The V.E.E. Study — Primary Vitrectomy Combined with 360° Endolaser or Encircling Band for Rhegmatogenous Retinal Detachment

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PURPOSE: Promising anatomical and functional results have been reported for pars plana vitrectomy (PPV) in the treatment of rhegmatogenous retinal detachments (RRDs), with a slightly better anatomical outcome when an encircling band was added to the surgical procedure. We designed a randomized clinical trial to evaluate the functional and anatomical outcome comparing two different surgical procedures for the treatment of more complex rhegmatogenous retinal detachments (RRDs).

METHODS: A clinical trial was designed to include sixty patients, assigned randomly to be treated with PPV combined with 360° endolaser photocoagulation (group 1) or with PPV combined with an encircling band (group 2). Gas or silicone oil was used as intraocular tamponade depending on the complexity of the RRD. Silicone oil removal was planned to be performed 3 to 6 months after RRD surgery. Main outcome measures were retinal redetachment rate, surgery-related complications, patients' comfort, refractive change, best-corrected visual acuity (BCVA), and optical coherence tomography (OCT). Patients were examined preoperatively, and at 1 week, 1 month, 3 to 6 months after RRD surgery, and after silicone oil removal respectively.

RESULTS: Up to now 23 cases with a mean follow-up of 10 ±7SD months were included into group 1, and 22 patients with a mean follow-up of 11 ± 6SD months were included into group 2. The retinal redetachment rate was 9% (n=2) in each group. No intraoperative complications occurred in both groups. Postoperative iris capture was found in 17% (n=4) in group 1, and in 9% (n=2) in group 2. An elevated IOP was found in 22% (n=5) in group 1, and in 27% (n=6) in group 2. Transient corneal disorders developed in 13% (n=3) in group 1, and in 36% (n=8) in group 2. Questionnaire responses showed lower levels of patients’ discomfort after surgery in group 1. Mean postoperative refractive error change was significantly lower in group 2 (-0.4 ± 0.9 diopters versus -1.3 ± 1.2 diopters). BCVA at 6 months improved by 3 or more lines in 83% (n=19) in group 1, and in 68% (n=15) in group 2. OCT images were comparable in both groups, with one patient in each group showing a cystoid macular edema after surgery.

CONCLUSIONS: Primary PPV combined with 360° endolaser therapy seems to be as effective as PPV combined with an encircling band, with the benefits of an improved patients’ comfort and a more stable refractive status.
The Effect of Symptom Duration on Outcomes Following Vitrectomy Repair of Primary Macula-off Retinal Detachments

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PURPOSE: To examine the effect of symptom duration on visual and anatomic outcomes following vitrectomy repair of primary macula-off retinal detachments.

METHODS: This is a retrospective, consecutive, interventional case series. All eyes underwent repair of the macula-off retinal detachment with a standard 3-port pars plana vitrectomy. Eyes with previous retinal surgery, giant retinal tear, grade C or higher proliferative vitreoretinopathy, or < 2 months follow-up were excluded from the study. The main outcome measures studied were final best-corrected visual acuity (BCVA) and single surgery anatomic success rate as dependent variables on the duration of macular detachment symptom. Visual acuity analysis was performed on all pseudophakic eyes by the final follow-up visit.

RESULTS: Ninety-three eyes of 92 patients met inclusion criteria, with a mean follow-up length of 26 months (range 2-121) and mean duration of macular detachment symptom of 9.4 days (range 0-60). The mean final BCVA was 20/40 (range HM-20/20), with 69% (n=64) of all patients obtaining 20/40 or better final BCVA. Patients with symptom duration of 7 days or less achieved better final BCVA (mean 20/30, n=46) than patients with longer symptom duration (mean 20/50, n=47) (T-test, p=0.019). After 7 days of macular detachment, no significant difference was seen in final BCVA (T-test, p>0.05). The overall single surgery anatomic success rate was 89% (83 of 93 eyes). There was no correlation between the single surgery anatomic success rate and duration of macular detachment symptom (Fisher’s exact test, p>0.10).

CONCLUSIONS: Vitrectomy results in good final visual outcome for patients with primary macula-off retinal detachments. Surgery within 7 days of the symptom onset yielded better visual outcomes. After 7 days, visual outcome was not affected by timing of surgery. Anatomic outcome following vitrectomy repair is not affected by symptom duration.
Epiretinal Membrane After Primary Pseudophakic Rhegmatogenous Retinal Detachment Repair by Pars Plana Vitrectomy Alone

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PURPOSE: To evaluate epiretinal membrane incidence, anatomic and functional outcomes, in patients who underwent pars plana vitrectomy (PPV) alone for repair of primary pseudophakic rhegmatogenous retinal detachment.

METHODS: Prospective study of 312 consecutive pseudophakic patients who underwent primary retinal detachment (RD) repair by pars plana vitrectomy alone during a 48-month period with a minimum follow-up of 12 months. Patients with traumatic RD, RD of more than 2 months duration, vitreoretinal proliferation grade B or more, or another visually significant ocular condition were excluded. After epiretinal membrane surgery minimum follow-up was 12 months.

RESULTS: Of 312 patients, 28 (8.9%) developed a postoperative epiretinal membrane. Twenty-two patients (78.5%) underwent a vitrectomy procedure with membrane peeling and internal limiting membrane dissection. The mean time from RD surgery to membrane peeling surgery was 6.2 months (range, 1 to 13). Mean preoperative BCVA was 20/60 (20/400 to 20/25) and mean postoperative BCVA was 20/45 (20/200 to 20/25). The average improvement in vision after repeated surgery was 1.3 Snellen chart line. Statistically significant differences were seen in older patients and low visual acuity before ERM surgery. Six cases (27.2%) developed macular edema after membrane surgery. Final BCVA equal to or greater than their BCVA after RD repair was obtained in 95% of patients. Mean follow-up was 23 months (range, 12 to 46).

