Continuing Medical Education:

Multimodal retinal imaging in central serous chorioretinopathy treated with oral eplerenone or photodynamic therapy

A Rabiolo¹, I Zucchiatti¹, A Marchese¹, G Baldin¹,
R Sacconi^{1,2}, D Montorio^{1,3}, MV Cicinelli¹,
L Querques^{1,4}, F Bandello¹ and G Querques¹

Release date: 21 December 2017; Expiration date: 21 December 2018

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

In support of improving patient care, this activity has been planned and implemented by Medscape, LLC and Springer Nature. Medscape, LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Medscape, LLC designates this Journal-based CME activity for a maximum of *1.00 AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

All other clinicians completing this activity will be issued a certificate of participation. To participate in this journal CME activity: (1) review the learning objectives and author disclosures; (2) study the education content; (3) take the post-test with a 75% minimum passing score and complete the evaluation at www.medscape.org/journal/eye; (4) view/print certificate.

Learning objectives

Upon completion of this activity, participants will be able to:

1. Evaluate pretreatment correlations among function, structural optical coherence tomography, and optical coherence tomography angiography measures in patients with central serous chorioretinopathy (CSC), based on a prospective, observational study
2. Assess multimodal retinal imaging changes associated with treatment of CSC, based on a prospective, observational study
3. Examine clinical implications of multimodal retinal imaging findings in patients with CSC, based on a prospective, observational study

Authors/editors disclosure information

Alessandro Rabiolo has disclosed no relevant financial relationships.
Ilaria Zucchiatti has disclosed no relevant financial relationships.
Alessandro Marchese has disclosed no relevant financial relationships.

Giovanni Baldin has disclosed no relevant financial relationships.

Riccardo Sacconi has disclosed no relevant financial relationships.

Daniela Montorio has disclosed no relevant financial relationships.

Maria Vittoria Cicinelli has disclosed no relevant financial relationships.

Lea Querques has disclosed no relevant financial relationships.

Francesco Bandello has disclosed the following relevant financial relationships: served as an advisor or consultant for: Allergan; Alimera; Bayer; F. Hoffmann-La Roche AG; Farmila Thea Farmaceutici SpA; Genentech; Novagali Pharma S.A.; Novartis; Sanofi-Aventis; Schering AG.

Giuseppe Querques has disclosed the following relevant financial relationships: served as an advisor or consultant for: Alimera; Allergan; Bayer; Novartis; Zeiss.

Journal CME author disclosure information.

Laurie Barclay has disclosed the following relevant financial relationships: Owns stock, stock options, or bonds from: Alnylam; Biogen; Pfizer Inc.

Multimodal retinal imaging in central serous chorioretinopathy treated with oral eplerenone or photodynamic therapy

A Rabiolo¹, I Zucchiatti¹, A Marchese¹, G Baldin¹,
R Sacconi^{1,2}, D Montorio^{1,3}, MV Cicinelli¹,
L Querques^{1,4}, F Bandello¹ and G Querques¹

Abstract

Purpose To correlate function and structural optical coherence tomography (OCT) to optical coherence tomography angiography (OCT-A) measures in patients affected by central serous chorioretinopathy (CSC) and to describe their changes after treatments (ie oral eplerenone, half-fluence photodynamic therapy (PDT)).
Patients and methods Twenty eyes of 16 consecutive patients with treatment-naïve CSC undergoing either eplerenone or PDT were enrolled in this prospective, observational study. All patients underwent structural OCT and OCT-A at baseline and after therapy at months 1 and 3.
Results Eleven eyes of nine patients and nine eyes of seven patients underwent eplerenone or PDT treatment, respectively. Central macular thickness (CMT) and subretinal fluid (SRF) correlated to fovea avascular zone (FAZ) area ($r = 0.74$ and $r = 0.71$, $P = 0.01$) and vessel density ($r = 0.77$ and $r = 0.68$, $P = 0.01$) at deep capillary plexus (DCP). CMT ($P = 0.0011$), SRF ($P = 0.0005$), SFCT ($P = 0.0016$), FAZ area at DCP ($P = 0.0334$) improved at 3-month visit. A significant reduction of deep FAZ area was appreciated in eplerenone ($P = 0.0204$) but not in PDT ($P = 0.5$) group. SFCT reduction was significantly higher in PDT than eplerenone group ($P = 0.0347$).
Conclusion Structural and vascular parameters are correlated in CSC and they improve after different treatments. Both half-fluence PDT and oral eplerenone do not permanently damage choriocapillaris or other choroidal layers as evaluated by OCT-A.
Eye (2018) 32, 55–66; doi:10.1038/eye.2017.290; published online 21 December 2017

Introduction

Central serous chorioretinopathy (CSC) is the fourth cause of vision-threatening retinopathy affecting people aged between 39 and 51 years with an estimated incidence of 9.9 and 1.7 per 100 000 individuals in men and women, respectively.^{1,2} CSC is characterized in its acute stage by accumulation of subretinal fluid (SRF) beneath the neurosensory retina and pigment epithelium detachment (PED).³ Despite being usually self-resolving, CSC sometimes evolves into a chronic, persistent form often accompanied by retinal pigment epithelium (RPE) and photoreceptors changes. Treatments of CSC include observation, discontinuation of drug at risk, laser photocoagulation, micropulse laser, rifampin, photodynamic therapy (PDT), anti-vascular endothelial growth factor (VEGF) and mineralocorticoid receptor (MR) antagonists (ie spironolactone, eplerenone).³

Multimodal imaging is extremely useful in the initial evaluation and follow-up of CSC after treatment. Beyond structural optical coherence tomography (OCT), several imaging modalities are routinely used in clinical practice of CSC, including fundus autofluorescence (FAF), fluorescein angiography (FA) and indocyanine green angiography (ICGA). Optical coherence tomography angiography (OCT-A) is a novel technology that allows the visualization of retinal and choroidal vessel vasculature in a rapid, non-invasive and dye-less fashion.⁴ Previous studies have shown that OCT-A is able to highlight qualitative defects and textural changes in affected eyes or to identify choroidal neovascularization (CNV) complicating CSC.^{5–8} Using en face OCT, Kuroda *et al*⁹ found increased choroidal vascular area in patients with CSC. No study evaluating quantitative

¹Department of Ophthalmology, University Vita-Salute, IRCCS San Raffaele, Milan, Italy

²Eye Clinic, Department of Neurological and Movement Sciences, University of Verona, Verona, Italy

³Eye Clinic, Department of Neurosciences, Reproductive Sciences and Dentistry, University of Naples Federico II, Naples, Italy

⁴G. B. Bietti Foundation-IRCCS, Rome, Italy

Correspondence: G Querques, Department of Ophthalmology, IRCCS Ospedale San Raffaele, University Vita-Salute San Raffaele, Via Olgettina 60, Milan 20132, Italy
Tel: +390 226 434 004; Fax: +390 226 433 643.
E-mail: giuseppe.querques@hotmail.it

Received: 3 April 2017
Accepted: 8 September 2017
Published online: 21 December 2017

changes in retinal and choroidal vasculature using OCT-A has been published yet. Moreover, correlation between novel OCT-A measures and well-known clinical and OCT features is still undetermined. Finally, effects of different therapies on OCT and OCT-A measures have not been elucidated.

