PHOTOBIOMODULATION THERAPY FOR LARGE SOFT DRUSEN AND DRUSENOID PIGMENT EPITHELIAL DETACHMENT IN AGE-RELATED MACULAR DEGENERATION

A Single-Center Prospective Pilot Study

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Purpose: To evaluate visual acuity and morphologic changes after photobiomodulation (PBM) for patients affected with large soft drusen and/or drusenoid pigment epithelial detachment associated with dry age-related macular degeneration.

Method: Twenty eyes with large soft drusen and/or drusenoid pigment epithelial detachment age-related macular degeneration were included and treated using the LumiThera Valeda Light Delivery System. All patients underwent two treatments per week for 5 weeks. Outcome measures included best-corrected visual acuity, microperimetry-scotopic testing, drusen volume, central drusen thickness, and quality of life score at baseline and month 6 (M6) follow-up. Data of best-corrected visual acuity, drusen volume, and central drusen thickness were also recorded at week 5 (W5).

Results: Best-corrected visual acuity significantly improved at M6 with a mean score gain of 5.5 letters ($P = 0.007$). Retinal sensitivity decreased by 0.1 dB ($P = 0.17$). The mean fixation stability increased by 0.45% ($P = 0.72$). Drusen volume decreased by 0.11 mm^3 ($P = 0.03$). Central drusen thickness was reduced by a mean of 17.05 μm ($P = 0.01$). Geographic atrophy area increased by 0.06 mm^2 ($P = 0.01$) over a 6-month follow-up, and quality of life score increased by 3,07 points on average ($P = 0.05$). One patient presented a drusenoid pigment epithelial detachment rupture at M6 after PBM treatment.

Conclusion: The visual and anatomical improvements in our patients support previous reports on PBM. PBM may provide a valid therapeutic option for large soft drusen and drusenoid pigment epithelial detachment age-related macular degeneration and may potentially slow the natural course of the disease.

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Age-related macular degeneration (AMD) accounts for approximately 10% of blindness in developed countries.[1] Disease progression unavoidably leads to significant visual loss and severely affects quality of life (QoL).[1] Early stages of AMD are characterized by accumulation of membranous lipidoproteic debris, including lipofuscin, extracellular material, and complement deposition.[1] The advanced late-stages of AMD are usually divided into exudative AMD (also called wet AMD) or geographic atrophy (GA) (also called dry AMD).[2] Dry AMD is characterized by complete or incomplete retinal pigment epithelium (RPE) and complete or incomplete outer retinal atrophy.[1,2] The pathogenesis of AMD is mainly genetically driven but remains partly understood.[2] Nevertheless, there is evidence that RPE dysfunction is involved in dry

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AMD.[1,2] It is caused by mitochondrial dysfunction, oxidative stress, lipidic deposition, and inflammation.[2] The early visible changes in the macular area are drusen and pigment changes.[1] Neovascular AMD is commonly treated by intravitreal injections of antivascular endothelial growth factor.[3] Limited treatment options are available for dry AMD, and only lifestyle changes and the use of antioxidant supplements can be proposed. A consequential alternate treatment plan is needed for the most frequent form of AMD.[3]

Photobiomodulation (PBM), also called low-level light therapy, involves specific use of selected wavelengths of visible to near infrared (NIR) light (510–800 nm). The light used for PBM is usually produced by noncoherent light source such as light-emitting diodes or a laser source.[3] The PBM procedure to selected tissues produces several positive cellular effects.[3] The entire mechanisms of this therapy are still not completely elucidated. It was demonstrated that the selective wavelengths increase the activity of mitochondrial cytochrome c oxidase and subsequently increase mitochondrial membrane activity and ATP production.[3] PBM therapy can also modulate retinal genes upregulation or downregulation.[4] The gene expression analysis identified an upregulation indicating rescued mitochondrial function.[5] Natoli et al confirmed increased expression of 126 neuroprotective retinal genes after PBM.[6,7] The antiinflammatory effect of PBM might be mediated by complement cascade downregulation.[4] Several studies analyzed the mitochondrial activity and demonstrated inhibition of intracellular superoxide but also increased expression of manganese superoxide dismutase, leading to antioxidative effect.[4] PBM seems as a potential noninvasive therapeutic option in several disorders.[8,9] A beneficial effect has been demonstrated on mitochondrial dysfunction, oxidative stress, and complement dysregulation.[3] For these reasons, it was proposed in prevention of macular apoptotic cell death in particularly against progression of GA in patients affected by AMD.[3]

The aim of this study was to evaluate visual acuity and morphologic changes after PBM in patients affected with large soft drusen and/or drusenoid pigment epithelial detachment (dPED) associated with dry AMD.

Methods

Type of Study

A prospective single-arm pilot study of 20 eyes (20) with dry AMD, age-related eye disease study (AREDS) categories 3 to 4, presenting soft drusen and/or dPED were treated using the LumiThera Valeda Light Delivery System (LumiThera, Inc. Poulsbo, Washington, DC).

