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Influence of Glycosylated Hemoglobin on the Efficacy of Ranibizumab for Diabetic Macular Edema

A Post Hoc Analysis of the RIDE/RISE Trials

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Purpose: To investigate the influence of glycosylated hemoglobin (HbA1c) on treatment outcomes in patients with diabetic macular edema (DME) receiving intravitreal ranibizumab.

Design: Post hoc analysis of 2 identical phase III clinical trials assessing the efficacy and safety of intravitreal ranibizumab in DME over 36 months (RIDE: NCT00473382/RISE: NCT00473330).

Participants: A total of 483 adults with vision loss from DME treated with ranibizumab were included in this analysis from RIDE/RISE. Participants received monthly intravitreal ranibizumab (0.3 or 0.5 mg).

Main Outcome Measures: Differences in visual and anatomic outcomes, and diabetic retinopathy (DR) severity score, between subgroups of patients with baseline HbA1c $\leq$7% versus HbA1c >7% at 36 months.

Results: There were 195 patients in RIDE/RISE who were treated with ranibizumab with a baseline HbA1c $\leq$7% and 288 patients with a baseline HbA1c >7% included in this analysis. The mean improvement in visual acuity (VA) at 36 months was +13 Early Treatment Diabetic Retinopathy Study (ETDRS) letters in patients with baseline HbA1c $\leq$7% compared with +11 ETDRS letters in the patients with a baseline HbA1c >7% ($P = 0.17$). After adjustment for baseline central foveal thickness (CFT) and duration of diabetes, the mean CFT reduction was −268 μm in patients with a baseline HbA1c $\leq$7% and −269 μm in patients with a baseline HbA1c >7% ($P = 0.98$; 95% confidence interval, −22.93 to 23.54). The proportion of patients with a $\geq$2-step improvement in DR severity score was 38% in patients with baseline HbA1c $\leq$7% compared with 41% in the patients with a baseline HbA1c >7% ($P = 0.53$). There was no correlation of baseline HbA1c with any visual or anatomic parameter.

Conclusions: The improvement in VA, anatomic reduction of macular edema, and improvement in DR severity score with ranibizumab treatment seem to be independent of baseline HbA1c. *Ophthalmology 2015;122:1573-1579 © 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.

On the basis of a recent multinational meta-analysis of the burden of diabetic eye disease, the global prevalence of diabetic macular edema (DME) is estimated to be 7.5%, affecting approximately 21 million individuals worldwide.[1] Vascular endothelial growth factor (VEGF) has been implicated as an integral target in the complex pathophysiology of DME.[2] Ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA) is a monoclonal antibody fragment specifically designed for intraocular use that binds and inhibits all isoforms of the VEGF molecule.[3] On the basis of 2 identical, prospective, randomized, phase III clinical trials (RIDE/RISE), intravitreal ranibizumab was approved by the US Food and Drug Administration for the treatment of DME.[4] Patients undergoing monthly treatment with intravitreal ranibizumab demonstrated statistically significant visual acuity (VA) gains with anatomic improvement compared with sham-treated patients over 36 months.[4,5] In RIDE/RISE, treatment with ranibizumab also significantly improved diabetic retinopathy (DR) severity scores from baseline compared with sham treatment at 36 months.[6]

Multiple large epidemiologic studies have shown that elevated glycosylated hemoglobin (HbA1c) confers an increased risk of developing DME.[1,7–9] However, once a patient develops DME and requires treatment, it is unknown whether the patient's underlying glycemic status may influence his or her responses to treatment. In fact, there is a paucity of data in the literature examining the influence of HbA1c on the response to treatment of DME. The few prior studies on this subject have yielded varying inconclusive results and are limited by their differing methodologies.[10–14]

http://dx.doi.org/10.1016/j.ophtha.2015.04.029
ISSN 0161-6420/15

The purpose of this analysis is to investigate both the influence of baseline HbA1c and the change in HbA1c on treatment outcomes in a large cohort of patients with DME treated with ranibizumab in the RIDE/RISE study population. The central hypothesis is that patients with DME and lower baseline HbA1c or improved HbA1c over the course of the study may have better visual and anatomic outcomes and improved DR severity scores when treated with ranibizumab compared with patients with higher baseline HbA1c or worsening HbA1c over the course of the study.

