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Relationship of Hemoglobin A1C and Outcomes of Treatment of Diabetic Macular Edema

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Authors' contributions

This work was carried out in collaboration between all authors. Author RBG wrote the protocol, and wrote the first draft and subsequent drafts of the manuscript. Author LJ managed the literature searches. Authors PEC and SON edited the manuscript. Author REC designed the study and edited the manuscript. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Aims: To evaluate the relationship between Hemoglobin A1c (HbA1c) and visual and anatomical outcomes in eyes following treatment with intravitreal anti vascular endothelial growth factor (VEGF) agents and corticosteroids for diabetic macular edema (DME).
Study Design: Retrospective observational case series.
Place and Duration of Study: Michael E. DeBakey Veterans Affairs Medical Center in Houston, Texas between January 2012 and November 2014.
Methodology: Case series from a single institution of 194 eyes from 134 consecutive patients with DME in the absence of concurrent retinal disease treated with at least 3 intravitreal injections of bevacizumab, ranibizumab, or aflibercept with at least 6 months of follow-up.
Results: On multivariate analysis, initial HbA1c and initial BCVA were each associated to predict final visual outcome (p = 0.003 and p =0.001, respectively). Subgroup analysis demonstrated no

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statistical difference in improvement in mean BCVA (p=0.11) or mean CSMT (p=0.11) among patients whose hemoglobin A1c stayed stable, increased during the study or decreased during the study, however the mean number of injections required were respectively 6.5, 9.0 and 8.1 (p=0.02).
Conclusions: The visual outcome following intravitreal bevacizumab, ranibizumab, or aflibercept with or without adjunctive triamcinolone acetonide are weakly related to glycemic control at initiation of treatment. Patients with stable glycemic control during treatment require fewer injections to treat diabetic macular edema compared to patients with improvement or worsening in glycemic control.

Keywords: Aflibercept; bevacizumab; diabetic macular edema; hemoglobin A1c; intravitreal injection; macular edema; ranibizumab; triamcinolone acetonide.

ABBREVIATIONS

DME : Diabetic Macular Edema
MPC : Macular Photocoagulation
IVT : Intravitreal
VEGF : Vascular Endothelial Growth Factor
MEDVAMC : Michael E. DeBakey Veterans Affairs Medical Center
HbA1c : Hemoglobin A1c
SD-OCT : Spectral Domain Optical Coherence Tomography
CSMT : Central Subfield Macular Thickness

1. INTRODUCTION

Macular edema is the leading cause of moderate visual loss in patients with diabetes mellitus [1,2]. There is evidence that strict glycemic control reduces the risk of development of diabetic macular edema (DME) and the risk of moderate visual loss in patients with diabetes mellitus [3-7]. Further, there is evidence that poor glycemic control may be associated with persistent DME following macular photocoagulation (MPC), which had been the standard treatment for DME until recently [8]. In the last decade, intravitreal (IVT) injections of the anti- vascular endothelial growth factor (VEGF) agents bevacizumab, ranibizumab and more recently aflibercept have been shown to be more effective in the treatment of DME than MPC, with aflibercept resulting in best visual outcomes in patients with initial visual acuity worse than 20/40 [9-15]. Triamcinolone acetonide with MPC has been found to be effective in the treatment of DME in pseudophakic patients, although it results in ocular hypertension in about 32% of eyes [16,17].

Some studies have examined the relationship between glycemic control and visual and anatomic outcomes following treatment with bevacizumab or ranibizumab [18,19]. However, these studies included a range of 60-150 patients for a maximum follow-up of 6 months. We therefore undertook the present study, using a larger group of patients treated in a clinical setting to further investigate this relationship of glycemic control with visual and anatomic outcomes following treatment with bevacizumab, ranibizumab, or aflibercept.

2. MATERIALS AND METHODS

This was a retrospective chart review of consecutive patients examined at the retina clinic at the Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC) between January 2012 and November 2014. The study was approved by the Baylor College of Medicine institutional review board and the research review board of the MEDVAMC.