The aims of our work were to (i) correlate functional and structural parameters to OCT-A measures in patients affected by CSC; (ii) describe changes in clinical, structural OCT and OCT-A measures after therapy using two different treatments (ie eplerenone, PDT).

Methods

Study population

Consecutive patients affected by CSC undergoing either eplerenone or PDT between January 2016 and June 2016 at the Medical Retina & Imaging Unit of the Department of Ophthalmology, University Vita-Salute, San Raffaele Hospital, Milan, Italy were enrolled in this non-randomized prospective study. The study was conducted in compliance with the Declaration of Helsinki and all patients signed a written general consent to participate in clinical studies, which was approved by the ethics committee of San Raffaele Hospital.

Inclusion criteria were: diagnosis of CSC with no spontaneous regression for at least 2 months; age ≥ 18 years old; refractive status between -6 and $+6$ diopters, no previous ocular surgery other than uncomplicated cataract extraction and intraocular lens implantation, no previous CSC therapy. Diagnosis of CSC was established on the basis of the following criteria: (i) SRF and/or PED within the macular area; (ii) idiopathic leakage from the RPE during FA/ICGA; (iii) exclusion of other possible causes of SRF/PED. CSC was further classified in acute or chronic whether its onset was ≤ 12 or > 12 weeks, respectively. Exclusion criteria were: presence of CNV; any other retinal disease; significant media opacity to ensure proper images quality; presence of systemic contraindication for eplerenone treatment (liver or renal disease, hyperkalemia, defined as > 5.5 mmol/l, or concomitant drugs that increase the potassium level, pregnancy).

Enrolled patients were evaluated at baseline and after therapy at months 1 and 3. The ophthalmologic examination included best-corrected visual acuity (BCVA) on Snellen charts, anterior segment biomicroscopy, intraocular pressure (IOP) measured with Goldmann applanation tonometry, indirect fundus exam, structural spectral-domain (SD)-OCT (Spectralis, HRA Heidelberg, Heidelberg, Germany) and 3×3 mm OCT-A (Angioplex, CIRRUS HD-OCT models 5000, Carl Zeiss Meditec, Inc., Dublin, OH, USA) scans of the macula. The

minimum strength of OCT-A images was 7 out of 10. BCVA was converted to the logarithm of the minimal angle of resolution (logMAR) for calculation purposes. Medical history and demographic data were also recorded.

Treatment regimen

Eplerenone (Inspra, Pfizer, Paris, France) was administrated orally 25 mg/day for a week followed by 50 mg/day for 4 weeks. The 50 mg/day eplerenone treatment was continued for other 8 weeks depending on the presence of SRF at SD-OCT scans. Treatment tolerance was assessed by blood analyses of kalemia and creatinine performed at baseline and every 4 weeks. The treatment was stopped in case of kalemia increase (> 5 mmol/l) or creatinine clearance rate decrease (< 60 ml/min).

Verteporfin (6 mg/m^2) PDT (Visudyne; Novartis Pharma, New York, NY, USA) with a half-fluence rate (25 J/cm) by one single experienced physician (GQ), as described elsewhere.¹⁰ Briefly, verteporfin was infused for 10 min and 15 min after the start of the infusion, a laser light at 689 nm was delivered at 25 J/cm , with an intensity of 300 mW/cm for 83 s.

Structural SD-OCT measurements

The structural SD-OCT acquisition protocol included: 19 horizontal raster linear B-scans, each composed by 9 averaged OCT B-scans (1024A-scans per line) at $240 \mu\text{m}$ intervals, covering an area of 20 degrees by 15 degrees; 6 radial linear B-scans, each composed by 25 averaged OCT B-scans (768A-scans per line) at 30 degrees centered on the fovea; 49 horizontal raster dense linear B-scans, each composed by 16 averaged OCT B-scans (384A-scans per line) at $30 \mu\text{m}$ intervals, covering an area of 15 degrees by 5 degrees. The latter two scan sequences were acquired in enhanced depth imaging (EDI) mode. All acquisition following baseline visit were acquired using the follow-up function. Central macular thickness (CMT) in the central 1-mm-diameter circle of the ETDRS thickness map was recorded with the Spectralis Software (Heidelberg Eye Explorer, Version 1.9.11.0, Heidelberg Engineering, Heidelberg, Germany). SRF, subfoveal choroidal thickness (SFCT) and PED height were manually measured by an independent operator (DM). SRF was defined as the vertical distance between the end of the outer segment and the RPE at the foveal center. SFCT measured vertically from the outer border of the RPE to the inner border of the sclera. PED height was calculated as the distance between the RPE at the base and the peak of the PED.

OCT-A images acquisition and analysis

OCT-A images were acquired with the Cirrus HD-OCT (Angioplex, CIRRUS HD-OCT models 5000, Carl Zeiss Meditec, Inc., Dublin, OH, USA). Automatic segmentation of full-thickness (internal limiting membrane to Bruch's membrane) retina vasculatures, superficial (SCP) and deep (DCP) capillary plexuses was evaluated by a single operator (AR) and manually adjusted in case of segmentation errors. All 3×3 OCT-A images were exported into the National Institutes of Health ImageJ 1.50 (National Institutes of Health, Bethesda, MD, USA) software and analyzed by a second independent operator (AR).

