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Outcomes with As-Needed Ranibizumab after Initial Monthly Therapy

Long-Term Outcomes of the Phase III RIDE and RISE Trials

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Purpose: To determine whether the efficacy and safety achieved with monthly ranibizumab as treatment for diabetic macular edema (DME) can be maintained with less-than-monthly treatment.

Design: Open-label extension (OLE) phase of randomized, sham-controlled phase III trials: RIDE (NCT00473382) and RISE (NCT00473330).

Participants: Five hundred of 582 adults who completed the 36-month randomized core studies elected to enter the OLE.

Methods: All patients participating in the OLE were eligible to receive 0.5 mg ranibizumab according to predefined re-treatment criteria: Treatment was administered when DME was identified by the investigator on optical coherence tomography or when best-corrected visual acuity (BCVA) worsened by ≥ 5 Early Treatment Diabetic Retinopathy Study letters versus month 36. Patients were observed at 30-, 60-, or 90-day intervals depending on the need for treatment.

Main Outcome Measures: The incidence and severity of ocular and nonocular events, proportion of patients with ≥ 15 -letter best-corrected visual acuity (BCVA) gain from baseline, mean BCVA change from month 36 (final core study visit), mean central foveal thickness (CFT), and mean CFT change from month 36.

Results: A mean of 4.5 injections were administered over a mean follow-up of 14.1 months. Approximately 25% of patients did not require further treatment based on protocol-defined re-treatment criteria. Mean BCVA was sustained or improved in these patients through the end of follow-up. Approximately 75% of patients received ≥ 1 criteria-based re-treatment; mean time to first re-treatment was approximately 3 months after the last masked-phase visit. Mean BCVA remained stable in re-treated patients; CFT was generally stable with a trend toward slight thickening in all patients when mandatory monthly therapy was relaxed.

Conclusions: Vision gains achieved after 1 or 3 years of monthly ranibizumab therapy were maintained with a marked reduction in treatment frequency; some patients required no additional treatment. These observations are consistent with other studies evaluating induction followed by maintenance ranibizumab therapy for DME. Patients whose treatment was deferred by 2 years (randomized initially to sham) did not ultimately achieve the same BCVA gains as patients who received ranibizumab from baseline. Ranibizumab's safety profile in the OLE appeared similar to that observed in the controlled core studies and other studies. *Ophthalmology* 2015;122:2504-2513 © 2015 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



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

The efficacy of intravitreal ranibizumab as a therapy for diabetic macular edema (DME) is now well established. Multiple randomized, controlled clinical trials, including DRCR.net Protocol I,^{1,2} RIDE and RISE,^{3,4} Ranibizumab for Edema of the macula in Diabetes 2 (READ-2),^{5,6} RESOLVE,⁷ and RESTORE⁸ have demonstrated superior visual outcomes with ranibizumab treatment compared with sham injection, intravitreal steroid therapy, or macular laser photocoagulation. In the RIDE and RISE phase III studies, monthly intravitreal injection with 0.3

or 0.5 mg ranibizumab for 24 months was superior to sham injection (with optional macular laser) across all the major outcomes assessed, including improvement in best-corrected visual acuity (BCVA), measured as the mean change from baseline or proportion of patients gaining ≥ 15 letters, and improvements in retinal anatomy as assessed on optical coherence tomography (OCT), color fundus photography, and fluorescein angiography. In addition, patients randomized to ranibizumab experienced significantly higher rates of improvement in diabetic retinopathy (DR)

severity and lower rates of worsening of DR, with fewer eyes worsening to proliferative DR compared with patients randomized to sham injections. Of note, patients initially randomized to sham injection who crossed over to monthly ranibizumab at month 24 did not experience the degree of improvements after 12 monthly injections as those patients randomized to ranibizumab from the beginning of the study.⁹

Outcomes of these studies underscore the importance of early diagnosis and initiation of anti-vascular endothelial growth factor (VEGF) therapy for patients with DME to achieve optimal visual and anatomic outcomes, as well as potential modification of the natural history of the underlying DR. In clinical practice, intravitreal ranibizumab has become an important frontline DME therapy. Thus, it is important to understand whether the efficacy observed in phase III studies is maintained in a long-term treatment setting.

Several studies in patients with DME inform this topic and show that less than monthly ranibizumab treatment in patients with DME may be effective for maintenance of vision and management of macular edema. For example, the RESTORE and DRCR.net Protocol I studies showed that after an initial period of intensive therapy, BCVA can be maintained with a significant decrease in treatment burden in patients with DME using a protocol-specified re-treatment algorithm.^{1,8,10} The design of the RIDE and RISE open-label extension (OLE) studies allowed further exploration of a less than monthly treatment strategy in patients with DME after an initial monthly treatment phase.

The RIDE and RISE OLE was designed to determine if the visual and anatomic benefits achieved during the 36-month monthly dosing period could be maintained while offering a lower treatment and visit burden when appropriate for patients on an individual basis. Patients who completed the 36-month masked phase of the study were eligible to continue, at their option, in the OLE phase, which consisted of a criteria-based pro re nata (PRN) treatment strategy in which 0.5 mg ranibizumab was administered on evidence of DME on OCT or visual acuity loss (≥ 5 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) from month 36. This allowed a continued evaluation of the ocular and nonocular safety of ranibizumab in patients with DME and further study of whether criteria-based PRN treatment could maintain the gains in visual acuity and anatomic measures achieved with monthly treatment. In this report, we describe the outcomes observed in the cohort of 500 patients who completed the phase III core studies and enrolled in the OLE.

Methods

Clinical Trial Design

RIDE (NCT00473382) and RISE (NCT00473330) were methodologically identical, randomized, phase III, double-masked, sham-injection-controlled clinical trials of ranibizumab in patients with DME. The design, baseline patient characteristics, and core efficacy and safety outcomes of the trials have been described.^{3,9} Study protocols were approved by institutional review

boards and ethics committees, and participants provided written informed consent.

