Changes in Oxygen Saturation Monitoring Reduces the Incidence of Retinopathy of Prematurity (ROP)

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PURPOSE: The deleterious effects of unrestricted, unmonitored oxygen therapy in retinopathy of prematurity (ROP) are well-accepted. However, the questions of optimal target ranges and optimal timing for maintaining blood oxygen in preterm infants remain controversial. Recent institutional changes in the delivery and monitoring of oxygen supplementation have allowed us the opportunity to examine the effect of systematic changes in target oxygen saturation on the incidence and severity of ROP.

METHODS: Retrospective, comparative cohort study using prospectively acquired data of all infants treated in our quaternary-care neonatal intensive care unit. During 2006, a desired O2 saturation range (85-93%) and oximeter alarm limits (80-95%) were defined, and protocols to meet these targets were implemented for all very low birth weight (VLBW) infants (<1500 g). Clinical outcomes of infants treated between 2005 and 2008 (i.e., before, during, and after the introduction of these institutional changes) were analyzed. Two cohorts were defined: cohort 1 included infants treated between 1/1/05 and 12/31/06, and cohort 2 included infants treated between 1/1/07 and 12/31/08. Main outcome measures were: (1) incidence of any ROP (Stage I or higher); (2) incidence of treatment-requiring ROP; (3) incidence of systemic comorbidities.

RESULTS: Cohort 1 included 178 infants, while cohort 2 included 181 infants. The incidence of any ROP (40% versus 25%, P=0.002) and of treatment-requiring ROP (12% versus 4%, P=0.01) were significantly lower in the later cohort. The incidences of chronic lung disease, severe intraventricular hemorrhage, periventricular leukomalacia and necrotizing enterocolitis were not statistically different between cohorts.

CONCLUSIONS: With contemporary neonatal practices, targeted oxygen saturation of 85-93% beginning within 24 hours of birth appears to reduce the incidence of ROP without additional adverse systemic effects. Systematic implementation of such a program of oxygen delivery and monitoring, by incorporating education of staff, revised order sets, and outcome assessment, appears practical and beneficial.
**Intravitreal Bevacizumab Therapy in the Treatment for Retinopathy of Prematurity: Four-year Follow-up**

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**Purpose:** To report the ocular and developmental findings after four years of follow up in a group of infants treated with intravitreal bevacizumab for treatment requiring retinopathy of prematurity (ROP).

**Methods:** A prospective, longitudinal follow-up study was performed in 18 eyes of 13 premature patients treated with intravitreal bevacizumab for ROP. Initially, the eyes were divided into three groups: group I, eyes with stage 4a or 4b ROP that had no response to conventional treatment (n=4); group II, eyes with threshold ROP that were difficult to treat with conventional treatment (n=5); group III, eyes with high risk prethreshold or threshold ROP (n=9). Neovascular regression, anatomical findings, functional testing, neurodevelopmental outcomes, visual acuity and refraction were recorded.

**Results:** Regression of neovascularization and normal neovascular growth was found in all patients. On four year follow up, no significant abnormalities were found in neurodevelopment. In groups II and III, retinal function was conserved 4 years after intravitreal injection of bevacizumab as assessed by electroretinography (ERG), refraction and visual acuity. Best corrected visual acuity (BCVA) in groups II and III at 4 years of age ranged from 20/30 to 20/200 (7 eyes with BCVA=20/30; 4 eyes with BCVA=20/40; 1 eye with BCVA=20/60; 1 eye with BCVA=20/80; 1 eye with BCVA=20/200). All except one patient in group I displayed visual acuity of 20/200 or worse.

**Conclusions:** Intravitreal bevacizumab as a treatment for retinopathy of prematurity seems to be a safe and effective therapy at 4 years of follow up in this small series.
Persistent Fetal Vasculature: New Thoughts on Pathogenesis and Treatment

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Purpose: Persistent Fetal Vasculature syndrome (PFVS) has historically been described as a unilateral sporadic anomaly of development. With improved diagnostics, surgical advancement, and genetic testing it is now recognized that this may be a more complex eye disease. We evaluated the eyes of children with apparently unilateral PFV for fellow-eye anomalies, management and surgical approaches and outcomes.

Methods: Children diagnosed with unilateral PFV underwent OCT, fundus photography, fluorescein angiography of both eyes. The affected eye also underwent surgical intervention (lens-sparing vitrectomy or lensectomy with vitrectomy). The diagnostics of both eyes were studied to investigate incidence of fellow-eye anomalies and evaluate surgical management and outcomes.

Results: Fluorescein angiography often revealed vascular anomalies in the fellow eye that was not detectable by ophthalmoscopy. The most common findings were peripheral avascular retina and/or anomalous foveal capillary formation. Surgical complications were due to anomalous retinal folds in the anterior retina, eccentric stalk tissue, or poorly formed pars plana. Both diagnostic findings and surgical structural remnants overlap with characteristics of Familial Exudative Vitreoretinopathy (FEVR). With improved genetic testing, patients with PFV may also have mutations in genes generally associated with FEVR, Norrie disease, and Osteoporosis Pseudoglioma syndrome. These findings suggest that PFVS may not be an isolated sporadic event but may represent a spectrum in vitreoretinal diseases of maldevelopment.

