• Comment and Response •

Comment on "Assessment of the long-term visual and anatomical outcomes of ranibizumab to treat neovascular age-related macular degeneration"

Dan Călugăru, Mihai Călugăru

Department of Ophthalmology, University of Medicine, Cluj-Napoca 400012, Romania

Correspondence to: Mihai Călugăru. Department of Ophthalmology, University of Medicine, Strada Brâncoveanu 11, Cluj-Napoca 400467, Romania. mihai.calugaru@mail.dntcj.ro

Received: 2018-05-24 Accepted: 2018-08-09

DOI:10.18240/ijo.2018.11.25

Citation: Călugăru D, Călugăru M. Comment on "Assessment of the long-term visual and anatomical outcomes of ranibizumab to treat neovascular age-related macular degeneration". *Int J Ophthalmol* 2018;11(11):1884-1886

Dear Editor,

The study by Kucuk *et al*[1] evaluated the long-term visual and anatomical outcomes in patients who underwent intravitreal ranibizumab (Lucentis, Novartis Pharma AG, Basel, Switzerland) monotherapy to treat neovascular age-related macular degeneration (AMD) and followed-up for at least 2y. The authors concluded that ranibizumab monotherapy can stabilize visual acuity for a mean period of 4y in patients with neovascular AMD.

We would like to address several challenges that have arisen from this study, which can be specifically summarized below.

1) The study was retrospectively conducted with a great number of patients (75.67%) that were lost from the assessment up to the end of the follow-up period. 2) Of the 6 angiographic types of choroidal neovascularization (CNV) existing in neovascular AMD patients, the study revealed only 3 of them, namely, the occult, the predominantly, and the minimally classic CNVs. The other 3 angiographic types [*e.g.* the mixed CNV, the retinal angiomatous proliferation (a distinct form of occult CNV associated with proliferation of intraretinal capillaries[2]), and the polypoidal choroidal vasculopathy (PCV)] were not screened and investigated in the study populations. The indocyanine green angiography (ICGA) should have been used to highlight patients with the 2 angiographic subtypes of PCV[3], namely, subtype 1, PCV sharing a common pathogenic background with neovascular AMD, and subtype 2, idiopathic PCV. Importantly, there is a difference in early treatment response with anti-vascular endothelial growth factor (VEGF) agent between the 2 subtypes of PCV[4]. The treatment would have had to be individualized according to the existing angiographic type. The ICGA should be a standard investigation for all patients with newly diagnosed neovascular AMD, especially those with occult neovascular AMD, to avoid missing this relevant subset. 3) The following pertinent data are missing from the study: the mean time duration of neovascular AMD from diagnosis to the initiation of the treatment; the forms of neovascular lesions that may arise secondary to neovascular AMD [*e.g.* the type 1 located under the retinal pigment epithelium (RPE), the type 2 located in the subretinal space, or the type 3 intraretinal]; the serous and/or hemorrhagic detachment of the neurosensory retina or RPE; the retinal hard exudates; the location of the intraretinal cystoid fluid if it existed in some cases (*e.g.* inner/outer nuclear layers or ganglion cell layer); the qualitative status of the ganglion cell complex, the external limiting membrane (ELM) band, the ellipsoid zone, and the interdigitation zone; the qualitative status of the RPE band-Bruch's membrane complex (*e.g.* pigment migration within the neurosensory retina, RPE porosity, micro-rips or blowouts in the RPE, focal RPE atrophy, and RPE thickening); the quantification of the subretinal hyperreflective material; the prevalence of vitreoretinal interface abnormalities (*e.g.* vitreomacular adhesion/traction and epiretinal membranes); the fluorescein angiographic findings including hyperfluorescence resembling occult CNV lesions in early or mid-phase of angiogram having lacy/stippled appearance, late hyperfluorescence only, and progressive leakage; the prevalence of the outer retinal tubulation; the subfoveal choroidal thickness; and the time to absence of retinal fluid (dryness) as well as the retinal fluid status at the end of the study [*e.g.* presence (wetness) or absence (dryness) of retinal fluid]. The effectiveness of the intravitreal ranibizumab monotherapy in routine clinical practice cannot be evaluated without considering these items. 4) The authors ascertained that the ranibizumab therapy can stabilize the visual acuity score for a mean follow-up time of 3.9y in patients with neovascular AMD. Of note, the mean central macular thickness (CMT)

