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EFFECT OF RESIDUAL FLUID ON VISUAL FUNCTION IN RANIBIZUMAB-TREATED NAOVASCULAR AGE-RELATED MACULAR DEGENERATION

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ABSTRACT

The authors are commenting on the study entitled**:** "Effect of residual fluid on visual function in ranibizumab-treated neovascular age-related macular degeneration" published by Holekamp *et al.* in American Journal Ophthalmology 2021 (doi.org/10.1016/j.ajo,2021.o6.029; Published on July 17, 2021), which assessed the relationship between retinal fluid and vision in 917 pactients aged ≥ 50 years with subfoveal neovascular age-related macular degeneration associated with subretinal and/or intraretinal fluid. Patients were treated with intravitreal ranivizumab 0.5 or 2.0 mg and best-corrected visual acuity and its change were evaluated from baseline at months 12/24. Eyes with residual subretinal fluid only exhibited the largest mean best-correected visual acuity gains followed by those with resolved subretinal/intraretinal fluid (dry retina), residual subretinal/intraretinal fluid, aud residual intraretinal fluid only. The authros concluded that vision outcomes through months 24 were better in ranibizumab-treated eyes with residual versus resolved subretinal fluid and worse with residual versus resolved intraretinal fluid.We believe that the validation, extrapolation, and generalizability of these findings can be made only by regression analyses including all the missing data referred to above by us in addition to the baseline characteristics already assessed in this study, serving to identify the potential prognosticators influencing the effect of residual retinal fluid on visual function in ranibizumab-treated neovascular age-related macular degeneration over 2 years of follow-up after the initiation of treatment.

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INTRODUCTION

The authors are commenting on the study entitled**:** "Effect of residual fluid on visual function in ranibizumab-treated neovascular age-related macular degeneration" published by Holekamp *et al.* in American Journal Ophthalmology 2021 (doi.org/10.1016/j.ajo,2021.o6.029; Published on July 17, 2021), which assessed the relationship between retinal fluid and vision in 917 pactients aged ≥ 50 years with subfoveal neovascular age-related macular degeneration (nAMD) associated with subretinal and/or intraretinal fluid. Patients were treated with intravitreal ranivizumab 0.5 or 2.0 mg and best-corrected visual acuity (BCVA) and its change were evaluated from baseline at months 12/24. Eyes with residual subretinal fluid (SRF) only exhibited the largest mean BCVA gains followed by those with resolved subretinal/intraretinal fluid (dry retina), residual subretinal/intraretinal fluid, aud residual intraretinal fluid only. The authors concluded that vision outcomes through months 24 were better in ranibizumab-treated eyes with residual versus resolved SRF and worse with residual versus resolved intraretinal fluid (IRF).

We would like to address several issues with this study which can be specifically summarized below. There was a selection bias due to the fact that all treated arms of patients were analyzed together without differentiating between those treated with different doses of intravitreal ranibizumab (0.5 or 2.0 mg) and those using different dosing regimens (monthly or pro re nata [PRN] treatment strategy following 3 loading doses). Taking together, these findings may have confounded the results.

This study investigated BCVA outcomes evaluated by the presence (residual) or absence (resolved) of SRF and/or IRF in ranibizumab-treated eyes who have been followed-up over 24 months. Although the authors consider that the disease activity on optical coherence tomography (OCT) in nAMD is indicated among other by any SRF, IRF or pigment epithelial detachment (PED), nothing has been stated about patients with sub-retinal pigment epithelium (RPE) fluid having different types of PED (drusenoid/serous/fibrovascular/mixed).

