The 1-year Results of CLEAR-IT 2, a Phase 2 Study of Vascular Endothelial Growth Factor Trap-Eye Dosed As-needed After 12-week Fixed Dosing

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Objective: To evaluate anatomic outcomes and vision, injection frequency, and safety during the as-needed (PRN) treatment phase of a study evaluating a 12-week fixed dosing period followed by PRN dosing to week 52 with vascular endothelial growth factor (VEGF) Trap-Eye for neovascular (wet) age-related macular degeneration (AMD).

Design: Multicenter, randomized, double-masked trial.

Participants: We included 159 patients with subfoveal choroidal neovascularization (CNV) secondary to wet AMD.

Methods: Patients were randomly assigned to 1 of 5 intravitreal VEGF Trap-Eye treatment groups: 0.5 mg or 2 mg every 4 weeks or 0.5, 2, or 4 mg every 12 weeks during the fixed-dosing period (weeks 1–12). From weeks 16 to 52, patients were evaluated monthly and were retreated PRN with their assigned dose (0.5, 2, or 4 mg).

Main Outcome Measures: Change in central retinal/lesion thickness (CR/LT), change in total lesion and CNV size, mean change in best-corrected visual acuity (BCVA), proportion of patients with 15-letter loss or gain, time to first PRN injection, reinjection frequency, and safety at week 52.

Results: The decrease in CR/LT at week 12 versus baseline remained significant at weeks 12 to 52 (−130 μm from baseline at week 52) and CNV size regressed from baseline by 2.21 mm^2 at 48 weeks. After achieving a significant improvement in BCVA during the 12-week, fixed-dosing phase for all groups combined, PRN dosing for 40 weeks maintained improvements in BCVA to 52 weeks (5.3-letter gain; $P<0.0001$). The most robust improvements and consistent maintenance of visual acuity generally occurred in patients initially dosed with 2 mg every 4 weeks for 12 weeks, demonstrating a gain of 9 letters at 52 weeks. Overall, a mean of 2 injections was administered after the 12-week fixed-dosing phase, and the mean time to first reinjection was 129 days; 19% of patients received no injections and 45% received 1 or 2 injections. Treatment with VEGF Trap-Eye was generally safe and well tolerated, with few ocular or systemic adverse events.

Conclusions: PRN dosing with VEGF Trap-Eye at weeks 16-52 maintained the significant anatomic and vision improvements established during the 12-week fixed-dosing phase with a low frequency of reinjections. Repeated dosing with VEGF Trap-Eye was well tolerated over 52 weeks of treatment.

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Vascular endothelial growth factor (VEGF) is a critical regulator of normal ocular vasculogenesis and angiogenesis during development.[1–3] Vascular endothelial growth factor also plays a central role in the abnormal growth of new blood vessels in the retina, as well as in vascular leakage that causes retinal edema and thickening, both of which characterize diseases such as neovascular (wet) age-related macular degeneration (AMD) and diabetic retinopathy that lead to loss of retinal function.[3–6] Of the various me

of the VEGF gene family, VEGF-A and placental growth factor (PlGF) are the factors implicated in pathologic angiogenesis and the pathogenesis of AMD (Invest Ophthalmol Vis Sci 50 [Suppl]: 2943,2009).[7–9]

An improved understanding of the pivotal role of VEGF in pathologic angiogenesis has resulted in the development and use of intravitreal anti-VEGF therapies in wet AMD and other eye diseases that have an angiogenesis-based

ligoribonucleotide aptamer,

and ranibizumab, a humanized monoclonal antibody fragment, are anti-VEGF therapies currently available for intravitreal treatment of neovascular AMD. In pivotal trials, pegaptanib mainly slowed loss of visual acuity, whereas ranibizumab improved visual function in a substantial proportion of patients.[13–16] Bevacizumab is an off-label intravitreal anti-VEGF therapy that has also been shown in less rigorous studies to improve visual function.[17–20]

