ISSN: 2230-9926

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

IJDR

International Journal of Development Research
Vol. 11, Issue, 10, pp. 51293-51294, October, 2021
https://doi.org/10.37118/ijdr.23010.10.2021

RESEARCH ARTICLE OPEN ACCESS

FOUR-YEAR OUTCOMES OF AFLIBERCEPT TREATMENT FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: RESULTS FROM REAL-LIFE SETTING

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ARTICLE INFO

Article History:
Received 17th August, 2021
Received in revised form
29th September, 2021
Accepted 03rd October, 2021
Published online 30th October, 2021

Key Words:
Age-related macular degenration; Fluorescein angiography; Anti-vascular endothelial growth factor therapy; Aflibecept.

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ABSTRACT

The authors are commenting on the study entitled: "Four-year outcomes of aflibercept treatment for neovascular age-related macular degeneration: results from rel-life setting" published by Lukic et al. in European Journal Ophthalmology 2020 (Doi: 10.1177/1120672120938565. Published on June 25, 2020), which assessed 4-year structural and functional outcomes in intravitreal aflibercept treatment for 89 patients (94 eyes) with neovascular age-related macular degeneration in a real-world setting. The authors concluded that there was a significant improvement in visual acuity and in anatomical outcomes in aflibercept-treated eyes at 4 years after commencing treatment. 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 neovascular age-related macular degeneration.

Citation: ***Dan Călugăru and Mihai Călugăru.*** "Four-year outcomes of aflibercept treatment for neovascular age-related macular degeneration: results from real-life setting*", International Journal of Development Research*, 11, (10), 51293-51294.

INTRODUCTION

We read with interest the study by Lukic *et al.* (2020) which assessed 4-year structural and functional outcomes in intravitreal aflibercept (Eylea; Regeneron Pharmaceuticals Inc., CA, USA) treatment for 89 patients (94 eyes) with neovascular age-related macular degeneration (nAMD) in a real-world setting. The mean number of aflibercept injections received over 4 years was 19.3. At 4 years the visual acuity (VA) improved significantly by 6.3 Early Treatment Diabetic Retinopathy Study (ETDRS) letters and central subfield macular thickness (CSMT) decreased significantly by 77.8 µm. Thirty three percent of eyes gained ≥ 15 ETDRS letters and 70% of eyes had no macular fluid at the end of the follow-up. The authors concluded that aflibercept treatment for nAMD can result in impressive long-term efficacy outcomes using a proactive treatment paradigm with pre-defined dosing in year 1 followed by treat-and-extend regimen. We would like to address several challenges that have arisen from this study which can be specifically summarized below.

The study was retrospectively conducted with a fairly high percentage of patients (35.9%) lost until the end of the follow-up period.

There was a treatment bias attributable to the treatment protocol that consisted of a combination of fixed and treat-and-extend regimens. Specifically, patients were treated in the first year followed fixed dosing regimen laoding phase of three monthly injections followed by bimonthly injections until the year 1 and then in 2nd, 3nd, and 4th year of treatment, the patients followed by treat-and-extend regimen. This resulted in a variable care strategy, that became more obvious in the third and fourth year of treatment suggesting that in eyes with no signs of macular fluid at that period may have continued on 12-weekly or even longer-interval injections while other may not have received additional injections if the clinician determines that they are stable after conversation with the patient. Thus 8.5%,28%,, and 37% of eyes had no injections in year 2, 3, and 4, respectively. Thirty-seven percent of those who had 0 injections in year 2 needed injections over year 3 and/or 4 and 8% of those who had no injections in year 3 needed injections over year 4. Taking together, these findings may have confounded the final results.

