myocardial infarction. One patient in the 2q4 group, with a history of cardiac disease, chronic obstructive pulmonary disease, peripheral vascular disease, kidney disease, hypercholesterolemia, and hypertension, experienced "sudden death." Many of the systemic AEs observed may be attributable in part to the underlying diabetic morbidity and cardiovascular comorbidities of the patients.

Discussion

In this phase 2 randomized clinical trial, intravitreal VEGF Trap-Eye was superior to macular laser treatment by the modified ETDRS protocol, the current clinical standard, for the treatment of DME over a 24-week period. VEGF Trap-Eye resulted in significantly better mean visual acuity outcomes (+8.5 to +11.4 letters gained) and greater mean reductions in retinal thickness (−127.3 to −194.5 μm) compared with laser alone. Moreover, the different doses (0.5 or 2 mg) and dosing regimens (given every 4 weeks, every 8 weeks, or on a PRN basis) of VEGF Trap-Eye were all individually superior to laser and resulted in statistically significant increases in visual acuity and reductions in retinal thickness at week 24. When individual patient outcomes are considered, the 2 mg dose of VEGF Trap-Eye almost completely eliminated vision loss at all dosing intervals (Fig 4, available at http://aaojournal.org). In addition, there did not seem to be substantial differences among the 4 VEGF Trap-Eye groups in terms of functional or morphologic outcomes, although the current study was not powered to detect differences between VEGF Trap-Eye groups.

The current study's results are consistent with the results of prior studies. A recently reported trial comparing laser, ranibizumab, and triamcinolone alone or in combination revealed a mean change of visual acuity of approximately +9 letters after 12 months in the ranibizumab groups with either prompt or deferred laser versus +3 letters in the laser-only group.[11] Similarly, in the RESOLVE phase 2 trial, the mean increase of visual acuity over 1 year was 7.8 letters with monthly ranibizumab treatment (Invest Ophthalmol Vis Sci 51[Suppl]: 5841). Comparable results were also achieved in the READ-2 study (+7.2 letters after 6 months in the ranibizumab monotherapy group; −0.4 letters after 6 months in the laser group).[10] Results from case series with bevacizumab reflect visual acuity changes of the same magnitude.[21] Despite the fact that each of these studies had differences in protocol design and study population, they are remarkably consistent with each other and with the current study's findings. A possible limitation of this study's findings is that study subjects were allowed to have received prior laser treatment up to 3 months before screening, and it is not known whether they may have perceived a difference between the sham and the true laser. However, it is unlikely that this knowledge would affect the primary and secondary outcomes of this clinical trial. These studies in conjunction with this short-term study provide evidence in support of the hypothesis that anti-VEGF therapy is in general superior to laser therapy in diabetic patients with DME. However, the long-term consequences of these anti-VEGF therapies for DME in diabetic patients remain undefined.

VEGF Trap-Eye differs from current monoclonal antibodies and antibody fragments that block VEGF-A in that it binds VEGF-A more tightly than its native receptors in a strict 1:1 fashion and also binds other VEGF family members, such as placental growth factor. The DA VINCI study provides some insight into the potential clinical impact of these specific properties because the study design included various dosing regimens. In the 2Q8 and 2 PRN arms, the treatment interval for VEGF Trap-Eye administration was prolonged after the loading phase without a trade-off in efficacy, because all VEGF Trap-Eye–treated groups manifested comparable gains in visual acuity versus baseline. The 2Q8 group appeared to have less improvement in BCVA than the other 2 mg groups, but because this difference was manifest at 4 weeks, it is unlikely to be related to

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dosing interval and more likely attributable to differences among the treatment groups at baseline; such effects in phase 2 studies are not unexpected given the typically smaller sample sizes for such studies. In fact, the 2Q8 group had a higher proportion of patients with a history of proliferative diabetic retinopathy, potentially indicating greater ischemia, which may account for the observed numeric difference in BCVA outcome for this group.

