

3:40 PM

Acute Macular Neuroretinopathy (AMN): New Insights into Diagnosis, Natural History and Pathogenesis as Revealed by Sequential Multimodal Imaging



- David Sarraf, MD
- Amani A. Fawzi, MD
- Rajeev Reddy Pappuru, MD
- Colin A. McCannel, MD
- Lucia Sobrin, MD
- Goldstein Debra
- Alexander Craig Walsh, MD
- Srinivas Reddy Sadda, MD
- Lee Jampol, MD

OBJECTIVE To describe novel findings of AMN in 8 patients (11 eyes) longitudinally evaluated with detailed multimodal imaging as early as 18 hours and as long as 14 months after disease onset.

PURPOSE To report the novel structural findings in acute macular neuro-retinopathy (AMN) and their long-term evolution as demonstrated by sequential multimodal retinal imaging including Fourier domain optical coherence tomography (FD-OCT), infrared (IR) reflectance and near IR autofluorescence (NIA).

METHODS Sequential multimodal imaging was performed in 8 patients (11 eyes) with AMN as early as 18 hours and as late as 14 months after disease onset. Manual segmentation of the FD-OCT volume scans was done of the AMN lesion to yield retinal sublayer topographic maps. Long term analysis with detailed multimodal imaging was conducted in all patients and a precise imaging map of the evolution of this disease was

formulated lending insight into the diagnosis, natural history and pathogenesis of this disease.

RESULTS Two patients were seen within 24 hours of disease onset and both showed outer nuclear and outer plexiform layer hyper-reflectivity with FD-OCT. Both patients developed darkening and enlargement of the lesion over the first week on IR reflectance imaging with corresponding outer retinal disruption on FD-OCT. OS/RPE and then IS/OS disruption was identified in all eyes with FD-OCT imaging within 1 to 2 weeks of disease onset. Thinning of the outer nuclear layer persisted in all patients with lesions >100 micron width, and in one patient this thinning worsened over the course of follow up, as noted on the sublayer maps. This structural abnormality correlated with long-term functional deficits, persisting up to 14 months after the initial episode.

CONCLUSION AMN lesions may initially only demonstrate OPL hyperreflectivity within the first 24 hours. OS/RPE and IS/OS disruption with FD-OCT ensues and correlates with progressive darkening of the AMN lesion with IR reflectance. The hallmark long-term changes are outer nuclear thinning on FD-OCT and a fading dark lesion on IR reflectance imaging.

TAKE HOME MESSAGE To demonstrate novel imaging findings by FD OCT and near infrared reflectance of the disease Acute Macular Neuroretinopathy

3:48 PM

Preclinical Evaluation and Intraoperative Human Retinal Imaging With a Microscope-Integrated Spectral Domain Optical Coherence Tomography Device



- Paul Hahn, MD, PhD
- Cynthia Ann Toth, MD
- Justin Migacz, MS
- Joseph Izatt, PhD
- Tomas A Moreno, BS
- Rachelle O'Connell

OBJECTIVE To provide updates on cutting-edge developments in the translation of a prototype Microscope-Integrated OCT (MIOCT) device into intraoperative human retinal imaging during vitreoretinal surgery.

PURPOSE We have recently developed a high-resolution Microscope-Integrated spectral domain Optical Coherence Tomography (MIOCT) device designed to enable OCT acquisition simultaneous with surgical maneuvers. The purpose of this report is to describe translation of this prototype device from preclinical testing into human intraoperative imaging.