The beneficial results with ranibizumab were obtained with a fixed-dosing regimen requiring an injection of ranibizumab 0.5 or 0.3 mg every month for 2 years in the pivotal phase 3 studies, Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) and Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR).[13,15] Several studies were undertaken to examine different dosing regimens for ranibizumab. In a large, randomized study in which patients were initially treated with a 3-month loading regimen of ranibizumab and then dosed at regular quarterly intervals, the initial gains after the loading regimen were not maintained at a year.[21] A 40-patient uncontrolled, open-label, single-site, Prospective Optical Coherence Tomography Imaging of Patients Treated with intra-Ocular ranibizumab (PrONTO) trial evaluated an as-needed (PRN) dosing regimen (based on monthly evaluation of changes in retinal thickness and edema using optical coherence tomography [OCT]) after 3 consecutive monthly injections. Visual acuity outcomes at 12 and 24 months were comparable with those observed in the pivotal phase 3 studies and were attained with fewer intravitreal injections.[22,23] However, in a larger randomized study, the gains in visual acuity after an initial 3-month loading regimen of ranibizumab were not maintained with subsequent protocol-defined retreatment.[24]

Vascular endothelial growth factor Trap-Eye (VEGF Trap-Eye) is a potent, specific VEGF antagonist that binds and inactivates circulating VEGF and VEGF in the extravascular space. It was developed specifically as an ultrapurified, isoosmotic solution for ophthalmic use.[25] Consisting of extracellular portions of VEGF receptors 1 and 2 fused to the Fc portion of human immunoglobulin G, VEGF Trap-Eye binds both VEGF-A or PlGF and forms an inert 1:1 complex with the growth factor dimers.[24,25] Thus, VEGF Trap-Eye has broader anti-VEGF activity compared with pegaptanib, which binds only the VEGF-A_{165} isoform,[26] and ranibizumab, which neutralizes all active isoforms of VEGF-A, but not PlGF.[27] Because VEGF Trap-Eye contains only human sequences, its potential for immunogenicity is low. A key differentiating feature of VEGF Trap-Eye is its picomolar affinity for VEGF ligands, which is substantially higher than that of the natural receptors or anti-VEGF monoclonal antibodies.[25,28,29] The clinical relevance of the higher binding affinity of VEGF Trap-Eye remains unknown, but it is thought that it might lead to more persistent VEGF blockade and a theoretically longer dosing interval between injections to maintain visual acuity relative to currently available anti-VEGF treatments.[30]

The clinical efficacy of VEGF-Trap Eye was initially demonstrated in the CLinical Evaluation of Anti-angiogenesis in the Retina Intravitreal Trial (CLEAR-IT 1), a 6-week phase 1 sequential cohort, single-ascending-dose (0.05 to 4 mg) study of intravitreal VEGF Trap-Eye in patients with neovascular AMD.[31] The efficacy and safety of repeated dosing with VEGF Trap-Eye were subsequently examined in the phase 2 CLEAR-IT 2 study, which consisted of an initial 12-week fixed dosing period with 1 of 5 monthly or quarterly regimens of VEGF Trap-Eye, followed by PRN dosing from weeks 16 to 52. Detailed results to 16 weeks for the fixed-dosing phase, including the primary endpoint at week 12, are presented in the accompanying article (Brown et al., in this issue, pp 1089-97). At 12 weeks, treatment with VEGF Trap-Eye resulted in a significant reduction in central retinal/lesion thickness (CR/LT) of -119 μm and a significant improvement in mean BCVA of 5.7 letters for all groups combined, and gains of >8 letters in the monthly dosing groups. The finding that improvements in visual acuity and retinal thickness were greater in the monthly dosing groups than in the quarterly dosing groups at week 12, support the need for an initial intensive monthly loading dose phase. Patients were treated with a PRN dosing regimen through week 52 to explore whether the high affinity of VEGF Trap-Eye for VEGF-A and PlGF could translate into the maintenance of initial visual acuity gains through 1 year with less frequent intravitreal injections. Results of the continued dosing phase of the CLEAR-IT 2 study are reported herein.

Materials and Methods

Study Design

The primary objectives of the study were to assess the effect of intravitreal VEGF Trap-Eye on CR/LT and to assess the ocular and systemic safety and tolerability of repeated doses of VEGF Trap-Eye in patients with choroidal neovascularization (CNV) associated with wet AMD. A key secondary objective was to assess the effect of VEGF Trap-Eye on BCVA.

