YERBA BUENA GARDEN — SFMOMA

SATURDAY
Digital Ultrasound and Optical Coherence Tomography-guided Measurement of Choroidal Thickness and Flow Following Systemic Sildenafil

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PURPOSE: To demonstrate anatomic and flow changes in the human choroid following systemic sildenafil.

METHODS: An index patient presented with vitreous hemorrhage one day following sildenafil (Viagra, Pfizer, New York NY) ingestion. Subsequently, a provocative test with Viagra demonstrated increased flow in the choroid by a factor of two. Based on this information, a pilot study was performed under Institutional Review Board approval. Seven normal eyes were evaluated using enhanced depth imaging-spectral domain OCT (EDI-OCT), digital very high frequency ultrasound, intraocular pressure screening, fluorescein angiography, and color vision screening. The measurement technique used swept scan very high frequency digital ultrasound analysis to demonstrate choroidal flow. Swept scan flow measurements offer significant advantage over Doppler techniques, in that flow can be accurately measured regardless of transducer orientation. With swept mode imaging, the transducer moves across different areas, allowing more accurate measurement in small vessels. Pre- and post-systemic Viagra, we also measured choroidal thickness with digital very high frequency ultrasound and EDI-OCT.

RESULTS: All subjects demonstrated increased choroidal flow measured very high frequency ultrasound, with the range of variation of 1.23 to 7.80 times baseline (p = 0.004). Fluorescein angiography showed no significant variation in fill time or vessel caliber. Choroidal thickness measured with EDI-OCT (mean pre: 281.3 µm, post: 311.8 µm, p = 0.0001) and ultrasound showed increased thickness for all eyes.

CONCLUSIONS: This study has characterized the changes in choroidal blood flow and choroidal thickening as a response to sildenafil which could secondarily affect retinal and retinal pigment epithelial function, and explain previously reported clinical symptoms. Also, sildenafil can be a potentially useful adjunct to treatment of ocular diseases which would benefit from increased choroidal blood flow in the eye.
The Effects of Sildenafil Citrate (Viagra®) on Choroidal Thickness as Determined by Enhanced Depth Imaging Spectral Domain Optical Coherence Tomography

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PURPOSE: To investigate the effects of the phosphodiesterase-5 (PDE-5) inhibitor, sildenafil citrate, on choroidal thickness using eye-tracked enhanced depth imaging spectral-domain optical coherence tomography (EDI-OCT).

METHODS: In an FDA and IRB approved prospective interventional protocol, 8 healthy subjects (4 male, 4 female) with no ocular history underwent EDI-OCT at baseline, 1 hour and 3 hours following the ingestion of 100 mg of sildenafil citrate. EDI-OCT choroidal thickness measurements for both eyes were taken by two masked readers at baseline and at 1 hour and 3 hour time points. Statistical analysis was performed to compare the measurements of choroidal thickness at each of the three intervals.

RESULTS: The mean age of the subjects was 35.9 years (range 30-46). Mean choroidal thickness at baseline was 334 um (± 57.2 um). Mean choroidal thickness increased by 12.3% to 375 um (± 67.6 um ) at 1 hour after ingestion (p < 0.001). At 3 hours after ingestion, the mean choroidal thickness remained elevated at 372 um (± 61.0 um), 11.6% thicker than baseline (p < 0.001). There was no significant difference in choroidal thickness between the 1 hour and 3 hour intervals (p=0.719).

CONCLUSIONS: Sildenafil citrate appears to increase choroidal thickness as measured by eye-tracked EDI-OCT measurements in healthy patients 1 hour and 3 hours after ingestion. These findings may be of relevance given that increased choroidal thickness appears to be a risk factor for central serous chorioretinopathy (CSC), and that several recent reports have suggested an association between PDE-5 inhibitors and this disorder.
High Resolution Imaging of Retinal and Choroidal Vasculature with Phase Contrast Optical Coherence Tomography (OCT)

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Jeff Fingler, PhD, Susanna Park, MD, PhD, Larry Morse, MD, PhD, John Werner, PhD, Robert Zawadzki, PhD

PURPOSE: To test whether phase contrast OCT can non-invasively image choroidal neovascularization and retinovascular disease comparably to fluorescein angiography.

METHODS: Phase contrast OCT software was used to analyze data from spectral domain OCT imaging in 8 patients (4 with exudative macular degeneration, 2 with diabetic retinopathy, 2 with retinal vein occlusion). Using imaging analysis tools, results of phase contrast OCT analysis were compared to fluorescein angiography to determine how accurately phase contrast OCT depicted choroidal neovascularization and retinovascular abnormalities (microaneurysms, regions of capillary non-perfusion).

RESULTS: Phase contrast OCT accurately depicted choroidal neovascularization and retinovascular abnormalities in these patients. Fine details of the retinal and choroidal vasculature were observed by phase contrast OCT with resolution that was comparable to fluorescein angiography. Regions of enhanced vascular permeability (leakage) evident with fluorescein angiography were not detected with phase contrast OCT.

CONCLUSIONS: Phase contrast OCT is a novel non-invasive imaging technique that may provide an alternative to fluorescein angiography for imaging choroidal neovascularization and retinovascular disease.
Operating Microscope Mounted Spectral Domain Optical Coherence Tomography

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PURPOSE: To demonstrate an operating microscope-based spectral domain optical coherence tomography (MMOCT) system for human retinal and animal surgery imaging.

METHODS: A prototype MMOCT system was designed and constructed to interface into an ophthalmic surgical microscope and was fitted into a Leica ophthalmic system. Retinal imaging was performed under IRB approved protocol in healthy volunteers, without surgery or pupil dilation. MMOCT imaging assistance was also applied while performing various operative maneuvers in purchased fresh cadaveric porcine eyes. Surgical instruments utilized in the study included forceps, scissors, subretinal needles (both metallic and polyamide), diamond dusted scrapers, and silicone tipped cannulas. Imaging was performed in numerous locations (mid-vitreous, retinal surface, and subretinal space). In both the human non-surgical imaging and in model surgical imaging, volume scanning and linear scanning were performed with a standard protocol.

RESULTS: High resolution images of the human retina were successfully obtained using the prototype system in healthy volunteers. During surgical maneuvers in the model eyes, metallic instruments (e.g., forceps, scissors, and needles) showed high reflectivity with total shadowing below the instrument. Polyamide material had a moderate reflectivity with subtotal shadowing. Silicone instrumentation showed moderate reflectivity with the least amount of shadowing of the materials. Summed voxel projection MMOCT images (retinal images) provided clear visualization of the instruments against the retinal background utilized. B-scans revealed details of the interactions between the tissues and the instrumentation. Imaging was achieved in all locations (e.g., mid-vitreous, retinal surface, subretinal space). Tissue manipulations and iatrogenic injuries were successfully imaged (e.g., subretinal space cannulation, retinal elevation, retinal breaks).

CONCLUSIONS: High quality retinal imaging of human subjects is feasible with the MMOCT system. MMOCT provides high resolution intraoperative imaging with depth information including visualization of instrumentation, tissue manipulation, and imaging of retinal deformation during intraoperative maneuvers. This study demonstrates a major component of an interactive platform that could provide enhanced information for the vitreoretinal surgeon. This research was funded in part by: NCRR 1UL1 RR024128-01 and NEI R21-EY-019411.
Intraoperative Optical Coherence Tomography of Full Thickness Macular Holes: Quantifying Changes in Hole Anatomy Following Vitrectomy and Internal Limiting Membrane Peeling

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Charlie Wykoff, MD, Tom Albini, MD, Timothy Murray, MD, William Smiddy, MD, Marco Uggiero, PhD

PURPOSE: Optical coherence tomography (OCT) is invaluable for diagnosing FTMH and confirming anatomic closure postoperatively. Intraoperative OCT imaging may be valuable in the perioperative care of patients with FTMH and may provide insight into the mechanical effects of our surgical approach to its treatment. Relief of traction by cortical vitreous removal and peeling of the perifoveal internal limiting membrane (ILM) may result in quantifiable intraoperative changes in the size and configuration of FTMH. The purpose of this study was to examine for such quantifiable changes by spectral domain OCT (SD-OCT).

METHODS: Intraoperative SD-OCT was performed during FTMH surgery in patients using a Spectralis (Heidelberg Engineering, Vista, California, USA) SD-OCT device modified for the operative setting with patients in a supine position by mounting the unit vertically. Postoperative SD-OCT imaging was performed using the horizontally oriented clinic-based Spectralis unit. Institutional review board approval was obtained.

RESULTS: Intraoperative SD-OCT was performed during FTMH surgery for 6 eyes of 6 different patients, including 5 left eyes, 2 males and 4 females. Two patients were children, aged 7 and 14 years, and 4 patients were adults (mean 65 years, range 60-71 years). Intraoperatively before vitrectomy, complete SD-OCT imaging was obtained for all eyes (n=6). Following vitrectomy and indocyanine green-assisted ILM-peeling, complete SD-OCT imaging was obtained for 4 eyes. Additionally, following vitrectomy and removal of all cortical vitreous from the posterior pole but before ILM peeling, complete SD-OCT imaging was obtained for 3 eyes. Quantifiable changes in macular hole area and volume were observed intraoperatively. By postoperative month 1, 5 of the 6 macular holes were anatomically closed and visual acuity improved in each of these 5 cases. The one macular hole that did not close was in a 7 year old female.

CONCLUSIONS: Intraoperative SD-OCT in the setting of surgery for FTMH is possible and can reveal immediate, quantifiable changes in the size and configuration of FTMH. Such changes in macular anatomy may allow prognostication of visual and anatomic outcomes and may allow avoidance of prone positioning for some patients with FTMH.
How Accurate is Optical Coherence Tomography (OCT) in Predicting Posterior Vitreous Detachment (PVD)?

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**PURPOSE:** Detachment of the cortical vitreous from the retina has been proposed to be involved in the pathogenesis of macular holes, age-related macular degeneration, diabetic macular edema, and ischemic optic neuropathy. A clear definition of PVD is not widely accepted. OCT is often used to predict the presence or absence of cortical vitreous attachment. In performing vitrectomies the use of intraoperative triamcinolone is helpful in identifying cortical vitreous attachment to the surface of the retina. This study correlates the pre-operative OCT visualization of a hyper-reflective line anterior to the surface of the retina with the intra-operative demonstration of triamcinolone adherence to residual vitreous on the surface of the retina.

