One-Year Outcomes of the DA VINCI Study of VEGF Trap-Eye in Eyes with Diabetic Macular Edema

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Purpose: To compare different doses and dosing regimens of Vascular Endothelial Growth Factor (VEGF) Trap-Eye with laser photocoagulation in eyes with diabetic macular edema (DME).

Design: Randomized, double-masked, multicenter, phase 2 clinical trial.

Participants: Diabetic patients (n = 221) with center-involved DME.

Methods: Participants were assigned randomly to 1 of 5 treatment regimens: VEGF Trap-Eye 0.5 mg every 4 weeks (0.5q4); 2 mg every 4 weeks (2q4); 2 mg every 8 weeks after 3 initial monthly doses (2q8); or 2 mg dosing as needed after 3 initial monthly doses (2PRN), or macular laser photocoagulation.

Main Outcome Measures: The change in best-corrected visual acuity (BCVA) at 24 weeks (the primary end point) and at 52 weeks, proportion of eyes that gained 15 letters or more in Early Treatment of Diabetic Retinopathy Study (ETDRS) BCVA, and mean changes in central retinal thickness (CRT) from baseline.

Results: As previously reported, mean improvements in BCVA in the VEGF Trap-Eye groups at week 24 were 8.6, 11.4, 8.5, and 10.3 letters for 0.5q4, 2q4, 2q8, and 2PRN regimens, respectively, versus 2.5 letters for the laser group ($P \leq 0.0085$ versus laser). Mean improvements in BCVA in the VEGF Trap-Eye groups at week 52 were 11.0, 13.1, 9.7, and 12.0 letters for 0.5q4, 2q4, 2q8, and 2PRN regimens, respectively, versus −1.3 letters for the laser group ($P \leq 0.0001$ versus laser). Proportions of eyes with gains in BCVA of 15 or more ETDRS letters at week 52 in the VEGF Trap-Eye groups were 40.9%, 45.5%, 23.8%, and 42.2% versus 11.4% for laser ($P = 0.0031$, $P = 0.0007$, $P = 0.1608$, and $P = 0.0016$, respectively, versus laser). Mean reductions in CRT in the VEGF Trap-Eye groups at week 52 were −165.4 μm, −227.4 μm, −187.8 μm, and −180.3 μm versus −58.4 μm for laser ($P < 0.0001$ versus laser). Vascular Endothelial Growth Factor Trap-Eye generally was well tolerated. The most frequent ocular adverse events with VEGF Trap-Eye were conjunctival hemorrhage, eye pain, ocular hyperemia, and increased intraocular pressure, whereas common systemic adverse events included hypertension, nausea, and congestive heart failure.

Conclusions: Significant gains in BCVA from baseline achieved at week 24 were maintained or improved at week 52 in all VEGF Trap-Eye groups. Vascular Endothelial Growth Factor Trap-Eye warrants further investigation for the treatment of DME.

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Diabetic macular edema (DME) is the most common cause of vision loss for patients with diabetes mellitus.[1] The Wisconsin Epidemiologic Study found that the prevalence of macular edema was associated with an increasing duration of diabetes.[2,3] Worldwide, the prevalence of adult diabetes is anticipated to rise from 4.0% in 1995 to 5.4% by 2025.[4] Given this rising prevalence, it is expected that diabetic retinopathy and DME will continue to be common and will be important causes of vision impairment.

The complex pathophysiology of DME has been under investigation in recent years. In individuals with diabetic retinopathy, fluid can accumulate within the retina as a result of a breakdown in the blood–retinal barrier. Hyperglycemia associated with diabetes stimulates an inflammatory response, which causes detrimental effects on the retinal vasculature.[5] Vascular occlusion and ischemia results, and can lead to local hypoxia.[6] Vascular endothelial growth factor (VEGF) and a host of other growth factors are upregulated during hypoxic conditions, and an inflammatory cascade of events can ensue.