This study was a double-masked, prospective, randomized, dose- and interval-ranging study in which 5 groups of approximately 30 patients each were assigned to a fixed-dose of intravitreal VEGF Trap-Eye in the study eye during the first 12 weeks of dosing, followed by PRN dosing from weeks 16 to 52 (Fig 1, available online at http://aaojournals.org). The VEGF Trap-Eye regimens were 0.5 mg or 2 mg at 4-week intervals (0.5q4 or 2q4 on day 1 and at weeks 4, 8, and 12 for a total of 4 treatments) or 0.5, 2, or 4 mg every 12 weeks (0.5q12, 2q12, or 4q12 on day 1 and week 12 for a total of 2 treatments). During the PRN dosing phase beginning at week 16, patients received the same dose of VEGF Trap-Eye (0.5, 2, or 4 mg) as received during the fixed-dosing phase (Fig 2).

The study protocol was approved by the ethics committee at every institution and was conducted according to the recommendations of Good Clinical Practice and 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 CLEAR-IT 2 study is registered with ClinicalTrials.gov (NCT00320788).

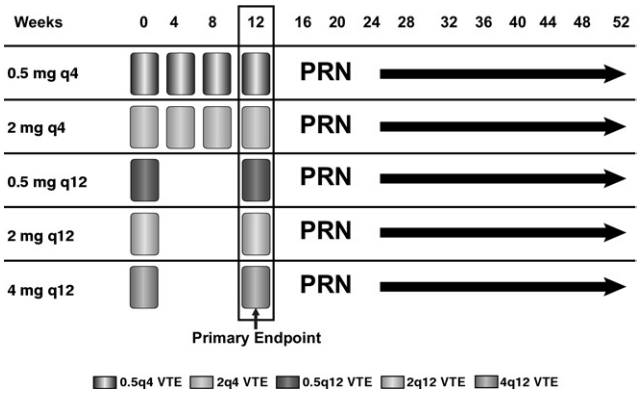

Figure 2. Study schedule. During the 12-week fixed dosing phase, patients in the monthly dosing groups received 0.5 or 2 mg of VEGF Trap-Eye every 4 weeks on day 0 and at weeks 4, 8, and 12 for a total of 4 doses; those in the quarterly dosing groups received 0.5, 2, or 4 mg of VEGF Trap-Eye every 12 weeks on day 0 and at week 12 for a total of 2 doses. Beginning at week 16 and continuing to week 52, patients were assessed every 4 weeks and, if needed, were retreated with the same dose of VEGF Trap-Eye as in the fixed dosing phase. The primary study endpoint was assessed at week 12. q = every; PRN = as-needed; VEGF = vascular endothelial growth factor; VTE = VEGF Trap-Eye; 0.5q4 = 0.5 mg every 4 weeks; 2q4 = 2 mg every 4 weeks; 0.5q12 = 0.5 mg every 12 weeks; 2q12 = 2 mg every 12 weeks; 4q12 = 4 mg every 12 weeks.

Patient Population

The study enrolled patients >50 years old who had a diagnosis of subfoveal CNV secondary to wet AMD and central retinal thickness ≥300 μm, Early Treatment of Diabetic Retinopathy Study (ETDRS) BCVA of 73 to 34 letters, loss of ≥5 ETDRS letters in BCVA over the preceding 6 months for previously treated patients with minimally classic or occult lesions, linear diameter of lesion ≤5400 μm by fluorescein angiography (FA), subretinal hemorrhage sparing the fovea and comprising ≤50% of total lesion, area of scar ≤25% of total lesion, and sufficient clarity of ocular media to allow retinal photography.

Key exclusion criteria were history of vitreous hemorrhage in preceding 4 weeks; aphakia or pseudophakia with absence of a posterior capsule (unless as a result of a yttrium aluminum garnet capsulotomy); significant subfoveal atrophy or scarring; presence of other causes of CNV in either eye; previous treatments for AMD in the study eye within 12 weeks for photodynamic therapy, 8 weeks for pegaptanib sodium, or 24 weeks for intravitreal or juxtascleral steroids; no other treatments for AMD (thermal laser, surgery, or intraocular/systemic anti-VEGF therapy) were allowed; any retinal vascular disease other than CNV in either eye; active ocular inflammation or infection; history of trabeculectomy or pars plana vitrectomy; history of myocardial infarction, stroke, transient ischemic attack, symptomatic peripheral vascular disease, or treatment for congestive heart failure within the last 6 months; and other conditions or laboratory abnormalities that might interfere with patient participation in the study.