**METHODS:** On a consecutive series of 84 primary vitrectomies performed by the author between 2/1/08 and 1/31/10 intra-operative triamcinolone was used to identify the presence or absence of cortical vitreous attachment to the surface of the macula or optic nerve. These observations were correlated with the presence or absence of a hyper-reflective line seen anterior to the surface of the retina on pre-operative spectral domain OCT (Topcon 3D OCT) imaging.

**RESULTS:** The average age was 73 ± 8.1 years with 38 females and 46 males. The indications for surgery were macular pucker (37), macular hole (34), acute subfoveal hemorrhage (5), diabetic macular edema (4), vitreo-macular traction syndrome (3), and floaters (1). On 54 patients in whom spectral domain OCT did not identify a hyper-reflective line anterior to the retina only 3 of those patients were found to have triamcinolone-identified vitreous attached to the retina at the time of surgery. Of 30 patients in whom spectral domain OCT identified a hyper-reflective line anterior to the retina 6 of these patients were not found to have triamcinolone-identified vitreous attachment to the retina. Spectral domain OCT therefore had a 6% false negative rate and a 20% false positive rate in predicting intra-operative triamcinolone-identified vitreous attachment.

**CONCLUSIONS:** Spectral domain OCT is reasonably reliable in predicting the presence or absence of triamcinolone-identified cortical vitreous attachment.
Acute Changes in Macular Thickness and Volume in Response to Pharmacologic Intervention

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PURPOSE: To describe the acute changes in the human macula in the hours and days immediately following pharmacologic intervention for edema secondary to retinal vein occlusion or diabetes mellitus by repetitive OCT examination and to characterize potential differences in measurement according to type of instrumentation employed.

METHODS: IRB approval was obtained to study nine patients undergoing either intravitreal triamcinolone 4.0 mg (n=7) or bevacizumab 1.25 mg therapy (n=2) for macular edema secondary to either retinal vein occlusion (n=4) or diabetes (n=5). Optical Coherence Tomography (OCT) scans were taken at both baseline, and 1,3,6,24, and 48 hours following injection as well as one one week later using both Spectral Domain and Time Domain Methods (Cirrus and Stratus Units, Carl Zeiss Meditech, Dublin, Ca). Resulting data were plotted and compared between patients and units for interpretative purposes including calculation of both central macular thickness (CMT) and volume, as well as clearance rates expressed in um’s or ul’s per minute.

RESULTS: Cirrus measurements of central macular thickness (CMT) were significantly reduced at 3 hours (p=0.03, paired t test) and volume at 6 hours (p=0.03) with continued decline thereafter. Measurements with the Stratus also showed a decline at 24 hours for both CMT and volume (p=.04) Measurements were 40.9 um thicker on the Cirrus compared with the Stratus while volume measurements were 3.47 cubic u’s higher with the Cirrus. Rates of decline were 0.02-0.3 um/min for CMT.

CONCLUSIONS: Significant CMT and volume reductions occur in the first 6 hours after injection and at a rate that may be related to the pump function of the retinal pigment epithelium. There were no appreciable differences in kinetics between the triamcinolone and bevacizumab although the sample sizes were small and the study not powered to detect such a difference. These data may be important in understanding the pathophysiology of macular edema and its treatment as well as comparing the potency of newer pharmacologic agents. Significant difference exist between measurements of the thickness and volume of the abnormal macula when taken with the Cirrus compared with the Stratus Units.
First Instructional Real Time Website for Contact B-Scan Ultrasonography

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Purpose: Establish a free, real time website for ultrasound education to include basic lectures with narrative as well as animations and a library of representative real time Contact B-Scan images to aid in pattern recognition.

Methods: Build an interactive website with audio, written content and real time imaging. Lecture content (8 in series) derived from 40 years of teaching Contact B-Scan. Animations in real time establish and demonstrate basic concepts. A video library is established from clinical cases provided from world wide contributions. An editorial board reviews movies for characteristic patterns prior to posting. Summaries of each movie provide instructional information. Analytics determine world penetration. Feedback options establish communication for surveys, changes in lectures or movie segments.

Results: Website launch occurred in January 2010. Video Library of 30 cases demonstrate real time, clinical examples of abnormal Contact B-Scan patterns. Real time movie segments provide critical information not available in print imaging. Review of site analytics include world penetration of 47 countries. Daily updates permit review of logistics for lecture use and case reviews. Survey and feedback information to be updated for the meeting.

Conclusions: The first instructional real time website for Contact B-Scan Ultrasonography has been established. The site is free of charge.
Evaluation of Augmented Reality Applications in Ophthalmology

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PURPOSE: Augmented Reality is the use of live video imagery, which is digitally processed and “augmented” by the addition of interactive 3D graphic objects, allowing the mix of real and virtual worlds together in real time. Recent technological progress enabled the development of Augmented reality solutions in ophthalmology. The purpose of this study is to assess Augmented Reality applications in Ophthalmology.

METHODS: A surgical microscope and a retinal Laser delivery prototype, both integrating Augmented Reality solutions were evaluated. Previously acquired image such as OCT and angiography were overlaid in real time on the real view of the surgeon. The performances of the Augmented Reality software including the tracking and the rendering capabilities were assessed on 20 eyes. Spatial and temporal accuracy of the overlay in the macular and the peripheral areas were measured for both prototypes.

RESULTS: The two tested prototypes demonstrated high temporal performances with maximal reaction time under 190 msec. Spatial accuracy depended mainly on the resolution of the live video imagery and the location of the overlaid image on the retina. Macular overlays showed higher spatial performances than peripheral overlays.

CONCLUSIONS: The introduction of Augmented reality in the ophthalmologic field gives to the surgeon most of the needed information overlaid in real time on the surgical target which would improve dramatically the safety, accuracy and solve the need of per-operative analyze of previously acquired images. The two tested prototypes demonstrated performances matching a potential use in clinical ophthalmologic applications. Although in its infancy and despite all the difficulties and limitations which have to be assessed, Augmented Reality technology may bring tremendous benefits to several medical fields such as intra-operative imaging, surgical training, pre-operative planning and enhanced visualization.
Spectral Domain Optical Coherence Tomography (OCT) Segmentation Analysis Reveals Significant Macular Thinning in Asymptomatic Patients with Sickle Cell Disease

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PURPOSE: Macular changes (foveal depression sign) have been reported in patients with sickle cell retinopathy. The purpose of this study was to investigate the prevalence and degree of macular thinning on spectral domain optical coherence tomography (SDOCT) in asymptomatic sickle cell patients without clinically evident macular disease.

METHODS: Fifty eyes of 26 sickle cell patients without clinical evidence of maculopathy or ocular disease aside from SCR underwent SDOCT imaging using the Heidelberg Spectralis OCT machine. The SDOCT images were then exported and manually segmented. The inner limiting membrane, nerve fiber layer (NFL), outer plexiform layer and retinal pigment epithelium were delineated using ImageJ. A computerized program (developed in the Matlab) was used to measure the thicknesses of the NFL, inner retina (IRT) and outer retina (ORT). The thicknesses were evaluated for the central macular area (central 1 mm of the OCT scan), parafoveal area (0.5 to 1.5 mm eccentric to the foveal center) and perifoveal area (1.5 to 3 mm eccentric to the foveal center) for each eye. Results were compared to age and gender-matched healthy African-American controls (20 eyes of 10 patients).

RESULTS: The central macular thickness (CMT) was 220 +/- 3 µ (mean +/- SEM) in sickle cell eyes versus 240 +/- 6 µ in controls (paired t-test, p < 0.0001). Parafoveal retinal thicknesses were 319 +/- 2 µ nasally and 301 +/- 2 µ temporally for sickle cell eyes versus 330 +/- 4 µ nasally and 312 +/- 2 µ temporally for controls (p < 0.004). There were no significant differences in IRT in parafoveal and perifoveal (1.5 to 3 mm eccentricity) regions. Central macular ORT was 173 +/- 2 µ in sickle cell eyes versus 185 +/- 2µm in controls (p < 0.0001). ORTs in temporal parafoveal and perifoveal regions were 141 +/- 2 µ and 119 +/- 1 µ, respectively versus 151 +/- 2 µ and 124 +/- 3 µ in corresponding controls (p < 0.001).

CONCLUSIONS: Asymptomatic sickle cell eyes without evident clinical macular disease have significant foveal thinning and splaying was compared with age-matched controls.
Human Cone Anatomy in Macular Disease: Serial Adaptive Optics Scanning Laser Ophthalmoscopic Imaging of Cones in Idiopathic Macular Teleangectasia

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PURPOSE: To serially investigate the photoreceptor (cone) array in different stages of perifoveal macular telangiectasia (mactel) with the adaptive optics scanning laser ophthalmoscope (AOSLO). This technology can acquire high-fidelity en face scans of the retina with two micron lateral resolution, and may have important clinical and research utility in the study of a broad range of conditions affecting the macula, including age-related macular degeneration.

METHODS: In this observational case series, high-resolution retinal images of 15 eyes from 8 patients were obtained with AOSLO. A number of patients were imaged at different time points, as much as 8 months apart. Conventional clinical measures including spectral domain OCT (SD-OCT), color fundus photos, autofluorescence and fluorescein angiograms were also obtained and included in data analyses. Qualitative measures of AOSLO images included the integrity and reflectivity of the cone array. Images were quantified by multiple measures including Voronoi analyses and cone spacing relative to the foveal center. Statistical comparisons were made with data from over 20 normal healthy eyes, and with data from the same maculae over time.

RESULTS: AOSLO imaging allowed visualization of cone arrays in mactel patients. Characteristic patterns included focal areas of cone loss (which were consistent with SD-OCT), hyper reflective and surrounding regions of contiguous cone arrays with spacing that was no different from healthy eyes. Hyper-reflective cone mosaics were observed to have increased polymorphism (p=0.032). New areas of focal cone loss were observed in eyes over time. Comparisons with data obtained from SD-OCT confirm the accuracy of the IS-OS junction as it relates to areas of cone loss. Motion contrast imaging demonstrates, in high resolution, abnormal capillary remodeling in the outer retina over time.