Vascular endothelial growth factor is thought to be a key factor in the pathogenesis of DME[5,7] and is a vasoactive cytokine that both induces vascular permeability and stimulates angiogenesis. It is approximately 50 000-fold more potent in inducing permeability than histamine[8–10] and affects endothelial tight junction proteins. Vascular endothelial growth factor is known to cause a breakdown of the blood–retinal barrier, followed by extracellular fluid accumulation and retinal edema.[11]

Vascular endothelial growth factor concentrations are elevated in both the vitreous fluid and aqueous humor of patients with active proliferative diabetic retinopathy.[12,13] One study reported that VEGF concentrations in aqueous humor were elevated nearly 5-fold in DME eyes compared with that of age-matched controls.[14] Another study showed that the VEGF concentrations in the aqueous humor of eyes with DME were 3-fold higher than in the plasma.[12] Moreover, these elevated VEGF levels were correlated significantly with the severity of DME.[12] Elevated VEGF concentrations are associated with extensive macular leakage in diabetic eyes, and numerous studies have shown that VEGF inhibitors are effective for reducing retinal thickness and improving visual acuity.[15–22]

Vascular Endothelial Growth Factor Trap-Eye is a 115-kDA recombinant fusion protein comprising the key VEGF binding domains of human VEGF receptors 1 and 2 fused to the Fc domain of human immunoglobulin G1.[23] Vascular Endothelial Growth Factor Trap-Eye is a panisoform VEGF-A inhibitor whose binding affinity to VEGF is substantially greater than that of either bevacizumab or ranibizumab,[23] leading to a mathematical model predicting it could have substantially longer duration of action in the eye.[24] In addition, VEGF Trap-Eye binds placental growth factors 1 and 2, which have been shown to contribute to excessive vascular permeability and retinal neovascularization.[25]

The phase 2 clinical trial DME And VEGF Trap-Eye: INvestigation of Clinical Impact (DA VINCI) was designed to compare intravitreal VEGF Trap-Eye with macular laser photocoagulation. Results at week 24 (primary end point data) from the current study have been published previously,[26] and all VEGF Trap-Eye arms showed significant gains in visual acuity compared with laser treatment ($P \leq 0.0085$) at week 24. Patients in this study continued with their assigned dosing regimen and continued follow-up to determine if these visual acuity gains were maintained through week 52. The 1-year results are reported here.

Patients and Methods

The DA VINCI study was a randomized, double-masked, active-controlled multicenter phase 2 clinical trial. Thirty-nine sites in the United States, Canada, and Austria participated in the trial, and patients were enrolled between December 2008 and June 2009. The primary objective was to assess the efficacy of various doses and dose intervals of intravitreal VEGF Trap-Eye (aflibercept injection) on BCVA. The primary end point was the change in BCVA from baseline to week 24. Secondary objectives were to assess the effects of intravitreal VEGF Trap-Eye on retinal thickness assessed by optical coherence tomography (OCT) and to assess safety and tolerability of intravitreal VEGF Trap-Eye in eyes with DME. Secondary outcomes were the change in BCVA from baseline at week 52, the proportion of eyes that gained at least 15 ETDRS letters in BCVA compared with baseline at weeks 24 and 52, the change in central retinal thickness (CRT; central subfield on OCT) from baseline to weeks 24 and 52, and the number of focal laser treatments given.

The study protocol was approved by the institutional review board or ethics committee at every institution and was conducted according to the recommendations of Good Clinical Practice and the tenets of the Declaration of Helsinki. The study was compliant with the rules and regulations under the Health Insurance Portability and Accountability Act of 1996. All patients provided written informed consent to participate in the study. The DA VINCI study is registered with ClinicalTrials.gov (NCT00789477).

Participants

The study enrolled adult patients 18 years of age or older with type 1 or 2 diabetes mellitus with clinically significant DME with center involvement of the fovea, defined as a central subfield measurement of 250 μm or more on time-domain OCT (Stratus OCT; Carl Zeiss Meditec, Jena, Germany). In addition, patients had an ETDRS BCVA letter score at 4 m of 73 to 24 (20/40 to 20/320) in the study eye.[27,28] Patients were excluded if any of the following were present in the study eye: history of vitreoretinal surgery, panretinal or macular laser photocoagulation within 3 months of screening, previous use of intraocular or periocular corticosteroids within 3 months of screening, or other ocular disorders that could contribute to vision loss and could confound the study results. In addition, previous treatment with antiangiogenic drugs for either eye (pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) was not allowed within 3 months of screening. Patients with uncontrolled diabetes mellitus or hypertension (systolic blood pressure >180 mmHg or >160 mmHg on 2 consecutive measurements or diastolic blood pressure >100 mmHg on optimal medical regimen) also were excluded from the study.

