Clinical Study

Systemic Factors Associated with Treatment Response in Diabetic Macular Edema

Wendy Meihua Wong1, Caroline Chee, Mayuri Bhargava, Charmaine Chai, Hazel Lin, Paul Zhao, Erlangga Ariadarma Mangunkusumo, Thet Naing, Yew Sen Yuen, Tien Yin Wong1,2, Xinyi Su1,2,3,4 and Gopal Lingam1,3

1National University Hospital, Singapore
2Singapore Eye Research Institute, Singapore
3National University of Singapore, Singapore
4Institute of Molecular and Cell Biology, A*STAR, Singapore

Correspondence should be addressed to Xinyi Su; xinyi_su@nuhs.edu.sg and Gopal Lingam; lingamgopal@gmail.com

Received 19 August 2019; Revised 15 February 2020; Accepted 26 February 2020; Published 23 March 2020

Guest Editor: Ali Dirani

Copyright © 2020 Wendy Meihua Wong et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Purpose. To identify systemic factors that may influence the response to anti-VEGF therapy in patients with diabetic macular edema (DME). Methods. 35 patients undergoing anti-VEGF injections for centre-involving DME were studied in this prospective observational study. The primary outcome was change in macular thickness one month after treatment, measured using spectral-domain optical coherence tomography (OCT). At baseline, information on various systemic factors was collected including glycosylated hemoglobin (HbA1c), serum VEGF levels, lipid profile and markers of renal function, and blood pressure. Thirty-three of the 35 patients were included in this study. Nonparametric statistical tests were used for the analysis of the data in view of the nonnormal distribution of the outcome variables. Multivariate analysis was performed using logistic regression. Stata 12.1 software was used for the analysis. Main Outcome Measures. Reduction in macular central subfield thickness (on spectral-domain OCT) and change in logMAR visual acuity at one month after injection. Results. Lower HbA1c levels (7% or less) were significantly associated with greater reduction in central macular subfield thickness at one month after injection of bevacizumab or ranibizumab on both univariate analysis ($p = 0.012$) and multivariate analysis ($p = 0.042$). Conclusions. Better glycemic control is associated with a greater reduction in central macular thickness after the first injection of bevacizumab or ranibizumab in diabetic macular edema. Patients with high levels of HbA1c and poor response to anti-VEGF may benefit from strict control of their blood glucose.

1. Introduction

Diabetic macular edema (DME) is a vision-threatening complication of diabetes. In DME, accumulation of fluid in the macula results in loss of central vision, which is important for facial recognition, reading, and driving. DME affects 1 in 15 people with diabetes [1] and is the leading cause of blindness in young adults in developed countries [2]. Intravitreal injections of antivascular endothelial growth factor (anti-VEGF) have revolutionized the treatment of patients with DME, causing visual impairment. Several landmark studies have demonstrated that anti-VEGF therapy, compared to laser photocoagulation, provides superior visual outcomes [3, 4]. In the Diabetic Retinopathy Clinical Research Network Protocol T, three commonly used anti-VEGF agents, bevacizumab, ranibizumab, and aflibercept, were shown in the randomized controlled trial to improve vision in centre-involving DME [5].

Despite the proven benefits of anti-VEGF therapy, a subgroup of patients has persistent DME after an initial course of anti-VEGF therapy. A secondary analysis of
Protocol T showed that after six monthly intravitreal anti-VEGF injections, persistent macular thickening was present in 65.6%, 41.5%, and 31.6% of eyes treated with bevacizumab, ranibizumab, and aflibercept, respectively [6]. The clinical challenge of predicting individual response to anti-VEGF therapy remains. Being able to do so will be invaluable for the physician to counsel patients and manage expectations.

The influence of systemic factors on the occurrence of diabetic retinopathy and other micro- and macrovascular complications has been well studied. Studies have shown that tight control of blood sugar and other associated systemic factors such as hypertension, serum cholesterol, and kidney function can significantly delay the onset of diabetic retinopathy [7–11]. However, it is not known if these systemic factors affect the anatomical and visual response to anti-VEGF intravitreal injections.