CONCLUSIONS: In our series, 8.9% of patients who underwent primary RD repair with PPV alone developed a postoperative macular pucker. Overall, the patients benefited from the repeated surgery for removal of macular epiretinal membranes, although the visual acuity gain was probably limited by the previous retinal detachment.
Scleral Buckling Remains Valuable for Retinal Reattachment

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PURPOSE: The use of a scleral buckling element in retinal detachment repair is decreasing. Reasons given are high rates of success with vitrectomy alone, and the elimination of complications at scleral buckling such as buckle erosion, and strabismus. We reviewed our cases of retinal reattachment surgery using a strategy that includes scleral buckling alone or with vitrectomy, and report anatomic and visual results as well as rates of buckle-related complications.

METHODS: This is a retrospective chart review of consecutive patients of two surgeons who performed repair of primary rhegmatogenous retinal detachment (RRD). All patients who had surgery in the calendar year 2008 were included (for the meeting, a larger series including 2009 will be reviewed). The choice of procedure was determined by the surgeon based on retinal detachment anatomy and lens status, among other factors. Data were collected on the type of procedure, scleral buckling element used (if any), preoperative macular status, pre-and postoperative acuity, length of follow-up, need for reoperation, and postoperative complications including strabismus, buckle erosion and epiretinal membrane.

RESULTS: A total of 139 cases were identified. Of the 128 who had surgery in the operating room, 49 had scleral buckling alone (SB), and 79 had scleral buckling combined with vitrectomy (SB/vit). All but one of the SB cases were phakic and 38/79 of the SB/vit cases were phakic. The macula was attached preoperatively in 32/49 of the SB group, and in 24/79 in the SB/vit group. Primary anatomic success occurred in 90% of patients in each group and final anatomic success was seen in 100%. The SB group showed final mean acuity of 20/34, with median 20/25. In the SB/vit group mean final acuity was 20/50 with median of 20/40. If macula on preop, final acuity in SB group was mean 20/24, median 20/20; in SB/vit group mean 20/36, median 20/25. If macula off preop, final acuity in SB group was mean 20/53, median 20/32; in SB/vit group mean 20/60, median 20/40. Phakic patients final acuity in SB group was mean 20/32, median 20/25; in SB/vit group mean was 20/70, median 20/50. Postoperative ERM was seen in 1/49 SB patients, and in 4/79 SB/vit patients. Re-detachment caused by PVR was seen in 4/79 of the SB/vit patients. No patients had strabismus requiring prisms or surgery, and no eroding buckles were seen.

CONCLUSIONS: RRD is a heterogenous condition, and current management is trending towards vitrectomy in a greater percentage of cases. Many patients who 20 years ago would have had SB, now get SB/vit or vitrectomy alone. In this series, patients who underwent SB had equivalent anatomic outcomes to those who had SB/vit, and slightly better visual outcomes whether the macula was on or off preoperatively. In phakic patients, visual acuity outcomes more significantly favored SB. These outcomes are consistent with those of the recent European SPR trial, which concluded that phakic patients had better visual outcomes with SB.
Incidence of Retinal Detachment After Small-incision, Sutureless Pars Plana Vitrectomy Compared to Conventional 20-gauge Vitrectomy in Macular Hole and Epiretinal Membrane Surgery

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PURPOSE: To evaluate the incidence of retinal detachment (RD) after small-incision, sutureless vitrectomy compared to conventional 20-gauge vitrectomy in macular hole (MH) and epiretinal membrane (ERM) surgery and to investigate clinical features and possible causing agents.

METHODS: We performed a computerized database analysis to identify retrospectively all patients which underwent vitrectomy at our institution between March 2001 and March 2009 for ERM and MH. We further investigated the clinical features of patients who showed RD within 6 months post-operatively in the study eye. Incidence rate and clinical features of the affected eyes were analyzed.

RESULTS: During the study period 2,432 vitrectomies were performed for ERM and MH. Incidence of RD was 1.7% (31 out of 1862) after sutureless 25-/23-gauge vitrectomy and 1.2% (7 out of 570) following conventional 20-gauge vitrectomy. The difference was not statistically significant. Moreover, the difference between 25-gauge surgery (28 out of 1580) and 23-gauge surgery (3 out of 282) was not statistically significant. In 9 out of 38 cases (24%) the RD was probably attributable to the underlying pathology (e.g. unclosed MH, reopening of pre-existing retinal tears). Twenty-one eyes (76%) presented new retinal tears which were not related to the sclerotomies in both groups.

CONCLUSIONS: The incidence of RD following macular surgery is not elevated in small-gauge, sutureless vitrectomy compared to the standard 20-gauge procedure. In most cases the RD is not caused by the surgical technique itself, but due to new retinal breaks.
Fovea-sparing Retinal Detachments: Time to Surgery and Visual Outcomes

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PURPOSE: To study the effect of the time interval from initial evaluation to repair on visual
and anatomic outcomes for fovea-sparing rhegmatogenous retinal detachment (RRD).

METHODS: This was a retrospective, consecutive case series of patients operated at a single
university medical center. Medical records were reviewed for preoperative and intraoperative factors
possibly associated with visual and anatomic outcomes for all patients undergoing scleral buckling
procedure (SBP) for fovea-sparing, primary RRD between 1989 and 2004.

RESULTS: Of the 199 study patients, 55% had symptoms for less than 7 days, 83% had best
corrected visual acuity (BCVA) of 20/40 or better, and 33% had a RRD that had extended to within
the macular arcade vessels. 85% were operated within 3 days including 56% within 24 hours.
One case progressed to fovea-off status before surgery 4 days after initial evaluation (0.5%). The
single operation success rate was 88% and final anatomic success was 99.5% (one patient refused
reoperation). 86% were examined postoperatively for at least 2 months; 73% had 20/40 or better
vision. The strongest predictor of postoperative BCVA was initial BCVA (r=0.47; p<0.001). There
was no statistically significant difference in postoperative BCVA or single operation success rate
when surgical repair was performed within 3 days of initial examination. No statistically significant
correlation was found between postoperative BCVA and duration of symptoms, RRD location,
direction of the closest approach of the RRD to the fovea, or need for reoperation.