Conclusions: The implications for management, consequently, change with a shift in evaluation. Not only does the fellow eye of unilateral PFV require a more thorough evaluation but more frequent examination may be prudent. The surgical approach also changes with this understanding. The pitfalls of anterior loop retina and anomalous stalk tissue is more easily addressed by observing the spectrum of disease phenotypes.
Anti-Apoptotic Therapy with the X-Linked Inhibitor of Apoptosis (XIAP) as an Adjunct to Gene Therapy for Hereditary Retinal Degeneration

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**Purpose:** To evaluate the photoreceptor-protective effect of AAV delivery of X-linked inhibitor of apoptosis (XIAP) in the rd10 mouse, a rodent model of autosomal recessive retinitis pigmentosa caused by a loss-of-function mutation of the —subunit of rod cGMP phosphodiesterase gene (Pde6b).

**Methods:** The rd10 mice were bred and reared in a dark environment. One eye received a subretinal injection of AAV-XIAP or AAV-GFP (as control) at postnatal age of 4 days or 3 weeks. The contralateral eye was not injected. After treatment, the animals were maintained for 4 weeks in the dark before they were moved to 12-hour/12-hour light/dark cycling environment. Histology, immunohistochemistry and ERG were performed at different stages up to 3 weeks after moving to the cycling light environment.

**Results:** Retinas treated with AAV- XIAP showed structural preservation of the outer nuclear layer up to 3 weeks after transfer to the light, whereas AAV-GFP injected eyes and untreated eyes showed severe degeneration after transfer to the light. Though present in the AAV-XIAP treated eyes, outer segments were disorganized and ERG analysis showed minimal functional improvement.

**Conclusions:** The results suggest that AAV-XIAP confers protection of photoreceptor numbers in rd10 mice for at least 3 weeks after moving to cycling light environment. We suspect that functional rescue was not achieved because the therapy did not address the underlying defect in the Pde6b gene. We propose that AAV-XIAP therapy may help extend the window of opportunity for preserving photoreceptor cell counts for subsequent gene therapy of the causative gene mutation. Combination therapy with both AAV-XIAP and subsequent AAV delivery of the Pde6b gene will also be discussed.
The Roundabout, Axon Guidance Receptor, Homolog1 (ROBO1), a Novel Age-related Macular Degeneration Susceptibility Gene

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PURPOSE: To examine the genetic contribution of ROBO1 to AMD susceptibility. ROBO1 is a gene identified using a systems biology based approach which included gene expression profiling and linkage analysis.

METHODS: We ascertained the genotypes of 1001 subjects including individuals with normal maculae, 65 years of age or older and individuals with varying levels of AMD severity, ranging from AREDS category 2 to neovascular disease. A combination of direct sequencing, TaqMan, and Sequenom iPLEX technology was employed to genotype 42 single nucleotide polymorphisms (SNPs) in a sibling cohort of 657 subjects and an unrelated case-control cohort of 344 subjects. Single SNP and haplotype analysis was conducted for AMD as a quantitative trait as well as for neovascular vs. dry AMD using Family Based Association Testing (FBAT), logistic regression, and UNPHASED while controlling for age, sex, and smoking.

RESULTS: We identified SNPs and haplotypes in ROBO1 that were associated with risk of neovascular AMD when compared to individuals with early and intermediate AMD. The haplotypes significantly associated with neovascular AMD in both cohorts contained alleles from SNPs rs7637338 and rs9832405, both located in the promoter of ROBO1. Additionally, variants in ROBO1 were found to significantly interact with variants in the AMD susceptibility genes ARMS2/HTRA1 and RORA.

CONCLUSIONS: These data demonstrate ROBO1 as a novel AMD susceptibility gene which may play a pathogenic role in progression to neovascular disease. Moreover, the interaction between genetic variants in ROBO1 with variants in ARMS2/HTRA1 and RORA suggests that these genes likely function in the same biologic pathway.
Normalizing the Retinal Vasculature and Protecting Neural Retinal Tissue with Insulin-like Growth Factor Binding Protein 3 (IGFBP-3) After Ischemic Injury

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PURPOSE: In an attempt to further understand and elucidate the mechanisms of neovascularization and modulate angiogenesis, we desired to determine the necessary steps to reduce retinal vascular permeability and preserve retinal neural tissue. Previously, we showed insulin-like growth factor binding protein 3 (IGFBP-3) to have vascular protective effects, including the ability to recruit endothelial progenitor cells (EPCs) to sites of injury. We, also, previously determined that IGFBP-3 increased the sphingosine/ceramide ratio, suggesting a role for acid sphingomylinase. In this work, we further explore the role of IGFBP-3 and acid sphingomylinase in reducing vascular permeability and protecting retinal tissue.

METHODS: Three different approaches were employed in this set of experiments. Two animal models of ischemia and injury were utilized: A. the ROP-OIR (retinopathy of prematurity oxygen induced retinopathy) model and B. our mouse laser photocoagulation injury model. Immunohistochemistry and electron microscopy were performed. A third aspect of this work, also in mice, looked at in-vivo permeability assays, after the intravitreal injections of various combinations of VEGF and IGFBP-3. Experiments were performed on chimeric and non-chimeric C57B1/6 mice. Retina flat mounts were analyzed for fluorescence. Acid sphingomylinase mRNA activity was measured.

