Letter to the Editor: Preventing Progression in Nonexudative Age-Related Macular Degeneration With Subthreshold Laser Therapy: A Systematic Review

Dear Editor,

We have read the manuscript entitled "Preventing Progression in Nonexudative Age-Related Macular Degeneration with Subthreshold Laser Therapy: A systematic Review" by Eng et al. (Vol. 50, No. 3). I would like to congratulate the authors for this successful systematic review and make some contributions. We believe that our insight can maximize the interpretation of their results.

In the article, it has been indicated that subthreshold retinal laser therapy is effective for reduction of drusen and has the potential to improve vision in patients with nonexudative age-related macular degeneration (AMD). The systematic review also showed that the therapy did not appear to show benefit (or harm) associated with the development of choroidal neovascularization (CNV) or geographic atrophy. After reviewing the nine studies that evaluated the occurrence of CNV cited in the systematic review, it came to our attention that none of them used optical coherence tomography angiography (OCTA) for their baseline analysis and follow-up. We think OCTA imaging should be included in the studies evaluating the occurrence of CNV. In a recent article, de Oliveira Dias et al. showed that swept-source OCTA identified subclinical macular neovascularization in 14.4% of 160 eyes with nonexudative AMD. In addition, their article showed that the risk of exudation at 1 year increases dramatically by a factor of 15.2 when compared to those without a subclinical CNV.[1] The use of fluorescein angiography, OCT, and funduscopic examination,[2] such as the case of the cited studies, could underestimate subclinical and occult CNVs. When designing a study on the laser for intermediate macular degeneration, OCTA should be used to differentiate two groups: those eyes with occult CNV and those without it. Subthreshold laser in eyes with occult CNV may have different outcomes, and these eyes may evolve faster to a classic CNV. This may be the reason why previous studies did not meet statistical significance in the prevention of wet AMD.

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Disclosures: The authors report no relevant financial disclosures.

Reply to Letter to the Editor: Preventing Progression in Nonexudative Age-Related Macular Degeneration With Subthreshold Laser Therapy: A Systematic Review

We thank the authors of the recent letter for their interest in our manuscript and for taking the time to highlight the value of implementing swept-source optical coherence tomography angiography (OCTA) in future trials that investigate subthreshold laser treatment for nonexudative AMD. The points raised by the authors are important considerations when interpreting the outcome of past age-related macular degeneration (AMD) trials with laser therapy

doi: 10.3928/23258160-20190905-12

and anti-vascular endothelial growth factor agents alike.

Similar to the cited paper by de Oliveira Dias et al., an earlier paper by Miller et al. also found the mean choroidal neovascularization (CNV) area measurements obtained by OCTA were significantly larger than area measurements of the same lesions using spectral-domain-OCT (SD-OCT).[1,2] The authors suggest that the higher scanning densities of OCTA allows for enhanced penetration through the retinal pigment epithelium and increases signal detection from deeper retinal layers. It is reasonable to also conclude that OCTA is also superior to SD-OCT in detecting subclinical CNVs. The better sensitivity of OCTA in detecting total lesion size may influence the predicted growth of CNVs and the retreatment decision.

We agree that this new imaging technology could be used to identify and stratify study participants who have a higher predisposition for developing CNV during the course of a clinical trial or would have needed more frequent retreatment. To our knowledge, no study has identified a difference in response to subthreshold laser therapy between eyes with and without subclinical CNV. Thus, eyes with subclinical CNVs may respond differently to subthreshold laser and may have contributed to the lack of significance found in these prior studies.

We remain optimistic that subthreshold laser has the potential to slow the progression toward exudative AMD. Although most of the studies reviewed in our manuscript were completed before the arrival of OCTA, a multicenter, prospective study sponsored by Boston Image Reading Center is currently using OCTA to track the natural history of 450 participants with nonexudative AMD (NCT03688243). We eagerly await the results from that study to determine if eyes with subclinical CNVs have different progression rate to exudative AMD and require a different treatment strategy.

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Disclosures: The authors report no relevant financial disclosures.