CONCLUSIONS: Visual and anatomic outcomes were favorable in this series when a
timely and selectively urgent, but not strictly emergent surgical approach was employed for fovea
sparing RRD. Progression to fovea-off status was rare and outcomes were equivalent when surgical
repair with a SBP was performed within 3 days of initial examination.
Macular Hole Surgery with and without Face Down Positioning, a Fifteen Year Journey Evaluating 204 Eyes with Idiopathic Macular Holes

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PURPOSE: The purpose of this presentation is to review my 15 year experience with macular hole repair with and without face down positioning, and to discuss which techniques made a difference.

METHODS: Between 1994 and 2009, 204 eyes with idiopathic macular holes were repaired. Twenty nine (14%) were positioned face down (FD) while 175 (86%) were not positioned face down (NFD) nor any other position, but asked not to sleep face up for a week. All eyes in the face down group were <50 years old and phakic. All eyes in the no face down group were pseudophakic and usually older than 50. Both groups were evaluated over three time periods or ‘episodes’.

In Episode I (1994-1999; n=64; 10FD), MHS surgery involved, #20 PPV, posterior hyaloid (PH) stripping, no formal ILM peeling, and frequently the use of autologous serum with 15% C3F8 or 20% SF6 gas. Episode II, 1999-mid 2006 (n=103; 18FD), involved #20 PPV, PH stripping, ICG guided ILM peeling, and 20% SF6 gas. Episode III, mid 2006 thru 2009 (n=37 eyes; 1FD), involved #23 PPV, PH stripping, ICG guided ILM peeling, and 25% SF6 gas.

RESULTS: In Episode I, MH were closed with one operation in: 80% FD group vs 87% NFD group; in Episode II: 94%FD vs 92% NFD; in Episode III: 100% FD vs 100% NFD. Combining all episodes the anatomic success rate was 90% (26/29) FD vs 92% (161/175) NFD. The incidence of VA >=20/50 was: Episode 1, 20% NFD vs 28% FD; Episode 2: 67% NFD vs 36% FD; Episode 3: 100% NFD vs 56% FD. Combining all episodes, VA>=20/50 in 52% (15/29) FD vs 38% (66/175) NFD. Combining all episodes, the incidence of RD was 10% (3/29) FD vs 3% (5/175) NFD.

CONCLUSIONS: There is no difference in the single operation macular hole closure rate in eyes treated with face down posturing versus no FD posturing. ICG assisted ILM peeling increases the MH closure rate regardless of positioning methods. Recent results (n=36)using #23 PPV surgery with ICG guided ILM peeling, 25% SF6 gas, and NO FD posturing, attained a closure rate of 100%, with 56% (20/36) of eyes reaching >=20/50 VA.
Repair of Retinal Detachment with Macular Hole in Eyes with Posterior Staphyloma After Unsuccessful Surgery

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Purpose: To analyze the factors that may have determined a relapse of retinal detachment (RD) with macular hole (MH) in highly myopic eyes with posterior staphyloma after pars plana vitrectomy (PPV) performed as first surgery.

Methods: The study includes 28 eyes of 28 patients (myopia ranging between 17 and 29 negative dioptres) underwent a second intervention for RD repair between April 2004 and January 2008 with a minimum follow up of 24 months.

Results: Before the first surgery all the 28 eyes had a shallow RD limited into the area of the posterior staphyloma. At baseline observation 15 out of the 28 eyes had silicone oil (SO) in the vitreous cavity. In 4 out of the 28 eyes a residual epiretinal tissue adherent to the macular area was detected; 16 of the 28 eyes had a severe atrophy of the choroid and of the retinal pigment epithelium (RPE) into the area of the staphyloma. In 6 out of the 15 eyes with SO the RD remained limited to the area of the staphyloma, while in the remaining 9 out of the 15 eyes with SO the RD extended also to the inferior quadrants. In 13 of the 28 eyes the RD extended from the area of the staphyloma toward the peripheral retina. The causative factors for the extension of the RD after a first unsuccessful surgery in eyes with posterior staphyloma are hypothesized.

Conclusions: The reduction of posterior staphyloma by means of posterior episcleral buckle is a method to use to repair unsuccessful cases.
The Diversity of Traction Mechanisms in Myopic Traction Maculopathy

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PURPOSE: There is growing consensus that myopic traction maculopathy is caused by a relative stiffness of the inner compared with the outer retina in the concavity of a posterior staphyloma in highly myopic eyes. The precise cause of the inner retinal stiffness remains uncertain, but is unlikely to be the same in all eyes. The purpose of this report is to illustrate that a variety of distinct traction mechanisms can lead to myopic traction maculopathy, and that surgery can be successfully tailored to the specific mechanism involved.

METHODS: We performed a retrospective chart review of consecutive patients that underwent vitreoretinal surgery for myopic traction maculopathy by a single surgeon at a tertiary referral center. Traction mechanisms were identified based on pre- and intra-operative findings, as well as post-operative response to a tailored surgical approach.

RESULTS: Six eyes of 6 patients, aged 46 to 81 years, with a minimum follow-up of 6 months were included. In addition to schisis-like retinal thickening throughout the macular area, one patient had a macular hole and one had macular detachment. Major pathogenic traction mechanisms included perifoveal PVD with vitreomacular traction in 3 eyes, poor elasticity of ILM in 2 eyes, epiretinal membrane in 1 eye, and remnant cortical vitreous following PVD in 1 eye. One eye exhibited 2 traction mechanisms. The surgical approach addressed only the major traction mechanism(s) identified in each eye. Postoperatively, the visual acuity improved by 2 or more lines in all eyes and macular thickening resolved completely in 5 of 6 eyes (83%) and partially in the remaining eye, with an average follow-up of 21 months.