Procedure and PBM Treatment

After pupillary dilatation using two drops of tropicamide placed in the treated eye with 15 minutes delay starting 30 minutes prior PBM treatment. All patients undertook two treatments per week for 5 weeks, a total of 10 treatments. The Valeda Light Delivery System deliver in 250 seconds (s) exposure time three different ranges of wavelengths in the yellow (590 nm; 4 mW/cm^2), red (660 nm; 65 mW/cm^2) and NIR (850 nm; 0.6 mW/cm^2) in 4 phases.[4] In the first and third phases, the yellow and NIR light are pulsed during 35 seconds on an open eye. In the second and fourth phases, a continuous red light is exposed during 90 seconds on a closed eye.[4] Valeda is CE-approved in the EU. Valeda was not FDA-approved in the United States at the time of this report.

Ethic Statement

Our report was conducted allowing to the International Conference on Harmonization Guidelines for Good Clinical Practice and the tenets of the Declaration of Helsinki. The ethic committee of the Macula French Federation gave its agreement to perform this pilot study. All patients in our study provided written informed consent.

Endpoints/Outcomes

Outcomes included changes from baseline in best-corrected visual acuity (BCVA), near visual acuity, retinal sensitivity (RS), fixation loss (FL), drusen volume (DV), central drusen thickness (CDT), GA surface, and QoL score.

Participant Criteria

Inclusion criteria were patients affected with dry AMD with at least one large soft drusen (diameter >125 μm) and/or dPED (diameter >250 μm) affecting the center of the macula diagnosed on multimodal imaging including fundus photographs, fundus blue autofluorescence, fluorescein and indocyanine green angiography, spectral domain optical coherence tomography (SD-OCT), and swept source optical coherence tomography angiography (SS-OCTA); subfoveal choroidal thickness >200 μm; age older than 50 years; BCVA in the treated eye between 20/200 and 20/20 Snellen chart (Early Treatment Diabetic Retinopathy Study (ETDRS) equivalent to 35 and 85 letters); and BCVA in the fellow eye better than or equal to 20/40 Snellen chart (ETDRS equivalent to 70 letters). Exclusion criteria were neovascular AMD, GA $>$ 0.5 mm, hypertensive or diabetic retinopathy, glaucomatous optic neuropathy, ocular surgery in the last

3 months or planned for the following 6 months in the study eye, all medications and systemic disorders inducing ocular involvements and/or visual dysfunction, migraine, epilepsy, and all allergies to adhesives or substance used.

Measurement of BCVA

BCVA was evaluated using a Snellen chart at 20 feet and then converted to equivalent ETDRS letters score. The BCVA line evaluated using the Snellen chart at 20 feet was validated in our study only when all letters of the line have been read by the patient. Near visual acuity was measured on the French Parinaud chart. RS and FL were recorded by microperimetry-scotopic testing after mydriasis and 40 minutes of dark adaptation using C10 to 2 grid with 68 tested points (MAIA; CenterVue, Padova, Italy). QoL score was assessed by using the Visual Function Questionnaire (VFQ-25) composite score. Fundus photographs by Solix FullRange OCT (Optovue Inc, Freemont CA). GA was assessed using blue autofluorescence imaging with 488 nm wavelength (SPECTRALIS OCT; Heidelberg Engineering). HRA SPECTRALIS system (Heidelberg Engineering, Heidelberg, Germany) was performed at baseline and at M6 for the acquisition of volume scans (15 × 10°) comprising the 49 parallel lines of OCT B-scans for the study eye. The automated real-time function averaged the 16 images for each scan. The volumetric analysis at baseline and at M6 of the large soft drusen and dPED was measured by using SPECTRALIS HRA system after semiautomatic segmentation of the RPE and Bruch membrane within the central 6 mm diameter of the macula comprising the 49 lines of the OCT B-scans. The automatic segmentation using SPECTRALIS HRA system was analyzed on each line of the 49 B-scan OCT by two expert readers (SYC and HO) and manually adjusted when the software failed in the recognition of the Bruch membrane and RPE lines. A third expert reader has been requested to make the final decision when the two experts did not agree (EHS). The volumetric analysis was compared between baseline and M6. GA area at baseline was quantitatively measured by the Region Finder Analyzer (Region Finder Software Heidelberg Engineering; Heidelberg Engineering) in the 488-nm blue autofluorescence images. The homogenous hypoautofluorescent surface of the blue autofluorescence images prior and M6 after PBM was assessed to evaluate the growth rate. This surface analysis was calculated by two expert readers and confirmed by a third reader (EHS) when the two expert readers disagree (SYC and HO). SS-OCTA AngioVue Retina 6 x 6 mm by Solix FullRange OCT (Optovue Inc, Freemont CA) was used to detect any quiescent macular neovascularization.

Assessments at W5

BCVA of 17 of 20 patients was evaluated the day of the 10th treatment, just before the PBM session, using the Snellen chart at 20 feet and then converted to ETDRS letters score. At this point, patients beneficiated from 9/10 PBM sessions. The 3 of 20 remaining patients came at this last session of treatment with an already dilated pupil, and then, BCVA measurement was not performed for these three patients. Data of DV and CDT were recorded using HRA SPECTRALIS system (Heidelberg Engineering, Heidelberg, Germany) with an acquisition of volume scans (15 × 10°) comprising the 49 parallel lines of OCT B-scans for the study eye. The automated real-time function averaged the 16 images for each scan. The volumetric analysis at W5 was performed with the same technique as at baseline and M6.

Adverse Events

All adverse events reported by patients were recorded over the time.