RESULTS: IGFBP-3 appears to have a variable effect on vascular permeability depending on location, relative to the vessel s lumen. In the OIR model, apoptotic death within the inner nuclear layer was greatly reduced in IGFBP-3 treated mice. In the laser injury model, increased retinal vascular permeability promoted by laser application was greatly reduced by IGFBP-3 treatment. Finally, it appeared that IGFBP-3 decreased acid sphingomylinase mRNA levels.

CONCLUSIONS: IGFBP-3 has variable effects on permeability after an ischemic insult. Overall, it appears to promote an increase in growth factors, which in turn, recruits the progenitor cells required for vascular repair. Ultimately, IGFBP-3 reduces acid sphingomylinase which leads to both, decreased apoptosis of cells in the inner nuclear layer of the retina and increased integrity of the blood-retinal barrier.
Efficacy of a Topical Tubulin Inhibitor, OC-10X, in a Non-human Primate Model of Exudative Age-related Macular Degeneration

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PURPOSE: To determine the efficacy of OC-10X in a non-human primate model of exudative AMD.

METHODS: Laser induced choroidal neovascularization, simulating exudative AMD, was generated in both eyes of 8 non-human primates. Intravitreal injection of OC-10X was preformed in one eye at baseline and two weeks, while the fellow control eye was observed. Animals were evaluated at two and four weeks for presence of ocular and systemic toxicity, and were sacrificed at 4 weeks. Area of CNV was measured by FITC-dextran technique.

RESULTS: A 43% reduction in the area of the CNV in OC-10X treated eyes compared to control eyes was measured (p=0.025). No toxic effects of the OC-10X or vehicle were noted in the anterior segment, posterior segment, or systemically.

CONCLUSIONS: OC-10X inhibits experimental CNV in a non-human primate model of AMD. Tubulin inhibition requires further investigation and may represent a safe, useful, alternative approach in the management of exudative AMD.
Targeting Complement Factor 5 in Combination with Vascular Endothelial Growth Factor (VEGF) Inhibition for Neovascular Age-related Macular Degeneration (AMD): Results of a Phase 1 Study

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PURPOSE: Genetic linkage and pathobiological studies have implicated activation of the complement system in AMD. Preclinical studies confirm a role for complement effector molecules in the induction and severity of choroidal neovascularization. This study assessed the safety of intravitreal injections of the aptamer ARC1905, which inhibits activation of complement factor 5, in combination with ranibizumab for the treatment of neovascular AMD.

METHODS: Forty-three treatment-naïve patients were enrolled in a phase 1, prospective, noncontrolled multicenter, dose escalating study of all subtypes of subfoveal neovascular AMD. These patients received six monthly intravitreal injections of the combination of ARC1905 (0.3 mg, 1 mg, 2 mg) and ranibizumab (0.5 mg). Secondary endpoints included change in visual acuity and OCT. Complement-associated SNP analysis was conducted in a cohort of patients.

RESULTS: Dose escalation was completed without evidence of dose-limiting toxicity. Two patients had non-ocular serious adverse events that were unrelated to study drug. Preliminary analysis revealed 51% of patients gained > 3 lines (> 15 ETDRS letters) of VA (46%, 47%, 60% for the 0.3 mg, 1 mg, and 2 mg dose groups, respectively) from baseline to Week 24. The mean change in OCT center point thickness was -150 µm (-141 µm, -171 µm, -137 µm for the 0.3 mg, 1 mg, and 2 mg dose groups, respectively) at Week 24. Baseline OCT center point thickness did not influence the response to therapy.

CONCLUSIONS: The combination of C5 and VEGF inhibition in neovascular AMD is well tolerated without evidence of acute toxicity.
Purposed: Recently developed thermo-responsive hydrogel has been shown to be effective in encapsulating and releasing active protein in vitro and may have various significant applications for the eye. The main objective of this study was to characterize the thermo-responsive hydrogel in an in vivo animal model.

Methods: All experiments were performed on anesthetized adult pigmented rats. Thermo-responsive hydrogel was synthesized using poly(N-isopropylacrylamide) (PNIPAAm) and crosslinked with polyethylene glycols-diacylate (PEG-DA). Approximately 5 µl of sterile hydrogel was injected into the vitreous cavity via a 30 gauge needle. Three in vivo testings were performed: SD-OCT to measure the thickness of the retina and injected hydrogel; SLO to assess size and location of the hydrogel; and ERG to measure the retinal cellular function. Data were acquired at prior to injection and weekly up to 4 weeks post injection.

Results: Both the retina and hydrogel were imaged at the same time with SD-OCT. The retinal thickness near the hydrogel was determined to be 259 ± 15 µm compared to the non-exposed area of 247 ± 19 µm. The cross-sectional thickness of the hydrogel was ~400 µm. Using 2-dimensional SLO infrared reflectance images, the area of the hydrogel was estimated to be ~4 mm2. The location and size of the hydrogel remained constant throughout the investigated period. There was a transient small change (~10%) in the retinal blood flow after one week but it recovered to the normal level. A corresponding small change in the a- and b-wave ERG amplitudes were noted after one week but recovered to the normal pre-injection level.

