The Impact of Systemic Factors on Clinical Response to Ranibizumab for Diabetic Macular Edema

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Purpose: To evaluate the effect of systemic factors on best-corrected visual acuity (BCVA) achieved with ranibizumab (Lucentis; Genentech, Inc, South San Francisco, CA) for treatment of diabetic macular edema (DME) in the RIDE and RISE phase 3 studies.

Design: Exploratory, post hoc analysis of 2 randomized, double-masked, sham-injection controlled studies.

Participants: Adults with DME, BCVA of 20/40 to 20/320 Snellen equivalent, and central foveal thickness of 275 μm or more.

Methods: Analysis of RIDE (clinicaltrials.gov identifier, NCT00473382) and RISE (clinicaltrials.gov identifier, NCT00473330) pooled ranibizumab data through month 24. Change in BCVA was assessed for association with the following covariates: age, body mass index (BMI), blood pressure, serum glucose, glycosylated hemoglobin (HbA1c), blood urea nitrogen, serum creatinine, estimated glomerular filtration rate, and blood chemistry variables. Change in BCVA at month 24 was assessed according to the following categories of diabetes medication use history: insulin only (n = 193), insulin plus other medications (n = 221), or other noninsulin medications (n = 331).

Main Outcome Measures: Change in BCVA from baseline assessed by randomized treatment group in pooled 0.3- and 0.5-mg monthly ranibizumab groups.

Results: In patients with DME, vision improvement with ranibizumab was not influenced by systemic factors such as diabetes medication history, serum glucose, HbA1c, renal function, BMI, and blood pressure. Patients taking insulin with or without other medications at baseline had longer diabetes disease duration (mean, 17.4 and 20.9 years, respectively) compared with those taking other noninsulin medications (mean, 11.9 years). At month 24, among ranibizumab-treated patients, the mean BCVA change from baseline (Early Treatment Diabetic Retinopathy Study letters ± standard deviation) was not different between patients taking only insulin (12.6±11.2 letters), insulin plus other medications (12.2±12.4 letters), or other noninsulin medications (14.0±13.7 letters). Mean BCVA change also was comparable among patients taking thiazolidinediones (12.9±9.7 letters) and those not taking thiazolidinediones (13.2±13.3 letters).

Conclusions: There were no associations between systemic factors (baseline values or change from baseline) and mean change of BCVA at month 24. These results suggest that visual response to ranibizumab therapy in DME was not influenced by nonocular factors related to systemic management of diabetes in the RIDE and RISE studies. *Ophthalmology 2016;123:1581-1587 © 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/).*

Intravitreal inhibitors of vascular endothelial growth factor (VEGF) A have become first-line treatment for patients with diabetic macular edema (DME), based on data from several large, prospective, randomized phase 3 clinical trials, including Diabetic Retinopathy Clinical Research Network protocol I,[1] RIDE/RISE,[2,3] RESOLVE,[4] RESTORE,[5] VIVID, and VISTA.[6] Given that DME and diabetic retinopathy are microvascular complications of diabetes, it is important to investigate whether control of the underlying disease has an impact on the outcomes with intravitreal VEGF inhibition. Several studies have demonstrated an association between the incidence or progression of DME, or both, with metabolic factors such as poor glycemic control[7–9] and hypertension.[8] The relationship between glycosylated hemoglobin (HbA1c) level and risk of microvascular complications is well established,[9] and HbA1c levels of 8% or more are associated with a greater risk of DME (e.g., central foveal thickness, ≥325 μm).[7] Several reports also suggest that abnormal values for metabolic factors related to the severity of systemic diabetes disease severity (e.g., serum creatinine, HbA1c, etc.) potentially may forecast visual or anatomic response, or both, to anti-VEGF therapies.[10–13] In a prospective study of 38 patients, inadequate control of serum creatinine and cholesterol levels was shown to correlate with poorer visual and anatomic outcomes with anti-VEGF therapy.[10] In a retrospective study of 124 patients, Matsuda et al[12] recently showed that, in patients

with HbA1c values of more than 7%, less robust anti-VEGF−mediated improvements in BCVA and central subfield macular thickness were achieved than in patients with HbA1c levels of 7% or less. Similar findings from 65 patients were reported by Ozturk et al,[13] wherein reduction in DME with anti-VEGF therapy was correlated negatively with HbA1c level. However, these studies were retrospective analyses, with variable follow-up and nonstandardized treatment regimens. In contrast, in the prospective, randomized, phase 3 RIDE and RISE studies, which enrolled 759 patients, there was no significant difference in best-corrected visual acuity (BCVA) gains or central foveal thickness (CFT) reduction in patients with HbA1c levels of more than 7% compared with those with HbA1c levels of 7% or less.[14]

Given the importance of understanding the relationship between overall course of the underlying disease and treatment outcomes in the eye and the conflicting findings reported in the literature, it is important to continue exploring the existing high-quality data from large phase 3 trials. In the present study, we analyzed data from the RISE and RIDE studies to determine whether any baseline systemic or metabolic factors influenced BCVA improvement with ranibizumab (Lucentis; Genentech, Inc, South San Francisco, CA).

