RADIANCE: A Randomized Controlled Study of Ranibizumab in Patients with Choroidal Neovascularization Secondary to Pathologic Myopia

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Objective: To compare the efficacy and safety of ranibizumab 0.5 mg, guided by visual acuity (VA) stabilization or disease activity criteria, versus verteporfin photodynamic therapy (vPDT) in patients with visual impairment due to myopic choroidal neovascularization (CNV).

Design: Phase III, 12-month, randomized, double-masked, multicenter, active-controlled study.

Participants: Patients (N = 277) with visual impairment due to myopic CNV.

Methods: Patients were randomized to receive ranibizumab on day 1, month 1, and thereafter as needed guided by VA stabilization criteria (group I, n = 106); ranibizumab on day 1 and thereafter as needed guided by disease activity criteria (group II, n = 116); or vPDT on day 1 and disease activity treated with ranibizumab or vPDT at investigators' discretion from month 3 (group III, n = 55).

Main Outcome Measures: Mean average best-corrected visual acuity (BCVA) change from baseline to month 1 through months 3 (primary) and 6, mean BCVA change and safety over 12 months.

Results: Ranibizumab treatment in groups I and II was superior to vPDT based on mean average BCVA change from baseline to month 1 through month 3 (group I: +10.5, group II: +10.6 vs. group III: +2.2 Early Treatment Diabetic Retinopathy Study [ETDRS] letters; both $P < 0.0001$). Ranibizumab treatment guided by disease activity was noninferior to VA stabilization-guided retreatment based on mean average BCVA change from baseline to month 1 through month 6 (group II: +11.7 vs. group I: +11.9 ETDRS letters; $P < 0.00001$). Mean BCVA change from baseline to month 12 was +13.8 (group I), +14.4 (group II), and +9.3 ETDRS letters (group III). At month 12, 63.8% to 65.7% of patients showed resolution of myopic CNV leakage. Patients received a median of 4.0 (group I) and 2.0 (groups II and III) ranibizumab injections over 12 months. No deaths or cases of endophthalmitis and myocardial infarction occurred.

Conclusions: Ranibizumab treatment, irrespective of retreatment criteria, provided superior BCVA gains versus vPDT up to month 3. Ranibizumab treatment guided by disease activity criteria was noninferior to VA stabilization criteria up to month 6. Over 12 months, individualized ranibizumab treatment was effective in improving and sustaining BCVA and was generally well tolerated in patients with myopic CNV. *Ophthalmology 2014;121:682-692 © 2014 by the American Academy of Ophthalmology.*

*Supplemental material is available at www.aaojournal.org.

Myopia is a common condition in many countries, particularly in East Asia, affecting approximately 40% of Chinese adults aged more than 40 years.[1,2] The most severe form of myopia, pathologic myopia, is a leading cause of visual impairment and one of the most frequent causes of blindness worldwide.[3–8] Although the definition of pathologic myopia is not standardized, it is historically classified in the clinical trial literature as a myopic refractive error greater than −6.00 diopters, or an axial length ≥26.5 mm, and degenerative changes involving the sclera, choroid, and retina.[9–11] The overall prevalence of pathologic myopia is approximately 1% to 4% in the general adult population, although there is a wide geographical variation. The associated prevalence of visual impairment due to pathological myopia is estimated to be 0.1% to 1.4%.[2,9,12–16]

Choroidal neovascularization (CNV) secondary to pathological myopia (myopic CNV) is a common vision-threatening complication and often affects adults of working age.[9,17,18] Myopic CNV develops in approximately 5% to 10% of patients with pathological myopia.[9,18–21] The overall prevalence of myopic CNV is therefore estimated to be approximately 0.04% to 0.05% in the general population.[20,21]

Until recently, verteporfin photodynamic therapy (vPDT) was the only approved treatment for subfoveal myopic

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CNV,[9] and additionally vPDT is also commonly used for juxtafoveal myopic CNV.[9,22,23] Although vPDT has been shown to stabilize vision in the short term, its longer-term benefits are limited, and improvement in vision is uncommon.[23–25] The Verteporfin In Photodynamic Therapy (VIP) study in patients with myopic CNV demonstrated that although vPDT showed better visual acuity (VA) benefits compared with placebo at month 12, there was a lack of VA stabilization over 24 months in the majority of patients.[23,24] Therefore, there is an unmet medical need for effective, well-tolerated treatments that can provide clinically relevant benefits in all types of myopic CNV, prevent disease progression, and improve vision.

As in the development of CNV secondary to neovascular age-related macular degeneration (AMD), vascular endothelial growth factor (VEGF)-A also plays a key role in the development of myopic CNV.[26,27] Ranibizumab (Lucentis; Novartis Pharma AG, Basel, Switzerland, and Genentech Inc., South San Francisco, CA) is a humanized monoclonal antibody fragment (Fab) that lacks the Fc domain. It has been specifically designed for ocular use, and it selectively binds to and inhibits all active isoforms of VEGF-A.[28] Ranibizumab is approved in many countries for the treatment of visual impairment due to neovascular AMD, diabetic macular edema, retinal vein occlusion, and more recently for CNV secondary to pathologic myopia.[29]

Several small uncontrolled studies have investigated the role of anti-VEGF treatment in myopic CNV. These preliminary studies have shown promising results in improving the functional and anatomic outcomes in patients with myopic CNV,[9,30–38] with some studies reporting a rapid VA gain of 10 to 15 letters over 12 months.[34–38] Ranibizumab for trEatment of CNV secondary to Pathological myopia: An Individualized Regimen (REPAIR), a larger, phase II, open-label, single-arm, multicenter, nonrandomized study of 65 patients from the United Kingdom, showed that ranibizumab was effective in preventing vision loss and improving vision with a median of 3.0 injections over 12 months.[39] While REPAIR has reported promising results, randomized controlled trials are required to evaluate the efficacy, safety, and optimal dosing regimen of ranibizumab in patients with visual impairment due to myopic CNV.