The FAZ area was manually measured using a previously published method.^{11,12} Briefly, the FAZ area was manually outlined using the polygon selection tool in all the three selected plexuses (full-thickness, superficial, SCP and DCP), and its dimension expressed as squared millimeters was calculated. The FAZ area was evaluated in full-thickness (internal limiting membrane to Bruch's membrane) OCT-A angiogram (ftFAZ), SCP (sFAZ) and DCP (dFAZ).

Vessel density was calculated through image thresholding and binarization, according to previous studies.^{13,14} Specifically, (i) the ImageJ mean threshold, which automatically calculates the threshold as the mean of the local greyscale distribution, was applied to each image; (ii) binarized 8-bit image was converted to RGB color model; (iii) FAZ area was contoured and colored to pure blue. White pixels were considered as vessel, black pixels as background, and blue pixels were automatically excluded from the analysis in order to prevent FAZ inclusion in vessel density calculation. Vessel density was calculated as the ratio between the white pixel and the total pixels after FAZ exclusion.

Statistical analysis

Variables included in the analysis were: age, sex, race, eye (right/left), BCVA, CMT, SRF, presence and height of PED, SFCT, FAZ area in the full-thickness, SCP and DCP; vessel density in full-thickness, SCP, DCP, choriocapillaris and Sattler-Haller layers. Differences between groups were calculated by means of student's *t*-test for continuous variables and χ^2 or Fisher exact test for categorical variables. Variables change during the follow-up period was assessed with analysis of variance (ANOVA) for repeated measures and Tukey test was used as *post-hoc* test. The relationship between variables was explored using Pearson correlation test and multiple correlations were adjusted by means of Benjamini-Hochberg test. All data were expressed as the mean $\pm$ standard deviation and all tests were two-sided.

A *P*-value less than 0.05, after adjustment when required, was considered to be significant. Prism 6.0 software (GraphPad Software, San Diego, CA, USA) was used to analyze the data.

Results

Baseline data and pre-treatment correlation analysis

Twenty eyes of 16 patients were enrolled. Eleven active eyes of nine patients and nine eyes of seven patients underwent to eplerenone or PDT treatment, respectively. No significant difference was appreciated between the two groups for clinical, OCT and OCT-A measures at the baseline visit (Table 1).

At correlation analysis, BCVA was not related to any of structural OCT variables, including CMT ($P=0.3$), SRF ($P=0.4$) and SFCT ($P=0.9$). No significant correlation was seen also between BCVA and OCT-A measures, including FAZ area and vessel density at every plexus.

Among OCT-parameters a robust association between CMT and SRF was disclosed ($r=0.90$, $P<0.01$); whereas no relationship was found between SFCT and CMT ($P=0.3$) or SRF ($P=0.5$). Both CMT and SRF strongly correlated to FAZ area ($r=0.74$ and $r=0.71$, $P=0.01$ and $P=0.01$, respectively) and vessel density ($r=0.77$ and $r=0.68$, $P=0.01$ and $P=0.01$, respectively) at DCP. Neither CMT or SRF significantly correlated to any other OCT-A-derived parameters, including arFAZ ($P=0.1$ and $P=0.3$, respectively) and sFAZ ($P=0.2$ and $P=0.3$, respectively) areas, vessel density at full thickness retina ($P=0.2$ and $P=0.2$, respectively), SCP ($P=0.13$ and $P=0.08$, respectively), choriocapillaris ($P=0.8$ and $P=0.3$, respectively) and Sattler-Haller ($P=0.7$ and $P=0.8$, respectively) vascular layers.

SFCT was negatively correlated to patient age ($r=-0.59$, $P=0.048$). SFCT was not significantly correlated to any other OCT-A variables ($P>0.05$).

Clinical, structural OCT and OCT-A changes after treatment

Enrolled patients were evaluated at 36 ± 5 and 103 ± 25 days after treatment (eplerenone or PDT). BCVA improved from 20/32 (0.20 logMAR) at baseline to 20/29.5 (0.17 logMAR) at 1 month and 20/28 (0.15 logMAR) at 3 months, although this difference was not statistically significant ($P=0.2$). BCVA improvement was more pronounced in patients who underwent eplerenone than PDT therapy, even if neither eplerenone ($P=0.12$) or PDT ($P=0.9$) group reached a significant change in BCVA from baseline. Moreover, no difference between eplerenone and PDT ($P=0.18$) was appreciated at

Table 1 Demographic, OCT and OCT-A measures at baseline

Variables	Overall	Eplerenone arm	PDT arm	P-value
<i>Demographic data</i>				
No. (Patients/Eyes)	16/20	9/11	7/9	n/a
Age years (Mean $\pm$ SD)	46.9 $\pm$ 8.3	44.1 $\pm$ 7.6	50.6 $\pm$ 9.5	0.2
Sex (Male/Female)	12/4	8/1	4/3	0.3
Eye (Right/Left)	13/7	7/4	6/3	
Race (Caucasian/Other)	16/0	9/0	7/0	
Duration of disease (Acute/Chronic)	5/15	4/7	1/8	0.3
Baseline BCVA, logMAR (Mean $\pm$ SD)	0.20 $\pm$ 0.21	0.18 $\pm$ 0.19	0.23 $\pm$ 0.23	0.6
Baseline BCVA, Snellen equivalent (Mean)	20/32	20/30	20/34	
<i>OCT measures</i>				
CMT, μ (Mean $\pm$ SD)	404.6 $\pm$ 120.3	442.8 $\pm$ 102.5	357.8 $\pm$ 129.6	0.12
SRF, μ (Mean $\pm$ SD)	155.3 $\pm$ 113.0	188.0 $\pm$ 95.1	115.3 $\pm$ 125.6	0.16
Serous PED (present/absent)	8/12	2/9	6/3	0.07
SFCT, μ (Mean $\pm$ SD)	426.6 $\pm$ 82.2	432.5 $\pm$ 83.0	419.3 $\pm$ 85.7	0.7
<i>OCT-A measures</i>				
<i>FAZ area, mm² (Mean $\pm$ SD)</i>				
ftRetina	0.342 $\pm$ 0.12	0.317 $\pm$ 0.11	0.381 $\pm$ 0.13	0.2
SCP	0.349 $\pm$ 0.13	0.332 $\pm$ 0.15	0.377 $\pm$ 0.11	0.5
DCP	1.966 $\pm$ 1.76	2.326 $\pm$ 1.53	1.353 $\pm$ 1.9	0.2
<i>Vessel density, % (Mean $\pm$ SD)</i>				
ftRetina	43.1 $\pm$ 2.3	43.0 $\pm$ 2.7	43.6 $\pm$ 1.6	0.5
SCP	41.9 $\pm$ 2.4	42.0 $\pm$ 2.8	42.4 $\pm$ 2.1	0.7
DCP	49.4 $\pm$ 6.3	49.5 $\pm$ 5.1	48.6 $\pm$ 7.8	0.8
CC	47.0 $\pm$ 2.1	46.4 $\pm$ 1.9	47.4 $\pm$ 2.3	0.3
Haller+Sattler	45.5 $\pm$ 1.0	45.3 $\pm$ 1.0	45.4 $\pm$ 1.4	0.8

