The Impact of Race on Short-term Treatment Response to Bevacizumab in Diabetic Macular Edema

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• PURPOSE: To determine the impact of race and ethnicity on efficacy of intravitreal bevacizumab for diabetic macular edema in anti–vascular endothelial growth factor (VEGF) treatment–naive patients.
• DESIGN: Retrospective cohort study.
• METHODS: SETTING: Urban-based academic institution with affiliated private offices. STUDY POPULATION: Intravitreal anti-VEGF naïve patients seen between 2010 and 2019 of White (W) race, Black (B) race, or Hispanic (H) ethnicity aged 18 years and older with diabetic macular edema who received intravitreal injections of bevacizumab. Exclusion criteria were prior intravitreal anti-VEGF treatment, invasive ophthalmologic interventions, and laser treatments within 3 months prior to first injection through the duration of the study. EXPOSURES: Intravitreal bevacizumab. MAIN OUTCOMES MEASURES: Percentage of patients with visual acuity (VA) improvement and mean percentage reduction in central macular thickness (CMT).
• RESULTS: Percentage with VA improvement was 27% vs 39% vs 50% after 1 injection (n = 314), and 34% vs 55% vs 59% after 3 injections (n = 150) for B, H, and W cohorts, respectively. Black patients experienced lower odds of VA improvement compared with White and Hispanic patients after 1 injection (odds of 0.480, CI 0.284-0.814, $P = .006$) and 3 injections (odds of 0.342, CI 0.149-0.782, $P = .008$) while controlling for age, sex, baseline glycated hemoglobin (HbA_{1c}), baseline CMT, baseline VA, laser history, injection time course, and follow-up delay.
• CONCLUSIONS: Black patients had a significantly lower likelihood of visual acuity improvement following intravitreal bevacizumab treatment compared with White and Hispanic patients. Further research is warranted to understand the effect of race and ethnicity on anti-VEGF efficacy to ensure optimal treatment for each individual. (Am J Ophthalmol 2021;222:310–317. © 2020 Elsevier Inc. All rights reserved.)

DIABETIC MACULAR EDEMA (DME) IS A LEADING cause of visual loss in patients with diabetes mellitus worldwide.[1] It is known that these patients exhibit increased levels of vascular endothelial growth factor (VEGF), resulting in abnormal retinal fluid accumulation and ultimately vision loss.[2] Historically, focal or grid laser photocoagulation had been the standard of care to mitigate vision loss from DME; however, with the more recent advent of angiogenesis inhibitors, intravitreal injection with agents such as bevacizumab has become the new standard of care.

Previous studies have reported that Black patients have a higher susceptibility for developing diabetic macular edema in comparison to White patients, despite controlling for confounding factors such as glycated hemoglobin (HbA_{1c}) values and duration of diabetes.[2,3] Studies comparing the efficacy of treatment with anti-VEGF agents in diabetic macular edema have a predominance of White subjects, and most do not represent the larger burden of disease experienced by minority subgroups. This indicates a disparity in prevalence of disease and the population studied for treatment. We are not aware of any studies as of this writing that have directly investigated the impact of race and ethnicity on anti-VEGF treatment effect.

We have anecdotally noted from our experience working with a diverse patient population that Black patients treated for diabetic macular edema with bevacizumab may have suboptimal outcomes compared with White patients. A post hoc analysis of the Diabetic Retinopathy Clinical Research Network Protocol T looking at risk factors in anti-VEGF treatment response also showed a trend that Black patients experienced lower visual acuity improvement compared to other races, while paradoxically having a larger reduction in central macular thickness following anti-VEGF therapy. The authors advised that these results should be interpreted with caution given the post hoc nature of the analysis.[4]

This retrospective study seeks to compare the impact of race and ethnicity on the short-term efficacy of intravitreal bevacizumab therapy for diabetic macular edema in anti-VEGF treatment–naïve patients. We hypothesize that

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Black patients are anatomically less responsive to and experience smaller visual acuity gains with bevacizumab therapy compared with their White and Hispanic cohorts.