Therefore, the first pivotal phase III randomized controlled trial, Ranibizumab And PDT [verteporfIn] evAluation iN myopic Choroidal nEovascularization (RADIANCE), has been conducted to evaluate the efficacy and safety of 2 individualized dosing regimens of ranibizumab versus vPDT in patients with visual impairment due to myopic CNV.

Methods

Study Design

RADIANCE was a 12-month, phase III, multicenter, randomized, double-masked, active-controlled study that enrolled patients with visual impairment due to myopic CNV from 76 centers worldwide. The study was conducted between October 2010 and August 2012 in accordance with the Declaration of Helsinki. The study protocol was reviewed and approved by the independent ethics committee or institutional review board for each contributing center. Patients provided written informed consent before entering the study. The study is registered with clinicaltrials.gov as NCT01217944.

Patients

The study population consisted of male or female patients aged ≥18 years with visual impairment due to myopic CNV. The key inclusion criteria at the screening visit were (1) diagnosis of active CNV secondary to pathologic myopia confirmed by complete ocular examination in the study eye using the following criteria: (a) presence of high myopia, greater than −6 diopters of spherical equivalence, (b) anteroposterior elongation of ≥26 mm, (c) presence of posterior changes compatible with pathologic myopia, (d) presence of active leakage from CNV, and (e) presence of intraretinal or subretinal fluid or increase of central retinal thickness (CRT); (2) presence of at least 1 of the following lesion types: (a) subfoveal, (b) juxtafoveal with involvement of the central macular area, (c) extrafoveal with involvement of the central macular area, and (d) margin of the optic disk with involvement of the central macular area; (3) best-corrected visual acuity (BCVA) ≥24 and ≤78 letters at a starting distance of 4 meters using Early Treatment Diabetic Retinopathy Study (ETDRS)-like VA chart (~20/32–20/320 Snellen equivalent); and (4) visual loss only due to the presence of any eligible types of CNV related to pathologic myopia, based on clinical ocular findings, fluorescein angiography (FA), and optical coherence tomography (OCT) data.

The key exclusion criteria were (1) history of (a) stroke, (b) pan-retinal or focal/grid laser photocoagulation with involvement of the macular area in the study eye at any time, (c) intraocular treatment with corticosteroids or intraocular surgery within 3 months prior to randomization and treatment with anti-VEGF or vPDT at any time in the study eye, or (d) hypersensitivity to ranibizumab or verteporfin or to drugs of similar class; (2) presence of CNV secondary to any cause other than pathologic myopia; (3) presence of active infectious disease or intraocular inflammation, active or suspected periocular infection, confirmed intraocular pressure (IOP) ≥25 mmHg, or iris neovascularization in either eye at the time of enrollment; and (4) pregnant or nursing women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin laboratory test (>5 mIU/ml).

Randomization and Treatment

A randomization list was produced by Novartis Drug Supply Management using a validated system that automates the random assignment of treatment groups to randomization numbers in the specified ratio. At enrollment, patients received the lowest available randomization number that then assigned them in a 2:2:1 ratio to 1 of the 3 treatment groups. For all patients, 1 eye was selected and treated as the study eye. If both eyes were eligible, then the eye with the worse VA (assessed at visit 1) was selected for the study treatment. However, if medical reasons and local ethical requirements dictated, the investigator could select the eye with the better VA as the study eye. If needed, the fellow eye was treated as per the investigator's discretion.

Group I: Ranibizumab Treatment Guided by Visual Acuity Stabilization Criteria. Patients received ranibizumab 0.5 mg injections on day 1 and month 1, with further treatment determined by the VA stabilization criterion, defined as no change in BCVA (the difference [gain or loss] in the number of ETDRS letters was not restricted/limited and was based on the judgment of the investigator) as compared with 2 preceding monthly visits. The first time point at which stability could be assessed was at month 2 (based on baseline and month 1 and 2 assessments) after a

minimum of 2 monthly injections were administered. Treatment was stopped if the VA stabilization criterion was fulfilled. Monthly treatment was resumed when there was a loss in VA due to disease activity and continued until stable VA was reached for 3 consecutive monthly assessments (Fig 1, available at www.aaojournal.org).

Group II: Ranibizumab Treatment Guided by Disease Activity Criteria. Patients received ranibizumab 0.5 mg injections on day 1. Starting from month 1, treatment was discontinued if no disease activity was observed, where disease activity was defined as visual impairment attributable to intraretinal or subretinal fluid or active leakage secondary to myopic CNV. Treatment was resumed if the disease activity criterion was fulfilled (Fig 1, available at www.aaojournal.org). The investigator advised the patients to follow all the precautions as mentioned in the vPDT label.

Group III: Verteporfin Photodynamic Therapy, with Ranibizumab Allowed as of Month 3. Verteporfin was administered intravenously at a dose of 6 mg/m^2 (in 30 ml 5% dextrose solution) over 10 minutes, followed by standard fluence photodynamic therapy (PDT) for 83 seconds (wavelength, 689 nm; dose, 50 J/cm^2; light intensity, 600 mW/cm^2) 15 minutes after start of the infusion. Patients received vPDT on day 1. From months 3 to 11, the treating investigator could treat the patients with either ranibizumab 0.5 mg guided by disease activity criteria, vPDT, or both. Treatment was administered if the disease activity criteria was fulfilled and suspended if no disease activity was observed (Fig 1, available at www.aaojournal.org).

Sham Treatment. Due to the different appearances and routes of administration between the 2 treatments, all patients received either sham injection or PDT sham in conjunction with the study treatment. The PDT sham consisted of intravenous injection of 5% dextrose solution followed by light application of PDT.

Masking. To ensure masking, 2 investigators were involved at each study center. All study assessments were made by the evaluating investigator, VA assessor, or other site personnel who were masked to the treatment assignment. The treating investigator was unmasked and administered the randomized study medication per the protocol; however, they were not involved in any other aspects of the study and could not communicate details of the treatment.