Methods

Summary of Literature Search

To identify any prior study in the literature regarding the influence of HbA1c on treatment outcomes in DME, we performed a broad literature search in PubMed from the 1950s to the present using a combination of the terms "anti-VEGF," "bevacizumab," "clinically significant macular edema," "diabetic macular edema," "diabetic retinopathy," "focal laser," "glycosylated hemoglobin," "grid laser," "HbA1c," "optical coherence tomography," "ranibizumab," and "vascular endothelial growth factor." The references of relevant articles were also reviewed to identify additional studies on the subject matter.

RIDE/RISE Trials and Glycosylated Hemoglobin Measurement

RIDE (registered on clinicaltrials.gov as NCT00473382; accessed at http://clinicaltrials.gov/show/NCT00473382) and RISE (registered on clinicaltrials.gov as NCT00473330; accessed at http://clinicaltrials.gov/show/NCT00473330) are methodologically identical, phase III, randomized, multicenter, double-masked, 36-month trials that were sham injection–controlled for the first 24 months.[4] Adults with decreased vision due to center-involved DME and presence of macular edema documented on time-domain optical coherence tomography (OCT) were eligible to enroll. Although spectral-domain OCT is the current imaging standard at the time of writing this article, patients in RIDE and RISE were recruited between 2007 and 2009, during which period time-domain OCT was the standard. 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 studies were approved by institutional review boards, ethics committees, or as applicable. All patients provided written informed consent before enrolling as participants.

Details of the study methods and key VA and safety findings have been reported.[4] Briefly, 1 eye per patient was randomized to monthly treatment with 0.3 mg ranibizumab, 0.5 mg ranibizumab, or sham injection for the first 24 months. Patients who were originally randomized to ranibizumab continued with monthly therapy at their assigned dosage through 36 months. Patients initially randomized to sham were switched to 0.5 mg ranibizumab monthly starting at month 25. The HbA1c values were drawn at baseline and 6, 12, 18, 24, and 36 months. The best-corrected VA (BCVA) of Early Treatment Diabetic Retinopathy Study (ETDRS) letter score, anatomic outcome of central foveal thickness (CFT) on time-domain OCT, and DR regression evaluated by the standardized ETDRS severity scale (using fundus photographs) were the same as previously described.[4,6]

Inclusion and Exclusion Criteria for Post Hoc Analysis

Because the baseline distributions of visual, anatomic, and DR outcomes were similar across both RIDE and RISE trials, data were pooled for these analyses. All patients in both the RIDE and RISE trials treated with 0.3 and 0.5 mg ranibizumab were pooled. For all analyses, visual, anatomic, and DR severity score outcomes are reported through 36 months for patients who were initially randomized to ranibizumab. Patients in the sham-treated group were excluded.

Baseline Glycosylated Hemoglobin Analysis

To investigate the influence of baseline HbA1c on treatment outcomes, patients were separated into 2 subgroups on the basis of baseline HbA1c $\leq$7% or >7%. This criterion was chosen on the basis of the 2014 American Diabetes Association position statement on the generally accepted threshold of diabetic control.[15] In addition, an identical analysis was performed by separating patients into 4 subgroups based on baseline HbA1c quartiles (group 1 had baseline HbA1c $\leq$6.6%, group 2 had baseline HbA1c >6.6% and $\leq$7.4%, group 3 had baseline HbA1c >7.4% and $\leq$8.5%, and group 4 had baseline HbA1c >8.5%). The quartiles' values were selected on the basis of baseline HbA1c distribution among ranibizumab-treated patients.