Retreatment Criteria

During the fixed-dosing phase, 1 eye was designated as the study eye and all evaluations were conducted on that eye as described previously (Brown et al, in this issue, pp 1089-97). Beginning at week 16, patients were evaluated every 4 weeks to determine the need for continued dosing. After week 16, the study eye was reinjected with VEGF Trap-Eye if any of the following changes were observed by the evaluating practitioner: An increase in CR/LT ≥100 μm as measured by OCT; a loss of ≥5 ETDRS letters in conjunction with recurrent fluid as indicated by OCT; persistent fluid as indicated by OCT; new-onset classic neovascularization; new or persistent leak on FA; or new macular hemorrhage.

Endpoints and Assessments

Assessments were performed at scheduled clinic visits on days 1 and 7, at week 4, and every 4 weeks thereafter to week 52. At each visit, patients underwent a full ophthalmologic examination, including visual acuity testing, indirect ophthalmoscopy and slit lamp examination, intraocular pressure (IOP) measurement, and OCT. Fundus photography and FA were performed at baseline and at weeks 4, 12, 24, 36, and 48.

The primary efficacy endpoint was reduction of CR/LT from baseline to 12 weeks, at the end of the fixed-dosing phase. The variables assessed during the PRN dosing phase included change from baseline in CR/LT and mean change from baseline in CNV size determined by FA at 48 weeks, the last mandatory FA in the study; BCVA at 52 weeks; proportions of patients with avoidance of moderate vision loss (loss of <15 letters); stabilization or improvement in visual acuity (gain of ≥0 letters); and significant vision gain (gain of ≥15 letters) at 52 weeks; time to first reinjection after week 12; and mean number of injections over the PRN period.

The CR/LT was determined from Stratus OCT (Version 4.0 or higher; CarlZeiss, Jena, Germany) scans read at a masked independent central reading center (Digital OCT Reading Center, Cleveland, OH). The CR/LT was defined as the distance between the inner limiting membrane and posterior border of retinal pigment epithelial/choriocapillaris complex including any subretinal fluid and thickness of any observable choroidal neovascular membrane or scar tissue in central 1 mm of posterior pole scan.

Changes in the size of the total lesion and the CNV component were evaluated with FA. The CNV size was defined as the area of visible CNV (classic or occult) with angiographic evidence of late leakage or pooling of dye. Angiographic images were transmitted to the masked reading center for review (Digital Angiography Reading Center, New York, NY). At least 1 designated photographer was certified by the Reading Center before enrollment of the first patient at each site.

Certified examiners assessed BCVA by using the ETDRS protocol at 4 m. Examiners were masked to treatment assignment, and performed no other study assessments.

Safety assessments included IOP (measured preinjection and approximately 30 minutes postinjection), ophthalmologic examinations for ocular toxicity, adverse events (AEs), serious AEs (SAEs), clinical laboratory tests, and vital signs.

Statistical Analysis

Efficacy assessments were made on the full analysis set, which included all patients who received study treatment and had a baseline and ≥1 postbaseline assessment. Safety assessments were performed on all patients who received study treatment.

The primary analysis was a paired comparison *t* test of the change in CR/LT from baseline to week 12 for all groups combined. If this was significant, an analysis of covariance was done on the 5 individual groups. A similar analysis was done for all continuous measures at all time points. Missing values were imputed using the last-observation-carried-forward method for continuous measures. The durability of the effect was assessed by evaluating all of the endpoints out to week 52. All of the analyses shown below were done using the same methods at week 12 and week 52 (week 48 for FA parameters).

Table 2. Baseline Demographic and Clinical Characteristics

Characteristic	All Treated Patients (n = 157)
Age, y (mean [range])	78.3 (53–94)
Gender (%M:%F)	38:62
Disease duration, months (mean [range])	3.9 (0–67)
Previous treatment	20 (12.7%)
Lesion size (mean ± SD) in disc area	3.11 ± 2.12
Lesion type (n [%])	
Predominantly classic	60 (38.2)
Minimally classic	37 (23.6)
Occult lesions	60 (38.2)
Disease status (mean [range])	
Central retinal/lesion thickness (μm)	456 (186–1316)
Foveal thickness (μm)	327 (116–1081)
Best-corrected visual acuity (ETDRS letters)	56 (27–83)

ETDRS = Early Treatment of Diabetic Retinopathy Study; F = Female; M = Male; SD = standard deviation.