Statistical Analysis

The difference between baseline and M6 variables was assessed with the Wilcoxon signed-rank test. A value of $P < 0.05$ was considered significant. Stata 17 SE software was used for statistical analysis (StataCorp, TX).

Results

Participant's characteristics are summarized in Table 1. This study included 20 eyes of 15 women and 5 men. The mean age was 74.45 years (51–87). The left eye was treated in 12 patients and the right eye in eight patients. The rate of eyes with AREDS category 3 AMD was 75% (15/20) and stage 4 was 25% (5/20).

Outcomes at M6, compared with baseline: BCVA improved significantly with a mean score gain of 5.5 letters ($P = 0.007$). Near vision improved with a mean score or 1.15 line of the Parinaud chart. The QoL score (VFQ-25) increased by 3.07 on average ($P = 0.05$). RS decreased by 0.1 dB on average ($P = 0.17$). The mean fixation stability increased by 0.45% ($P = 0.72$). DV decreased by 0.11 mm^3 ($P = 0.03$) on average. CDT was reduced by a mean of 17.05 μm ($P = 0.01$) (Figures 1, 2). GA surface increased by a mean of 0.06 mm^2 ($P = 0.01$) (Figure 3) (Table 2). Outcomes

Table 1. Summary Table of Results Comparison After Photobiomodulation Treatment From Baseline to M6 in Participants of Our Study

Patient	Age	Sex	AREDS	BCVA BL	BCVA W5	BCVA M6	DV BL	DV W5	DV M6	CDT BL	CDT W5	CDT M6	GA BL	GA M6	RS BL	RS M6	FL BL	FL M6	QOL BL	QOL M6
1	**86**	**F**	**3**	**80**	_	**75**	**0,31**	**0,24**	**0,14**	**89**	**43**	**32**	**0**	**0,03**	**23,2**	**23,4**	**0**	**11**	**72,76**	**75,33**
2	**69**	**F**	**4**	**75**	**75**	**85**	**2,13**	**2,13**	**0,43**	**132**	**96**	**16**	**0,26**	**0,3**	**16,8**	**22,9**	**0**	**0**	**71,98**	**83,14**
3	**74**	**F**	**3**	**80**	**80**	**80**	**0,5**	**0,48**	**0,48**	**34**	**42**	**36**	**0**	**0**	**23,2**	**22,1**	**13**	**0**	**83,07**	**83,07**
4	**82**	**F**	**3**	**80**	**85**	**85**	**0,6**	**0,54**	**0,5**	**38**	**38**	**27**	**0**	**0**	**23,6**	**23,9**	**14**	**0**	**86,28**	**94,32**
5	**74**	**F**	**3**	**70**	**60**	**75**	**1,41**	**1,42**	**1,83**	**342**	**351**	**289**	**0**	**0,8**	**16,3**	**14,6**	**0**	**0**	**63,14**	**41,80**
6	**68**	**F**	**4**	**70**	**75**	**80**	**0,48**	**0,54**	**0,49**	**37**	**43**	**22**	**0,24**	**0,27**	**20,5**	**19,3**	**11**	**0**	**45,75**	**48,92**
7	**73**	**M**	**3**	**85**	**85**	**85**	**0,52**	**0,56**	**0,46**	**75**	**70**	**41**	**0,42**	**0,46**	**21,9**	**21,8**	**20**	**0**	**71,98**	**83,51**
8	**56**	**M**	**3**	**85**	**85**	**85**	**1,5**	**1,35**	**1,48**	**204**	**181**	**164**	**0**	**0**	**22,9**	**22,2**	**0**	**13**	**75,33**	**83,72**
9	**74**	**F**	**3**	**70**	**80**	**85**	**0,8**	**0,75**	**0,67**	**38**	**38**	**33**	**0**	**0**	**21,3**	**22,6**	**0**	**0**	**72,76**	**76,13**
10	**51**	**M**	**3**	**80**	**80**	**85**	**0,66**	**0,66**	**0,7**	**151**	**152**	**154**	**0**	**0**	**26**	**25,7**	**0**	**13**	**80,04**	**88,49**
11	**70**	**F**	**3**	**85**	**85**	**85**	**0,74**	**0,81**	**0,69**	**70**	**68**	**45**	**0**	**0**	**23,1**	**21,6**	**0**	**0**	**83,07**	**83,14**
12	**86**	**F**	**4**	**65**	**70**	**80**	**0,3**	**0,36**	**0,34**	**103**	**122**	**120**	**0,31**	**0,33**	**21**	**20,1**	**0**	**0**	**46,99**	**67,96**
13	**69**	**F**	**3**	**75**	_	**85**	**0,97**	**1,02**	**1,02**	**142**	**162**	**161**	**0**	**0**	**23**	**23,5**	**0**	**0**	**80,07**	**75,73**
14	**83**	**F**	**3**	**70**	_	**75**	**0,5**	**0,46**	**0,46**	**62**	**52**	**56**	**0**	**0**	**23,8**	**21,9**	**0**	**0**	**83,75**	**87,91**
15	**76**	**F**	**3**	**70**	**60**	**60**	**0,94**	**0,82**	**0,86**	**260**	**231**	**255**	**0**	**0**	**11,8**	**11,3**	**0**	**13**	**41,52**	**54,12**
16	**77**	**F**	**4**	**85**	**85**	**85**	**0,75**	**0,64**	**0,6**	**59**	**47**	**49**	**0,07**	**0,07**	**12,4**	**11,6**	**0**	**0**	**71,06**	**57,31**
17	**87**	**M**	**4**	**75**	**80**	**85**	**0,58**	**0,49**	**0,5**	**25**	**18**	**15**	**0,22**	**0,38**	**15,1**	**14,3**	**0**	**0**	**83,63**	**80,86**
18	**86**	**F**	**3**	**80**	**80**	**85**	**0,48**	**0,46**	**0,5**	**20**	**18**	**26**	**0**	**0**	**21,4**	**19,7**	**11**	**10**	**50,01**	**50,97**
19	**79**	**M**	**3**	**55**	**70**	**85**	**0,49**	**0,47**	**0,47**	**25**	**31**	**32**	**0**	**0**	**21,7**	**24,1**	**0**	**0**	**93,93**	**97,91**
20	**69**	**F**	**3**	**85**	**85**	**85**	**0,61**	**0,61**	**0,57**	**39**	**34**	**31**	**0**	**0**	**21,1**	**21,4**	**0**	**0**	**93,75**	**97,91**