METHODS

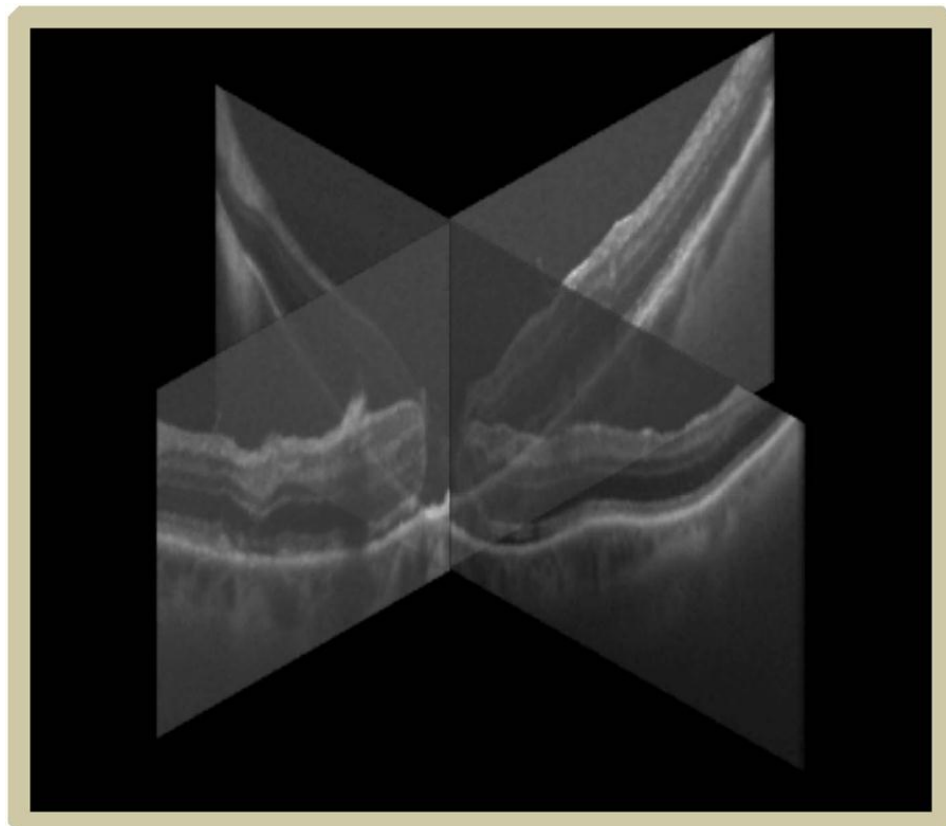
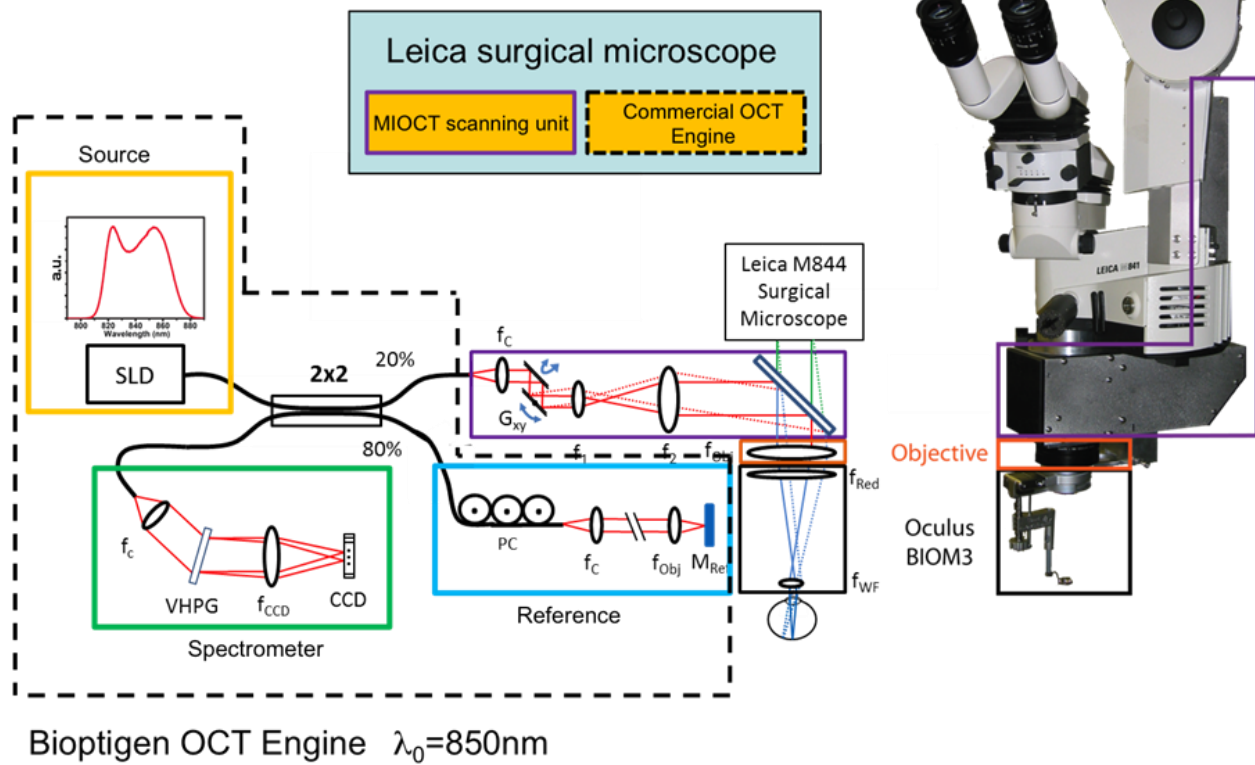
Prior to human imaging, surgical conditions were fully simulated for extensive preclinical MIOCT evaluation. MIOCT images were then acquired in normal human volunteers and in patients during vitreoretinal surgery. Intraoperative MIOCT images were obtained before and at pauses in surgical maneuvers and were compared based on pre-determined diagnostic criteria to images obtained with a handheld spectral domain OCT system (HHOCT, Bioptigen Inc., Research Triangle Park, NC) at the same time point. Cohorts of five consecutive patients were imaged. Successful endpoints were predefined, including correlation in identification of pathology between MIOCT and HHOCT in 80% of patients.