Results

Patient Disposition

Of 159 patients who were randomized, 157 were treated and 134 (85.4%) completed 52 weeks in the study (Table 1 available online at http://aaojournal.org). For the 23 patients (14.6%) who were withdrawn before completion of 52 weeks, 6 (3.8%) withdrawals were at the request of the patient.

Baseline Characteristics

The study population was representative of the AMD population in the United States. Patients ranged in age from 53 to 94 years (mean, 78.3) and the majority were women (62%; Table 2). The mean time from diagnosis was 3.9 months (range, 0–67), and 12.7% of patients had received previous treatment. The distribution of CNV lesions was 38.2% predominantly classic, 23.6% minimally classic, and 38.2% occult with no classic. The treatment groups were well-balanced overall for baseline disease severity, but mean CR/LT and mean foveal thickness were somewhat higher in the 4 mg q12wk group (Table 3).

Change in Central Retinal/Lesion Thickness

The primary efficacy endpoint of the study was mean change in CR/LT at week 12. In all treatment groups combined, the significant decrease from baseline in CR/LT observed at week 12 (−119 μm) was maintained to week 52 (−130 μm; $P<0.0001$) after 40 weeks of PRN dosing with VEGF Trap-Eye (Fig 3A). The decrease in CR/LT was also maintained in all individual dosing groups after PRN dosing and was significant compared with baseline values. The greatest decreases in CR/LT at week 52 versus baseline occurred in the 4 mg q12wk group (−161 μm; $P = 0.0002$) and the 2 mg q4wk group (−143 μm; $P<0.0001$; Fig 3B).

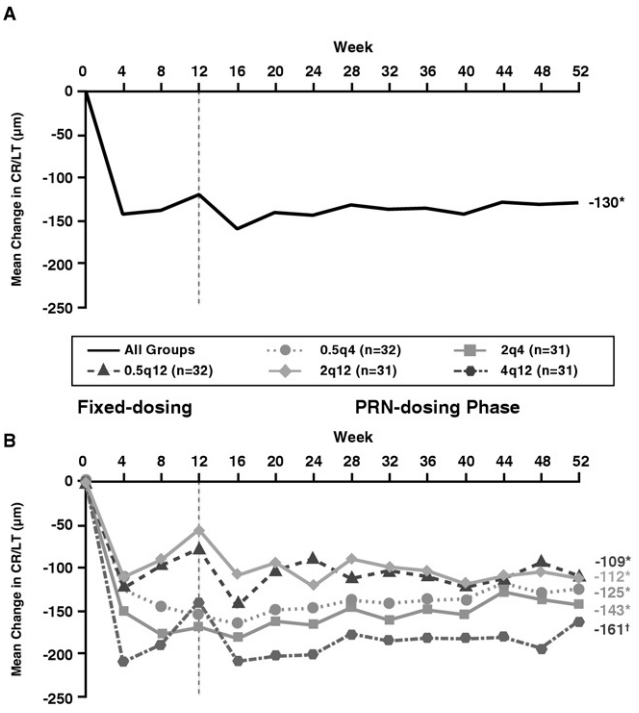

Figure 3. Mean change in central retinal/lesion (CR/LT) thickness in (**A**) all treatment groups combined and (**B**) individual treatment groups. The CR/LT was measured with optical coherence tomography. Change in CR/LT from baseline at 12 weeks was the primary study endpoint. In the combined treatment group, a significant (*$P<0.0001$) decrease in CR/LT at week 12 was maintained to week 52 (−130 μm). The decrease in CR/LT in individual treatment groups was maintained between weeks 12 and 52 with PRN dosing was significant (*$P<0.0001$; †$P = 0.0002$) compared with baseline values. The last-observation-carried-forward method was used to impute missing data. CR/LT = central retina/lesion thickness; PRN = as-needed; 0.5q4 = 0.5 mg every 4 weeks; 2q4 = 2 mg every 4 weeks; 0.5q12 = 0.5 mg every 12 weeks; 2q12 = 2 mg every 12 weeks; 4q12 = 4 mg every 12 weeks.

