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RESEARCH ARTICLE

THE IMPACT OF RACE ON SHORT TERM TREATMENT RESPONSE TO BEVACIZUMAB IN DIABETIC MACULAR EDEMA

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ABSTRACT

The authors are commenting on the study entitled**:**"The impact of race on short term treatment response to bevacizumab in diabetic macular edema" published by Osathanugrah *et al*. in Am J Ophthalmology 2021;222(February):310-317, which reported the impact of race and ethnicity on efficacy of intravitreal bevacizumab for diabetic macular edema in anti-vascular endothelial growth factor treatment naïve patients after one and three injections.The authors found that the race is a risk factor for treatment effect in diabetic macular edema. However, the validation, extrapolation, and generalizability of this finding can only be validated by statistical analyses including all the missing baseline potential risk factors referred to above by us in addition to the baseline characteristics already evaluated in this study, serving to emphasize the key metrics assessing the impact of race and ethnicity on efficacy of intravitreal bevacizumab for diabetic macular edema in anti-vascular endothelial growth factor treatment naïve patients.

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INTRODUCTION

We read with great interest the study by Osathanugrah *et al.* (2021), which reported the impact of race and ethnicity on efficacy of intravitreal bevacizumab (Avastin; Genentech, Inc., San Francisco, CA, USA) for diabetic macular edema (DME) in anti-vascular endothelial growth factor (VEGF) treatment naïve patients after one and three injections. Percentage with visual acuity (VA) improvement was 36% vs 39% vs 50% after 1 injection (n=314), and 34% vs 55% vs 59% after 3 injections (n=150) for Black, Hispanic, and White cohorts, respectively. Percent central macular thickness (CMT) reductions were 12.30% vs 17.01% vs 20.66% after 1 injection, and 24.36% vs 16.13% vs 25.38% after 3 injections in Black, Hispanic, and White patients, respectively. After controlling for sex, age, baseline A1c, baseline CMT, baseline VA, prior laser history, injection time course, and follow up delay, the authors concluded that Black patients had a significantly lower likelihood of VA improvement following intravitreal bevacizumab treatment compared to White and Hispanic patients. We would like to address several issues that have arisen from this study, which can be specifically summarized below.

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There were no details regarding the DME defined as retinal thickening or hard exudates at or within 1 disc diameter of the macula center and which is most commonly classified into either being clinically significant or not. Moreover, the criteria used to define the clinically significant DME, if it was present in some patients, were not indicated. There were no data on the duration of the diabetes and DME before entering the study after diabetes onset, the staging of diabetic maculopathy (early, advanced, severe, and atrophic maculopathy), the spectral domain-optical coherence tomography (SD-OCT) patterns of the DME (sponge-like swelling/cystoid macular edema/serous neuroretinal detachment/mixed type), and the location of the cystoid type (ganglion cell layer/inner/outer nuclear layers) (Călugăru *et al.* 2017). Without taking all these characteristics of DME into account, no judgment can be made on the efficacy of intravitreal bevacizumab in Black, White, and Hispanic patients.

There was a key differentiation in the assessment of the main outcomes measures highlighted by Table 2A of this study. Specifically, while the VA improvement criterion was well established by an increase of at least 0.1 points on the Log MAR scale, the CMT change was evaluated as a percentage without indicating the value in microns of decrease in CMT as a requisite criterion to certify a CMT improvement. These findings may have confounded the results and could explain the discordance between VA improvement and CMT changes in this study. Of note, the currently available assertion

considers that evaluation of the results has to be guided primarily by anatomical measure data with visual changes as a secondary guidance (Freund *et al.* 2015).

There were 2 series of VA improvements evaluated differently in Black, Hispanic, and White patients, that is, the first serie within the abstract section with percentage assessments of 36%, vs 39% vs 50% after one injection, and 34% vs 55% vs 59% after three injections, and the second serie within the text of the manuscript (section results) and the Table 2A, with percentage point LogMAR scale assessments of 26.71% vs 39.39% vs 50% after one injection and 33.82% vs 54.76% vs 58.54% after three injections, respectively. Which of them should be taken into account ? Of note, the difference between the 2 series of improvement percentages for Black patients after one injection was very large (9.29%), what calls into question the conclusion of this article that the race is a risk factor for treatment effect in DME.

The following critical data that should have been included into statistical analyses, are missing from the study: the SD-OCT patterns of vitreoretinal interface abnormalities (for example, incomplete/complete posterior vitreous detachment, epiretinal membranes, vitreomacular adhesion/traction, full-thickness macular hole, lamellar macular hole, and combined epiretinal membranes and vitreomacular traction); the existence or not of the disorganization of the retinal inner layers and grading of its severity (mild, severe, or severe with damaged ellipsoid zone [EZ]); the qualitative status of the photoreceptor cell layer (the disorganization/thinning of the outer nuclear layer; the disruption/absence of the external limiting membrane (ELM) band, the EZ, and the interdigitation zone; the changes of the retinal pigment epithelial band-Bruch membrane complex (pigment migration within the neurosensory retina, retinal pigment epithelium [RPE] porosity, microrips or blowouts in the RPE, focal RPE atrophy, RPE thickening, presence of reticular pseudodrusen); the number of hyperreflective intraretinal foci; and the subfoveal choroidal thickness (Călugăru *et al.*2019).

Nothing was stated regarding the influence which intravitreal bevacizumab injections can exert on the diabetic choroidopathy in Black, White, and Hispanic patients, which consists in intrachoroidal vascular abnormalities and may directly induce choroidal ischemia, leading to RPE dysfunction. The progressive thickening of the choroid layer caused by increasing the severity of diabetic retinopathy (DR) (from no DR to proliferative DR) and development of DME (being thickest in eyes with serous neuroretinal detachment type of DME) denotes progression of the diabetic choroidopathy (Kim *et al.* 2013).

The authors of this study did not take into account the European School for Advanced Studies in Ophthalmology international classification of the diabetic maculopathy based on the SD-OCT microstructural alterations of the outer/inner retina and vitreoretinal interface going through the center of the fovea (Panozzo *et al.* 2020).

Of the seven distinct qualitative and quantitative features included in this classification (for example, the central subfoveal thickness, the size of intraretinal cysts, the state of the EZ and ELM, the occurrence of disorganization of the retinal inner layers, the presence and number of hyperreflective intraretinal foci, the presence of subretinal fluid, and the characteristics of the vitreoretinal interface) the authors of this study documented only one of them, namely, the CMT.

Altogether, the authors found that the race is a risk factor for treatment effect in DME. We believe that this finding can only be validated by statistical analyses including all the missing baseline potential risk factors referred to above by us in addition to the baseline characteristics already evaluated in this study, serving to emphasize the key metrics assessing the impact of race and ethnicity on efficacy of intravitreal bevacizumab for DME in anti-VEGF treatment naïve patients.

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