Change in Glycosylated Hemoglobin Analysis

To investigate the influence of the change in HbA1c on treatment outcomes, patients were separated into 3 subgroups on the basis of a $\pm$0.5% absolute change in HbA1c from baseline to month 36. Group 1 represented "improved" patients whose baseline HbA1c decreased by >0.5% at month 36. Group 2 represented "stable" patients whose baseline HbA1c remained within 0.5% at month 36. Group 3 represented "worsened" patients whose baseline HbA1c increased by >0.5% at month 36. This criterion was chosen on the basis of the clinically accepted threshold by which physicians managing diabetes may expect a clinically meaningful response in improvement or worsening in glycemic status.[16]

Statistical Analysis

Missing data were imputed using the last-observation-carried-forward method on BCVA, CFT, and ETDRS DR severity scale end points. Analysis of variance or *t* test was used to compare the mean change from baseline in BCVA and CFT at month 36 between HbA1c subgroups. Additional sensitivity analyses were performed for mean change from baseline in CFT using the covariate-adjusted analysis of covariance model with baseline CFT value and duration of diabetes as the covariates. The proportions of patients gaining $\geq$15 letters from baseline, achieving $\geq$20/40 Snellen equivalent BCVA, reaching a CFT $\leq$250 μm, and attaining $\geq$2-step improvement in DR severity score at month 36 between the subgroups were compared using Pearson chi-square tests. The Kruskal–Wallis test or Wilcoxon rank-sum test was used to examine the median difference in DR severity score between HbA1c subgroups. In addition, the correlation between baseline HbA1c and visual, anatomic, and DR severity score was assessed using the Spearman correlation coefficient.

Table 1. Influence of Baseline Glycosylated Hemoglobin on Outcomes: Baseline Characteristics and Summary of Results

Characteristic or Outcome	Baseline HbA1c ≤7% (n = 195)	Baseline HbA1c >7% (n = 288)	*P* Value
Baseline characteristics			
HbA1c, %	6.4 (0.4)	8.5 (1.2)	–
Age, yrs	63 (9.8)	61 (10.2)	–
Male sex, n (%)	123 (63)	156 (54)	–
Duration of diabetes, yrs	14 (9.9)	17 (9.1)	<0.01
BCVA, ETDRS letters	56 (12.5)	57 (11.4)	0.37
approximate Snellen equivalent	20/80	20/80	
CFT, μm	494 (187.2)	456 (140.1)	0.02
Median DR severity score†	47‡	47‡	0.90
Vision outcomes at month 36			
Change in BCVA from baseline, ETDRS letters	+13 (13.1)	+11 (14.5)	0.17
BCVA, ETDRS letters	69 (14.4)	68 (14.8)	0.57
approximate Snellen equivalent	20/40	20/50	
Patients gaining ≥15 letters from baseline, n (%)	92 (47)	117 (41)	0.15
Patients with Snellen ≥20/40, n (%)	116 (59)	172 (60)	0.96
Anatomic outcomes at month 36			
Change in CFT from baseline, μm	−292 (204.8)	−253 (178.0)	0.03
Change in CFT from baseline, μm, adjusted LS mean (SE)*	−268 (9.1)	−269 (7.4)	0.98
CFT, μm	203 (129.9)	204 (115.7)	0.93
Patients with CFT ≤250 μm, n (%)	157 (81)	236 (82)	0.69
DR severity score at month 36†			
Median DR severity score	35‡	35‡	0.64
Patients with ≥2-step improvement, n (%)	69 (38)	110 (41)	0.53

Data are mean (standard deviation) unless otherwise indicated.
BCVA = best-corrected visual acuity; CFT = central foveal thickness; DR = diabetic retinopathy; ETDRS = Early Treatment Diabetic Retinopathy Study; HbA1c = glycosylated hemoglobin; LS = least squares; SE = standard error.
*Analysis of covariance model with baseline CFT and duration of diabetes as covariates was used to estimate the adjusted LS mean.
†ETDRS DR severity was available for analysis in 451 patients treated with ranibizumab included.
‡Severity level: 47 = moderate to severe nonproliferative DR; 35 = mild nonproliferative DR.

Results

Baseline Glycosylated Hemoglobin Analysis (Baseline Characteristics)

A total of 759 patients with DME were enrolled and randomized to ranibizumab or sham treatment in RIDE/RISE. This analysis focuses on the 483 patients who were treated with ranibizumab with baseline HbA1c data available (baseline HbA1c ≤7%: n = 195; baseline HbA1c >7%: n = 288). Baseline demographics are summarized in Table 1. Baseline BCVA and DR severity of the study eye were not significantly different between HbA1c subgroups ($P = 0.37$ and 0.90, respectively). Baseline CFT was significantly thicker in the subgroup of patients with baseline HbA1c ≤7% compared with patients with baseline HbA1c >7% ($P = 0.02$).