Study Objectives

The primary objective of this study was to demonstrate the superiority of ranibizumab 0.5 mg treatment, guided by VA stabilization and/or disease activity criteria, over vPDT at month 3. The key secondary objective was to demonstrate the noninferiority of ranibizumab 0.5 mg guided by disease activity criteria versus VA stabilization criteria at month 6.

Other secondary objectives were to (1) evaluate the efficacy of all treatment groups for (a) the mean change in BCVA and CRT, (b) the proportion of patients with categorized change in BCVA between treatment groups, and (c) the anatomical outcomes across the treatment groups; (2) assess treatment exposure; and (3) evaluate the safety of the different treatment regimens over 12 months.

Efficacy and Safety Assessments

Best-Corrected Visual Acuity. The BCVA in the study eye was assessed at every visit using the ETDRS-like VA testing charts at a starting distance of 4 meters (ETDRS letters). The primary endpoint was the mean average change in BCVA from baseline to month 1 through month 3, which is the mean difference of BCVA versus baseline over all monthly post-baseline assessments from month 1 to month 3. This end point provides a more robust estimate than a mean change assessed at a single time point (month 3, which was the last month before ranibizumab was allowed in group III). The secondary endpoints included the mean average change in BCVA from baseline to month 1 through month 6, the mean change in BCVA from baseline over time, the proportion of patients gaining $\geq$10 and $\geq$15 ETDRS letters (or reaching 84 letters) at month 12, and the proportion of patients losing $\geq$10 and $\geq$15 ETDRS letters at month 12.

Optical Coherence Tomography. Optical coherence tomography was performed on the study eye at all visits, except at day 8. The images were reviewed by a central reading center to ensure standardized evaluation. Subretinal fluid, intraretinal edema, intraretinal cysts (volume scan and crosshair scan), and mean change in CRT were measured by OCT.

Color Fundus Photography and Fluorescein Angiography. Trained technicians conducted FA after color fundus photography, at screening, and at the end of the study to assess the choroid and retinal vasculature. The fundus photography and FA images were independently reviewed by the central reading center (CRC) to ensure standardized evaluation. Additional assessments for retreatment were performed from month 1 to 11, as needed, in the study eye.

Treatment Exposure. The number of ranibizumab injections administered to each group and the number of vPDT treatments administered were evaluated over 12 months.

Safety Assessments. Safety was assessed by incidence of adverse events (AEs) and serious AEs (SAEs), by ophthalmic examinations, IOP measurements, and changes in vital signs and laboratory results over the 12-month study/assessment period. All ocular/nonocular AEs and SAEs were recorded, including information on their relationship to study drug and/or ocular injection procedure. All AEs were summarized by the proportion of patients experiencing AEs, based on the standardized Medical Dictionary for Regulatory Activities by system organ class and preferred term.

Statistical Analysis

A sample size of 110 patients in each of the ranibizumab groups and 55 patients in the vPDT group was considered to have $\geq$91% power to reject 1 of the primary hypotheses using Cochran–Mantel–Haenszel tests. A treatment difference of 8 letters was assumed between each of the ranibizumab groups and vPDT with a standard deviation (SD) of 10 BCVA letters with the Hochberg procedure at multiple 1-sided alpha level of 0.001. By assuming a SD of 10 for the key secondary variable and equal means for the 2 ranibizumab groups, then 110 patients per treatment group were sufficient to achieve a power of 91% to reject the key secondary hypothesis. The primary and key secondary objectives were achieved at the multiple alpha level of 1-sided 0.025.

The randomized set consisted of all randomized patients. Patients were considered randomized when they had been given a randomization number. The full analysis set (FAS) consisted of all randomized patients who received at least 1 application of the study treatment (ranibizumab [sham] or vPDT [sham]) and had at least 1 post-baseline record of study eye VA data.

The primary analysis was performed on the FAS with a modified last observation carried forward (LOCF) approach, wherein the missing values occurring between the observed values were computed from the mean of the observed values before and after the missing time point. The primary endpoint variable was the difference between the average level of BCVA letter score over all monthly post-baseline assessments from month 1 to month 3 and the baseline level of BCVA letter score. The ranibizumab treatment groups were considered superior to vPDT if the corresponding 1-sided P value was $\leq$0.001/2=0.0005 or if both 1-sided P values were $\leq$0.001. Pairwise comparisons between the ranibizumab groups and the vPDT group were performed using a stratified

Cochran–Mantel–Haenszel test with the observed values as scores. The key secondary endpoint was the difference between the average level of BCVA (letters) over all monthly post-baseline assessments from month 1 to month 6 and the baseline level of BCVA. The 2-sided 95% confidence interval of the average changes in BCVA and the corresponding pairwise difference between both treatments arms was calculated using the least square means for treatment differences from an analysis of variance (ANOVA) model with treatment and baseline BCVA category (≤60 vs. >60 letters) as factors, and the hypothesis tests were evaluated at a 2-sided 0.05/1-sided 0.025 level of significance. The key secondary variable was compared between both ranibizumab treatment arms using a 5-letter noninferiority margin, and the comparison was based on a stratified Cochran–Mantel–Haenszel test. For the secondary objectives, descriptive statistics were used for each treatment group.

All safety analyses were performed on the safety set that consisted of all patients who received at least 1 application of study treatment (ranibizumab [sham] and/or vPDT [sham]) and had at least 1 post-baseline safety assessment. To describe the safety profile for patients randomized to vPDT, group III was further split into 2 groups: patients who received ranibizumab and patients who did not receive ranibizumab as of month 3.

Results

Patient Disposition and Demographics

Of the 334 patients screened, 277 patients were randomized: 106 to receive ranibizumab guided by VA stabilization criteria (group I), 116 to receive ranibizumab guided by disease activity criteria (group II), and 55 to receive vPDT (group III). Overall, baseline patient demographics and ocular and disease characteristics were comparable across the 3 treatment groups (Table 1). The majority of the patients across the 3 treatment groups completed the 12-month study period (group I: 94.3%; group II: 96.6%; group III: 100%). No patients discontinued due to AEs (Fig 2).