AREDS, age-related eye disease study score; BCVA, best corrected visual acuity in EDTRS (early treatment diabetic retinopathy study) letters score; BL, baseline; CDT, central drusen thickness (μm); DV, Drusen volume; FL, fixation loss; GA, geographic atrophy (mm^2); M6, Month 6 follow up; QOL, quality of life score using the visual function questionnaire-25 (VQF-25); RS, retinal sensitivity (dB); W5, Week 5 follow up.

Table 2. Six Months Change After Photobiomodulation Treatment From Baseline in Functional and Anatomical Outcome Measures for the 20 Participants of Our Study

Measure	Mean (BL)	Mean (M6)	Change BL-M6	*P*
BCVA (letters)	76.00 (±8.04)	81.50 (±6.30)	+ 5.5	0.007
DV (mm^3)	0.76 (±0.45)	0.65 (±0.39)	- 0.11	0.03
CDT (μm)	97.25 (±86.56)	80.2 (±82.02)	- 17.05	0.01
GA (mm^2)	0.07 (±0.13)	0.13 (±0.22)	+ 0.06	0.01
RS (db)	20.5 (±3.91)	20.40 (±4.16)	- 0.1	0.17
FL (%)	3.45 (±6.36)	3.00 (±5.35)	- 0.45	0.72
QOL score	72.54 (±15.59)	75.61 (±16.71)	+ 3.07	0.05

Means beside the SD (bracketed) values are indicated. The *P*-values is analyzed by the Wilcoxon signed-rank test. It is related to the significant difference in mean change in our study.

BL, baseline; M6, at 6 months follow-up; AREDS category, age-related eye disease study category; BCVA, best-corrected visual acuity in ETDRS (Early Treatment Diabetic Retinopathy Study) letters score; DV, drusen volume (mm^3); CDT, central drusen thickness (μm); GA, geographic atrophy (mm^2); RS, retinal sensitivity (dB); FL, fixation loss; QOL, quality of life score using the Visual Function Questionnaire-25 (VFQ-25).

at W5: We observed a nonstatistically significant improvement in BCVA ($P = 0.44$) and nonstatistically significant decrease in DV ($P = 0.23$) and CDT ($P = 0.27$) (Table 3).

Outcomes between W5 and Month 6: A statistically significant BCVA improvement was noted, with a mean score gain of 3.68 letters ($P = 0.007$). CDT decreased significantly ($P = 0.02$). However, decrease of DV ($P = 0.21$) was not statistically significant (Table 3) (Figures 1, 2).

Compliance was high with 100% of participants presented to all treatment procedures. A rupture of dPED was diagnosed at M6 follow-up in one patient with a decreased dPED volume and thickness (Figure 4). Vitreous floaters were reported in one patient.

Discussion

LIGHTSITE I was a sham-controlled, double-masked, single-center, and randomized study that reported several functional and structural benefits of PBM therapy in eyes presenting intermediate AMD.[3] The improvement of BCVA was estimated at 3.8 letters at M1 and 4.1 letters at M3 in previous studies.[3] The visual benefit of PBM therapy on BCVA seemed to diminish at M6 with a main gain score of 2.4 letters.[3] In the LIGHTSITE II study, the main gain score of BCVA at M9 was 2.30 letters.[10] The TORPA 1 study revealed a statistically significant amelioration of BCVA at M12.[11] The TORPA 2 study confirmed this outcome with a main gain score of 5.90 letters at M1 and 5.14 letters at M3.[12] Our study supports this favorable effect of PBM with a 5.5 letters improvement at M6. This outcome is in accordance with the recently released results of the LIGHTSITE III study (5.5 letters at M13) (SEATTLE, March 22, 2022/PRNewswire/LumiThera Inc) (https://eu.lumithera.com/category/press-releases/). According to the TORPA 2 study, the main gain score in BCVA seemed to be more important at the end of treatment and diminished after, which differs from our result (W5).[12] This difference may be explained by the differences in devices, time duration, NIR dosages used, and GA surface of eyes (7.01 mm^2 ±5.22 in the TORPA 2 study vs. 0.07 mm^2 ±0.13 in our study).[12] The LIGHTSITE I study reported a best mean score gain of 4.1 letters at M3 after PBM.[3] In our study, BCVA improvement was statistically significant particularly from W5 to M6 with a mean score gain of 3.86 letters