METHODS

THIS IS A RETROSPECTIVE COHORT STUDY OF PATIENTS receiving treatment at Boston University Eye Associates, affiliated with Boston Medical Center (BMC), an urban-based academic institution with a large international and diverse patient population, and its affiliated private offices between the years 2010 and 2019. This study was conducted according to the Declaration of Helsinki and was approved by the Institutional Review Board at Boston University School of Medicine. Inclusion criteria included intravitreal anti-VEGF–naïve patients aged ≥18 years with a diagnosis of diabetic macular edema who received intravitreal injections of bevacizumab. Data were collected at baseline, 1-3 months following a single injection, and 1-3 months following 3 injections. Primary outcomes were improvement in visual acuity as determined by an increase of at least 0.1 points on the logarithm of minimum angle of resolution (logMAR) scale and percentage reduction in central macular thickness (CMT) compared with baseline on Heidelberg spectral-domain optical coherence tomography (SD-OCT). Additional data points collected included age, race, sex, hemoglobin A_{1c}, prior laser history, baseline visual acuity, baseline visual acuity worse than or equal to 20/50, baseline central macular thickness, compliance, visual acuity, and CMT after the first and third dose, interval from the first dose to the next follow-up visit, interval between the first and third doses of bevacizumab, and the interval between the third dose and follow-up. Compliant participants were defined as individuals who did not miss any appointments and who adhered to treatment plans created for them. The number of individuals with visual acuity of 20/50 or worse were identified in our analysis as Protocol T indicates that in subjects entering with visual acuity at this level, bevacizumab resulted in less visual acuity improvement than aflibercept and ranibizumab. Subjects were excluded from the analysis if they had received any prior intravitreal anti-VEGF treatment, any invasive ophthalmologic interventions including cataract surgery, or any laser treatments within 3 months prior to the initiation of anti-VEGF injections.

Race and ethnicity information was initially abstracted from the medical chart from hospital intake questionnaires. Per the US Census Bureau standards, race was defined as White, Black or African American, American Indian or Alaska Native, Asian, and Native Hawaiian or Other Pacific Islander.[5] Ethnicity was defined as Hispanic or Latino and Not Hispanic or Latino. We collected self-reported information on race and ethnicity. Patients in the Hispanic group included all patients who identified as Hispanic or Latino regardless of their reported race. The White and Black patient groups contained only patients who did not also identify as Hispanic or Latino. To ensure that our language was free of bias, we consulted the American Psychological Association guidelines for talking about racial and ethnic identity with inclusivity and respect.[6] For patients who met inclusion criteria for the study, phone calls were placed to obtain verbal consent for this study as well as to confirm their race and ethnicity. Multivariate logistic and linear regression analyses were performed using SAS v 9.4 to evaluate for statistical significance between our 3 groups: Black, Hispanic, and White. Analysis was completed separately after 1 dose and after 3 doses, with a P value of .05 considered statistically significant. Based on the similarity of outcomes for the White and Hispanic groups in initial statistical analysis, we performed a secondary analysis merging those groups, resulting in a Black vs White/Hispanic comparison.

RESULTS

DATA FROM 314 MEDICAL CHARTS WERE INCLUDED FOR SINGLE injection analysis and 151 for the 3-injection analysis. Race cohorts were similar with regard to age, compliance, baseline hemoglobin A_{1c}, proportion with prior laser, time interval between the first and third doses of bevacizumab, time intervals between the first and follow-up, first and third dose, and third dose and follow-up, baseline visual acuity, proportion with baseline visual acuity worse or equal to 20/50, post-treatment visual acuity, and baseline CMT values (Table 1). The single-dose analysis was controlled for age, sex, baseline HbA_{1c}, baseline CMT, baseline vision, prior laser history, and time interval between the first dose and follow-up visual acuity and CMT measurement. The 3-dose analysis was controlled for age, sex, baseline HbA_{1c}, baseline CMT, baseline vision, prior laser history, time interval between first and third doses of bevacizumab, and time interval between the third dose and follow-up visual acuity and CMT measurement. The Black patient cohort had a higher percentage of female patients. There were no other statistically significant differences in demographic data between the 3 race groups. The post-treatment logMAR change in visual acuity was significantly less for Black individuals in both the single-dose ($P = .03$) and 3-dose ($P = .008$) analysis.

After a single injection of bevacizumab, 26.71% of Black patients versus 39.39% of Hispanic and 50% of White patients experienced improved visual acuity of at least 0.1 on the logMAR scale ($P = .002$). Our 3-injection analysis showed a similar trend, with a significantly smaller proportion of Black patients experiencing improved visual acuity (33.82% of Black patients vs 54.76% of Hispanic and 58.54% of White patients; $P = .02$). No significant difference in the visual acuity response rate was found between

TABLE 1. Comparison of Demographic Data and Clinical Characteristics of Racial/Ethnic Groups

