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Predictors of Diabetic Macular Edema Treatment Frequency with Ranibizumab During the Open-Label Extension of the RIDE and RISE Trials

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Purpose: To investigate the role of baseline demographics, disease characteristics, and treatment responses to ranibizumab during RIDE/RISE in predicting long-term treatment frequency with a criteria-based pro re nata (PRN) regimen during the open-label extension (OLE).

Design: Pooled, retrospective, post hoc analysis from the phase III, randomized RIDE/RISE studies and subsequent OLE.

Participants: Five hundred patients enrolled in the OLE after completion of the 36-month RIDE/RISE studies.

Methods: Summary statistics of RIDE/RISE baseline characteristics and treatment responses were generated by PRN ranibizumab 0.5 mg annualized injection frequency in the OLE (0 and >7 annualized injections). Univariable regression and analysis of variance, and multivariable analysis of covariance were performed on the annualized number of ranibizumab injections administered during the OLE versus baseline characteristics and response to treatment during the RIDE/RISE studies.

Main Outcome Measures: Association of patient characteristics and responses to treatment during RIDE/RISE with the observed ranibizumab treatment burden during the OLE.

Results: During the OLE, 121 patients required no treatment, 132 required >0 to ≤3 annualized injections, 159 required >3 to ≤7 annualized injections, and 88 required >7 annualized injections. Parameters identified in the multivariable analysis as related to the annualized number of injections included the total number of rescue focal macular lasers received during the core studies ($P = 0.0203$), central foveal thickness at baseline ($P = 0.0002$) and month 36 ($P < 0.0001$), fluorescein leakage area at month 36 ($P = 0.0137$), and glycated hemoglobin (HbA_{1c}) levels at month 36 ($P = 0.0054$). Patients receiving 0 versus >7 annualized injections during the OLE had, on average, a shorter duration of diabetes and diabetic macular edema (DME) at baseline, were less likely to have proliferative diabetic retinopathy at baseline, received fewer rescue focal macular laser treatments, and were more likely to experience diabetic retinopathy severity scale improvement of ≥2 steps.

Conclusions: Patients who received less frequent injections during the RIDE/RISE OLE tended to have less advanced disease at baseline and responded better to initial ranibizumab treatment, suggesting that earlier anti–vascular endothelial growth factor treatment of center-involving DME with visual acuity loss may decrease long-term treatment burden. *Ophthalmology 2016;■:1–6 © 2016 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/).*

Diabetic macular edema (DME) is a leading cause of visual impairment and blindness in working-age patients with diabetic retinopathy (DR) in many developed countries.[1] The first validated treatment for DME, focal macular laser, was established through the Early Treatment of Diabetic Retinopathy Study (ETDRS) in the 1980s.[2] More recently, pharmacologic management has progressively replaced focal macular laser as the primary treatment for center-involved DME.[3–6] Vascular endothelial growth factor (VEGF)-A is a key cytokine in the development and progression of DME and DR,[7,8] and its clinical blockade has proven remarkably effective at improving visual acuity (VA) and reducing VA losses in populations with center-involved DME with VA loss.[3–6,9]

On the basis of the results of the phase III RIDE/RISE trials,[6,10] ranibizumab (Lucentis, Genentech, Inc, South San Francisco, CA) was the first anti-VEGF pharmaceutical agent approved by the US Food and Drug Administration for the treatment of DME, becoming commercially available in 2012.[11] During the RIDE/RISE studies, patients receiving 0.3 mg or 0.5 mg monthly ranibizumab injections rapidly experienced significantly greater gains in mean best-corrected visual acuity (BCVA) and decreases in retinal thickness compared with those receiving

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sham injections with rescue focal macular laser.[3] All patients who completed the RIDE/RISE 36-month trials (n = 582) were eligible to continue in the open-label extension (OLE), of whom 500 (85.9%) elected to participate. There did not seem to be meaningful differences in the baseline characteristics of patients who did or did not enroll in the RIDE/RISE OLE.[12]

During the OLE, all patients were eligible to receive pro re nata (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 optical coherence tomography (OCT) (evaluated by the investigator and defined as the presence of intraretinal fluid or cysts, or subretinal fluid due to DME and not another cause; 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).[12] Through a mean of 14.1 months of OLE follow-up, overall the BCVA gains and anatomic OCT thickness improvements achieved with monthly dosing during RIDE/RISE were maintained. During the OLE the mean annualized number of injections was 3.8, and there was wide variability in the frequency of the required PRN injections, with approximately one-quarter of patients (24.2%) requiring no ranibizumab injections.