CONCLUSIONS: This study suggests cone anatomy and pathology can be observed in various stages of macular telangiectasia. Statistical analyses of cone spacing may correlate with disease presence, severity and possibly prognosis. Motion contrast imaging provides a high-resolution view of abnormal macular vasculature and its changes over time, although the relationship to cone pathology and loss remains undetermined. Serial imaging of cone anatomy, and cone reflectivity may or may not prove to be a meaningful prognostic indicator and / or provide a quantitative clinical endpoint capable of measuring disease progression or response to intervention. AOSLO imaging substantiates the clinical importance of following the IS-OS junction with SD-OCT and may provide important insights into the pathophysiology of cone loss in macular diseases.
Quantitative Analysis of Peripheral Ultra-wide Field Angiographic Hyperfluorescence in Patients with Macular Degeneration

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PURPOSE: To assess and quantify vascular and peripheral angiographic findings of patients with age-related macular degeneration (AMD) and quantify the therapeutic affect of Anti-VEGF treatment.

METHODS: A retrospective quantitative analysis was performed on 185 subjects: 80 with wet AMD, 60 with dry AMD and 45 controls who had undergone imaging with ultra-wide field fluorescein angiography (Optos). The analysis was to assess peripheral changes, vascular patterns, and luminance. Each image was normalized for luminance gamma and the maximum arterial luminance was calculated to give a baseline measurement. The area of evaluation was standardized and color segmentation was created based on pixel luminance, enabling an analysis of extrapolated quantitative value for the region. VA (Early Treatment Diabetic Retinopathy Study [ETDRS] letters), central foveal thickness (CFT), fluorescein leakage, and quantitative image analysis were performed.

RESULTS: Of 80 wet AMD patients, mean age (+SD) 82.9 ± 9.2, mean VA (+ SEM) of was 45.6 ± 13.5 ETDRS Letters, CFT (± SEM) of 371.6 ± 130.4, peripheral FA hyper-fluorescence in 82.5%. Extrapolated quantitative luminance value mean 1134.4, range 137 to 2117.6. Of 60 dry AMD patients, mean age (+SD) 77.9 ± 6.2, mean VA (+ SEM) of was 69.6 ± 10.1 ETDRS Letters, CFT (± SEM) of 301.6 ± 30.4, peripheral FA hyper-fluorescence in 73.3%. Extrapolated quant luminance value mean 784.4, range 151.3 to 1701.7. Of 45 control eyes, mean age (+SD) 62.9 ± 9.2, mean VA (+ SEM) of was 45.6 ± 13.5 ETDRS Letters, CFT (± SEM) of 371.6 ± 130.4, peripheral FA hyper-fluorescence in 82.5%. Extrapolated quant luminance value mean 276.8, range 0 to 503.2.

CONCLUSIONS: Quantification of peripheral perfusion and relative ischemia, based on normalized gamma pixel luminance is possible using ultra-wide field fluorescein angiography. This objective, numerical value may be a useful adjunct in the determining the efficacy and choice of anti-VEGF therapy in controlling macular leakage in these patients. Dynamic wide field angiographic quantitative analysis can possibly allow for eyes with wet AMD to be treated more specifically, or may correlate and indicate those dry AMD patients who may be at greater risk for converting to wet AMD. A statistically powered prospective trial is planned to further examine the utility of quantifying peripheral angiographic hyperfluorescence in macular degeneration.
AWARD OF MERIT IN RETINA RESEARCH
CHARLES L. SCHEPENS LECTURE
Retinitis Pigmentosa: Advances in Diagnosis and Treatment

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PURPOSE: To present some advances in the diagnosis and treatment of retinitis pigmentosa (RP).

METHODS: Electroretinograms, molecular genetic analyses, clinical trials.

RESULTS: Patients with progressive forms of RP can be detected in early life based on reduced and delayed ERGs often many years before diagnostic changes are seen with the ophthalmoscope. Molecular genetic analyses have revealed more than 50 causative genes that account for 50-60% of cases in the United States. A cone ERG actuarial table has been developed to estimate long-term visual prognoses. The typical forms of RP are treatable as follows: vitamin A palmitate 15,000 IU/day, on average, slows the course; docosahexaenoic acid (DHA) 1200 mg/day further slows the course for 2 years among those starting vitamin A for the first time; and lutein 12 mg/day slows decline in midperipheral visual field sensitivity among those on vitamin A. Patients on a high omega-3 fish diet (i.e. 1-2 three-ounce servings of oily fish/week of which DHA is a major constituent) have a slower course than those on a low omega-3 fish diet. Some rare forms (e.g. abetalipoproteinemia, Refsum disease, and familial vitamin E deficiency) are also treatable with nutritional interventions.

CONCLUSIONS: Both typical and rare forms of RP have yielded to nutritional therapies. Patients with typical RP, who would be expected to lose vision by age 60 without treatment, could achieve an estimated 20-year benefit by starting vitamin A, DHA, and lutein in their mid-30s and retain vision until age 80.
FELLOWSHIP RESEARCH AWARD

The Effect of HMG-CoA Reductase Inhibitors on the Development of Age-related Macular Degeneration

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David Zacks, MD, PHD, Nidhi Talwar, MS, Bin Nan, PHD, Joshua Stein, MD, MS

PURPOSE: To determine if HMG-CoA Reductase Inhibitors (statins) have an effect on the development of age-related macular degeneration (ARMD).

METHODS: Claims data from a large, national U.S. managed care network was reviewed to identify individuals age > 55 who had one or more visits to an eye care provider from 2001-2007. ICD-9 billing codes were used to identify enrollees who were diagnosed with non-exudative or exudative AMD during this time period. Beneficiaries were excluded if they had not been previously diagnosed with hyperlipidemia. A one year look back was then used to determine the total number of months each beneficiary was taking statins. A Cox regression analysis was performed to determine the relative hazard of developing ARMD based on statin use with adjustment for sociodemographic factors, ocular and medical conditions.

RESULTS: Complete claims and prescription medication data was available for 553,585 beneficiaries who met the inclusion criteria of which 57.4% used statins during the observation period. The average age of the sample was 63.0 years old and had an age range of 55-87. A total of 36,180 new cases of ARMD were diagnosed. After adjustment for sociodemographics, other ocular and medical conditions, for every additional month of statin use, the hazard of developing ARMD was reduced by 0.1% (p = 0.0586). Enrollees receiving statins continuously over an entire year had a 1.2% decreased hazard of developing ARMD relative to others who received no statins.

CONCLUSIONS: The findings from this analysis suggest that the use of statins can reduce the development of ARMD. This data, taken with other previous reports, suggest a randomized controlled trial is warranted to better understand whether statins are protective against ARMD.
RAYMOND R. MARGHERIO AWARD

En Face Spectral Domain Optical Coherence Tomography Outer Retinal Analysis and Relation to Visual Acuity

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PURPOSE: To describe a novel method of en face visualization of the outer retina, including the photoreceptor inner segment/outer segment junction (IS/OS), using spectral domain Cirrus optical coherence tomography (SD OCT), quantification of the area within the central macula, and its association with visual acuity in patients with and without retinal pathology compared to standard Cirrus SD OCT measurements including central subfield thickness (CST), macular volume (MV) and average macular thickness (AMT).

METHODS: Case control study of seventy-four eyes of 53 patients using Cirrus SD OCT advanced visualization RPE slice mode. The central 1 mm and 400 um foveal zones were analyzed with Metamorph computer software, set to the same threshold value for all images.

RESULTS: Thirty eyes (40.5%, group 1) had no previous or established retinal pathology on clinical examination, and an average logMAR visual acuity (VA) = 0.116. Twenty-five eyes (33.7%, group 2) had intraretinal edema on clinical examination due to either retinal vein occlusion, diabetic macular edema, idiopathic epiretinal membrane, pseudophakic cystoid macular edema, neovascular age-related macular degeneration or vitreomacular traction and a VA = 0.494. Nineteen eyes had non-neovascular (dry) AMD (25.6%, group 3) on clinical examination a VA= 0.392. In all eyes, central 1 mm and 400 um en face outer retinal areas were 58.3 ± 25.0% and 56.4 ± 26.0% respectively, which showed significant correlation with VA (Pearson correlation, r = -0.66 and -0.56, respectively, p<0.001 for both.) This correlation was greater than that of VA compared to mean CST (r=0.39, p<0.001), MV (r=0.36, p=0.002), or AMT (r=0.37, p=0.001). In all eyes and every sub-analysis, both en face area measurements demonstrated greater correlation than retinal thickness or volume, although it was not significant for group 3. Excluding eyes with dry AMD, all measurements demonstrated statistically significant correlation with VA, although it was highest for 1 mm and 400 um en face areas (r= -0.81 and -0.71, p<0.001).

CONCLUSIONS: Central outer retinal en face OCT area measurements are modestly correlated with VA in both healthy and eyes with retinal disease. It may be a better predictor of VA than other routine SD OCT values, including CST. The presence of dry AMD may affect this correlation by irregular disruption of the retinal pigmented epithelium and IS/OS plane used to formulate the en face display. Advancements in Cirrus SD OCT software may allow for the routine analysis of en face visualization and analysis.
**J. DONALD M. GASS AWARD**

**To See and To Be Seen**

**URSULA SCHMIDT-ERFURTH, MD**

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**Purpose:** To visualize mechanisms relevant in the pathophysiologic origin and therapeutic response of retinal disease.

**Methods:** Development of novel strategies in retinal imaging, including topographic fluorescein and indocyanine angiography, high-resolution optical coherence tomography with three-dimensional analysis, polarization-sensitive OCT.

**Results:** Confocal angiography with topographic representation provides a realistic identification of the morphology of choroidal neovascularization (CNV) and leakage phenomena in exudative age-related macular degeneration (AMD) for diagnosis and detection of recurrence and choroidal atrophy during therapeutical follow-up. Spectral domain optical coherence tomography (SD OCT) is modified with appropriate algorithms to image different retinal compartments before and during therapy and allows to identify parameters relevant for visual recovery, e.g. subretinal fluid. All location raster scanning provides three-dimensional imaging with analysis of volumetric data. Morphologic changes in diabetic maculopathy (DMP) can be characterized by focal analysis of SD-OCT findings and correlated with function. The effects of laser photocoagulation and antiangiogenic therapy are monitored closely with imaging of focal changes at specific neurosensory levels. Polarization-sensitive OCT (PS OCT) is a novel method to identify intraretinal lipid exudation which highlights the pathogenetic mechanisms in DMP in vivo. The retinal pigment epithelium (RPE) may be selectively represented by PS OCT in atrophic as well as neovascular AMD allowing early diagnosis and prognostic evaluation during therapy.