Patients and Treatment

Patients who had not previously discontinued study drug treatment and completed month 36 of RIDE or RISE were eligible for participation in the OLE phase. All patients were eligible to receive PRN 0.5 mg ranibizumab on the basis of predefined re-treatment criteria that assessed visual and anatomic stability. At each visit, treatment was administered if there was evidence of DME on OCT (evaluated by the investigator and defined as the presence of intraretinal fluid or cysts, subretinal fluid, or subretinal pigment epithelium fluid; there were no absolute macular or central subfield thickness criteria that mandated treatment) or if patients demonstrated a decrease in BCVA of ≥ 5 ETDRS letters from the month 36 value (due to DME and not another cause). Because the OLE study design was finalized and the study was carried out before the US Food and Drug Administration (FDA) approval of 0.3 mg monthly ranibizumab for patients with DME, the determination to use the 0.5-mg dose was made on the basis of the efficacy and safety data in patients with DME that existed at the time, such as the RESTORE study.^{1,8,11}

A flexible visit schedule was used, with per-protocol visits every 30 (± 7) days for patients who had received a ranibizumab injection during the last visit and extension of the interval at the discretion of the evaluating physician to 60 (± 7) or 90 (± 7) days if no treatment was given during the last visit. The month 48 visit was mandatory for all patients participating in the OLE, regardless of the scheduled visit interval, to provide for an annual assessment from the month 36 visit. Follow-up was planned to end at month 60 from the original study baseline or 30 days after FDA approval of ranibizumab for DME, whichever occurred first. On FDA approval, the trial ended, resulting in varying durations of follow-up time for individual patients in the OLE phase.

Objectives

The objectives were to evaluate the long-term safety, tolerability, and efficacy of multiple intravitreal injections of 0.5 mg ranibizumab administered using a criteria-based PRN treatment regimen. The treatment criteria were designed to maintain the visual and anatomic stability achieved in patients with DME during the RIDE and RISE core studies, while allowing additional flexibility in dosing and office visit intervals for patients achieving disease stability.

Statistical Analysis

Data from the OLE phases of RIDE and RISE were pooled for these analyses. Because of the variable follow-up time and patient attrition during the OLE, descriptive statistics are provided based on observed data. Efficacy and safety analyses for the OLE phase are presented with observed values and no imputation for missing data. For key efficacy measures, estimates and confidence intervals (CIs) are provided for continuous variables for each treatment group. For binary variables, the proportion is provided from baseline or from month 36 for each treatment group. All CIs were 2 sided and at the 95% level. Month 36 (final scheduled visit in the core study) was used as a baseline for calculations of change in visual and anatomic parameters during the OLE. Key efficacy results are also presented from core study baseline.

Efficacy Assessments

Although all patients were eligible to receive 0.5 mg ranibizumab PRN in the OLE, some efficacy analyses are presented by prior

Table 2. Patient Disposition in the RIDE and RISE Open-Label Extension by Prior Treatment Group During Core Phase (Pooled Data)

	Sham/Crossover	Ranibizumab 0.3 mg	Ranibizumab 0.5 mg
Enrollment at baseline	257	250	252
Patients completing month 36, n (%)	188 (73.2)	196 (78.4)	198 (78.6)
Patients enrolled in OLE, n (%)	165 (64.2)	172 (68.8)	163 (64.7)
Follow-up during OLE, mean (SD), mos	13.8 (5.4)	14.5 (5.4)	14.1 (5.8)
Patients receiving re-treatment in OLE, n (%)	121 (73.3)	130 (75.6)	128 (78.5)
Patients not receiving re-treatment in OLE, n (%)	44 (26.7)	42 (24.4)	35 (21.5)

OLE = open-label extension; SD = standard deviation.

treatment group in the core studies (prior sham/crossover to monthly 0.5 mg ranibizumab, prior monthly 0.3 mg ranibizumab, and prior monthly 0.5 mg ranibizumab). Efficacy assessments included mean BCVA and central foveal thickness (CFT) by prior treatment group in the core studies, mean BCVA and CFT change from month 36 by prior treatment group, and mean BCVA and CFT change from month 36 in patients treated during the OLE and in those not requiring treatment based on stability criteria. Month 36 was used as a baseline for comparison of outcomes during the OLE to determine the efficacy of PRN 0.5 mg ranibizumab for maintaining outcomes achieved at the end of the core studies.

The University of Wisconsin Fundus Photograph Reading Center evaluated study eye macular OCT images from OLE visits at months 42, 48, and 60, and early termination if applicable, as prespecified in the protocol. The Reading Center also evaluated the fundus photographs and fluorescein angiograms taken at months 48 and 60. Changes in ETDRS DR severity score (DRSS) and the rate of worsening to proliferative DR were assessed as previously described.⁹

Progression of DR was comprehensively evaluated in a time-to-event analysis of first new proliferative diabetic retinopathy (PDR) event using a composite outcome end point that included both changes in DR severity on fundus photographs plus the occurrence of clinically significant adverse events (AEs) or procedures. A new PDR event was defined by the first occurrence of (1) progression from nonproliferative DR (DRSS <60) at baseline to PDR (DRSS ≥60) at a later time point, (2) use of pan-retinal photocoagulation laser, (3) vitreous hemorrhage (AE or slit-lamp grade 0 at baseline to >0 at a later time point), (4) cases identified by ophthalmoscopy, (5) use of vitrectomy for reasons related to DR or its complications, (6) iris neovascularization AE, or (7) retinal neovascularization AE.

Safety Assessments

Safety for all patients enrolled in the OLE was summarized for the following outcome measures: incidence and severity of ocular and nonocular AEs and serious adverse events (SAEs), and incidence of deaths. In the OLE phase of the study, the population used for safety analyses included all patients enrolled in the OLE. Safety analysis results are summarized by prior treatment group in the core studies.

