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THE EVOLUTION OF FIBROSIS AND ATROPHY AND THEIR RELATIONSHIP WITH VISUAL OUTCOMES IN ASIAN PERSONS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

***Dan Călugăru and Mihai Călugăru**

Department of Ophthalmology, University of Medicine Cluj-Napoca/Romania

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****Corresponding author: Mihai Călugăru***

ABSTRACT

The authors are commenting on the study entitled "The evolution of fibrosis and atrophy and their relationship with visual outcomes in Asian persons with neovascular age-related macular degeneration" published by Cheung *et al*. in Ophthalmology Retina; 2019; 3 (12):4045-4055 Published online June 11, 2019. The validation, extrapolation, and generalizability of the 12-month visual outcomes of this study can be made only by statistical analyses including all the missing baseline potential predictors referred to above by us in addition to the baseline characteristics already assessed in this study, which serve as putative biomarkers predicting the occurrence and progression of fibrosis and macular atrophy in Asian persons with neovascular age-related macular degeneration.

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INTRODUCTION

The prospective study by Cheung *et al.* (2019) assessed the rate of development and progression of fibrosis and macular atrophy (MA) and their relationship with 12-month visual outcomes in Asian persons with treatment-naïve neovascular age-related macular degeneration (nAMD). Worse baseline visual acuity (VA) and presence of subretinal hyperreflective material (SHRM) at month 12 were associated with worse VA at month 12, whereas polypoidal choroidal vasculopathy (PCV) was associated with better VA at month 12. The authors concluded that fibrosis is the most important prognosticator of outcomes highlighting the need for therapy beyond anti-vascular endothelial growth factor (VEGF) inhibition in Asian nAMD. We would like to address several challenges that have arisen from the study of Cheung *et al.* (2019) which can be specifically summarized below.

First, the authors considered the existence of MA should complete retinal pigment epithelium (RPE) and outer retinal atrophy be present. Importantly, the currently available definition for the MA associated with nAMD based on optical coherence tomography (OCT) imaging encompasses ≥ 3 criteria, that is, a zone of hypertransmission of ≥ 250 µm, a zone of attenuation or disruption of RPE band of ≥ 250 µm in diameter, and evidence of overlying photoreceptor degeneration whose features include outer nuclear layer (ONL) thinning, external limiting membrane (ELM) loss, and ellipsoid zone (EZ) or interdigitation zone (IZ) loss (Sadda *et al.,* 2018). Although the authors thoroughly assessed the fibrotic scars, nothing was stated regarding the nonfibrotic scars and extramacular geographic atrophy (GA) whose prevalences (the rate at baseline) and incidences (the rate at 1-year without baseline prevalence) should have been evaluated. Of note, pathogenesis of the GA in treated nAMD is currently unclear and may or may not be distinct from GA that develops in the setting of de novo GA lesions (purely dry AMD). Atrophic lesions associated with treated choroidal neovascularization (CNV) are clinically indistinguishable from the GA that most clinicians historically think of as arising in dry AMD.

Second, the following pertinent data are missing from the study: the mean time duration of symptoms of the nAMD from diagnosis to the initiation of the treatment; the OCT patterns of the vitreoretinal interface abnormalities (e.g., epiretinal membranes, vitreomacular adhesion/traction, full-thickness macular hole, lamellar macular hole, and combined epiretinal membranes and viteomacular traction); the existence or not of the disorganization of retinal inner layers and its severity (mild, severe, and severe with damaged EZ); the

prevalence of the 2 angiographic types of CNV which were not included in the statistical analyses (the occult CNV and retinal angiomatous proliferation); the prevalence of the 2 angiographic subtypes of PCV (Jeong *et al.* 2017) with different pathophysiology, genetic backgrounds, early treatment response, and disease progressions (subtype 1, PCV sharing a common pathogenic background with nAMD and subtype 2, idiopathic PCV); the location of the MA and GA (foveal/extrafoveal, within the bed of previous CNV, in close proximity or clearly outside of the area of total CNV lesions); the location of the intraretinal fluid (e.g., inner/outer nuclear layers or ganglion cell layer); the alterations of the photoreceptor cell layer (disorganization/thinning of the ONL, ELM defects, disruption of the EZ, and IZ); and the prevalence, number, size, and shape of the tubular structures affecting the outer retina and RPE termed outer retinal tubulation (Călugăru *et al.*2019).

Third, in the assessment of the 12-month results of this study, we considered the current assertion that evaluation of outcomes has to be guided by anatomical measure data with visual changes as a secondary guide (Freund *et al.*2015). Accordingly, the effectiveness of the treatment in this series was unsatisfactory. Specifically, although the VA improved significantly by about 5 Early Treatment Diabetic Retinopathy Study letters, the rates of fibrosis and MA increased significantly from 13.0% to 37.8% and 9.7% to 17.2%, respectively, between baseline and month 12. In addition, subretinal fluid was present in the vast majority of eyes (96.1% - 100%) at month 12 and there was an increase in the proportion of SHRM resulting from fibrosis (82.5%). Importantly, the mean central subfield thickness decreased significantly from 471.1 µm to 343.4 µm, a value being much more than the cutoff for the upper level of the normal macular thickness plus 2 standard deviations (315.2 µm).These findings highlight unresolved macular edema owing to significant undertreatment administered (overall average number of 5.1 anti-vascular endothelial growth factor injections) with insufficient macular deturgescence and indicate that the disease process is still active and progressive, requiring further treatment with antiangiogenic agents.

Altogether, the authors of this study showed that the presence of fibrosis and SHRM were associated with poorer visual outcomes, regardless of subtype of nAMD and treatment exposure. However, the validation, extrapolation, and generalizability of the authors' conclusion can be made only by statistical analyses including all the missing baseline potential predictors referred to above by us in addition to the baseline characteristics already assessed in this study, which serve as putative biomarkers predicting the occurrence and progression of fibrosis and MA in Asian persons with nAMD.

Dan Călugăru, MD, PhD
Mihai Călugăru, MD, PhD

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