The efficacy analyses were performed on the FAS consisting of 105 patients (group I), 116 patients (group II), and 55 patients (group III). The safety analyses were conducted on the safety set comprising 106 patients (group I), 118 patients (group II), and 53 (group III) patients. Two patients in group III received ranibizumab before month 3 and were placed in group II for safety analysis.

Efficacy

Best-Corrected Visual Acuity. Ranibizumab treatment guided by VA stabilization and/or disease activity retreatment criteria was superior to vPDT with respect to mean average change ± SD in BCVA from baseline to month 1 through month 3 (group I: +10.5±8.2 ETDRS letters; group II: +10.6±7.3 ETDRS letters vs. group III: +2.2±9.5 ETDRS letters; both $P < 0.00001$; Fig 3).

Ranibizumab treatment guided by disease activity criteria was noninferior to ranibizumab treatment guided by VA stabilization criteria with respect to mean average change ± SD in BCVA from baseline to month 1 through month 6 (group II: +11.7±8.2 vs. group I: +11.9±8.8 ETDRS letters; $P < 0.00001$).

Ranibizumab treatment in groups I and II led to a rapid improvement in BCVA as early as month 3, and a continuous numerical improvement in BCVA (mean ± SD) was observed up to month 12 (group I: +13.8±11.42 ETDRS letters; group II: +14.4±10.20 ETDRS letters; Fig 4). In group III, the mean BCVA change observed at month 3 was lower than that observed in groups I and II. However, with the allowance of ranibizumab as of month 3 in group III, a steady improvement in BCVA (mean ± SD) was observed up to month 12 (+9.3±11.33 ETDRS letters; Fig 4).

Table 1. Baseline Patient Demographics and Ocular and Disease Characteristics (Randomized Set*)

Characteristics	Ranibizumab 0.5 mg		vPDT
	Group I, Guided by VA Stabilization (n=106)	*Group II, Guided by Disease Activity (n=116)*	*Group III (n=55)*
Mean age (SD), yrs	54.0 (14.0)	56.1 (14.4)	57.4 (12.8)
Sex, n (%)			
Male	24 (22.6)	29 (25.0)	15 (27.3)
Female	82 (77.4)	87 (75.0)	40 (72.7)
Race, n (%)			
Caucasian	60 (56.6)	70 (60.3)	32 (58.2)
Asian	45 (42.5)	46 (39.7)	23 (41.8)
Other	1 (0.9)	0 (0.0)	0 (0.0)
Mean BCVA (SD), letters	55.4 (13.4)	55.8 (12.6)	54.7 (13.8)
Mean CRT (SD), μm	350.2 (95.1)	373.1 (127.4)	355.1 (102.4)
Mean IOP (SD), mmHg	15.1 (2.8)	15.1 (3.2)	14.8 (3.0)
Mean axial length (SD), mm	29.3 (1.9)	28.8 (1.8)	29.4 (1.9)
Mean refraction-sphere (SD), diopters†	13.7 (5.2)	11.6 (4.7)	12.2 (4.9)
CNV location, n (%)‡			
Subfoveal	71 (67.0)	81 (69.8)	38 (69.1)
Juxtafoveal	26 (24.5)	24 (20.7)	16 (29.1)
Extrafoveal	7 (6.6)	3 (2.6)	1 (1.8)

BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; CRT = central retinal thickness; IOP = intraocular pressure; SD = standard deviation; VA = visual acuity; vPDT = verteporfin photodynamic therapy.
Percentages are based on the total number of patients in the randomized set.
*Consisted of all randomized patients who received at least 1 application of study treatment (ranibizumab [sham] and/or vPDT [sham]) and had at least 1 post-baseline record of study eye VA data.
†Refraction-sphere values were collected as negative diopters but are presented as positive values to facilitate the interpretation.
‡Subfoveal: presence of abnormal vasculature in the avascular central fovea; juxtafoveal: presence of abnormal vasculature not under the center of fovea but <200 μm from the center; extrafoveal: presence of abnormal vasculature >200 μm from the center of the fovea.