Baseline Glycosylated Hemoglobin and Visual Outcomes

Visual, anatomic, and DR severity score results are summarized in Table 1. At month 36, patients with baseline HbA1c ≤7% gained a mean of +13 letters from baseline (standard deviation [SD], 13.1) compared with patients with baseline HbA1c >7%, who gained a mean of +11 letters from baseline (SD, 14.5) (Fig 1). The mean improvement between the HbA1c subgroups was not significantly different ($P = 0.17$; 95% confidence interval [CI], −0.78 to 4.31). From baseline to month 36, 47% of patients with baseline HbA1c ≤7% gained ≥15 letters compared with 41% of patients with baseline HbA1c >7% ($P = 0.15$). At month 36, 59% of patients with baseline HbA1c ≤7% achieved BCVA of ≥20/40 compared with 60% of patients with baseline HbA1c >7% ($P = 0.96$).

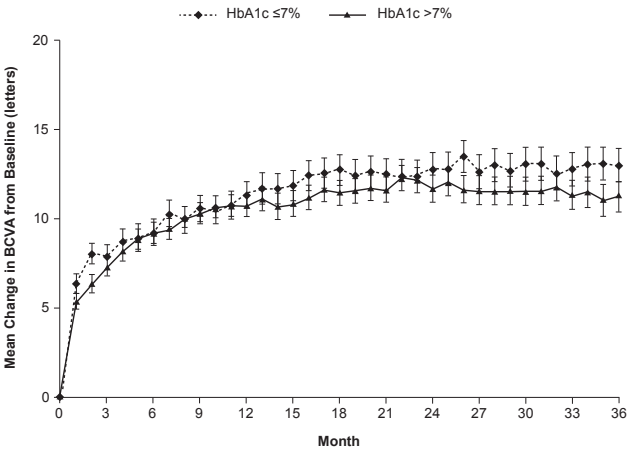

Figure 1. Mean change in best-corrected visual acuity (BCVA) over 36 months in ranibizumab-treated patients with baseline glycosylated hemoglobin (HbA1c) ≤7% compared with HbA1c >7%. Error bars represent ±1 standard error.

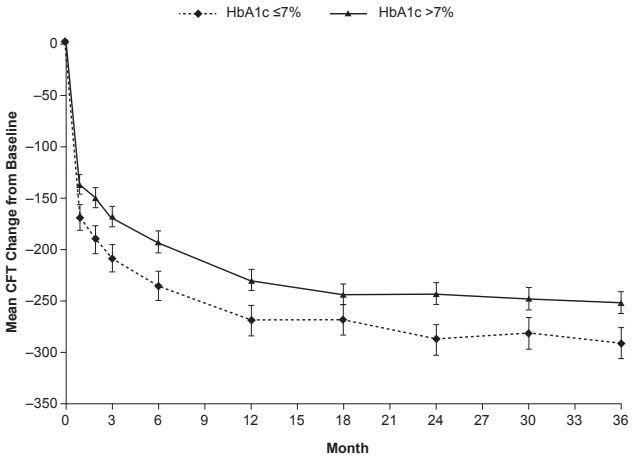

Figure 2. Mean change in central foveal thickness (CFT) over 36 months in ranibizumab-treated patients with baseline glycosylated hemoglobin (HbA1c) ≤7% compared with HbA1c >7%. Error bars represent ±1 standard error.

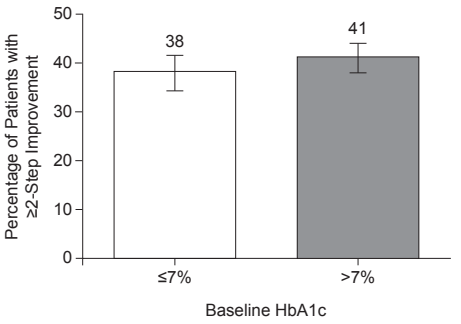

Figure 3. Percentage of patients with ≥2-step improvement in diabetic retinopathy severity score at month 36 among ranibizumab-treated patients with baseline glycosylated hemoglobin (HbA1c) ≤7% compared with HbA1c >7%. Error bars represent ±1 standard error.