	Single-Dose Analysis					Three-Dose Analysis				
	Total (N = 314; 100%)	Black (n = 146; 46.5%)	Hispanic (n = 84; 26.8%)	White (n = 84; 26.7%)	*P*	Total (n = 151; 100%)	Black (n = 68; 46.8%)	Hispanic (n = 42; 27.8%)	White (n = 41; 27.2%)	*P*
Age, y, mean (SD)	62 (10)	62 (10)	61 (9)	61 (11)	.67	61 (10)	62 (10)	61 (9)	61 (11)	.67
% female	48	62	38	35	.00004	44	57	36	32	.01
% compliance	94	93	92	99	.1	94	95	95	93	.89
Baseline A_{1c}, % mean (SD)	8.7 (2.2)	8.9 (2.3)	8.9 (1.9)	8.4 (2.4)	.18	8.8 (2.3)	9.1 (2.3)	8.9 (2.2)	8.2 (2.3)	.13
% with prior laser	17	19	17	13	.50	14	16	14	10	.64
Dose 1-3 interval, days, mean (SD)	N/A	N/A	N/A	N/A	N/A	97 (35)	95 (31)	97 (39)	102 (38)	.52
Dose 1–follow-up interval, days, mean (SD)	44 (24)	46 (26)	45 (25)	40 (17)	.16	42 (16)	44 (16)	41 (14)	39 (18)	.26
Dose 3–follow-up interval, days, mean (SD)	N/A	N/A	N/A	N/A	N/A	42 (16)	44 (16)	41 (14)	39 (18)	.26
Baseline VA logMAR, mean (SD)	0.46 (0.30)	0.44 (0.28)	0.47 (0.31)	0.49 (0.32)	.43	0.48 (0.29)	0.43 (0.26)	0.51 (0.28)	0.52 (0.36)	.50
Post-treatment VA logMAR, mean (SD)	0.37 (0.27)	0.38 (0.28)	0.36 (0.27)	0.37 (0.28)	.85	0.35 (0.24)	0.37 (0.25)	0.33 (0.27)	0.33 (0.20)	.68
Post-treatment logMAR change, mean (SD)	0.087 (0.20)	0.055 (0.19)	0.11 (0.20)	0.12 (0.22)	.03	0.129 (0.23)	0.066 (0.16)	0.174 (0.28)	0.185 (0.24)	.008
% baseline VA ≤20/50	58	57	61	57	.84	59	57	64	56	.70
Baseline CMT, mean (SD)	314 (35)	398 (105)	401 (122)	425 (116)	.19	430 (122)	420 (109)	431 (147)	444 (117)	.63

CMT = central macular thickness, logMAR = logarithm of minimum angle of resolution, VA = visual acuity.
Standard deviation (SD) is listed in parentheses.

TABLE 2. Percentage of Patients With Improved Visual Acuity (VA) and Percentage Change in Central Macular Thickness (CMT) by Racial/Ethnic Group

	Single-Dose Analysis					Three-Dose Analysis				
	Total (N = 314)	Black (n = 146)	Hispanic (n = 84)	White (n = 84)	*P*	Total (n = 151)	Black (n = 68)	Hispanic (n = 42)	White (n = 41)	*P*
% with improved VA, mean (SD)	36.31 (48.2)	26.71 (44.4)	39.39 (49.1)	50 (50.3)	.002	46.36 (50.0)	33.82 (47.7)	54.76 (50.4)	58.54 (49.9)	.02
% CMT change, mean (SD)	−15.79 (35.5)	−12.30 (38.9)	−17.01 (34.5)	−20.66 (29.5)	.20	−22.35 (44.7)	−24.36 (58.1)	−16.13 (28.0)	−25.38 (31.3)	.57

Standard deviation is listed in parentheses.