Given the societal impact of DME-associated vision loss, coupled with the substantial burden to patients and the health care system of delivering intravitreal anti-VEGF treatments regularly,[13] there is a need to identify and better understand clinical markers that may be predictive in assessing long-term treatment burdens for patients. The objective of this analysis was to characterize those patients who required less re-treatment during the OLE. Baseline patient demographics, disease characteristics, and treatment responses to ranibizumab during RIDE/RISE were studied as potential predictors of long-term treatment burden.

Methods

Study Design

Full methods of RIDE (NCT00473382) and RISE (NCT00473330) have been described previously.[6,10] Briefly, patients with DME (N = 759) were randomized to receive monthly intravitreal ranibizumab (0.3 or 0.5 mg) or sham injections with rescue laser according to prespecified criteria. At month 25, patients in the sham arm crossed over to receive monthly ranibizumab (0.5 mg), and patients originally assigned to ranibizumab continued to receive monthly injections of their original dose through month 36. All patients enrolled in the OLE (N = 500) were eligible to receive PRN 0.5 mg ranibizumab according to predefined re-treatment criteria. Treatment was administered when DME was identified by the investigator on OCT or when BCVA worsened by ≥5 ETDRS letters versus month 36 (start of the OLE) as the result of DME. Patients receiving ranibizumab treatment at any visit during the OLE were subsequently observed every 30 (±7) days. At the discretion of the investigator, this could be extended to 60 (±7) days or 90 (±7) days for patients who did not receive treatment. The difference between arms in the distribution of time to first injection during the OLE was determined by using the log-rank test.

Both trials were designed and conducted in accordance with the principles of the Declaration of Helsinki and in compliance with the Health Insurance Portability and Accountability Act. The study protocols were approved by institutional review boards, ethics committees, or as applicable. All patients provided written informed consent before enrolling as study participants.

Variables Selected for Analysis

In this exploratory analysis, RIDE/RISE study baseline and treatment response characteristics were summarized by the number of criteria-based PRN injections received per follow-up year during the OLE. The following baseline continuous or categoric variables were examined: duration of diabetes, duration of DME, glycated hemoglobin (HbA_{1c}), BCVA, central foveal thickness (CFT), DR severity, age, gender, race, blood pressure, kidney function, fluorescein angiography (FA) leakage, capillary loss, and focal/diffuse edema. The following treatment response continuous or categoric variables were examined at months 24 and 36 of the core studies: BCVA, CFT, DR severity, HbA_{1c}, FA leakage, capillary loss, focal/diffuse edema, blood pressure, and kidney function. The following continuous variables also were considered: the number of laser treatments received by months 24 and 36, including rescue focal macular laser and panretinal photocoagulation.

To illustrate the clinical relevance of the variables identified in the univariable analysis, summary statistics for continuous variables (mean [standard deviation]) and categoric variables (n [%]) were examined by the number of annualized injections and provided for patients receiving the least frequent versus most frequent treatment.

Univariable Regression/Analysis of Variance

A univariable regression analysis was performed on the number of annualized injections received in the OLE versus RIDE/RISE baseline and response to treatment characteristics for all patients enrolled in the OLE. Patients were excluded from the analysis if they were marked as "missing," "cannot grade," "not available," "not applicable," or "questionable" for the corresponding variables. Parameter estimates, their standard errors, and P values based on t test for continuous variables and F-test for categoric variables were reported.

Multivariable Analysis of Covariance

A multivariable analysis of covariance was performed on the number of annualized injections in the OLE versus variables selected from the univariable regression analysis that had overall effect P values < 0.20, without the initial assigned treatment group variable forced in, using stepwise selection (entry P value cutoff = 0.20, stay P value cutoff = 0.05).

Results

The median time to first injection in the OLE was 65 days, 59 days, and 64 days for patients in the sham, ranibizumab 0.3 mg, and ranibizumab 0.5 mg arms, respectively (log-rank P value = 0.64). The frequency distribution of the annualized number of criteria-based PRN injections administered during the RIDE/RISE OLE is provided in Figure 1. Patient demographics, baseline disease characteristics, and responses to treatment variables from the RIDE/RISE studies were correlated with the number of annualized injections administered during the OLE. The continuous and categoric variables that were significant (at $\alpha = 0.2$ level) in the univariable analysis are presented in Table 1. A multivariable analysis was then performed using these variables. The parameters

