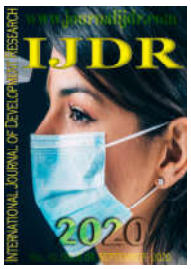
ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 10, Issue, 09, pp. 40816-40817, September, 2020
https://doi.org/10.37118/ijdr.20055.09.2020



RESEARCH ARTICLE OPEN ACCESS

RANIBIZUMAB OR AFLIBERCEPT FOR DIABETIC MACULAR EDEMA. COMPARISON OF 1-YEAR OUTCOMES FROM THE FIGHT RETINAL BLINDNESS REGISTRY

Călugăru and Mihai Călugăru*

Department of Ophthalmology, University of Medicine Cluj-Napoca/Romania

ARTICLE INFO

Article History:
Received 14th June 2020
Received in revised form
28th July 2020
Accepted 07th August 2020
Published online 30th September 2020

Key Words:

Aflibercept; Ranibizumab; Visual Acuity; Central subfiled thickness; Diabetic Macular Edema.

Corresponding author: Mihai Călugăru

ABSTRACT

The authors are commenting on the study entitled "Ranibizumab or aflibercept for diabetic macular edema. Comparison of 1-year outcomes from the fight retinal blindness registry", published by Bhandari et al. in Ophthalmology 2020;127(5):608-615, which compared the 12-month treatment outcomes of ranibizumab and aflibercept in 383 treatment-naïve eyes with diabetic macular edema. The authors found that aflibercept had somewhat better anatomic outcomes and larger visual acuity gains only in eyes receiving aflibercept treatment when the initial visual acuity was 68 letters or fewer. We believe that these findings can only be validated 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 comparative efficacy of ranibizumab and aflibercept in diabetic macular edema.

Citation: ***Călugăru and Mihai Călugăru. 2020.*** "Ranibizumab or aflibercept for diabetic macular edema. comparison of 1-year outcomes from the fight retinal blindness registry", *International Journal of Development Research*, 10, (09), 40816-40817.

INTRODUCTION

The study by Bhandari *et al.* (2020) compared the 12-month treatment outcomes of ranibizumab (Lucentis; Genentech, Inc, South San Francisco, CA, USA) and aflibercept (Eylea; Regeneron Pharmaceuticals Inc., Tarrytown, NY, USA) in 383 treatment-naïve eyes with diabetic macular edema (DME). Eyes in the aflibercept group received more median injections than the ranibizumab group (8 vs. 6 injections, respectively). Significantly more eyes in the aflibercept group were lost to follow-up within 12-months (21% vs. 9% ranibizumab). The authors concluded that aflibercept-treated eyes showed larger central subfield thickness (CST) reductions and larger visual acuity (VA) gains when the initial VA was 20/50 or worse. 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 the fact that the patients in the 2 groups of treatments (aflibercept and ranibizumab) had completely different baseline characteristics that were not ideally matched making them inappropriate for comparison. Specifically, there were significant differences with respect to the diabetes duration, diabetic retinopathy grade, and baseline age of patients as well as statistically borderline differences in terms of the baseline VA and CST.

Although the authors stated that eyes receiving treatment for clinically significant diabetic macular edema (CSME) were eligibile in the DME module, 2% of the included aflibercept-treated eyes, however, had no CSME. Importantly, all treatment decisions, including selection of cases, choice of treatment regimen, and frequency of visits based on VA and spectral domain optical coherence tomography (SD-OCT) were at the discretion of the practitioner in consultation with the patient at sites across the 5 countries included in this study. Taken together, these findings may have confounded the final results. Of note, the statistical analysis that adjusted for baseline factors with potential impact such as VA, age, and CST further deepened the confusion.