**Conclusion:** Advances in retinal imaging provide superior understanding of retinal function and finally morphology. It is a crucial base for the development of efficient therapies to optimally treat retinal disease.
Driving Ability in Neovascular Age-related Macular Degeneration Patients Following Treatment with Ranibizumab: Self-reported Perceptions

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PURPOSE: To evaluate the impact of intravitreal ranibizumab on self-reported driving status, self-reported driving function, and likelihood of maintaining or achieving visual acuity levels required for driving in patients with neovascular age-related macular degeneration (AMD).

METHODS: Self-reported driving status and perception of driving ability using the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) as well as best-corrected visual acuity were assessed at baseline and at months 1, 2, 3, 6, 9, 12, 18, and 24 in two multicenter, double-masked, controlled clinical trials in which patients with AMD were randomized to ranibizumab treatment versus sham (MARINA) or photodynamic therapy (PDT) with verteporfin (ANCHOR).

RESULTS: In MARINA, among patients who reported driving at baseline, a greater proportion of patients in the 0.5-mg ranibizumab group reported that they were still driving at 12 months compared with patients in the sham group (87.8% vs 74.8%, P < .002). Mean change from baseline to 12 months in NEI VFQ-25 driving subscale score was 0.4 points in the 0.5-mg ranibizumab group vs 12.4 points in the sham group (P < .0001). In ANCHOR, among patients who reported driving at baseline, a greater proportion of patients in the 0.5-mg ranibizumab group reported that they were still driving at 12 months compared with patients in the PDT group (94.2% vs 80.5%, P < .008). Mean change from baseline to 12 months in NEI VFQ-25 driving subscale score was +3.9 points in the 0.5-mg ranibizumab group vs 4.1 points in the PDT group (P < .005). In both the MARINA and ANCHOR trials, ranibizumab-treated patients were more likely to maintain or achieve a visual acuity letter score of 70 or better (Snellen equivalent approximately 20/40 or better) in the better-seeing eye (a cutoff for driver license requirements in many U.S. states) compared with sham or PDT-treated patients.

CONCLUSIONS: Neovascular AMD patients treated with ranibizumab appear more likely to report that they are driving, to perceive that they have better driving function, and to maintain or achieve visual acuity required for a driver license compared with patients treated with sham or PDT.
Ranibizumab for Treating Vascularized Pigment Epithelial Detachment (vPED) Due to Age-related Macular Degeneration, a Prospective Randomized Study

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Purpose: To study the efficacy and safety of intravitreal ranibizumab injections for patients with a vascularized pigment epithelial detachment (vPED) due to AMD randomized to monthly versus as needed injections.

Methods: Ten eyes in 10 patients were enrolled in this prospective investigator sponsored trial from December, 2008 to December, 2009. Five eyes (Group 1) received mandatory monthly injections of 0.5 mg ranibizumab for up to 12 months, and 5 eyes (Group 2) received monthly injections of same for 4 months and subsequent as needed monthly injections for up to 12 months. Outcome measures included pre- and post-injection vision, central-1mm thickness, sizes and heights of PED and choroidal neovascularization (CNV), amount of subretinal fluid (SRF) and cystoid macular edema (CME), and adverse ocular and systemic events. Baseline and follow-up ETDRS VA (letters score [LS]), fundus and fluorescein photography, biomicroscopy, and OCT were performed.

Results: The mean age of the entire study cohort was 83.7 (range 71-94), with a mean follow-up of 9.9 months (range: 6-12.0 months). There were 9 females and 1 male. The mean pre- and post-injection ETDRS VA for the entire cohort were 51.2±11 LS (20/100) and 54.7±22.76LS (20/99), respectively (P=0.66, Paired-T test). When comparing between groups, 2-way analysis of variance (ANOVA) showed comparable baseline features and no differences in pre- and post-injection results. When comparing within group, 2-way ANOVA showed reduced post-injection vPED height and central 1-mm thickness for both groups (p=0.03 and 0.05, respectively). When combining both groups for analysis, there were less post-injection vPED height (mean: 302.39±165.8 microns) and central 1-mm thickness (mean: 217.0±46.2microns) in comparison to pre-injection results (P=0.023 and 0.037, respectively). There was also less post- than pre-injection SRF and CME (Wilcoxon Signed-Rank test, P=0.02 and 0.01, respectively). Serious ocular adverse events included only marked cataract progression in 1 eye (Group 1), and RPE tear in 1 eye (Group 2).

Conclusions: There were equivalent results of mandatory monthly injections vs. as needed injections of 0.5 mg of ranibizumab for decreasing the SRF, CME, and PED height in eyes with vPED. Although the vPEDs were not flattened, ranibizumab monotherapy provided consistent benefits for such eyes associated with a sound safety profile.
Ranibizumab Monotherapy in Neovascular Age-related Macular Degeneration with Pigment Epithelial Detachment

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Purpose: To evaluate the effect of ranibizumab monotherapy in patients with neovascular age-related macular degeneration (ARMD) associated with a pigment epithelial detachment (PED).

Methods: A retrospective chart review of neovascular ARMD with associated PED treated using initial three monthly doses of ranibizumab followed by as needed dosing. The patients included in the study were treated from July 2006 to March 2010 at the Retina Service of Boston University Medical Center (BUMC). This study was approved by the BUMC institutional review board. The response to treatment was assessed by evaluating changes in visual acuity and central macular thickness (CMT) by ocular coherence tomography. The total ranibizumab injections needed was also assessed. The data was analyzed using paired t-tests on a SAS 9.1 system.

Results: A total of 15 eyes from 13 patients were included in this study. Eleven of thirteen patients (85%) were female, with an average age of 79 years (range 61-94yrs). All patients were Caucasians. The average follow up period was 22 months (range 5 to 48 months). The mean pre-treatment logMAR visual acuity was 0.678 (Snellen = 20/80-) with a SD 0.434 and the mean final logMAR VA was 1.036 (Snellen = 20/200-) with SD 0.771. Analysis of data showed a statistically significant worsening of vision (p-value=0.041) in the post treatment eyes. The average pretreatment central macular thickness (CMT) was 261.583 microns (SD 62.873) and the average final post treatment CMT was 272.583 microns (SD 72.732). There was no significant difference in the two CMT values (p-value=0.702), indicating that this treatment does not improve the macular thickness. An average of 6.5 ranibizumab injections per eye (range 3-16 injections) was administered over the duration of the study.

Conclusions: This case series of 15 eyes from 13 patients who underwent ranibizumab monotherapy for neovascular ARMD with PED demonstrate worsening visual acuity and no improvement of macular thickness post treatment. Our pilot study suggests that ranibizumab alone is not effective, and combined treatment approaches may be necessary at an early stage to prevent visual loss in these cases.
REACT Trial: Response to Monthly Ranibizumab for Active Wet AMD as Guided by SD-OCT, 18-54 Month Data

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PURPOSE: To determine the difference in response between Asian and Caucasian patients with Wet AMD who switch from intermittent therapy targeting vascular endothelial growth factor (anti-VEGF therapy: pegaptanib, bevacizumab, or ranibizumab) to monthly ranibizumab therapy.

METHODS: Treatment data was analyzed in 100 consecutive patients (121 eyes, 54 Asian and 67 Caucasian) who had received anti-VEGF induction, maintenance, and pro re nata (PRN) therapy in the preceding 4 to 42 months. Patients with active angiographic leakage and edema on SD-OCT were prospectively enrolled into an open-label phase 2 study of intravitreal ranibizumab (0.5 mg) administered monthly for the first 6 months and PRN for the next 6 months. Qualitative SD-OCT, changes in VA (Early Treatment Diabetic Retinopathy Study [ETDRS] letters), central foveal thickness (CFT), fluorescein leakage, and resolution of macular edema were assessed monthly. The last-observation-carried-forward method is used to impute missing data. Safety monitoring includes monthly evaluation of ocular and systemic adverse events.

RESULTS: During the initial 4 to 42 months of anti-VEGF therapy, the 121 eyes of Asian and Caucasian patients experienced a mean VA improvement of 3.56 and 4.24 ETDRS letters, respectively. When these patients were switched from PRONTO guided PRN treatment, Asian patients demonstrated an additional VA improvement of 2.76 and 5.57 ETDRS letters at 6 and 12 months respectively, while Caucasian patients gained 3.91 and 5.34 ETDRS letters at 6 and 12 months respectively. CFT improved by a mean of 30.93 µm and 46.44 µm at 6 and 12 months in Asian patients and 45.54 µm and 42.04 µm at 6 and 12 months in Caucasian patients. At study conclusion, compared with baseline: Asian patients previously treated for <12 months VA improved 7.57 letters; those previously treated for 12 to 18 months VA improved 7.94 letters; and those previously treated for over 18 months VA improved 3.64 letters. The VA improvement after switching to monthly therapy for Caucasian patients was 3.94, 7, and 5.49 ETDRS letters for those previously treated for <12 months, 12-18 months, and over 18 months, respectively. One patient experienced a transient ischemic attack, and 1 had an RPE tear prior to month 6.

CONCLUSIONS: When fluid was identified on SD-OCT, switching patients with neovascular AMD, from Pronto style PRN anti-VEGF therapy to monthly ranibizumab therapy demonstrated additional improvement in both VA and CFT. The observed improvement was evident in all subgroups regardless of the disease chronicity.
SAVE (Superdose Anti-VEGF) Trial — 2.0 mg Intravitreal Ranibizumab for Recalcitrant Neovascular Age-related Macular Degeneration

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PURPOSE: Many patients with neovascular AMD have persistent edema or fluorescein leakage despite monthly anti-VEGF intravitreal injections. As the MARINA and ANCHOR trials both demonstrated a dose-response curve favoring 0.5 mg ranibizumab over 0.3 mg ranibizumab dosing, the SAVE trial was designed to test if a higher dose of ranibizumab could potentially lead to further anatomic and visual acuity improvements in these patients with recalcitrant disease.