In this prospective study, we explored whether systemic factors, such as blood pressure, glucose control, cholesterol, triglyceride, and creatinine levels at the time of intravitreal anti-VEGF injection, affect the visual or anatomic response at one month after initiating the treatment.

2. Materials and Methods

2.1. Study Design. This prospective, single-centre, observational study was conducted with Institutional Review Board approval and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all study participants. Eligible participants had centre-involved DME confirmed on spectral-domain optical coherence tomography (OCT) (Spectralis HRA + OCT, Heidelberg Engineering, Heidelberg, Germany). Patients who had prior vitreoretinal surgery, laser, or anti-VEGF injections to the study eye within 2 months or were unable to come for review one month after the injection were excluded. The study recruited consecutive patients who required anti-VEGF treatment for DME and were able to provide informed consent.

2.2. Assessment of Systemic and Metabolic Parameters. The following baseline clinical characteristics were recorded: age; gender; duration of diabetes; diabetic medications; and associated systemic conditions such as hypertension, nephropathy, and ischemic heart disease.

On the day of injection, blood was collected to check the glycosylated hemoglobin (HbA1c) and serum VEGF levels, lipid profile (triglyceride, total cholesterol, and fractions), and markers of renal function (estimated glomerular filtration rate (eGFR) and serum creatinine). The brachial systolic and diastolic blood pressures (BP) were recorded twice with a digital manometer, at intervals of 10 minutes, with the lower of the two recordings taken as the final value.

2.3. Assessment and Treatment of DME. The Snellen best corrected visual acuity (BCVA) was recorded. The central subfield thickness (CST) was measured on spectral-domain optical coherence tomography (OCT). The change in BCVA and CST, between baseline and one month after IVT anti-VEGF, was used to assess the functional and morphological response to treatment, respectively. Study participants received either intravitreal bevacizumab (1.25 mg in 0.05 ml) or ranibizumab (0.5 mg in 0.05 ml).

2.4. Statistical Analysis. The Snellen BCVA was converted to LogMAR units and the ETDRS letter score for statistical analysis.

Continuous variables were dichotomised as normal and abnormal. The value for dichotomisation was based on published literature (>140 mmHg for systolic BP [12]; >90 mm/hg for diastolic blood pressure [5]; >7.0% for HbA1c [13]; and >308 pg/mL for serum VEGF levels [14]) or the laboratory-specific reference range (>5.2 mmol/litre for cholesterol; >2.2 mmol/litre for triglycerides; >3.3 mmol/litre for LDL; <1 mmol/litre for HDL; >3.5 for total cholesterol; HDL ratio; >120 μmol/litre for serum creatinine; and <90 ml/min/1.73 m² for eGFR).

Univariate analysis was performed with nonparametric tests as the distribution of the outcome variables were significantly skewed to the right. Evaluation of the effect of each of the systemic factors (normal vs abnormal) on the change in CST and BCVA was performed with Mann–Whitney U test. Spearman correlation test was performed for testing correlation between linear variables such as visual acuity and central subfield thickness. Multivariate analysis was performed using logistic regression analysis and step-wise backward selection of variables to be included in the final model. The Strata 12.1 software was used for statistical analysis.

3. Results

3.1. Baseline Characteristics. Over a one-year period, 35 eyes of 35 participants received either intravitreal bevacizumab (n = 25, 71.4% of eyes) or ranibizumab (n = 10, 28.6% of eyes). Data were analyzed for 33 eyes that completed the one-month follow-up visit.

The baseline demographic and study eye characteristics are summarized in Table 1. The mean duration of diabetes for study participants was 11.8 ± 9.5 years. The mean baseline CST was 440.5 ± 136.3 microns. There was no statistically significant difference in the mean baseline CST of patients with HbA1c ≤7.0% and patients with HbA1c >7.0% (p = 0.27).