RESULTS MIOCT was favorably evaluated by study surgeons and scrub nurses, all of whom responded that they would consider participating in human intraoperative imaging trials. The MIOCT transition into clinical human research was smooth. MIOCT of normal human volunteers demonstrated high-resolution imaging comparable to tabletop scanners. In the operating room, after an initial learning curve, surgeons successfully acquired human macular MIOCT images before and after surgical maneuvers. MIOCT imaging confirmed preoperative diagnoses, such as full-thickness macular hole and vitreomacular traction, and demonstrated post-surgical changes in retinal morphology. Two cohorts of five patients were imaged. In the second cohort, the predefined endpoints were exceeded with 80% correlation between MIOCT and HHOCT imaging in 100% of patients.

CONCLUSION

This report describes high-resolution MIOCT imaging using our prototype device in human eyes during vitreoretinal surgery, with successful achievement of predefined endpoints for imaging. Further refinements and investigations will be directed towards fully integrating MIOCT with vitreoretinal and other ocular surgery to image surgical maneuvers in real time.

TAKE HOME MESSAGE Our group at the Duke Eye Center is actively developing a microscope-integrated SDOCT system to enable intrasurgical OCT imaging concurrent with surgical maneuvers and surgical viewing.



4:00 PM

PIONEER: A Prospective Intraoperative and Perioperative OCT Study--6 Month Vitreoretinal Results



- Justis P. Ehlers, MD
- Peter K. Kaiser, MD
- Alex Yuan, MD
- Gina M. Smith
- Sunil Srivastava, MD

OBJECTIVE To demonstrate the feasibility and results of intraoperative optical coherence tomography (*i*OCT) and perioperative OCT during vitreoretinal surgery.

PURPOSE The cross-sectional anatomic information obtained with OCT provides a natural complement to the retinal surgeon, but the specific role of OCT in surgery remains unknown. PIONEER is a prospective single-center study examining the utility of *i*OCT and perioperative OCT in the management of vitreoretinal surgical diseases.