Included were patients with a diagnosis of DME who received at least 3 intravitreal injections and had follow-up of at least 6 months. Exclusion criteria were the presence of concurrent retinal pathology, other possible causes of macular edema, loss to follow-up, previous treatment with intravitreal injections, treatment with focal MPC or no hemoglobin A1c (HbA1c) measured at 4-month intervals. Patients were not excluded if they had co-morbid ophthalmic conditions that did not contribute to macular edema. Subjects were analyzed from the initiation of their therapy until the end of the chart review period.

Every 4 weeks subjects underwent a comprehensive ophthalmologic examination that included determination of distance best corrected visual acuity (BCVA) on electronic ETDRS chart and spectral domain optical coherence tomography (SD-OCT) with a central subfield macular thickness (CSMT) measurement. An intravitreal injection was given if center involving DME resulting in decreased BCVA was present or, in the presence of normal visual acuity, if the diabetic macular edema was considered to be disruptive to the normal foveal architecture from intraretinal cystic cavities on SD-OCT or if the

CSMT was greater than 300 microns. Retreatment for DME was based on persistence of intraretinal cystic spaces on SD-OCT or persistence of CSMT greater than 300 microns. The choice of treatment medication was at the attending physician's discretion with a change in medication made if there had been no improvement of at least 10% of CSMT on SD-OCT at 2 consecutive visits. Therapy was withheld when it was determined by the attending physician that BCVA was not affected by macular edema and the patient was observed on a monthly basis to assess for recurrence. HbA1c was measured every 3-4 months.

A linear regression model was fit with final BCVA as the dependent variable and patient age, number of intravitreal injections, initial HbA1c, initial CSMT, initial BCVA, final HbA1c, and final CSMT tested as independent variables. Secondary outcome measurements included a comparison in change in BCVA, change in CSMT and number of injections required between a group in which the HbA1c stayed the same during the study, a group in which the HbA1c improved by greater than 3% of baseline value and a group in which the HbA1c worsened by 3% of baseline value. The 3% cutoff for change in baseline HbA1c was chosen based on the accepted variable error and total analytic imprecision of the analyzer determining HbA1c levels [20].

For the purposes of data analysis electronic ETDRS visual acuities were converted to logarithmic minimum angle of resolution (logMAR). There were 7 patients with count finger visual acuities that were assigned a logMAR value of 1.6 as has been described previously [21]. The factors predictive of significant improvement in BCVA were analyzed using linear regression model. Additional data analysis was performed with paired sample t-test and ANOVA statistical analysis. The accepted p-value for statistical significance was set to p=0.05. Data were analyzed using SPSS 22 (copyright 2015 IBM, Inc.).

3. RESULTS AND DISCUSSION

Included were 194 eyes of 134 patients whose demographic characteristics are shown in Table 1. During an average follow-up time of18 months (range 6-34 months), the average number of injections that subject eyes received over the course of their treatment was 7.95 (range 3-30). There was no significant difference in the mean HbA1c value during follow-up (8.36 vs. 8.37, p= 0.61).

Table 1. Baseline characteristics

	Patients (n=134)
Mean age (SD, Range)	63 (7.7, 48-88)
Sex	
Male	133 (98.9%)
Female	1(1.1%)
Ethnicity	
Caucasian	75 (56.1%)
African American	40 (29.5%)
Hispanic	10 (7.6%)
Asian	3 (2.6%)
Other	6 (4.1%)
Hemoglobin A1c	8.36%
Insulin dependent, n (%)	75 (56%)
Initial BCVA (logMAR)	20/60 (0.48)
Initial CSMT	425 µm

There was significant improvement in overall visual acuity with mean BCVA improving from logMAR 0.48 (Snellen equivalent 20/62) to 0.43 (Snellen equivalent 20/53, p=0.05). Overall anatomic improvement was noted with mean CSMT decreasing from 423 µm to 345 µm (p= <0.001). During the study, more than a single medication was required in 134 eyes (71.6%) and variations in treatment regimens can be seen in Table 2.