The systemic and metabolic factors at time of anti-VEGF treatment are shown in Table 2. The serum HbA1c was greater than 7.0% in 57.1% of participants.

No correlation was found between the baseline CST and BCVA (Spearman correlation test).

3.2. Effect of Treatment on Visual Acuity. The final visual acuity was 6/12 (70 letters) or better in 51.4%; >6/60 to <6/12 (36 to 69 letters) in 34.3%; and less than or equal to 6/60 (35 letters) in 8.6%. The visual acuity was unchanged in 12 eyes (36.4%). The visual acuity improved in 11 eyes (33.3%), with an increase in the visual-acuity letter score ranging from 3 to
35 letters. An improvement of ≥15 letters was observed in 2 eyes (18.2%). The visual acuity worsened in 10 (30.3%) eyes, with 3 eyes (30%) having a ≥15 letters decline in the visual-acuity letter score.

3.3. Effect of Treatment on Retinal Thickening. At 4 weeks after injection, the CST decreased, on average by 82.03 ± 150.19 microns (range: −519 μm to +138 μm). By percentage (with reference to baseline) the change ranged from −65.6% to +28.9%. The Spearman correlation test did not reveal any correlation between the change in the level of vision and the change in CST.

3.4. Association of Systemic Factors with Anatomical and Visual Response. Tables 3 and 4 summarize the results of univariate and multivariate analysis of influence of various independent variables on the outcome variables.

On univariate analysis, only the HbA1c level was significantly associated with reduction of CST after anti-VEGF treatment (p = 0.012). The mean reduction in CST was 130 μm in the group with HbA1c ≤7.0% and 41.9 μm in the group with HbA1c >7.0%. On multivariate logistic regression analysis, the HbA1c level was associated with reduction in CST after anti-VEGF therapy (odds ratio −0.019, 95% confidence interval 0.042 to 0.944). The serum levels of VEGF had a moderate correlation with the reduction of CST, but this difference did not achieve statistical significance (p = 0.1894).

The change in BCVA after treatment did not have any correlation with the systemic factors that were tested.

4. Discussion

In the management of diabetic macular edema, following several landmark trials [3, 12, 13], anti-VEGF therapy has become the standard of care. However, a subgroup of patients lacks “good” visual or anatomical response for unclear reasons. Postulated factors include local factors, such as poor retinal pigment epithelium health. In this study, we hypothesized that systemic factors have an important role in the clinical response to anti-VEGF treatment.

4.1. Association of Systemic Factors with Anatomical Response after Treatment. Our study has identified that HbA1c levels of 7% or less, at the time of intravitreal anti-VEGF injection, is
In this study, the serum creatinine and glycosylated hemoglobin (gHbA1c) did not show an association with CST after anti-VEGF therapy. Additionally, patients on dialysis did not show a preferential lack of response to treatment, although our study may not be sufficiently powered to address this.

4.2. Association of Systemic Factors with Visual Outcome after Treatment. Our study showed a significant association between lower Hba1c and CST reduction, but a similar association was not found for BCVA. However, changes in the CST and the visual acuity do not necessarily correlate. In the DRCR.net Protocol I, the CST and VA of eyes treated with laser had a modest correlation [17]. In the DRCR.net Protocol T, the change in CST at 12 weeks and visual acuity at 2 years did not have a strong association [18].