Baseline Glycosylated Hemoglobin and Anatomic Outcomes

At baseline, there was a significant difference in CFT between the subgroups (baseline HbA1c ≤7%: 494 μm vs. baseline HbA1c >7%: 456 μm; $P = 0.02$). At month 36, the mean CFT reduction from baseline was −292 μm (SD, 204.8 μm) and −253 μm (SD, 178.0 μm) in patients with baseline HbA1c ≤7% and >7%, respectively ($P = 0.03$; 95% CI, −74.44 to −3.53) (Fig 2). However, after adjustment for baseline CFT and duration of diabetes, the mean CFT reduction was −268 μm in patients with a baseline HbA1c ≤7% and −269 μm in patients with a baseline HbA1c >7% ($P = 0.98$; 95% CI, −22.93 to 23.54). The percentage of patients with a CFT ≤250 μm at month 36 was similar between baseline HbA1c subgroups (baseline HbA1c ≤7%: 81%; baseline HbA1c >7%: 82%; $P = 0.69$).

Baseline Glycosylated Hemoglobin and Early Treatment Diabetic Retinopathy Study Diabetic Retinopathy Severity Outcomes

At baseline, the median ETDRS DR severity level was 47 in both HbA1c subgroups, which corresponds to moderate to severe nonproliferative DR (moderate severe nonproliferative DR).[17] The median ETDRS DR severity level at month 36 was 35 in both HbA1c subgroups, which corresponds to mild nonproliferative DR. The proportion of patients with a ≥2-step improvement in DR severity score was 38% among patients with baseline HbA1c ≤7% compared with 41% among patients with a baseline HbA1c >7% ($P = 0.53$) (Fig 3).

Baseline Glycosylated Hemoglobin Analysis Using Quartile Stratification

An identical analysis to the one just described was carried out, separating patients into 4 subgroups using quartiles of baseline HbA1c. Group 1 had baseline HbA1c ≤6.6% (n = 116), group 2 had baseline HbA1c >6.6% and ≤7.4% (n = 140), group 3 had baseline HbA1c >7.4% and ≤8.5% (n = 113), and group 4 had baseline HbA1c >8.5% (n = 114). There was no difference among any subgroups regarding VA, anatomic, or DR severity score outcomes (Table 2, available at www.aaojournal.org).

Correlation of Baseline Glycosylated Hemoglobin to Visual, Anatomic, and Diabetic Retinopathy Severity Score

In the pooled analysis of ranibizumab-treated patients, there was no correlation between baseline HbA1c and improvement in BCVA, 36-month BCVA, change in CFT, 36-month CFT, improvement in DR severity score, or 36-month DR severity score.

Change in Glycosylated Hemoglobin Analysis (Baseline Characteristics)

Of the 483 patients treated with ranibizumab, 371 had HbA1c data available at month 36 for analysis. Group 1 represented "improved" patients whose baseline HbA1c decreased by >0.5% at month 36 (n = 93), group 2 represented "stable" patients whose baseline HbA1c remained within 0.5% at month 36 (n = 139), and group 3 represented "worsened" patients whose baseline HbA1c increased by >0.5% at month 36 (n = 139). Baseline demographics are summarized in Table 3. Baseline BCVA, CFT, and DR severity level of the study eye were not significantly different between HbA1c subgroups ($P = 0.30$, 0.34, and 0.17, respectively).

Change in Glycosylated Hemoglobin and Visual Outcomes

At month 36, patients with "improved" HbA1c gained a mean of +12 letters from baseline (SD, 15.9) compared with patients with "stable" HbA1c, who gained a mean of +13 letters from baseline (SD, 13.1), and compared with patients with "worsened" HbA1c, who gained a mean of +15 letters from baseline (SD, 13.4; $P = 0.23$). There was no statistically significant difference in the other VA outcome parameters among the 3 subgroups (Table 3).

