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TREATMENT OUTCOMES OF RANIBIZUMAB VERSUS AFLIBERCEPT FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION. DATA FROM THE FIGHT RETINAL BLINDNESS REGISTRY

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ABSTRACT

The authors are commenting on the study entitled "Treatment outcomes of ranibizumab versus aflibercept for neovascular age-related macular degeneration. Data from the fight retinal blindness registry", published by Bhandari *et al.* in Ophthalmology 2020;127(3):369-376, which compared the 3-year treatment outcomes of ranibizumab and aflibercept in 965 treatment-naive eyes with neovascular age-related macular degeneration. The authors of this study found that treatment outcomes of neovascular age-related macular degeneration in routine clinical practice with either ranibizumab or aflibercept were similar at 3 years in terms of visual outcomes, treatment frequency, and visits. We believe that 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, serving to emphasize the key metrics assessing the comparatve efficacy of ranibizumab and aflibercept in neovascular age-related macular degeneration.

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INTRODUCTION

The study by Bhandari *et al.* (2020) compared the 3-year treatment outcomes of ranibizumab (Lucentis; Genentech, Inc, South San Francisco, CA, USA) and aflibercept (Eylea; Regeneron Pharmaceuticals Inc., Tarrytown, NY, USA) in 965 treatment-naive eyes with neovascular age-related macular degeneration (nAMD). The crude mean visual acuity (VA) change was +1.5 letters in the ranibizumab group and +1.6 letters in the aflibercept group at 3-years in all eyes while the adjusted mean VA change was +0.3 letters versus +1.0 letters, respectively. Significantly more switches from ranibizumab to aflibercept took place than vice versa. The proportion of eyes that did not complete 3 years of treatment in each group was similar. The authors concluded that neither ranibizumab nor aflibercept was superior to the other in terms of VA outcomes and treatment frequency at 3 years for nAMD. We would like to address several challenges that have arisen from this study, which can be specifically summarized below.

There was a selection bias assigned to the fact that the patients of the 2 groups of treatments (ranibizumab and ranibizumab) had some significantly different characteristics that were not ideally matched making them inappropriate for comparison. That is, there were significant differences with respect to the baseline age (82 years and 79 years, respectively) and the proportion of women (66% and 57%, respectively) as well as the mean number of intravitreal injections (11 and 14, respectively) received for all eyes within the 3-year follow-up. Although the longitudinal models were adjusted for age, baseline VA, lesion type, and practice, the adjustment was not carried out for the proportion of women at baseline. Importantly, all treatment decisions, selection of cases, drug choice, and visit schedule were at the discretion of the practitioner in consultation with the patient at 38, 2, and 1 practices in Australia, New Zeland, and Switzerland without adjudication from a reading center or guidance by study protocols. Of note, the fundus angiography was performed only if deemed necessary by the treating physician. Taken together, these findings may have confounded the final results.

Although the authors asserted that they included in the study treatment-naïve eyes with nAMD that began treatment with either ranibizumab of aflibercept, there were also some eyes that started treatment with 1 injection of bevacizumab (Avastin; Genentech, Inc.). In addition, no details were given referring to the schedule of procedures for switching

treatments (15%) occurring during the 3 years studied, significantly more frequent from ranibizumab (25.45 %) to aflibercept than vice versa (4.50 %). That is why, the comparative efficacy of the treatment with aflibercept and ranibizumab could not be evaluated because the design of this study lacked a real washout period, which is essential among the 2 or 3 periods of treatment in terms of aliased effects. Thus, the impact of the significant carryover effects of the bevacizumab/or treatment switches may be confounded with direct treatment effects of the aflibercept and ranibizumab because these effects could not be estimated separately; carryover effects may bias the interpretation of data analysis.

The following relevant data are missing from this article: the mean time duration of symptoms of nAMD from diagnosis to the initiation of treatment; the spectral domain-optical coherence tomography (SD-OCT) patterns of vitreoretinal interface abnormalities (for example, incomplete/complete posterior vitreous detachment, epiretinal membranes, vitreomacular adhesion/traction, full-thickness macular hole, lamellar macular hole, and combined epiretinal membranes and vitreomacular traction) at baseline and at the end of the study; the existence or not of the disorganization of retinal inner layers and its severity (e,g., mild, severe, and severe with damaged ellipsoid zone [EZ] at presentation and at the end of year 3; the location of the intraretinal fluid (e.g., inner/outer nuclear layers or ganglion cell layer) at baseline 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 and interdigitation zone) at presentation and at the end of the study; the existence or otherwise at baseline and at the completion of the study of the type 3 macular neovascularization (MNV), located intraretinal and coming from the deep capillary plexus in the retina with growing toward the outer retina, in addition to the type 1 and type 2 of the MNVs already highlighted in this study ; the SD-OCT patterns of the 3 phenotypes of the lesions within the fibrotic spectrum (3 main pathways of progression from original neovascular lesion to fibrotic scar), 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 the completion of the study; the existence or not of the 2 distinct phenotypic subgroups of advanced fibrotic lesions (final morphologies of the fibrotic process) at the end of the study, 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) (Călugăru *et al*.2020); the rate of patients with nonfibrotic scars at the end of year 3; the composition the subretinal hyperreflective material (e.g., fibrosis, blood, fibrin, exudation, lipid, vitelliform material, or neovascular tissue) at baseline and at the end of the study; the SD-OCT patterns of the pigment epithelial detachment (drusenoid/ fibrovascular/ serous/ mixed) at presentation and at the completion of the study (Călugăru *et al.* 2018, 2019).

The comparative assessment of the treatment efficacy between ranibizumab and aflibercept remains questionable due to the high rates of noncompleters (43.4% and 51,7% respectively), the high proportions of eyes with active lesions at the final study visit (37% and 35%, respectively), and the significantly lower percentage of visits graded as active at last visit completed for noncompleters in the ranibizumab group that switched treatments than the aflibercept group (45% and 57%, respectively).

Altogether, the authors of this study found that treatment outcomes of nAMD in routine clinical practice with either ranibizumab or aflibercept were similar at 3 years in terms of visual outcomes, treatment frequency, and visits. We believe that the validation, extrapolation, and generalizability of these findings can be made only by adequately adjusted 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, serving to emphasize the key metrics evaluating the comparatve efficacy of ranibizumab and aflibercept in nAMD (Călugăru *et al*. 2020a).

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