Abbreviations: BCVA, best corrected visual acuity; logMAR, logarithm of the minimal angle of resolution; OCT, optical coherence tomography; OCT-A, optical coherence tomography angiography; SD, standard deviation; PDT, photodynamic therapy; CMT, central macular thickness; SRF, subretinal fluid; PED, pigmented epithelium detachment; SFCT, subfoveal choroidal thickness; FAZ, fovea avascular zone; ft, full-thickness; SCP, superficial capillary plexus; DCP, deep capillary plexus; CC, choriocapillaris.

3 months regarding BCVA. Figure 1a shows BCVA changes after treatments.

CMT significantly decreased from $404.6 \pm 120.3 \mu$ at baseline to $337.1 \pm 97.9 \mu$ and $286.8 \pm 76.6 \mu$ at 1 and 3 months, respectively ($P = 0.0011$). CMT reduction from baseline was significant at both 1 ($P = 0.049$) and 3 ($P = 0.0037$) months; a significant difference was appreciated also between 1- and 3-month visit ($P = 0.0203$). A significant CMT reduction from baseline was appreciated in the eplerenone ($P = 0.0022$) but not in the PDT ($P = 0.18$) group, although no difference between the two groups was found at 3 months ($P = 0.5$). In the eplerenone group, CMT significantly decreased both at 1 ($P = 0.033$) and 3 ($P = 0.0079$) months; conversely no difference between 1- and 3-month visits was disclosed ($P = 0.09$). Figure 1b shows CMT changes after treatments.

Similarly, SRF decreased from $155.3 \pm 113.0 \mu$ at baseline to $87.5 \pm 75.5 \mu$ and $34.6 \pm 57.4 \mu$ at 1 and 3 months, respectively ($P = 0.0005$). SRF reduction from baseline was significant at 1 ($P = 0.0379$) and 3 ($P = 0.0018$) months and also between those two follow-up visits

($P = 0.01$). A significant reduction in SRF was disclosed in eplerenone ($P = 0.0015$) but not in PDT ($P = 0.14$) group, although no difference between the two groups was found at 3 months ($P = 0.7$). In the eplerenone group, SRF reduction from baseline was significant at both 1 ($P = 0.0239$) and 3 ($P = 0.0058$) months and also between the two follow-up visits ($P = 0.0239$). Figure 1c shows SRF changes after treatments.

PED completely resolved in only one eye after treatment and PED mean height did not significantly improve during the follow-up period ($P = 0.6$). The case of PED resolution occurred in the eplerenone group.

SCFT significantly decreased from $426.6 \pm 82.2 \mu$ at baseline to $398.1 \pm 66.9 \mu$ and $359.4 \pm 72.6 \mu$ at 1 and 3 months, respectively ($P = 0.0016$). SFCT at 3-month visit was significantly lower than at both baseline ($P = 0.0053$) and 1-month ($P = 0.0007$) visits, whereas SCFT at 1 month did not differ from baseline ($P = 0.4$). Significant reduction of SFCT was appreciated in both eplerenone ($P = 0.0212$) and PDT ($P = 0.0267$) groups; however, magnitude of reduction at 3 months was significantly higher in PDT

Figure 1 Functional and structural variables at baseline and at 1- and 3-month visit after treatment (ie overall, eplerenone, photodynamic therapy (PDT)). (a) Best corrected visual acuity (BCVA), (b) central macular thickness (CMT), (c) subretinal fluid (SRF), (d) subfoveal choroidal thickness (SFCT). LogMAR indicates the logarithm of the minimal angle of resolution.

Figure 2 Optical coherence tomography angiography-derived measures at baseline and at 1- and 3-month visit after treatment (ie overall, eplerenone, photodynamic therapy (PDT)). Full-thickness retina foveal avascular zone (FAZ) area (a) and vessel density (b); superficial capillary plexus (SCP) FAZ area (c) and vessel density (d), deep capillary plexus (DCP) FAZ area (e) and vessel density (f); choriocapillaris (CC) (g) and Sattler+Haller (h) vessel densities.

Figure 3 Structural optical coherence tomography (OCT) and optical coherence tomography angiography (OCT-A) at deep capillary plexus (DCP) at baseline and at 3-month visit after oral eplerenone (a,b) and photodynamic therapy (PDT) (c,d). Structural OCT (a) revealing serous neuroretinal detachment, intraretinal hyperreflective dots, atrophy of outer retinal layers, thicken subfoveal choroid and dilated choroidal vessels prior to eplerenone treatment. OCT-A at DCP (b) after binarization (c) discloses increased foveal avascular zone (FAZ) area (depicted in blue) and higher vessel density. At 3-month visit after eplerenone, structural OCT (d) shows a marked reduction of subretinal fluid; OCT-A (e) after image binarization (f) reveals recovery in FAZ area and vessel density at DCP. Structural OCT (g) revealing serous neuroretinal detachment, intraretinal hyperreflective dots, thicken subfoveal choroid and dilated choroidal vessels prior to PDT. OCT-A at DCP (h) after binarization (i) discloses moderate increase in foveal avascular zone (FAZ) area (depicted in blue) and vessel density. At 3-month visit after PDT, structural OCT (j) shows a resolution of subretinal fluid; OCT-A (k) after image binarization (l) mild improvement in FAZ area and vessel density.

than eplerenone group ($P=0.0347$). Figure 1d shows SRF changes after treatments.

Regarding full thickness retina vasculature, no significant change in FAZ area and vessel density was found overall ($P=0.5$ and $P=0.7$, respectively), in the eplerenone ($P=0.3$ and $P=0.9$, respectively) or in the PDT ($P=0.4$ and $P=0.9$, respectively) group, as shown in Figures 2a and b.