Change in Glycosylated Hemoglobin and Anatomic Outcomes

At month 36, patients with improved, stable, or worsened HbA1c had similar CFT (209, 193, and 176 μm, respectively; $P = 0.08$)

Table 3. Influence of Change of Glycosylated Hemoglobin on Outcomes: Baseline Characteristics and Summary of Results

Characteristic or Outcome	HbA1c Improved* (n = 93)	HbA1c Stable* (n = 139)	HbA1c Worsened* (n = 139)	*P* Value
Baseline characteristics				
HbA1c, %	8.5 (1.5)	7.3 (1.2)	7.4 (1.2)	–
Age, yrs	63 (8.6)	63 (10.4)	61 (10.0)	–
Male, n (%)	51 (55)	92 (66)	76 (55)	–
Duration of diabetes, yrs	16 (11.1)	16 (9.8)	15 (8.7)	0.41
BCVA, ETDRS letters	55 (11.9)	58 (10.4)	57 (13.2)	0.30
approximate Snellen equivalent	20/80	20/80	20/80	
CFT, μm	457 (144.6)	489 (175.7)	480 (161.8)	0.34
Median DR severity score†	47‡	47‡	47‡	0.17
Vision outcomes at month 36				
Change in BCVA from baseline, ETDRS letters	+12 (15.9)	+13 (13.1)	+15 (13.4)	0.23
BCVA, ETDRS letters	67 (14.9)	70 (13.3)	71 (15.1)	0.07
approximate Snellen equivalent	20/50	20/40	20/40	
Patients gaining ≥15 letters from baseline, n (%)	41 (44)	66 (47)	70 (50)	0.64
Patients with Snellen ≥20/40, n (%)	51 (55)	90 (65)	96 (69)	0.08
Anatomic outcomes at month 36				
Change in CFT from baseline, μm	−248 (176.8)	−295 (200.1)	−304 (178.3)	0.06
Change in CFT from baseline, μm, adjusted LS mean (SE)§	−267 (11.8)	−285 (9.7)	−301 (9.6)	0.08
CFT, μm	209 (126.4)	193 (111.0)	176 (99.4)	0.08
Patients with CFT ≤250 μm, n (%)	75 (81)	115 (83)	127 (91)	0.04
DR severity score at month 36†				
Median DR severity score	35‡	35‡	35‡	0.86
Patients with ≥2-step improvement, n (%)	33 (38)	58 (44)	64 (50)	0.21

Data are mean (standard deviation) unless otherwise indicated.
BCVA = best-corrected visual acuity; CFT = central foveal thickness; DR = diabetic retinopathy; ETDRS = Early Treatment Diabetic Retinopathy Study; HbA1c = glycosylated hemoglobin; LS = least squares; SE = standard error.
*Improved defined as >0.5% absolute value decrease in HbA1c at month 36 from baseline; Stable defined as an increase or decrease of ≤0.5%; worsened defined as >0.5% absolute value increase in HbA1c at month 36 from baseline.
†ETDRS DR severity was available for analysis in 348 patients treated with ranibizumab included.
‡Severity level: 47 = moderate to severe nonproliferative DR; 35 = mild nonproliferative DR.
§Analysis of covariance model with baseline CFT and duration of diabetes as covariates was used to estimate the adjusted LS mean.

(Table 3). The mean reduction in CFT from baseline at month 36 was −248 μm (SD, 176.8 μm), −295 μm (SD, 200.1 μm), and −304 μm (SD, 178.3 μm) in the improved, stable, and worsened HbA1c groups, respectively ($P = 0.06$).

Change in Glycosylated Hemoglobin and Early Treatment Diabetic Retinopathy Study Diabetic Retinopathy Severity Outcomes

At month 36, there was no statistically significant difference in the median DR severity score or percentage of patients with a ≥2-step improvement in DR severity score among the subgroups of patients with improved, stable, or worsened HbA1c (Table 3).

Discussion

Prior studies investigating the relationship of HbA1c on the response to treatment of DME have varied greatly in their methodology, ranging from disease state studied (treatment-naive DME vs. refractory DME), intervention (ranibizumab vs. bevacizumab vs. laser), outcome measures (final VA vs. change in VA), and correlation of HbA1c to various outcome parameters (baseline VA or CFT, final VA or CFT, or change in VA or CFT). These differences coupled with smaller sample sizes and retrospective design limit the clinician's ability to draw meaningful conclusions regarding this fundamental and important clinical question: Does HbA1c influence the outcomes in patients treated for DME?