There is conflicting evidence on correlation of Hba1c and visual response to anti-VEGF from large phase 3 trials [19, 20]. An analysis of ranibizumab-treated patients from the RISE and RIDE trials did not find an association between mean change in BCVA at weeks 52 and 100, with the baseline Hba1c [19]. This is in contrast to an analysis of aflibercept-treated patients from the VISTA and VIVID

Table 3: Association of various systemic factors with change in central subfield thickness (CST) and change in logMAR visual acuity (N = 33), (Mann–Whitney U test).

| S/N | Systemic factor | Reduction in CST | Change in logMAR visual acuity | p value | p value |
|-----|-----------------|------------------|--------------------------------|---------|---------|
|     |                 | Mean (SD)        | Mean (SD)                      |         |         |
| 1   | IHD             | No (n = 23) 98.43 (44.3) | 0.013 (0.239) | 0.3371 | 0.7479 |
|     |                 | Yes (n = 10) 105.2 (165.38) | 0.06 (0.193) | 0.006 | 0.2105 |
| 2   | On dialysis     | No (n = 30) 77.63 (126) | 0.06 (0.193) | 0.006 | 0.2105 |
|     |                 | Yes (n = 3) 145.77 (222.7) | 0.234 | 0.7542 |         |
| 3   | Systolic BP     | ≤ 140 (n = 11) 71.73 (180.23) | 0.29 | 0.4337 |         |
|     |                 | > 140 (n = 22) 87.18 (137.18) | 0.29 | 0.035 |         |
| 4   | Diastolic BP    | ≤ 90 (n = 29) 79.31 (155.30) | 0.228 | 0.6994 |         |
|     |                 | < 90 (n = 4) 122.09 (101.75) | 0.16 (0.192) | 0.016 | 0.1492 |
| 5   | Creatinine      | ≤ 120 (n = 18) 77.61 (134.9) | 0.212 | 0.6255 |         |
|     |                 | < 120 (n = 15) 171.47 (87.3) | 0.243 | 0.008 | 0.2582 |
| 6   | eGFR            | > 90 (n = 8) 82.13 (172.0) | 0.267 | 0.8831 |         |
|     |                 | ≤ 90 (n = 25) 146.44 (82) | 0.212 | 0.058 |         |
| 7   | Total cholesterol | ≤ 5.2 (n = 24) 72.67 (147.39) | 0.179 | 0.7464 |         |
|     |                 | > 5.2 (n = 9) 163.7 (107.25) | 0.283 | 0.018 |         |
| 8   | Triglycerides   | < 2.2 (n = 22) 91.14 (166.77) | 0.153 | 0.9239 |         |
|     |                 | > 2.2 (n = 11) 114.99 (63.82) | 0.283 | 0.054 |         |
| 9   | HDL cholesterol | ≥ 1 (n = 27) 69.67 (134.7) | 0.164 | 0.7794 |         |
|     |                 | < 1 (n = 6) 213.2 (137.67) | 0.322 | 0.002 |         |
| 10  | LDL cholesterol | ≤ 3.3 (n = 25) 69.76 (145.02) | 0.307 | 0.005 |         |
|     |                 | > 3.3 (n = 8) 169.67 (120.38) | 0.267 | 0.5015 |         |
| 11  | Hba1c           | ≤ 7 (n = 15) 130.13 (158.44) | 0.192 | 0.017 |         |
|     |                 | > 7 (n = 18) 134.32 (41.94) | 0.2627 | 0.096 |         |
| 12  | Serum VEGF      | ≤ 308 (n = 10) 41.1 (132.49) | 0.157 | 0.0841 |         |
|     |                 | > 308 (n = 23) 156.64 (99.83) | 0.5558 | 0.054 |         |

CST, central subfield thickness; IHD, ischemic heart disease; BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoproteins; Hba1c, glycosylated hemoglobin; VEGF, vascular endothelial growth factor.

Table 4: Multivariate logistic regression analysis using stepwise backward selection for influence of various factors on reduction in central macular thickness with anti-VEGF injection.

| S/N | Parameter          | Odds ratio | p value | Confidence interval |
|-----|--------------------|------------|---------|---------------------|
| 1   | Hba1c              | 0.019      | 0.042   | 0.042               |
| 2   | LDL: total cholesterol | 3.19      | 0.021   | 0.042               |

Other factors were dropped during the stepwise backward selection.
trials, which found that the mean improvement in VA at 2 years was dependent on HbA1c levels [21]. More recently, an exploratory analysis of DRCR.net Protocol T, in which participants were randomized to receive bevacizumab, ranibizumab, or aflibercept, similarly found the magnitude of vision improvement after anti-VEGF treatment to be associated with HbA1c levels [20].

