Effect of glycosylated hemoglobin on response to ranibizumab therapy in diabetic macular edema: real-world outcomes in 312 patients

Zaid Shalchi, FRCOphth, MRCP, Mali Okada, MD, Alice Bruynseels, MBChB, BMedSc, David Palethorpe, MBBS, BSc, Ammar Yusuf, MBBS, Rohan Hussain, MBBS, BSc, Christina Herrspiegel, MD, Antonio Scazzarriello, BN, Abubakar Habib, MBChB, MSc, Razia Amin, MSc, BA, Ranjan Rajendram, FRCOphth, MD

ABSTRACT •

Objective: To investigate the effect of serum glycosylated hemoglobin (HbA1c) on the outcomes of ranibizumab therapy for diabetic macular edema (DME).

Design: Retrospective cohort study.

Participants: Patients receiving ranibizumab injections for centre-involving DME in a National Health Service setting.

Methods: The Moorfields OpenEyes database was used to study eyes with DME treated with ranibizumab from October 2013 to November 2015 at the Moorfields City Road, Ealing, Northwick Park, and St George's Hospital sites. Only eyes receiving a minimum of 3 injections and completing 12 months of follow-up were included. If both eyes received treatment, the first eye treated was analyzed. When both eyes received initial treatment simultaneously, random number tables were used to select the eye for analysis. HbA1c was tested at the initiation of ranibizumab treatment. Multivariate regression analysis was used to identify relationships between HbA1c and the outcome measures.

Outcomes: The primary outcome was change in visual acuity (VA) Early Treatment of Diabetic Retinopathy study (ETDRS) letters. The secondary outcomes were change in central subfield thickness (CSFT) and macular volume (MV), as well as number of injections in year 1.

Results: Three hundred and twelve eyes of 312 patients were included in the analysis. HbA1c was not related to change in VA ($p = 0.577$), change in CSFT ($p = 0.099$), change in MV ($p = 0.082$), or number of injections in year 1 ($p = 0.859$).

Conclusions: HbA1c is not related to functional or anatomical outcomes at 1 year in DME treated with ranibizumab.

The management of diabetic macular edema (DME) has been revolutionized by agents targeting vascular endothelial growth factor (VEGF). Ranibizumab has shown remarkable efficacy and safety in several clinical trials, including RESOLVE, RESTORE, RISE/RIDE, and Diabetic Retinopathy Clinical Research Network (DRCR.net).[1–4]

Systemic factors such as glycosylated hemoglobin (HbA1c) have been shown to be related to the incidence and progression of DME.[5–7] However, there is limited knowledge of the effect of HbA1c on the functional and anatomical outcomes of treatment. Recent post hoc analysis of data from the RISE and RIDE trials has shown HbA1c to have no effect on visual gain or retinal thickness change after ranibizumab treatment.[8] However, this clinical trial excluded patients with HbA1c levels over 12% and hence may underestimate the true effect of this factor. Clinical trials may not reflect the full range of the population that is seen in a real-world clinical practice such as the U.K. National Health Service. In addition, the act of enrollment in a clinical trial may influence the glycemic control of participants, leading to a tightening of control over the study that is not reflected in the results.

We wanted to investigate the effect of HbA1c levels on outcome of ranibizumab therapy for DME in a real-world population.

METHODS

Institutional review board approval for this study was obtained at Moorfields Eye Hospital (reference number ROAD17/0008), and its conduct adhered to the tenets of the Declaration of Helsinki.

The Moorfields OpenEyes (Across Health, Gent, Belgium) database was used to identify patients treated with ranibizumab for DME in the period October 2013 to November 2015. Patients treated at the City Road, Ealing, Northwick Park, and St George's Hospital sites were included. Patients were seen and treated as part of the National Health Service, a public health system in the United Kingdom.

Only eyes receiving a minimum of 3 injections and completing 12 months of follow-up were included. Only 1 eye per patient was included for analysis. When both eyes were treated, the first eye treated was included. When both eyes received the first injection on the same date,

https://doi.org/10.1016/j.jcjo.2017.10.008
ISSN 0008-4182/17

Canadian Ophthalmological Society | Société canadienne d'ophtalmologie
EYE PHYSICIANS AND SURGEONS OF CANADA | MÉDECINS ET CHIRURGIENS OPHTALMOLOGISTES DU CANADA

random number tables were used to select the eye for analysis (odd number = left; even number = right).