Conclusions: There was a small transient change in blood flow and ERG after the intravitreal injection of the hydrogel. However, these changes fully recovered back to baseline after one week. OCT images remained stable throughout the course of the study. Current results suggest that thermo-responsive hydrogels appear to be a safe and promising minimally invasive drug delivery platform to the posterior segment of the eye.
**iSONEP, an Anti-Sphingosine-1-Phosphate Monoclonal Antibody for Investigation in Exudative Age-related Macular Degeneration: Results from a Phase 1 Trial**

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**PURPOSE:** To evaluate the safety, maximum tolerated dose (MTD) and preliminary biologic activity of escalating doses of iSONEP in subjects with exudative AMD.

**METHODS:** Subjects with all sub-types of CNV secondary to AMD were enrolled in a Prospective Open-Label Dose-Escalating Multi-Center Study. Fifteen subjects (3/dose group) received a single intravitreal (ivt) injection of iSONEP (0.2, 0.6, 1.0, 1.4 or 1.8 mg/eye) in one eye. The study duration was 30 days with 11 months of safety follow-up. Primary outcome measures were safety and tolerability. Secondary outcome measures included assessments of preliminary biologic activity as determined by OCT and FA (area of CNV).

**RESULTS:** Nine females and 6 males were enrolled. Median age was 76. Most subjects had received prior AMD treatment including anti-VeGF and triple therapy. No SAEs related to iSONEP were reported. Only 3 AEs occurred: subconjunctival hemorrhage, post-injection eye pain, and a 3 msec increase in the QTcB interval in a subject (0.2 mg) with a history of arrhythmia. All AEs resolved without sequelae. Ten subjects were evaluable for biologic activity, as 3 were deemed to have disciform scars at screening as determined by an independent reading center and 2 were excluded from analysis due to protocol violation. Biologic activity (by OCT and/or FA) was noted in 8/10 evaluable subjects. There was a clinically meaningful regression in CNV area for the 5/10 subjects with occult CNV. Pigment epithelium detachment (PED) was noted in 2 subjects entry; complete resolution of PED was noted by Day 45.

**CONCLUSIONS:** While the MTD was not reached, a single dose of ivt iSONEP up to 1.8 mg was well tolerated. Although the study is limited by a small sample size and lack of a control group, results suggest sphingosine-1-phosphate is a biologic mediator in some patients with exudative AMD.
Hydroxychloroquine Screening and the Retina Specialist

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Purpose: 1) To provide retina specialists with new data on the risk of hydroxychloroquine (HCQ) maculopathy and on the use (and relative sensitivity) of the latest technology for screening. 2) To provide an insider view to pending revisions of the American Academy of Ophthalmology screening guidelines, revisions that change some expectations and practice.

Methods: Recent literature is reviewed, including a new demographic study (In Press) based on the largest reported group of 1538 unselected HCQ users. Material from the new AAO guidelines (still under review at time of abstract submission) will be presented.

Results: Analysis of bull’s eye maculopathy among 1538 HCQ users shows that the risk of retinopathy is low within 5 years of administration, but then rises towards 1% and will reach 2-3% by 10-20 years. Most patients nowadays receive 400 mg daily, and within this dosage range (excepting very small individuals) the precise daily dose by weight is not related to toxicity. Years of usage and cumulative dose is most critical. The AAO guidelines will continue to recommend baseline screening, and then annual examination beginning after 5 years (unless there are special risk factors), but with recognition of duration of use as a key risk factor. Underlying maculopathy is a contraindication for HCQ usage because it confounds the recognition of early toxicity. Dosage should not exceed 400 mg/day and should be less for individuals with short stature. Although retinal examination and 10-2 fields remain the core of screening recommendations, SD-OCT, fundus autofluorescence and mfERG are recognized to be more sensitive in many patients.

Conclusions: The risk of HCQ retinopathy is higher than previously appreciated in long-time users, ranging from 1-3% depending on years of use. This is an incidence that should justify screening. The new AAO guidelines will put more emphasis on duration of use (cumulative dose) than daily dose (except for short stature). Newer retinal test procedures such as mfERG, SD-OCT and fundus autofluorescence may be more sensitive than fundus examination and 10-2 fields, but cannot be mandated because of limited availability. However, retina specialists should consider the use of these tests on a routine basis where practicable, to increase the likelihood of recognizing early HCQ toxicity.

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Purpose: To evaluate nosocomial, acute-onset postoperative endophthalmitis rates occurring at an university teaching hospital from a contemporary series (2002-2009) and to compare these to prior rates over the last 25 years.

Methods: This was a retrospective, consecutive case series. Medical records were reviewed for all patients diagnosed with acute-onset, postoperative nosocomial endophthalmitis from 2002 through 2009 associated with surgery at Bascom Palmer Eye Institute.

