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RESEARCH ARTICLE

SPECTRAL-DOMAIN OCT ANALYSIS OF RISK FACTORS FOR MACULAR ATROPHY DEVELOPMENT IN THE HARBOR STUDY FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

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ABSTRACT

The authors are commenting on the study entitled **:**"Spectral-domain OCT analysis of risk factors for macular atrophy development in the Harbor study for neovascular age-related macular degeneration" published by Sadda *et al*. in Ophthalmology 2020;127(10):1360-1370,which identified the baseline risk factors for macular atrophy development in patients with neovascular age-related macular degeneration treated with ranibizumab over 24 months of follow-up. The following baseline risk factors for macular atrophy were confirmed from prior analyses that used color fundus photography and fluorescein angiography data: absence of subretinal fluid, presence of intraretinal cysts, presence of Type 3 neovascularization, and presence of atrophy in the fellow eye. This analysis using Spectral-domain optical tomography data revealed new baseline risk factors for macular atrophy: higher central drusen volume, lower choroidal thickness, presence of nascent atrophy, presence of reticular pseudodrusen, and increased central foveal thickness. Ranibizumab treatment regimen and dose level were not found to be risk factors for macular atrophy development. However, the validation, extrapolation, and generalizability of the authors' conclusions can be made only by statistical analyses including all the missing baseline potential risk factors referred by us in addition to the new risk factors identified in this study, which serve as putative biomarkers predicting the occurrence and progression of macular atrophy in neovascular age-related macular degeneration patients.

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INTRODUCTION

We read with interest the article by Sadda *et al.* (2020) which identified the baseline risk factors for macular atrophy (MA) development in patients with neovascular age-related macular degeneration (nAMD) treated with ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA, USA) over 24 months of follow-up. The following baseline risk factors for MA were confirmed from prior analyses that used color fundus photography and fluorescein angiography data: absence of subretinal fluid, presence of intraretinal cysts, presence of Type 3 neovascularization, and presence of atrophy in the fellow eye. This analysis using Spectral-domain optical tomography (SD-OCT) data revealed new baseline risk factors for MA: higher central drusen volume, lower choroidal thickness, presence of nascent atrophy, presence of reticular pseudodrusen, and increased central foveal thickness.

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Ranibizumab treatment regimen and dose level were not found to be risk factors for MA development. We would like to address several issues that have arisen from this study, which can be specifically summarized below.

There was a selection bias attributable to the fact that the 4 treatment groups with ranibizumab (group 1, 0.5 mg monthly; group 2, 0.5 mg pro re nata [PRN] after 3 loading doses; group 3, 2.0 mg monthly; and group 4, 2 mg PRN) included patients with subfoveal choroidal neovascularization (CNV) who had totally different baseline characteristics, namely, with definite MA (n = 131), with questionable MA (n = 49), and without MA (n= 761). Taken together, these findings may have confounded the results.

Identification of the risk factors for MA development should have been made for each of the 4 phenotypes of MA proposed by the Classification of Atrophy Meetings (CAM) group (Sadda *et al*.2018), that is, complete retinal pigment epithelium (RPE) and outer retinal atrophy (cRORA), incomplete RPE and outer retinal atrophy (iRORA), complete outer retinal atrophy (cORA), and incomplete outer retinal atrophy (iORA).

Unlike the concise and explicit terminology established by the CAM (Sadda *et al*.2018) and the Consensus on nAMD

Nomenclature groups (Spaide *et al.* 2020), the terms used in this article e.g. definite MA, questionable MA, or nascent atrophy, are questionable and confusing. Specifically, the introduction of the nascent atrophy term in this article created a total confusion among the ophthalmologists. According to its definition given by the authors of this paper (e.g., loss of outer retinal layers with no loss or thinning of RPE, regardless of drusen presence), the nascent atrophy would rather correspond to the cORA and iORA types established by the CAM group (Sadda *et al.* 2018). Likewise, although the 3 inclusive criteria used for diagnosis of MA or cRORA on OCT are in accordance with the CAM group, nothing was stated referred to the exlusive criteria, namely, scrolled RPE or other signs of RPE tear (Sadda *et al.*2018).

