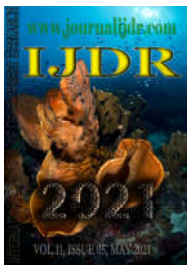
ISSN: 2230-9926

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

IJDR

International Journal of Development Research
Vol. 11, Issue, 05, pp. 46945-46946, May, 2021
https://doi.org/10.37118/ijdr.21885.05.2021



RESEARCH ARTICLE OPEN ACCESS

MACULAR ATROPHY INCIDENCE AND PROGRESSION IN EYES WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION TREATED WITH VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS USING A TREAT-AND-EXTEND OR A PRO RE NATA REGIMEN. FOUR YEAR RESULTS OF THE MANEX STUDY

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ARTICLE INFO

Article History:
Received 04th February, 2021
Received in revised form
19th March, 2021
Accepted 25th April, 2021
Published online 22th May, 2021

Key Words:

Neovascular age-related macular degeneration; Fluorescein angiography; Anti-vascular endothelial growth factor therapy; Treat-and-extent retimen; Pro re nata regimen.

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ABSTRACT

The authors are commenting on the study entitled**:** "Macular atrophy incidence and progression in eyes with neovascular age-related macular degeneration treated with vascular endothelial growth factor inhibitors using a treat-and-extend or a pro re nata regimen. Four-year results of the Manex study" by Spooner *et al.* in Ophthalmology 2020;127(12):1663-1673, compared the incidence and progression of macular atrophy in eyes with neovascular age-related macular degeneration treated with anti-vascular endothelial growth factor agents using either a treat-and-extend or a pro re nata regimen over 4 years in a real-world setting. The authors concluded that treat-and-extend may be the preferred treatment regimen because it allows for better functional outcomes with no increased risk for macular atrophy. 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 key drivers influencing the incidence and progression of macular atrophy in eyes with neovascular age-related macular degeneration treated with anti-vascular endothelial growth injections using treat-and-extend and pro re nata approaches.

Citation: Dan Călugăru and Mihai Călugăru, 2021. "Macular atrophy incidence and progression in eyes with neovascular age-related macular degeneration treated with vascular endothelial growth factor inhibitors using a treat-and-extend or a pro re nata regimen. four year results of the Manex study", *International Journal of Development Research*, 11, (05), 46945-46946.

INTRODUCTION

We read with interest the study by Spooner *et al.* (2020) which compared the incidence and progression of macular atophy (MA) in 264 eyes with neovascular age-related macular degeneration (nAMD) treated with vascular endothelial growth factor (VEGF) inhibitors using either a treat-and-extend (T&E) (n=163) or a pro re nata (PRN) (n=101) regimen over 4 years in a real-world setting. At baseline MA was present in 24% and 20% of study eyes in T&E and PRN groups, respectively. At year 4, 27% and 25% of eyes without baseline MA showed detectable MA in the T&E and PRN groups, respectively. Multivariate analysis for baseline predictors of MA growth demonstrated that older age, poorer baseline visual acuity, and presence of retinal angiomatosis proliferation had a higher risk of greater MA progression. Regression analysis showed no association between T&E and PRN treatment strategies with the risk of new MA developing during the 4 years of follow-up or the progression of pre-existing MA at year 4. Eyes treated with a T&E regimen received significantly more injections and achieved significantly better visual outcomes compared with those treated with a PRN approach.

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 of patients undergoing anti-VEGF therapy for nAMD from 2 retinal clinics in Sydney, Australia, and Milan, Italy, where strict criteria for follow-up and retreatment were not pre-established and each site followed their own internal guidelines for the management of patients with nAMD. During the 4-year follow-up period 130 eyes (49%) switched anti-VEGF agents at least once (62 eyes in the PRN group and 68 eyes in the T&E group) and the difference in the development or incidence of MA between anti-VEGF agents was not compared. Likewise, being a retrospective study, the both cohorts of patients represent only a subgroup of treated patients, that is, those with 4 years of follow-up and adequate imaging. Although the Heildeberg Region Finder software is so far the only validated method to assess atrophy in choroidal neovascularization, it has limitations such as masking because of fibrosis and disease activity. Taking together, these findings may have confounded the final results.

Second, MA was defined by the authors as sharp, delineated hypoautofluorescence with corresponding attenuation of the retinal pigment epithelial band and loss of the overlying ellipsoid zone (EZ) and external limiting membrane with thinning of the outer nuclear layer, together with enhanced signal transmission into the choroid as evidenced on optical coherence tomography (OCT). On the other hand, MA that was confluent with peripapillary atrophy was excluded. Nothing was stated about the 4 phenotypes of the MA which may occur in nAMD, whose prevalence (detected at baseline) and incidence during the 4 years should have been separately estimated. That is, the complete and incomplete retinal pigment epithelial and outer retinal atrophies (the differentiation 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 EZ and interdigitation zone usually with corresponding loss of thickness of the outer nuclear layer) (Spaide *et al.* 2020).

Third, 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 (ie, 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; and the type 3 intraretinal MNV which grows from the deep capillary plexus toward the outer retina); the mixed type 1 and type 2 minimally classic MNV (e.g., OCT findings of both type 1 and type 2 MNV together and OCT angiography demonstrates neovascularization in the sub-retinal pigment epithelial and subretinal compartments) at presentation and at the end of the study; the 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); 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]); 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 qualitative status of the photoreceptor cell layer (disorganization/ thinning of the outer nuclear layer, external limiting membrane defects, disruption of the EZ, and interdigitation zone) at baseline 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 years 4; the proportion of eyes with dry macula at year 4; and the subfoveal choroidal thickness at baseline and at the end of the study (Călugăru *et al.*2020.

Altogether, the authors found no significant difference in the incidence or progression of MA in eyes with nAMD treated with anti-VEGF intravitreal injections using T&E or PRN regimen over 4 years. They concluded that T&E may be the preferred treatment regimen because it allows for better functional outcomes with no increased risk for MA. 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 putative biomarkers influencing the incidence and progression of MA in eyes with nAMD treated with anti-VEGF injections using T&E and PRN approaches.

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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