Results

Demographic and baseline characteristics were similar to the baseline characteristics of the overall population enrolled in the RIDE and RISE core studies and were well balanced among the 3 prior treatment groups (Table 1, available at www.aaojournal.org). A total of 759 patients were originally randomized in the 2 core

studies; 582 completed month 36, of whom 500 elected to enter the OLE (Table 2). There did not seem to be meaningful differences in the baseline characteristics of patients who did or did not enroll in the OLE. Ranibizumab was approved for treatment of DME in the United States on August 10, 2012, and the per-protocol conclusion of the OLE occurred approximately 30 days later. The majority of the 211 patients (42.2% of those enrolled in the OLE) who did not complete the month 48 visit discontinued because of the conclusion of the study (n = 160), and the same was true of those who did not complete the month 60 visit. Few patients who entered the OLE were lost to follow-up by month 48 (n = 7) or month 60 (n = 12). In the data collected up to the point of study conclusion, the mean follow-up duration during the OLE was 14.1 months (Fig 1A).

Overall, 24.2% of patients enrolled in the OLE continued to meet visual and anatomic stability criteria, and thus did not require any additional therapy with 0.5 mg ranibizumab during follow-up to maintain the visual and anatomic gains achieved at the end of the core studies (Fig 1B). The remaining 75.8% of patients received at least 1 criteria-based injection in the OLE, with a mean of 2.5, 2.4, and 2.1 months for the prior 0.5 mg ranibizumab, prior 0.3 mg ranibizumab, and prior sham/crossover groups, respectively, from month 36 to the first open-label ranibizumab re-treatment. Per the core study protocol, no injection was given to patients at the month 36 visit as part of the masked treatment phase, and month 36 injections occurred only if patients met the PRN re-treatment category; therefore, this corresponds to a 3.1- to 3.5-month interval from the last injection administered during the core phase of RIDE and RISE. Of 298 patients in the OLE who had at least 12 months of additional follow-up from month 36, 58 (19.5%) maintained vision with no further therapy.

Overall, an annualized rate of 3.8 ranibizumab injections was administered during the OLE (mean of 4.5 injections over a mean 14.1 months of follow-up); among the subgroup of patients requiring treatment, an annualized rate of 4.8 injections was given (mean of 5.9 injections over a mean 14.6-month follow-up period). In 30% of cases in which no injection was given at a visit, the subsequent visit was extended beyond 30 days (Table 3, available at www.aaojournal.org).

Visual Acuity and Anatomic Outcomes

The mean change in BCVA from baseline during the core and extension studies is presented in Figure 2. After the transition from monthly to PRN therapy, mean BCVA gains achieved by patients at the end of the core studies were maintained throughout the extension study, with patients initially randomized to

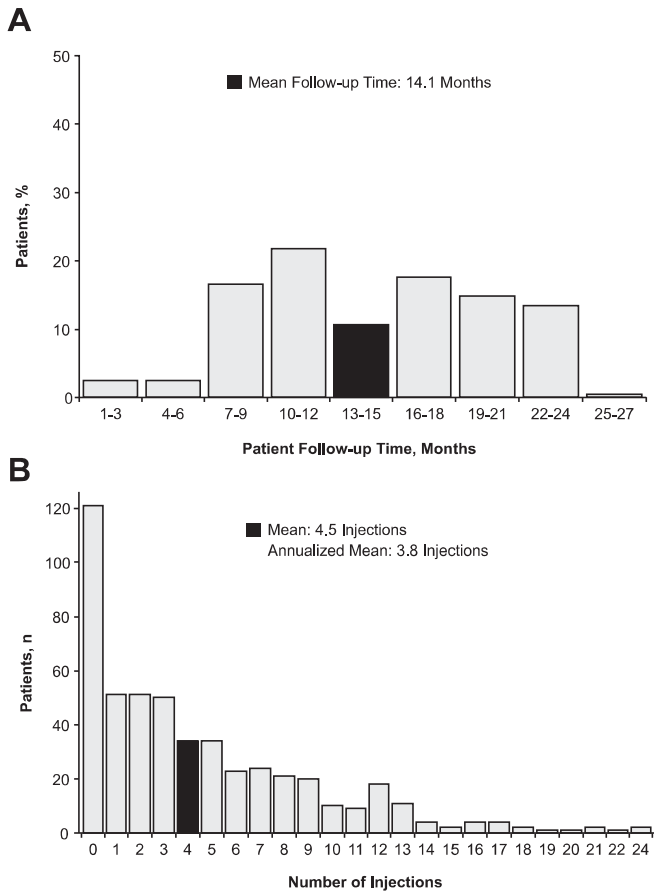


Figure 1. Distribution of (A) patient follow-up time and (B) ranibizumab exposure in the pooled RIDE and RISE open-label extension (OLE) phase.

ranibizumab treatment continuing to demonstrate improved functional outcomes compared with patients in the sham/crossover group who had ranibizumab treatment deferred for 24 months. Because of the variable follow-up time in the OLE, the data beyond month 54 became unstable because of the low number of patients with follow-up beyond that point. The actual mean BCVA during the core and extension studies (Fig 3, available at www.aajournal.org) showed similar results.

Month 36 (end of the core studies) was used as a new baseline for assessing BCVA change after the transition to PRN therapy. Among all patients entering the OLE, the mean BCVA change from month 36 was within ± 5 ETDRS letters at all time points, demonstrating the efficacy of the PRN regimen for maintaining visual outcomes in this study (Fig 4A). This remained true when patients were analyzed by prior treatment group in the core studies (Fig 4B). Furthermore, patients who met PRN stability criteria and therefore did not require treatment with ranibizumab during the OLE experienced a mean change in BCVA of +1.9 letters from month 36 to month 48 (Fig 4C). Patients who received at least 1 ranibizumab injection under the protocol-specified criteria experienced a mean change of -1.0 letter over this same time period. Likewise, CFT remained stable under the PRN regimen, with a trend toward a small ($<50 \mu\text{m}$) increase in retinal thickness for all patients after transitioning from monthly to as-needed therapy (Fig 4D–F).