Table 3. Changes in Best-Corrected Visual Acuity and Anatomical Outcome Measures After Photobiomodulation Treatment in Our Study From Baseline to 5 Weeks and From 5 Weeks to 6 Months

Measure	Total of Patients	Mean (BL)	Mean (W5)	Mean (M6)	Change BL-W5	Change W5-M6	*P* BL-W5	*P* W5-M6
BCVA (letters)	17	76.17 (±8.57)	77.64 (±8.31)	81.50 (±6.30)	+ 1.47	+3.86	0.44	0.007
DV (mm^3)	20	0.76 (±0.45)	0.74 (±0.44)	0.65 (±0.39)	- 0.02	−0,09	0.23	0.21
CDT (μm)	20	97.25 (±86.56)	91.85 (±85.71)	80.2 (±82.02)	- 5.4	−11.65	0.27	0.02

Means beside the SD (bracketed) values are indicated. The *P*-values is analyzed by the Wilcoxon signed-rank test. It is related to the significant difference in mean change in our study.

BL, baseline; W5, at 5 weeks follow-up from baseline, the end of photobiomodulation (PBM) treatment; BCVA, best-corrected visual acuity in ETDRS (Early Treatment Diabetic Retinopathy Study) letters score; DV, drusen volume (mm^3); CDT, central drusen thickness (μm).

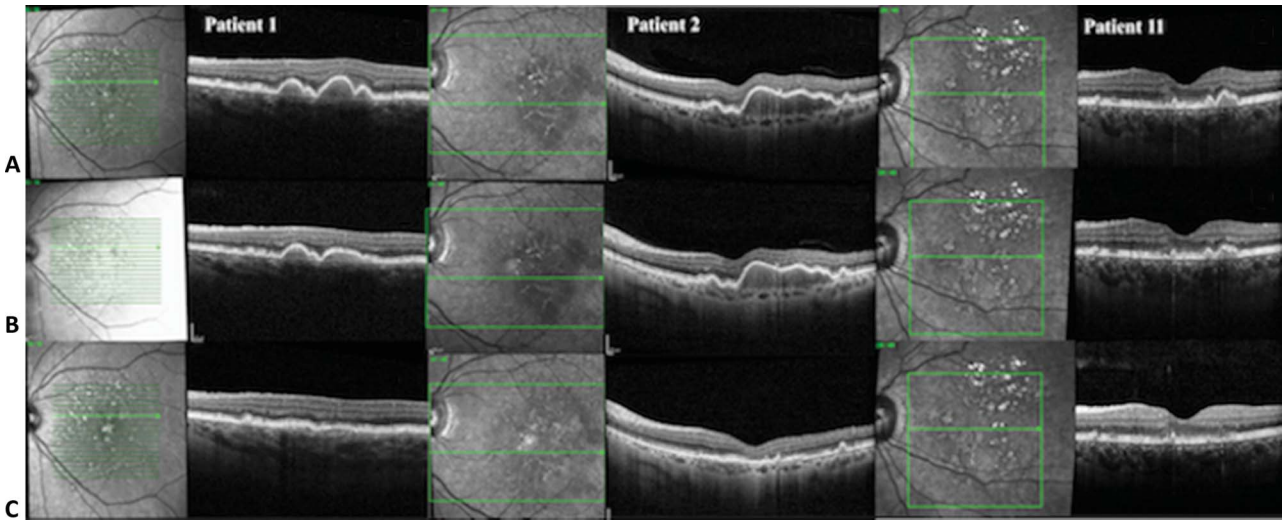

Fig. 1. B-scan spectral domain optical coherent tomography (SD-OCT) demonstrating drusen reduction in a left eye with dry AMD treated by PBM. Baseline (**A**) imaging showing large macular drusenoid pigment epithelial detachment (PED) in patients 1 and 2 and soft drusen in patient 11. Week 5 (**B**) B-scan SD-OCT showing drusen volume evolution with a main reduction at the time points between week 5 and month 6. Month 6 (**C**) imaging illustrates the complete reduction of the drusenoid PED and soft drusen after a series of 10 photobiomodulation (PBM) treatments.

(P = 0.07). This result is in accordance with the LIGHTSITE I study that used the same device, same parameters, and regimen but a higher rate of eye with GA (66.7% vs. 30% in our study). Therefore, the main visual benefit probably continues to grow 5 months after treatment ended.[3] These preliminary results suggest that PBM may provide a therapeutic option for patients with dry AMD mainly in its early stages and may potentially slow the progression of the disease. Microperimetry improvement is controverted in the lines has been revealed.

