CORRESPONDENCE

Conbercept for Treatment of Neovascular Age-related Macular Degeneration: Results of the Randomized Phase 3 Phoenix Study

EDITOR:

WE WOULD LIKE TO ADDRESS SEVERAL ISSUES WITH THE study of Liu and associates.[1]

Of the 6 angiographic types of choroidal neovascularization (CNV) existing in neovascular age-related macular degeneration (AMD) patients, the study revealed only 3 of them, namely, the occult, the predominantly classic, and the minimally classic CNVs. The other 3 angiographic types (eg, mixed CNV, retinal angiomatous proliferation, and polypoidal choroidal vasculopathy [PCV]) were not screened and investigated in the study populations. Indocyanine green angiography (ICGA) should have been used to highlight patients with the 2 angiographic subtypes of PCV,[2] 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 aflibercept (Eylea, Regeneron, Tarrytown, New York, 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. Of note, 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.

There were no data on the forms of neovascular lesions existing in the 2 groups of patients (eg, type 1, located under the retinal pigment epithelium [RPE]; type 2, located in the subretinal space; or type 3, intraretinal), as well as the optical coherence tomography patterns of macular edema (eg, subretinal fluid, sub-RPE fluid, intraretinal cystic changes, or mixed type) at the beginning of the treatment with intravitreal conbercept (Lumitin; Chengdu Kanghong Biotech Co, Ltd, Chengdu, China) and the location of the intraretinal cystoid fluid if it existed in some cases (eg, inner/outer nuclear layers or ganglion cell layer).

Initially, a comparison had to be carried out between the 2 groups of patients to establish whether or not they are comparable. Accordingly, this comparison should have been conducted only if there were no significant baseline differences between all variables of these 2 groups. Of note, there were obvious baseline differences between the conbercept group and the sham control group concerning the following findings: the age of patients, the previous treatment applied, the central retinal thickness, the leakage area on fluorescein angiography, and the angiographic types of CNV.

There are no data with regard to the changes produced by conbercept treatment in the choroid. Notably, unlike bevacizumab (Avastin; Genentech, South San Francisco, California, USA), which has a protective effect against occlusion of choriocapillaris induced by photodynamic therapy,[5] and ranibizumab (Lucentis, Genentech), which does not impair the choroidal thickness,[6] aflibercept treatment may result in a significant subfoveal choroidal thickness loss by suppressing the choroidal vascular hyperpermeability and vasoconstriction.[6]

The following relevant data are missing from the study: the existence or not of the disorganization of the retinal inner layers; the qualitative status of the photoreceptor cell layer (outer nuclear layer thinning, external limiting membrane band disruption, discontinuity of the ellipsoid zone, and the interdigitation zone loss); the grading of the RPE changes (pigment migration within the neurosensory retina, RPE porosity, microrips or blowouts in the RPE, focal RPE atrophy, RPE thickening, presence of reticular pseudodrusen); and the proportion of eyes with sustained retina dryness at the end of the study.

Altogether, the validation, extrapolation, and generalizability of the authors' conclusion concerning 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, which serve as potential prognosticators influencing functional and anatomic improvements.

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REFERENCES

1. Liu K, Song Y, Xu G, et al. Conbercept for treatment of neovascular age-related macular degeneration: results of the randomized phase 3 Phoenix study. *Am J Ophthalmol* 201810.1016/j.ajo.2018.08.026. 2018.08.24.
2. Kawamura A, Yuzawa M, Mori R, et al. Indocyanine green angiographic and optical coherence tomographic findings support classification of polypoidal choroidal vasculopathy into two types. *Acta Ophthalmol* 2013;91(6):e474–e481.
3. 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.
4. Cheung CMG, Lai TYY, Ruamviboonsuk P, et al. Polypoidal choroidal vasculopathy. Definition, pathogenesis, diagnosis, and management. *Ophthalmology* 2018;125(5):708–724.
5. Mukai R, Kishi S, Sato T, et al. Protective effect of intravitreal bevacizumab and sub-tenon triamcinolone acetonide against occlusion of choriocapillaris induced by photodynamic therapy. *Ophthalmologica* 2010;224(5):267–273.
6. Gharbiya M, Cruciani F, Mariotti C, et al. Choroidal thickness changes after intravitreal antivascular endothelial growth factor therapy for age-related macular degeneration: ranibizumab versus aflibercept. *J Ocul Pharmacol Ther* 2015;31(6):357–362.

REPLY

WE WOULD LIKE TO REPLY TO THE ISSUES ADDRESSED BY Dan Călugăru and Mihai Călugăru.

In our study, 3 types of choroidal neovascularization (CNV) of neovascular age-related macular degeneration (AMD) were revealed: the occult, the predominantly classic, and the minimally classic. The classification was based on the results of Fundus Fluorescein Angiography (FFA). This classification has been adopted not only in the PHOENIX study, but also in the previous VIEW study (aflibercept vs ranibizumab),[1] MARINA study (ranibizumab vs sham),[2] and ANCHOR study (ranibizumab vs verteporfin).[3] Though there are now different ways to classify CNV according to optical coherence tomography, optical coherence tomography angiography, or indocyanine green (ICG) angiography, the way we used in the study was still the classic method as used in the previous anti-VEGF studies.

Considering the prevalence of polypoidal choroidal vasculopathy (PCV) in Chinese people, the PHOENIX study initially planned to exclude PCV patients by using ICG angiography examination, which was regarded as the gold standard for diagnosing PCV. However, the supply of ICG agents ran out in the year 2012 in China, which made it impossible to give patients ICG examinations. Without ICG, PCV could not be accurately diagnosed.

In the end, pooling PCV may influence interpretation of the data, which we have already stated in the paper and analyzed in the discussion.

Best-corrected visual acuity (BCVA) was our main outcome measure. There is no statistical difference of BCVA between the 2 groups of patients at baseline, so it is for sure that the 2 groups are comparable.

We find several suggestions from the correspondence letter quite constructive and we really appreciate that. It should be noted that the main purpose of the present paper was to demonstrate the main results of the PHOENIX study. In the future, we would consider further analyzing the data, including the changes in the choroid and different layers of the retina.

Till now, other anti-VEGF agents cannot support this dosing regimen. Treatment using conbercept has the potential to be a more patient-friendly treatment than are existing treatments.

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REFERENCES

1. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology* 2012;119(12):2537–2548.
2. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006;355(14):1419–1431.
3. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006;355(14):1432–1444.

Boston Type I Keratoprosthesis: Antibacterial Resistance and Microbiota Evaluation of Soft Contact Lenses

EDITOR:
WE READ WITH GREAT INTEREST THE ARTICLE BY TORRES-Netto and associates titled "Boston Type I Keratoprosthesis: Antibacterial Resistance and Microbiota Evaluation of Soft Contact Lenses."[1] Infections after Boston keratoprosthesis are devastating, and any evidence of an antibacterial resistance pattern in this field will be an essential addition to the existing literature.

However, we have some concerns. The authors concluded that "prophylaxis with topical 5% povidone-