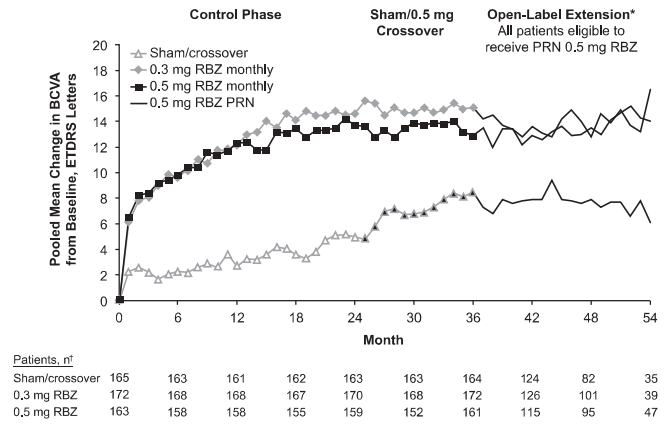


Figure 2. Pooled (RIDE and RISE) mean change from baseline in best-corrected visual acuity (BCVA) among patients enrolled in the open-label extension (OLE) (observed data). ETDRS = Early Treatment Diabetic Retinopathy Study; PRN = pro re nata; RBZ = ranibizumab. *Data become unstable after month 54 because of the low number of patients at that point. [†]Treatment during core study.

The PRN regimen was effective for maintaining categoric visual acuity outcomes achieved with monthly therapy. Although not all patients enrolled in the core studies enrolled in the extension, at month 48, the proportion of patients in the extension who achieved a ≥ 15 ETDRS letter visual gain from original baseline (day 0) was similar to the proportions seen at month 36 for patients randomized in the core studies (Table 4). Among patients enrolled in the OLE, approximately 45%, 49%, and 20% of patients had gained ≥ 15 ETDRS letters from baseline at month 48 in the prior 0.5 mg ranibizumab, prior 0.3 mg ranibizumab, and prior sham/crossover groups, respectively. Among all patients enrolled in the core study (not limited to only those who enrolled in the extension), 41%, 44%, and 21% of patients gained ≥ 15 ETDRS letters from baseline at month 36 in the 0.5 mg ranibizumab, 0.3 mg ranibizumab, and sham/crossover groups, respectively.

For patients enrolled in the OLE, approximately 65%, 64%, and 51% of patients achieved a Snellen equivalent of 20/40 or better at month 48 in the prior 0.5 mg ranibizumab, prior 0.3 mg ranibizumab, and prior sham/crossover groups, respectively. This was also similar to the results seen at month 36 for the original study population: For all patients enrolled in the core study (not limited to those who enrolled in the extension), 59%, 59%, and 42% of patients reached a Snellen equivalent of 20/40 or better at month 36 in the 0.5 mg ranibizumab, 0.3 mg ranibizumab, and sham/crossover groups, respectively.

Diabetic Retinopathy Severity

At the end of the 24-month sham-controlled phase of the RIDE and RISE studies, the rates of ≥ 2 - and ≥ 3 -step DRSS improvement in patients randomized to sham injections were 5.4% and 1.3%, respectively,⁹ and the respective rates of ≥ 2 - and ≥ 3 -step DRSS worsening were 9.6% and 5.0%. These rates represent the natural history of ≥ 2 - and ≥ 3 -step DRSS improvement and worsening in contemporaneous patients with DME not receiving ranibizumab (treated only with macular laser when indicated). Under monthly 0.3 mg ranibizumab treatment, 37.6% and 13.2% of patients achieved ≥ 2 - and ≥ 3 -step DRSS improvement, respectively,⁹ and 1.3% and 1.3% of patients experienced ≥ 2 - and ≥ 3 -step

