• Comment and Response •

Comment on "Intravitreal conbercept injection for neovascular age-related macular degeneration"

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Dear Editor,

We would like to address several issues with the study of Wu *et al*[1], which can be specifically summarized below.

The study was retrospectively conducted with a pretty high proportion of patients (23.80%) lost until the end of the follow-up period.

Nothing was stated with regard to the 6 angiographic types of choroidal neovascularization (CNV) existing in patients with neovascular age-related macular degeneration (AMD), namely, the occult, classic, predominantly classic, minimally classic, mixed CNVs, and polypoidal choroidal vasculopathy (PCV). Indocyanine green angiography (ICGA) should have been used to highlight patients with the 2 angiographic subtypes of PCV, that is, subtype 1, PCV sharing a common pathogenic background with neovascular AMD, and subtype 2, idiopathic PCV[2]. Notably, there is a difference in early treatment response with aflibercept (Eylea, Regeneron, Tarrytown, NY, USA) between the 2 subtypes of PCV[3]. Thus, the subtype 1 polypoidal CNV showed better visual improvement, with higher percentage of polyp regression comparable to that of AMD, than did the subtype 2 idiopathic PCV. The distinct treatment effects may be attributable to their different pathophysiology, genetic backgrounds, and disease progressions. Importantly, the proportion of PCV based on ICGA findings in clinic-based case series of Asian patients with neovascular AMD, was estimated to be fairly high, namely between 20% and 60%[4]. That is why 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.

The following critical data are missing from the study: the previous treatments of patients prior to entry in the study; the classification of the neovascular lesions *e.g.*, as type 1 CNV when expanding through Bruch's membrane into the space beneath the retinal pigment epithelium (RPE) and as type 2 when spreading into the subretinal space; the optical coherence tomography patterns of macular edema (*e.g.*, subretinal fluid, sub-RPE fluid, intraretinal cystic changes, or mixed type) and the location of the intraretinal cystoid fluid if it existed in some cases (*e.g.*, inner/outer nuclear layer or ganglion cell layer) at beginning of the treatment and at the completion of the follow-up period; the existence or not of the disorganization of the retinal inner layers and grading of its severity; the qualitative status of the photoreceptor cell layers; the grading of the RPE changes; the prevalence of vitreoretinal interface abnormalities (*e.g.*, vitreomacular adhesion/traction and epiretinal membranes); the prevalences of fibrotic and nonfibrotic scars and geographic atrophy at presentation and their incidences at month 12; and the proportion of eyes with sustained retina dryness at the end of the follow-up period.

In the assessment of the final outcomes of this study we considered the current assertion[5] that evaluation of outcomes should be guided by the anatomical measure data with visual changes as a secondary guide. Despite significant visual improvements in the best-corrected visual acuity after treatment [*e.g.*, a mean gain of approximately 14 Early Treatment Diabetic Retinopathy Study (ETDRS) letters from baseline], the structural outcomes of this study were unsatisfactory. Thus, the central macular thickness (CMT) decreased significantly from a mean of 547.59 μm at baseline to a mean of 333.87 μm at month 12. Of note, this final CMT value is much more than the cutoff (315.2 μm) for the upper level of the normal CMT (270±22.5 μm)[6] plus 2 standard deviations. We believe that the persistence of high values of the CMT after treatment highlights unresolved macular edema due to insufficient macular deturgescence and indicates that the disease process is still active and progressive requiring further treatment with anti-angiogenic agents.

There is no data concerning the changes produced by conbercept (Lumitin; Chengdu Kanghong Biotech Co, Ltd., China) treatment in the choroid. Of note, unlike bevacizumab (Avastin, Genentech, South San Francisco, CA, USA), which has a protective effect against occlusion of choriocapillaris induced by photodynamic therapy[7], and ranibizumab (Lucentis, Genentech), which does not impair the choroidal thickness[8], aflibercept treatment may result in a significant subfoveal choroidal thickness loss by suppressing the choroidal vascular hyperpermeability and vasoconstriction as well as by more pronounced reductions of choriocapillaris endothelium thickness and number of fenestrations[9].

The authors of this study concluded that intravitreal injection of conbercept appears to significantly improve visual acuity and anatomical outcomes in patients with neovascular AMD with no serious adverse reactions and complications. However, the validation, extrapolation, and generalizability of the authors' conclusion with respect to the efficiency of conbercept treatment and its advantages over other anti-vascular endothelial growth factor treatments can be made only by statistical analyses including all the missing baseline potential predictive factors mentioned by us in addition to the baseline characteristics already evaluated in this study, serving to identify the putative biomarkers influencing functional and anatomic improvements.

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

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Author Reply to the Editor

Dear Editor,

Thanks a lot for Dr. Dan Călugăru and Dr. Mihai Călugăru's comments on our manuscript entitled "Intravitreal conbercept injection for neovascular age-related macular degeneration". We have studied your comments carefully.

