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/).
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., 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. 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 or better), and were not based on statistical hypotheses. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

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, 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%.13 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).

Laboratory parameters and blood pressure values at baseline and at month 24 were assessed 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
Table 1. Systemic Patient Characteristics at Baseline and Month 24

<table>
<thead>
<tr>
<th>Systemic Characteristics, Mean (Standard Deviation)</th>
<th>Sham Injection</th>
<th>Ranibizumab (0.3-mg and 0.5-mg Groups Pooled)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (n = 257)</td>
<td>Month 24 (n = 204)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>62.7 (10.3)</td>
<td>62.2 (10.1)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>31.6 (7.0)</td>
<td>31.7 (6.5)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>76.5 (10.7)</td>
<td>77.5 (10.2)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>135.9 (19.4)</td>
<td>138.1 (18.1)</td>
</tr>
<tr>
<td>Blood chemistry profile (g/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>3.9 (0.4)</td>
<td>3.9 (0.4)</td>
</tr>
<tr>
<td>Total protein</td>
<td>7.2 (0.5)</td>
<td>7.2 (0.5)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>12.8 (1.5)</td>
<td>12.6 (1.6)</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>38.8 (4.5)</td>
<td>38.4 (4.6)</td>
</tr>
<tr>
<td>Glycemic control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood glucose (mg/dl)</td>
<td>150.0 (64.7)</td>
<td>168.4 (84.6)</td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td>7.7 (1.4)</td>
<td>7.7 (1.7)</td>
</tr>
<tr>
<td>Renal function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dl)</td>
<td>24.4 (11.6)</td>
<td>26.5 (14.3)</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.1 (0.5)</td>
<td>1.4 (0.9)</td>
</tr>
<tr>
<td>Estimated GFR (ml/minute/1.73 m²)</td>
<td>74.1 (26.5)</td>
<td>64.1 (25.5)</td>
</tr>
</tbody>
</table>

— = age and body mass index not determined at month 24; GFR = glomerular filtration rate.

Data are mean ± standard deviation.

diabetes was longer in patients taking insulin only (20.9±10.7 years) or taking insulin with other agents (17.4±8.4 years) versus those taking other antidiabetic agents (11.9±8.5 years) or taking no diabetes medications (11.0±8.5 years). Mean ± SD duration of DME was comparable across medication use categories: 2.3±2.7 years in those taking insulin only, 2.2±2.7 years in those taking insulin with other agents, 1.9±2.3 years in patients taking non-insulin agents, and 1.4±1.7 years in patients not taking diabetes medications. There were no apparent differences among visual outcomes in patients taking insulin alone, patients taking insulin with other antihyperglycemic medications, patients taking only noninsulin antihyperglycemic medications, or those taking or not taking thiazolidinediones (Fig 4).

Discussion

Previous assessment of data from RIDE and RISE using a categorical distribution showed that patients with an HbA1c level of more than 7% had visual outcomes that were comparable with those in patients with an HbA1c level of 6% to 7.5%, whereas only 13% had HbA1c levels of more than 7.5%, whereas only 13% had HbA1c levels of more than 8%, whereas only 13% had HbA1c levels of more than 9%.13 We conducted a more detailed assessment of the relationship between changes in BCVA in patients randomized to 24 months of ranibizumab treatment in the RISE and RIDE trials with a range of systemic and metabolic characteristics, both at baseline and as they may have changed during treatment. With the exception of age, we found no compelling evidence that systemic factors such as glycemic control, blood chemistry, or renal function were associated with BCVA outcomes in response to ranibizumab treatment. Similarly, we found no evidence that BCVA outcomes differed according to the class of antihyperglycemic medications being used for treatment of diabetes. Although thiazolidinediones are associated with macular edema, the lack of difference in visual outcomes between patients taking or not taking thiazolidinediones suggests equal efficacy of ranibizumab in these 2 groups.

It should be noted that patients with severely uncontrolled diabetes, as evidenced by an HbA1c level of more than 12%, were excluded from the RIDE and RISE trials. As expected for patients living with diabetes on average for 15 years (mean, 14.5±16.6 years at baseline), laboratory values at baseline reflected chronically abnormal glucose metabolism and microvascular disease (Table 1). The RIDE and RISE trial participants seemed to be reasonably well controlled during the 24-month period, with a mean HbA1c level of approximately 7.7% and changes in laboratory values not indicating meaningful change in clinical severity in the sham or ranibizumab arms. The lack of patients with severely uncontrolled diabetes represents a potential limitation of our analysis. However, these patients constitute a minority of those seen in clinical practice. For example, the Centers for Disease Control and Prevention reported that, among patients with diabetes between 2003 and 2006, most (87%) had HbA1c levels between 6% and 9%, whereas only 13% had HbA1c levels of more than 9%.13