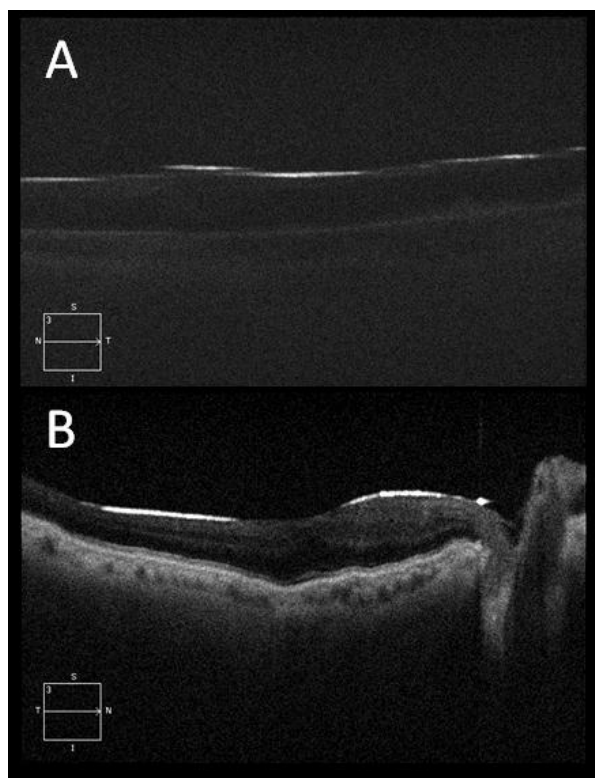
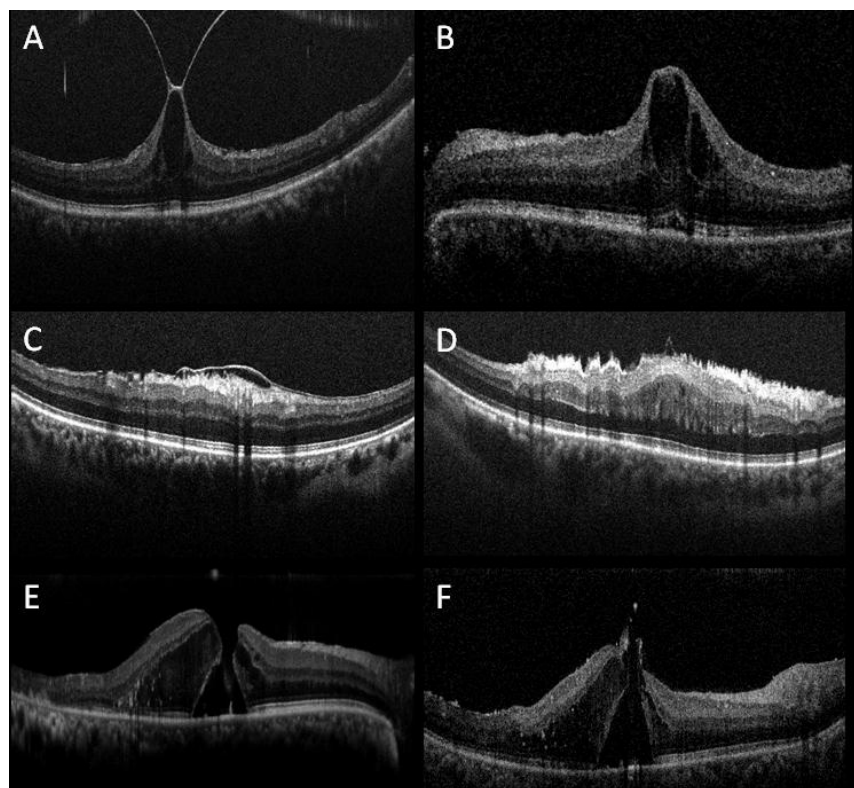
METHODS An IRB-approved prospective study was initiated including patients undergoing incisional vitreoretinal surgery. A custom surgical microscope-mount system was constructed for a handheld spectral domain OCT probe. A prespecified imaging protocol was developed to provide for robust image analysis and

standardization across surgeons. Fifty-one subjects were enrolled. Images were obtained using the *i*OCT system prior to initiating surgery and following key surgical milestones (e.g., after elevating the hyaloid). Additionally, trans-tamponade (e.g., gas) OCT scans were obtained 1 hour and 1 day postoperatively to assess early post-surgical architectural dynamics (e.g., macular hole closure).

RESULTS Forty-nine of 51 subjects were included due to 2 subjects exiting the study prior to imaging. Surgical diagnosis was epiretinal membrane in 15 eyes, retinal detachment in 11 eyes, macular hole in 10 eyes, proliferative diabetic retinopathy in 10 eyes, vitreomacular traction in 2 eyes, and optic pit in 1 eye. Successful *i*OCT imaging was achieved in all cases. Novel *i*OCT findings included subclinical alterations in foveal architecture, increased hyporeflectivity under IS/OS line after membrane peeling, and macular hole configuration changes following surgical manipulation. Trans-tamponade OCT was attempted for 10 eyes at post-op 1-hour and for 34 eyes on post-op day 1. Post-op 1-hour scans were successfully obtained in 9 of 10 eyes although quality was generally poor. On post-op day 1, scans were successfully obtained in 34 of 34 eyes with improved quality compared to post-op 1-hour scans. The main variable associated with trans-tamponade scan quality was pseudophakia.