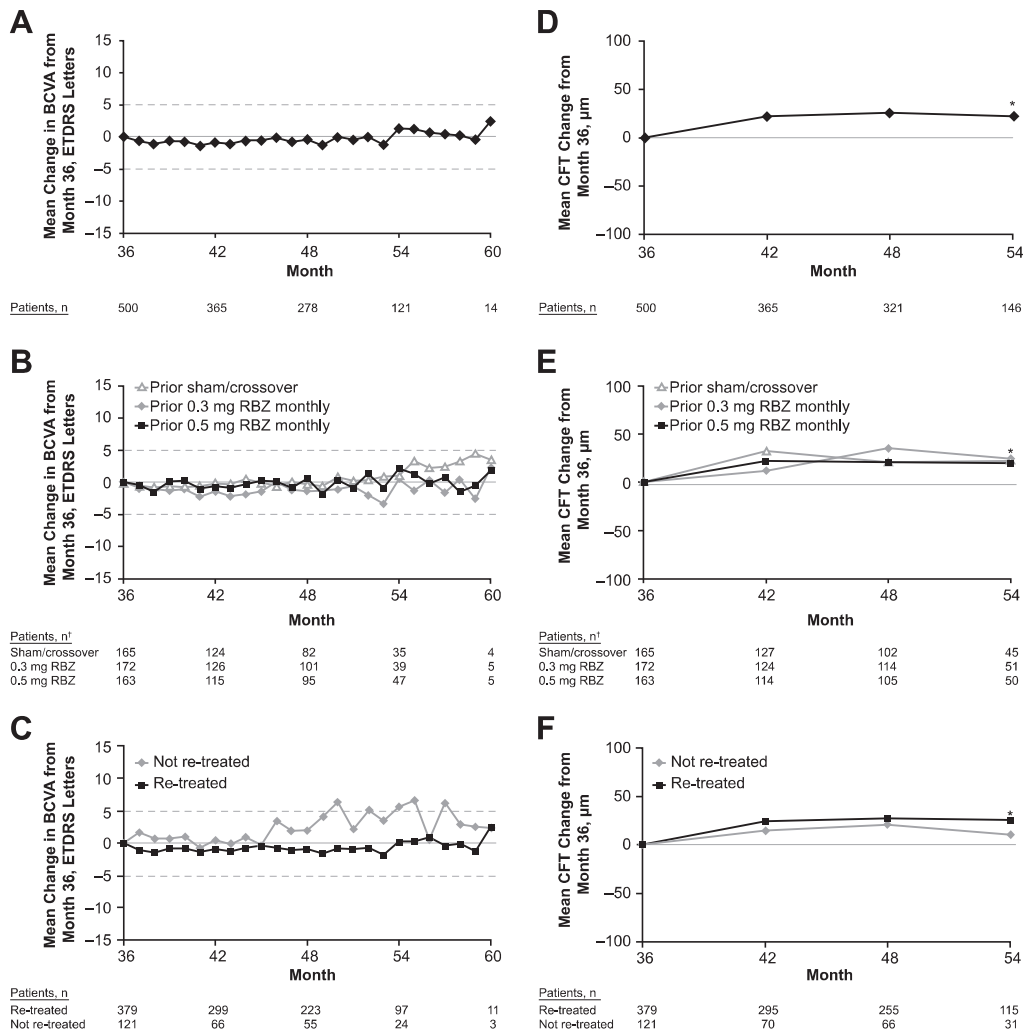


Figure 4. Pooled (RIDE and RISE) mean change in best-corrected visual acuity (BCVA) and central foveal thickness (CFT) in study eye from month 36. Mean change in BCVA from month 36 for (A) all patients in the open-label extension (OLE), (B) patients by prior treatment group in the core studies, and (C) patients receiving or not receiving criteria-based pro re nata (PRN) treatment in the extension phase. Mean change in CFT from month 36 for (D) all patients in the OLE, (E) patients by prior treatment group in the core studies, and (F) patients receiving or not receiving criteria-based PRN treatment in the extension phase. Dashed horizontal lines in A, B, and C indicate ± 5 Early Treatment Diabetic Retinopathy Study (ETDRS) letters. *Insufficient data were available beyond month 54. [†]Prior treatment group during the core studies. BCVA = best-corrected visual acuity; RBZ = ranibizumab.

DR worsening, respectively, at month 24. At month 36, after 12 monthly ranibizumab injections, patients initially randomized to sham injections showed 23.8% and 3.8% rates of ≥ 2 - and ≥ 3 -step DRSS improvement, respectively, and the respective rates of ≥ 2 - and ≥ 3 -step DRSS worsening were 9.2% and 3.8%.¹² Among patients receiving 0.3 mg ranibizumab, 38.9% and 15.0% experienced ≥ 2 - and ≥ 3 -step DRSS improvement, respectively, and 2.6% and 1.3% experienced ≥ 2 - and ≥ 3 -step DRSS worsening, respectively, at month 36.¹²

Given the substantial effect of monthly ranibizumab on increasing the likelihood of DRSS improvement and decreasing the likelihood of DRSS worsening, we also wanted to examine the effect of initiating less-frequent therapy on DR severity. Of note, PRN re-treatment criteria were not related to changes in DRSS. Among patients with evaluable DR outcomes at month 48, under the PRN regimen, 27.2% and 11.2% of patients from the prior 0.3 mg treatment group who continued in the OLE (n = 125) demonstrated ≥ 2 - and ≥ 3 -step DRSS improvement, respectively,

and 2.4% and 1.6% experienced ≥ 2 - and ≥ 3 -step DRSS worsening, respectively (Table 5). Similar efficacy was noted with the 0.5 mg ranibizumab group (n = 118).

A time-to-event analysis was used to assess time to development of a new proliferative DR event (Fig 5), using the previously reported composite methodology for assessing disease worsening by this metric⁹ and as described earlier. Patients treated with ranibizumab had a low rate of development of PDR in the OLE phase. Patients originally randomized to ranibizumab had a lower risk of developing a new PDR event compared with patients originally randomized to sham over time through month 54.

Safety

Treatment with PRN 0.5 mg ranibizumab during the OLE was generally well tolerated. Because the data were not controlled and patients had variable treatment exposure and durations of

Table 4. Efficacy Outcomes in the RIDE and RISE Open-Label Extension by Prior Treatment During the Core Studies

	RIDE			RISE		
	Sham/ Crossover	Ranibizumab 0.3 mg	Ranibizumab 0.5 mg	Sham/ Crossover	Ranibizumab 0.3 mg	Ranibizumab 0.5 mg
Month 48 BCVA change from month 36, mean (95% CI), ETDRS letters	-2.6 (-5.6 to 0.5)	-0.9 (-3.6 to 1.8)	0.6 (-1.2 to 2.4)	1.3 (-0.3 to 2.9)	-1.7 (-3.6 to 0.2)	0.8 (-1.1 to 2.7)
Month 48 CFT change from month 36, mean (95% CI), μm	9.6 (-18.4 to 37.6)	46.1 (-2.6 to 94.8)	44.1 (16.1-72.1)	29.6 (3.4-55.7)	23.3 (-7.7 to 54.3)	4.2 (-17.1 to 25.4)
No. of patients in analysis						
Month 24	130	125	127	127	125	125
Month 36	130	125	127	127	125	125
Month 48	34	39	39	48	62	56
% of patients with ≥ 15 -letter gain from baseline at:						
Month 24	12.3	33.6	45.7	18.1	44.8	39.2
Month 36	19.2	36.8	40.2	22.0	51.2	41.6
Month 48	17.6	48.7	41.0	22.9	50.0	48.2
% of patients with < 15 -letter loss from baseline at:						
Month 24	91.5	98.4	96.1	89.8	97.6	97.6
Month 36	92.3	96.8	96.1	91.3	99.2	97.6
Month 48	94.1	97.4	97.4	97.9	100	100
% of patients achieving BCVA Snellen equivalent $\geq 20/40$ at:						
Month 24	34.6	54.4	62.2	37.8	60.0	63.2
Month 36	42.3	55.2	59.1	42.5	63.2	59.2
Month 48	47.1	64.1	56.4	54.2	62.9	73.2