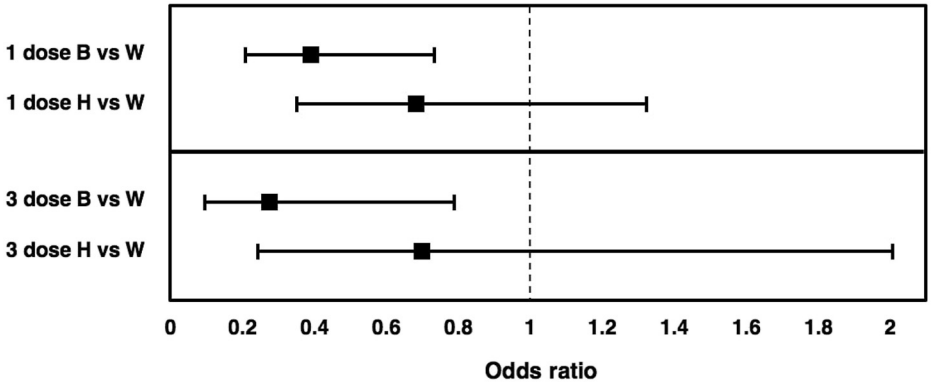

FIGURE 1. Odds ratio comparing proportions of individuals with visual acuity improvement of at least 0.1 on the logMAR scale between racial/ethnic groups. The odds of visual acuity improvement of Black patients (B) and Hispanic patients (H) are listed in comparison to White patients (W) following a single dose and 3 doses of bevacizumab. Black patients experienced significantly less odds of visual acuity improvement compared with White patients in the single-dose (odds of 0.392, range 0.209-0.734; $P = .003$) and in the 3-dose (odds of 0.259, range 0.094-0.714; $P = .012$) analysis. Hispanic and White patients experienced similar visual acuity improvement in the single- ($P = .26$) and 3-dose ($P = .48$) analysis.

the White and Hispanic groups after 1 or 3 injections. CMT reductions were 12.30% in Black patients, 17.01% in Hispanic patients, and 20.66% in White patients after 1 injection, and 24.36% in Black patients, 16.13% in Hispanic patients, and 25.38% in White patients after 3 injections. There were no statistically significant differences in the reduction of central macular thickness between the race groups ($P = .3$; Table 2 and Figures 1 and 2).

Given the similarity in visual acuity outcomes between the White and Hispanic groups, race cohorts were regrouped under "Black" and "White and Hispanic" and the data were reanalyzed. This new combined White and Hispanic cohort had similar visual acuity outcomes to the White-only and Hispanic-only groups. After 1 injection, 44.64% of the combined White and Hispanic cohort showed visual improvement. After 3 injections, 56.63% showed improvement. The new groups revealed a statistically significant trend that Black patients were less likely to exhibit improvement in visual acuity compared with the combined White and Hispanic cohort following both 1 and 3 injections ($P = .006$, $P = .008$). There was no significantly different change in CMT across the racial/ethnic groups for the single-dose ($P = .10$) and 3-dose ($P = .62$) analyses (see Table 3 and Figure 3).

DISCUSSION

RACIAL DISPARITIES IN MAJOR EYE DISEASES AND IN THE USE of eye care services have been well documented.[7–9] In particular, the prevalence of diabetic retinopathy and its serious sequelae are highest among non-Hispanic Black individuals, the less educated, and the impoverished.[10] Even while controlling for confounding factors, studies have shown Black individuals experience more than a 2-fold increased risk of having clinically significant macular edema compared with non-Hispanic Whites.[11] This

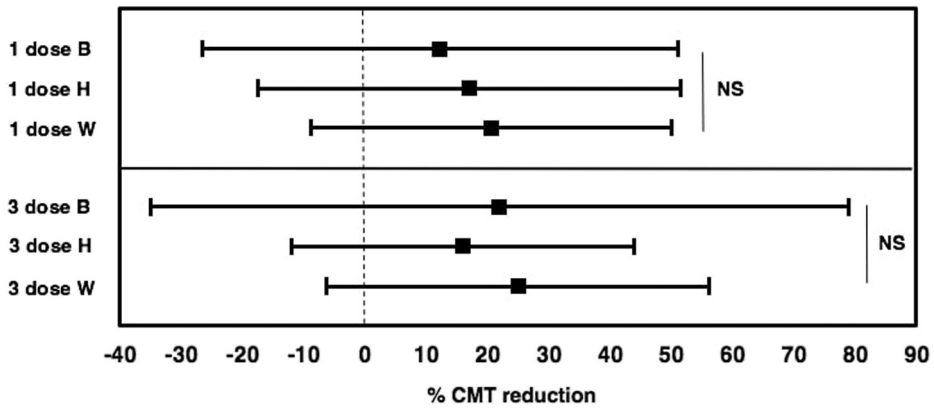

FIGURE 2. Percentage reduction in central macular thickness (CMT) following a single-dose and 3 doses of bevacizumab by racial/ethnic group. There is no significant difference in CMT reduction among Black (B), Hispanic (H), and White (W) patients in the single- ($P = .20$) or 3-dose ($P = .57$) analysis.