No significant difference was disclosed in SCP for FAZ area and vessel density overall, in eplerenone or in PDT group, as shown in Figures 2c and d.

With regards to DCP, dFAZ area (Figure 2e) significantly decreased from $1.966 \pm 1.76 \text{ mm}^2$ at baseline to $1.25 \pm 1.03 \text{ mm}^2$ and $0.88 \pm 0.55 \text{ mm}^2$ at 1 and 3 months,

respectively ($P=0.0334$). A significant reduction of dFAZ area was appreciated in eplerenone ($P=0.0204$) but not in PDT ($P=0.5$) group. DCP vessel density reduction following treatment disclosed a nearly significant trend ($P=0.058$), as shown in Figure 2f. Interestingly, vessel density significantly changed after eplerenone ($P=0.0397$) but not PDT ($P=0.4$) treatments. Figure 3 shows changes in structural OCT and DCP at OCT-A after oral eplerenone and PDT.

Vessel density in both choriocapillaris (Figure 2g) and Sattler+Haller (Figure 2h) vascular layers did not exhibit any significant modification after treatment ($P=0.3$ and $P=0.5$, respectively), even when considering the eplerenone ($P=0.6$ and $P=0.3$, respectively) and the PDT

Figure 4 Structural optical coherence tomography (OCT) and optical coherence tomography angiography (OCT-A) at choriocapillaris (CC) at baseline and at 3-month visit after oral eplerenone (a,b) and photodynamic therapy (PDT) (c,d). Both oral eplerenone and PDT cause a reduction or marked reduction of subretinal fluid at 3-month visit detected by means of structural OCT, respectively. No difference in CC vessel density after image binarization is disclosed between baseline and 3-month visit in both groups.

($P=0.4$ and $P=0.6$, respectively) groups separately. Figure 4 shows structural OCT and CC at OCT-A changes after eplerenone or PDT treatments.

Discussion

In the present study, we investigated the relationship between clinical (ie BCVA), structural OCT (ie CMT, SRF, SFCT) and vascular OCT-A (ie FAZ area, vessel density) data in patients affected by treatment naïve CSC. In this cohort of patients, a positive correlation has been found between structural, namely CMT and SRF, and vascular variables, namely FAZ area and vessel density at DCP. In addition, changes in such measures have been prospectively evaluated over a 3-month period following two different treatment modalities: oral eplerenone and PDT. Most of the structural parameters (ie CMT, SRF, SFCT) as well as vascular parameters (ie dFAZ) significantly improved after treatment. Although structural OCT is the primary test in most macular diseases, diagnosis and follow-up of CSC are based on a multimodal approach. Structural OCT reveals several features of acute (ie SRF, CMT, PED) and chronic (ie

photoreceptor elongation, RPE hypertrophy or atrophy, outer nuclear layer thinning, disruption of the ellipsoid zone (EZ) or external limiting membrane (ELM), cystoid macular degeneration) disease. EDI-OCT identified thicker choroid in both affected and unaffected eyes.^{15,16} FAF may provide useful information about the status of RPE, especially in chronic disease.¹⁷ FA is useful in order to individuate origin of leakage at baseline³; whereas ICGA allows to identify choroidal vascular changes (ie delayed filling, congestion, hyperpermeability, punctate hyperfluorescent spots) and to exclude the presence of CNV.^{18–21}

Structural OCT and OCT-A assessment of eyes with CSC could provide information about the anatomical status of the retinal and choroidal structure and vessels, which can result altered even after therapy and episode resolution. Although the choroid plays a major pathogenic role, neuroretina may be subjected to several pathological changes in chronic as well acute CSC, which could cause secondary alterations in retinal vasculature.³ An impairment in retinal vein dilation in response to flicker light has been recently described in eyes with active CSC and this could reflect either a primary

dysregulation linked to autonomic imbalance or a secondary phenomenon caused by SRF accumulation.²²

Thus, we designed a prospective study in order to quantitatively investigate the structural and vascular status of eyes affected by CSC using respectively structural OCT and OCT-A at baseline and their modifications following two different treatments (ie eplerenone, PDT). Even though some qualitative abnormalities have been previously described on OCT-A, such as textural changes or presence of CNV complicating CSC, no quantitative assessment was attempted.⁵⁻⁸ Moreover, no study has characterized the quantitative OCT-A modifications following treatment in the retina as well in the choroid vasculatures. To obtain quantitative data, OCT-A angiograms were post-processed and two indices, namely FAZ area and vessel density, were calculated. In correspondence to the foveola, the superficial and deep plexuses interrupt to form a capillary-free zone called FAZ.²³ Macular vessel density reflects the percentage of vessels covering the macular area in the retina as well in the underlying choroidal layers. Both indices are stable and reliable parameters commonly adopted in quantitative analysis of OCTA, and they reflect the vascular status of the macular area.²⁴⁻²⁶

In accordance with previous studies,²⁷ we did not observe any correlation between BCVA and CMT, SRF or SFCT. In addition, our data indicate that none of OCT-A measure is significantly associated with BCVA. A strong positive correlation among CMT, SRF and vessel analysis at DCP (ie FAZ area, vessel density) was observed. We hypothesize that such correlation can be explained by the mechanic effect exerted by the fluid beneath the neuroretina, causing a centrifugal displacement and squeezing of retinal vessels, which could, in turn, generate enlargement of FAZ and increasing of vessel density.

Several treatment strategies have been proposed in CSC including observation, discontinuation of drug at risk, laser photocoagulation, micropulse laser, PDT, anti-VEGF agents and MR antagonists (ie spironolactone, eplerenone). However, evidence for those treatment strategies is low and current literature does not provide enough information about the best approach with regard to safety and efficacy in CSC.²⁸ Among interventional modalities, PDT is the preferred practice pattern of retina specialist.²⁹ Therapeutic effect of PDT is accomplished through the production of oxygen-free radical in choroidal vasculature with subsequent vascular obliteration. PDT improves choroidal morphology and functionality leading to a reduction in choroidal congestion, vascular hyperpermeability, and extravascular leakage.³⁰ However, several sight-threatening adverse events following PDT have been reported, including RPE tear, sub-RPE hemorrhage, RPE

atrophy, and choriocapillaris nonperfusion.^{31,32} In order to avoid side effects of standard PDT, other regimens have been applied including half-dose or lower-fluence PDT. According to a recent meta-analysis, those regimens seem to be as effective as standard PDT.³³