Treatments

Eyes were assigned randomly using a 1:1:1:1:1 ratio to one of the following treatment regimens (Fig 1): (1) 0.5 mg VEGF Trap-Eye every 4 weeks (0.5q4); (2) 2 mg VEGF Trap-Eye every 4 weeks (2q4); (3) 2 mg VEGF Trap-Eye every 8 weeks after 3 initial monthly doses (2q8); (4) 2 mg VEGF Trap-Eye, with dosing as needed after 3 initial monthly doses (2PRN); (5) laser photocoagulation using a modified ETDRS protocol[27] at baseline and then as needed (but no more frequently than every 16 weeks). Eyes in the laser group also received a sham injection every 4 weeks.

Vascular Endothelial Growth Factor Trap-Eye, provided by Regeneron Pharmaceuticals, Inc (Tarrytown, New York), was administered by intravitreal injection with a 30-gauge needle using standard ophthalmic techniques. Vascular Endothelial Growth Factor Trap-Eye was formulated as a sterile liquid to a final concentration of either 10 mg/ml or 40 mg/ml VEGF Trap-Eye. The injection volume was 50 μl (0.05 ml), which provided the delivery of 0.5 mg or 2 mg of VEGF-Trap-Eye. Sham injections were performed following the identical treatment protocol used for the active injections, but only gentle application of the hub of the syringe (without the needle) to the sclera was used to mimic an injection.

Laser photocoagulation was performed using the modified ETDRS protocol (baseline treatment at week 1).[3,28] After topical anesthesia and placement of a contact lens, grid therapy was applied to the thickened areas of the retina with diffuse leakage, focal therapy, or both being applied to leaking microaneurysms within the areas of retinal thickening. Sham laser treatments 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, while the laser remained in the off position.

Retreatment Criteria

After the 3 initial monthly doses, eyes assigned to the 2PRN arm received an injection of study drug if any one of the following criteria were present: a more than 50-μm increase in CRT com-

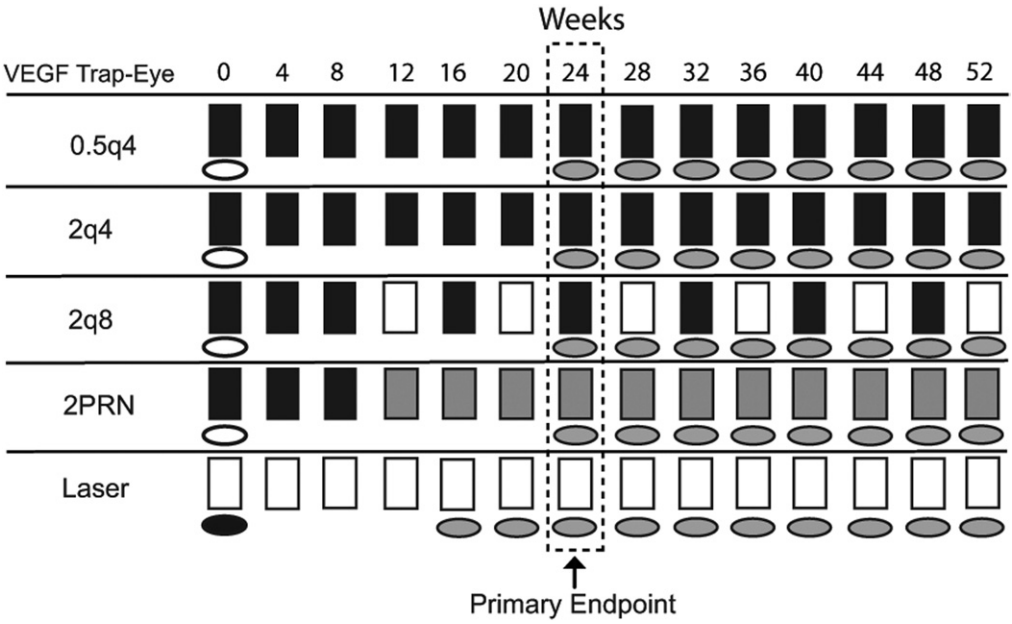

Figure 1. Diagram showing study design with interventions and schedule of visits throughout the course of the 12-month study. 0.5q4 = 0.5 mg every 4 weeks; 2q4 = 2 mg every 4 weeks; 2q8 = 2 mg for 3 initial monthly doses then every 8 weeks; 2PRN = 2 mg for 3 initial monthly doses then as needed; box = injection; grey = as needed; oval = laser; outline = sham; solid = active; VEGF = vascular endothelial growth factor.