In this study, there were no significant safety signals to suggest that VEGF inhibition using VEGF Trap-Eye is associated with an increased risk of systemic side effects, such as arterial thrombotic events or increased risk of mortality. Three patients randomized to VEGF Trap-Eye experienced arterial thromboembolic events. Despite the randomization, there was an imbalance in the baseline history of cardiac disease, with patients randomized to VEGF Trap-Eye having approximately 2 times the prior incidence than those randomized to laser (39.4% vs. 18.2%). This comorbid history may contribute to the higher rate of arterial thrombotic events seen in the VEGF Trap-Eye group. There were 3 deaths among the patients randomized to VEGF Trap-Eye; this equates to a 6-month rate of 0.0028 deaths per person-month among all 4 VEGF Trap-Eye groups, which compares favorably to the 8-month rate of 0.0034 deaths per person-month (19 deaths among 693 patients) reported in a recent trial in diabetic patients of laser versus intravitreal triamcinolone for DME.[22] Each of the patients received a different dose of VEGF Trap-Eye, so there seemed to be no dose-dependent risk of death. The results are consistent with mortality rates in a diabetic population, considering that diabetes itself is known to increase the risk of mortality as much as 2- to 4-fold.[23] Because this phase 2 clinical trial was not powered to evaluate the relationship between VEGF inhibition and arterial thrombotic events, cardiovascular events, or mortality, larger clinical trials are needed to investigate whether a true risk exists. This study has insufficient power to fully evaluate potential safety issues. However, at the present time, intravitreal VEGF blockade with VEGF Trap-Eye seems to be a safe treatment in patients with DME with a favorable risk–benefit ratio.

In conclusion, the DA VINCI study demonstrates that intravitreal VEGF Trap-Eye has a statistically significant beneficial effect on visual acuity when compared with macular laser treatment in patients with DME. The results of this clinical trial provide additional support for the hypothesis that VEGF plays an important role in the pathogenesis of DME and suggests that VEGF inhibition may become of increasing importance in future treatment of DME. A prolongation of the retreatment interval from 4 to 8 weeks based on this data and the rationale of the improved binding properties of VEGF Trap-Eye represents an opportunity to potentially reduce the treatment and monitoring burden in antiangiogenic therapy for chronic retinal diseases such as DME.

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Footnotes and Financial Disclosures

Originally received: September 28, 2010.
Final revision: February 9, 2011.
Accepted: February 9, 2011.
Available online: May 5, 2011. Manuscript no. 2010-1342.

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Financial Disclosure(s):
The author (s) have made the following disclosure (s): Diana V. Do: Genentech (financial support), Regeneron Pharmaceuticals (financial support). Ursula Schmidt-Erfuth: Alcon Labs (consultant, lecturer), Bayer Healthcare (consultant, lecturer), Novartis (consultant, lecturer), Regeneron Pharmaceuticals (lecturer), Pfizer (lecturer). Victor H. Gonzalez: Pfizer (consultant, lecturer), Genentech (lecturer), Eyetech (consultant, lecturer), Regeneron (lecturer). Carmelina M. Gordon: Allergan (consultant), Regeneron Pharmaceuticals (lecturer), Novartis (consultant, lecturer). Michael Tolentino: Genentech (consultant, lecturer), Eyetech (consultant, lecturer), Regeneron Pharmaceuticals (consultant, lecturer). Alyson J. Berliner: Regeneron Pharmaceuticals (employee, equity owner). Robert Vitti: Regeneron Pharmaceuticals (employee, equity owner). Rene Rückert: Bayer Schering Pharma (employee). Rupert Sandbrink: Bayer Schering Pharma (employee). David Stein: Regeneron Pharmaceuticals (employee, equity owner). Ke Yang: Regeneron Pharmaceuticals (employee, equity owner). Karola Beckmann: Bayer Schering Pharma (employee). Jeff S. Heier: Genentech (consultant, lecturer), Regeneron Pharmaceuticals (consultant, lecturer), Fovea (consultant).

Funding: Sponsored by Regeneron Pharmaceuticals, Inc., Tarrytown, New York.

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