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HAWK AND HARRIER: PHASE 3, MULTICENTER, RANDOMIZAED, DOUBLE-MASKED TRIALS OF BROLUCIZUMAB FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

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ABSTRACT

The authors are commenting on the study entitled "Hawk and Harrier: phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration" published by Dugel *et al.* in Ophthalmology 2020;127(1):72-84, which prospectively compared the efficacy of brolucizumab (a single-chain antibody fragment that inhibits vascular endothelial growth factor-A) with aflibercept in patients with active, chronic, treatment-naïve choroidal neovascularization secondary to neovascular age-related macular degeneration in two similarly designed trials (Hawk and Harrier). After 48 weeks brolucizumab demonstrated noninferioriy to aflibercept in best-corrected visual acuity change from baseline and > 50% of brolucizumab 6 mg-treated eyes were maintained on an injection every 12 week dosing interval through week 48. However, the validation, extrapolation, and generalizability of these findings 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.

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INTRODUCTION

We read with interest the study by Dugel *et al.* (2020) which prospectively compared the efficacy of brolucizumab (a single-chain antibody fragment that inhibits vascular endothelial growth factor [VEGF]-A) with aflibercept (Eylea; Regeneron Pharmaceuticals, Inc, Tarrytown, NY, USA) in patients with active, chronic, treatment-naïve choroidal neovascularization (CNV) secondary to neovascular age related macular degeneration (nAMD) in two similarly designed trials (Hawk and Harrier). After loading with 3 monthly injections, brolucizumab-treated eyes received an injection every 12 weeks (q12w) and were interval adjusted to every 8 weeks (q8w) should the disease activity have been present while aflibercept-treated eyes received q8w fixed dosing. The authors concluded that the anatomic outcomes favored brolucizumab over aflibercept and overall safety with brolucizumab was similar to aflibercept. We would like to address several challenges that have arisen from this study, which can be specifically summarized below.

There was a bias assigned to the fact that after loading with 3 monthly injections the dosing intervals for the brolucizumab were completely different from those for the aflibercept what favored the brolucizumab-treated patients in achieving better final results. Specifically, the treatment dosing paradigm for brolucizumab given every q12w was continuously adjusted with the q8w dosing interval if the disease activity was identified while the aflibercept-treated eyes received invariably q8w dosing regimen for the entire study period regardless of the activity of the disease.

The indocyanine green angiography (ICGA) was applied only to patients screened at sites in Japan to evaluate patients with polypoidal choroidal vasculopathy (PCV). Of note, ICGA should have been performed at all sites in Asia and Europe because the proportions of PCV based on ICGA findings in Asian patients and in white European patients were quite high (20% - 60% and 8% - 13%, respectively) (Cheung *et al.* 2018). Importantly, the ICGA should have been used to highlight patients with the 2 angiographic subtypes of PCV, namely, subtype 1, PCV sharing a common pathogenic background with nAMD, and subtype 2, idiopathic PCV. There is a difference in early treatment response with aflibercept between the 2 subtypes of PCV (Jeong *et al.* 2017). Thus, the subtype 1 polypoidal CNV showed better visual improvement, with higher percentage of polyp regression comparable to that of

nAMD, than did the subtype 2 idiopathic PCV. The distinct treatment effects may be attributable to their different pathophysiology, genetic backgrounds, and disease progressions. Therefore, the ICGA should be a standard investigation to be useful in evaluating specific forms of newly diagnosed nAMD, such as pigment epithelial detachment (PED), poorly defined CNV, occult CNV, and lesions including retinal angiomatous proliferation or idiopathic PCV.

The comparison of the effectiveness of the brolucizumab q12w/q8w and aflibercept q8w was in appropriate because the treatment paradigms of the two anti-vascular endothelial growth factor (VEGF) agents were completely different, namely, a treat and extend simplified regimen for the brolucizumab-treated eyes and a fixed-interval paradigm for the aflibercept-treated eyes. Likewise, the role of the disease activity (e.g., presence of retinal fluid and increased central subfield thickness) in the establishment of the effective treatment scheduling could not be comparatively evaluated because the dosing intervals for brolucizumab were continuously adjusted according to the activity of the disease while they remained fixed without adjustment for aflibercept for the entire study period regardless of the disease activity. It is assumed that the comparison of the brolucizumab dosing paradigm with a pro re nata regimen for aflibercept (e.g., patients monitored monthly and treated only if signs of active disease are present) would have been more appropriate and more closer to the real life than that with aflibercept fixed interval regimen (q8w).

The following pertinent data, which should have been included in the statistical analyses, are missing in patients treated with brolucizumab and aflibercept: the mean time duration of symptoms of nAMD from diagnosis to the initiation of treatment; the optical coherence tomography patterns of vitreoretinal interface abnormalities at baseline and at week 48 (epiretinal membranes, retinomacular adhesion/traction, full-thickness macular hole, lamellar macular hole, and combined epiretinal membranes and vitreomacular traction); the existence or not of the disorganization of retinal inner layers and its severity at presentation and at the end of the study (e,g., mild, severe, and severe with damaged ellipsoid zone); the location of the intraretinal fluid at presentation and at week 48 (e.g., inner/outer nuclear layers or ganglion cell layer); the optical coherence tomography of the 3 phenotypes of the lesions within the fibrotic spectrum (3 main pathways of progression to macular fibrosis), that is, the type A located underneath the retinal pigment epithelium (RPE), the type B located above the RPE with intact RPE, and the type C located subretinal with the RPE indistinguishable at week 48; the existence or not of the 2 types of advanced fibrotic lesions (final stages of fibrotic lesions) at week 48, e.g., 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 scars and geographic atrophy affecting the central subfield at week 48; the quantification of the sub retinal hyper reflective material at baseline and at the end of the study and its composition (e.g., fibrosis, blood, fibrin, exudation, lipid, vitelliform material, and neovascular tissue) at baseline and at month 12; the prevalence, number, size, and shape of the tubular structures affecting the outer retina and RPE termed outer retinal tubulation; the proportion of the PED and their type (fibrovascular/serous/mixed) at baseline and at month 12; and the subfoveal choroidal thickness at presentation and at the end of the study (Călugăru *et al*., 2020).

Altogether, the authors of this study concluded that after 48 weeks brolucizumab demonstrated noninferioriy to aflibercept in best-corrected visual acuity change from baseline and > 50% of brolucizumab 6 mg-treated eyes were maintained on the q12w dosing interval through week 48. However, the validation, extrapolation, and generalizability of these findings 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.

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Acknowledgments/disclosure

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