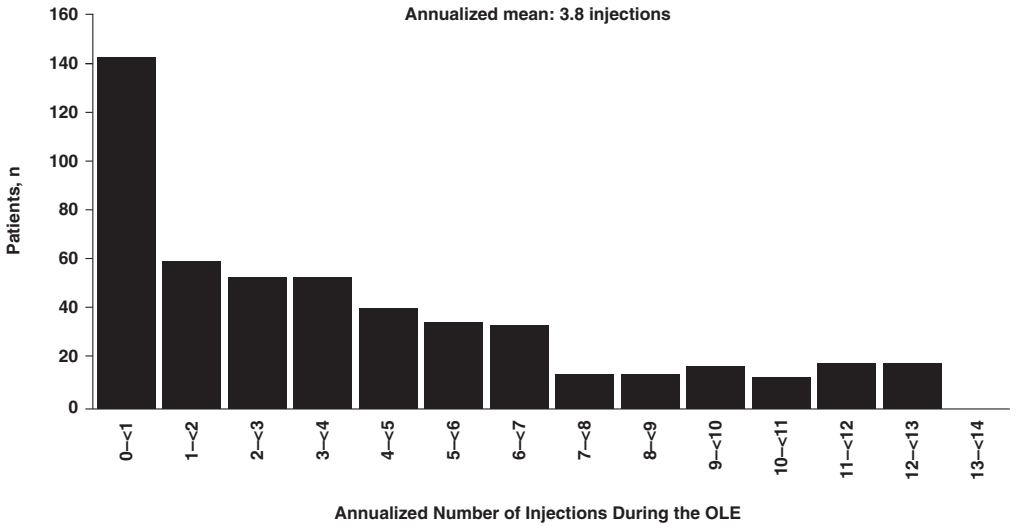

Figure 1. Frequency distribution of the annualized number of criteria-based pro re nata (PRN) injections administered during the RIDE/RISE open-label extension (OLE).

that remained significant at $\alpha = 0.05$ level in the multivariable analysis are presented in Table 2. Less frequent injection during the OLE was associated with thinner CFT at baseline and month 36, less FA leakage at month 36, and fewer rescue focal macular laser treatments needed through month 36. HbA_{1c} level at month 36 was inversely proportional to the number of annualized injections during the OLE.

To further assess clinically relevant trends identified in the univariable analysis, we compared the characteristics of patients who required no injections (n = 121; 24.2%) with those of patients who received >7 annualized injections (n = 88; 17.6%) during the OLE (Table 3). Among patients who required the least frequent treatment during the OLE (0 annualized injections) compared with those who required the most (>7 annualized injections), the mean duration of DME was shorter at baseline by approximately 9.6 months (25.2 vs. 34.8 months on average, respectively). The proportion of patients with proliferative DR at baseline was lower among those who required 0 annualized injections (27.3%) than among patients requiring >7 annualized injections (47.7%). Furthermore, the patients who required 0 annualized injections during the OLE were more likely to experience a ≥2-step improvement on the Diabetic Retinopathy Severity Scale at months 24 and 36 (21.5% and 33.9%, respectively) compared with patients requiring >7 annualized injections (12.5% and 17.0%, respectively).

Discussion

In the RIDE/RISE trials, patients with center-involved DME causing VA loss to 20/40 or worse were treated monthly with intravitreal ranibizumab for 36 (0.3 mg and 0.5 mg) or 12 (sham/crossover to 0.5 mg) months[6,12] before enrolling in the OLE, a PRN treatment regimen that continued for a mean of 14.1 months.

The DRCR.network Protocol I trial also evaluated the efficacy of ranibizumab for center-involved DME causing VA loss using monthly treatment followed by criteria-based PRN re-treatment.[4] In Protocol I, patients randomized to ranibizumab (0.5 mg) received 4 monthly injections followed by visits every 4 weeks with PRN injections for the first year. By using this protocol through 1 year of treatment, patients received a median of 8 to 9 injections. During subsequent years of Protocol I, the median numbers of ranibizumab injections decreased substantially while earlier visual gains were maintained.[14,15] This is concordant with findings from the OLE that initial mean visual gains achieved with monthly ranibizumab dosing can be sustained with substantially fewer mean injections.[12]

The OLE was stopped when ranibizumab was approved by the US Food and Drug Administration for treatment of DME.[12] During the OLE, the need for treatment varied greatly. Approximately one-quarter (24.2%) of patients required no additional ranibizumab injections to maintain the visual and anatomic improvements achieved during RIDE/RISE. Conversely, some patients continued to require frequent treatment, with 17.6% receiving >7 annualized injections.