values before treatment (303 μm) and at the end of the study (251 μm) were under the cutoff (315.2 μm[5]) of the upper level of normal CMT plus 2 standard deviations. However, the final visual and anatomical outcomes of this study were unsatisfactory. Specifically, there was a loss of 2.4 letters in visual acuity, the fibrotic scars developed in 63.5% of the eyes, and the geographic atrophy (GA) was evident in 8.1% of the eyes. Nothing was stated related to the locations of the fibrotic scars (subfoveal/subretinal fibrosis) as well as the GA (foveal/extrafoveal; contiguous with or clearly outside of the area of total CNV lesion). Potential reasons for these suboptimal outcomes include multiple factors. Most likely, there was a permanent VEGF receptor 2-mediated breakdown of the inner blood-retinal barrier and a permanent VEGF receptor 1-mediated rupture of the RPF junctions induced by long-term VEGF overexpression. This permanent chronic retinal capillaropathy caused by persistent subretinal and intraretinal fluid was temporarily relieved by reduction of the edematous component with ranibizumab therapy. However, the pathology was incurable because of irreversible ischemic changes to the macular ganglion cell complex, close to the foveola, with macular edema being a minor factor[6] .

Altogether, regardless of the anti-vascular endothelial growth factor agents used and regardless of the treatment dosing paradigms chosen (*e.g.* treat-and-extend, *pro re nata*, fixed-interval, or escalated algorithm), the efficacy of therapy depends primarily on the promptness of the therapy after the onset of neovascular AMD[6-11].

ACKNOWLEDGEMENTS

All authors were involved in design and conduct of the study; collection, management, analysis and interpretation of the data; and preparation, review or approval of the manuscript.

Conflicts of Interest: Călugăru D, None; **Călugăru M,** None.

REFERENCES

1 Küçük B, Kadayıfçılar S, Eldem B. Assessment of the long-term visual and anatomical outcomes of ranibizumab to treat neovascular age-related macular degeneration. *Int J Ophthalmol* 2018;11(4):645-649.

2 Călugăru D, Călugăru M. Long-term remission of neovaascular age-related macular degeneration with as-needed anti-vascular endothelial growth factor therapy. *Retina* 2017;37(9):108-110.

3 Kawamura A, Yuzawa M, Mori R, Haruyama M, Tanaka K. Indocyanine green angiographic and optical coherence tomographic findings support classification of polypoidal choroidal vasculopathy into two types. *Acta Ophthalmol* 2013;91(6):e474-e481.

4 Jeong S, Sagong M. Short-term efficacy of intravitreal aflibercept depending on angiographic classification of polypoidal choroidal vasculopathy. *Br J Ophthalmol* 2017;101(6):758-763.

5 Grover S, Murthy RK, Brar VS, Chalam KV. Normative data for macular thickness by high-definition spectral-domain optical coherence tomography (Spectralis). *Arch Ophthalmol* 2009;148(2):266-271.

6 Călugăru D, Călugăru M. Long-term results of pro re nata regimen of aflibercept treatment in persistent neovascular age-related macular degeneration. *Am J Ophthalmol* 2017;173(1):145-146.

7 Călugăru D, Călugăru M. High-frequency aflibercept injections in persistent neovascular age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol* 2017;255(10):2067-2068.

8 Călugăru D, Călugăru M. Visual and anatomic outcomes after conversion to aflibercept in neovascular age-related macular degeneration: 12-month results. *Eur J Ophthalmol* 2017;27(4):134.

9 Călugăru D, Călugăru M. Long-term outcomes of aflibercept treatment for neovascular age-related macular degeneration in a clinical setting. *Am J Ophthalmol* 2017;174(2):185-186.

10 Călugăru D, Călugăru M. Comparison of time to retreatment and visual function between ranibizumab and aflibercept in age-related macular degeneration. *Am J Ophthalmol* 2017;174(2):181-182.