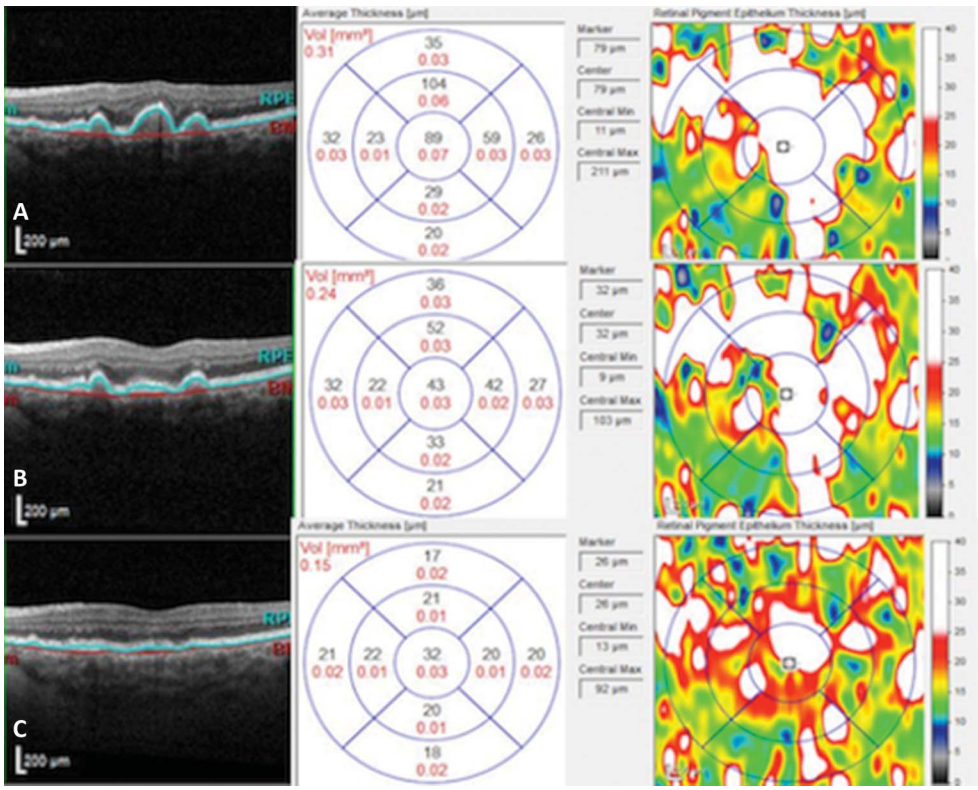

Fig. 2. Illustrative example of volumetric evaluation of a low-reflective homogenous drusen larger than 125 μm using SPECTRALIS HRA system after segmentation of the RPE and Bruch membrane (BM) within the central 6-mm diameter of the macula. Analysis of each ETDRS subgrid showed drusen volume (DV) and mean central drusen thickness reduction in an eye categorized as AREDS 3 treated by photobiomodulation (PBM) (patient N1). Baseline (**A**) SD-OCT illustrates DV of 0.31 mm^3 with CDT of 89 μm. On the left side, the color-coded drusen thickness map illustrated the anatomical improvement. Week 5 (**B**) SD-OCT showed DV reduction to 0.24 mm^3 with CDT of 43 μm. On the left side, the color-coded drusen thickness map illustrated the anatomical improvement. At month 6 after PBM therapy (**C**) SD-OCT demonstrated a global decrease in DV (0.15 mm^3) and CDT (32 μm). SD-OCT confirmed no newly development of geographic atrophy (GA), or irregularity of the photoreceptor

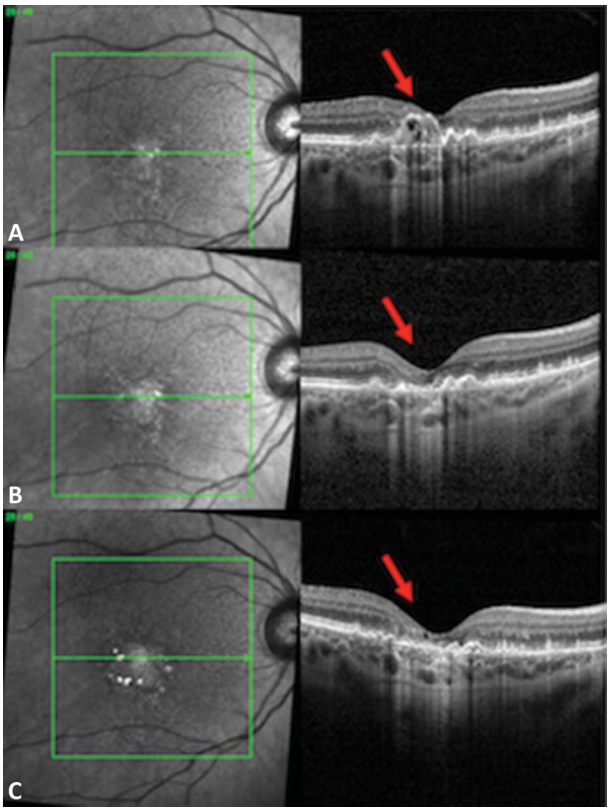

Fig. 3. B-scan spectral domain optical coherent tomography (SD-OCT) illustrating drusen reduction and GA in a right eye with dry AMD categorized as AREDS 4 treated by photobiomodulation (PBM). Baseline (**A**) imaging showing macular drusen. Week 5 (**B**) B-scan SD-OCT showing incomplete drusen resolution. Month 6 (**C**) imaging revealing GA after drusen resolution.

literature.[3,11] We noted a nonstatistically significant decrease of FL and RS in our study.