CONCLUSIONS: The traction mechanisms causing myopic traction maculopathy are diverse and vary from one eye to another. Vitreoretinal surgical repair of this condition is successful when the major traction mechanisms are identified and relieved.
A Comparison of Macular Hole Surgery with Indocyanine Green (ICG) versus Kenalog

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PURPOSE: To compare visual and anatomic outcomes in eyes undergoing macular hole surgery with Indocyanine Green (ICG) versus Kenalog to stain the internal limiting membrane (ILM)

METHODS: This is a retrospective, single surgeon, consecutive case series study. Due to a temporary shortage of ICG in early 2007 I began using Kenalog, instead of ICG, to stain the ILM in all macular hole surgery cases. This study compares outcomes in 38 eyes operated on prior to the switch with 20 eyes operated on since the switch. Except for the type of stain, the operative technique used in the two groups was substantially the same. The data was obtained through chart review. Snellen acuities were converted to logmar. Phakic eyes with less than six months follow-up were excluded.

RESULTS: Nineteen of 19 (100%) Kenalog eyes and 34 of 37 (92%) ICG eyes had closed macular holes at the most recent follow up exam, p=ns. Thirteen of 19 (68%) Kenalog eyes and 15 of 37 (42%) ICG eyes obtained visual acuity of 20/40 or better, p <.05 (chi squared). The mean logmar visual acuity outcomes were 0.28 in the Kenalog group and 0.52 in the ICG group (snellen equivalent 20/38 and 20/66), p<.004 (t test).

CONCLUSIONS: The use of Kenalog to assist in ILM peeling during macular hole surgery enhances visual acuity outcomes and does not decrease the anatomic success rate compared with the use of Indocyanine Green.
Triamcinolone as an Adjuvant to Reduce Post-operative Epiretinal Membrane Peel Edema

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PURPOSE: A cellophane maculopathy contracts in advanced stages, leading to macular pucker with wrinkling of the inner retinal layers and compromise of the inner retinal blood barrier. This can lead to significant visual consequences, necessitating an epiretinal membrane (ERM) peel. Surgical ERM peeling may lead to mechanical stretching of the layers of the neurosensory retina, which can exacerbate edema and explain delay in resolution of post-operative metamorphopsia. Although the precise mechanism of action of steroids on retinal edema is unknown, steroids are known to have a direct effect on consolidating the retinal endothelial barrier, and may play a role in down-regulating important mediators of blood retinal barrier breakdown, including vascular endothelial growth factor (VEGF). The purpose of this study is to determine the efficacy of intravitreal triamcinolone injection peri-operatively after ERM peel to reduce macular edema and expedite postoperative visual rehabilitation.

METHODS: All patients with visually significant ERMs who opted for surgery were included in the study. Exclusion criteria were glaucoma and other significant ocular comorbidity. Informed consent was obtained from all patients pre-operatively. After surgical peeling, patients received a peri-operative intraocular injection of triamcinolone (4mg in 0.1cc). Post-operative follow-up included complete ophthalmologic exams at 1, 3, and 6 months with OCT. Case-matched controls were established that had not received triamcinolone injection for data comparison.

RESULTS: Nineteen patients enrolled in the study, and 15 of these patients have presented for 1-month followup with 5 having completed OCT examination at this time. Current data is compared to case-matched controls. At 1-month followup, control group mean best-corrected distance visual acuity (LogMAR) = .33, (Snellen acuity = 20/61); experimental group mean best-corrected distance visual acuity (LogMAR) = .48, (Snellen acuity = 20/43), (p=0.028, t-test). Central macular thickness (CMT) was 343 microns preoperatively and 323 microns postoperatively in the control group compared with 398 microns preoperatively and 233 microns postoperatively in the treatment group (n=5), demonstrating a trend toward improvement. 12/15 patients in the treatment group reported post-operative improvement in metamorphopsia symptoms.

CONCLUSIONS: On-going data demonstrate statistically significant (p <0.05) improved 1-month post-operative visual acuity using intraoperative triamcinolone after ERM peeling when compared to case-matched controls. Continued follow-up of these patients with OCT examination post-operatively will allow comparison of pre-operative and post-operative macular thickness and more objective assessment of triamcinolone efficacy in reducing post-operative ERM peel edema and patient’s satisfaction.
One Year Follow-up of Non-Vitrectomizing Epiretinal Membrane Peeling Using 25- and 27-gauge Techniques

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Purpose: To evaluate the safety and efficacy of epiretinal membrane peeling without vitreous removal using 25- and 27-gauge technique. To evaluate postoperative visual acuity (VA) and progression of cataract at one year follow-up.

Methods: Twenty-three eyes affected by epiretinal membrane (ERM), underwent complete ocular examination included VA, OCT, lens status. Eyes with previous vitrectomy, cataract or cataract surgery were excluded. Peeling of the ERM was performed using 25 or 27 gauge forceps without vitreous removal. Intraoperative and postoperative complications were considered and the follow-up was at 1, 3, 6 and 12 months post-operatively.

Results: Sixteen eyes underwent ERM peeling using 25 gauge and 7 using 27 gauge technique. Mean patient age was 56 y.o. and mean preoperative VA was 20/40. Six of 23 eyes were converted during surgery in conventional 25g vitrectomy, two for retinal bleeding during peeling and 4 for membrane floating in the vitreous. No post-operative complications were observed, mean VA at 12 month was 20/32. Of the 6 eyes converted into vitrectomy 1 developed cataract at 1 year follow-up, while none of the 17 eyes who underwent successful no-vitrectomy peeling developed cataract.