11 Călugăru D, Călugăru M. Treat-and-extend therapy using aflibercept for neovascular age-related macular degeneration: a prospective clinical trial. *Am J Ophthalmol* 2017;182(4):204-205.

Authors Reply to the Editor

Dear Editor,

We thank Călugăru *et al* for their interest in our article[1] and their comments.

First of all, the follow up time for each patient was not the same for every patient in the study, and we have already stated in the Discussion that decreasing patient number over the 5 year period was a limitation of our study[1].

In our routine clinical practice ICGA can not be performed in all the patients newly diagnosed with neovascular AMD as the dye can not be found readily at state university hospitals, and even if it is found from outside resources, it is not reimbursed. In other studies as well ICGA has not been performed in all patients for the diagnosis of neovascular AMD[2-3]. Our study is a retrospective study involving cases treated starting from December 2006. At those days it was common practice to classify neovascular AMD according to fluorescein fundus angiogrophy characteristics. As patients with retinal angiomatous proliferation and PCV lesions may differ in their response to anti-VEGF treatment we did not include those cases in the study.

All the patients in the study were treated within 1wk of diagnosis of neovascular AMD. We thank the authors for giving us the chance to add this important information. However many patients especially the ones with unilateral neovascular AMD present late.

Our study was conducted with a time domain optical coherence tomography (OCT; Zeiss Stratus, Oberkochen Germany), which was the only available OCT at our clinic at the beginning of the study, in December 2006, therefore we were unable to perform a detailed OCT analysis with regard to exact location of fibrosis, presence of outer retinal tubulations,

status of ELM, ellipsoid zone and the other stated parameters. Three patients had significant epiretinal membrane both at baseline and at the end of the follow up.

The CMT was measured with time-domain Stratus OCT. The mean macular thickness at fovea taken with Stratus OCT in USA was reported to be 212±20 microns and in Japan 209.5±26.7 microns[4]. Stratus OCT measurements are converted to spectralis measurements with the formula y=1.029x+72.49[5]. When this formula is applied the baseline CMT in our study is 384.28 microns, and the final CMT is 330.77 microns. With regard to location of geographic atrophy, all 6 cases had GA at the fovea.

In our study, the mean period between two visits was long, and the number of injections was less which may have resulted in poorer visual acuity and higher rates of atrophy/scarring, as also reported in other studies[6].

REFERENCES

1 Küçük B, Kadayıfçılar S, Eldem B. Assessment of the long-term visual and anatomical outcomes of ranibizumab to treat neovascular age-related macular degeneration. *Int J Ophthalmol* 2018;11(4):645-649.

2 Cohen SY, Mimoun G, Oubraham H, Zourdani A, Malbrel C, Queré S, Schneider V. Changes in visual acuity in patients with wet age-related macular degeneration treated with intravitreal ranibizumab in daily clinical practice. *Retina* 2013;33(3):474-481.

3 Souied EH, Oubraham H, Mimoun G, Cohen SY, Quere S, Derveloy A. Changes in visual acuity in patients with wet age-related macular degeneration treated with intravitreal ranibizumab in daily clinical practice. *Retina* 2015;35(9):1743-1749.

4 Oshitari T, Hanawa K, Adachi-Usami E. Macular and retinal nerve fiber layer thickness in Japanese measured by Stratus optical coherence tomography. *Clin Ophthalmol* 2007;1(2):133-140.

5 Ibrahim MA, Sepah YJ, Symons RCA, Channa R, Hatef E, Khwaja A, Bittencourt M, Heo J, Do DV, Nguyen QD. Spectral- and time-domain optical coherence tomography measurements of macular thickness in normal eyes and in eyes with diabetic macular edema. *Eye* 2011;26(3):454-462.

6 Rofagha S, Bhisitkul RB, Boyer DS, Sadda SR, Zhang K; SEVEN-UP Study Group. Seven-year outcomes in ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON. *Ophthalmology* 2013;120(11):2292-2299.

Bekir Küçük, Sibel Kadayıfçılar, Bora Eldem

Department of Ophthalmology, Hacettepe University, Ankara 06100, Turkey