Before the anti-VEGF era, Do et al[10] reported that patients with "persistent" DME had higher HbA1c concentrations compared with patients with resolved DME, suggesting that tighter glycemic control may prevent persistent DME. However, the study was limited by its selection bias given its small retrospective design and lack of VA outcomes reported. In a small prospective study of 30 patients, Schmid et al[13] found that there was no correlation between the baseline HbA1c and the reduction of CFT after focal laser for DME.

In the anti-VEGF era, we identified 3 prior studies that compared the differences in treatment outcomes between subgroups of patients on the basis of baseline HbA1c concentrations (≤7% or >7%). In a small prospective analysis of 38 patients treated with a single intravitreal injection of bevacizumab for refractory clinically significant DME, Warid Al-Laftah et al[14] demonstrated that a greater proportion of patients with HbA1c <7% gained 2 lines of VA compared with those with HbA1c >7%, suggesting that poorer glycemic control may lead to worse visual outcomes. By contrast, in a prospective study of 52 patients, Macky and Mahgoub[11] reported that there was

no difference in the 6-month VA or CFT between patients with baseline HbA1c <7% or ≥7% treated with 3 injections of bevacizumab plus laser for treatment-naive DME.

More recently, in a retrospective analysis of 124 patients treated with approximately 6 injections of bevacizumab for treatment-naive DME over 12 months, Matsuda et al[12] demonstrated that patients with an initial HbA1c ≤7% had better 12-month VA (20/43) compared with patients with an initial HbA1c >7% (20/62). However, there was no significant difference in the final CFT between the 2 groups; that is, both groups had significant reductions in CFT after treatment regardless of their glycemic control. The authors concluded that "patients with more optimal HbA1c achieve better final BCVA after one year of bevacizumab treatment." However, it is worthwhile to note that patients in this study with HbA1c >7% had worse baseline vision compared with patients with HbA1c <7%, which alone may confound the results.

In the present study, we demonstrate that patients treated with monthly intravitreal ranibizumab have improvement in VA, reduction in CFT, and improvement in DR severity score independent of their baseline HbA1c or change in HbA1c. We found no significant differences in the 36-month vision, change in vision, or 36-month CFT between patients with baseline HbA1c ≤7% and >7%, or between patients stratified by quartiles of baseline HbA1c. Our results are similar to those of Ozturk et al,[18] who found no relationship between the baseline HbA1c and improvement in VA after a single intravitreal injection of ranibizumab. Although there was a statistically significant difference in the change in CFT from baseline at 36 months between the 2 groups, this could be accounted for by the fact that the baseline CFT was significantly thicker in the group with baseline HbA1c ≤7%. Matsuda et al[12] and Macky and Mahgoub[11] reported similar findings. It is unclear why patients with baseline HbA1c ≤7% had thicker CFT at baseline compared with those with HbA1c >7%, but it is a finding that warrants further investigation. After adjustment for baseline CFT values and duration of diabetes, there was no statistically significant difference between the 2 groups in change in CFT from baseline to 36 months. Furthermore, the proportion of patients with CFT ≤250 μm at month 36 was high (>80%) and similar between both groups.

In addition to analyzing the effect of baseline HbA1c, we also found no difference in the 36-month vision, change in vision, proportion of patients gaining 15 letters, proportion of patients with ≥20/40 BCVA, 36-month CFT, or DR severity score outcomes among the 3 subgroups of patients with improved, stable, or worsened HbA1c throughout the study. The question of how best to evaluate a clinically meaningful change in HbA1c is a challenging one, and one that currently has no consensus in the diabetic literature. After a thorough review of the literature, we chose a plausible threshold of ±0.5% which is the criterion many physicians managing diabetes use to evaluate response to systemic treatments.[16] We acknowledge that this cutoff may not represent an equally meaningful change based on differing levels of HbA1c. For instance, a change from HbA1c of 10.1% to 9.6% may be more clinically relevant than a change from HbA1c of 6.8% to 6.3%. Further work is needed to better define clinically meaningful change in HbA1c when examining clinical studies.

