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MACULAR ATROPHY IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

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ABSTRACT

The authors are commenting on the study entitled "Macular atrophy in neovascular age-related macular degeneration" published by Gillies *et al*. in Ophthalmology 2020;127(2):198-210, which analyzed the differences in the development and growth of macular atrophy over 24 months between treat-and-extend ranibizumab and aflibercept in patients with active, chronic, treatment-naïve subfoveal choroidal neovascularization secondary to neovascular age-related macular degeneration. The authors of this study concluded that no significant differences in the rate of development or growth of macular atrophy over 24 months were achieved between ranibizumab and aflibercept. 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 Gillies *et al.*(2020) which prospectively analyzed the differences in the development and growth of macular atrophy (MA) over 24 months between treat-and-extend ranibizumab (Lucentis; Genentech, Inc, South San Francisco, CA, USA) and aflibercept (Eylea; Regeneron Pharmaceuticals, Inc, Tarrytown, NY, USA) in patients with active, chronic, treatment-naïve subfoveal choroidal neovascularization secondary to neovascular age-related macular degeneration (nAMG). The proportion of patients with MA increased from 7% to 37% for ranibizuamb and from 6% to 32% for aflibercept from baseline to month 24 while the average number of injections received per year was similar between both groups (9.6 and 9.5, respectively). The mean change in best-corrected visual acuity (BCVA) from baseline to month 24 was +6.6 letters for ranibizuamb and +4.6 for aflibercept group. No statistical difference between ranibizumab 0.5 mg and aflibercept 2.0 mg was found in the development of MA in nAMD patients treated over 24 months. We would like to address several challenges that have arisen from this study, which can be specifically summarized below.

The study had a prospective design with a follow-up period of 2 years, which was far too short to effectively assess the development of new MA known to be a very relentless slow process. The relatively high discontinuation rate of 19.9% at 2 years influenced the aggregate data and might have caused an inadvertent bias. On the other hand, there was a selection bias attributable to the fact that the assessment of 2 of the 3 criteria for disease activity (e.g., the loss of BCVA of 5 letters or more than the BCVA recorded since treatment started and the presence of new retinal hemorrhage) was at the discretion of the 24 investigators at the 24 sites across Australia. Taken together, these findings may have confounded the results. Of the 6 angiographic types of choroidal neovascularization (CNV) existing in patients with nAMD, the study analyzed at presentation only 3 of them, namely, the occult, the predominantly and minimally classic CNVs. The other 3 angiographic types (e.g., the mixed CNV, the retinal angiomatous proliferation, and the polypoidal choroidal vasculopathy [PCV]) were not screened and investigated in the study populations as potential predictive factors influencing the occurrence and progression of the MA. The indocyanine

green angiography (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. Importantly, 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. Moreover, there were no data on the forms of neovascular lesions that may arise secondary to nAMD, namely, the type 1 located under the retinal pigment epithelium (RPE), the type 2 located in the subretinal space, or the type 3 intraretinal.

The MA was defined by the authors using the multimodal imaging as the loss of the RPE, ellipsoid zone (EZ), and external limiting membrane (ELM) with visible underlying large choroidal vessels and with concomitant subsiding of the outer retinal layers together with increased signal transmission below Bruch's membrane of 100 μm or more in the longest linear dimension on optical coherence tomography (OCT). Of note, the currently available international consensus definition for atrophy associated with nAMD (Sadda *et al.,* 2018) based on multimodal imaging encompasses the following criteria: 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 (ONL) thinning, ELM loss, and EZ or interdigitation zone loss with increased visibility of choroidal vessels.

The following pertinent data, which should have been included in the statistical analyses, are missing in the 2 study groups: the mean time duration of symptoms of nAMD from diagnosis to the initiation of treatment; the OCT patterns of vitreoretinal interface abnormalities at baseline and at month 24 (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 month 24 (e.g., mild, severe, and severe with damaged EZ); the location of the intraretinal fluid at presentation and at the end of the study (e.g., inner/outer nuclear layers or ganglion cell layer); the rate of the fibrotic and nonfibrotic scars at presentation and at month 24; the quantification of the subretinal hyper reflective material at the end of the study and its composition (e.g., fibrosis, blood, fibrin, exudation, vitelliform material, lipid, and neovascular tissue) at baseline and at month 24; 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 (solid/hollow/mixed) at month 24; and the subfoveal choroidal thickness at the end of the study.

The effectiveness of the treatment in this series was unsatisfactory. Specifically, although the BCVA increased by 6.5 letters for the ranibizumab group and 5.3 letters for the aflibercept group and the central subfield foveal thickness decreased to the normal limits in both groups at month 24, there were relatively high proportions of patients with wet retinas (subretinal fluid or intraretinal fluid) both at 12 months (44% and 36% in the ranibizumab and aflibercept group, respectively) and at 24 months (43% and 39%, respectively). 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).

The authors of this study concluded that no significant differences in the rate of development or growth of MA over 24 months were achieved between ranibizumab and aflibercept. However, we have to take into account the structural differences between the 2 molecules of these antiangiogenic agents. Specifically, aflibercept therapy results in greater more sustained reduction in systemic VEGF levels than ranibizumab. On the other hand, unlike ranibizumab, which does not impair the choroidal thickness, aflibercept treatment may result in a significant subfoveal choroidal thickness loss (Gharbiya *et al.* 2015), by suppressing the choroidal vascular hyperpermeability and vasoconstriction, as well as by more pronounced reductions of choriocapillaris endothelium thickness and number of fenestrations. On short-term, the significant subfoveal choroidal thickness thinning by aflibercept does not seem to result in visual deleterious changes. However, on long-term, the prolonged inhibition of the RPE-derived VEGF using aflibercept may affect the integrity of the choriocapillaris, considering the key role of VEGF-A in the normal function of the retina and in the regulation of the survival and permeability of the choriocapillaris. Thus, choroidal vascular impairment may affect the integrity of the RPE and outer retina favoring the development of the fovea-involving geographic atrophy with subsequent visual damaging effects 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. In addition, through the fragment crystallizable (Fc) domain, aflibercept can bind to the Fc receptor of both choriocapillaris endothelial cells and red blood cells, leading to complement-mediated cell death.

Altogether, the validation, extrapolation, and generalizability of the authors' conclusions 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 [Avastin; Genentech, Inc]/ 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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REFERENCES

Călugăru D, Călugăru M. High-dose high frequency aflibercept for recalcitrant neovascular age-related macular degeneration. *Retina* 2017;37(11):e139-e141.

Gharbiya M, Cruciani F, Mariotti C, et al. Choroidal thickness changes after intravitreal antivascular endothelial growth factor therapy for age-related macular degeneration: ranibizumab versus aflibercept. *J Ocul Pharmacol Ther* 2015; 31(6):357-362.

Gillies MC, Hunyor AP, Arnold JJ, *et al*. Macular atrophy in neovascular age-related macular degeneration. *Ophthalmology* 2020;127(2):198-210.

Jaffe GJ, Kaiser PK, Thompson D, *et al.* Differential response to anti-VEGF regimens in age-related macular degeneration patients with early persisted retinal fluid. *Ophthalmology* 2016;123(9):1856-1864.

Jeong S, Sagong M. Short-term efficacy of intravitreal aflibercept depending on angiographic classification of polypoidal choroidal vasculopathy. *Br J Ophthalmol* 2017;101(6):753-763.

Sadda SR, Guymer R, Holtz FG *et al.* Consensus definition for atrophy associated with age- related macular degeneration on OCT. *Ophthalmology* 2018;125(4):537-548.

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