pared with the lowest previous measurement; new or persistent cystic retinal changes, subretinal fluid, or persistent diffuse edema of 250 μm or more on OCT; a loss of 5 or more letters of BCVA from the best previous measurement in conjunction with any increase in CRT; and an increase in BCVA between the current and most recent visit of 5 letters or more. Eyes assigned to the 2PRN arm received sham injections if none of the retreatment criteria above were met.

Eyes in the laser photocoagulation arm of the study received their initial laser at week 1 (Fig 1). Starting at week 16, eyes were assessed for retreatment according to the following ETDRS criteria and were retreated if any one of the criteria were met: an increase in retinal thickness 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; zone(s) of retinal thickening 1 disc area or larger (any part of which was within 1 disc diameter of the center of the macula).

Starting at week 24 (month 6), these same three criteria were used to assess eyes in the VEGF Trap-Eye arms for laser rescue. Eyes in the VEGF Trap-Eye arms that met the criteria for laser rescue received laser 1 week after the scheduled visit, which they qualified for laser rescue. Subsequent laser rescue treatments could be performed at 16-week intervals.

Masking

Treatments (study drug injection, sham injection, laser or sham laser photocoagulation) were performed by an unmasked physician. A separate masked physician was assigned to assess adverse events (AEs) and retreatment and rescue criteria and to supervise the masked assessment of efficacy. Every effort was made to ensure that all other study site personnel remained masked to treatment assignment to facilitate an unbiased assessment of efficacy and safety.

Measurements

Visual acuity was measured using the ETDRS protocol.[28] Retinal and lesion characteristics of the study eye were evaluated using time-domain OCT (Zeiss Stratus OCT equipped with software version 3.0 or greater; Carl Zeiss Meditec, Jena, Germany). The study eye was evaluated by dilated funduscopic examination, fundus photography, and fluorescein angiography. The severity of each patient's diabetic retinopathy was assessed using the Diabetic Retinopathy Severity Score.[29] Intraocular pressure of the study eye was measured using Goldmann applanation tonometry (Haag-Streit AG, Köniz, Switzerland) or the Tono-Pen (Reichert Technologies, DePew, New York) before dosing and again approximately 5 to 10 minutes after dosing. Safety assessments included ophthalmic examinations, clinical AEs, laboratory measures, and serum samples for potential development of anti-VEGF Trap-Eye antibodies.

Concomitant Medications

Patients were not allowed to receive any treatment for their DME in the study eye other than the assigned study treatment with VEGF Trap-Eye or laser until week 52 or until the early termination visit assessments were completed.

Statistical Analyses

The full analysis set, which was used for the efficacy analysis, included all randomized patients who received any study medication and had at least 1 assessment after baseline. The safety analysis set, used for all safety and tolerability assessments, included all participants who received any study medication. The last observation carried forward approach was used to account for missing data. A sample size of 200 patients (40 per group) provided 84% power to detect an 8-letter difference between each of the 4 VEGF Trap-Eye arms and the laser arm (assuming a standard

Table 3. Treatment and Exposure Summary for Vascular Endothelial Growth Factor Trap-Eye and Laser Treatments over the Course of the First 48 Weeks

Study Arm	Mean No. of Vascular Endothelial Growth Factor Trap-Eye Injections (SD)	Mean No. of Laser Treatments (SD)
0.5q4 (n = 44)	11.7 (2.49)	0.8 (0.83)
2q4 (n = 44)	10.8 (2.87)	0.5 (0.66)
2q8 (n = 42)	7.2 (1.74)	0.8 (0.86)
2PRN (n = 45)	7.4 (3.19)	0.7 (0.77)
Laser (n = 44)	N/A	2.5 (0.87)

0.5q4 = 0.5 mg every 4 weeks; 2q4 = 2 mg every 4 weeks; 2q8 = 2 mg for 3 initial monthly doses then every 8 weeks; 2PRN = 2 mg for 3 initial monthly doses then as needed; N/A = not applicable; SD = standard deviation.