Markers of longer disease duration and more advanced disease correlated with an increased frequency of long-term treatment when comparing clinically relevant categories of treatment burden during the OLE: patients receiving 0 versus patients receiving >7 annualized injections. Shorter duration of both diabetes mellitus and DME correlated with fewer PRN treatments in the OLE. Furthermore, the patients requiring >7 annualized injections during the OLE were more likely to have proliferative DR at baseline and less likely to experience Diabetic Retinopathy Severity Scale improvements of ≥2 steps. The current multivariable analyses similarly indicated reduced long-term treatment burden during the OLE in patients with less retinal thickening due to DME at baseline.

These data indicate that earlier anti-VEGF treatment of DME causing VA loss may reduce the long-term treatment burden. Correspondingly, earlier anti-VEGF treatment appears to result in better ultimate visual outcomes on a population basis. During RIDE/RISE, delayed anti-VEGF treatment resulted in less robust visual gains compared with the outcomes achieved in patients initially randomized

Table 1. Candidate Variables Selected from Univariable Analyses with $P < 0.20$

Parameter	Overall Effect P Value
Continuous variables	
Age, yrs	0.0654
Duration of diabetes at randomization, yrs	0.1206
Duration of diabetes at start of extension study, yrs	0.1207
Duration of DME at randomization, yrs	0.0312
Duration of DME at start of extension study, yrs	0.0312
Parent baseline BCVA, ETDRS letters (0–100)	0.0075
Parent BCVA at month 24, observed ETDRS letters	0.0010
Parent BCVA at month 36, observed ETDRS letters	0.0031
Parent baseline CFT (derived), μm	<0.0001
Parent CFT (derived) at month 24, μm	<0.0001
Parent CFT (derived) at month 36, μm	<0.0001
DR severity score at baseline (1–10)	0.1633
Parent DR severity score at month 24	0.0113
Parent DR severity score at month 36	0.0018
Parent change from baseline DR severity score at month 24	0.0119
Parent change from baseline DR severity score at month 36	0.0018
Parent number of laser treatments by month 24	<0.0001
Parent number of laser treatments by month 36	<0.0001
Parent number of macular rescue laser treatments by month 24	<0.0001
Parent number of macular rescue laser treatments by month 36	<0.0001
Parent baseline HbA_{1c}, %	0.1634
Parent HbA_{1c} at month 24, %	0.0126
Parent HbA_{1c} at month 36, %	0.0006
Parent change from baseline HbA_{1c} at month 24, %	0.1741
Parent change from baseline HbA_{1c} at month 36, %	0.0028
Parent baseline LOG HbA_{1c}	0.1690
Parent LOG HbA_{1c} at month 24	0.0136
Parent LOG HbA_{1c} at month 36	0.0007
Parent change from baseline LOG HbA_{1c} at month 24	0.1843
Parent change from baseline LOG HbA_{1c} at month 36	0.0030
Parent baseline total area of fluorescein leakage, disc areas	0.0562
Parent total area of fluorescein leakage at month 24, disc areas	<0.0001
Parent change from baseline leakage area at month 24, disc areas	0.0049
Parent total area of fluorescein leakage at month 36, disc areas	<0.0001
Parent change from baseline leakage area at month 36, disc areas	0.0011
Parent diastolic blood pressure at month 36, mm Hg	0.1002
Parent change from baseline in diastolic blood pressure at month 36, mm Hg	0.0909
Parent change from baseline in BUN at month 36, mg/dl	0.0956
Parent baseline glomerular filtration rate, ml/min/1.73 m^2	0.1883
Parent glomerular filtration rate at month 24, ml/min/1.73 m^2	0.0878
Categoric Variables	
Race	0.0678
Parent CFT ≤250 μm at month 24	<0.0001
Parent CFT ≤250 μm at month 36	<0.0001
Parent baseline DR severity scale categories (60, 61 separate)	0.1372
Parent baseline DR severity category (60, 61 combined)	0.0962
Parent baseline DR severity score ≤53 (NPDR) vs. >53 (PDR)	0.0078
Parent baseline DR severity score ≤60 vs. >60	0.1834
Parent change from baseline DRSS (≥2-step improvement) (yes/no) at month 24	0.0437
Parent change from baseline DRSS (≥2-step improvement) (yes/no) at month 36	0.0003
Presence of fluorescein leakage (yes/no) at month 24	0.0034
Presence of fluorescein leakage (yes/no) at month 36	<0.0001

BCVA = best-corrected visual acuity; BUN = blood urea nitrogen; CFT = central foveal thickness; DME = diabetic macular edema; DR = diabetic retinopathy; DRSS = Diabetic Retinopathy Severity Scale; ETDRS = Early Treatment Diabetic Retinopathy Study; HbA_{1c} = glycated hemoglobin; LOG = logarithm; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy.