In a recent study, Zhao *et al*³⁴ demonstrated that choroidal vascular dilation and leakage induced by high-dose glucocorticoid or aldosterone was reverted by MR antagonists. Following this observation, oral MR antagonists have been applied in CSC treatment. Of the two commercially available oral MR antagonist, eplerenone is usually preferred to spironolactone for the highest specificity toward MR and, thus, less anti-androgen (ie gynecomastia, feminization, loss of libido, erectile dysfunction) and metabolic (hyperglycemia, hypercortisolism) side effects.³⁵

In our study, both half-fluence PDT and eplerenone had similar outcomes. BCVA did not change significantly after treatments, although a trend toward improvement was observed, especially in the eplerenone group. Lack of statistically significant change in BCVA could be related to several factors, including (i) small sample size, (ii) high BCVA at baseline, (iii) high percentage of long-standing CSC which is often accompanied by photoreceptor injury. CMT and SRF were strongly correlated at baseline, and significantly improved after treatment. Interestingly, CMT and SRF changes were significant in the eplerenone group, while a trend toward reduction was observed also in the PDT group. With regards to retinal vascular indices, reduction of FAZ area and vessel density in DCP was appreciated, and this difference was driven by the eplerenone group. We speculate that normalization of OCT-A measures in DCP could be linked to SRF decrease and, thus, related to the reduction of mechanical vascular displacement exerted by the fluid. SRF reduction was more pronounced in eplerenone than PDT group and this finding may explain why modifications in DCP were more pronounced in eplerenone group. Given that PED, which can exert a displacement of retinal vessels, actually did not improve after therapy, the higher number of PED in PDT group could at least in part explain the differences between those two groups at OCT-A. Since eplerenone, differently from PDT that acts locally, is a systemic treatment, it is possible to hypothesize a global circulatory improvement seen at DCP.

On the other hand, OCT-A did not disclose any vascular modifications of FAZ area and vessel density at SCP. This might be explained by the fact that CSC is a disease characterized by the involvement of the choroid and outer retina, while inner retinal layers are generally preserved.

Choroidal thickening has been extensively described in affected and fellow eyes of CSC patients due to choriocapillaris hyperpermeability and dilation of large

vessels in Haller layer.^{36,37} In the present study, we have investigated the choroid using both structural OCT (ie SFCT) and OCT-A (ie vessel density in choriocapillaris and in Sattler+Haller layer). In accordance with previous studies,^{38,39} our results indicate that SFCT significantly improved after treatment overall and in both subgroups. Notably, we observed a reduction in SFCT significantly greater in eyes treated with PDT than eplerenone. A recent study by Kinoshita *et al*⁴⁰ showed that reduction in SFCT following half-dose PDT may be ascribed both to a decrease of exudation from choriocapillaris in the inner choroidal stroma and a reduction of vessel dilation in Haller layer. The reduction of SFCT exerted by both treatments could be due to a reduction in choroidal hyperpermeability and, thus, in stromal exudation. Another interesting finding of our work is that no significant change in choriocapillaris and Sattler+Haller layers has been found using OCT-A. Histopathological studies have shown that standard PDT induces selective damage and obliteration of choriocapillaris.⁴¹ Interestingly, we did not find any change in both choriocapillaris and Sattler+Haller layers following either eplerenone or half-fluence PDT. This observation suggests that half-fluence PDT, opposite to standard PDT, exerts its action without significantly damaging choroidal vascular structure similarly to other less invasive therapeutic strategies (ie eplerenone).

The main limitation of our study relies on the small sample size and, thus, some correlation and differences during the follow-up could have been therefore missed. Furthermore, our study provides a relatively short follow-up period and long-term modifications could occur. Finally, visualization of the choroid, especially in the case of thickening (as in CSC), could have been improved using a swept source instead of spectral domain OCT and OCT-A. Despite the above limitations, our study has got several strengths including its prospective design and the quantitative assessment of OCT and OCT-A images.

Several conclusions can be drawn from the present study. A correlation between structural (ie CMT, SRF) and vascular (ie FAZ area and vessel density at DCP at OCT-A) parameters exists and all those parameters significantly improve after different treatments. SFCT decreases with both treatments, although the change is more pronounced following half-fluence PDT. A significant reduction of dFAZ area was appreciated in eplerenone but not in PDT group, possibly related to the systemic effects of MR antagonists. Finally, both half-fluence PDT and oral eplerenone do not permanently damage choriocapillaris or other choroidal layers as evaluated by OCT-A.

Summary

What was known before

- Structural OCT-derived parameters (eg subfoveal choroidal thickness, subretinal fluid, central macular thickness) are affected in CSC.
- OCT-A is able to identify choroidal neovascularization complicating CSC.
- OCT-A revealed qualitative defects and textural changes in the choroid of affected eyes.

What this study adds

- Vascular and structural parameters in patients with central serous chorioretinopathy are affected and mutually correlated.
- Both vascular and structural parameters improve after different treatments, including mineralocorticoid receptor antagonist and half-fluence PDT.
- Both half-fluence PDT and oral eplerenone do not permanently damage choriocapillaris or other choroidal layers as evaluated by OCT-A.

Conflict of interest

The authors declare no conflict of interest.

References

- 1 Kitzmann AS, Pulido JS, Diehl NN, Hodge DO, Burke JP. The incidence of central serous chorioretinopathy in Olmsted County, Minnesota, 1980–2002. *Ophthalmology* 2008; **115**(1): 169–173.
- 2 Wang M, Munch IC, Hasler PW, Prunte C, Larsen M. Central serous chorioretinopathy. *Acta Ophthalmol* 2008; **86**(2): 126–145.
- 3 Daruich A, Matet A, Dirani A, Bousquet E, Zhao M, Farman N *et al*. Central serous chorioretinopathy: recent findings and new physiopathology hypothesis. *Prog Retin Eye Res* 2015; **48**: 82–118.
- 4 Rabiolo A, Carnevali A, Bandello F, Querques G. Optical coherence tomography angiography: evolution or revolution? *Exp Rev Ophthalmol* 2016; **11**(4): 243–245.
- 5 Bonini Filho MA, de Carlo TE, Ferrara D, Adhi M, Bauman CR, Witkin AJ *et al*. Association of choroidal neovascularization and central serous chorioretinopathy with optical coherence tomography angiography. *JAMA Ophthalmol* 2015; **133**(8): 899–906.
- 6 Costanzo E, Cohen SY, Miere A, Querques G, Capuano V, Semoun O *et al*. Optical coherence tomography angiography in central serous chorioretinopathy. *J Ophthalmol* 2015; **2015**: 134783.
- 7 Quaranta-El Maftouhi M, El Maftouhi A, Eandi CM. Chronic central serous chorioretinopathy imaged by optical coherence tomographic angiography. *Am J Ophthalmol* 2015; **160**(3): 581–587 e581.
- 8 Teussink MM, Breukink MB, van Grinsven MJ, Hoyng CB, Klevering BJ, Boon CJ *et al*. OCT angiography compared to fluorescein and indocyanine green angiography in chronic central serous chorioretinopathy. *Invest Ophthalmol Vis Sci* 2015; **56**(9): 5229–5237.
- 9 Kuroda Y, Ooto S, Yamashiro K, Oishi A, Nakanishi H, Tamura H *et al*. Increased choroidal vascularity in central serous chorioretinopathy quantified using swept-source optical coherence tomography. *Am J Ophthalmol* 2016; **169**: 199–207.