Without considering the prevalent (detected at baseline) and incident (developed and progressed during the 4 years) macular atrophy (MA) and subretinal fibrosis, the 4-year outcomes of treatment with aflibercept in patients with nAMD cannot be assessed. Nothing was stated about of the 4 phenotypes of the MA which may occur in nAMD, whose prevalence and incidence should have been separately

estimated. That is, the complete and incomplete retinal pigment epithelial and outer retinal atrophies (the differentiation between these 2 forms is made according to the diameter of the abnormality zone, namely, more or less than 250 μm, respectively) and the complete and incomplete outer retinal atrophies (loss of the ellipsoid zone [EZ] and interdigitation zone [IZ] usually with corresponding loss of thickness of the outer nuclear layer) (Spaide *et al.* 2020). Likewise, the optical coherence tomography (OCT) patterns of the 3 phenotypes of the lesions representing 3 main pathways of progression from original neovascular lesions to fibrotic scar at the end of the study (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) were not highlighted as well as the existence or otherwise of the 2 distinct phenotypic subgroups of advanced fibrotic lesions at the completion of the study (the fibroatrophic lesions [absence of proliferation under the subretinal space] and the fibroglial lesions [fibroglial proliferation in the subretinal space after RPE erosio]).

In the assessment of the 4-year results of this study, we considered the current assertion that evaluation of outcomes has to be guided by anatomical measure data with visual changes as a secondary guide (Freund *et al.*2015). Although the VA improved significantly by 6.3 letters and the CSMT decreased significantly by 77.8 μm, the evidence of macular fluid on OCT imaging was found in 30% of eyes at the end of year 4, namely, 10% of eyes had still presence of subretinal fluid (SRF), whilst 16% and 3% of eyes had presence of intraretinal fluid (IRF) and IRF + SRF at the end of 4 years, respectively. These findings highlight unresolved macular edema owing to undertreatment administered (overall average number of 19.3 injections over 4 years) with insufficient macular deturgescence and indicate that the disease process is still active and progressive, requiring further treatment with antiangiogenic agents.

The following pertinent data, that should have been included in the statistical analyses, are missing from the study: the mean time duration of symptoms of the nAMD from diagnosis to the initiation of treatment; the OCT patterns of the vitreoretinal interface abnormalities at baseline and at the end of the study (e.g., epiretinal membranes, vitreomacular adhesion/traction, full-thickness macular hole, lamellar macular hole, and combined epiretinal membranes and viteomacular traction); the existence or otherwise of the disorganization of retinal inner layers and its severity at enrollment and at completion of the study (mild, severe, and severe with damaged EZ); the forms of the macular neovascularization (MNV) lesions at the completion of the study, that may arise secondary to nAMD (the type 1 occult MNV located under the RPE; the type 2 classic MNV which proliferates in the subretinal space; the mixed type 1 and type 2 minimally classic MNV with OCT findings of both type 1 and type 2 MNV together; and the type 3 intraretinal MNV which grows from the deep capillary plexus toward the outer retina); the rate of patients with nonfibrotic scar at enrollement and at the completion of the study; the location of the intraretinal fluid (e.g., inner/outer nuclear layers or ganglion cell layer) at presentation 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 IZ) at enrollment and at the end of the study; the prevalence, number, size, and shape of the tubular structures affecting the outer retina and RPE termed outer retinal tubulation at presentation and at the completion of the study; the quantification of the subretinal hyperreflective material and its composition at baseline and at the end of the study (for example, fibrosis, blood, fibrin, exudation, lipid, vitelliform material, or neovascular tissue); the OCT patterns of the pigment epithelial detachment (drusenoid/fibrovascular/serous/mixed) at presentation and at the end of the follow-up period; the proportion of eyes with reticular pseudodrusen at baseline and at year 4; and the subfoveal choroidal thickness at enrollment and at the completion of the study (Călugăru *et al*. 2017).

Altogether, the authors showed that good long-term morphological and functional treatment results can be achieved using aflibercept for nAMD in a real-life setting. We believe that the validation, extrapolation, and generalizability of these findings can be made only by regression analyses including all the missing data referred to above by us in addition to the baseline characteristics already assessed in this study, serving to identify the potential prognosticators influencing outcomes of aflibercept treatment for nAMD over 4 years of follow-up after the initiation of treatment.

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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.

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