METHODS: Forty patients with recalcitrant neovascular AMD (defined as having morphologic evidence of leakage on SD OCT despite monthly or near monthly 0.5 mg ranibizumab injections) were treated with 2.0 mg ranibizumab injections monthly for 3 loading doses followed by randomization to either 4 week or 6 week follow-up examinations. All patients in the follow-up period received a capped PRN treatment with 2.0 mg ranibizumab injections mandated at each quarterly visit and 2.0 mg ranibizumab PRN injections given at follow-up visits (treatment given if any morphologic evidence of CNVM activity exists on OCT, FFA, or clinical exam). All patients received ETDRS 4 meter refractions, clinical exam, and Stratus OCT, Cirrus HD OCT, and Spectralis OCT at every visit.

RESULTS: Forty patients were enrolled with evidence of fluid on OCT (intraretinal, subretinal, or sub-RPE). Patients had (on average) 26.2 ranibizumab injections prior to enrollment and 10.3 injections in the preceding 12 months. Mean refracted VA was 66.77 ETDRS letters at baseline and mean central subfield was 359µ. Anatomically, mean OCT central subfield thickness improvement from baseline was -37µ at day 7, -29.6µ at month one, and -37.8µ at month two. Mean visual acuity gain over baseline was +4.3 ETDRS letters at day 7, +4.8 ETDRS letters at month 1, and +6.6 ETDRS letters gain by month 2. No unexpected adverse events were observed in any subject.

CONCLUSIONS: 2.0 mg ranibizumab intravitreal injections led to anatomic improvements and visual acuity gains even in patients with multiple prior 0.5 mg injections. This data provides strong support for the rationale of the HARBOR phase III trial and implies that some patients with neovascular AMD may require a higher dose of ranibizumab than is commercially available.
Three-year Results Using Constant Interval Dosing with Ranibizumab

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PURPOSE: To evaluate the outcome of patients who have received three years of treatment with ranibizumab on a constant interval dosing schedule.

METHODS: Using billing records we located the charts of our patients who had received three years of ranibizumab using a constant interval dosing schedule. Two groups of patients were identified. Group 1 patients were treatment naive. Group 2 patients had received other treatments (photodynamic therapy, pegaptanib, steroids, or laser) prior to beginning ranibizumab. Visual acuities were recorded on each visit and followed for three years. Snellen acuities were converted to LogMAR vision and mean vision was calculated for the groups. Average change was also calculated.

RESULTS: We located 28 patients who had received constant interval dosing for at least three years and who received injections at intervals no greater than 6 weeks. Average visual acuity rapidly increased from 0.5 to 0.3 (20/60 to 20/40) over four months and then was stable for the rest of the three year period. There was no detectable decline during the treatment period. Group 1 responded better to treatment than group 2 although if non-responders were separated from group the visual acuities were similar in both groups.

CONCLUSIONS: Unlike the patients in the HORIZON study (extension of MARINA and ANCHOR studies) where patients were switched to PRN dosing after two years and subsequently lost vision, our patients maintained their vision over a three year period. Constant interval dosing may be a better strategy to preserve sight than PRN dosing of anti-VEGF drugs.
Subgroup Analyses of Month 12 Visual Acuity Outcomes in the CRUISE Study

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PURPOSE: Evaluate treatment group differences in visual acuity (VA) outcomes at Month 12 in the CRUISE study according to age, prior therapy, baseline VA, and baseline central foveal thickness (CFT).

METHODS: Phase III, double-masked, controlled study. Patients with macular edema (central subfield thickness ≥250 µm) following central retinal vein occlusion (CRVO) were randomized to receive 6 monthly intravitreal injections of 0.3 mg (n=132) or 0.5 mg (n=130) ranibizumab or sham injections (n=130) followed by 6 months of observation, during which all patients could receive ranibizumab PRN if they met prespecified criteria. For retreatment, 0.3 mg and 0.5 mg groups received their assigned dose; sham group received 0.5 mg ranibizumab. Primary efficacy endpoint was mean change from baseline best-corrected VA (BCVA) at Month 6. Secondary endpoints included mean change from baseline BCVA over time to Month 12. Prespecified subgroup analyses included change from BCVA according to baseline BCVA (≤34 [approximate Snellen equivalent 20/200 to <20/80], ≥55 [approximate Snellen equivalent ≥20/80]).

RESULTS: Mean changes from baseline BCVA letter score at Month 6 were significantly greater for patients who received 0.3 mg (+12.7) or 0.5 mg (+14.9) ranibizumab compared with sham injections (+0.8). Month 6 improvement in BCVA was, on average, maintained at Month 12 with PRN treatment in the 0.3 mg (+1.2 letters at Month 12 compared with Month 6) and 0.5 mg (-1.0 letters at Month 12 compared with Month 6) ranibizumab groups. Relative to Month 6, sham patients who crossed over to PRN 0.5 mg ranibizumab had gained 6.5 letters at Month 12. Treatment group differences in BCVA outcome were maintained when analyzed by subgroup. At Month 12 the differences in mean change from baseline BCVA between the 0.3/0.5 mg ranibizumab and sham treatment groups, analyzed by BCVA ≤34, and 35-54, and ≥55, were +6.7/+5.1, +8.9/+6.8, and +3.7/+6.6 letters, respectively. At Month 12 the differences in mean change from baseline BCVA between the 0.3/0.5 mg ranibizumab and sham treatment groups, analyzed by CFT.

CONCLUSIONS: Visual acuity outcomes following monthly ranibizumab in patients with macular edema following CRVO at Month 6 were maintained at Month 12, following 6 months of PRN treatment. Differences in VA outcomes between the sham and ranibizumab treatment groups at Month 12 favored the ranibizumab groups and were, in general, not influenced by baseline VA or CFT, age, or prior treatment.
Subgroup Analyses of Month 12 Visual Acuity Outcomes in the BRAVO Study

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PURPOSE: Evaluate treatment group differences in visual acuity (VA) outcomes at Month 12 in the BRAVO study according to age, prior therapy, baseline VA, and baseline central foveal thickness (CFT).

METHODS: Phase III, double-masked, controlled study. Patients with macular edema (central subfield thickness >250 µm) following branch retinal vein occlusion (BRVO) were randomized to receive 6 monthly intravitreal injections of 0.3 mg (n=134) or 0.5 mg (n=131) ranibizumab or sham injections (n=132) followed by 6 months of observation, during which all patients could receive ranibizumab PRN if they met prespecified criteria. For retreatment, 0.3 mg and 0.5 mg groups received their assigned dose; sham group received 0.5 mg ranibizumab. Primary efficacy endpoint was mean change from baseline best-corrected visual acuity (BCVA) at Month 6. Secondary endpoints included mean change from baseline BCVA over time to Month 12. Prespecified subgroup analyses included change from baseline BCVA according to baseline BCVA (>34 approximate Snellen equivalent).

RESULTS: Mean changes from baseline BCVA letter score at Month 6 were significantly greater for patients who received 0.3 mg (+16.6) or 0.5 mg (+18.3) ranibizumab compared with sham injections (+7.3). Month 6 improvement in BCVA was, on average, maintained at Month 12 with PRN treatment in the 0.3 mg (-0.2 letters at Month 12 compared with Month 6) and 0.5 mg (0.0 letters at Month 12 compared with Month 6) ranibizumab groups. Relative to Month 6, sham patients who crossed over to PRN 0.5 mg ranibizumab had gained 4.8 letters at Month 12. Treatment group differences in BCVA outcome were maintained when analyzed by subgroup. At Month 12, the differences in mean change from baseline BCVA between the 0.3/0.5 mg ranibizumab and sham treatment groups, analyzed by BCVA >34, and 35-54, and >55, were +9.4/+9.9, +5.9/+8.5, and +3.0/+3.4, respectively. At Month 12 the differences in mean change from baseline BCVA between the 0.3/0.5 mg ranibizumab and sham treatment groups, analyzed by CFT.

CONCLUSIONS: Visual acuity outcomes following monthly ranibizumab in patients with macular edema following BRVO at Month 6 were maintained at Month 12, following 6 months of PRN treatment. Differences in VA outcomes between the sham and ranibizumab treatment groups at Month 12 favored the ranibizumab groups and were, in general, not influenced by baseline VA or CFT, age, or prior treatment.
Intravitreal Lucentis (ranibizumab) for Radiation Maculopathy

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PURPOSE: To report our interim results of treatment with intravitreal ranibizumab for radiation maculopathy following plaque radiotherapy for choroidal melanoma.

METHODS: Ten patients were enrolled in an investigator sponsored, prospective, non-randomized consecutive case trial of patients treated for uveal melanoma with plaque radiotherapy who subsequently developed radiation maculopathy. Entry criteria also included 1) more than 6 months after radiotherapy; 2) initial visual acuity of 20/400 or better; 3) subjective or objective loss of vision. Intravitreal injections of ranibizumab were given every 30 days (+/-7 days). Outcome measures included safety as measured by visual acuity (ETDRS), fundus photography, angiography, optical coherence tomography (OCT) and B-scan ultrasound imaging.

RESULTS: Patients were treated with palladium-103 ophthalmic plaque brachytherapy for 7 days. The median tumor apex dose was 77.8 Gy (range 58.8-85.7), and median macular dose was 56.6 Gy (range 15.0-138.5). The median time from plaque radiotherapy to enrollment in the trial was 21.5 months (range 6-67) with a median study follow-up of 12.5 months (range 5-16). Intravitreal ranibizumab was found to reduce retinal hemorrhages, exudation and macular edema. The most common and reproducible finding was decreased edema, with secondary restoration of the normal anatomy of the macula. Our six (n=10) and twelve (n=5) month analysis demonstrated 1) mean change in visual acuity of +7.2 (0 to +18) letters and +4.4 (+4 to 14) letters using ETDRS charts, respectively; 2) mean reduction in central foveal thickness of 31% (range 1-65) and 45% (20-72) on OCT imaging compared to baseline, respectively; and 3) all patients demonstrated either a reduction or stabilization in tumor thickness on B-scan ultrasonography from pre-ranibizumab baseline, respectively. There was one case of bacterial endophthalmitis, and one unrelated death due to respiratory and cardiac failure.

