Photobiomodulation For Dry AMD: Ready For Its Day in The Sun?

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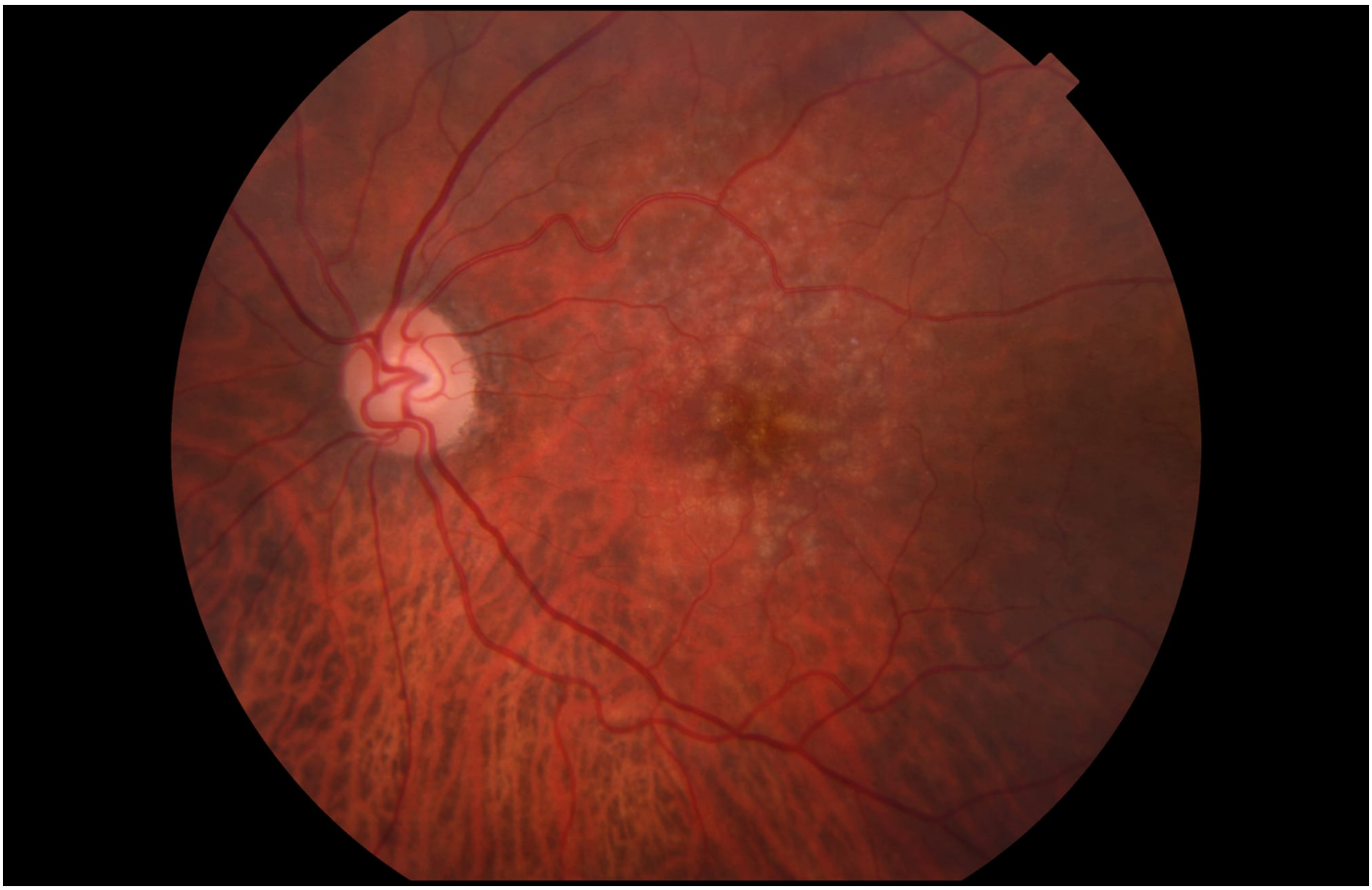

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Saumya M. Shah, MD, Daniel Su, MD, David S. Boyer, MD, of Retina Vitreous Associates Medical Group review what is known, and promised, about photobiomodulation, following the completion of 2 major trials.

