



ISSN: 2230-9926

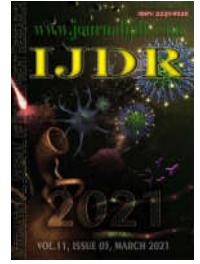
Available online at <http://www.journalijdr.com>

IJDR

International Journal of Development Research

Vol. 11, Issue, 03, pp.45047-45048, March, 2021

<https://doi.org/10.37118/ijdr.21271.03.2021>



RESEARCH ARTICLE

OPEN ACCESS

ONE-YEAR REAL-LIFE RESULTS ON EFFECT OF INRAVITREAL AFLIBERCEPT IN PATIENTS WITH DIABETIC MACULAR EDEMA SWITCHED FROM RANIBIZUMAB

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ARTICLE INFO

Article History:

Received 19th December, 2020
Received in revised form
24th January, 2021
Accepted 14th February, 2021
Published online 15th March, 2021

Key Words:

Aflibercept; Ranibizumab;
Diabetic Macular edema;
Anti-vascular endothelial growth
Factor treatment.

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ABSTRACT

The authors are commenting on the study entitled :“One-year real-life results on th effect of intravitreal aflibercept in patient with diabetic macular edema switched from ranibizuamab” published by Lukic *et al.* in Eur J Ophthalmol 2020; Doi: org/101177/1120672120927275. Published online: May 26, 2020, which assessed the visual and optical coherence tomography-derived anatomical outcomes of treatment with intravitreal aflibercept for diabetic macular edema in patients switched from intravitreal ranibizumab. The authors found that there was a significant improvement in visual acuity and in anatomical outcomes in the switched group at 12 months after commencing treatment with aflibercept for diabetic macular edema. However, the validation, extrapolation, and generalizability of this findings can only be validated through 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 putative biomarkers assessing the visual acuity and anatomical benefits in switching anti-vascular endothelial growth factor agent in diabetic macular edema patients.

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Citation: Dan Călugăru, MD, PhD and Mihai Călugăru, MD, PhD. 2021. “One-year real-life results on effect of inravitrealaflibercept in patients with diabetic macular edema switched from ranibizumab”, *International Journal of Development Research*, 11, (03) , 45047-45048.

INTRODUCTION

The study by Lukic *et al.* (2020) evaluated visual and anatomical results of treatment with intravitreal aflibercept (Eylea; Regeneron Pharmaceuticals Inc., Tarrytown, NY, USA) for diabetic macular edema (DME) in 90 eyes of 67 patients switched from intravitreal ranibizumab (Lucentis; Genentech, Inc, South San Francisco, CA, USA). At 12 months after starting treatment with aflibercept the authors found the following benefits in the switched group: the mean change in visual acuity (VA) of +4 Early Treatment Diabetic Retinopathy Study letters ($p = 0.0053$), the mean change in macular volume of -1.53 mm^3 ($p = 0.21$), and the change in central foveal thickness of $-136.8 \mu\text{m}$ ($p = 0.69$). We would like to address several challenges that have arisen from this study which can be specifically summarized below.

First, there was a selection bias attributable to inclusion in the study and pooled analysis of patients with type 1 and 2 diabetes mellitus and all decisions on switch as well as on treatment and retreatment were based on the opinion of the treating ophthalmologists and were at their discretion.

Likewise, for 87.7% of eyes, the 12-month tracking data were available with non-attendance in which case the last valid set data were carried forward. Of note, twenty-five proportion of overall switched patients experienced macular laser prior to baseline. Taken together, these findings may have confounded the results.

Second, the comparative efficacy of the treatment with ranibizumab and aflibercept can not be actually evaluated because nothing was stated whether or not a washing period existed between macular laser performed in 25 patients of the overall switched group and aflibercept commencing. In addition 53 eyes were switched from ranibizumab to aflibercept with an interval of less than 3 months. Thus, the impact of the significant carryover effects of the macular laser/ranibizumab on previously presented patients may be confounded with direct treatment effects of aflibercept what can bias the interpretation of data analysis.

Third, there were completely different p-values for the changes in the central foveal thickness and macular volume during the study, that is, 0.69 and 0.21, respectively, in the Abstract section (total insignificant) and < 0.0001 and < 0.0001 , respectively, in the Post-switched data section (significantly high). Which of them are real and

hence the legitimate question of whether all these results are significant or not.

Fourth, the authors of this study did not consider the currently available recommendations of the European School for Advanced Studies in Ophthalmology international classification (Panozzo *et al.* 2020) that classified the diabetic maculopathy based on the spectral domain optical coherence tomography (SD-OCT) microstructural alterations of the outer/inner retina and vitreoretinal interface. From the seven distinct parameters of an SD-OCT structural image going through the center of the fovea only one was highlighted in this study, namely, the foveal thickness/macular volume. The remaining 6 distinct features of this classification, which should have been assessed separately in this study, are as follows:

- Intraretinal cysts with specification of their location if they existed (inner/outer nuclear layers or ganglion cell layers);
- Ellipsoid zone (EZ) or external limiting membrane status;
- Presence of disorganization of the retinal inner layers and grading of its severity (mild, severe, and severe with damaged EZ);
- Number of hyperreflective foci;
- Subretinal fluid with serous neuroretinal detachment;
- Patterns of vitreoretinal interface abnormalities (epiretinal membranes, vitreomacular adhesion/traction, full-thickness macular hole, lamellar macular hole, and combined epiretinal membranes and vitreomacular traction).

Fifth, there were no data referring to the reasons for switching, namely, tachyphylaxis (caused by depletion of the amount of neurotransmitter responsible for creating the drug's effect or by depletion of receptors available to which the drug or neurotransmitter can bind) or pharmacodynamic tolerance (determined by increased expression of vascular endothelial growth factor [VEGF] due to elevated numbers of macrophages, increased expression of VEGF receptors or a shift of the stimulus towards other growth factors, e.g., VEGF-B and placental-derived growth factor).

Differentiation between the 2 reasons is mandatory because each of them requires specific therapy, that is, tachyphylaxis can be defeated by switching to a similar drug but with different properties while tolerance requires an increased dosage or shorter dosing time intervals (Călugăru *et al.* 2017).

Altogether, the authors of this study found that there was a significant improvement in visual acuity and in anatomical outcomes in the switched group at 12 months after commencing treatment with aflibercept for diabetic macular edema. However, the validation, extrapolation, and generalizability of this finding 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 putative biomarkers assessing the anatomical and functional benefits in switching anti-VEGF agent in DME patients.

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