CONCLUSIONS: While reductions in retinal hemorrhage, exudate and macular edema were documented by photography and angiography; the most common finding was decreased or stabilized macular retinal thickness seen on OCT that was maintained over a 12 month interval.
Pattern Electroretinography After Ranibizumab in Naive Age-related Macular Degeneration

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PURPOSE: To determine if chronic vascular endothelial growth factor (VEGF) inhibition would be toxic to the retina by utilizing pattern electroretinography (PERG) in patients with neovascular age-related macular degeneration (AMD) receiving monthly injections of ranibizumab.

METHODS: Seventeen treatment naïve patients were treated with intravitreal ranibizumab monthly for 6 months. These patients were followed by an assessment of retinal function using PERG. Baseline visual acuity (VA), optical coherence tomography (OCT), and fluorescein angiography were obtained. PERG was performed prior to and at 1 month, 3 months, and 6 months after initial treatment. PERGs were interpreted by a trained reader masked to the clinical data.

RESULTS: At 6 months, mean VA prior to treatment was 20/85 with improvement to a mean of 20/55 (p = .004). At baseline, mean P50 and N95 amplitudes were 1.3 + 0.69 µV and 1.5 + 0.71 µV respectively. At the end of the study period, there was no decrease in P50 or N95 amplitudes from baseline (1.4 + 0.47 µV p = 0.461 and 1.8 + 0.96 µV p = 0.139 respectively).

CONCLUSIONS: It has been shown that there is a significant role for VEGF in the prevention of apoptosis of retinal Müller cells, photoreceptors, and ganglion cells. This study found no decrease in P50 and N95 amplitudes in patients treated with ranibizumab for neovascular AMD. These findings indicate that VEGF inhibition with monthly injections of ranibizumab over 6 months likely do not lead to retinal cell damage.
Changes in the Retinal Nerve Fiber Layer in Patients Receiving Intravitreal Anti-VEGF Agents

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PURPOSE: To determine if change in retinal nerve fiber layer thickness develops in patients receiving anti-VEGF injections and compare two potential mechanisms of glaucomatous damage.

METHODS: A retrospective chart review.

RESULTS: Eighty-six eyes were treated with intravitreal bevacizumab or ranibizumab between January 2008 and December 2009. RNFL was determined with OCT prior to injection and at final follow up visit. Each eye received a minimum of 3 injections with a range of 3-13 injections. Follow up ranged from 14 to 82 weeks, mean of 44.84 weeks. Paracentesis was performed in 28 of 86 eyes.

In 48 patients only receiving bevacizumab injections the mean change in OCT measured retinal nerve fiber layer thickness from baseline in all patients was 0.15 (SD 7.62) microns over a mean follow up of 42.73 (SD 19.97) weeks. Of the group receiving paracentesis there was a mean change of 0.87 (SD 7.57) microns and those not receiving paracentesis a mean change of -0.97 (SD 6.582) microns. The data was not statistically significant. In 38 patients only receiving ranibizumab injections the mean change in OCT measured retinal nerve fiber layer thickness from baseline in all patients was -1.21 (SD 5.46) microns over a mean follow up of 47.50 (19.35) weeks. Of the group receiving paracentesis there was a mean change of -0.83 (5.83) microns and those not receiving paracentesis a mean change of -1.38 (5.40) microns. The data was not statistically significant. The P-values were calculated using the Chi-square test for categorical variables, the 2-sample T-test for means, and the Wilcoxon’s Rank Sum Test for medians.

CONCLUSIONS: Transient elevation of intraocular pressure and ischemia may lead to optic nerve injury. The use of OCT in evaluation of the thickness of the retinal nerve fiber layer has allowed for a more sensitive means of assessing glaucomatous changes associated with anti-VEGF injections. Theoretically, if an ischemic mechanism of glaucomatous damage is at work, a decrease in retinal nerve fiber layer thickness should have been seen in both groups. If transient elevated intraocular pressure is at work than less RNFL thinning should have been seen in the group receiving a paracentesis when compared to the group not receiving a paracentesis. There was no statistically significant change in the RNFL thickness in the entire group of patients receiving intravitreal anti-VEGF injections regardless of whether a paracentesis was performed. Although there may be a trend towards increased retinal nerve fiber layer loss in patients not receiving a paracentesis compared with those receiving a paracentesis, the difference is small, and not statistically significant. A larger study size and longer follow up time may be needed to achieve statistically significant values.
Comparison of Treatment Outcomes for Diabetic Macular Edema Using Short Duration Focal Macular Laser with and without Intravitreal Bevacizumab

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PURPOSE: To compare the visual acuity (VA) and spectral domain optical coherence tomography (OCT) thickness results at 4 months using short duration focal macular laser photocoagulation with and without the concomitant use of intravitreal bevacizumab (IVB) in the treatment of clinically significant macular edema (CSME) due to diabetes.

METHODS: Consecutive retrospective analysis of VA and OCT data from eyes treated in a modified Early Treatment Diabetic Retinopathy Study (ETDRS) style using only short duration laser compared to eyes in which patients received IVB (1.25 mg/0.05 mL) within 2 weeks prior to the laser treatment. All subjects were treated with the same laser unit using 100 µm spot size, 10 millisecond pulse duration, and varying power to create a light graying tissue change.

RESULTS: A total of 138 eyes from 102 patients met study criteria. One-hundred eyes were treated with laser only, and 38 eyes were treated with laser plus IVB. At 4 months in the laser only group, there was an average improvement in visual acuity (VA) of .060 LOGMar (an improvement from 20/45 to 20/40, or ~3 ETDRS letters, p = 0.0007) and a reduction of central OCT thickness of 40 µm (p = 0.0049). At 4 months in the combination laser plus IVB group, there was an average improvement in visual acuity (VA) of .097 LOGMar (an improvement from 20/70 to 20/56, or ~9 ETDRS letters, p = 0.0001) and a reduction of central OCT thickness of 66 µm (p = 0.0002).

CONCLUSIONS: Short duration focal macular laser photocoagulation has a biological treatment effect for CSME at 4 months both with and without concomitant administration of IVB. Short duration focal macular laser appears safe and effective in the short term both with and without IVB, with 4 month VA gains and reduction in OCT thickness greater when short duration focal macular laser is performed in conjunction with IVB.
**Serum Cortisol After Posterior Sub-Tenons Triamcinolone Acetonide Injection**

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**PURPOSE:** To assess the pharmacokinetics of triamcinolone acetonide (TA) and effects on serum cortisol after posterior sub-Tenon’s (PST) injection.

**METHODS:** This IRB-approved, prospective, interventional study assessed via mass spectrometry and High Performance Liquid Chromatography the TA levels in undiluted vitreous and serum samples from 57 patients undergoing vitrectomy for macular hole or epiretinal membrane. At least five pairs of samples were collected at each of seven time points (1 day, 3 days, and 1, 2, 3, 4, and 8 weeks) after PST TA injection, with six controls who did not receive a steroid injection. Serum cortisol concentrations were measured in 31 samples to assess systemic effects of PST TA.

**RESULTS:** Average vitreous levels of TA peaked at 111 ng/ml at day 1, then reached a plateau around 15-25 ng/mL for at least one month. Average serum TA levels peaked at day 3 near 35 ng/mL, due largely to one sample with an elevated concentration, and ranged from 2-8 ng/mL at all other time points. Vitreous and serum TA concentrations were significantly correlated (Spearman coefficient of 0.64709, p<0.001) while serum cortisol levels were inversely correlated with serum TA levels (Spearman -0.41851, p=0.0214).

**CONCLUSIONS:** Posterior sub-Tenon’s injection of TA resulted in serum TA levels that were about one quarter of the vitreous TA levels and were highly correlated, supporting trans-scleral delivery of TA into the choroid and vitreous. The low serum TA levels measured in this study were sufficient to inhibit serum cortisol levels and thus warrant further investigation.
**Key Differential Gene Expression Pathways Affected by Intravitreal Injections of Two Steroids Triamcinolone Acetonide (TA) and Dexamethasone (Dex) in Mouse Retina and Retinal Pigment Epithelial Tissue**

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**PURPOSE:** To identify key early and late differential gene expression pathways affected by intravitreal injections of two steroids, Triamcinolone Acetonide (TA) or Dexamethasone (Dex) in the C57BL/6J mouse retina and RPE/choroid tissues.

**METHODS:** All research was conducted in compliance with the ARVO statement for the use of animals in ophthalmic and vision research. Intravitreal injections were performed transconjunctivally in anesthetized C57BL/6J mice with Hamilton syringes and 33g needles delivering 2 ul of solution according to institutional protocol. In group 1 (n=3) animals received balanced intravitreal salt solution (BSS), in group 2 (n=3) TA (20µg), in group 3 (n=3) Dex (2µg). At 1, 4 and 12 weeks after the injections, mice from each group were sacrificed by pentobarbital sodium overdose (120mg/kg) and the eyes were harvested for retinal and RPE/choroid tissue dissection and total RNA isolation from each tissue. Microarray analysis of 45,101 genes was performed using Affymetrix MOE-430-2 GeneChip arrays. Data analysis was performed using Affymetrix Expression Console, GeneSpring 11 GX, and Ingenuity Pathway (IPA) software.

**RESULTS:** Differences between Dex and TA induced gene expression were seen affecting the Th1, Th2, and Th17 cytokine immune response pathways. At one week, Dex acts primarily through Th17 (upregulation of IL-22 and downregulation of IL-17) in the RPE, while TAA modifies Th1 CD4+ helper T cell response (modulation of IL1 expression in retina and RPE). At one month, modulation of genes affecting Th2 type cytokines (IL-6 and IL-10) occurs for both Dex and TAA, but in the opposite manner Dex upregulates IL-6 and downregulated IL-10 in the retina, while TAA downregulates IL-6 in RPE. At week 1 TAA upregulates PDGFC in retina and Dex downregulates VEGF in RPE. At week 4, only TAA downregulates PEDF and VEGF in the retina.

**CONCLUSIONS:** The balance of Th1, Th2, and Th17 cytokine production influences many pathological processes and plays both causative and protective roles in retinal disease. Microarray pathway analysis shows the full complexity of steroid effects on retinal and RPE/choroid gene expression of these cytokines. Our data suggest that each of the steroids has a preferential pathway or set of genes that it affects. Differential gene expression in the retina and RPE/choroid tissues may have clinical implications.
Pharmacogenomics of the Steroid Response

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PURPOSE: We are investigating a possible pharmacogenomic association regarding the steroid response following treatment with intravitreal triamcinolone acetonide (IVTA).