Change in Angiographic Measures

Fluorescein angiography (FA) was performed at baseline and at weeks 4, 12, 24, 36, and 48. In all groups combined and in each treatment group, there were no significant changes in total lesion

Table 3. Baseline Disease Status by Treatment Group

Mean (Range)	0.5q4 (n = 32)	2q4 (n = 31)	0.5q12 (n = 32)	2q12 (n = 31)	4q12 (n = 31)	All Groups (n = 157)
CR/LT (μm)	434 (282–710)	453 (232–960)	442 (186–762)	447 (265–948)	507 (240–1316)	456 (186–1316)
Foveal thickness (μm)	329 (212–509)	307 (171–524)	319 (116–559)	334 (186–762)	360 (177–1081)	327* (116–1081)
BCVA (ETDRS letters)	54 (27–76)	58 (32–83)	56 (30–72)	57 (32–72)	53 (28–80)	56 (27–83)

BCVA = best-corrected visual acuity; CR/LT = central retinal/lesion thickness; ETDRS = Early Treatment of Diabetic Retinopathy Study; q = every.
*In all groups (n = 157), 25 patients at week 52 showed foveal thickness measurements of <150 μm.

size from baseline to week 12 and week 48 (data not shown). The decrease in total lesion size for the 2 mg q4wk group at week 12 (−0.75 mm^2; −0.30 disc area [DA]) and week 48 (−1.75 mm^2; −0.69 DA; $P<0.04$) achieved significance.

The area of CNV (defined as classic and/or occult CNV demonstrating angiographic evidence of late leakage or pooling of dye) was also measured. In all treatment groups combined, PRN treatment with VEGF Trap-Eye resulted in a consistent decrease in the CNV size versus baseline at weeks 12 and 48, with a decrease of −2.21 mm^2 (−0.87 DA) at week 48 ($P<0.001$; Fig 4A, available online at http://aaojournal.org). All treatment groups other than the 0.5 mg q12wk group experienced a decrease in active CNV size at 48 weeks (−1.42 to −3.41 mm^2; −0.56 to −1.34 DA), with the greatest reduction in the 2 mg q4wk group (−3.41 mm^2, −1.34 DA; $P<0.001$; Fig 4B).

Change in Visual Acuity

The significant improvement from baseline in BCVA that was noted at 12 weeks was maintained through the PRN dosing phase to week 52. The combining of all treatment groups showed a mean gain of 5.7 letters at week 12 and 5.3 letters at week 52 ($P<0.0001$ vs baseline; Fig 5A). The greatest improvement in BCVA occurred in the 2 mg q4wk treatment group, with a mean increase of 8.3 letters at week 12 and of 9.0 letters at week 52 ($P<0.0001$ vs baseline; Fig 5B). Visual acuity improvements compared with baseline were also maintained in all other treatment groups at week 52.