BCVA = best-corrected visual acuity; CFT = central foveal thickness; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study. Months 24 and 36 are based on patients randomized in the core study. Month 48 is based on patients enrolled in the open-label extension (OLE) phase.

follow-up, only limited comparisons and conclusions can be drawn from the safety data. Ocular AEs (Table 6, available at www.aaojournal.org) were similar to those observed during the core, sham-controlled studies through month 24. The most common ocular AEs in the study eye observed during the OLE were macular edema, retinal hemorrhage, conjunctival hemorrhage, vitreous floaters, eye pain, and cataract. Ocular AEs typically seen in patients with DME, such as vitreous hemorrhage, were uncommon ($< 3\%$ of patients during the OLE). Ocular SAEs in the study eye occurred infrequently and were reported in 9 of 500 patients (1.8%). A small percentage ($< 3\%$) of ocular AEs were reported as severe. Two of 500 patients withdrew from the study because of AEs, 1 patient with retinal detachment and 1 patient

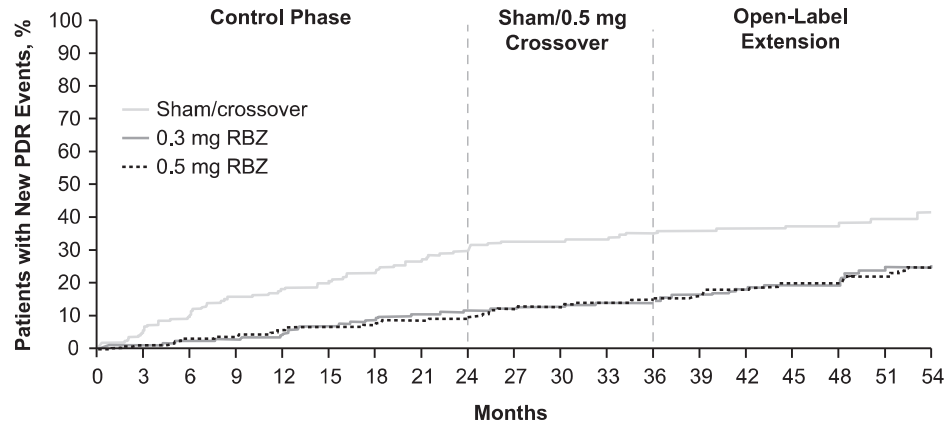
with retinal hemorrhage and blindness. Overall, 2225 injections were administered during the OLE, and no cases of endophthalmitis were reported.

Systemic AEs observed during the OLE were also similar to those observed during the core, sham-controlled studies through month 24. Nonocular SAEs potentially related to VEGF inhibition occurred in 8.4% of patients in the OLE (Table 7, available at www.aaojournal.org). No increase in SAEs was noted among patients who required re-treatment during the OLE versus those who did not require re-treatment (Table 8). During the OLE, the incidence of stroke in all patients enrolled was 2.2% and the incidence of myocardial infarction was 2.4%. Eighteen deaths occurred during the OLE; causes of death included cardiac

Table 5. Patients in the RIDE and RISE Open-Label Extension with Early Treatment Diabetic Retinopathy Study Diabetic Retinopathy Severity Score Change from Baseline at Months 36 and 48 by Treatment Group During the Core Studies (Pooled, Observed Data*)

Patients, n (%)	Month 36: End of Core Studies			Month 48: OLE Phase		
	Sham/Crossover (n = 123)	Ranibizumab 0.3 mg (n = 124)	Ranibizumab 0.5 mg (n = 117)	Sham/Crossover (n = 124)	Ranibizumab 0.3 mg (n = 125)	Ranibizumab 0.5 mg (n = 118)
DRSS Improvement						
≥ 3 steps	7 (5.7)	22 (17.7)	22 (18.8)	6 (4.8)	14 (11.2)	9 (7.6)
≥ 2 steps	36 (29.3)	57 (46.0)	52 (44.4)	26 (21.0)	34 (27.2)	42 (35.6)
≥ 1 step	61 (49.6)	77 (62.1)	70 (59.8)	53 (42.7)	56 (44.8)	60 (50.8)
DRSS Worsening						
≥ 3 steps	4 (3.3)	1 (0.8%)	1 (0.9)	8 (6.5)	2 (1.6)	1 (0.8)
≥ 2 steps	10 (8.1)	2 (1.6%)	3 (2.6)	14 (11.3)	3 (2.4)	3 (2.5)
≥ 1 step	12 (9.8)	4 (3.2%)	4 (3.4)	17 (13.7)	11 (8.8)	8 (6.8)

*Patients enrolled in the open-label extension (OLE) with diabetic retinopathy (DR) outcomes at baseline and month 48.



Patients at Risk, n*	
Sham/crossover	165 156 148 139 135 131 127 120 116 111 111 110 107 104 101 84 55 43 28
0.3 mg RBZ	172 170 168 167 164 160 156 154 152 151 150 148 147 142 136 120 90 72 47
0.5 mg RBZ	163 161 158 157 154 152 150 148 147 143 142 140 138 132 124 105 79 62 35

Figure 5. Time to development of new proliferative diabetic retinopathy (PDR) event, pooled, observed data from RIDE and RISE among patients enrolled in the open-label extension (OLE). New PDR event defined by the first occurrence of (1) progression from nonproliferative diabetic retinopathy (NPDR) (DR severity score [DRSS] <60) at baseline to PDR (DRSS ≥60) at a later time point, (2) use of pan-retinal photocoagulation laser, (3) vitreous hemorrhage (adverse event [AE] or slit-lamp grade 0 at baseline to >0 at a later time point), (4) cases identified by ophthalmoscopy, (5) use of vitrectomy for any reasons related to DR or its complications, (6) iris neovascularization AE, or (7) retinal neovascularization AE. A patient is no longer at risk once he or she develops the first PDR event. *Treatment during core study. RBZ = ranibizumab.

conditions, multiorgan failure, aggravated renal failure, squamous cell carcinoma of the lung, metastatic ovarian cancer, and decubitus ulcer; in 2 patients the cause of death was unknown (Table 9, available at www.aaojournal.org).