deviation of 10 letters per group, with a 2-sided *t* test at an α level of 5%/4 = 0.0125). Change from baseline in BCVA and OCT were analyzed using analysis of covariance, models with the baseline value as covariate and the treatment as fixed factor. Hochberg's procedure was used for the primary analysis to control for the multiple comparisons. No adjustments for multiplicity were made for the secondary variables. The proportions of patients in the VEGF Trap-Eye arms gaining 10 letters or more (15 letters or more) were compared with the laser arm using the Fisher exact test. Other secondary end points, as well as demographic, baseline, and safety data, were evaluated using summary statistics.

Results

Patient Disposition and Demographics

A total of 221 eyes were randomized, 219 were treated, and 176 completed the 52-week study (Table 1, available at http://aaojournal.org). Forty-three patients discontinued the study after receiving at least 1 treatment for the following reasons: lost to follow-up (n = 11), withdrew consent (n = 11), death (n = 6), treatment failures (n = 2), AE (n = 7), protocol deviation (n = 2), other (n = 4). Discontinuations were distributed evenly among all the treatment groups. Demographic information and baseline characteristics are provided in Table 2 (available at http://aaojournal.org). The groups generally were similar, although the VEGF Trap-Eye 2q8 group had a higher prevalence of proliferative diabetic retinopathy (regressed at baseline) compared with the other treatment groups. In addition, a history of cardiac disease was more common in the VEGF Trap-Eye groups compared with the laser group.

Treatment and Exposure Summary

Over the 52 weeks of the study, the mean number of VEGF Trap-Eye injections administered was similar to the number of required injections for the group (Table 3). The VEGF Trap-Eye groups received an average of less than 1 laser treatment between month 6 and month 12 (up to 2 laser treatments were allowed from week 24 to week 48). For the laser treatment group, the mean number of laser treatments was 2.5 (up to 4 laser treatments were allowed from baseline to week 48).

Efficacy

Treatment with VEGF Trap-Eye produced statistically significant improvements in BCVA in all treatment groups compared with laser at both week 24 (the primary outcome) and week 52 (week 52, $P<0.001$; Fig 2).[27] The ranges of improvement were +8.5 to +11.4 letters at week 24 and +9.7 to +13.1 letters at week 52. No significant differences were observed among the VEGF Trap-Eye treatment groups. Waterfall plots displaying BCVA changes for individual eyes indicate that few patients in the VEGF Trap-Eye groups experienced any loss of vision (Fig 3). At week 52, the proportion of eyes that gained 15 letters or more was statistically greater ($P\leq0.001$) than that in the laser treatment group in all VEGF Trap-Eye groups except 2q8 (Fig 4). The percentages of eyes that gained 10 letters or more were 57%, 71%, 45%, 62%, and 30%, for the 0.5q4, 2q4, 2q8, 2PRN, and the laser groups, respectively.

Eyes treated with each VEGF Trap-Eye dosing regimen experienced statistically significant reductions in CRT compared with eyes undergoing laser treatment (week 52, $P < 0.0001$; Fig 5). For eyes on the VEGF Trap-Eye treatment regimens, CRT continued to decrease through week 52.

For each study eye, baseline diabetic retinopathy severity was recorded using the Diabetic Retinopathy Severity Score (Table 2, available at http://aaojournal.org). At week 52, 40%, 31%, 64%, and 32% of the 0.5q4, 2q4, 2q8, and 2PRN VEGF Trap-Eye groups, respectively, had an improvement in their Diabetic Retinopathy Severity Score compared with 12% in the laser group. In addition, eyes treated with VEGF Trap-Eye were less likely to have worsening of their Diabetic Retinopathy Severity Score compared with laser-treated eyes (0%, 13%, 0%, and 14% in the 0.5q4, 2q4, 2q8, and 2PRN VEGF Trap-Eye groups and 24% in the laser group).