One possible explanation for the discrepancy between studies is that patients with similar HbA1c levels can have marked differences in their daily glucose profiles, with variable frequency and duration of glucose excursions [22, 23]. Transient hyperglycemic spikes can be a HbA1c-independent risk factor for diabetes-related complications, due to transient episodes of oxidative stress [24]. Most studies have used HbA1c levels measured at the time of injection which reflects the blood glucose control in the previous 2 months and not prospectively after administering treatment. This could also be a limitation in understanding the correlation between HbA1c levels and response to anti-VEGF treatment.

4.3. Study Strengths and Limitations. The principal strength of this study is the prospective evaluation of the impact of other comorbidities on the short-term anatomical or visual response to anti-VEGF treatment. There are several limitations to this study, including the small sample size and inclusion of study participants receiving different anti-VEGF agents.

5. Conclusion

Although HbA1c has been demonstrated to be a marker and strong predictor of vascular complications in diabetic patients [7], its prognostic significance during treatment of DME and its effect on the efficacy is not clear. In our study, we identified that good glycemic control, as defined by an HbA1c level of less than 7%, in the period preceding anti-VEGF treatment, is associated with greater reduction in central subfield thickness on macular OCT. This has significant implications for our clinical management of DME patients with suboptimal response to initial anti-VEGF therapy. If the HbA1c levels are high in these patients, one can enforce rigid control of blood glucose, continue with the same therapy, and reassess, rather than switch to a different drug. This is because the initial lack of optimal response might be due to the lack of proper blood glucose control. Our results also will help with patient counselling and management of their expectations after their first intravitreal anti-VEGF injection.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

This study was supported by a grant from Singapore Eye Research Institute (R1034/49/2013).

References

[1] J. W. Yau, S. L. Rogers, R. Kawasaki et al., “Global prevalence and major risk factors of diabetic retinopathy,” Diabetes Care, vol. 35, no. 3, pp. 556–564, 2012.
[2] P. Romero-Aroca, “Managing diabetic macular edema: the leading cause of diabetes blindness,” World Journal of Diabetes, vol. 2, no. 6, pp. 98–104, 2011.
[3] Q. D. Nguyen, D. M. Brown, D. M. Marcus et al., “Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE,” Ophthalmology, vol. 119, no. 4, pp. 789–801, 2012.
[4] M. J. Elman, L. P. Aiello, R. W. Beck et al., “Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema,” Ophthalmology, vol. 117, no. 6, pp. 1064–1077, 2010.
[5] J. A. Wells, A. R. Glassman, A. R. Ayala et al., “Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial,” Ophthalmology, vol. 123, no. 6, pp. 1351–1359, 2016.
[6] N. M. Bressler, W. T. Beaulieu, A. R. Glassman et al., “Persistent macular thickening following intravitreal aflibercept, bevacizumab, or ranibizumab for central-involved diabetic macular edema with vision impairment: a secondary analysis of a randomized clinical trial,” JAMA Ophthalmology, vol. 136, no. 3, pp. 257–269, 2018.
[7] The Diabetes Control and Complications Trial Research Group, “The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial,” Diabetes, vol. 44, no. 8, pp. 968–983, 1995.
[8] UK Prospective Diabetes Study (UKPDS) Group, “Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33),” The Lancet, vol. 352, no. 9134, pp. 837–853, 1998.
[9] UK Prospective Diabetes Study Group, “ Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38,” BMJ, vol. 317, no. 7160, pp. 703–713, 1998.
[10] Diabetes Control and Complications Trial/Epidemiology Of Diabetes Interventions and Complications Research Group, J. M. Lachin, S. Genuth et al., “Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive insulin therapy,” New England Journal of Medicine, vol. 342, no. 6, pp. 381–389, 2000.
[11] T. Y. Wong, C. M. G. Cheung, M. Larsen, S. Sharma, and R. Simó, “Diabetic retinopathy,” Nature Reviews Disease Primers, vol. 2, no. 1, p. 16012, 2016.
[12] J.-F. Korobelnik, D. V. Do, U. Schmidt-Erfurth et al., “Intravitreal aflibercept for diabetic macular edema,” Ophthalmology, vol. 121, no. 11, pp. 2247–2254, 2014.
[13] M. Michaelides, A. Kaines, R. D. Hamilton et al., “A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: report 2,” Ophthalmology, vol. 117, no. 6, pp. 1078–1086, 2010.
[14] B. T. Ozturk, H. Kerimoglu, M. Adam, K. Gunduz, and S. Okudan, "Glucose regulation influences treatment outcome in ranibizumab treatment for diabetic macular edema," *Journal of Diabetes and its Complications*, vol. 25, no. 5, pp. 298–302, 2011.