CONCLUSION Significant subclinical architectural alterations to retinal anatomy are noted with *i*OCT following surgical maneuvers. Identifying these changes may help facilitate our understanding of functional and anatomic outcomes, potentially improving surgical success. This study helps to lay the foundation for future disease-specific validation of *i*OCT utility and the impact of *i*OCT findings on outcomes.

TAKE HOME MESSAGE Intraoperative OCT is feasible in numerous vitreoretinal surgical diseases. Novel findings associated with surgical maneuvers may help improve our understanding of functional/anatomic outcomes.



4:04 PM

Automated Drusen Segmentation and Quantification in SD-OCT Images



- Theodore Leng, MD, MS
- Daniel Rubin, MD, MS

OBJECTIVE To describe a novel automatic drusen segmentation method for SD-OCT retinal images, which leverages *a priori* knowledge of normal retinal morphology and anatomical features.

PURPOSE To design a novel algorithm to automatically and quantitatively segment drusen in patients with age-related macular degeneration. Biomarkers for potential disease progression, such as drusen area and volume were correlated to clinical information.

METHODS An automated algorithm was developed for analyzing SD-OCT scans of AMD patients, which consisted of the following: 1. Image denoising with a modified bilateral filtering algorithm. 2. Removal of the RNFL. 3. Extraction of the RPE layer through interpolation. A fitting procedure was used in areas where the RPE was distorted by drusen. 4. Segmentation of drusen in the areas located between the interpolated and fitted RPE. 5. Refinement of the initial drusen segmentation by using an *en face* drusen projection image restricted to the sub-volume of the image containing the RPE and

drusen segmentation. 6. Elimination of false positive drusen. 7. Drusen refinement 8. Drusen smoothing.

RESULTS After image denoising, each SD-OCT cube (128 B-scans) was segmented in ~ 6 minutes. A total of 19 SD-OCT scans were analyzed. We compared the automated segmentations to a manual gold standard and found a close correlation (0.75). Thickness maps and 3D renderings were generated based on automated segmentations. Drusen areas and volumes were able to be generated over multiple timepoints and plotted over a 32 month time frame to be correlated with clinical data and disease status.

CONCLUSION A novel automated drusen segmentation algorithm for SD-OCT images was developed, which incorporates the 3D spatial information of the retina with information from drusen projection images. The algorithm was able to effectively segment different patterns of drusen. The qualitative and quantitative evaluations may be clinically useful for evaluating the progress of drusen.

TAKE HOME MESSAGE A lot of previously unused data can be extracted from SD-OCT scans and help to quantify disease and monitor disease status and progression.

4:08 PM

Does Spectral Domain OCT Provide Any Additional Information to Non-mydriatic Fundus Photography Screening?



- Rishi P. Singh, MD
- Richard Lang, MD, MPH
- Raul Seballos, MD
- Akshay Thomas, BS

OBJECTIVE To determine whether SDOCT improved the diagnostic capability of non-mydriatic fundus imaging.

PURPOSE Non-mydriatic fundus imaging has been used previously for the screening evaluation of patients for diseases such as glaucoma, age related macular degeneration, and diabetic retinopathy. The purpose of this study was to examine whether Spectral Domain OCT (SD-OCT) added any additional useful information to non-mydriatic single-field fundus photography screening.

METHODS Combined SD-OCT and non-mydriatic imaging was performed (Topcon OCT 2000) in both eyes of 568 consecutive patients. The SD-OCT scans were read independently. Images were obtained with sections through the macula and the optic

disk and corresponding fast macular thickness map and NFL analyses were performed. The 50 degree field fundus photographs were first read by two blinded graders. The reviewers were then presented with the OCT data and asked whether it confirmed, was non contributory, or refuted their initial diagnosis. In addition, two blinded graders reported cup to disc ratio and this was compared to the automated cup to disc ratio performed with the SD-OCT device.