Consistent with our findings, a Diabetic Retinopathy Clinical Research Network analysis of 361 eyes of patients with DME treated using ranibizumab with prompt or deferred laser photocoagulation found no association of changes in BCVA or central subfield thickness for HbA1c, hypertensive, or renal disease, whereas younger age (<60 years vs. ≥60 years) was found to be associated with greater improvements in BCVA.11

Findings from smaller studies are less consistent. For example, a case-series study of the anti-VEGF treatment bevacizumab in 38 patients (45 eyes) with DME found, as in the present study, that there was no association of treatment benefits with hypertension.10 However, that
Figure 1. Scatterplots showing change in best-corrected visual acuity (BCVA) at month 24 versus (A) baseline age, (B) baseline body mass index, (C) systolic and (D) diastolic blood pressure at baseline, and 24-month change in (E) systolic and (F) diastolic blood pressure. Lines represent local regression smoothing, and shaded areas represent 95% confidence intervals. \( P \) values are from linear regression models. ETDRS = Early Treatment Diabetic Retinopathy Study.
study suggested that factors including poor glycemic control, longer duration of diabetes, serum creatinine levels, and nephropathy may predict a poor response to treatment. An additional retrospective case series of 124 patients with DME identified that glycemic control lasting for more than 1 year was associated with an improved response to bevacizumab, but no association of treatment outcomes was found for patient age, duration of diabetes, serum creatinine, BMI, or blood pressure.12 Finally, a retrospective case-series study of 65 patients (65 eyes) found that short-term changes in central subfield thickness were correlated negatively with HbA1c levels after a single injection of ranibizumab.13 There is no clear explanation for the differences between our findings and those of earlier studies. However, comparisons made across different studies may be affected by differences in study design and patient populations. For example, patients in the clinical trial setting typically are monitored more closely than in real-world circumstances, and studies differ in sample size (i.e., earlier studies had smaller sample sizes), inclusion criteria, study duration, study medications, or a combination thereof. These may be contributing factors to the differences observed across published analyses of HbA1c levels in patients receiving anti-VEGF for DME.

The size and prospective nature of the RIDE and RISE clinical trials, on which the present ad hoc analysis is based, are relative strengths compared with the retrospective design of other earlier studies.7 The lack of consistency among previous studies and in consideration of the present data illustrate the challenges inherent in the use of post hoc analyses, which are not powered to provide definitive evidence for associations of treatment benefit. Nonetheless, it is important to consider that in the large, well-selected patient population derived from the RIDE and RISE studies, we did not observe any association between metabolic factors and BCVA change in response to ranibizumab treatment over the 24-month study period, further confirmed on multivariate analysis. Based on these data from the RIDE and RISE studies, improvement in vision with ranibizumab was independent of patient characteristics such as glycemic control, diabetes medication history, blood pressure, BMI, or renal function.

Figure 2. Scatterplots showing change in best-corrected visual acuity (BCVA) at month 24 versus (A) glycosylated hemoglobin (HbA1c) at baseline, (B) blood glucose at baseline, and 24-month change in (C) HbA1c and (D) blood glucose. Lines represent local regression smoothing, and shaded areas represent 95% confidence intervals. P values are from linear regression models. ETDRS = Early Treatment Diabetic Retinopathy Study.
Figure 3. Scatterplots showing change in best-corrected visual acuity (BCVA) at month 24 versus (A) baseline serum creatinine, (B) baseline estimated glomerular filtration rate (eGFR), and 24-month change in (C) serum creatinine and (D) eGFR. Lines represent local regression smoothing, and shaded areas represent 95% confidence intervals. P values are from linear regression models. ETDRS = Early Treatment Diabetic Retinopathy Study.

Figure 4. Bar chart showing change in best-corrected visual acuity (BCVA) in ranibizumab-treated patients as a function of antihyperglycemic medications class. Bars indicate standard deviation. Not shown: 7 subjects were not taking medication at baseline. ETDRS = Early Treatment Diabetic Retinopathy Study; TZD = thiazolidinedione.
References


Footnotes and Financial Disclosures


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I.S.: Employee – Genentech, Inc. (South San Francisco, CA); Member – the Roche group; Equity owner – Roche.

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Analysis and interpretation: Singh, Habbu, Ehlers, Lansang, Hill, Stoilov
Data collection: Hill, Stoilov
Obtained funding: none
Overall responsibility: Singh, Habbu, Ehlers, Lansang, Hill, Stoilov

Abbreviations and Acronyms:

BCVA = best-corrected visual acuity; BMI = body mass index; DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; HbA1c = glycosylated hemoglobin; SD = standard deviation; VEGF = vascular endothelial growth factor.

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