[15] S. Matsuda, T. Tam, R. P. Singh et al., "The impact of metabolic parameters on clinical response to VEGF inhibitors for diabetic macular edema," *Journal of Diabetes and Its Complications*, vol. 28, no. 2, pp. 166–170, 2014.

[16] F. A. Warid Al-Laftah, M. Elshafie, M. Alhashimi, A. Pai, and M. Farouq, "Pretreatment clinical variables associated with the response to intravitreal bevacizumab (Avastin) injection in patients with persistent diabetic macular edema," *Saudi Journal of Ophthalmology*, vol. 24, no. 4, pp. 133–138, 2010.

[17] D. J. Browning, D. J. Browning, A. R. Glassman et al., "Relationship between optical coherence tomography-measured central retinal thickness and visual acuity in diabetic macular edema," *Ophthalmology*, vol. 114, no. 3, pp. 525–536, 2007.

[18] N. M. Bressler, W. T. Beaulieu, M. G. Maguire et al., "Early response to anti-vascular endothelial growth factor and two-year outcomes among eyes with diabetic macular edema in protocol T," *American Journal of Ophthalmology*, vol. 195, pp. 93–100, 2018.

[19] R. P. Singh, K. Habbu, J. P. Ehlers, M. C. Lansang, L. Hill, and I. Stoilov, "The impact of systemic factors on clinical response to ranibizumab for diabetic macular edema," *Ophthalmology*, vol. 123, no. 7, pp. 1581–1587, 2016.

[20] S. B. Bressler, I. Odia, M. G. Maguire et al., "Factors associated with visual acuity and central subfield thickness changes when treating diabetic macular edema with anti-vascular endothelial growth factor therapy: an exploratory analysis of the protocol T randomized clinical trial," *JAMA Ophthalmol*, vol. 137, no. 4, p. 382, 2019.

[21] R. P. Singh, C. C. Wykoff, D. M. Brown et al., "Outcomes of diabetic macular edema patients by baseline hemoglobin A1c: analyses from VISTA and VIVID," *Ophthalmology Retina*, vol. 1, no. 5, pp. 382–388, 2017.

[22] S. E. Siegelaar, F. Holleman, J. B. L. Hoekstra, and J. H. DeVries, "Glucose variability; does it matter?" *Endocrine Reviews*, vol. 31, no. 2, pp. 171–182, 2010.

[23] H. Chehregosha, M. E. Khamsheh, M. Malek, F. Hosseinpahanah, and F. Ismail-Beigi, "A view beyond HbA1c: role of continuous glucose monitoring," *Diabetes Therapy*, vol. 10, no. 3, pp. 853–863, 2019.

[24] F. Giacco and M. Brownlee, "Oxidative stress and diabetic complications," *Circulation Research*, vol. 107, no. 9, pp. 1058–1070, 2010.