- 10 Casalino G, Del Turco C, Corvi F, Rafaeli O, Bandello F, Querques G. Short-term retinal sensitivity and metamorphopsia changes following half-fluence photodynamic therapy in central serous chorioretinopathy. *Ophthalmic Res* 2016; **56**(1): 23–29.
- 11 Samara WA, Say EA, Khoo CT, Higgins TP, Magrath G, Ferenczy S *et al*. Correlation of foveal avascular zone size with foveal morphology in normal eyes using optical coherence tomography angiography. *Retina* 2015; **35**(11): 2188–2195.
- 12 Shahlaee A, Pefkianaki M, Hsu J, Ho AC. Measurement of foveal avascular zone dimensions and its reliability in healthy eyes using optical coherence tomography angiography. *Am J Ophthalmol* 2016; **161**: 50–55 e51.
- 13 Battaglia Parodi M, Cicinelli MV, Rabiolo A, Pierro L, Bolognesi G, Bandello F. Vascular abnormalities in patients with Stargardt disease assessed with optical coherence tomography angiography. *Br J Ophthalmol* 2016; **101**(6): 780–785.
- 14 Chidambara L, Gadde SG, Yadav NK, Jayadev C, Bhanushali D, Appaji AM *et al*. Characteristics and quantification of vascular changes in macular telangiectasia type 2 on optical coherence tomography angiography. *Br J Ophthalmol* 2016; **100**(11): 1482–1488.
- 15 Goktas A. Correlation of subretinal fluid volume with choroidal thickness and macular volume in acute central serous chorioretinopathy. *Eye (Lond)* 2014; **28**(12): 1431–1436.
- 16 Maruko I, Iida T, Sugano Y, Ojima A, Sekiryu T. Subfoveal choroidal thickness in fellow eyes of patients with central serous chorioretinopathy. *Retina* 2011; **31**(8): 1603–1608.
- 17 Lee WJ, Lee JH, Lee BR. Fundus autofluorescence imaging patterns in central serous chorioretinopathy according to chronicity. *Eye (Lond)* 2016; **30**(10): 1336–1342.
- 18 Hayashi K, Hasegawa Y, Tokoro T. Indocyanine green angiography of central serous chorioretinopathy. *Int Ophthalmol* 1986; **9**(1): 37–41.
- 19 Menchini U, Virgili G, Lanzetta P, Ferrari E. Indocyanine green angiography in central serous chorioretinopathy. ICG angiography in CSC. *Int Ophthalmol* 1997; **21**(2): 57–69.
- 20 Tsujikawa A, Ojima Y, Yamashiro K, Ooto S, Tamura H, Nakagawa S *et al*. Punctate hyperfluorescent spots associated with central serous chorioretinopathy as seen on indocyanine green angiography. *Retina* 2010; **30**(5): 801–809.
- 21 Yannuzzi LA. Indocyanine green angiography: a perspective on use in the clinical setting. *Am J Ophthalmol* 2011; **151**(5): 745–751 e741.
- 22 Tomasso L, Benatti L, Rabiolo A, Carnevali A, Zucchiatti I, Querques L *et al*. Retinal vessels functionality in eyes with central serous chorioretinopathy. *Br J Ophthalmol* 2017; e-pub ahead of print 9 June 2017; doi: 10.1136/bjophthalmol-2017-310398.
- 23 Cicinelli MV, Carnevali A, Rabiolo A, Querques L, Zucchiatti I, Scordia V *et al*. Clinical spectrum of macular-foveal capillaries evaluated with optical coherence tomography angiography. *Retina* 2017; **37**(3): 436–443.
- 24 La Spina C, Carnevali A, Marchese A, Querques G, Bandello F. Reproducibility and reliability of optical coherence tomography angiography for foveal avascular zone evaluation and measurement in different settings. *Retina* 2016; **37**(9): 1636–1641.
- 25 Yanik Odabas O, Demirel S, Ozmert E, Batioglu F. Repeatability of automated vessel density and superficial and deep foveal avascular zone area measurements using optical coherence tomography angiography: diurnal findings. *Retina* 2017; e-pub ahead of print 2 May 2017; doi: 10.1097/IAE.0000000000001671.
- 26 Venugopal JP, Rao HL, Weinreb RN, Pradhan ZS, Dasari S, Riyazuddin M *et al*. Repeatability of vessel density measurements of optical coherence tomography angiography in normal and glaucoma eyes. *Br J Ophthalmol* 2017; e-pub ahead of print 24 July 2017; doi: 10.1136/bjophthalmol-2017-310637.
- 27 Yalcinbayir O, Gelisken O, Akova-Budak B, Ozkaya G, Gorkem Cevik S, Yucel AA. Correlation of spectral domain optical coherence tomography findings and visual acuity in central serous chorioretinopathy. *Retina* 2014; **34**(4): 705–712.
- 28 Salehi M, Wenick AS, Law H, Evans JR, Gehlbach P. Interventions for central serous chorioretinopathy: a network meta-analysis. *Cochrane Database Syst Rev* 2015; (12): CD011841.
- 29 Mehta PH, Meyerle C, Sivaprasad S, Boon C, Chhablani J. Preferred practice pattern in central serous chorioretinopathy. *Br J Ophthalmol* 2016; **101**(5): 587–590.
- 30 Chan WM, Lam DS, Lai TY, Tam BS, Liu DT, Chan CK. Choroidal vascular remodelling in central serous chorioretinopathy after indocyanine green guided photodynamic therapy with verteporfin: a novel treatment at the primary disease level. *Br J Ophthalmol* 2003; **87**(12): 1453–1458.
- 31 Lim JJ, Glassman AR, Aiello LP, Chakravarthy U, Flaxel CJ, Spaide RF *et al*. Collaborative retrospective macula society study of photodynamic therapy for chronic central serous chorioretinopathy. *Ophthalmology* 2014; **121**(5): 1073–1078.
- 32 Reibaldi M, Cardascia N, Longo A, Furino C, Avitabile T, Faro S *et al*. Standard-fluence versus low-fluence photodynamic therapy in chronic central serous chorioretinopathy: a nonrandomized clinical trial. *Am J Ophthalmol* 2010; **149**(2): 307–315 e302.
- 33 Ma J, Meng N, Xu X, Zhou F, Qu Y. System review and meta-analysis on photodynamic therapy in central serous chorioretinopathy. *Acta Ophthalmol* 2014; **92**(8): e594–e601.
- 34 Zhao M, Celerier I, Bousquet E, Jeanny JC, Jonet L, Savoldelli M *et al*. Mineralocorticoid receptor is involved in rat and human ocular chorioretinopathy. *J Clin Invest* 2012; **122**(7): 2672–2679.
- 35 Delyani JA. Mineralocorticoid receptor antagonists: the evolution of utility and pharmacology. *Kidney Int* 2000; **57**(4): 1408–1411.
- 36 Chung YR, Kim JW, Kim SW, Lee K. Choroidal thickness in patients with central serous chorioretinopathy: assessment of Haller and Sattler layers. *Retina* 2016; **36**(9): 1652–1657.
- 37 Maruko I, Iida T, Sugano Y, Ojima A, Ogasawara M, Spaide RF. Subfoveal choroidal thickness after treatment of central serous chorioretinopathy. *Ophthalmology* 2010; **117**(9): 1792–1799.
- 38 Gergely R, Kovacs I, Schneider M, Resch M, Papp A, Recsan Z *et al*. Mineralocorticoid receptor antagonist treatment in bilateral chronic central serous chorioretinopathy: a comparative study of exudative and nonexudative fellow eyes. *Retina* 2016; **37**(6): 1084–1091.
- 39 Oh BL, Yu HG. Choroidal thickness after full-fluence and half-fluence photodynamic therapy in chronic central serous chorioretinopathy. *Retina* 2015; **35**(8): 1555–1560.
- 40 Kinoshita T, Mitamura Y, Mori T, Akaiwa K, Semba K, Egawa M *et al*. Changes in choroidal structures in eyes with chronic central serous chorioretinopathy after half-dose photodynamic therapy. *PLoS One* 2016; **11**(9): e0163104.
- 41 Schmidt-Erfurth U, Laqua H, Schlotzer-Schrehard U, Viestenz A, Naumann GO. Histopathological changes following photodynamic therapy in human eyes. *Arch Ophthalmol* 2002; **120**(6): 835–844.