The following relevant data, which should have been included in the statistical analyses, are missing from the study: the location of the

IRF (inner/outer retinal layers, ganglion cell layer); the evaluation in μm of the thickness of residual subfoveal SRF and its relationship with macular atrophy; the amount of SRF tolerated without detrimental or harmful effect to the visual gains; the mean time duration of symptoms of the nAMD from diagnosis to the initiation of treatment; the OCT patterns of the vitreoretinal interface abnormalities at baseline and at the end of the study (ie, epiretinal membranes, vitreomacular adhesion/traction, full-thickness macular hole, lamellar macular hole, and combined epiretinal membranes and vitreomacular traction); the existence or otherwise of the disorganization of retinal inner layers and its severity at enrollment and at completion of the study (mild, severe, and severe with damaged ellipsoid zone [EZ]); the forms of the macular neovascularization (MNV) lesions at baseline and the completion of the study, that may arise secondary to nAMD (the type 1 occult, the type 2 classic, the type 3 intraretinal, the mixed type 1 and type 2 minimally classic MNVs; the 3 phenotypes of the lesions representing 3 main pathways of progression from original neovascular lesions to fibrotic scar at the end of the study (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); the existence or otherwise of the 2 distinct phenotypic subgroups of advanced fibrotic lesions at the completion of the study (the fibroatrophic and the fibroglial lesions); the qualitative status of the photoreceptor cell layer (disorganization/thinning of the outer nuclear layer, external limiting membrane defects, disruption of the EZ zone, and interdigitation zone) at baseline and at the end of the study; the proportion of eyes with reticular pseudodrusen at baseline and at years 2; and the subfoveal choroidal thickness at baseline and at the end of the study (Călugăru *et al.* 2021).

The extremely valuable statement of the authors that presence of SRF was associated with a lower incidence of macular atrophy was not documented in this study as well as the assertion that IRF was associated with macular atrophy which was identified as a baseline risk factor for atrophy development or as an indicator of existing atrophy. However, the authors suggested in this study that completely resolving SRF may not be necessary for achieving the best visual outcomes and that the presence of residual SRF may not be harmful or deleterious and has a benefical effect to vision to protect from atrophy and to reduce rates of atrophy when regular anti-vascular endothelial growth factor treatment is maintaining.

The authors admit existence in the nAMD of two types of fluid, result of exudative and transudative mechanisms, that is neovascular (exudative) and non-neovascular (degenerative or transudative processes) fluid (Sharma *et al*.2021). Likewise, that the development of non-neovascular fluid is the result of degenerative pathways such as retinal pigment epithelial pump failure and Muller cell loss or both which may be considered factors explaining the occurrence of transudative fluid in nAMD due to impaired mechanisms of fluid clearance. The authors discussed the mechanisms of occurrence and clearance of the non-neovascular fluid but nothing was documented about the qualitative status of the retinal pigment epithelial band – Bruch's membrane complex in this study (pigment migration within the neurosensory retina, sub-RPE fluid, RPE porosity, micro-rips or blowouts in the RPE, focal RPE atrophy, and RPE thickening) or other possible causative biomarkers that may indicate development of degeneration fluid such as the prevalence, number, size, and shape of the tubular structures affecting the outer retina and RPE termed outer retinal tubulation. Likewise, that intraretinal cysts or pseudocysts overlying areas of atrophy with complete RPE and outer retinal atrophy might be additional markers of degenerative fluid formation.

The authors did not explain the clearly higher gains in BCVA in patients with residual SRF compared with those with resolved SRF at month 12 (11.9 letters and 9.5 letters, respectively), and month 24 (11.7 letters and 8.6 letters, respectively).

Altogether, residual SRF associated with MNV may be the result of both exudative and degenerative pathways. After adjusting for the baseline BCVA discrepancies, which were only present in the SRF group, the authors concluded that eyes with only residual SRF were associated with the best visual outcomes, while the eyes with only residual IRF were associated with the worst visual outcomes after 12 and 24 months of monthly or PRN ranibizumab treatment. We believe that the validation, extrapolation, and generalizability of these findings can be made only by regression analyses including all the missing data referred to above by us in addition to the baseline characteristics already assessed in this study, serving to identify the potential prognosticators influencing the effect of residual retinal fluid on visual function in ranibizumab-treated nAMD over 2 years of follow-up after the initiation of treatment.

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