Safety

Vascular Endothelial Growth Factor Trap-Eye was well tolerated, and the most common ocular AEs that occurred were typical of those associated with intravitreal injections (Table 4, available at http://aaojournal.org). The most frequent were conjunctival hemorrhage, eye pain, increased intraocular pressure, ocular hyperemia, cataract, and vitreous floaters. Approximately 11% of patients treated with VEGF Trap-Eye experienced an AE of increased intraocular pressure immediately after the intravitreal injection; however, only 2 of these patients had an increase of more than 10 mmHg. Two patients who were randomized to

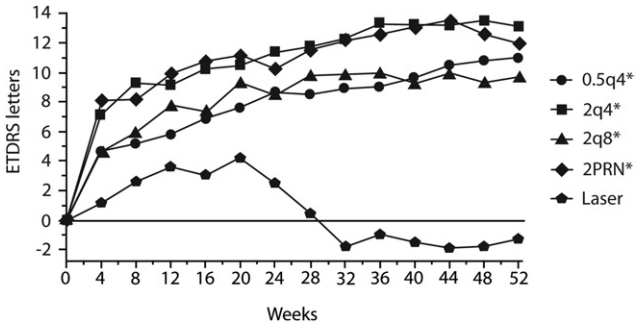

Figure 2. Graph showing mean changes in best-corrected visual acuity letter score by treatment groups (laser and Vascular Endothelial Growth Factor [VEGF] Trap-Eye) using last observation carried forward analysis: n = 44 (laser; VEGF Trap-Eye 0.5 mg every 4 weeks [0.5 q4] and 2 mg every 4 weeks [2q4]); n = 42 (VEGF Trap-Eye 2 mg for 3 initial monthly doses then every 8 weeks [2q8]); n = 45 (VEGF Trap-Eye 2 mg for 3 initial monthly doses then as needed [2PRN]). Difference between each treatment versus laser at week 52 was assessed using an analysis of covariance. *$P < 0.0001$. ETDRS = Early Treatment Diabetic Retinopathy Study.

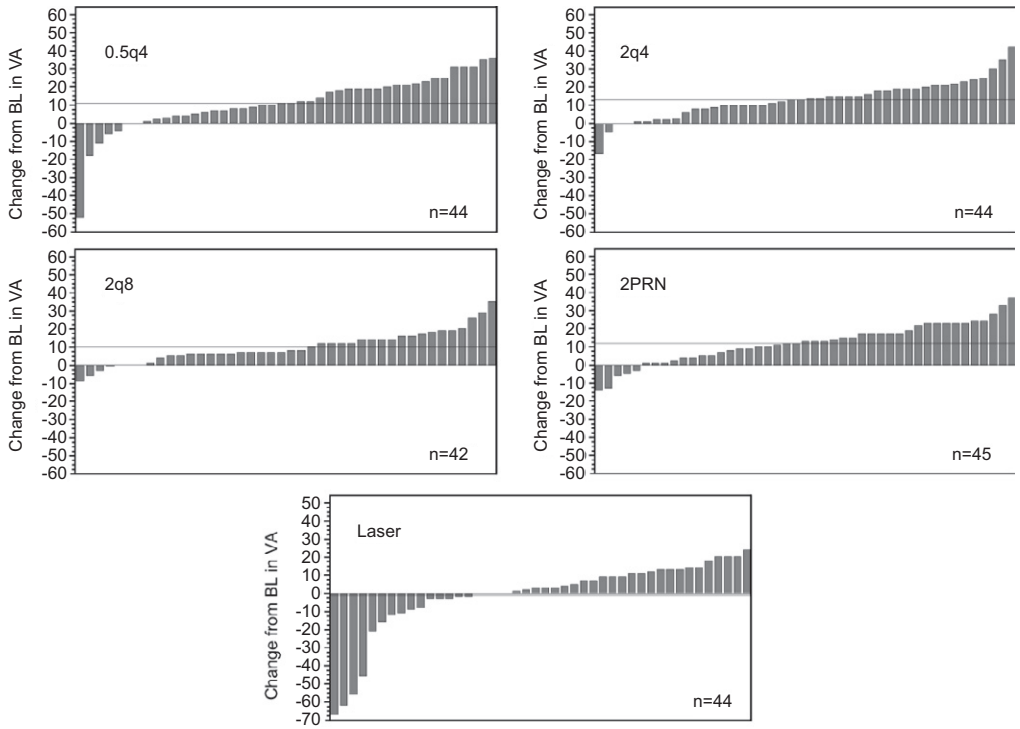

Figure 3. Graphs showing individual changes in best-corrected visual acuity (BCVA) letter score by treatment groups (laser and Vascular Endothelial Growth Factor Trap-Eye). Each bar corresponds to an individual patient. Dotted line represents median BCVA. 0.5q4 = 0.5 mg every 4 weeks; 2q4 = 2 mg every 4 weeks; 2q8 = 2 mg for 3 initial monthly doses then every 8 weeks; 2PRN = 2 mg for 3 initial monthly doses then as needed; BL = baseline; PRN = as needed; VA = visual acuity.