In the TORPA 2 study, OCT monitoring showed a reduction in CDT by a mean of 3.78 μm at M3 (vs. 17.05 μm at M6 in our study).[12] In the LIGHTSITE I study, 70% of eyes included presented a reduction in DV at M12 (vs. 70% at M6 in our study).[3] As reported in the LIGHTSITE II study, DV was not increased at M9 in PBM-treated eyes while it was increased in the sham-treated group.[10] In our study, mean decrease of DV and CDT was statistically significant over a period of 6 months from baseline. The CDT decrease was statistically significant only from W5 to M6. The DV decrease from baseline to W5 and from W5 to M6 was nonstatistically significant. Moreover, as reported in the literature, the statistically significant change in mean DV in AMD requires a long-period assessment, at least one year.[3,13] This outcome highlights the interest of long-term assessment after PBM treatment. It suggests that anatomical benefit continues probably to increase over time after treatment ended. Previous studies suggest that PBM therapy is preferably suitable to AREDS stages 2 to 4 AMD.[4] All treated patients in our study were in AREDS stages 3 to 4 AMD (stage 3 [75%] and stage 4 [25%]). We previously demonstrated that PBM on reticular pseudodrusen, in five cases, showed a decreased number of stage 3 reticular pseudodrusen, which is in accordance with anatomical benefits in our study.[14]

Previous reports revealed that drusen development and resolution are in a constant course of change.[3,15] Drusen resolution can leave behind GA.[3] Large dPED can also collapse and disappear without leading to additional photoreceptors and RPE disruption and loss.[3] The mean rate of GA progression for total populations reported in available studies is 1.78 mm^2/year.[16] Regardless of the lack of the group control in our study, 35% patients increased or developed GA with a mean rate of 0.06 mm^2/6 months, which is not significant compared with the half of the rate (1.78 mm^2/year) corresponding to the natural progression of GA. Moreover, Markowitz SN and al. through a sham-controlled, randomized, double-masked study of 46 eyes with dry AMD showed no progression of GA lesion was recorded in the PBM-treated study eyes in comparison with the sham-treated eyes at M12 ($P > 0.05$).[3] Furthermore, the LIGHTSITE II study reported a 20% less growth of GA in the PBM-treated patients at M9 compared with sham-treated eyes.[10] This outcomes suggested that PBM therapy can probably protect patients with large drusen and dPED associated with dry AMD from appearance and/or progression of GA.

Querques et al suggested that lesion preceding RPE apertures of the avascular PED is focal atrophic progression of the drusenoid material.[17] Therefore, drusenoid materiel regression related to PBM therapy may possibly be involved of the dPED rupture in our study. Moreover, several studies investigated the relationships between RPE and DV changes during the PED lifecycle.[18–20] However, further long-term studies, with control groups, are needed to determinate whether GA and dPED rupture are associated with the natural progression of the disease or a consequence of PBM treatment.

PBM treatment provided an increased QoL at M6 in our study. This outcome is in accordance with the other quantitative clinical outcome measures and the (VFQ-25) composite score analysis in PBM-treated patients for dry AMD in the previous studies.[3] This improvement in QoL can potentially provide more independence and decrease the limitations in lifestyle for these patients. Actually, there is no consensus on PBM therapy regimens.[2] Indeed, different duration, dosages, and frequency of the NIR light have been experienced in previous studies with varying efficiency.[2] In the LIGHTSITE I study, patients were treated with the LumiThera Valeda Light Delivery

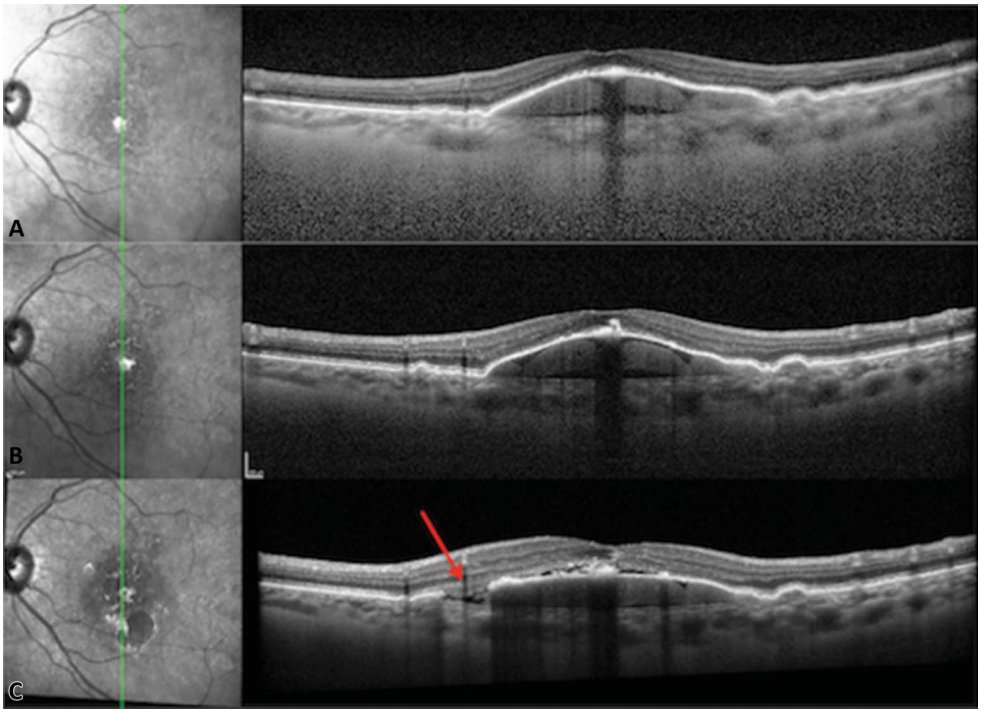

Fig. 4. B-scan spectral domain optical coherent tomography (SD-OCT) showing the pigment epithelial detachment (PED) at baseline (**A**) and week 5 (**B**). The PED rupture (red arrow) occurred at month 6 (**C**) after photobiomodulation (PBM) treatment in our patient.