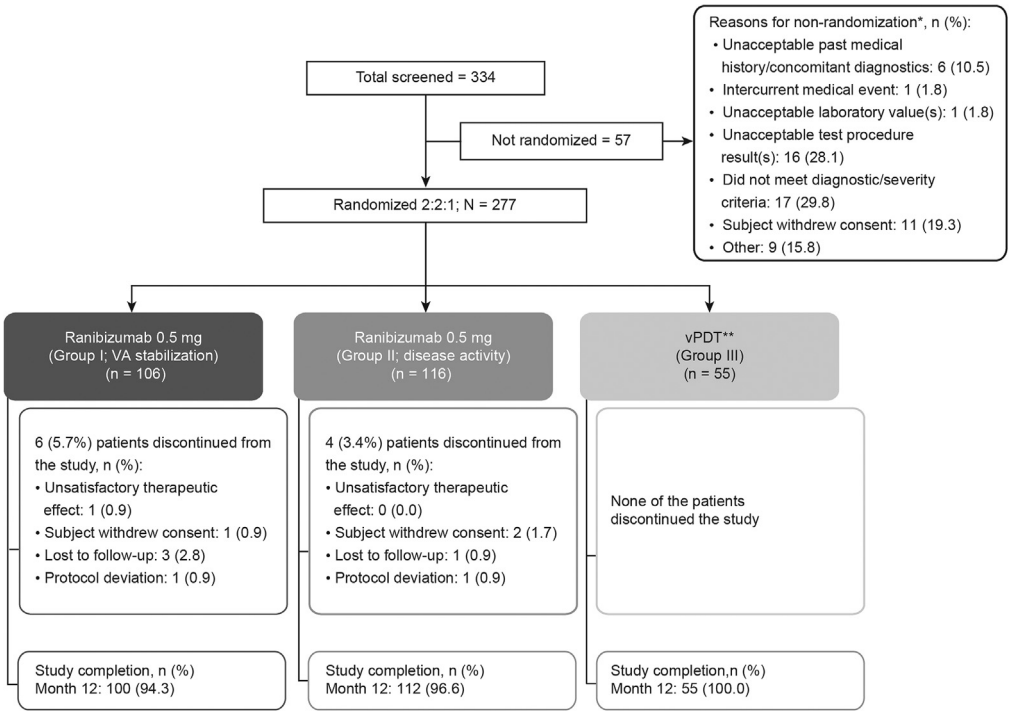

Figure 2. Patient disposition. *Percentages are based on the total number of patients screened but not randomized. **Patients randomized to verteporfin photodynamic therapy (vPDT) were allowed to receive vPDT at day 1, and from month 3 to 11 the investigator had the options to treat the patient's disease activity with ranibizumab 0.5 mg or vPDT (as per label) or both. VA = visual acuity.

At month 3, more than a 2-fold greater proportion of patients gained ≥10 and ≥15 ETDRS letters (or reached 84 letters) in both the ranibizumab treatment groups (groups I and II) versus patients treated with vPDT. At month 12, 69.5% (group I) and 69.0% of patients (group II) gained ≥10 ETDRS letters, while 53.3% (group I) and 51.7% of patients (group II) gained ≥15 ETDRS letters (or reached 84 letters) with continued individualized ranibizumab treatment (Fig 5). In patients treated with vPDT (group III), 49.1% and 32.7% gained ≥10 and ≥15 ETDRS letters (or reached 84 letters), respectively, at month 12 after the allowance of ranibizumab as of month 3. The proportion of patients losing ≥10 and ≥15 ETDRS letters across the treatment groups at month 3 and month 12 is shown in Figure 6 (available at www.aaojournal.org). With the allowance of ranibizumab as of month 3 in group III, fewer patients lost ≥10 and ≥15 ETDRS letters (3.6% each) at month 12 versus month 3.

Anatomic Outcomes

At month 12, the proportion of patients with subretinal fluid, intraretinal edema, and intraretinal cysts decreased from baseline across all treatment groups (Fig 7, available at www.aaojournal.org). The mean CRT decrease observed in patients in both ranibizumab groups at month 3 (−61.0 [group I] and −77.6 μm [group II]) was maintained with continued individualized ranibizumab treatment at month 12 (−66.6 and −71.3 μm for groups I and II, respectively). However, in group III the mean change in CRT decreased progressively from −12.0 μm at month 3 to −60.8 μm at month 12. At month 12, 63.8% to 65.7% of patients had resolution of CNV leakage across the treatment groups. Finally, in terms of lesion size, the mean change ± SD from baseline to month 12 was −0.31±1.65 (group I), −0.57±1.94 (group II), and 0.28±2.96 mm^2 (group III).

Treatment Exposure

Ranibizumab Injections. The median number of ranibizumab injections from day 1 until prior to month 12 was numerically higher in group I (4.0 injections) compared with group II (2.0 injections; Table 2). The mean number of ranibizumab injections was 4.6 and 3.5 for groups I and II, respectively. In group II, 62.9% of the patients did not require ranibizumab injections from months 6 to 11. Of the 55 patients who received vPDT at baseline (group III), 38 received ranibizumab injections as of month 3 until before month 12. These patients received a median of 2.0 ranibizumab injections (mean 2.4). Fifteen of 55 patients in group III did not receive ranibizumab treatment during the 12-month study period (Table 2).

Verteporfin Photodynamic Therapy. All patients randomized to ranibizumab (groups I and II) received sham PDT, while all patients in group III received active vPDT at baseline. In group III, 2 patients received ranibizumab prior to month 3 and were included in group II for safety analysis. As of month 3, 2 out of 53 patients in group III received a second active vPDT treatment over 12 months (Table 3, available at www.aaojournal.org).

Safety

Serious Adverse Events. Two cases of ocular SAEs in the study eye were reported over the 12-month study period (1 [0.9%] in group I [corneal erosion] and 1 [0.8%] in group II [retinoschisis]; Table 4, available at www.aaojournal.org). The case of corneal erosion was suspected to be related to the ocular injection procedure. Overall, nonocular SAEs were reported in 11 patients (6 [5.7%] in group I and 5 [4.2%] in group II; Table 4, available at www.aaojournal.org); none were suspected to be related to study drug or ocular injection. No ocular or nonocular SAEs were reported in group III during the study. There were no deaths and no cases of endophthalmitis, retinal

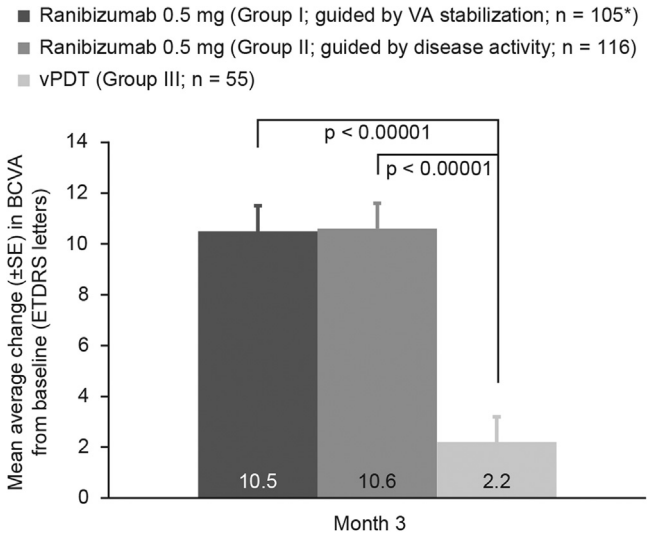

Figure 3. Mean average change in best-corrected visual acuity (BCVA) from baseline to month 1 through month 3 (primary end point; full analysis set [modified last observation carried forward]). *Of the 106 enrolled patients, 1 patient withdrew from the study before having a post-baseline visual acuity (VA) assessment and was excluded from this analysis. $P < 0.00001$ (for both groups I and II) versus verteporfin photodynamic therapy (vPDT). One-sided P values for treatment difference are derived from the 2-sided stratified Cochran–Mantel–Haenszel test using the row means score statistics. The primary objective was achieved at the multiple 1-sided alpha level of 0.001. ETDRS = Early Treatment Diabetic Retinopathy Study; SE = standard error.

detachment, myocardial infarction, or cerebrovascular events reported in any treatment group (Table 4, available at www.aaojournal.org).