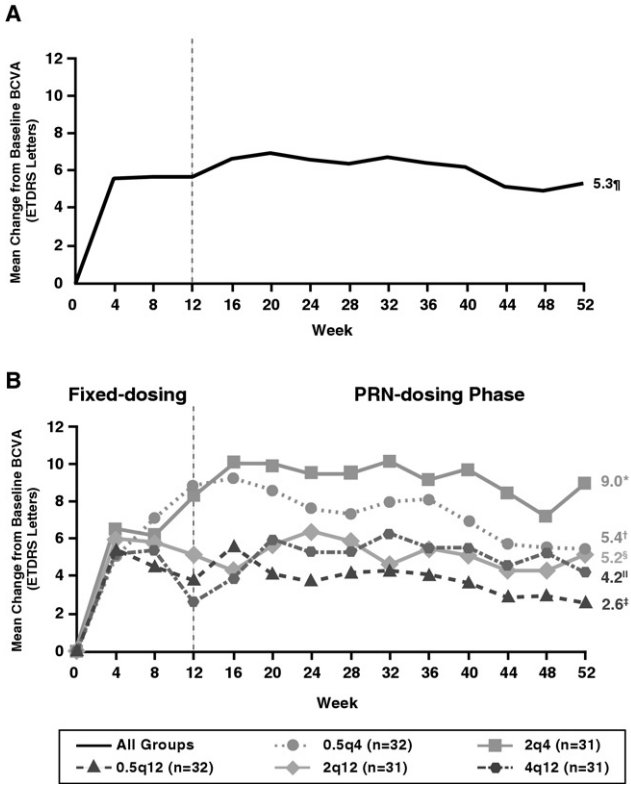

Figure 5. Mean change in best-corrected visual acuity (BCVA) in (**A**) all treatment groups combined and (**B**) individual treatment groups. The BCVA was assessed with the Early Treatment of Diabetic Retinopathy Study protocol at 4 m. Significant improvements from baseline in BCVA were noted in all treatment groups combined at week 12 (5.7 letters) and were maintained to week 52 (5.3 letters; ¶$P<0.0001$). The 2 mg q4wk group showed the greatest gain in BCVA at 12 weeks, which was maintained to 52 weeks (9.0 letters; *$P<0.0001$; †$P = 0.085$; ‡$P = 0.0412$; §$P = 0.0154$; and ‖$P = 0.344$ for individual groups versus baseline). The last-observation-carried-forward method was used to impute missing data. ETDRS = Early Treatment of Diabetic Retinopathy Study; PRN = as-needed.

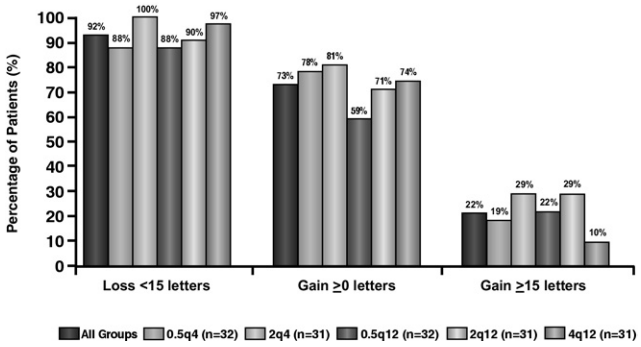

Figure 6. Visual acuity changes at week 52. The proportions of patients who avoided moderate vision loss (≥15 letters), had an improvement in visual acuity (gain of ≥0 letters), or had a significant vision gain (≥15 letters) in the treatment groups combined and individual dosing groups at week 52 are shown. In the treatment groups combined, only 8% of patients experienced moderate loss of vision, whereas 22% showed a significant gain in vision of ≥15 letters at week 52 after 40 weeks of as-needed (PRN) dosing. The last-observation-carried-forward method was used to impute missing data. 0.5q4 = 0.5 mg every 4 weeks; 2q4 = 2 mg every 4 weeks; 0.5q12 = 0.5 mg every 12 weeks; 2q12 = 2 mg every 12 weeks; 4q12 = 4 mg every 12 weeks.

Frequency of Patients with Visual Acuity Changes

In all treatment groups combined, moderate loss of vision (loss of ≥15 letters) was avoided in 98% of patients at week 12 and 92% at week 52 after treatment with VEGF Trap-Eye. In the individual treatment groups, 88% to 100% of patients avoided moderate loss of vision at week 52 (Fig 6). Overall, 12 patients experienced moderate vision loss at week 52, including 4 in the 0.5 mg q4wk group, 4 in the 0.5 mg q12wk group, 3 in the 2 mg q12wk group, and 1 in the 4 mg q12wk group. None of the patients in the 2 mg q4wk group experienced moderate vision loss.

Stabilization or improvement in visual acuity (gain of ≥0 letters) occurred in 74.5% of patients in all treatment groups combined at week 12 and in 73% of patients at week 52. In the individual treatment groups, the proportion of patients experiencing stable or improved visual acuity ranged between 59% and 81%, with the highest proportion in the 2 mg q4wk group. Overall, these proportions remained steady from week 12 to week 52.

The frequency of patients in all treatment groups combined with a significant gain in vision (≥15 letters) was 18.5% at week 12 and 22% at week 52. Groups treated with 2 mg, either monthly or quarterly, had the highest frequency of patients with significant visual gain (26% and 16%, respectively, at week 12, and 29% in each group at week 52).

The proportion of patients with ≤20/200 vision in all treatment groups combined was 11.5% at baseline and remained stable at 10.8% at week 52. The proportion of patients with ≥20/40 vision increased from baseline (15%) to week 52 (41%) for all groups combined, with the 0.5mg q4wk and 2mg q4wk groups increasing from 13% and 16% to 47% and 45%, respectively (Fig 7, available online at http://aaojournal.org).

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