Table 2. Intravitreous medication regimens

Medication used	Total eyes (n=194)
Monotherapy bevacizumab, n (%)	42 (21.6%)
Monotherapy ranibizumab, n (%)	15 (7.73%)
Monotherapy aflibercept, n (%)	3 (1.55%)
Bevacizumab switched to ranibizumab, n(%)	42 (21.6%)
Bevacizumab switched to aflibercept, n(%)	27 (13.9%)
Ranibizumab switched to bevacizumab, n(%)	6 (3.01%)
Ranibizumab switched to aflibercept, n(%)	4 (2.06%)
Triamcinolone switched to anti-VEGF, n(%)	11 (5.67%)
Anti-VEGF switched to triamcinolone, n(%)	22 (11.3%)
Bevacizumab, ranibizumab and aflibercept, n(%)	16 (8.25%)
Bevacizumab, ranibizumab, aflibercept and triamcinolone, n(%)	6 (3.10%)

Multivariate analysis shown in Table 3 demonstrated the following factors to be associated with better final BCVA: 1) initial HbA1c (p = 0.003); and 2) initial BCVA (p=0.001).

Table 3. Linear regression model with final BCVA as outcome variable

Independent variable	T-statistic value	P-value
Age	1.03	P=0.31
Total Injections	1.11	P= 0.27
Initial CSMT	-0.28	P=0.78
Final CSMT	1.23	P=0.22
Initial HbA1c	2.97	P=0.003
Final HbA1c	-1.34	P=1.18
Initial BCVA	9.12	P=0.001

There were 68 patients with improved glycemic control, 57patients with stable glycemic control and 69 patients with worse glycemic control during the study (Table 4). Mean logMAR improved by 0.01, 0.02 and 0.10 respectively (p=0.17), while mean change in CSMT was -59 um, -108 µm, and -82 µm, respectively (p=0.18). The average number of injections was 8.1, 6.5, and 9.0 respectively (p=0.02).

Of phakic eyes, a total of 19 eyes (12%) underwent cataract extraction during the period of their treatment with intravitreal injections for DME.

In this study, we found that with mean follow-up of 18 months, baseline visual acuity and HbA1c prior to first injection are significant predictors of final visual acuity following intravitreal bevacizumab, ranibizumab or aflibercept. Conversely, baseline and final CSMT, age, number of injections and final HbA1c do not correlate with final best-corrected visual acuity when considered together in a mathematical model. These results are consistent with prior studies of patients receiving IVT anti-VEGF injections that patients with low HbA1c measurements show a more robust improvement in BCVA than other patients receiving injections for DME [22,23]. Matsuda et al demonstrated that glucose regulation can impact the response of DME to IVT bevacizumab as patients with an initial HbA1c of less than 7.0% had a greater improvement in BCVA over the course of 12 months [22]. A recent investigation by Pemp and colleagues also provided evidence that with intravitreal ranibizumab or bevacizumab, maximum gains in visual acuity are achieved in patients with a HbA1c less than 7% at the start of therapy [23]. Our data also correlates with previously published data suggesting that patients with worse glycemic control have more significant microvascular damage over time [23]. Therefore patients with mild disease will have better results as there has been less significant changes in the endothelium from excessive glycemic exposure that has occurred [12]. These results, however contradict a dichotomous analysis of patients from the VIVID/VISTA studies which suggested that there was no difference in final visual and anatomic outcomes comparing patients with hemoglobin A1c of greater or less than 8.0% at baseline (Wykoff CC. Intravitreal aflibercept in the VISTA-DME and VIVID-DME studies: subgroup analysis by baseline demographics and systemic disease characteristics, Retina Society 2014 Annual Meeting, Philadelphia, PA). A dichotomous analysis may lack the power to show a significant difference and such an analysis of our dataset would have also failed to detect a difference. Moreover, the choice of 8.0% is arbitrary. Indeed, in prior investigations of patients receiving a single anti-VEGF medication, patients with a HbA1c <7% at the start of treatment showed a significantly larger reduction in retinal thickness [22-25]. Matsuda and colleagues demonstrated a larger reduction in CSMT in patients with glycemic control of 7.0% or less with bevacizumab, and Ozturk et al showed similar results using IVT ranibizumab to treat DME [22,25]. An investigation with either IVT ranibizumab or bevacizumab confirmed these results of marked reduction in CSMT in patients with HbA1c less than 7.0% as well [23]. This discrepancy between our results and previous investigations is likely based on the difference in injection protocols. While we did demonstrate that initial HbA1c is a predictor of final visual outcome, the approach to treatment of varying anti-VEGF medication appears to be effective in improving even the most severe forms of diabetic macular edema.