Adverse Events (Study Eye). Ocular AEs were reported in 46 patients (43.4%) in group I, 44 patients (37.3%) in group II, 16 patients (42.1%) in group III with ranibizumab, and 4 patients (26.7%) in group III without ranibizumab (Table 5). The most frequent ocular AEs were conjunctival hemorrhage (group I: 11.3%; group II: 10.2%; group III with/without ranibizumab: 5.3%/0%) and punctate keratitis (group I: 7.5%; group II: 2.5%; group III with/without ranibizumab: 5.3%/0%; Table 5). Ocular AEs suspected to be related to study drug/ocular injection are summarized in Table 6 (available at www.aaojournal.org).

Nonocular AEs were reported in 48 patients (45.3%) in group I, 51 patients (43.2%) in group II, 19 patients (50.0%) group III with ranibizumab, and 5 patients (33.3%) in group III without ranibizumab (Table 5). The most frequent nonocular AEs were nasopharyngitis (group I: 11.3%, group II: 10.2%, group III with/without ranibizumab: 2.6%/13.3%), and headache (group I: 7.5%, group II: 9.3%, and group III with/without ranibizumab: 2.6%/0%; Table 5). The nonocular AEs suspected to be related to study drug/ocular injection are presented in Table 6 (available at www.aaojournal.org).

Discussion

The RADIANCE study is the first randomized controlled trial in patients with myopic CNV to demonstrate that intravitreal ranibizumab treatment, with re-treatment guided by either VA stabilization or disease activity criteria, was superior (statistically significant) compared with vPDT. From baseline to month 1 through month 3, ranibizumab treatment resulted in a mean average BCVA gain of more than 10 ETDRS letters for either dosing regimen compared with approximately 2 ETDRS letters for vPDT; therefore, the primary endpoint of the study was met. Furthermore, this study demonstrated that there were no differences in efficacy between the 2 commonly used individualized ranibizumab dosing regimens, with mean average BCVA change from baseline to month 1 through month 6 of more than 11 ETDRS letters for re-treatment guided by either VA stabilization criteria or disease activity criteria. Thus, the key secondary objective of the study was also met.

Both ranibizumab dosing regimens led to rapid and similar improvements in mean BCVA from baseline up to month 3 that were sustained with continued individualized ranibizumab treatment up to month 12, with BCVA gain of approximately 14 letters in both groups. At month 3, in

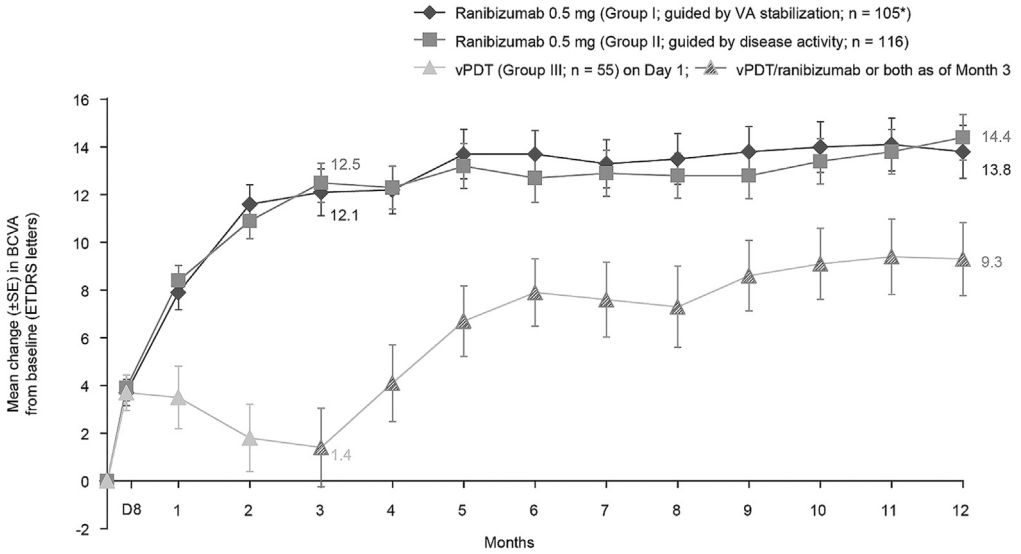

Figure 4. Mean change in best-corrected visual acuity (BCVA) from baseline over time up to month 12 (full analysis set [modified last observation carried forward]). *Of the 106 enrolled patients, 1 patient withdrew from the study before having a post-baseline visual acuity (VA) assessment and was excluded from this analysis. D8 = day 8; ETDRS = Early Treatment Diabetic Retinopathy Study; SE = standard error; vPDT = verteporfin photodynamic therapy.

