TO THE EDITOR: We would like to address several challenges that have arisen from the study by Li et al.1

There was a selection bias due to inclusion in the study of patients treated with different anti-vascular endothelial growth factor (VEGF) agents, namely, bevacizumab (Avastin, Genentech, Inc., South San Francisco, CA), ranibizumab (Lucentis, Genentech, Inc.), and aflibercept (Eylea, Regeneron Pharmaceuticals Inc., Tarrytown, NY) or a combination of them. Likewise, the choice of anti-VEGF drug and treatment intervals were based on the treating physician’s discretion in a large multidisciplinary ophthalmological practice. Taken together, these findings may have confounded the results.

Of the 5 angiographic types of choroidal neovascularization (CNV) existing in patients with neovascular age-related macular degeneration (nAMD), the study revealed only 3 of them, namely, the occult and classic CNVs, and the retinal angiomatous proliferation. The other 2 angiographic types (e.g., the mixed CNV and the polypoidal choroidal vasculopathy) were not screened and investigated in the study populations.

The following key data, which would have had to be included in the univariate logistic regression model, are missing in the study; the visual acuity stratification; the duration of the nAMD before entry into the study; the location of the macular atrophy (MA) (foveal or extrafoveal; within or in close proximity to the total CNV lesion); the serous or hemorrhagic detachment of the neurosensory retina or retinal pigment epithelium (RPE); the retinal hard exudates; the location of the intraretinal cystoid fluid if it existed in some cases (inner/outer nuclear layers or ganglion cell layer); the qualitative status of the ganglion cell complex; the qualitative status of the external limiting membrane band, the ellipsoid zone (EZ), the interdigitation zone, and the RPE band-Bruch’s membrane complex; the quantification of the subretinal drusenoid deposits; the prevalence of vitreoretinal interface abnormalities (e.g., vitreomacular adhesion/traction and epiretinal membranes); the prevalence of the outer retinal tubulation; the fluorescein angiographic findings; and the subfoveal choroidal thickness. The effectiveness of the anti-VEGF agents in routine clinical practice cannot be evaluated without considering these items.2

For the manual measurements of the MA on spectral-domain OCT, the authors of this study used stringent criteria that included disruption of the outer retina (e.g., RPE or EZ loss) and increased signal transmission into the choroid. Of note, the currently available definition for MA associated with nAMD based on OCT imaging3 encompasses at least 2 criteria, that is, 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 thinning, external limiting membrane loss, and EZ or interdigitation zone loss.

The authors documented that age was the strongest predictor of MA progression. Conceivably, the number of such predictive factors would have been higher if all the missing baseline potential prognosticators mentioned by us had been included in the final analysis, in addition to the baseline characteristics already evaluated in this study.

The final outcomes of this series are beneficial. Specifically, the authors achieved visual acuity stabilization and normalization of the central subfield thickness. However, the percentage of 53.6% of the eyes that have developed MA in the eyes without baseline MA is fairly high, namely, among the highest existing in the ophthalmic literature. Anti-VEGF therapy might be one of the potential determinants of this high value of the cumulative incident MA because it can interfere with the maintenance of the ocular vasculature. Specifically, the VEGF-A plays a key role in the normal function of the retina and in the regulation of the survival and permeability of the choriocapillaris. In the long term, the prolonged inhibition of the VEGF using anti-VEGF agents may affect the integrity of the choriocapillaris by suppressing the choroidal vascular hyperpermeability and vasoconstriction, as well as by more pronounced reductions of choriocapillaris endothelium thickness and number of fenestrations. Thus, choroidal vascular impairment may affect the integrity of the RPE and outer retina, favoring development of the MA, because the choroid is involved in maintaining the perfusion of the outer retinal layers and is the sole source of metabolic exchange (nourishment and oxygen) for the fovea.

Altogether, the pathogenesis of the MA in treated nAMD is currently unclear and may or may not be distinct from geographic atrophy that develops in the setting of de novo geographic atrophy lesions. Regardless of the anti-VEGF agents used (e.g., bevacizumab/ranibizumab/aflibercept), the treatment dosing paradigms chosen (e.g., treat-and-extend/pro re nata/fixed-interval/escalated algorithm), the patient age, the baseline visual acuity, and the angiographic type, the efficacy of the treatment depends primarily on the promptness of the therapy after the onset of nAMD.3,4,5

DAN CĂLUGĂRU, MD, PhD
MIHAI CĂLUGĂRU, MD, PhD
Department of Ophthalmology, University of Medicine, Cluj-Napoca, Romania

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