Conclusions: The mininvasive epiretinal membrane peeling without vitreous removal seems to be effective and safe for lens preservation at one year in selected eyes (small cases). Conversion to vitrectomy does not seem to be a complication of this surgery. Peeling result more difficult for the vitreous presence above all for 27 gauge technique. Internal limiting membrane staining is not possible with this technique.
Determination of Retinal and Vitreous Temperature During Vitreous Surgery

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Purpose: Therapeutic hypothermia of 90-93°F is used in medicine with increasing frequency and success. Temperatures below this are avoided because of greater incidence of side effects. There are no reports in the literature of the degree of ocular hypothermia induced during routine vitrectomy. We measured the temperature of the mid-vitreous and retinal surface before, during, and after vitrectomy.

Methods: In this prospective study, the temperatures of the mid-vitreous and retinal surface of 7 patients undergoing routine vitrectomy using room-temperature infusion fluid were measured using a 21 or 23 gauge flexible wire thermoprobe. The retinal temperature was measured in four locations: the nasal, temporal, and inferior retina, and fovea. This was done at three separate time points: before opening the infusion line, during the vitrectomy with an open infusion line, and after the vitrectomy was complete and the infusion line was closed for 5 minutes. The patients temperature, the room temperature and the temperature of the infusion fluid were also recorded before and after vitrectomy.

Results: Before vitrectomy, the average temperature was 92.7°F of the mid-vitreous cavity and 94.8-95.3°F on the surface of the retina and fovea. During vitrectomy, the average temperatures were significantly cooler: the temperature of the mid-vitreous cavity was 77.2°F and the temperature of the surface of the retina and fovea were 82.7-85.1°F. After vitrectomy and with the infusion line closed, the ocular temperatures rapidly rewarmed: the average temperature of the mid-vitreous cavity was 87.0°F and 90.1-90.9°F on the surface of the retina and fovea. The temperatures of the patient, room, and infusion fluid fluctuated minimally during the vitrectomies.

Conclusions: In vitrectomy the vitreous cavity and retina are cooled to much lower temperatures than those typically used in therapeutic hypothermia, and rapid re-warming of the eye begins once the infusion line is closed. These low temperatures, coupled with rapid rewarming, could contribute to post-surgical cataract formation and also increase the risk of intra- and post-operative intraocular hemorrhage.
Polyethylene Glycol (PEG) Hydrogel Polymer Sealant for Closure of Sclerotomies: A Variable Intraocular Pressure (IOP) and Histologic Study

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Purpose: To test a synthetic PEG-based hydrogel ocular bandage (Ocular Therapeutix, Inc., Bedford, MA) for its ability to secure sutureless pars plana vitrectomy incisions. The availability of a sealant to prevent entry of ocular surface fluid as well as prevent the leakage of intraocular fluid in the early postoperative period may help decrease the incidence of endophthalmitis and hypotony, respectively.

Methods: For testing IOP variation, 23 and 20 G incisions were constructed in fresh human cadaveric eyes. 20 G straight incisions were either sutured or sealed with the ocular bandage. 23 G beveled incisions were either left bare or sealed with the ocular bandage. All incisions were monitored for leaks as intraocular pressure was elevated. To test fluid ingress, 23 and 20 G incisions were constructed in fresh human cadaver eyes. 20 G straight incisions were either sutured or sealed with the ocular bandage. 23 G beveled incisions were either left bare or sealed with the ocular bandage. India ink was applied over the incision sites while the IOP was varied. The presence of India ink particles along various incisions was later evaluated by histologic analysis.

Results: 23 G incisions: hydrogel sealant application to the incisions significantly increased the leak pressure relative to bare incisions, 131.8 ± 8.2 vs. 39.5 ± 5.2 mm Hg, respectively (p=0.000001). Only 1/8 of the sealant treated incisions leaked below 140 mmHg, compared to 8/8 of bare incisions. 20 G incisions: no difference in leak pressure between hydrogel sealed and sutured incisions; 140 ± 0 mmHg vs. 136.3 ± 3.8 mm Hg, respectively (p=NS). None (0/8) of the sealant treated incisions leaked below 140 mmHg, compared to 1/8 of the sutured incisions. On histological analysis, the hydrogel bandage prevented the entry of ink particles in all covered incisions after IOP modulation and incision manipulation. Four bare 23 G incisions showed the presence of ink within the inner aspect of the incisions (p=0.0455, relative to 23 G sealed incisions). One 20 G sutured incision showed partial ink ingress.

Conclusions: The use of a hydrogel bandage to close sutureless sclerotomies may be an alternative to bare incisions or sutures. Closure of sutureless sclerotomies may reduce the likelihood of entry of ocular surface fluid into these incisions and may prevent leakage of intraocular fluid in the immediate postoperative period theoretically decreasing the incidence of endophthalmitis and hypotony, respectively.
**Intrector® — A Hand-held Vitrectomy Device: Fluidics**

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**PURPOSE:** To compare the fluidic properties of the Intrector® syringe-based vitrectomy device with other commercially available systems to evaluate its safety in the treatment of vitreoretinal diseases.

**METHODS:** Mean operator comfortable sustainable syringe plunger pull force was determined using a spring-loaded digital scale. Vacuum levels for syringes of different volumes (3, 5, and 10 mL) and pulling forces were quantified with a pressure transducer. Flow rates of water and egg white were measured both with the cutter at 600 cuts/min and in the off position with the port open. Infusion flow of water was evaluated using a 1 mL syringe.

**RESULTS:** The mean plunger pull force among operators (n=8) was 0.80 kg (s.d.=0.20 kg). Using the 3 mL syringe with 0.91 kg of pull force, mean vacuum level was 135.9 (s.d.=4.8) mmHg and mean cutter-on flow rates of water and egg white were 1.9 (s.d.=0.1) and 0.5 (s.d.=0.1) mL/min, respectively. Larger bore syringes generated lower vacuum levels and liquid flow rates.