Methods

Study Design and Participants

Details of methods and key findings from the RISE and RIDE trials (ClinicalTrials.gov identifiers NCT00473330 and NCT00473382, respectively) have been described in detail elsewhere.[2] Briefly, RISE and RIDE were methodologically identical phase 3, multicenter, double-masked, sham-injection−controlled, randomized studies of intravitreal ranibizumab (0.3 or 0.5 mg monthly) for the treatment of DME. Studies were conducted in accordance with the tenets of the Declaration of Helsinki and its amendments. Both studies received approval from the relevant institutional review boards and ethics committees, and all participants provided informed consent. Enrolled participants were 18 years of age or older, had decreased vision resulting from DME (study eye BCVA, 20/40−20/320 Snellen equivalent), and central subfield thickness of at least 275 μm (measured with time-domain optical coherence tomography). Patients were randomized to monthly sham injections or intravitreal ranibizumab 0.3 mg or 0.5 mg through month 24. Macular laser was permitted beginning at month 3 as per protocol-specified criteria and an assessment by the evaluating physician that macular laser will be beneficial. In the third year, sham patients, while still masked, were eligible to cross over to monthly 0.5-mg ranibizumab treatment.

Assessments

The current analysis considered only double-masked, sham-injection−controlled data from the 2 ranibizumab arms up to the primary end point at month 24. Because efficacy outcomes in the RISE and RIDE trials were similar for the 0.3-mg and 0.5-mg ranibizumab treatment groups,[2] data for these groups were pooled for this analysis. The relationship between change in BCVA with ranibizumab treatment from baseline through month 24 and the following covariates related to systemic or metabolic function, or both, were assessed: age; body mass

index (BMI); blood pressure (systolic and diastolic); markers of glycemic control factors, including HbA1c and blood glucose levels; blood chemistry, including albumin, hemoglobin, hematocrit, and total protein; and markers of renal function, including baseline serum creatinine, estimated glomerular filtration rate, and blood urea nitrogen.

In a separate analysis of data from the RIDE and RISE studies, the effect of HbA1c on BCVA and central foveal thickness was analyzed according to better or worse glycemic control, using a cutoff threshold of 7.0%.[14] Herein, we conducted a more detailed assessment of the potential effects of systemic covariates and change in BCVA over time using ordinary least-squares regression and locally weighted linear regression smoothing curves. The association between systemic factors and BCVA was assessed according to baseline covariate values versus change in BCVA over time and according to change in systemic covariates from baseline versus change in BCVA over time. Systemic characteristics of patients at baseline were evaluated using Student's t test. A multivariate analysis was planned for any variables found to be significant at the 0.2 significance level in univariate analysis. Diabetes medication status at baseline and change in BCVA at month 24 also were assessed. Medication categories were defined as insulin alone, insulin in combination with other antidiabetic drugs, only noninsulin antihyperglycemic medications, and no antidiabetic drugs. Additionally, we looked at use of thiazolidinediones at baseline and change in BCVA at month 24. These analyses were exploratory and were not based on statistical hypotheses. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

Results

Laboratory parameters and blood pressure values at baseline and at month 24 (Table 1) were similar for the patients randomized to sham injection or ranibizumab (pooled 0.3-mg and 0.5-mg groups). In patients receiving ranibizumab, mean HbA1c level was 7.7% (standard deviation [SD], 1.4%) at baseline and 7.8% (SD, 1.6%) at month 24 ($P = 0.08$). The directionality of the changes from baseline to month 24 was similar between the sham and ranibizumab patients. Systolic and diastolic blood pressure, total protein, and estimated glomerular filtration rate all decreased at month 24 with respect to baseline. Blood glucose, blood urea nitrogen, and serum creatinine increased at month 24 compared with baseline. However, in both univariate and multivariate analyses, the only characteristic that was associated significantly with BCVA change at month 24 was patient age ($P = 0.03$; Fig 1A).

Change in BCVA at month 24 was not associated with baseline BMI ($P = 0.49$; Fig 1), baseline systolic blood pressure ($P = 0.38$), baseline diastolic blood pressure ($P = 0.36$), change in systolic blood pressure ($P = 0.82$), or change in diastolic blood pressure ($P = 0.83$). In addition, there was no relationship between month 24 BCVA change and baseline HbA1c level ($P = 0.83$; Fig 2), baseline blood glucose level ($P = 0.23$), or change in either of these parameters at month 24 ($P = 0.23$ and $P = 0.26$, respectively). Measures of blood chemistry and renal factors yielded similar results, with baseline and month 24 change in serum creatinine ($P = 0.97$ and $P = 0.76$, respectively) and baseline and month 24 change in estimated glomerular filtration rate ($P = 0.78$ and $P = 0.88$, respectively) all showing no association with change in BCVA at month 24 (Fig 3).

Month 24 change in BCVA was analyzed as a function of antihyperglycemic medication use. Mean ± SD duration of