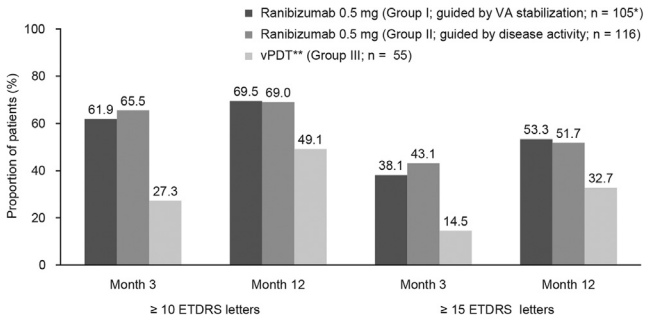

Figure 5. Categorized best-corrected visual acuity gain at months 3 and 12 (full analysis set [modified last observation carried forward]), representing the proportion of patients who gained ≥10 and ≥15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (or reaching 84 letters). *Of the 106 enrolled patients, 1 patient withdrew from the study before having a post-baseline visual acuity (VA) assessment and was excluded from this analysis. **Patients in group III were eligible to receive ranibizumab 0.5 mg and/or verteporfin photodynamic therapy (vPDT) as of month 3 at the investigators' discretion.

patients randomized to the vPDT group, the mean BCVA gain was considerably lower (+1.4 ETDRS letters) compared with that observed in ranibizumab-treated patients (>12 ETDRS letters). However, with the allowance of ranibizumab as of month 3, a steady increase in BCVA was observed in the vPDT group, although the mean improvement at month 12 (+9.3 ETDRS letters) was still numerically lower than that observed in groups I and II (no formal superiority testing performed). A similar observation was made with respect to the proportion of patients gaining ≥10 or ≥15 ETDRS letters (or reaching 84 letters). With the allowance of ranibizumab after month 3, a greater proportion of patients in the vPDT group gained ≥10 and ≥15 ETDRS letters (or reached 84 letters) at month 12 compared with month 3. Nevertheless, at month 12 the proportion of patients in the vPDT group was still numerically lower than observed in the ranibizumab groups. These results may indicate that it is important to initiate ranibizumab treatment early in patients with myopic CNV.

The anatomical outcomes of this study mirrored the overall treatment effect observed in the improvements of BCVA. There was a reduction in the proportion of patients with subretinal fluid, intraretinal edema, and/or intraretinal cysts from baseline to month 12 across the 3 treatment groups. At month 12, the mean reductions in CRT from baseline were comparable across the treatment groups.

The available data for ranibizumab treatment from trials across neovascular AMD, diabetic macular edema, and retinal vein occlusion support the concept of individualized dosing regimens to achieve optimal VA benefits while minimizing the risk of overtreatment or undertreatment.[40–42] An important secondary endpoint in the RADIANCE study was to evaluate the effects of 2 flexible individualized dosing regimens of ranibizumab to address the individual patient variability with respect to treatment requirement. While the VA stabilization–guided regimen required VA loss for re-treatment, the disease activity–guided regimen aimed to treat the anatomical changes that often precede the actual VA loss and

Table 2. Ranibizumab Treatment Exposure from Day 1 until Prior to Month 12 (Full Analysis Set*)

Exposure	Ranibizumab 0.5 mg		vPDT
	Group I, Guided by VA Stabilization (n=105)	*Group II, Guided by Disease Activity* (n=116)	*Group III*† (n=55)
No. of injections			
Total	488	404	131‡
Mean (SD)	4.6 (2.6)	3.5 (3.0)	2.4 (2.6)‡
Median	4.0	2.0	2.0‡
Frequency (month) of injections, n (%)§			
0	0 (0.0)	0 (0.0)	15 (27.3)
1	1 (1.0)	36 (31.0)	10 (18.2)
2	26 (24.8)	23 (19.8)	10 (18.2)
3	19 (18.1)	13 (11.2)	8 (14.5)
4	15 (14.3)	11 (9.5)	3 (5.5)
5	9 (8.6)	16 (13.8)	3 (5.5)
6	9 (8.6)	4 (3.4)	1 (1.8)
7	10 (9.5)	2 (1.7)	0 (0.0)
8	4 (3.8)	0 (0.0)	1 (1.8)
9	6 (5.7)	1 (0.9)	4 (7.3)
10	3 (2.9)	3 (2.6)	0 (0.0)
11	3 (2.9)	2 (1.7)	0 (0.0)
12	0 (0.0)	5 (4.3)	0 (0.0)

SD = standard deviation; VA = visual acuity; vPDT = verteporfin photodynamic therapy.
*Consisted of all randomized patients who received at least 1 application of study treatment (ranibizumab [sham] and/or vPDT [sham]) and had at least 1 post-baseline record of study eye VA data.
†Patients randomized to vPDT were allowed to receive vPDT at day 1, and from month 3 to 11 the investigator had the option to treat the patient's disease activity with ranibizumab 0.5 mg, vPDT (as per label), or both.
‡Ranibizumab injections received over months 3 to 12.
§Frequency denotes the number of injections received by patients (n, %) during the 12 months (e.g., [1] in group 3, 15 [27.3%] patients did not receive any injection [0 injection] during the whole of 12 months; [2] in group 1, 26 [24.8%] patients received 2 injections over 12 months.

Table 5. Most Frequent Ocular (Study Eye) and Nonocular Adverse Events (≥5% of Patients in any Group) from Day 1 to Month 12 (Safety Set*)

	Ranibizumab 0.5 mg		vPDT	
Preferred Term	*Group I, Guided by VA Stabilization (n=106)*	*Group II, Guided by Disease Activity (n=118)*	*Group III with Ranibizumab 0.5 mg as of Month 3 (n=38)*	*Group III without Ranibizumab 0.5 mg as of Month 3 (n=15)*
Ocular AEs, total	46 (43.4)	44 (37.3)	16 (42.1)	4 (26.7)
Conjunctival hemorrhage	12 (11.3)	12 (10.2)	2 (5.3)	0 (0.0)
Punctate keratitis	8 (7.5)	3 (2.5)	2 (5.3)	0 (0.0)
Dry eye	4 (3.8)	2 (1.7)	0 (0.0)	1 (6.7)
Eye pain	4 (3.8)	4 (3.4)	1 (2.6)	1 (6.7)
Injection site hemorrhage	3 (2.8)	3 (2.5)	2 (5.3)	0 (0.0)
Increased IOP	3 (2.8)	7 (5.9)	4 (10.5)	0 (0.0)
Cataract	1 (0.9)	2 (1.7)	0 (0.0)	1 (6.7)
Visual impairment	0 (0.0)	0 (0.0)	2 (5.3)	0 (0.0)
Nonocular AEs, total	48 (45.3)	51 (43.2)	19 (50.0)	5 (33.3)
Nasopharyngitis	12 (11.3)	12 (10.2)	1 (2.6)	2 (13.3)
Headache	8 (7.5)	11 (9.3)	1 (2.6)	0 (0.0)
Hypertension	3 (2.8)	5 (4.2)	3 (7.9)	0 (0.0)
Pain in extremity	2 (1.9)	1 (0.8)	0 (0.0)	1 (6.7)
Cystitis	1 (0.9)	1 (0.8)	2 (5.3)	0 (0.0)
Dental caries	0 (0.0)	2 (1.7)	0 (0.0)	1 (6.7)
Laryngitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)
Localized infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)
Lower respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)
Tinea pedis	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)
Tinnitus	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)