RESULTS OCT scans were adequate in both eyes of 534 (94%) patients. OCT findings were normal in both eyes of 36.7% of patients. VMT was seen in at least one eye of 13.7% patients. PVD was seen in 26.18% patients. ERM was seen in 20 (3.75%) patients. An abnormal foveal contour was found in 17 (3.2%) patients. Drusen was seen in 14 (2.62%) patients. Lamellar holes and pseudoholes were each seen in 2 (0.38%) patients. Cystoid macular edema and sub-RPE fluid were each seen in 1 (0.19%) patient. The mean central retinal thickness was $253 \pm 14 \mu\text{m}$ (SD: $28.9 \pm 14 \mu\text{m}$). The SD-OCT imaging confirmed the diagnosis in 64% of patients, refuted it in 12%, and was non contributory in 24%.

CONCLUSION The addition of SD OCT has some additive benefit to non mydriatic imaging when confirming the initial diagnosis and rarely refuted the initial diagnosis for most disease states. In cases of ERM and VMT however, SDOCT improved the ability to detect these conditions over fundus photography alone.

TAKE HOME MESSAGE SD-OCT provides an additive benefit when evaluating patients in a non-mydriatic screening program.

4:12 PM

Functional Retinal Imaging with Triple-Wavelength Imaging Reflectometry (TIR)



- Kristie L. Lin, MD
- Jeff Fingler, PhD
- Xiquan Cui
- Michael J. Davis, MD
- Tom S. Chang, MD
- Scott Fraser, PhD

OBJECTIVE To describe the novel use of Triple-wavelength Imaging Reflectometry (TIR) as a functional assessment of photoreceptors and RPE cells as a biomarker of disease progression and response to treatment.

PURPOSE To describe the novel use of a direct, quantitative and high-resolution technology for functional retinal imaging, using Triple-wavelength Imaging Reflectometry (TIR). This technology measures the bleaching and recovery of rhodopsin as an assay for photoreceptor and RPE function. Objective measures from TIR may serve as useful adjunctive measures in clinical trials guided by functional outcomes.

METHODS Normal subjects and patients with dry AMD were dark adapted and exposed to light of 3 different wavelengths. A comparative study design was employed to evaluate

the hypothesis that functional retinal imaging using TIR could provide adjunctive measures for clinical management. TIR maps the density and recovery speed of rod rhodopsin over a field-of-view of 30° with a resolution better than 0.5°. Imaging time was shortened to a few minutes, as the regeneration of rhodopsin in human is faster than in rats. The method can also permit analysis of other photoreceptor cell types (e.g. L, M, S cones) by using different wavelengths.

RESULTS Eyes from 10 patients and normal subjects were imaged. Disease entities included early and advanced dry macular degeneration. We successfully demonstrated the measurement of rod rhodopsin with high sensitivity, without interference of transient photoproducts (metarhodopsin III), and free of eye motion artifacts. Changes to photoreceptor function in diseased eyes when compared to normal subjects were largely consistent with visual function variations. Often, retinal functional changes preceded visual complaints. Overall, the system provided easy clinical access to measuring and assessing the functional health of the retina *in vivo*. The objective measurements from TIR may serve as useful adjunctive measures in clinical trials guided by functional outcomes.

CONCLUSION TIR is a non-invasive, high resolution and easy-to-use functional retinal imaging technology that allows us to measure longitudinal changes in photoreceptor function for patients with central macular diseases like dry AMD. As newer therapeutics are developed, the distinctive and quantitative biomarkers from TIR may become an increasingly important biomarker of disease progression or improvement.

TAKE HOME MESSAGE As newer therapeutics are developed, the distinctive and quantitative biomarkers offered by TIR may become an increasingly important biomarker of disease progression and response to treatment.

4:24 PM

Microglia in Retina - Can We See Them In Vivo?



- Gennady Landa, MD
- Jonathan A Barnett
- Patricia Garcia
- Richard B. Rosen, MD

OBJECTIVE To evaluate inner plexiform layer reflectivity variations among patients with different outer retinal diseases in vivo.

PURPOSE Histological studies have suggested that only microglial cells have their cell bodies located in the inner plexiform layer (IPL), which functional significance is not well understood. We propose that IPL reflectivity may be related with the status of microglial population. Our purpose was to evaluate IPL reflectivity variations among patients with different outer retinal diseases in vivo.

METHODS Using High Resolution Spectral Domain OCT (SD-OCT) imaging, the inner plexiform layer appears highly reflective and can be identified between the ganglion cell layer and inner nuclear layer. Normal subjects, patients with dry AMD, geographic

atrophy, wet AMD and patients with retinitis pigmentosa were imaged using high resolution SD OCT and IPL reflectivity was retrospectively analyzed using Photoshop software. Mean luminosity, which is the brightness of the IPL reflectivity, was the primary outcome measurement.