The retrospective study is about 66 eyes of 63 patients diagnosed neovascular age-related macular degeneration (AMD) which were received 0.5 mg intravitreal injection of conbercept monthly for 3 consecutive months, 48 eyes of 48 patients were followed at least 1y. 15 patients were lost, because of the length of disease and the status of lesion mostly, also including economic reasons. First of all, thank you for your explanations of the basic knowledge of AMD, which benefited me a lot. This paper is only a retrospective cross-sectional study, excluding special types of choroidal neovascularization (CNV), such as retinal angiomatous proliferation and polypoidal choroidal vasculopathy (PCV). It is true that there is no detailed grouping of CNV types, which will be one of the research directions of our next step.

You point out the directions for us to design research programs and write articles in the future. Thank you very much for your suggestions. At present, I can only answer one of your questions. All patients were treated initially, without any history of anti-vascular endothelial growth factor (VEGF) drugs or surgery. However, no detailed statistics have been made on the classification of CNV and the optical coherence tomography patterns of macular edema *etc*.

The 3+PRN treatment regimen adopted in this study, which does not mean that all patients will stop treatment at 1y. We only performed cross-sectional statistics on the central macular thickness (CMT) of 48 patients who were followed up for 1y, and the patients continued to receive treatment according to the retreatment principle. The CMT is affected by the late scar, the formation of subretinal fibrosis and choroidal atrophy which caused by the organization of the lesion, as shown in the following patient (Figure 1).

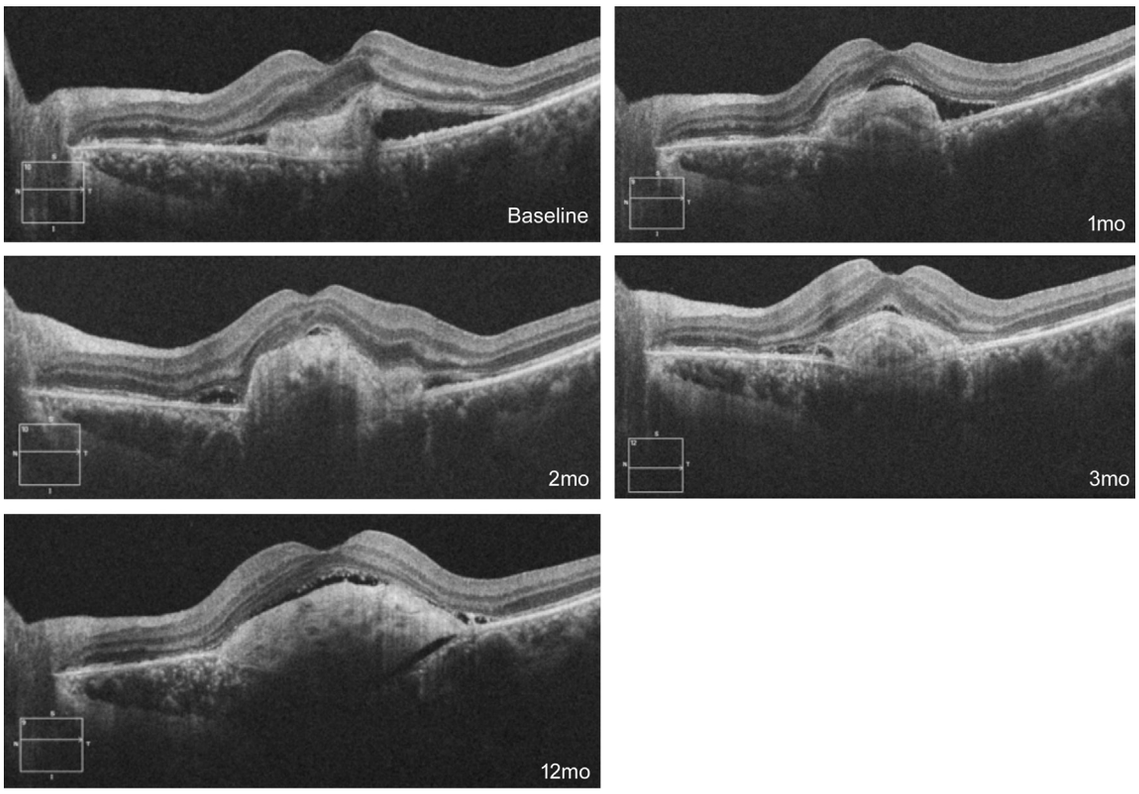

Figure 1 Study eye The CMT measurement of this patient at baseline (461 μm); conbercept injection No.1 was given at this visit. At 1st, 2nd and 3rd month, CMT is 543, 577, and 560 μm, respectively. At 12th month due to choroidal atrophy caused by the organization of the lesion, with an increase in the CMT to 717 μm.

Conbercept and aflibercept are both the fusion protein anti-angiogenesis drugs, which are different from monoclonal antibodies. The effective results of many domestic clinical trials in China, including PHOENIX, ensure that the development and treatment of conbercept is fully recognized by the Food and Drug Administration (FDA) of the United States, so it has obtained the approval of the phase III clinical study through the FDA.

Our conclusion only focuses on the efficacy and safety of conbercept in the treatment of wet AMD, and has not been compared and statistically analyzed with other anti-VEGF drugs, which is not enough to demonstrate that this drug is superior to other anti-VEGF drugs.

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