**CONCLUSIONS:** The fluidic parameters of the Intrector® vitrectomy device measured in this study suggest that, at comfortable sustainable syringe pull forces, vacuum levels and liquid aspiration rates are safe and similar to some other commercially available systems.
Slow Motion Videography Analysis of Vitreous Base Motion During Vitrectomy

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Purpose: What is known about the fluidics of vitrectomy, particularly as relates to the effect of cutting rates, duty cycle, flow rates and instrument gauge, has been determined by studying saline liquid moving into the vitrectomy probe. Removing real vitreous in situ is much more complex, and often doesn’t seem to adhere to the same principles as removing fluid. This study uses slow motion videographic analysis of tracers within porcine vitreous within the eye to determine the true fluidic characteristics of vitrectomy, with special attention to how forces are transmitted to the vitreous base during core vitrectomy.

Methods: Twenty-five freshly enulcleated pig eyes were prepared with a Miyake-style set up, removing the back 30% of the globe and sealing the sclera with optical glass. Standard vitrectomy setups were then utilized comparing 20 ga, 23 ga, and 25 ga Ultravit™ vitrectomy probes from the Constellation™ Vision System (Alcon Surgical, Ft. Worth, Tx). Vitreous was marked with a thin column of triamcinolone crystals injected through the pars plana, incarcerating the steroid into the vitreous base. Vitrectomies were carried out at various cut rates, vacuum levels and flow rates, while recording the vitreous motion with high speed videography at 1000 fps using the Phantom v210 high speed digital camera (Vision Research, Inc., Wayne, NJ). Individual frame analysis was done to determine patterns in vitreous motion, amounts of vitreous movement, and related traction to the vitreous base.

Results: Four types of vitreous motion are seen: 1. Direct linear traction, 2. Distant linear traction, 3. Bullwhip amplified traction, and 4. Recoil redistribution. The collagen fibers within vitreous extend a long distance, and pull at one end of the fibers can transmit traction over 20 mm away from the port. Motion is pulled linearly in distant directions due to the cross-linking of the fibers. Traction is also amplified, similar to cracking a bull whip, increasing the motion as much as 600%. Fibers are put on stretch, storing energy, so that when cut they will recoil away, hitting other fibers and redistributing the vitreous. Central vitrectomy commonly significantly transmits traction to the vitreous base as much as 16 mm from the tip, regardless of cut rate and gauge size. Higher cut rates and smaller gauge size still dampen the traction, particularly by reducing the bullwhip amplification phenomenon. As the vitreous is trimmed shorter and shorter, only the direct traction style of motion predominates.

Conclusions: Although vitreous movement during vitrectomy appears complex, it can be broken down to a few defined patterns of vitreous movement. The beneficial effect of high cutting rates and small gauge size is easily demonstrated with fluid removal, but is less beneficial in actual vitreous. Vitreous traction near the vitreous base is universally seen even at the highest cut rates and lowest flow levels. Still, high cut rates and low flow levels are still desirable as they result in the lowest amount of measurable traction.
Novel Method to Quantify Traction in a Vitrectomy Procedure

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Anderson Texeira, MD, Naoki Matsuoka, MD, Adrian Rowley, MD, Prashant Bhadri, PhD

PURPOSE: Report a novel method to quantify traction applied to the retina using vitreous cutters during pars plana vitrectomy.

METHODS: Fresh porcine eyes were positioned in a specially developed holder and transfixed to the retinal layers with a wire and the other end fixed to the load cell of a strain gauge. Twenty, 23 and 25 gauge pneumatic and electric vitrectors were introduced into the eye at a 45-degree angle and positioned at a distance of either 3 or 5 mm from theretina. Data from the strain gauge was acquired and the traction force computed.

RESULTS: (p<.05 for all)

<table>
<thead>
<tr>
<th>Gauge</th>
<th>Vacuum varied</th>
<th>Cut rate varied</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 g pneumatic</td>
<td>+4.96d/100mm Hg</td>
<td>-3.41d/500 cpm</td>
</tr>
<tr>
<td>23 g pneumatic</td>
<td>+3.14d/100 mm Hg</td>
<td>-2.85d/500 cpm</td>
</tr>
<tr>
<td>25 g pneumatic</td>
<td>+3.40d/100 mm Hg</td>
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<tr>
<td>20 g electric</td>
<td>+7.90d/100 mm Hg</td>
<td>-2.51d/500 cpm</td>
</tr>
<tr>
<td>25 g electric</td>
<td>-3.24 /100mm Hg</td>
<td>-4.17 /500 cpm</td>
</tr>
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CONCLUSIONS: It is possible to predict traction at a fixed distance from the retina based on cut rate and vacuum for the individual cutters we tested. Traction caused by vitrectors is much less than reported retinal adhesion forces. Traction created by small gauge vitrectors is affected less by vacuum but more by cut rate than large vitrectors. To our knowledge this is the first time retinal traction by vitreous cutters has been measured.
The Effect of Cutting Rates on Flow Rates and Microbead Displacement, Velocity and Acceleration in Porcine Vitreous and Clinical Application

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PURPOSE: The purpose is to determine if 5000 cuts per minute vitrectomy reduces pulsatile vitreoretinal traction while providing sufficient flow rates.

METHODS: The effect of varying cutting rates on flow rates in saline and porcine vitreous was measured using a digital scale. An Alcon Constellation Vision System vitrectomy console and 25 UltraVit probes at various cutting rates was used to study the motion of 75 micron multicolored microbeads in porcine vitreous using high speed cameras and Vision Research 3-D Video Analysis Software. A single surgeon series of over 750 cases using the Alcon Constellation Vision System and 25 gauge UltraVit cutter was performed. The case mix included PVR, diabetic traction retinal detachments, rhegmatogenous retinal detachment, dislocated lens material, vitreomacular surgery, vitreous hemorrhage and a variety of other cases.