For treatment with ranibizumab, eyes needed to have centre-involving DME with central subfield thickness equal to or greater than 350 μm on Topcon 3D OCT-2000 (Topcon Corporation, Tokyo, Japan). This approximately equates to the 400 μm on the Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) and is required to ensure compliance with national guidelines. Topcon 3D OCT-2000 measurements were used throughout this study.[9] Typically, eyes were treated with 3 injections spaced monthly and reviewed 1 month thereafter. Re-treatment was at the discretion of the ophthalmologist and was typically employed in eyes with a good functional and/or anatomical response to the loading 3 injections but in which there was persistent or recurrent DME. Macular laser and panretinal photocoagulation was permitted alongside ranibizumab treatment. The full treatment protocol has been outlined previously.[10]

HbA1c levels were extracted from a nursing database at each site. HbA1c readings were obtained using the DCA Vantage Analyzer (Siemens AG, Berlin, Germany).

The primary outcome was change in Early Treatment of Diabetic Retinopathy study (ETDRS) visual acuity (VA) in year 1. The secondary outcomes were change in central subfield thickness (CSFT) and change in macular volume (MV) as measured by spectral domain optical coherence tomography (OCT) (3D OCT-2000), as well as the number of ranibizumab injections used in year 1.

Statistical analysis was performed using the Statistical Package for the Social Sciences v22 (IBM SPSS Inc. Armonk, N.Y.). Multivariate linear regression was used to identify significant correlation between the outcome measures and baseline HbA1c. Significance was defined as $p < 0.05$.

Results

Three hundred and twelve eyes of 312 patients were included in this study.

Figure 1 shows the spread of HbA1c values for all patients. The mean HbA1c was 62.6 mmol/mol (7.9%) with an SD of 18.2 mmol/mol. Twelve patients had HbA1c over 12% (107.7 mmol/mol). Of these, 6 patients showed HbA1c ≥130 mmol/mol (14.0%), this being the upper limit of the detection of the device.

Table 1 displays the functional and anatomical characteristics of the cohort at baseline and 1 year. There was a mean ± SD increase in VA of 6.5 ± 12.4 ETDRS letters ($p < 0.001$), together with mean reduction in CSFT of 102.7 ± 137.9 μm ($p < 0.001$) and reduction of MV of 1.17 ± 1.67 mm^3 ($p < 0.001$). The mean number of ranibizumab injections was 6.18 ± 2.35.

Baseline characteristics and HbA1c

At baseline, there was no significant correlation between HbA1c levels and any features of diabetic macular edema, including baseline VA ($p = 0.74$), CST ($p = 0.07$), or MV ($p = 0.15$).

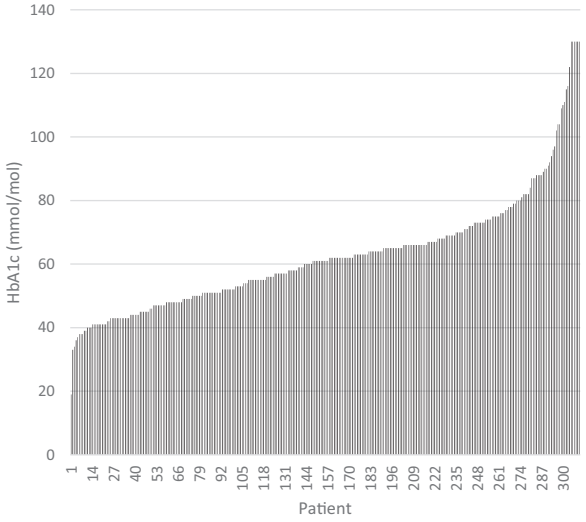

Fig. 1—Baseline HbA1c values for all patients arranged consecutively in ascending order. Six patients showed HbA1c 130 mmol/mol (14.0%), this being the upper limit of the detection of the device.

Change in visual acuity

HbA1c was not correlated with change in VA on multivariate analysis ($p = 0.577$) (Fig. 2). There was, however, a positive association between increasing number of injections and a larger change in VA ($p = 0.002$). Furthermore, the better the baseline VA, the less the visual gain observed at year 1 ($p < 0.001$).

Change in central subfield thickness

HbA1c was not correlated with change in CSFT on multivariate analysis ($p = 0.099$) (Fig. 3).

Change in macular volume

Although HbA1c was significantly correlated with change in MV on univariate testing ($p = 0.029$), this was not the case for multivariate analysis once baseline MV was considered ($p = 0.082$) (Fig. 4).

Number of injections in year 1

HbA1c was not correlated with number of ranibizumab injections required in the first year ($p = 0.859$) (Fig. 5).

Discussion

We have found that baseline HbA1c is not correlated with the change in VA, CSFT, or MV in eyes treated with

Table 1—Ocular characteristics at baseline and 1 year

	Baseline	1 Year	*p*
Mean ± SD baseline VA (letters)	54.9 ± 16.6	61.3 ± 12.4	<0.001
Mean ± SD baseline CSFT (μm)	441.9 ± 117.8	338.2 ± 120.6	<0.001
Mean ± SD baseline MV (mm^3)	9.99 ± 1.95	8.86 ± 1.52	<0.001

VA, ETDRS visual acuity; CSFT, central subfield thickness; MV, macular volume.