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LONG-TERM ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR TREATMENT FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: THE LATAR STUDY

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ABSTRACT

The authors are commenting on the study entitled**:** "Long-term anti-vascular endothelial growth factor treatment for neovascular age-related macular degeneration: the Latar study" published by Spooner *et al.* in Ophthalmology Retina. (Doi.org/101016/j.oret.2020.09.019), which assessed the 10-year outcomes in 293 neovascular age-related macular degeneration eyes treated with vascular endothelial growth factor agents. The authors concluded that eyes with neovascular age-related macular degeneration maintained starting visual acuity when treated with vascular endothelial growth factor inhibitors for 10 years. However, the validation, extrapolation, and generalizability of this finding 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 stabilization of the visual acuity over 10 years of follow-up after the initiation of treatment.

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INTRODUCTION

We read with interest the study by Spoonner K *et al.* (2020) which assessed the 10-year outcomes in 293 neovascular age-related macular degeneration (nAMD) eyes treated with vascular endothelial growth factor (VEGF) agents. The median baseline visual acuity (VA) was 60 letters, which improved significantly by 9 letters after the first year of treatment and then these initial gains were lost over time with a final VA change of +3 letters. The proportion of eyes with VA ≥ 20/40 (minimum vision required to hold a driver's licence) significantly increased from 29% at baseline to 35% at 10 years and the proportion of eyes at baseline with VA ≤ 20/200 was 14% and 17% at 10 years. The mean central macular thickness (CMT) significantly decreased from 355.5 µm to 264.2 µm with a mean of 58.1 injections during the 10 years. The authors concluded that eyes with nAMD maintained starting VA when treated with VEGF inhibitors for 10 years. We would like to address several challenges that have arisen from this study which can be specifically summarized below.

There was a selection bias attributable to inclusion in the study and pooled analysis of patients of 4 practitioners treated initially as per local label instructions (i.e., monthly), then patients were converted over time to a modified treat-and-extend regimen according to the treating physician (e.g., the extension did not follow specific rules), and finally the treat-and-extend regimen became more accepted, and the treating physicians followed a more typical approach that is, extending the interval by 1 to 2 weeks to a maximum of 12 weeks in eyes without fluid or hemorrhage, and stable VA.

Likewise, treatment schedules after the initial loading phase, which might have influenced long-term outcomes, were at the discretion of the treating ophthalmologist and patient and 31 eyes (11%) had suspended injection therapy for at least 6 months and resumed treatment during the study. Taking together, these findings may have confounded the final results.

In the assessment of the 10-year 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 due to the formation of macular atrophy (MA) and/or undertreatment. Specifically, although there was a hold of the starting VA and the CMT decreased significantly from 355.5 µm to 264.2 µm when treated with VEGF inhibitors for 10 years, the MA increased from 22% at baseline to 59% at 10 years, 43% of the eyes developed subretinal fibrosis at the completion of the study, and evidence of fluid on optical coherence tomography (OCT) imaging was found in 120 eyes (30 eyes with subretinal fluid and 90 eyes with intraretinal fluid) at the end of the study. During the 10 years of follow-up 5 eyes developed retinal pigment epithelium (RPE) tears (1.7%), 9 eyes (3%) developed disciform scarring, and there were 2 cases of endophthalmitis.

The following pertinent data that should have been included in the statistical analyses, are missing from the study: 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 (e.g., epiretinal membranes, vitreomacular adhesion/traction, full-thickness macular

hole, lamellar macular hole, and combined epiretinal membranes and viteomacular 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 existence or not of the 4 phenotypes of de novo atrophies at baseline and at the end of the study (the complete and incomplete retinal pigment epithelial and outer retinal atrophies and the complete and incomplete outer retinal atrophies); the forms of the macular neovascularization (MNV) lesions at the completion of the study, that may arise secondary to nAMD (the type 1 occult MNV located under the RPE, the type 2 classic MNV which proliferates in the subretinal space; the mixed type 1 and type 2 minimally classic MNV; and the type 3 intraretinal MNV which grows from the deep capillary plexus toward the outer retina); the proportion of eyes with subretinal fibrosis at baseline; the OCT patterns of 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 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 scar at enrollement and at the completion of the study; the location of the intraretinal fluid (e.g., inner/outer nuclear layers or ganglion cell layer) at presentation and at the end of the study; the alterations 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 enrollment 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 quantification of the subretinal hyperreflective material and its composition at baseline and at the end of the study (for example, fibrosis, blood, fibrin, exudation, lipid, vitelliform material, or neovascular tissue); the OCT patterns of the pigment epithelial detachment (drusenoid/ fibrovascular/serous/mixed) at presentation and at the end of the follow-up period; the proportion of eyes with reticular pseudodrusen at baseline and at years 10; and the subfoveal choroidal thickness at enrollment and at the completion of the study.

Altogether, the authors showed after an initial improvement in vision, this gradually decreased over the 10 years of follow-up to mean baseline levels. They concluded that patients who sustain continuous anti-VEGF therapy may be able to maintain VA over a 10-year time period. Still, the validation, extrapolation, and generalizability of this finding 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 stabilization of the VA over 10 years of follow-up after the initiation of treatment.

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