AE = adverse event; IOP = intraocular pressure; VA = visual acuity; vPDT, verteporfin photodynamic therapy.
Data are n (%). A patient with multiple occurrences of an AE under 1 treatment is counted only once in the AE category for that treatment.
*Consisted of all patients who received at least 1 application of study treatment (ranibizumab [sham] and/or vPDT [sham]) and had at least 1 post-baseline safety assessment.

therefore aimed to control disease progression earlier.[43] Patients treated with ranibizumab guided by VA stabilization criteria (group I) received a median of 4.0 injections compared with a median of 2.0 injections in patients treated with ranibizumab guided by disease activity criteria (group II). This difference in injection number between the 2 groups may be largely dictated by the loading dosage regimen in the protocol wherein a minimum of 2 injections were administered in group I before the VA stability could be assessed, whereas in group II, only 1 mandatory injection was administered at day 1 and disease activity was then assessed during the subsequent visit. The findings from this study appear to corroborate those from Muether et al,[43] suggesting that treatment guided by OCT and other disease activity criteria may provide a more sensitive approach to evaluate recurrence and provide similar BCVA gains with fewer injections and thus may be preferred over treatment guided by VA stabilization criteria. Patients in the vPDT group (group III) received a median of 2.0 injections between months 3 and 11. The efficacy results of this study are comparable to those observed in the phase II, single-arm REPAIR study, wherein ranibizumab was effective in preventing vision loss and improving vision (+13.76 ETDRS letters at month 12) with a median of 3.0 injections.[39] The observed numeric difference in the efficacy outcomes and injection frequency between these studies could be attributed to the differences in the baseline disease and ocular characteristics of the enrolled patients and the different re-treatment criteria employed in these studies. Furthermore, the results from the current study show that a median of 2.0 (group II) to 4.0 (group I) injections was adequate to provide clinically meaningful VA benefits in patients with myopic CNV. This is lower than the number of ranibizumab injections required to provide VA benefits in other indications, such as neovascular AMD. The difference in ranibizumab injection frequency across indications may be due to inherent differences in the pathophysiology of the diseases and the self-limiting nature of myopic CNV.[44]

The results from the current study showed that ranibizumab and vPDT treatments were generally well tolerated in patients with myopic CNV. Overall, there were low incidences of ocular (0.7%) and nonocular (4.0%) SAEs reported in groups I and II and none in group III. No deaths or cases of endophthalmitis, retinal detachment, myocardial infarction, or cerebrovascular events were reported across the treatment arms during the 12-month study period. Ocular AEs were reported in 36.4% to 43.4% of patients across the 3 treatment groups. The reported cases of increased IOP were transient and did not require IOP-lowering treatment. Overall, nonocular AEs were reported in 43.2% to 45.3% of patients across the 3 treatment groups. The 12-month safety results from the RADIANCE study corroborate the safety findings of the REPAIR study. Also, the overall safety of ranibizumab treatment in patients with myopic CNV was comparable to the previously established safety profile of ranibizumab in other

indications, such as neovascular AMD, diabetic macular edema, and retinal vein occlusion.

In the current study, patients with myopic CNV had a mean axial length of 29 mm and a mean refraction sphere of −12.5 diopters, which is representative of the general patient population with myopic CNV and is considered to be appropriate to evaluate the effect of ranibizumab.[9–11] Thus, there are no obvious limitations to the interpretation of the study results with respect to the external validity of the study population. In terms of study limitations, this study was designed to allow ranibizumab treatment as of month 3 in patients randomized to vPDT, thereby limiting the longer-term comparison between ranibizumab and vPDT. However, on the basis of the results from previous clinical trials with ranibizumab in patients with myopic CNV,[34–38] it was evident that ranibizumab treatment was able to provide relevant VA improvements; thus, it was important to design the study such that the patients in the vPDT group also may benefit from ranibizumab treatment. Therefore, in this study, the patients randomized to vPDT were allowed to receive ranibizumab after the evaluation of the primary end point at month 3. Ongoing studies such as LUMINOUS (Observe the Effectiveness and Safety of Ranibizumab in Real Life Setting) conducted in a real-life setting may provide valuable information on the long-term safety and effectiveness of ranibizumab in routine clinical practice.[45]

In conclusion, RADIANCE, the first phase III randomized controlled trial evaluating anti-VEGF treatment in patients with myopic CNV, demonstrated that individualized ranibizumab treatment provides superior VA benefits versus vPDT up to month 3. Continued individualized ranibizumab treatment was effective in further improving and sustaining BCVA in patients with myopic CNV over 12 months. In patients randomized to vPDT, allowing ranibizumab treatment as of month 3 provided BCVA improvements up to month 12. Ranibizumab retreatment guided by disease activity criteria was able to provide similar VA benefits with fewer injections than ranibizumab treatment guided by VA stabilization criteria. Overall, ranibizumab was well tolerated in patients with myopic CNV over 12 months. The phase II REPAIR and the phase III RADIANCE studies provide robust clinical evidence for the efficacy and safety of ranibizumab in patients with myopic CNV.[39]

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Footnotes and Financial Disclosures

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Appendix 1 (Continued)

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