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Real-World Vision in Age-Related Macular Degeneration Patients Treated with Single Anti-VEGF Drug Type for 1 Year in the IRIS Registry

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To the Editor

We would like to address several challenges that have arisen from the study by Rao et al., [1] which can be specifically summarized below.

The following pertinent baseline data, which would have had to be included in the univariate logistic regression model, are missing in the study: the angiographic subtypes of neovascular age-related macular degeneration (nAMD), namely, the occult, classic, and mixed choroidal neovascularization, the retinal angiomatous proliferation, and the polypoidal choroidal vasculopathy; the duration of the nAMD before entry into the study; the optical coherence tomography (OCT) characteristics, that is, the qualitative status of the geographic atrophy, intraretinal/subretinal fluid, ganglion cell complex, external limiting membrane band, ellipsoid zone, interdigitation zone, retinal pigment epithelium (RPE)-Bruch complex, outer retinal tubulation, and subretinal drusenoid deposits; and the subfoveal choroidal thickness. Additionally, the following covariates, which were significantly different between the 3 drug groups were not encompassed in the ultimate multivariate analysis after multivariate logistic adjustment for the baseline differences: pseudophakia, primary open-angle glaucoma, and epiretinal membrane. Taken together, these findings may have confounded the results.

The clinical significance of the minimal gain in visual acuity (VA) achieved in this series over 1 year of treatment with bevacizumab (Avastin, Genentech, Inc, South San Francisco, CA), ranibizumab (Lucentis, Genentech, Inc.) or aflibercept (Eylea, Regeneron Pharmaceuticals Inc., Tarrytown, NY) (approximately 3, 2, and 2 Early Treatment Diabetic Retinopathy Study letters, respectively) cannot be assessed because of the lack of the OCT characteristics that should guide the evaluation of outcomes with visual changes as a secondary guide. Most likely, there was a permanent vascular endothelial growth factor (VEGF) receptor 2-mediated breakdown of the inner blood-retinal barrier and a permanent VEGF receptor 1-mediated rupture of the RPE junctions induced by long-term VEGF overexpression and high vitreous levels of placental growth factor in patients with nAMD. This permanent retinal capillaropathy caused by persistent

subretinal or intraretinal fluid was temporarily relieved by reduction of edematous component with antiangiogenic agents. However, the pathology was incurable because of irreversible ischemic changes to the macular ganglion cell complex, close to the foveola, with macular edema being a minor factor.

The presumed pharmacologic advantages of aflibercept over bevacizumab or ranibizumab—for example, a higher binding affinity to all isoforms of VEGF-A, activity against VEGF-B, placental-derived growth factor, and galectin-1, as well as a prolonged time of the intraocular VEGF-A suppression—were not confirmed by the results of this series, which demonstrated that all 3 drugs improved VA similarly over 1 year of monotherapy, with no overall differences in mean VA improved between drug types. However, the authors emphasized that a great percentage of patients in the aflibercept group maintained or lost ≥ 3 lines in VA compared with bevacizumab only after multivariate adjustment. Importantly, nothing was stated with regard to the adverse effects of these drugs. Specifically, unlike bevacizumab, which has a protective effect against occlusion of choriocapillaris induced by photodynamic therapy [2], and ranibizumab, which does not impair the choroidal thickness, aflibercept treatment may result in a significant subfoveal choroidal thickness loss [3] by suppressing the choroidal vascular hyperpermeability and vasoconstriction as well as by more pronounced reductions of choriocapillaris endothelium thickness and number of fenestrations. In the short-term, the significant subfoveal choroidal thickness thinning by aflibercept does not seem to result in visual deleterious effects. However, in the long-term, the prolonged inhibition of VEGF using aflibercept may affect the integrity of the choriocapillaris, considering the key role of VEGF-A 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 development of the fovea-involving geographic atrophy, 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 domain, aflibercept can bind to the fragment crystallizable receptor of both choriocapillaris endothelial cells and red blood cells, leading to complement-mediated cell death [4].

Altogether, regardless of the anti-VEGF agents used (e.g., bevacizumab/ranibizumab/ aflibercept), and regardless of the treatment dosing paradigms chosen (e.g., treat-and-extend/pro re nata/fixed-interval/escalated algorithm), the efficacy of the treatment depends primarily on the promptness of the therapy after the onset of nAMD [5].

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