RESULTS: With simultaneous cutting and aspiration at 500-5000cpm and vacuums of 250, 450, and 650 mmHg, BSS flow rates were 73.4%-97.8% higher than vitreous flow rates. The vitreous flow data shows a much less difference between 20, 23, 25 gauge than is observed with BSS flow data. The amount of vitreous aspirated per port open-close cycle is the same at 500 cpm as 5000 cpm because the port open time is the same for both cut rates. If there is an increase in the amount of times the port opens and closes, there is an increase in the amount of vitreous aspirated explaining why higher cutting rates do not decrease flow. The average displacement of microbeads for 2500 and 5000 cpm was very similar. 2500 cpm cut rate generates 10.76% faster velocity than 5000 cpm and 2500 cpm cut rate generates 10.07% higher acceleration than 5000 cpm. Clinical results demonstrated that a 25 gauge UltraVit cutter at 5000 cuts per minute produced effective flow rates for all tasks and all cases. Pulsatile vitreoretinal traction and retinal motion appears to be significantly less than prior series using the Alcon Accurus at 2500 cpm.

CONCLUSIONS: Higher cutting rates reduce pulsatile vitreoretinal traction without slowing down surgery. 5000 cutting rates should be used for all tasks and all cases.
Finite Element Analysis of Displacement of Detached Retina by Intraocular Gas

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PURPOSE: To determine if finite element analysis (FEA) of all forces on the retina can model the effect of a gas bubble on detached retina better than simpler models (models with fewer forces) or models in which forces act on subretinal fluid or hemorrhage rather than directly on the retina.

METHODS: Displacement forces on detached retina are modeled by a computer program written with Mathematica software. In the program, the retina is divided into multiple tiny segments. For each segment, forces resulting from bubble surface tension, bubble pressure, vitreous fluid pressure, subretinal fluid pressure, retina stretching force, retinal pigment epithelial adhesion, and retinal weight are determined. The retinal segments are moved by these forces, subject to constraints, over a period of approximately one thousandth of a second, and the process is repeated until the retina reaches equilibrium and no longer moves. The results are output as video files showing the movement of the retina and bubble inside the eye, and these video files are incorporated into a PowerPoint presentation. Modeling is done for several situations including an eye with a macular hemorrhage and an eye with a detachment treated with a gas bubble during vitreous surgery.

RESULTS: This model confirms the importance of published reports of surface tension forces from an intraocular bubble. The model also shows the importance of other equally powerful forces, some of which are not obvious. The vertical pressure gradient in subretinal fluid moves detached retina when it is covered with a gas bubble. Adhesion of the retina to the RPE limits displacement of subretinal fluid, but under conditions when sufficient force is present, this adhesion can be broken. The constraint that the volume of subretinal fluid must remain constant when there is no open retinal break exerts powerful positive and relative negative pressure forces on detached retina. In the video output from the program, the retina seems to behave as it does clinical situations. Additional FEA modeling of the bubble meniscus, the shape of which is analytically known, shows that the model is accurate in that situation as well.

CONCLUSIONS: Finite element analysis offers a useful tool for understanding the effect of an intraocular bubble on a retinal detachment.
Mixed Gauge Vitrectomy: A Practical Approach with Evolving Technology

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PURPOSE: Transconjunctival 23 and 25 gauge vitrectomy techniques and instrumentation are now widely disseminated and coexist with conventional 20 gauge instruments and systems. Nevertheless, the choice of instrumentation remains quite varied, even for the same surgical goals, and is highly surgeon dependent. The author reviews and outlines his current experience and preferences, and, in particular, illustrates the advantages of mixed gauge surgery for a variety of indications.

METHODS: Retrospective review of all vitrectomies performed by the author from January 1, 2008 thru March 31, 2010.

RESULTS: There were 273 consecutive vitrectomies, and all were available for review. The indications for surgery spanned the gamut of retinal diseases encountered in an university referral practice but also included some unusual indications such as vitrectomy in association with permanent keratoprosthesis, chorioretinal biopsy, and vascular tumor excision. A completely 25 gauge setup was used in 114 cases, 23 gauge in 27 cases, mixed gauge 25/20 in 35 cases, and 23/20 in 34 cases. Conventional 20 gauge surgery was performed in 63 cases, and these were clustered early in the series. Typical indications for 25 gauge surgery included macular pucker and holes, vitreous hemorrhage, primary retinal detachment, and papillary membrane excision. Twenty-three gauge instrumentation was preferred for diabetic traction detachment as well as proliferative vitreoretinopathy. Mixed gauge surgery with one or two 20 gauge sclerotomies was selected in order to 1) place or remove silicone oil, 2) remove the lens by fragmentation, 3) utilize subretinal forceps, 4) deliver biopsy materials, and 5) permit the use of robust forceps during membrane peeling; certain other miscellaneous cases were combined with 20 gauge sclerotomies due to need to open the conjunctiva for other reasons such as AC IOL placement. It should be noted that even though 20 gauge sclerotomies were created for the mixed gauge cases, the 25 and 23 gauge vitrectors were used as the cutter when needed. Furthermore, the 20 gauge cutter was not used at all in the second half of the series. The 25 gauge infusion cannula was invariably sufficient in all cases, including 25/20 mixed gauge silicone oil removal, but 23 gauge cannulas were also (reluctantly) used as provided in 23 gauge packs.

CONCLUSIONS: In this single surgeon series, straightforward 25 gauge surgery was the clear preference, but was followed by mixed gauge surgery 25/20 and 23/20. Although 20 gauge sclerotomies remain advantageous for certain maneuvers, the actual 20 gauge vitrector is no longer used by this author. Also, a 25 gauge infusion cannula, particularly of newer design, provides excellent infusion for all cases with more secure closure on removal than 23 gauge cannulas and would be routinely employed if it was provided within every surgical pack.
Air Tamponade May Reduce Complications in 23-gauge Vitrectomy

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**PURPOSE:** To assess if air tamponade may reduce the risk of hypotony and endophthalmitis in 23-gauge vitrectomy as compared to fluid-filled eyes.