The authors of this study did not use the currently available state-of-the-art nomenclature (Spaide *et al.* 2020) to define the forms of macular neovascularization (MNV) that may arise secondary to nAMD, for example, the type 1 occult MNV, the type 2 classic MNV, the mixed types 1 and 2 minimally classic MNV, and the type 3 intraretinal MNV.

The following pertinent data, which should have been included in statistical analyses, are missing from the study: the mean time duration of symptoms of the nAMD from diagnosis to the initiation of treatment; the diagnosis criteria for iRORA, cORA, and iORA; the SD-OCT patterns of the vitreoretinal interface abnormalities (e.g., incomplete/complete posterior vitreous detachment, epiretinal membranes, vitreomacular adhesion/traction, full-thickness macular hole, lamellar macular hole, and combined epiretinal membranes and vitreomacular traction) at baseline and at the completion of the study; the existence or not of the disorganization of retinal inner layers and its severity (mild, severe, and severe with damaged ellipsoid zone [EZ]) at presentation and at the end of the study; the location of the MA (foveal/extrafoveal, within the bed of previous CNV, in close proximity or clearly outside of the area of total CNV lesions) at month 24; the location of the intraretinal fluid (e.g., inner/outer nuclear layers or ganglion cell layer) at baseline and at month 24; the alterations of the photoreceptor cell layer (disorganization/thinning of the outer nuclear layer, external limiting membrane defects, disruption of the EZ, and interdigitation zone) at presentation and at the end of the study; the prevalence, number, size, and shape of the tubular structures affecting the outer retina and RPE termed outer retinal tubulation at presentation and at the completion of the study; the SD-OCT patterns of the 3 phenotypes of the lesions within the fibrotic spectrum (3 main pathways of progression from original neovascular lesion to fibrotic scar), that is, the type A located underneath the RPE, the type B located above the RPE with intact RPE, and the type C located subretinal with the RPE indistinguishable at month 24; the existence or not of the 2 distinct phenotypic subgroups of advanced fibrotic lesions (final morphologies of the fibrotic process) at month 24, e.g., the fibroatrophic lesions (absence of proliferation under the subretinal space) and the fibroglial lesions (fibroglial proliferation in the subretinal space after RPE erosio); the rate of patients with nonfibrotic scars at month 24; the composition of the subretinal hyperreflective material at baseline and at the end of the study (e.g., fibrosis, blood, fibrin, exudation, lipid, vitelliform material, or neovascular tissue);and the SD-OCT patterns of the pigment epithelial detachment (drusenoid/ fibrovascular/ serous/mixed) at presentation and at month 24.

The authors of this study concluded that monthly treatment with ranibizumab 0.5% was not found to be a risk factor for MA development over 24 months and that the lower choroidal thickness was a baseline risk factor for MA although SD-OCT scans were obtained in non-enhanced depth imaging mode, thus resulting in approximately 25% of scans not allowing visualization of the choroid. Based on the evidence we have postulated (Călugăru *et al.*2020) that the subfoveal choroidal thickness thinning – emergent choroidal insufficiency centered primarily on that of choriocapillaris and determined by prolonged inhibition of the vascular endothelial growth factor (VEGF) using anti-VEGF therapy may affect integrity of the choriocapillaris, considering the key role of the VEGF-A in the normal function of the retina and in the regulation of the survival and permeability of the choriocapillaris. It serves as a trophic factor for vascular endothelial cells and maintains the fenestrated and highly permeable structure of the choroidal vascular endothelium. Without space Thus, the choroidal vascular impairment induced by suppressing the choroidal vascular hyperpermeability and vasoconstriction as well as by more pronounced reductions of choriocapillaris endothelium thickness and number of fenestrations in choriocapillaris endothelial cells, may involve the integrity of the RPE and outer retina favoring MA development because the choroid is involved in maintaining the perfusion of the outer retina layers and is the sole source of metabolic exchange for the fovea (Călugăru *et al*. 2017).

Altogether, the validation, extrapolation, and generalizability of the authors' conclusions can be made only by statistical analyses including all the missing baseline potential risk factors referred to above by us in addition to the new risk factors identified in this study, which serve as putative biomarkers predicting the occurrence and progression of MA in nAMD patients.

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