Our study also found that, in follow-up period from 6 to 34 months, treatment with IVT bevacizumab, ranibizumab, aflibercept and/or triamcinolone acetonide led to similar improvements in visual acuity and macular thickness irrespective of improvement, stability or worsening of glycemic control during the course of the study. However, ANOVA testing revealed that significantly fewer injections were needed to achieve these similar outcomes with stable glycemic control while patients with worsening glycemic control required the most injections.

Table 4. Subgroup analysis based on change in HbA1c

	Net Decrease HbA1c (n=68)	No Net Change HbA1c (n=57)	Net Increase HbA1c (n=69)	P-value
Number of injections	8.1	6.5	9.0	P=0.018
Initial BCVA (logMAR)	20/56 (0.45)	20/54 (0.43)	20/73(0.56)	P=0.11
Overall change in BCVA, logMAR	0.01	0.02	0.10	P=0.17
Initial CSMT	400 µm	444 µm	434 µm	P= 0.11
Overall change in CSMT	-59 µm	-108 µm	-82 µm	P= 0.18

These are novel results, as prior studies have not investigated, to our knowledge, the relationship between changes in hemoglobin A1c levels and injection frequency. This relationship may be explained by the need for additional suppression of cytokine-mediated vascular permeability in diabetics with worsening glycemic control, and the transient progression of retinopathy that occurs in part due to alteration in blood flow and induced ischemia in patients with improving glycemic control [26-33].

Our study results are from a clinical treatment setting where patients were not excluded based on visual acuity, CSMT, or overall diabetes control and where patients were treated based on an OCT-guided treatment protocol with the treating physician changing anti-VEGF agent or adding triamcinolone acetonide based on their best judgment. We acknowledge that patients may respond uniquely to the different anti-VEGF medications available, and recent investigations have shown that aflibercept may work initially for more significant vision loss [34]. However, when taking cost-effectiveness into account a recent article suggested that the benefits of bevacizumab may outweigh the benefits of other anti-VEGF medications in certain populations [35]. The number of patients in this study is one of the largest to date for a single-center study on the treatment of diabetic macular edema. Limitations of this study include the limitations inherent to retrospective studies (including selection bias), the reliance on physician discretion for the choice of intravitreal injection agent and decision to inject, lack of standardization in visit intervals and variable follow-up. Additionally, the patient population was predominantly male, and Caucasian or African American with poorly controlled diabetes due to the nature of the patient base at the MEDVAMC. This may contribute to a limited ability to generalize the results to a standard population model. Further investigations that use a standardized treatment regimen may be beneficial to better understand the relationship of HbA1c and response to treatment. Also, additional studies that include fluorescein angiography and/or OCT-angiography may add a better understanding of the role of macular ischemia in limitations of BCVA in patients with DME.

4. CONCLUSION

Baseline glycemic control affects the visual outcome following treatment of diabetic macular edema with intravitreal bevacizumab, ranibizumab, aflibercept and/or triamcinolone acetonide in the intermediate term. Further, improvement, stability or worsening of glycemic control do not seem to have any effect on visual or anatomic outcomes, although, on average, stability of glycemic control is associated the fewest injections while worsening of glycemic control is associated with the most injections for treatment of diabetic macular edema.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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