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INTRAVITREAL AFLIBERCEPT FOR DIABETIC MACULAR OEDEMA IN REAL-WORLD: 36-MONTH VISUAL ACUITY AND ANATOMICAL OUTCOMES

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ABSTRACT

The authors are commenting on the study entitled**:** "Intravitreal aflibercept for diabetic macular oedema in real-world: 36-month visual acuity and anatomical outcomes" published by Lukic *et al.* in European Journal Ophthalmology 2020 (Doi: 10.1177/1120672120925034. Published on May 19, 2020), which assessed structural and functional outcomes of treatment with aflibercept for centre-involving diabetic macular oedema in 57 patients (64 eyes) with diabetes. The authors concluded that there was a significant improvement in visual acuity and in anatomical outcomes in aflibercept-treated eyes at 36 months after commencing treatment for diabetic macular oedema in real-life settings. However, the validation, extrapolation, and generalizabilty of these findings can only be made by statistical analyses including all the missing baseline potential risk 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 efficacy of intravitreal aflibercept for diabetic macular oedema in patients with diabetes mellitus.

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INTRODUCTION

We read with interest the study by Lukic *et al.* (2020) which assessed structural and functional outcomes of treatment with aflibercept (Eylea; Regeneraon Pharmaceuticals Inc., Tarrytown, NY, USA) for centre-involving diabetic macular oedema (DMO) in 57 patients (64 eyes) with diabetes. At months 36, visual acuity (VA) improved significantly by 6.89 Early Treatment Diabetic Retinopathy Study (ETDRS) letters, central foveal thickness (CFT) decreased significantly by 119 µm, and macular volume decreased significantly by 1.16 mm^3. Sixteen (25%) eyes gained > 15 ETDRS letters at month 36, and 33 eyes (51.56 %) had a decrease in CFT of ≥ 100 µm at the same time. The good vision and anatomical outcomes were maintained over second and third year of treatment with a mean of 2.93 and 2.57 intravitreal injections, respectively. We would like to address several challenges that have arisen from this study which can be specifically summarized below.

There was a selection bias attributable to inclusion in the study and pooled analysis of patients with type 1 and type 2 diabetes mellitus (DM) as well as those who had prior macular laser surgery (32.81%). The treatment was initiated on a loading phase of five 1-monthly intravitreal aflibercept injections followed by injections, if needed as per clinicians' discretion on the basis of treating towards VA and optical coherence tomography (OCT) scan stability. Notably, eleven percent of included eyes had less than five monathly loading doses due to either clinicians'discretion or patients'choice (they did not attend or they cancelled appointments). Nine eyes included had active proliferative disease at baseline and had platelet-rich plasma treatment before baseline and between intravitreal injections. Twenty-eight percent of eyes included were pseudophakic at baseline and nineteen percent of phakic eyes had cataract surgery during the 36-month follow-up. Taking together, these findings may have confounded the final results.

There were no details regarding the DMO defined as retinal thickening or hard exudates at or within 1 disc diameter of the macula center and which is most commonly classified into either being clinically significant or not. Moreover, the criteria used to define the clinically significant DMO, if it was present in some patients, were not indicated. There were no data on the duration of the diabetes and DMO before entering the study after diabetes onset, the existence or otherwise of the diabetic retinopathy (DR) and its forms (nonproliferative/proliferative DR), the staging of diabetic maculopathy (early, advanced, severe, and atrophic maculopathy), the OCT patterns of the DMO (sponge-like swelling/cystoid macular edema/serous neuroretinal detachment/mixed type), and the location of the cystoid type (ganglion cell layer/inner/outer nuclear layers). Without taking all these characteristics of DMO into account, no judgment can be made on the efficacy of intravitreal aflibercept for DMO in real-world.

The following critical data that should have been included into statistical analyses, are missing from the study: the existence or not of the disorganization of the retinal inner layers and grading of its severity (mild, severe, or severe with damaged ellipsoid zone [EZ]); the qualitative status of the photoreceptor cell layer (the disorganization/thinning of the outer nuclear layer; the disruption/absence of the external limiting membrane [ELM] band, the EZ, and the interdigitation zone); the changes of the retinal pigment epithelial band-Bruch membrane complex (pigment migration within the neurosensory retina, retinal pigment epithelium [RPE] porosity, microrips or blowouts in the RPE, focal RPE atrophy, RPE thickening, presence of reticular pseudodrusen); the proportion of eyes considered "dry" on OCT at the end of the study; the number of hyperreflective intraretinal foci; and the subfoveal choroidal thickness (Călugăru *et al.* 2018).

Nothing was stated regarding the influence which intravitreal aflibercept injections can exert on the diabetic choroidopathy, which consists in intrachoroidal vascular abnormalities and may directly induce choroidal ischemia, leading to RPE dysfunction. The progressive thickening of the choroid layer caused by increasing the severity of DR (from no DR to proliferative DR) and development of DMO (being thickest in eyes with serous neuroretinal detachment type of DMO) denotes progression of the diabetic choroidopathy (Kim *et al.* 2013). In the treatment of DMO with antiangiogenic agents, two adverse effects of aflibercept should be considered and accounted for. Specifically, unlike bevacizumab, which has a protective effect against occlusion of choriocapillaris induced by photodynamic therapy (Mukai *et al.* 2010), and ranibizumab, which does not impair the choroidal thickness (Gharbiya *et al.* 2015), 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. The thinning of the choroid consisted of the loss of small and medium vessels with baring of larger vessels, as well as the loss of pigmented cells, with clumping of preserved pigmented cells in various regions of the choroid. 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 vascular endothelial growth factor (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.

The authors of this study stated that their data showed that at the end of Year 1, Year 2 and Year 3, the subgroup with initially better VA (≥ 69 letters) had statistically significant better VA as compared to the one which had initially worse vision (< 69 letters). In reality, the situation is the reverse, that is, the subgroup with initially better VA had minimal, insignificant gain in VA (+ 0.88 ETDRS letters; p = 0.60) because of the ceiling effect, compared with the subgroup with initially worse VA, which had significant improvement (+ 11.2 ETDRS letters; p = 0.0001) in VA.

On the other hand the authors asserted in the abstract of this study that they had included only treatment-naïve patients. Furher on the main text we found that the study actually included also patients (32.81%) who had macular laser surgery 6 months or more prior initiation of treatment with intravitreal aflibercept.

The authors of this study did not take into account the European School for Advanced Studies in Ophthalmology international classification of the diabetic maculopathy based on the OCT microstructural alterations of the outer/inner retina and vitreoretinal interface going through the center of the fovea (Panozzo *et al.* 2020). Of the seven distinct qualitative and quantitative features included in this classification, which should have been assessed separately (for example, the CFT/macular volume, the size of intraretinal cysts with specification of their location if they existed, the state of the EZ and ELM, the occurrence of disorganization of the retinal inner layers, the presence and number of hyperreflective intraretinal foci, the presence of subretinal fluid with serous neuroretinal detachment, and the OCT patterns of vitreoretinal interface abnormalities) the authors of this study documented only one of them, namely, the CFT/macular volume.

Altogether, the authors of this study found that there was a significant improvement in VA and in anatomical outcomes in aflibercept-treated eyes at 36 months after commencing treatment for DMO in real-life settings. We believe that these findings can only be validated by statistical analyses including all the missing baseline potential risk 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 efficacy of intravitreal aflibercept for DMO in patients with DM.

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