TABLE 3. Percentage of Patients With Improved Visual Acuity (VA) and Percentage Change in Central Macular Thickness (CMT) by Race, With White and Hispanic Patients Grouped Together

	Single-Dose Analysis				Three-Dose Analysis			
	Total (N = 314)	Black (n = 146)	White/Hispanic (n = 164)	*P*	Total (n = 151)	Black (n = 68)	White/Hispanic (n = 83)	*P*
% with improved VA, mean (SD)	36.31 (48.16)	26.71 (44.4)	44.64 (49.9)	.001	46.36 (50.0)	33.82 (47.7)	56.63 (49.9)	.005
% CMT change, mean (SD)	−15.79 (35.5)	−12.30 (38.9)	−18.83 (32.1)	.10	−22.35 (44.7)	−24.36 (58.1)	−20.69 (29.9)	.62

Standard deviation (SD) is listed in parentheses.

underscores a critical need for more research regarding optimal treatment options that serve all racial groups.

Boston Medical Center is the largest safety net hospital in New England, and our institution provides care for a diverse and international patient population.[12] As many of our patients rely on government payors for health coverage, bevacizumab is often the initial treatment choice given its low cost, followed by more expensive options, aflibercept and ranibizumab, if the response to treatment with bevacizumab is inadequate or has plateaued. This is the primary reason we studied bevacizumab over the other agents. The possibility of studying other agents was considered; however, similar to the treatment at our institution, bevacizumab is given first line for DME by many retina specialists in the United States. According to the 2019 Preferences and Trends survey conducted by the American Society of Retina Specialists, bevacizumab is the first line of treatment for DME for 64.8% of Americans who responded to the survey and 31.5% of international respondents.[13]

Our results show that Black patients are half as likely to show visual acuity improvement 1 month after the first and third bevacizumab injections compared with White and Hispanic patients. This finding may not be surprising. Research and development of anti-angiogenesis therapy for eye disease was focused initially on the treatment of age-related macular degeneration (AMD) which is a disease that predominantly affects White individuals of northern European descent. Virtually all medications, from pegaptanib sodium to ranibizumab, which is a daughter molecule to off-label bevacizumab, and eventually aflibercept, were initially studied for treatment of AMD, and only after efficacy for AMD was established (for the latter 3 medications) were they subsequently studied for diabetic retinopathy, DME, and vein occlusions. Other factors may also contribute to our findings. Intrinsic genetic variation is another possible explanation for the differential response rate.[14] A polymorphism in the *VEGF* gene, C634G, has been identified as a genetic risk factor for DME as well as an indicator that an individual would have a positive response to bevacizumab.[15] The effect of the C634G VEGF polymorphism is variable across individuals, and its expression across racial groups is not yet determined,[16] but varying distributions of similar genetic polymorphisms between racial groups would explain different response rates to bevacizumab treatment, and may be worth investigating in a prospective study. Socioeconomic differences as manifest by factors such as disease severity and treatment adherence between races may further account for the

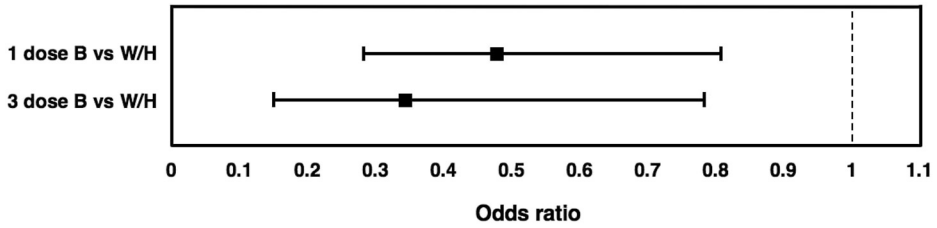

FIGURE 3. Odds ratio comparing proportions of Black (B) to combined White and Hispanic (W/H) individuals with visual acuity improvement of at least 0.1 on the logMAR scale. Black patients experienced significantly smaller odds of visual acuity improvement compared with White and Hispanic patients in the single- (odds of 0.480, range 0.284-0.814; $P = .006$) and 3-dose (odds of 0.342, range 0.149-0.782; $P = .008$) analysis.

difference in visual acuity response rate. However, we attempted to at least mitigate these differences by controlling for disease severity through hemoglobin A_{1c} and baseline central macular thickness, as well as controlling for compliance rates with missed or skipped appointments and patient refusal of treatment when recommended.

Although this study was not specifically designed to assess the predictive value of a single bevacizumab injection on the chances of response after multiple injections, our results show that patients who did not exhibit visual acuity improvement after the first injection (n=87) had only a 23% chance of improving after the third injection. Those who did improve after the first injection (n=57) had an 82% chance of retaining that improvement at the third injection mark. This trend was consistent among all racial/ethnic groups and suggests that a patient who did not improve after 1 injection may continue to not respond after a series of injections. Further studies would be required to substantiate this finding.