VEGF Trap-Eye experienced injection-related endophthalmitis, and uveitis developed in 1 patient. Serious nonocular AEs were infrequent in all treatment groups (Table 5). The most common systemic AEs were hypertension, nausea, and congestive heart failure. Because of its limited sample size, this phase 2 study was not powered adequately to assess the significance of differences in AEs among the treatment arms.

Seven deaths occurred during the study. One patient in the laser group died of cardiac arrest. One patient in the 0.5q4 group died of multiorgan failure. Three patients in the 2q4 group died: one of cerebral infarction, another from non–small-cell lung cancer, and the third from sudden death. Two patients in the 2q8 group died: one of renal failure and the other of acute coronary syndrome. None of the events that led to death in these patients was judged by

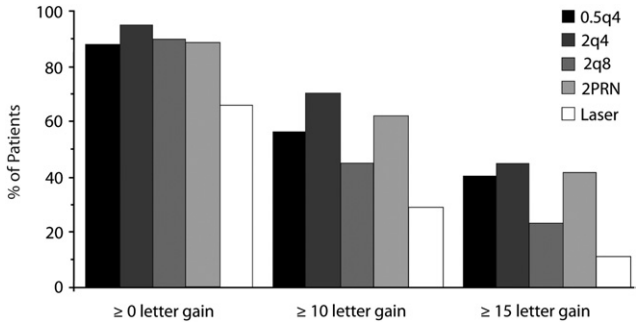

Figure 4. Bar graph showing percentage of patients with changes in changes in best-corrected visual acuity at 12 months by treatment groups (laser and Vascular Endothelial Growth Factor [VEGF] Trap-Eye) using last observation carried forward analysis: n = 44 (laser; VEGF Trap-Eye 0.5 mg every 4 weeks [0.5q4], 2 mg every 4 weeks [2q4]); n = 42 (VEGF Trap-Eye 2 mg for 3 initial monthly doses then every 8 weeks [2q8]); n = 45 (VEGF Trap-Eye 2 mg for 3 initial monthly doses then as needed [2PRN]). $P = 0.0031$, 0.5q4; $P = 0.0007$, 2q4; $P = 0.1608$, 2q8; $P = 0.0016$, 2PRN; all are compared with laser (analysis of covariance).

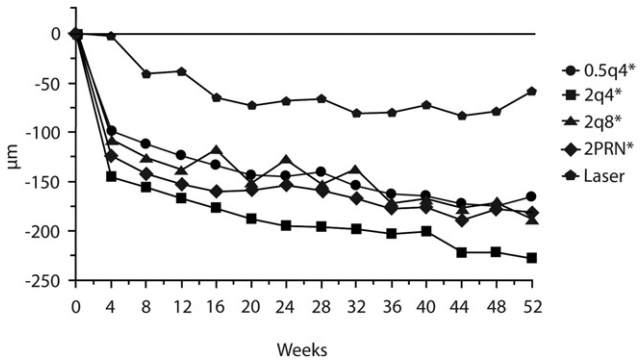

Figure 5. Graph showing mean change in central retinal thickness (in micrometers) by treatment groups (laser and Vascular Endothelial Growth Factor [VEGF] Trap-Eye) over the course of 12 months using last observation carried forward analysis: n = 44 (laser; VEGF Trap-Eye 0.5 mg every 4 weeks [0.5q4], 2 mg every 4 weeks [2q4]); n = 42 (VEGF Trap-Eye 2 mg for 3 initial monthly doses then every 8 weeks [2q8]); n = 45 (VEGF Trap-Eye 2 mg for 3 initial monthly doses then as needed [2PRN]). *$P < 0.0001$, difference between each treatment versus laser analysis of covariance.

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