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SHORT COMMUNICATION **OPEN ACCESS**

LONG-TERM OUTCOMES OF SWITCHING TO AFLIBERCEPT FOR TREATMENT-RESISTANT NEOVACULAR AGE-RELATED MACULAR DEGENERATION

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ABSTRACT

The authors are commenting on the study entitled "Long-term outcomes of switching to aflibercept for treatment-resistant neovascular age-related macular degeneration" published by Spooner et al. in Acta Ophthalmologica 2019;97(5):e706-e7012. The conclusion of this study was that aflibercept was an effective alternative therapy for treatment-resistant active, chronic neovascular age-related macular degeneration. However, the validation, extrapolation, and generalizability of the authors'finding can be made only by statistical analyses including all the missing baseline potential predictive factors referred to above by us in addition to the baseline characteristics already evaluated in this study. Regardless of the anti-vascular endothelial growth factor agents chosen (e.g., ranibizumab/bevacizumab/aflibercept), and regardless of the treatment dosing paradigms used (e,g., treat-and-extend, pro re nata, fixed-interval, or escalated regimen), the efficacy of therapy depends primarily on the precociousness of the therapy after the neovascular age-related macular degeneration diagnosis.

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INTRODUCTION

We read with interest the study by Spooner *et al*. (2019) which prospectively reported the 4-year outcomes following the switch to aflibercept (Eylea; Regeneron Pharmaceuticals, Inc, Tarrytown, NY, USA) in 39 patients with treatment-recalcitrant active, chronic neovascular age-related macular degeneration (nAMD). The mean best-corrected visual acuity (BCVA) improved significantly by 4.9 Early Treatment Diabetic Retinopathy Study letters following 12 months of treatment, a value that was not maintained and dropped significantly below the baseline (62.03 letters), by a mean difference of -0.4 letters after 48 months. The reduction in central retinal thickness (CRT) from baseline was significantly (170.3 µm) at the end of month 48. The authors concluded that aflibercept was an effective alternative therapy for treatment-resistant active, chronic nAMD. We would like to address several challenges with the study of Spooner et al. (2019), which can be specifically summarized below.

1. There were no details with respect to the prior treatment (ranibizumab [Lucentis; Genentech, Inc, South San Francisco, CA, USA] and/or bevacizumab [Avastin; Genentech, Inc]) given to patients, that is the number of injections, the scheme of treatment applied, and should a washout period have existed or otherwise between the two periods of treatment (e.g., the first period including ranibizumab and/or bevacizumab treatment and the second period consisting of aflibercept for the first 48 weeks, then an individualized regimen for further 36 months following previous treatment with ranibizumab and/or bevacizumab. Of note, a real washout period is essential between these 2 periods of treatment in terms of aliased effects. In the absence of it, the impact of the significant carryover effects of the prior treatment may be confounded with direct treatment effects of the second period because these effects could not be estimated separately; carryover effects may bias the interpretation of data analysis.

2. The following relevant data, which should have been included in the statistical analyses, are missing from the study: the nAMD duration before the entry in the study; the existence or not of the disorganization of retinal inner layers and its severity (mild, severe or severe with damaged ellipsoid zone); the location of the intraretinal fluid (e.g., inner/outer nuclear layer or ganglion cell layer); the prevalence of the subretinal hyperreflective material and its composition (fibrosis, blood, exudation, fibrin, choroidal neovascularization [CNV]); the

prevalence, number, size, and shape of the tubular structures affecting the outer retina and retinal pigment epithelium (RPE) termed outer retinal tubulation; and the location of the geographic atrophy (foveal/extrafoveal, within the bed of previous CNV, in close proximity or clearly outside the area of total CNV lesions).

3. The effectiveness of the treatment in this series was unsatisfactory. Specifically, although the BCVA was maintained across 4 years and CRT decreased significantly to normal values, the BCVA loss of ≤ 5 letters occurred at 31% of the eyes, the pigment epithelial detachment persisted at 82.75% of the eyes although their heights decreased significantly, and the retinal fluid persisted at 43.58% of the eyes at the end of the study. Importantly, the authors of this study did not consider the currently available recommendations (Jaffe *et al*. 2016), which stated that when early persistent retinal fluid or exudation was present, eyes treated with monthly aflibercept had better visual acuity at week 52 than those treated with aflibercept less frequently or those treated with ranibizumab. Furthermore, a dry retina was more likely to be sustained in eyes treated with monthly aflibercept than in those treated with aflibercept every 2 months or ranibizumab every month. Notably, should this regimen be not effective, then the optimal results might have been obtained by high-dose high-frequency aflibercept, that is, intravitreal aflibercept 4 mg dosed every month (Călugăru *et al*. 2017). Conceivably, the design and the final outcomes of this study would have been different if the patients had been treated early after the exudative changes were detected with this stepwise dose escalation of the anti-vascular endothelial growth factor (VEGF) agent injections instead of the presently employed regimens.

4. The authors defined the geographic atrophy (GA) as one or more well-defined patches of partial or complete depigmentation of the RPE. Importantly, the currently available definition for the atrophy associated with nAMD based on optical coherence tomography 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 thinning, external limiting membrane loss, and EZ or interdigitation zone loss (Sadda *et al.* 2018).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 CNV are clinically indistinguishable from the GA that most clinicians historically think of as arising in dry AMD.

Altogether, regardless of the anti-VEGF agents chosen (e.g., ranibizumab/bevacizumab/aflibercept), and regardless of the treatment dosing paradigms used (e,g., treat-and-extend, pro re nata, fixed-interval, or escalated regimen), the efficacy of therapy depends primarily on the precociousness of the therapy after the nAMD diagnosis.

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