• Comment •

Comment on: Impact of switching from ranibizumab to aflibercept on the number of intravitreous injection and follow up visit in wet AMD: results of real-life ELU study

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Dear Editor,

The study by Queguiner *et al*[1] compared the number of follow up visits and intravitreal injections in 33 patients with wet age-related macular degeneration (AMD) treated initially with ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA, USA; phase 1) and then switched to aflibercept (Eylea; Regeneron Pharmaceuticals Inc., Tarrytown, NY, USA; phase 2) because of suboptimal response (loss of treatment efficacy). The number of monthly follow up visits and intravitreal injections was significantly lower in patients treated with aflibercept while the mean visual acuity (VA) evolution (VA final-VA initial) was similar with the both anti-vascular endothelial growth (VEGF) agents and did not show any statistically significant difference between the two phases. We would like to address several challenges that have arisen from this study which can be specifically summarized below.

The comparative efficacy of the treatments with ranibizumab and aflibercept cannot be evaluated because the design of this study lacked a real washout period, which is essential among the 2 phases of treatment in terms of aliased effects. Thus, the impact of the significant carryover effects of ranibizumab in this study may be confounded with direct treatment effects of aflibercept because these effects could not be estimated separately; carryover effects may bias the interpretation of data analysis[2].

The authors detailed the presumed pharmacologic advantages of aflibercept over ranibizumab which were not confirmed by the results of this series (*e.g.*, a higher binding affinity for VEGF-A, activities against VEGF-B and placental-derived growth factor as well as a half-life of aflibercept slightly greater than that of ranibizumab suggesting a longer duration of effect). However, nothing was stated with respect to the two adverse effects of aflibercept that should be considered and accounted for. That is, unlike ranibizumab, which does not impair the choroidal thickness, aflibercept treatment may result in a significant subfoveal choroidal thickness loss[3], by suppressing the choroidal vascular hyperpermeability and vasoconstriction, as well as by more pronounced reductions of choriocapillaris endothelium thickness and number of fenestrations. The thinning of the choroid consisted of the loss of small and medium vessels with baring of larger vessels, as well as the loss of pigmented cells, with clumping of preserved pigmented cells in various regions of the choroid. On short-term, the significant subfoveal choroidal thickness thinning by aflibercept does not seem to result in visual deleterious changes. However, on long-term, the prolonged inhibition of VEGF using aflibercept may affect the integrity of the choriocapillaris, considering the key role of VEGF-A in the normal function of the retina and in the regulation of the survival and permeability of the choriocapillaris. Thus, choroidal vascular impairment may affect the integrity of the retinal pigment epithelium (RPE) and outer retina favoring the development of the fovea-involving geographic atrophy with subsequent visual damaging effects because the choroid is involved in maintaining the perfusion of the outer retinal layers and is the sole source of metabolic exchange (nourishment and oxygen) for the fovea. In addition, through the fragment crystallizable (Fc) domain, aflibercept can bind to the Fc receptor of both choriocapillaris endothelial cells and red blood cells, leading to complement-mediated cell death[4].

The currently available classification of the forms of the macular neovascularization (MNV) based on the state-of-the-art consensus nomenclature for reporting neovascular AMD data[5] has not been used for the assessment of the 5 types of choroidal neovascularization (CNV) included in this series. Accordingly, the types 2 (42.1%) and 5 (36.8%) from this

study belong to the type 1 MNV (originating initially from the choriocapillaris and ingrowing into and within the sub-RPE space); the type 1 (7.9%) of this study corresponds to the type 2 MNV (arising from the choroid, traverses Bruch's membrane and the RPE monolayer and then proliferates in the subretinal space); and the types 3 (10.5%) and 4 (2.6%) of this study belong to the mixed type 2 and type 1 MNV, respectively (neovascularization in the subretinal and sub-retinal pigment epithelial compartments). Noting was stated with regards to the existence or otherwise in this study of the type 3 MNV (originating from the retinal circulation, typically the deep capillary plexus and growing toward the outer retina).

In the assessment of the efficacy of treatment with ranibizumab and aflibercept we considered the current assertion that evaluation of the outcomes has to be guided by anatomical measure data with visual changes as a secondary guide[6]. Accordingly, the actual evaluation of the treatment effectiveness cannot be made due to lack of the anatomical parameters measured by optical coherence tomography (OCT) which had not been analyzed at baseline and at the end of the study. On the other hand there were no significant difference between initial and final VA with each of the anti-VEGF agents used before and after switch. A possible explanation of the lack of change in VA regardless of the treatment used during the study period is the high percentage of patients (78.9%) with the type 1 MNV. Of note, unlike the type 2 MNV (angiogenesis) which responds well to antiangiogenic agents, the type 1 MNV (arteriogenesis) with vascularization limited to the region beneath the RPE with no involvement of subretinal or inner retinal layers, is refractory to anti-VEGF therapy as it contains more mature vessels requiring adjunctive therapy[7].

Concerning the reasons for "switching" the authors featured only one of them, namely the loss of treatment efficacy. The other 2 (tachyphylaxis and tolerance problems) were not detailed for patients in this series with respect to their causes and the ways in which they should have been removed to improve the efficacy of treatment. Specifically, tachyphylaxis could be caused by the depletion or marked reduction of the amount of neurotransmitter responsible for creating the drug's effect or by the depletion of receptors available to which the drug or neurotransmitter can bind. This state was not overcome by switching to aflibercept in this study, a similar drug with different properties. Pharmacodynamic tolerance may be caused by the increased expression of VEGF due to elevated numbers of macrophages in CNV, increased expression of VEGF receptors, changes in signal transduction, or a shift of the stimulus for CNV growth towards other growth factors (*e.g.*, VEGF-B and placental-derived growth factor). The tolerance requires an increased dosage or shorter dosing time intervals to achieve the desire effect[8].

Altogether, the findings of this study showed that switching from ranibizumab to aflibercept in "suboptimal" patients significantly reduce the number of follow up visits and intravitreal injections with a comparable efficacy[1]. However, the authors did not document whether these reductions were beneficial for patients in the sense that they were not only improving patients' quality of life but also increased or otherwise the proportion of patients with inactivation of the disease (lesion drying measured on OCT) after switch to aflibercept at the completion of the study. Of note, taking into account the lack of the structural changes highlighted by OCT at the end of the study and considering only the VA-existing minimal insignificant alterations between the 2 phases of the study, we inferred that the efficiency of the switching procedure remained suboptimal just like it was after ranibizumab therapy.

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

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