METHODS: This study was approved by the Institutional Review Board of the University of Miami. We obtained peripheral blood samples from 53 adult patients who were treated with IVTA (4 mg in 0.1 cc) for a variety of indications. Our primary clinical outcome measure was the maximum change in intraocular pressure (delta IOP) recorded following treatment with IVTA. We performed a genome-wide association study (gWAS) on the blood samples using the GeneChip® Human Mapping 500K Array Set (Affymetrix, Santa Clara, CA) to identify polymorphisms which associated with magnitude of delta IOP.

RESULTS: GWAS identified 48 polymorphisms within 33 genes that correlated (p < 0.001) with delta IOP. The strongest correlation (p = 3.05 * 10^-8) involved an orphan G-protein coupled receptor (orphan GPCR) which is expressed in the brain, RPE/choroid, and optic nerve. Using the PC-3 prostate cancer cell line, expression of the orphan GPCR increased approximately 4-fold upon exposure to exogenous triamcinolone and dexamethasone, peaking at 4 and 8 hours after exposure, respectively. Similarly, exposure to exogenous triamcinolone and dexamethasone increased orphan GPCR production in a concentration-dependent manner in PC-3 cells.

CONCLUSIONS: In this pilot study, we have identified a group of polymorphisms that correlate with the magnitude of IOP elevation following treatment with IVTA. The polymorphism with the strongest association (p = 3.05 * 10^-8) involves an orphan GPCR that appears inducible by exogenous corticosteroids in a prostate cancer cell line. Further studies are necessary to validate these findings.
**Ozurdex™ (Dexamethasone Intravitreal Implant) as Adjunctive Therapy to Lucentis® in Patients with Choroidal Neovascularization Secondary to Age-related Macular Degeneration**

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**PURPOSE:** Evaluate the safety and efficacy of Ozurdex™ (dexamethasone intravitreal implant) 0.7 mg when given with Lucentis® (ranibizumab) in patients with choroidal neovascularization (CNV) secondary to exudative age-related macular degeneration (AMD).

**METHODS:** This 6-month, randomized, single-masked, multicenter, sham-controlled study enrolled patients requiring ranibizumab treatment for CNV secondary to AMD. At screening, all patients received an intravitreal injection of ranibizumab 0.5 mg. 4 weeks later at the baseline (day 1) visit, patients who met OCT and clinical examination criteria for retreatment with ranibizumab were randomized to receive DeX Implant (n=123) or sham procedure (n=120). Patients were given a second ranibizumab injection 7-14 days after the baseline visit. For patients meeting retreatment criteria, up to 5 additional ranibizumab injections were given prior to study exit (week 25). Primary efficacy outcome measure was injection-free interval.

**RESULTS:** Adjunctive therapy with DeX Implant significantly delayed first as-needed ranibizumab injection based on Kaplan-Meier product-limit method (P = .016). The 75th percentile of injection-free interval was 12 weeks in DeX Implant group vs 8 weeks in control group. Relative risk of not requiring additional as-needed ranibizumab injection was 3.28 (DeX Implant vs sham, P = .048). No significant between-group differences in visual acuity or improvement in central retinal thickness noted. Treatment-related adverse events were similar between groups, except increased IOP (9.9% vs 3.4%) and conjunctival hemorrhage (6.6% vs 0.8%) in the DeX Implant group vs control group (P > .044).

**CONCLUSIONS:** DeX Implant delayed the time to as-needed injection of ranibizumab and reduced the need for repeated ranibizumab treatment in patients with CNV secondary to AMD.
Dexamethasone Intravitreal Implant for Treatment of Diabetic Macular Edema in Vitrectomized Patients: A Prospective, 6-month, Open-label Study

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PURPOSE: Pharmacologic treatment of macular edema in vitrectomized eyes can be difficult due to increased intravitreal drug clearance. To evaluate the safety and efficacy of Ozurdex™ (dexamethasone intravitreal implant, DEX Implant) 0.7 mg in the treatment of diabetic macular edema (DME) after vitrectomy.

METHODS: This prospective, multicenter, 6-month, open-label study enrolled 56 patients with DME and a history of pars plana vitrectomy in the study eye at least 3 months prior to the baseline study visit. Patients received a single intravitreal injection of 0.7 mg DEX Implant in the vitrectomized eye and were followed for 26 weeks. The primary efficacy endpoint was change in central retinal thickness from baseline to week 26 by optical coherence tomography. Other key outcome measures were best-corrected visual acuity (BCVA) and safety measures including adverse events and intraocular pressure.

RESULTS: Fifty-five patients (mean age, 62 years) received DEX Implant. Mean duration of DME was 43 months. DEX Implant significantly decreased central retinal thickness (CRT) from baseline and improved BCVA at week 1 through week 26. Mean change in CRT from baseline at week 8 (peak effect) was -155.8 µm (P < .001) and at week 26 was -38.9 µm (P = .004). BCVA improved by >10 letters in 30.4% of eyes at week 13 and in 21.4% at week 26. Conjunctival hemorrhage and hyperemia were the most common adverse events. No patient had intraocular pressure ≥25 mmHg at week 26.

CONCLUSIONS: Treatment with DEX Implant safely reduced DME and improved visual acuity in a difficult-to-treat vitrectomized population with chronic DME. Intravitreal corticosteroid sustained-release delivery with DEX Implant may be particularly beneficial for treatment in vitrectomized eyes.
Safety and Efficacy of Intravitreal Dexamethasone Implant Plus Laser Photocoagulation Versus Laser Alone for Treatment of Diffuse Diabetic Macular Edema

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Purpose: To report the design and endpoints of a clinical trial comparing the safety and efficacy of dexamethasone intravitreal implant (DEX Implant) plus laser photocoagulation to that of laser alone for treatment of diffuse diabetic macular edema (DDME).

Methods: This prospective, masked, phase 3b study randomized (1:1) DDME patients with retinal thickness of >275 microns and best-corrected visual acuity (BCVA) >34 to <70 letters to receive DEX Implant 0.7mg at day 0 followed by laser photocoagulation at month 1 (DEX Implant + laser) or laser alone at month 1. If needed, patients were retreated with DEX Implant at month 6 or 9 and with laser at months 4, 6, and 9. Outcomes were evaluated at baseline and months 4, 6, 9, and 12, with an additional 3-month follow-up for those who were retreated with DEX Implant at month 9.

Results: The primary efficacy measure was the proportion of patients with a BCVA improvement of >10 letters from baseline at month 12. The secondary efficacy measures were BCVA, optical coherence tomography, fundus photography, fluorescein angiography, laser treatment parameters, number of DEX Implant and laser re-treatments, time to re-treatment with DEX Implant, and vision-related quality of life. Safety evaluation included adverse events, intraocular pressure, and biomicroscopic findings. The results are expected by April 2010.

Conclusions: The study will provide evidence on the effectiveness of DEX/laser versus laser alone for treatment of patients with diffuse diabetic macular edema.
Microplasmin for Treatment of Vitreomacular Adhesion: Results of the Phase III MIVI-TRUST Program

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on behalf of the MIVI-TRUST Investigators

PURPOSE: Focal vitreomacular adhesion (VMA) is implicated in the pathobiology of disorders including vitreomacular traction syndrome and macular hole, and is associated with more severe disease in other conditions such as diabetic retinopathy and AMD. Therefore, a pharmacologic means of resolving focal vitreomacular adhesion could fill a significant unmet need in the treatment of vitreoretinal disease. Preclinical experiments and Phase II clinical trials indicate that microplasmin, a recombinant truncated form of plasmin, may be useful for the pharmacologic separation of vitreomacular adhesion. The MIVI-TRUST program is composed of two Phase III trials evaluating microplasmin (generic name ocriplasmin) for the treatment of focal VMA (the MIVI-006 and the MIVI-007 trials). Both studies have identical inclusion/exclusion criteria, treatment regimens, and visit schedules, and are therefore suitable for pooling of results.

METHODS: The MIVI-TRUST program consists of the MIVI-006 and the MIVI-007 studies. Both studies are Phase III, multicenter, randomized, placebo controlled, double-masked clinical trials designed to investigate intravitreal microplasmin 125 µg for the nonsurgical treatment of focal VMA (www.clinicaltrials.gov, Registration #s NCT00781859 and NCT00798317, respectively). Exclusion criteria included proliferative retinopathy, MH diameter >400um, high myopia, prior RD/macular laser/vitrectomy. Subjects were randomized to microplasmin or placebo intravitreous injection (allocation ratio 2:1 in MIVI-006; 3:1 in MIVI-007). The primary endpoint was nonsurgical resolution of fVMA at day 28, determined by Central Reading Centre OCT evaluation. Secondary endpoint assessments included total PVD at day 28, nonsurgical MH closure, avoidance of vitrectomy, visual acuity, and VFQ-25. Eyes were followed for 6 months.

RESULTS: Between December 2008 and December 2009, 652 eyes were treated (326 in each study). Mean age at baseline was 72 y.o. (Range 18 to 97), with 67% Female and 92% Caucasian. In addition to focal VMA, 23% had full-thickness MH; 39% had eRM; and 6% had diabetic retinopathy. The mean baseline BCVA was 64 letters (Range 8-88).

The first of these two trials, MIVI-006, demonstrated highly statistically significant improved rate of nonsurgical resolution of focal VMA in microplasmin group compared to placebo (p=0.003). Further, over 40% of patients with FTMH at baseline treated with microplasmin achieved nonsurgical resolution of FTMH. The results of the second trial, MIVI-007, will be available in time to allow presentation of the pooled results of the Phase III program at the Retina Society Annual Meeting.

CONCLUSION: The MIVI-TRUST program is the largest Phase III program ever conducted to evaluate a pharmacologic intervention for treatment of focal vitreomacular adhesion. Therefore, the results of these trials, both individually and pooled, allow the opportunity to increase our understanding of the clinical relevance of the vitreoretinal interface in various disorders, and potentially may lead to a new nonsurgical treatment option for such disorders.
Vascular Changes in Patients Treated with Dexamethasone Intravitreal Implant for Macular Edema Due to BRVO or CRVO Over 12 Months

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PURPOSE: To report the angiographic findings from 2 identical randomized clinical trials evaluating the safety and efficacy of a sustained-release dexamethasone intravitreal implant (OZURDEX™) for the treatment of branch and central retinal vein occlusions (BRVO and CRVO).