Results: The 8 year (2002-2009) frequency of acute-onset postoperative endophthalmitis was 0.025% (14 of 56,672 intraocular surgeries). The rate was 0.028% (8/28,568) for cataract surgery and 0.011% (2/18,492) for pars plana vitrectomy (PPV). Both PPV endophthalmitis cases followed 20-gauge surgery and no cases followed small gauge, transconjunctival PPV (n=2,262). Three cases occurred following penetrating keratoplasty (3/2,788, 0.108%). The most common bacterial isolate was Staphylococcus (n=7, 50%). Initial treatment involved ocular paracentesis (n=8, 57%) or vitrectomy (n=5, 36%), in combination with injection of intraocular antibiotics. Vancomycin and ceftazidime were used in 13 (93%) eyes and intraocular steroids were given initially to 9 (64%) eyes. Final visual acuity was >20/200 in 9 (64%) eyes and 2 (14%) eyes were no light perception. At this institution since 1984, there has been a statistically significant trend for a decreasing rate of acute-onset postoperative endophthalmitis (1984-1994: 0.09%; 1995-2001: 0.05%; 2002-2009: 0.025%; p<0.001).

Conclusions: At a university teaching hospital involving resident, fellow and faculty surgeons, the frequency of nosocomial, acute-onset postoperative endophthalmitis is low. When compared to prior time periods from the same institution, the rate of postoperative endophthalmitis has not increased in the era of sutureless clear corneal cataract surgery or transconjunctival sutureless pars plana vitrectomy.
Clinical Outcomes in Patients with Large Uveal Melanomas Treated with Proton Therapy

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PURPOSE: To determine ocular outcomes and survival after proton therapy in patients with large tumors ineligible for the Collaborative Ocular Melanoma Study (COMS).

METHODS: We evaluated 392 patients treated with proton therapy for large choroidal melanomas (> 8mm in height and >16 mm in basal diameter). Maximum tumor height was 17.1 mm and maximum LTD was 24 mm. Rates of survival, visual acuity changes, tumor recurrence, treatment-related complications, and enucleation were calculated using the Kaplan-Meier method. Median follow-up was 8 years.

RESULTS: The tumor recurred in approximately 10% of the cohort by ten years after proton therapy. Of 15 documented recurrences, 6 (40%) were marginal recurrences, and 4 (27%) were uncontrolled tumors. Approximately one-third of these patients (n=140) died from metastatic disease while under observation. Of 282 patients with a visual acuity of at least 20/200 at diagnosis, 18.8% retained visual acuity of at least 20/200 and 44.8% retained visual acuity of counting fingers or better 5 years after treatment. Patients with tumors located near critical structures (within 1 disc diameter of the optic nerve and/or 2 disc diameters of the fovea) were likely to experience more severe vision loss; 5 years after treatment 8% had visual acuity of 20/200 or better compared to 42% for patients with tumors farther away from these structures. Overall, rates of radiation papillopathy and maculopathy were approximately 22% and 37%, respectively, by five years after treatment. Higher rates were observed in patients with large tumors that were also in close proximity to the optic nerve or fovea, with five year rates of 31% for papillopathy and 43.5% for maculopathy. Enucleation was performed in 61 cases (15.6%), with NVG the most common reason for the procedure (n=28).

CONCLUSIONS: Proton irradiation should be considered for patients with large tumors especially when the tumors are located away from the optic nerve and macula. Eye conservation is possible in approximately 85% of patients with preservation of vision (counting fingers or better) in 44% of cases.
Outcomes and Risk Factors Associated with Endophthalmitis After Intravitreal Injection of Anti-VEGF Agents

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Purpose: To describe the visual outcomes in patients with presumed infectious endophthalmitis following intravitreal injection of anti-VEGF agents and to evaluate modifiable risk factors.

Methods: This single-center, non-randomized, unmasked, prospective series includes all patients who developed presumed infectious endophthalmitis after intravitreal bevacizumab or ranibizumab injection. All intravitreal anti-VEGF injections were administered between Jan 1, 2009 and Feb 28, 2010 by one of 16 retina surgeons. All eyes were prepped with topical 5% povidone-iodine prior to injection. Each surgeon administered the anti-VEGF injections using his or her preferred technique; the variables examined included bladed lid speculum use, conjunctival displacement, hemisphere of injection, and outcomes associated with bevacizumab vs. ranibizumab. A two-sample test of proportion was performed using Stata 9 (College Park, TX).

Results: 22,058 anti-VEGF injections were performed. 18 eyes underwent vitreous ± aqueous tap and intravitreal antibiotic injection. 5 cases were culture-positive, each with a different organism. All patients presented with pain and vitritis, on average 3.3 days (range 1-5) after injection, with no difference between culture-positive and negative groups. 14 of 18 eyes (78%) had a hypopyon. Of 16 cases that had at least 3 months follow-up, 10 returned to baseline vision (+/- 2 lines) within 3 months. 2 more eyes returned to baseline vision at 6 months. 2 of the 4 eyes that had > 2 lines of vision loss were culture-positive. Neither lid speculum use (0.10% vs. 0.066% in the no use group, p = 0.38), conjunctival displacement (0.12% vs. 0.073% no displacement, p = 0.38), hemisphere of injection (0.070% superior vs. 0.083% inferior, p = 0.81), or bevacizumab (0.11%) vs. ranibizumab ((0.060%, (p = 0.17)) affected risk. There were no trends associated with lot numbers. Endophthalmitis after ranibizumab was 5 times more likely to be culture-positive than after bevacizumab (50% vs. 10%, p = 0.060), suggesting a greater prevalence of non-infectious endophthalmitis with bevacizumab.