No details were given referring to the schedule of administration of the additional treatments to patients (macular laser sessions, triamcinolone and Ozurdex injections [Allergan Inc., Irvine, CA, USA]) and the treatment switches occurring within 12 months (more frequent from ranibizumab to aflibercept than vice versa). 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 additional treatment and/or the 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 crude mean VA and CST changes at 12 months for all eyes highlighted significantly better results for aflibercept than ranibizumab regardless of the VA at presentation. Instead, the adjusted VA changes for aflibercept remained significant only for the VA $\leq$ 68 letters but not for the VA $\geq$ 69 letter, while the adjusted CST changes showed significantly higher reductions for aflibercept in both strata of VA at presentation. Additionally, the analysis of the 61 eyes that discontinued treatment before completing 12 months of follow-up also pleaded for a greater effectiveness of aflibercept over ranibizumab. That is, at last visit before discontinuing treatment the aflibercept-treated patients showed obviously better gains of VA and significantly better mean drop in CST although their maculae had been significantly thicker than those of the eyes in the ranibizumab group when they had started the treatment. The stronger effect of aflibercept over ranibizumab also resulted from the treatment switches (5%) occurring within 12 months which were significantly higher from ranibizumab to aflibercept than vice versa. And yet, the 12-month outcomes of this series are questionable due to the noncompletion rate of patients that has been significantly higher in the aflibercept group (21%) vs 9% in eyes receiving ranibizumab. Importantly, aflibercept–treated patients received more median injections (8 vs 6 injections, respectively), what created an inadvertent bias.

The following critical data are missing at presentation and at completion of the study: the staging of diabetic maculopathy in accordance with the European School for Advanced Studies in Ophthalmology (ESASO) classification (early, advanced, severe, and atrophic maculopathy) (Panozzo *et al.* 2020); the 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); 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 SD-OCT patterns of the DME (for example, sponge-like swelling/cystoid macular edema/serous neuroretinal detachment/mixed type) and the location of the intraretinal cystoid fluid (e.g., inner/outer nuclear layer or ganglion cell layer) (Călugăru *et al.* 2019); 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 number of hyperreflective intraretinal foci; and the subfoveal choroidal thickness (Călugăru *et al.* 2018).

Nothing was stated regarding the influence which aflibercept and ranibizumab can exert on the diabetic choroidopathy, which consists in intrachoroidal vascular abnormalities and which may directly induce choroidal ischemia, leading to RPE dysfunction. The progressive thickening of the choroid layer caused by increasing the severity of diabetic retinopathy (DR) (from no DR to proliferative DR) and development of DME (being thickest in eyes with serous neuroretinal detachment type of DME) denotes progression of the diabetic choroidopathy (Kim *et al.* 2013).

The authors of this study did not take into account the ESASO international classification of the diabetic maculopathy based on the SD-OCT microstructural alterations of the outer/inner retina and vitreoretinal interface going through the center of the fovea. From the seven distinct qualitative and quantitative features included in this classification (for example, the central subfoveal thickness, the size of intraretinal cysts, 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, and the characteristics of the vitreoretinal interface) the authors of this study documented only one of them (central subfoveal thickness).

Altogether, the authors found that aflibercept had somewhat better anatomic outcomes and larger VA gains only in eyes receiving aflibercept treatment when the initial VA was 68 letters or fewer (Bhandari *et al*. 2020). We believe that these findings can only be validated 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 DME.

Acknowledgments/disclosure

All authors have completed and submitted the ICMJE form for disclosure of potential conflicts of interest. No financial disclosures. Both authors (D.C and M.C) were involved in the design and conduct of the study; collection, management, analysis and interpretation of the data; and preparation, review or approval of the manuscript. The authors have full control over the primary data and they agree to allow the International Journal of Development Research to review their data if requested.

REFERENCES

Bhandari S, Nguyen V, Fraser-Bell S, et al. Ranibizumab or aflibercept for diabetic macular edema. Comparison to 1-year outcomes from the fight retinal blindness registry. *Ophthalmology* 2020; 127(5):608-615.

Panozzo G, Cicinelli MV, Augustin AJ, et al. An optical coherence tomography based grading of diabetic maculopathy proposed by an international expert panel: the European School for Advanced Studies in Ophthalmology classification. *Eur J Ophthalmol* 2020; 30(1):8-18.

Călugăru D, Călugăru M. Comment on "Thickness and volume of the choroid outer retinal layers and retinal pigment epithelium layer changes in patients with diabetic retinopathy". *Int J Ophthalmol* 2019; 12(8):1366-1368.

Călugăru D, Călugăru M. Early response to intravitreal dexamethasone implant therapy in diabetic macular edema may predict visual outcome. *Am J Ophthalmol* 2018; 186(February): 164-165.

Kim JT, Lee DH, Joe SG. Changes in choroidal thickness in relation to the severity of retinopathy and macular edema in type 2 diabetic patients. *Invest Ophhalmol Vis Sci* 2013; 54(5):3378-3384.

****