Discussion

The OLE phase of RIDE and RISE showed that a criteria-based PRN regimen effectively maintained the visual and anatomic gains achieved with initial monthly ranibizumab, including clinically significant benefits on DR severity. In addition, to the extent that comparisons may be made

between the controlled and uncontrolled portions of the study, the safety profile of criteria-based re-treatment with ranibizumab seems consistent with previous observations. Overall, on the basis of the additional ranibizumab exposure achieved in the RIDE and RISE OLE, the 0.5 mg ranibizumab PRN regimen used here seemed to be generally well tolerated in patients with DME, with similar types of AEs reported as those observed in the RIDE and RISE core and other studies.

The overall plateau of visual acuity improvement continuing from the end of the core studies throughout the OLE, as seen in Figure 2, illustrates 2 important points relevant to real-world implementation of clinical trial data.

Table 8. Summary of Nonocular Serious Adverse Events Potentially Related to Vascular Endothelial Growth Factor Inhibition (Pooled Data for Patients Enrolled in the Open-Label Extension [OLE] Phase) by Need for Criteria-Based Pro Re Nata Re-treatment During Extension Study

Patients, n (%)	Received Treatment During OLE			Not Treated During OLE		
	Prior Sham/ Crossover (n = 120)	Prior RBZ 0.3 mg (n = 131)	Prior RBZ 0.5 mg (n = 128)	Prior Sham/ Crossover (n = 44)	Prior RBZ 0.3 mg (n = 42)	Prior RBZ 0.5 mg (n = 35)
Any nonocular SAE	8 (6.7)	15 (11.5)	8 (6.3)	6 (13.6)	2 (4.8)	3 (8.6)
Any bleeding/hemorrhage SAE	1 (0.8)	6 (4.6)	3 (2.3)	2 (4.5)	1 (2.4)	1 (2.9)
CNS/cerebrovascular	1 (0.8)	5 (3.8)	2 (1.6)	1 (2.3)	0	1 (2.9)
Non-CNS	0	1 (0.8)	1 (0.8)	1 (2.3)	1 (2.4)	0
Congestive heart failure	4 (3.3)	5 (3.8)	3 (2.3)	3 (6.8)	1 (2.4)	2 (5.7)
Hypertension	1 (0.8)	2 (1.5)	0	0	0	0
Thromboembolic event						
Arterial	3 (2.5)	9 (6.9)	4 (3.1)	2 (4.5)	2 (4.8)	1 (2.9)
Venous	0	0	1 (0.8)	0	0	0

CNS = central nervous system; PRN = pro re nata; RBZ = ranibizumab; SAE = serious adverse event.

First, mean BCVA remained stable for at least 1 year using less than monthly ranibizumab. Patients were followed for a mean 14.1 additional months after the completion of the core studies, and a mean 4.5 injections were administered, with approximately 25% of patients not requiring reinjection during the OLE. This corresponds to a mean annualized rate of 3.8 injections/year, a significant reduction in treatment burden relative to monthly therapy. Of note, the visit interval was extended, and patients did not have to return monthly unless they were treated at the previous visit. Visits could be extended to 60- or 90-day intervals at the discretion of the investigator; therefore, the maintenance of vision in the OLE was possible with a decrease in visit burden. Second, these data further speak to the impact of delayed anti-VEGF therapy on visual acuity outcomes, a key observation from the RIDE and RISE core studies that stems from the study design. Patients randomized to the control group in the core studies received 24 months of sham injections and rescue laser therapy before initiating treatment with ranibizumab; once these patients crossed over to active therapy, their visual gains failed to achieve those of patients who were randomized to active therapy from the start of the core studies. With continued PRN therapy in the OLE, these prior sham-treated patients maintained what visual gains they had achieved with a year of monthly ranibizumab therapy, but their overall mean improvement in BCVA remained smaller than in those who had received earlier treatment. This failure to reach the same level of improvement could be due to delay in initiation of ranibizumab therapy, due to retinal damage from more extensive focal laser treatment compared with the group originally randomized to ranibizumab (Table 2 in Brown et al⁴), or due to a need for further monthly therapy before transitioning to as-needed therapy; because the study was not specifically designed to address outcomes of immediate versus delayed ranibizumab therapy, it is not possible to address this point with certainty. However, the overall outcome underscores the importance of early anti-VEGF therapy in real-world clinical practice for patients newly diagnosed with DME, because early anti-VEGF therapy seems to result in the best treatment outcomes and minimizes the need for tissue-destructive therapies such as macular laser.

One limitation of the OLE study is the relatively limited number of patients who reached the month 48 or later visits. Although the mean follow-up period in the OLE was 14.1 months, 42.2% of patients did not complete the month 48 visit. However, this was due to conclusion of the study after FDA approval of ranibizumab for treatment of DME and not to loss to follow-up. Although this affected the robustness of data after month 48, patients with longer follow-up were not selected on the basis of their response to drug or randomized treatment, but only by the time at which they were enrolled in the original studies. We would speculate that longer-term results for the entire group would be similar to results for those who completed month 48, based on the 4- and 5-year data from DRCR.net Protocol I, which demonstrate generally similar results to the RIDE/RISE OLE.¹³