Conclusions: Most patients who develop endophthalmitis after anti-VEGF injection will regain baseline vision within 6 months. Neither lid speculum use, conjunctival displacement, hemisphere of injection, or type of anti-VEGF agent affect risk. Culture-negative endophthalmitis occurs more commonly after bevacizumab than after ranibizumab injection. The presence of pain, vitritis, or hypopyon does not differentiate culture-positive from culture-negative cases.
Timing of Povidone-Iodine Prophylaxis for Intravitreal Injections

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PURPOSE: To report the optimal contact time of 5% povidone-iodine on the ocular surface prior to intravitreal injection.

METHODS: A prospective randomized controlled study of 60 patients undergoing intravitreal injection. The study eye was prepared with 5% povidone-iodine with a contact time of either 30, 60, 90, 120, 150, or 180 seconds. The fellow eye served as a control. Swabs were taken from both eye’s conjunctiva prior to application and after the corresponding time intervals. Proportion of positive bacterial cultures, mean number of specimens, and growth of isolates were compared.

RESULTS: Use of 5% povidone-iodine for 60 seconds or greater resulted in a statistically significant reduction in proportion of positive cultures and swabs (83% versus 30%, p=<0.001).

CONCLUSIONS: The administration of 5% povidone-iodine for 60 seconds prior to intravitreal injections achieves a significant reduction in bacterial cultures. This should be considered the minimal amount of contact time with povidone-iodine necessary prior to intravitreal injection.
Barrier Effect of Lidocaine Gel with Povidone Iodine Antisepsis of the Ocular Surface

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Purpose: Anesthetic gels are being used more frequently for intravitreal injection preparations. This study evaluates the effect of lidocaine gel on betadine antisepsis of bacterial colonies.

Methods: Blood agar plates inoculated with Staphylococcus epidermidis were prepared using 2% lidocaine gel and 5% povidone-iodine solution in 8 groups as follows: 1) no treatment; 2) application of lidocaine gel; 3) application of lidocaine gel, followed by povidone-iodine for 30 seconds; 4) application of lidocaine gel, followed by povidone-iodine for 5 seconds; 5) application of povidone-iodine for 30 seconds; 6) application of povidone-iodine for 5 seconds; 7) application of povidone-iodine for 30 seconds, followed by lidocaine gel; 8) application of povidone-iodine for 5 seconds, followed by lidocaine gel. The plates were then incubated at 37 degrees Celsius for 24 hours, and the bacterial growth was independently determined by two separate graders.

Results: Control plates and plates treated with lidocaine gel alone or before povidone-iodine had no statistically significant difference in bacterial counts. Plates on which povidone-iodine was applied alone or prior to lidocaine gel demonstrated no bacterial growth, regardless of whether the antiseptic was retained on the plate for 5 seconds or for 30 seconds.

Conclusions: Povidone-iodine is effective at reducing bacterial counts when applied prior to lidocaine gel, regardless of whether the antiseptic has been present for 5 seconds or 30 seconds prior to administration of the anesthetic gel.
A Systematic Review/Meta-analysis of the Effects of the Timing of Pars Plana Vitrectomy (PPV) for Removal of Intravitreal Retained Lens Fragments (RLF) After Surgery for Age-related Cataracts

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PURPOSE: The retina community is divided over PPV timing and the feasibility of same-day PPVs. Since mixed results of timing on patient outcomes persist, a thorough understanding of existing data is needed in the absence of an RCT. The goal was to estimate rates of good (≥20/40) and bad (≤20/200) visual acuity (VA), retinal detachment (RD), and increased intraocular pressure (IOP) for time periods between cataract surgery and PPV.

METHODS: Meta-analysis can increase statistical power and detect subgroup differences. A PubMed search (limits: English; published after 01/01/1985) yielded 191 articles, with 64 more identified from reference lists: total 255. After review, 52 articles remained for the systematic review, with data from 35 unique studies for the meta-analysis (2385 eyes). All studies were retrospective case series.

RESULTS: Determination of timing to PPV was based on clinical conditions and practice patterns, with greater inflammation, persistent increased IOP, greater percent of lens fragments retained, and/or other complications indicating earlier PPV and/or faster referral from the cataract surgeon. Several authors indicated that results for earlier PPVs may be biased by greater patient severity. After 20+ years, PPV timing remains controversial and an RCT is demanded.

Rates of good VA and RD were similar for 0-7 and 8-30 days, and better than more than 30 days (month+) (all statistically significant at p<0.05 except VA 8-30 days vs. month+). Rates of bad VA and increased IOP were better for 0-7 than 8-30 days, which were better than month+ (statistically significant at p<0.05 IOP 0-7 days vs. month+). Analysis of VA results for 0-7 days indicated that 0-2 days was worse than 3-7 days. Reanalysis indicated better VA results for 3-7 days than any other time period (statistically significant at p<0.05 0-2 vs. 3-7 days (bad VA) & 3-7 vs. month+ (good VA)). Analysis of same-day PPV, showed that 7 centers achieved excellent results (averaging good VA results 40% higher and bad VA results 15% lower) than 7 other centers.