METHODS: In 2 identical studies, patients with ME due to RVO were randomized and received DEX Implant 0.7 mg (n=427) or sham procedure (n=426). At day 180, patients could receive open-label treatment with DEX Implant 0.7 mg if best-corrected visual acuity (BCVA) was 250 µm. After completing the first 6 months, 341 patients from the DEX Implant 0.7-mg group and 327 from the sham group entered the open-label phase and were followed for an additional 6 months. Fluorescein angiography (FA) with transit of the study eye was obtained prospectively for all patients at baseline, 6 month, and at 12 month (study end). After the completion of the study, FA data were collected retrospectively from a subset of sites that were requested to submit FAs for analysis at a masked, centralized reading center.

RESULTS: FAs were received for 487 patients (183 with CRVO, 304 with BRVO), who were similar and well-matched to the total cohort for all major characteristics at baseline including age, gender, concomitant disease, visual acuity, and OCT central subfield thickness. For ease of analysis, BRVO and CRVO results were pooled, and DEX implant 0.7 mg (FDA-approved dose) was compared with sham. Neovascularization (NV) on FA was observed in 12/151 DEX implant 0.7 mg and 16/157 sham patients at baseline (P=ns). By Day 180, active NV was present in 11/146 (7.5%) DEX implant 0.7 mg and 23/142 (16.2%) sham patients. Global nonperfusion could be assessed in fewer than 50% of patients at baseline, primarily due to extensive hemorrhage but was gradable by Day 180 in 82% of DEX implant 0.7 mg and 71% of sham patients, demonstrating a mean of 5.9 MPS disk areas (DA) of nonperfusion in the DEX implant 0.7-mg group compared with 5.1 MPS DA in the sham. Only 21.1% of DEX implant 0.7 mg and 18.3% of sham patients demonstrated >10 MPS DA on nonperfusion by Day 180. Severity of macular capillary nonperfusion was similar between DEX implant and sham at baseline and during the study, with severe nonperfusion in foveal central subfield present in 15.9% DEX-treated patients and 13.1% in sham patients.

CONCLUSIONS: Extensive capillary nonperfusion (>10 MPS DA) and NV were relatively uncommon, consistent with the prespecified enrollment criteria. Though the sham and DEX implant groups were well-balanced for most FA features, including macular leakage, DEX-treated patients appeared to have a greater extent of nonperfusion. Despite this, patients receiving DEX implant 0.7 mg appeared to have a lower rate of development of NV compared with sham. Macular leakage declined in both treated and sham patients over time and appeared to mirror the OCT results.
Double-masked, Sham-controlled, Randomized Study of Dexamethasone Intravitreal Implant for the Treatment of Uveitis

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Purpose: To evaluate the dexamethasone intravitreal implant (DEX Implant, Ozurdex™) in patients with uveitis.

Methods: In this 26-week trial, patients with non-infectious intermediate or posterior uveitis were randomized to receive DEX Implant 0.7 mg (n=77), DEX Implant 0.35 mg (n=76), or a sham procedure (n=76). The primary endpoint was the proportion of patients with vitreous haze score of 0 at week 8. Other endpoints included best-corrected visual acuity (BCVA) and safety.

Results: The proportion of patients with vitreous haze score of 0 at week 8 was 46.8% with DEX Implant 0.7 mg, 35.5% with DEX Implant 0.35 mg, and 11.8% with sham (P15 letters from baseline BCVA was seen in significantly more patients in the DEX Implant groups than the sham group at all visits (P25 mmHg peaked at 7.1% for DEX Implant 0.7 mg, 8.7% for DEX Implant 0.35 mg, and 4.2% for sham (P = ns, all visits). Cataracts developed or worsened in 11 Dex Implant 0.7 mg, 10 DEX Implant 0.35 mg, and 8 sham patients.

Conclusions: In patients with non-infectious intermediate or posterior uveitis, a single dose of DEX Implant was well-tolerated and produced significant improvements in intraocular inflammation and visual acuity persisting for 6 months. Overall, DEX Implant 0.7 mg demonstrated greater efficacy than DEX Implant 0.35 mg with similar safety.
Intravitreal TNF Inhibitors in the Treatment of Refractory Diabetic Macular Edema: A Pilot Study from the Pan American Collaborative Retina Study Group

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PURPOSE: To report the short term visual and anatomic outcomes following intravitreal injections of 2 different tissue necrosis factor (TNF) alpha inhibitors in eyes with refractory diabetic macular edema (DME).

METHODS: An interventional, retrospective, multicenter study of 39 eyes with refractory DME that were injected with adalimumab (n=5 for 2 mg) or infliximab (n=15 for 1 mg; n=19 for 2 mg). The main outcome measures were the best corrected visual acuity (BCVA) and the central macular thickness (CMT) at 3 months of follow-up.

RESULTS: In the 1 mg infliximab group the logMAR BCVA improved from 1.49 ± 0.58 at baseline to 1.38 ± 0.56 at 3 months (p=0.6991). In the 2 mg infliximab group, the logMAR BCVA worsened from 0.76 ± 0.54 to 1.03 ± 0.69 at 3 months (p=0.5995). In the adalimumab group, the logMAR BCVA improved from 1.44 ± 0.77 to 1.08 ± 0.85 at 3 months (p=0.2500). The CMT in the 1 mg infliximab group decreased from 459 ± 125 µm at baseline to 388 ± 131 µm at 3 months (p=0.1178). In the 2 mg infliximab group, the CMT remained unchanged from 378 ± 97 µm at baseline to 349 ± 118 µm at 3 months (p=0.2162). In the adalimumab group, the CMT remained unchanged from 521 ± 163 µm at baseline to 526 ± 390 µm at 3 months (p=0.1250). There were no systemic side effects reported in any of the patients. None of the eyes injected with either adalimumab or 1 mg of infliximab had ocular adverse events. In the 2 mg of infliximab group, 42% (8/19) of eyes developed a severe uveitis. Three of these eyes (37.5%) required pars plana vitrectomy. The uveitis in the remaining 5 eyes resolved with topical steroid therapy.

CONCLUSIONS: Both intravitreal adalimumab and infliximab do not appear to benefit eyes with refractory DME. Intravitreal injections of infliximab may elicit a severe intraocular inflammatory reaction.
iCo-007 for Treatment of Diffuse Diabetic Macular Edema (DME) Results from the Phase I, Open Label, Dose Escalation Study Using a Single Intravitreal Injection of iCo-007

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Purpose: To investigate safety, tolerability and efficacy of iCo-007 in patients with refractory DME. This novel agent is a second-generation antisense drug reducing expression of C-raf kinase, a component of the mitogen-activated protein (MAP) kinase signaling pathway. Down-regulating the MAP kinase pathway has the potential to block the signaling of multiple growth factors.

Methods: The Phase I, open label, dose escalation (110µg, 350µg, 700µg and 1,000µg) clinical trial at four clinical centers in the USA. A total of 15 patients with diffuse DME received treatment and were followed for 6 months after a single intravitreal injection of iCo-007 to investigate safety, PK profile and signs of efficacy based on optical coherence tomography and visual acuity testing at all visits.

Results: Patients had a history of chronic diffuse DME resistant to other treatments, including photocoagulation, steroids and anti-VEGF treatments. There were no drug-related serious adverse events in any of the cohorts and the drug was consistently undetectable in the blood plasma regardless of the drug dose injected. Signs of biologic activity were observed in a number of patients (retinal thickness reduction ranging between 115-743 microns at their last visit). Onset of effect was observed toward the end of the follow-up period. The results of the treatment of all cohorts will be available and presented.

Conclusions: iCo-007 injected intravitreally was found to be safe and showed a biologic effect in the treatment of patients who previously failed treatment for DME. Based on the Phase I study, future clinical trial doses may only be required every 3 to 6 months which would be an improvement over the current treatment regimen.
Fluorescein Angiographic Findings in PEARL Study of Ranibizumab Therapy for PCV — Importance of ICG Angiography Due to Therapeutic Response Differences Between PCV and AMD

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Purpose: To demonstrate the potential role of ICG angiographic findings in influencing therapeutic decision making in patients presenting with serosanguinous maculopathy with choroidal neovascularization and leakage on fluorescein angiography.

Methods: The fluorescein angiographic (FA) findings of patients screening for the prospective ranibizumab trial for polypoidal choroidal vasculopathy (PEARL study – BJO EPUB 9/1/09) were reviewed for type of choroidal neovascularization and location of leakage on FA. All patients screening into this study had polypoidal choroidal vasculopathy (PCV) documented on ICG angiography.

Results: The FA findings in the 16 Asian patients with documented PCV on ICG angiography showed occult choroidal neovascularization in 10/16 eyes (62.5%), vascularized RPED in 5/16 eyes (31.2%), and predominantly classic CNV in 1 eye (6.3%). The location of leakage was subfoveal in 11/16 eyes (68.8%) and extrafoveal in 5/16 eyes (31.2%). Many of the FA findings did not show findings that would be suspicious for PCV. All 16 patients had PCV on ICG angiography in the macular region, which is typical for the Asian PCV population, with 1 patient also having peripapillary polyps. The 6 month results of ranibizumab therapy for PCV in the PEARL trial recently e-published in the BJO showed a 17% chance of 3 lines or more vision improvement, which is less than that noted in the MARINA and ANCHOR studies in exudative AMD. The 2 patients with PCV responding with 3 lines of vision gain on ranibizumab therapy had occult CNV in one eye and predominantly classic CNV in one eye. Recently, EVEREST trial results show a much higher anatomic closure rate of PCV complexes on ICG angiography with combined PDT and ranibizumab than with ranibizumab alone.

Conclusions: ICG angiography is important to differentiate PCV from exudative AMD, especially with the more variable and less robust response to anti-VEGF monotherapy, and the much higher anatomic PCV closure results with PDT and ranibizumab than ranibizumab monotherapy alone. Fluorescein angiographic findings alone are not adequate to make the diagnosis of PCV in many cases.