System, which delivers a total of 250 seconds (4 minutes 10 seconds) three distinct wavelengths in the yellow (590 nm), red (660 nm), and NIR (850 nm) ranges.[3] Patients underwent two series of PBM treatments over 1 year using a regimen of three sessions per week for 3 weeks with a total of nine treatment sessions per series.[3] The LIGHTSITE II and LIGHTSITE III studies also used the Valeda device.[10] The regimen adopted in both studies is approximately three sessions per week for 3 weeks in LIGHTSITE II and 3 to 4 weeks for LIGHTSITE III.[10] Treatment duration was different in the LIGHTSITE II study approximately 5 minutes per session with a frequency of three series of PBM treatment per year at baseline, M4, and M8.[10] The frequency of treatment in the LIGHTSITE III study was approximately six series over 24 months at baseline, M4, M8, M12, M16, and M20 (SEATTLE, March 22, 2022/PRNewswire/LumiThera Inc; https://eu.lumithera.com/category/press-releases/).

The prospective interventional case series TORPA I treated dry AMD patients with a regimen of 18 sessions over a 6-week period using two devices.[11] The first one is Warp 10 (Quantum Devices, Newark, OH) with treatment parameters of 670 nm ± 15 nm at 50 to 80 mW/cm^2, 4 to 7.68 J/cm^2, for 88 ± 8 seconds.[11] The second device is GentleWaves (Light Bioscience, Virginia Beach, VA) using treatment parameters of 590 nm ± 8 nm at 4 mW, 790 nm ± 60 nm at 0.6 mW, for 30 seconds.[11] In the TORPA 2 study, the regimen used was nine sessions over a limited 3-week period using sequentially the same two devices operated in the TORPA 1 study.[12] The PBM treatment parameters for the Warp 10 were wavelength 670 ± 15 nm delivering 50 to 80 mW/cm^2 (4–7.68 J/cm^2) for 88 ± 8 seconds and for the GentleWaves were wavelengths of 590 ± 8 nm at 4 mW and 790 ± 60 nm at 0.6 mW, both for 35 seconds, pulsed at 2.5 Hz (250 milliseconds on, 150 milliseconds off, delivering 0.1 J/cm^2/treatment).[12] In the LIGHTSITE II, patients had three PBM treatments per week for 3 to 4 weeks, every 4 months.[10] The PBM exposure regimen used in our study is limited to two treatments per week for 5 weeks with a total of 10 treatment sessions. This regimen was determined for convenience reasons for elderly patients to decrease the number of visits per week. We hypothesized that reduction of the number of visits per week would make the treatment more acceptable by the patients and their accompanying person. Finally, we observed a total (20/20) compliance in our study. In addition, we hypothesized that, with our protocol, the benefit of the treatment could be observed for 6 months that could allow reducing the number of series per year. Thus, patients could benefit for a series of treatment every 6 months instead of a series of treatments every 4 months, as performed in the LIGHTSITE II study.[10]

Ferroptosis, the recently revealed programmed cell death pathway, is a consequence of lipid peroxidation leading to iron-dependent accumulation.[21] Previous studies revealed present iron accumulation and lipid

peroxidation increase in the aging retina. These outcomes evidenced ferroptosis involvement in AMD pathogenesis.[21]

Lederman et al[22] validated that exogenous oxidative stress caused by intravitreal injection of paraquat leads to an upregulation of an iron transporter called transferrin, and the main intracellular iron storage molecule termed ferritin, in mice degenerating retinas. Therefore, this upregulation may reduce the availability of iron to the Fenton reaction, improving consequently oxidative damage. Lederman et al suggested that the amelioration of the oxidative defense mechanism can probably protect retinas underdoing chronic oxidative stress.[21] Thereby, we highlight the relevance of clarifying through further studies whether additional origins of oxidative injury as photic damage, light and PBM, are implicated in iron metabolism upregulation in AMD, explaining accordingly visual and anatomical improvements in our study. A better understanding of the mechanism of action of PBM therapy could likely improve the procedure and the protocol of use. It could probably extend its use to other pathologies, in particular those secondary to the dysfunction of RPE cells with limited therapeutic options.

Despite the lack of control group and limited number and follow-up of included patients, the outcomes of this study highlighted the overall efficacy and safety of PBM for treatment of large soft and dPED drusen associated with dry AMD, supporting prior reports.[4] Nevertheless, long-term and larger studies are needed to determine whether the effectiveness is stable or whether repeated PBM procedures are needed to maintain the visual improvement.

Key words: age-related macular degeneration, drusen, photobiomodulation, retinal sensitivity, visual acuity.

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