There could be several reasons for the differences in our results and those of prior studies. First, DME is undoubtedly a complex condition that occurs after patients have diabetes for an extended period of time, the improvement or worsening of which likely depends on a multitude of fluctuating systemic and local factors, such as blood pressure, cholesterol, obesity, and genetics, and not purely on HbA1c or VEGF inhibition alone. Second, direct comparison of our results taken from a standardized clinical trial with those of a small retrospective study is difficult. The key strengths of our analysis include data derived from a large, prospectively obtained sample size treated with regular ranibizumab and close follow-up in a standardized fashion. Of note, we are able to provide long-term follow-up (36 months), which allowed comparisons at various time points. Glycemic control undoubtedly fluctuates from month to month and year to year; therefore, capturing long-term data over 36 months is critical to assessing any effect of glycemic control on treatment outcomes. Notwithstanding, we acknowledge that RIDE/RISE patients had diabetes for more than 15 years on average, and a 3-year time period is a relatively small window in the total life of a diabetic patient.

Study Limitations

There are certain limitations to this study. As with any post hoc analysis, we must exercise caution in interpreting our results as causal and not purely coincidental. Patients in the RIDE/RISE trials were closely monitored and treated monthly regardless of VA or OCT findings, a practice that is infrequently encountered in clinical practice outside of a formal clinical trial. As such, it is possible that the group with baseline HbA1c ≤7% could have achieved excellent VA with less frequent dosing. Conversely, it is possible that patients with baseline HbA1c >7% required frequent monthly treatment to maintain their excellent visual and anatomic results. At some point, there may be a threshold beyond which VA fails to improve despite additional treatment. In addition, patients in the RIDE/RISE trials may have had better controlled and stable HbA1c than what is typically seen in clinical practice because of the controlled clinical trial setting. To fully explore our hypothesis and isolate HbA1c as an independent risk factor, patients with DME who have similar baseline vision and CFT would need to be randomized according to HbA1c and prospectively studied according to a certain treatment protocol. A study of this nature would be technically and financially unfeasible.

Because of our large sample size, relatively balanced subgroups at the outset, and same treatment protocol for each subgroup, we are confident that our results may guide clinicians in answering a common clinical question: What is the role of glycemic control in the treatment of DME? Although HbA1c remains an important marker for systemic control of diabetes mellitus, our results suggest that patients with DME treated with regular intravitreal ranibizumab on average achieve improvement in visual, anatomic, and DR

outcomes independent of their baseline HbA1c or change in HbA1c.

Acknowledgment. Support for third-party writing assistance for this article was provided by Emma A. Platt, PharmD, of Envision Scientific Solutions and funded by Genentech, Inc.

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Footnotes and Financial Disclosures

Originally received: November 24, 2014.
Final revision: April 22, 2015.
Accepted: April 22, 2015.
Available online: June 4, 2015. Manuscript no. 2014-1880.

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Presented at: the American Diabetes Association Annual Meeting, June 13−17, 2014, San Francisco, California.

Financial Disclosure(s):
The author(s) have made the following disclosure(s): R.N.K.: Consultant to and receives grants − Allergan; consultant to and is on the Speakers Bureau of − Genentech, Inc.; Consultant to, receives research grants from, and is on the Speakers Bureau of − Regeneron. M.R.W.: Consultant − Genentech, Inc.

P-.W.W. and L.T.: Employees − Genentech, Inc.

S.A.V.E.: Employee − Genentech, Inc., at the time of the manuscript development; currently is an employee of Avalanche Biotechnologies.

Funded by Genentech, Inc. The sponsor participated in the design and conduct of the studies; data collection, analysis, and interpretation of results; and preparation, review, and approval of the manuscript.

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Abbreviations and Acronyms:
BCVA = best-corrected visual acuity; **CFT** = central foveal thickness; **CI** = confidence interval; **DME** = diabetic macular edema; **DR** = diabetic retinopathy; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **HbA1c** = glycosylated hemoglobin; **OCT** = optical coherence tomography; **SD** = standard deviation; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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