Our visual acuity results were not supported by objective OCT measurements like CMT, as our data show that race and ethnicity did not seem to have an impact on change in CMT. The incongruity in vision and CMT aligns with other previous studies that have shown a similar discordance between visual acuity improvement and CMT change.[17] This may be due to the variable duration of edema and ischemia, which affects CMT and visual acuity differently. In those studies, measuring the disorganization of the inner retinal layers was found to have a moderately better correlation with visual acuity improvement.[17,18]

The strengths of this study include a highly selective criteria for inclusion of treatment-naïve patients who adhered to a narrow follow-up window, which reduced the effect of variability in follow-up time on our results and eliminated any potential confounding factors such as previous anti-VEGF injection treatments. Additionally, because of the diverse patient base at Boston Medical Center, we were able to include a significant number of Black and Hispanic patients who are typically not well represented in larger prospective studies of diabetic macular edema. This is also the first study that has focused on race as a risk factor for treatment effect in diabetic macular edema.

This study has limitations, many of which are inherent to its retrospective design, including incomplete control of potential confounding variables such as blood pressure, duration of diabetes, duration of diabetic macular edema, and other medical comorbidities including concurrent renal disease. Racial disparities in health care are heavily documented and encompass factors such as socioeconomic status, access to care, health literacy, insurance coverage, and discordance between patients and providers.[16] The controls used in this study account for several of these differences; however, they may not fully encompass the many racial disparities that exist. The Institute of Medicine report on racial/ethnic disparities in health care describe that these differences contribute to delays in screening, diagnosis, and timely treatment.[16] This results in higher rates and severity of microvascular complications, diabetic retinopathy, and macular edema, which can worsen a patient's response to bevacizumab but may not be best represented by a single hemoglobin A_{1c} level or central macular thickness measurement.[1,3] Additionally, although we controlled for A_{1c} levels, there is evidence that HbA_{1c} may not be a comprehensive measure of glycemia. One explanation offered for this variability is blood cell 2,3-diphosphoglycerate, which is responsible for liberating oxygen from hemoglobin and may exhibit differences between races due to varying degrees of protein glycation.[19] Other studies suggest that ocular complications of diabetes may begin to occur at lower HbA_{1c} levels in Black individuals; however, no conclusive evidence has been identified.[20] Other independent predictors of diabetic retinopathy, including more comprehensive measures such as regular use of diabetes medications, waist-to-hip ratio, hypertension history, and marital status[3] may further aid in controlling for these differences. Additionally, because of our strict selection criteria, the number of patients who qualified for this study was limited, resulting in larger confidence intervals of the odds ratio estimates. Subjects who were not able to appear for follow-up visits within the defined follow-up window were excluded from

the study. Hence, our 3-dose analysis was not completely powered to assess the full extent of patient compliance on bevacizumab efficacy. To power a study to 80% with similar results, 110 individuals per group would be needed for the single-dose analysis (our study had 146 and 164 in each group), and 72 individuals per group would be needed for the 3-dose analysis (our study had 68 and 83 in each group). Our data were limited to best available visual acuity, and future studies could be strengthened by prospectively collecting best-corrected visual acuity. Our use of Snellen visual acuity measurements may be considerably different from the Early Treatment Diabetic Retinopathy Study (ETDRS) system used in Protocol T, as patients may score more poorly on the Snellen scale. As such, the true proportion of individuals in each racial/ethnic group with a visual acuity of 20/50 or worse on ETDRS is likely lower than reported. Lastly, the relationship between compliance and treatment efficacy could be assessed as a future direction of the study.

The implication that Black patients are more resistant to bevacizumab treatment, as found in our study, as well as evidence cited in prior studies that Black patients carry a significantly higher disease burden of DME demonstrates the need to make every effort to incorporate an equal representation of racial groups in future studies. Black individuals represent 13.4% of the US population[21] but carry at least twice the prevalence of DME compared with White individuals[11] and should be represented in DME research accordingly.

In summary, Black patients appear to have a significantly lower likelihood of short-term visual acuity improvement following intravitreal bevacizumab compared with White and Hispanic patients. Further research controlling for additional variables, including duration of diabetes, other comorbidities, and end-organ complications, is warranted to elucidate the efficacy of bevacizumab as well as other anti-VEGF agents in different races to ensure optimal treatment for each individual patient.

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