In exudative age-related macular degeneration (wet AMD), significant strides — such as the development of anti-vascular endothelial growth factor (anti-VEGF) therapies — have pushed the treatment possibilities forward and rewritten the likely course of the disease for many patients. However, for most patients, AMD is nonexudative (dry), and treatments for those patients remain largely limited.[1,2] Recent developments in the form of complement inhibitor treatments (such as pegcetacoplan and avacincaptad pegol) are showing promise in slowing progression rates of geographic atrophy (GA) — an advanced, vision-threatening form of dry AMD affecting nearly 1 in 5

patients. But for the dry AMD patients without GA, a tremendous gap in therapeutic avenues persists.[3-5]

Photobiomodulation (PBM) is an emerging therapy that has shown promising potential as a possible treatment for patients with nonexudative intermediate AMD. In truth, this low-level laser therapy (LLLT) technology has existed for more than 50 years, and researchers have been reviewing its potential ocular applications for at least 20 of those years. But with a CE mark issued in 2018, the completion of a major clinical trial last year, and this year's appeal to the US Food & Drug Administration (FDA) by a manufacturer to market the technology as a noninvasive treatment option for dry AMD, PBM seems ready to shine.[6,7]

Its utilization will require an understanding of the technology's history as it applies to dry AMD, and the lessons learned from the extensive clinical trials it has undergone.

How Photobiomodulation Works

Mechanistically, there are a multitude of ways in which photobiomodulation is hypothesized to assist in treating nonexudative AMD. It involves the use of targeted wavelengths of visible light to near-infrared (NIR) spectrum (500-1000 nm) produced by a noncoherent light source such as light-emitting diodes (LEDs) or a laser. This light induces a chemical reaction at the cellular level in the electron transport chain, specifically against an enzyme called cytochrome c oxidase within complex IV. Activation of complex IV directly increases mitochondrial activity within the cells in retinal layers such as RPE cells, ganglion cell nuclei, and inner/outer plexiform nuclei, which then promotes adenosine triphosphate (ATP) production, the cell's major source of energy.[8,9] Additionally, the NIR also decreases nitric oxide activity, which inhibits complex IV, thereby indirectly increasing complex IV activity. This then leads to improved photoreceptor function.

Photobiomodulation has been shown to decrease the activity of

inflammatory markers such as vimentin, glial fibrillary acidic protein (GFAP), and tumor necrosis factor (TNF).*10,11* It also has been found to directly reduce expression of C2 and C3 complement expression within the outer retina.[12,13] By these anti-inflammatory effects, PBM may downregulate the complement factor cascade, which plays a major role in the progression of AMD.

Finally, photobiomodulation can also alter gene expression, leading to rescued mitochondrial function that then caused neuroprotective effects on blue-light damaged murine primary photoreceptors.[14,15]

Photobiomodulation On Trial

The use and effectiveness of PBM for AMD has been tested in several studies. In a 2008 study, a semiconductor laser diode emitting continuous 670 nm light was given to 348 eyes in 4 treatments for more than 2 weeks. Best-corrected visual acuity (BCVA) improved significantly, but no details were provided regarding VA measures, type of AMD, or any structural parameters.[16]

The Toronto and Oak Ridge Photobiomodulation Study for Dry Age-Related Macular Degeneration (TORPA; ClinicalTrials.gov Identifier: NCT00940407) studied the impact of PBM on patients with intermediate AMD with VA between 20/20 and 20/200. Eighteen patients were treated with 2 transpupillary diode lasers for 18 treatments spanning 6 weeks and primary endpoints were changes in BCVA and contrast sensitivity. Statistically significant improvements were noted in BCVA and contrast sensitivity at 6 months and 1 year after treatment, while fixation stability remained unchanged.[17]

This was followed by the TORPA II study, which expanded on the previous study by including patients with vision worse than 20/200. Primary outcome measures were changes in BCVA and CS from baseline. Secondary efficacy endpoints included changes in optical coherence tomography (OCT) and

fundus autofluorescence (FAF) at 3 months compared with baseline. At 3-month follow-up after photobiomodulation treatment, there was an average of +5.9 letter improvement, with 59.5% of patients having gained more than 1 line on the Snellen visual acuity chart. Drusen volume and thickness was also noted to be significantly reduced, but the overall central retinal thickness remained the same.[18]

While the TORPA II study showed a promising role for PBM in the treatment of dry AMD, the sample size was small, a randomized control group was not included, and the follow-up time only extended to 3 months.