CONCLUSIONS: Superior visual acuity results for PPVs 3-7 days have not been previously detected due to authors tendency to group together all PPVs 0-7 days post cataract surgery, which masked the heterogeneity of results for this time period. Overall results may also be confounded, since patients with more severe reactions to RLF tended to receive earlier referral and/or PPV. Continued analysis and risk adjustment is needed to inform an RCT comparing PPV timings. In addition, practice patterns for same-day PPV should be assessed to determine which lead to the best patient outcomes.
Combined Cataract Extraction, PCIOL, Pars Plana Vitrectomy, Retisert Implant, and Pars Plana Tube (CPR-PT) in Chronic, Advanced, Non-infectious Uveitis with Cataract and Glaucoma

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PURPOSE: To assess the safety and efficacy of combined cataract extraction (CE) with posterior chamber intraocular lens (PCIOL), pars plana vitrectomy (PPV), Fluocinolone Acetonide intravitreal implant (Retisert), and Ahmed valve with pars plana tube (PPT) in eyes with advanced, chronic, non-infectious uveitis with cataract and glaucoma.

METHODS: A retrospective chart review was performed of all patients who had Retisert implants, since its FDA approval in 2005, for posterior non-infectious uveitis combined with CE/PCIOL, PPV, and PPT. Outcome measures included visual acuity (VA), control of intraocular pressure (IOP), inflammation, and complications. Patients with at least 6 months of follow up were included. The Wilcoxon signed rank test was used for statistical analysis.

RESULTS: Eight eyes of 5 pts, ages 40 to 62, were included, with a mean follow up of 14 months (range 7-27). All eyes had a single procedure consisting of synechiolysis, CE/PCIOL, Retisert implant, PPV, and PPT (CPR-PT procedure). Two eyes had pre-existing anterior chamber tubes which were diverted to the PP secondary to corneal erosion. Mean VA improved significantly from pre-op LogMar 1.89 (SD 0.93, Snellen ~CF 2) (range 20/200 to HM) to post-op LogMar 0.17 (SD 0.13, Snellen ~20/30) (range 20/20 to 20/50) (p=0.01). Mean post-op IOP (14 mmHg, SD 2.51) was significantly lower than pre-op IOP (20.1 mmHg, SD 6.8) (p=0.04). All patients were on fewer glaucoma drops post-op (0.25, SD 0.46) than pre-op (2.9, SD 0.8) (p=0.01). No patients were on systemic prednisone compared to a mean pre-op dose (49 mg, SD 33) (p=0.004). Three pts were on systemic immunosuppressives pre-op which were discontinued. Inflammation was well controlled in all eyes at final follow up. Two eyes developed iris bombe, which were relieved with YAG peripheral laser iridotomy.

CONCLUSIONS: The CPR-PT procedure appears to be a reasonable option for patients with chronic, advanced, non-infectious uveitis, with cataract and glaucoma. The combined CPR-PT procedure allows rapid visual rehabilitation with good control of intraocular inflammation and IOP with less dependency on glaucoma medications, systemic steroids and immunosuppressive therapy, and without major short term complications.
Role of Pars Plana Vitrectomy for Medically Non-responsive Cystoid Macula Edema (CME) in Uveitis

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PURPOSE: To explore the role for pars plana vitrectomy in medically non-responsive CME in various types of uveitis.

METHODS: A retrospective case series of four patients (n=6 eyes) with various types of uveitis had persistent CME that was non-responsive to medical therapy despite control of intraocular inflammation. They underwent pars plana vitrectomy, with/without peeling of the ILM. Patient age, sex, clinical examination, best corrected pre- and post-operative VA, as well as pre- and post-operative TD-OCT were recorded.

RESULTS: Four patients, 6 eyes (4 right and 2 left), with a mean age of 49 years (range: 23-68) were followed for 4.3 months (range: 3-8 months) following surgery. At the time of surgery, each patient had an adherent posterior hyaloid over the macula despite the pre-operative appearance of a total posterior vitreous detachment. A typical pattern of adherent vitreous was encountered a small peripapillary circle with an isthmus connecting to a larger circle encompassing both retinal vascular arcades. After removal of the vitreous, with/without peeling of the ILM, BCVA improved from 20/97 (range: 20/40-20/200) to 20/45 (range: 20/25-20/80) [P=0.138] and central foveal thickness decreased from 318.8 (range: 216-389) to 247.7 (range: 0.082). No surgical complications occurred.

CONCLUSIONS: Medically non-responsive CME associated with uveitis, even with control of intraocular inflammation, may result from an adherent posterior hyaloid over the macula and/or contracture of the ILM. Pars plana vitrectomy, with/without ILM peeling, should be considered to achieve an improvement in vision.
Treatment and Long-term Follow-up of Choroidal Tumors with Benign FNAB Cytopathology

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PURPOSE: We assessed long-term outcome of choroidal lesions >4.5mm thick and suspicious enough for a malignancy on standard ophthalmic oncologic evaluation to have undergone intraoperative fine needle aspiration biopsy and were shown to have a benign cytopathologic result.

METHODS: Retrospective review of database for all choroidal tumors with a benign cytopathology result that were either followed with intervention (mainly atypical melanocytomas or lesions without subretinal fluid and/or documented growth) (19 cases) or treated with 20GyE of charged particle radiation (8 cases).