These results are consistent with other studies that have demonstrated the efficacy of less than monthly ranibizumab

for patients with DME. For example, in the RESTORE phase III trial, patients were randomized to treatment with ranibizumab + focal/grid laser photocoagulation or 1 of 2 sham control groups: sham intravitreal injections + laser or sham laser + ranibizumab. After 3 consecutive loading doses, 0.5 mg ranibizumab was administered according to a criteria-based PRN regimen. Stability criteria were defined as Snellen equivalent $\geq 20/20$ for ≥ 2 visits or no further BCVA improvement for 2 consecutive visits. During the 8-month PRN phase, patients received approximately 4 ranibizumab injections, and the visual and anatomic gains achieved with initial monthly therapy in RESTORE were maintained with a PRN regimen. The 12-month core phase of the RESTORE study was followed by a 2-year extension study,¹⁰ with all patients treated under the 0.5 mg ranibizumab criteria-based PRN regimen. In the RESTORE extension, visual and anatomic benefits were also maintained with criteria-based ranibizumab re-treatment. Taken together, the results of the RIDE, RISE, and RESTORE OLEs (N = 720 patients) provide compelling evidence supporting the efficacy of criteria-based regimens for maintaining visual and anatomic gains achieved with initial, intensive ranibizumab therapy in DME. The efficacy of less than monthly ranibizumab for maintaining vision also has been demonstrated in the DRCR.net Protocol I study.¹ During years 4 and 5 of Protocol I, patients in both the ranibizumab plus prompt and deferred laser groups required very little additional treatment (median 0–1 injections) to maintain vision gains achieved. The estimated mean change in BCVA from baseline was +7.4 at 4 years and +7.2 at 5 years for those who received prompt laser treatment and +9.4 letters and +9.8 letters, respectively, for those who received deferred laser treatment.¹³

In addition to the maintenance of visual acuity benefits, a continued benefit on DR severity was also observed in the RIDE and RISE extensions. Clinically significant improvements in DRSS and reduced rates of significant DR worsening were both observed in patients initially randomized to monthly ranibizumab therapy compared with patients randomized to sham.⁹ It was unclear whether these improvements in DR severity would persist with reduced-intensity therapy. We have now demonstrated that DR improvements continue to be observed with relaxation of treatment intensity. After a 1- to 3-year period of monthly ranibizumab injections, 21.0% to 35.6% of participants in the RIDE and RISE OLE with DR outcomes at month 48 (1 year of less than monthly injections) experienced a ≥ 2 -step improvement in DRSS from baseline. These data, along with the fact that many patients required no additional therapy for DME (discussed further in the next paragraph), suggest that anti-VEGF therapy may modify the course of disease in patients with DR and DME.

A key finding of the RIDE and RISE OLE was that approximately 25% of patients continued to meet visual and anatomic stability criteria without any further ranibizumab treatment during the OLE period. This raises 2 important issues: First, because these patients appear to have reached disease stability with 1 or 3 years of monthly ranibizumab injections, continued treatment of these patients under a

fixed interval regimen may result in unnecessary intervention. Therefore, an individualized PRN approach could offer fewer treatments, decreasing burden on patients and providers. Second, the success of these patients raises questions regarding the underlying pathophysiology of diabetic retinal disease and the potential modification of the disease course through VEGF inhibition. What underlying physiologic mechanisms might explain the difference between patients who required no re-treatment and those who required some re-treatment after the initial intensive anti-VEGF period? For example, is it possible that retinal vascular inflammation or levels of capillary nonperfusion are different in patients whose disease is modified to the extent that no further therapy is required? These questions cannot be easily addressed by the current study, but provide tantalizing areas for focusing additional research. Furthermore, it will be important to explore the possibility of prospectively identifying patients who do or do not require prolonged anti-VEGF therapy; this will be useful not only for patient counseling but also for designing future clinical trials in DR and DME.

In conclusion, the results of the RIDE and RISE OLE provide further evidence for the efficacy of a clinically relevant ranibizumab treatment paradigm in DME: initial, intensive therapy followed by observation and maintenance therapy when indicated. Consistent results were observed across anatomic and visual acuity outcomes. Finally, the long-term visual outcomes of patients who received delayed-onset therapy (patients initially randomized to sham) continue to underscore the importance of appropriate screening for patients with DR, so that DME may be identified and treated at a stage when the best outcomes are likely.

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*The RIDE and RISE Research Group is listed in the Appendix (available at www.aaojournal.org).

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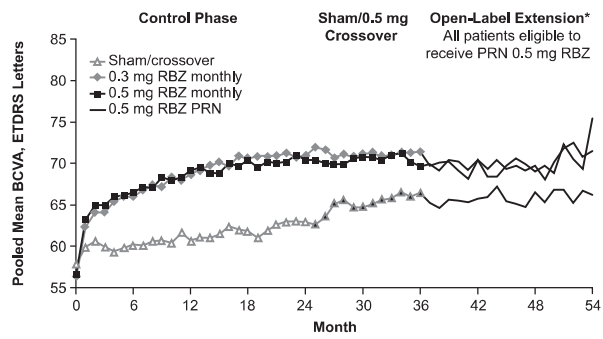
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Abbreviations and Acronyms:

AE = adverse event; **BCVA** = best-corrected visual acuity; **CFT** = central foveal thickness; **DME** = diabetic macular edema; **DR** = diabetic retinopathy; **DRSS** = diabetic retinopathy severity score; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **FDA** = Food and Drug Administration; **NPDR** = nonproliferative diabetic retinopathy; **OCT** = optical coherence tomography; **OLE** = open-label extension; **PDR** = proliferative diabetic retinopathy; **PRN** = pro re nata; **SAE** = serious adverse event; **VEGF** = vascular endothelial growth factor.

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Patients_n ₁	165	163	161	162	163	163	164	124	82	35
Sham/crossover	165	163	161	162	163	163	164	124	82	35
0.3 mg RBZ	172	168	168	167	170	168	172	126	101	39
0.5 mg RBZ	163	158	158	155	159	152	161	115	95	47

Figure 3. Pooled (RIDE and RISE) mean best-corrected visual acuity (BCVA) among patients enrolled in the open-label extension (OLE) (observed data). ETDRS = Early Treatment Diabetic Retinopathy Study; PRN = pro re nata; RBZ = ranibizumab. *Data become unstable after month 54 because of the low number of patients at that point. †Treatment during core study.