to ranibizumab. After 12 months of active treatment, patients initially randomized to sham treatment gained a mean of 4.5 letters from baseline, compared with 10.6 and 11.1 mean letters with 0.3 mg and 0.5 mg ranibizumab, respectively.[3] Analogous findings have been reported from the VISTA/VIVID phase III trials assessing aflibercept for the treatment of DME.[5]

Furthermore, in the current series, improved anatomic markers of DME, including less retinal thickening and less FA leakage at the end of RIDE/RISE, correlated with fewer treatments during the OLE. Of note, patients requiring more injections during the OLE did so despite receiving more focal macular laser treatments during RIDE/RISE, suggesting that these patients may have had more chronic DME with limited responsiveness to laser therapy. The role of supplemental treatments in such patients with more recalcitrant DME in the face of ongoing anti-VEGF therapy requires further study.

In the current analysis, there was no clinically meaningful correlation between HbA_{1c} and annualized PRN

Table 2. Multivariable Analysis of Covariance for Number of Annualized Injections versus Independent Variable by Naïve Stepwise Selection, without Core Study Treatment Forced In

Characteristics	Estimates	
	Coefficient (SE)	*P Value*
No. of rescue lasers by month 36	0.18 (0.08)	0.0203
CFT at baseline	0.004 (0.001)	0.0002
CFT at month 36	0.013 (0.002)	<0.0001
Fluorescein leakage at month 36	0.11 (0.05)	0.0137
HbA_{1c} at month 36	−0.23 (0.08)	0.0054

CFT = central foveal thickness; HbA_{1c} = glycated hemoglobin; SE = standard error.

Table 3. Selected Variables by Annualized Injections Received in the Open-Label Extension

	Annualized Number of Injections	
	0 (n = 121)	*>7 (n = 88)*
Duration of diabetes at baseline, yrs	16.0 (9.8)	18.0 (10.6)
Duration of DME at baseline, mean (SD), yrs	2.1 (2.37)	2.9 (2.89)
Patients with PDR at baseline, %	27.3	47.7
Patients with ≥2-step improvement from baseline in DR severity, n (%)		
Month 24	26 (21.5)	11 (12.5)
Month 36	41 (33.9)	15 (17.0)
No. of rescue lasers by month 36, mean (SD)	0.9 (1.51)	2.3 (2.77)
CFT at baseline, mean (SD), μm	440.5 (150.27)	525.5 (160.78)
CFT at month 36, mean (SD), μm	145.9 (38.35)	271.7 (168.52)
FA leakage at month 36, mean (SD), disc areas	1.3 (2.71)	4.1 (4.37)
HbA_{1c} at month 36, mean (SD), %	8.2 (1.91)	7.5 (1.40)

CFT = central foveal thickness; DME = diabetic macular edema; DR = diabetic retinopathy; FA = fluorescein angiography; HbA_{1c} = glycated hemoglobin; PDR = proliferative diabetic retinopathy; SD = standard deviation.

injection frequency during the OLE. Multiple prospective trials have confirmed the value of improving long-term blood glucose control toward minimizing the development and progression of DR.[16,17] Of note, patients with HbA_{1c} >12% were excluded from the RIDE/RISE trials, thereby potentially limiting our ability to detect a meaningful relationship between HbA_{1c} and visual or anatomic outcomes.

Study Strengths and Limitations

Strengths of the current analysis include the randomized, prospective design of the RIDE/RISE phase III trials and the high retention rate of patients entering the OLE after completion of the core studies, as well as the prespecified anatomic and visual re-treatment criteria used in the OLE. Limitations of the current study include its post hoc exploratory approach and variable follow-up intervals of patients within the OLE due to cessation of the study at a given date unrelated to duration of patient participation in the study.

The current data indicate that disease characteristics at baseline and response to monthly ranibizumab treatment may correlate with anti-VEGF treatment burden during long-term DME management. Overall, patients who received less frequent injections during the OLE tended to have less advanced disease at baseline and responded better to initial ranibizumab treatment, suggesting that earlier anti-VEGF treatment of center-involving DME with VA loss may decrease long-term treatment burden.

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Abbreviations and Acronyms:
BCVA = best-corrected visual acuity; **BUN** = blood urea nitrogen; **CFT** = central foveal thickness; **DM** = diabetes mellitus; **DME** = diabetic macular edema; **DR** = diabetic retinopathy; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **FA** = fluorescein angiography; **HbA_{1c}** = glycated hemoglobin; **OCT** = optical coherence tomography; **OLE** = open-label extension; **PRN** = pro re nata; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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