RESULTS: None of these patients had growth documented after FNAB. In the group of 8 cases with either documented growth (5) or subretinal fluid (3) that were shown to have benign cytology on FNAB, all responded to low dose charged particle radiation with tumor shrinkage. Complete follow-up was available in all cases, and no patient died of metastatic melanoma.

CONCLUSIONS: In very atypical moderate to large choroidal tumors (4.5-11mm thick on ultrasonography), a small percentage are benign on cytopathologic evaluation. In those without evidence of growth or exudative detachment long-term follow-up showed no tumor activity. In a small number with growth or sub-retinal fluid, treatment with low dose radiation was effective in controlling the lesions.
Surgical Attenuation of Radiation in the Treatment of Choroidal Melanoma: Report of a Technique

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PURPOSE: Although iodine-125 brachytherapy successfully achieves local tumor control, visual loss secondary to radiation affects most patients. Currently, no treatments for radiation vasculopathy are effective at saving vision. We have found that Silicone Oil 1000 cs attenuates iodine-125 by approximately 50% (Oliver et al, 2010). We report our technique of using iodine-125 brachytherapy in combination with vitrectomy and silicone oil in patients undergoing treatment for choroidal melanoma.

METHODS: Vitrectomy surgery with silicone oil 1000 cs was performed immediately following iodine-125 plaque placement for local treatment of choroidal melanoma. After appropriate dose of radiation had been applied to the tumor, the plaque was removed and silicone oil was removed from the eye. Tumor response to treatment and surgical outcomes were evaluated.

RESULTS: The technique of iodine-125 brachytherapy and vitrectomy with silicone oil 1000 cs was technically feasible and expected tumor response to treatment was achieved.

CONCLUSIONS: Iodine-125 brachytherapy and vitrectomy with silicone oil 1000 cs is a feasible strategy to potentially reduce radiation exposure to non-tumor tissue of eyes being treated for choroidal melanoma. Long-term clinical follow-up is warranted to evaluate effects of treatment including radiation attenuation on visual function.
Clinical Course of Choroidal Osteoma Following Radiation Therapy by Proton Treatment

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PURPOSE: To describe the clinical course of a growing choroidal osteoma in a 4 year old child by OCT and Fluorescein Angiography as well as visual function following treatment with fractionated proton beam therapy.

METHODS: Following the proof of growth within the papillomacular bundle towards the foveola the choroidal osteoma was treated in four sessions in general anesthesia at 5 Gy each on 4 consecutive days up to 20 Gy. The success was controlled by measuring visual function, binocular vision, Spectralis OCT and angiography following treatment.

RESULTS: After treatment the tumor showed no further increase following continuous growth towards the foveola with increasing thickness as measured by Spectralis OCT until the time of radiation. Instead the choroidal compartment within the tumor area became flatter and the exudative reaction diminished. The bony structures appear to dissolve. The angiography showed no significant leakage and the visual acuity stayed at 0.9 with normal binocular vision.

CONCLUSIONS: We were able to show the arrest of tumor growth in area and height following proton treatment of a choroidal osteoma. Whether this will influence visual function on the longterm follow up remains to be seen.
10,000 Intravitreal Injections: Analysis of Impact on the Ocular Oncology Service at Bascom Palmer Eye Institute

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PURPOSE: To report the indications, complications, cost and benefit of the first 10,000 intravitreal vascular targeting agent injections within a single service setting (Ocular Oncology) at the Bascom Palmer Eye Institute.

METHODS: An IRB approved, HIPAA compliant retrospective review of a consecutive series of 10,142 intravitreal injections of vascular targeting agents between June 1, 2007 and January 31, 2010 performed within the Ocular Oncology Service (TGM), Bascom Palmer Eye Institute, University of Miami Miller School of Medicine. All patients were identified through EMR for demographic analysis. Clinical indications for treatment, fundus and OCT imaging, and ophthalmologic follow-up were abstracted from direct chart review. Patient data was obtained for each injection and at pre-injection, one month, three months, six months, one year and two year intervals. A standard injection protocol was utilized including povidone-iodine, topical lidocaine, lid speculum and topical antibiotic.

RESULTS: 3,381 patients were treated with 10,142 intravitreal injections of bevacizumab (7,315), triamcinolone acetonide (1,846) or ranibizumab (981). The average number of injections per patient eye was 2.0 (range 1 to 34) with a median interval between injections of 63 days. Indications for injection were radiation retinopathy (54.2%), neovascular AMD (18.3%), non-AMD neovascularization (15.1%), VMT/ERM/CME (4.8%) and diabetic retinopathy (3.6%). The incidence of clinically suspected and culture positive endophthalmitis was 0.0098% (1/10,142). For the largest injection subset, visually compromising radiation retinopathy, Visual acuity was maintained within 2 lines of presenting visual acuity in 74% of patients over the three year study window.

CONCLUSIONS: Intravitreal vascular targeting therapy has significant impact within a large University Ocular Oncology service. This single service cohort, using a standardized protocol, enables evaluation of clinical applicability of therapy and documents a reassuringly low infection rate of 0.0098%. Cost and benefit had potentially large differentials between the anti-vascular targeting agents utilized and led the service to employ bevacizumab as its primary anti-VEGF agent for these unique “off label” treatments.