RESULTS Sixty-nine eyes of 62 patients composed study population. In comparison to normal subjects (91.7 ± 10.4), the mean luminosity of the IPL was significantly lower in patients with geographic atrophy (74.0 ± 15.8 ; $p=0.018$) and retinitis pigmentosa (71.8 ± 19.1 ; $p=0.0003$).

CONCLUSION Evaluation of the IPL reflectivity may be important in ocular diseases with primary involvement of outer retina, such as AMD and RP. The microglial status in vivo can be indirectly evaluated based on alteration in reflectivity of the inner plexiform layer seen on SD-OCT. Further studies are warranted to further investigate a role of microglia in patients with various ocular diseases.

TAKE HOME MESSAGE Variations of the inner plexiform layer reflectivity may be related to the microglial status in ocular diseases with primary involvement of outer retina, such as AMD and RP.

4:28 PM

Effect of Area of Peripheral Retinal Non-perfusion on Treatment Response in Branch and Central Retinal Vein Occlusion



- Michael A. Singer, MD
- Colin S Tan, MBBS, MMed (Ophth), FRCSEd (Ophth)
- Darren J. Bell, MD
- Joe Pollard, MPH, CCRC
- Srinivas Reddy Sadda, MD

OBJECTIVE To evaluate the amount of retinal non-perfusion in patients with retinal vein occlusion and determine the effect of area on treatment response.

PURPOSE To evaluate the extent of peripheral retinal non-perfusion in patients with branch or central retinal vein occlusion (BRVO & CRVO) and to determine the effect of the area of ischemia on the response to treatment, and requirement for re-treatment.

METHODS Thirty-two patients presenting with BRVO or CRVO at the Medical Center Ophthalmology Associates, San Antonio, were treated with intravitreal injections of anti-VEGF and/or dexamethasone intravitreal implant (Ozurdex). At all visits, patients underwent 200-degree widefield fluorescein angiography (FA) and color fundus

photography using the Optos 200Tx, and spectral domain optical coherence tomography (OCT) using the Cirrus OCT. The FA images were centered on the fovea, then steered peripherally. All images were graded by a masked investigator. The areas of ischemia were mapped out using a validated software (GRADOR), and this was calculated as a percentage of the total area of retina visible.

RESULTS The mean area of retinal ischemia was 13.4% (range, 0% to 51.4%, SD $\hat{A}\pm 15.5$), with 18 patients (56.2%) having ischemia of $\hat{A}\leq 10\%$, while the remaining 14 (43.8%) had areas of ischemia $>10\%$. The area of non-perfusion was larger when macular edema was present compared to when the edema had resolved (14.8% vs. 10.3%, $p<0.001$). With macular edema, the mean central subfield thickness on OCT showed a trend to be thicker in those with total areas of ischemia $>10\%$ compared to those $\hat{A}\leq 10\%$ ($513.9\text{ }\mu\text{m}$ vs. $435.3\text{ }\mu\text{m}$, $p=0.177$). Similarly, the decrease in OCT thickness in response to treatment was greater for those with ischemia $>10\%$ ($289.4\text{ }\mu\text{m}$ vs. $177.8\text{ }\mu\text{m}$, $p=0.05$). Patients with $>10\%$ ischemia had worse visual acuity (VA) with macular edema present (54.6 letters vs. 69.7) and experienced a larger gain in VA with treatment (12.6 letters vs. 1.6). The time to recurrence of macular edema was slightly longer for those with areas of ischemia $\leq 10\%$ (3.5 vs. 2.9 months).

CONCLUSION Patients with BRVO and CRVO demonstrate considerable variability in the extent of peripheral retinal non-perfusion at baseline, which affects the initial amount of retinal thickening and the magnitude of reduction in retinal thickness on OCT and improvement in VA with treatment. Increased areas of peripheral retinal non-perfusion may drive VEGF production and result in more severe macular edema.

TAKE HOME MESSAGE Anti-VEGF injections in Retinal Vein Occlusion patients are associated with changes in peripheral ischemia as well as reduction in OCT thickness.