LIGHTSITE Clinical Trials

Following this, the LIGHTSITE I (ClinicalTrials.gov Identifier: NCT02725762) trial was the first single-center randomized sham-controlled study to evaluate PBM efficacy in AMD.[19] It used the Valeda Light Delivery System (LumiThera, Inc., USA), which emits 3 distinct wavelengths of light, including yellow (590 nm), red (660 nm), and near-infrared (850 nm) within 250 seconds in a total of 4 phases. Patients received 9 sessions of treatment within 3 to 4 weeks at baseline and after 6 months. Forty-six eyes of 30 patients with intermediate dry AMD and vision between 20/40 and 20/200 were enrolled. BCVA was noted to increase by an average of 4 letters, then declined to baseline at the 6-month follow up and was noted to once again increase after the retreatment at 6 months, followed by another decrease in BCVA to baseline at the subsequent 6-month follow-up. This suggests a possible role for the need for consistent repetitive therapy to maintain efficacy. A significant decrease in drusen volume was also noted in patients treated with PBM vs the control group.[19]

This was followed by the LIGHTSITE II (ClinicalTrials.gov Identifier: NCT03878420) study, which further explored the efficacy of PBM in 53 eyes of 44 patients with intermediate dry AMD and BCVA between 20/32 and 20/100.[20] This was a randomized controlled multi-center study with the

primary outcome of change in BCVA between baseline at 9-month follow-up. The PBM-treated group had a significant improvement in vision (2.3 letters) and had a slower rate of growth of GA lesion size. However, the limitations of this study were its small sample size and relatively higher rate of patient drop-out rate.

These limitations in the prior LIGHTSITE studies led to the development of the LIGHTSITE III study. This was a prospective randomized controlled multi-center study including 148 eyes of 100 patients with intermediate dry AMD and BCVA between 20/32 and 20/100. Over a 24-month period, patients received six series of PBM or sham treatments using the Valeda system (LumiThera, Inc.), administered 3 times per week for 3 to 4 weeks and repeated every 4 months. The 13-month preliminary results showed a significant improvement in BCVA (5.5 letters) in the PBM-treated group with 55% of patients having an average of 9.7 letter improvement compared to the control group.[21] The 24-month follow-up results were recently published and showed a similar statistically significant increase BCVA in the PBM groups compared with the control group (5.9 vs 1.0 letters; P =.0015). Only 1.1% of the PBM-treated patients progressed to GA, compared with 9.1% of the control group who developed new GA.

The conversion rate from dry to wet AMD was higher for the PBM group (5.4% vs 1.8% for the control group). Approximately 58% of the PBM-treated eyes experienced a gain of more than 5 letters, with a mean letter gain of 8.5±0.5. Similar to the 13-month results, at 24 months of follow-up, 5.7% of PBM-treated patients vs 21.6% of the control group had progressed to new GA (P =.025). There were minimal safety risks and high patient compliance at the 24-month mark.[22] An extension of the trial to a third year is in progress investigating longer term treatment.

A Future in AMD Management

There are some limitations in comparing these results to other

photobiomodulation studies, including varying wavelengths, time intervals of treatment , and length of sessions across different studies, as well as lack of specificity regarding which stage of AMD the treatment is best targeted towards. Further research is needed with larger sample sizes and longer follow-up times to determine the appropriate standards for which patients would most benefit from treatment, as well as the parameters for the most efficacious PBM application.

Additionally, thorough investigation also needs to be conducted in determining whether PBM will be more applicable to prevent progression of early AMD or later stage GA, as well as the most appropriate imaging modalities for monitoring the effects of PBM. In any event, these studies show a promising role for the use of PBM in patients with intermediate AMD and pave the way for more effective treatment modalities in the future for patients with AMD.

- Wong WL, Su X, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health*. 2014;2(2):e106-16. doi:10.1016/S2214-109X(13)70145-1