Multimodal retinal imaging in central serous chorioretinopathy treated with oral eplerenone or photodynamic therapy

To obtain credit, you should first read the journal article. After reading the article, you should be able to answer the following, related, multiple-choice questions. To complete the questions (with a minimum 75% passing score) and earn continuing medical education (CME) credit, please go to <http://www.medscape.org/journal/eye>. Credit cannot be obtained for tests completed on paper, although you may use the worksheet below to keep a record of your answers.

You must be a registered user on <http://www.medscape.org>. If you are not registered on <http://www.medscape.org>, please click on the "Register" link on the right hand side of the website.

Only one answer is correct for each question. Once you successfully answer all post-test questions you will be able to view and/or print your certificate. For questions regarding this

activity, contact the accredited provider, CME@medscape.net. For technical assistance, contact CME@medscape.net. American Medical Association's Physician's Recognition Award (AMA PRA) credits are accepted in the US as evidence of participation in CME activities. For further information on this award, please go to <https://www.ama-assn.org>. The AMA has determined that physicians not licensed in the US who participate in this CME activity are eligible for *AMA PRA Category 1 Credits™*. Through agreements that the AMA has made with agencies in some countries, AMA PRA credit may be acceptable as evidence of participation in CME activities. If you are not licensed in the US, please complete the questions online, print the AMA PRA CME credit certificate, and present it to your national medical association for review.

1. Your patient is a 43-year-old man with untreated central serous chorioretinopathy (CSC). On the basis of the prospective, observational study by Rabiolo and colleagues, which one of the following statements about pretreatment correlations among function, structural optical coherence tomography (OCT), and optical coherence tomography angiography (OCT-A) measures in patients with CSC is correct?
 - A Central macular thickness (CMT) and subretinal fluid (SRF) correlated to fovea avascular zone (FAZ) area ($P = .01$) and vessel density ($P = .01$) at the deep capillary plexus (DCP)
 - B Best-corrected visual acuity (BCVA) was significantly associated with structural OCT findings
 - C BCVA was significantly associated with OCT-A measures, including FAZ area and vessel density at every plexus
 - D Subfoveal choroidal thickness (SFCT) was significantly associated with CMT
2. According to the prospective, observational study by Rabiolo and colleagues, which one of the following statements about changes in function, structural OCT, and OCT-A after treatment of CSC is correct?
 - A Structural, but not vascular, measures improved after eplerenone
 - B Vascular, but not structural, measures improved after photodynamic therapy (PDT)
 - C OCT-A showed permanent damage of choriocapillaris and other choroidal layers after half-fluence PDT
 - D At 3 months after treatment, there were significant improvements in CMT ($P = .0011$), SRF ($P = .0005$), SFCT ($P = .0016$), and FAZ area at DCP ($P = .0334$)
3. According to the prospective, observational study by Rabiolo and colleagues, which one of the following statements about clinical implications of multimodal retinal imaging findings in patients with CSC is correct?
 - A Sight-threatening adverse events have not been reported after PDT
 - B Fluid under the neuroretina may centrifugally displace and squeeze retinal vessels, enlarging FAZ and increasing vessel density
 - C No mechanisms have been proposed to explain the therapeutic action of PDT
 - D The study proved that either half-fluence PDT or eplerenone significantly improved BCVA