**METHODS:** A prospective, randomized, single-surgeon comparative case series was undertaken. All eyes were phakic and none had previously undergone vitrectomy. All eyes had povidone-iodine placed on the conjunctiva prior to entry. All eyes had same entry: Conjunctival displacement followed by two-step, beveled incision and 23-gauge vitrectomy with or without air tamponade. All air-filled eyes had 70% or greater tamponade; light-pipe assisted cannula removal was performed on all eyes; eyes subsequently requiring gas or silicone oil tamponade were excluded. All study eyes were evaluated by a separate, masked ophthalmologist on postoperative days 1, 3 and 7 in terms of intraocular pressure and anterior segment inflammation only; Fundus exam was then performed by the surgeon on POD 1 and 7 only.

**RESULTS:** Case series included 53 eyes (52 patients) in the air-tamponade group (AT) and 47 eyes (46 patients) in the fluid-filled group (FF). Intraocular pressure measurements at postoperative day 1 were 16.8 +/- 2.2 (AT group) and 11.2 +/- 2.6 (FF group) (P=0.17). No choroidals were noted. On POD 7, IOP levels were 17.9 +/- 1.2 (AT group) and 16.3 +/- 2.4 (FF group). Intraocular inflammation was graded as follows: All AT eyes on POD 1 had 0-trace anterior segment cell while only 28 FF eyes had same findings; 15 FF eyes had 1+ cell and 4 eyes had 2+ cell. On POD 7, 10 eyes still had trace to 1+ cell; No eyes developed endophthalmitis.

**CONCLUSIONS:** Air tamponade in 23-gauge vitrectomy may reduce the risk of hypotony and, consequently, decrease fluid inflow/fluid egress through the wound in the first three postoperative days after vitrectomy; this latter effect may also reduce the risk of endophthalmitis.
Non-damaging Retinal Phototherpay: The Dynamic Range of Heat Shock Protein Expression

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Christopher Sramek, MS, Mark Mackanos, PhD, Ryan Spitler, BS, Hiroyuki Nomoto, MD, PhD, Chris Contag, PhD

PURPOSE: Recent trials of sub-threshold retinal phototherapy have shown its clinical efficacy in the treatment of diabetic macular edema. Laser energy was applied without visible effect or fluorescein leakage, as observed acutely and in subsequent clinical exams. The underlying mechanism of this treatment is assumed to be tissue hyperthermia below the threshold of cell death, although the details of this interaction remain unclear. Heat shock proteins act as molecular chaperones that stimulate damage repair following thermal and other forms of cellular stress, and may be responsible for this effect. To assess the range of cellular response to hyperthermia we evaluate the expression of heat shock protein following laser irradiation below the threshold of cell death. A transgenic reporter mouse is used to determine the minimum thresholds of heat shock protein (Hsp70) expression and of retinal pigment epithelium (RPE) damage.

METHODS: 532-nm laser exposures of 100 ms in duration and 400 µm spot-size were applied to the retina surrounding the optic nerve in 30 transgenic Hsp70-L2G reporter mice. Increase in Hsp70 expression relative to the control fellow eye was measured with a luciferase bioluminescence assay 7 hours after laser application. RPE viability threshold was determined with propidium iodide cell viability assay. A finite-element computational model was developed to estimate temperature rise and the extent of cell damage (as determined by the value of the Arrhenius integral) at both thresholds.

RESULTS: A significant increase in Hsp70 expression was found at exposures over 20 mW—half the threshold of RPE cell death occurring at 40 mW. Computational modeling determined that the peak temperature at the Hsp70 expression threshold was 49 degrees C, while the peak temperature at the damage threshold was 62 degrees C. Thermal damage at the threshold for Hsp70 expression was calculated to be significantly reduced (by a factor of 10) relative to damage at the threshold of angiographic visibility. Similar temperatures and indices of thermal damage were found when modeling treatment of the human retina with clinical sub-threshold laser settings.

CONCLUSIONS: It is likely that the beneficial effects of laser therapy extend beyond those resulting from the destruction of tissue. Careful application of laser energy below the threshold of cellular death can induce the expression of heat shock and other stress-induced proteins such as Hsp70. Hsp70 may serve a protective role, activating cellular repair mechanisms as well as slowing or preventing apoptotic and inflammatory pathways that lead to cellular damage. With 100ms exposures, Hsp70 expression occurred at laser power approximately half of that required for RPE damage. A computational model of retinal response to laser treatment may help with further optimization of laser parameters to maximize the dynamic range of non-damaging phototherapy.
Clinical Experience with a Second Generation Retinal Navigating Laser, the NAVILAS, in a Series of 120 Eyes with Clinically Significant Macular Edema from Diabetes or Other Retino-vascular Disease

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Igor Kozak, MD, PhD, MAS

Purpose: To report clinical experience with a Retinal Navigating Laser, the Navilas® system (OD-OS GmbH Teltow, Germany), in a series of 120 eyes with clinically significant macular edema from diabetes or other retino-vascular disease.

Methods: The Navilas® system integrates a scanning slit fundus camera with fluorescein angiographic, color, red-free and IR imaging capabilities with a computer steerable, therapeutic 532 nm laser, allowing registered image overlay and laser stabilization on the retina utilizing image processing. This allows digital angiograms to be overlaid onto the patient’s fundus together with pre-planned laser treatment locations identified on the angiogram. While the patient is positioned in front of the device laser photocoagulation can then be performed as the laser is positioned and stabilized onto the retina to the preplanned treatment locations. Preliminary results were reported at the 2009 AAO retina meeting utilizing a prototype version. Further hardware and software enhancements have been integrated into a first product version of the device and FDA approved, allowing now more clinical evaluation of which accuracy data has now been compiled. Herein we report on a consecutive series of 120 eyes treated by our group. Accuracy was determined in diabetic eyes by image analysis and recording the number of microaneurysms directly hit versus missed by overlaying fluorescein angiograms and post op color photographs using the overlay software in the device.

Results: The new Navilas® system provided valuable improvements such as more robust registration and tracking, the ability to treat patients without a treatment contact lens, and semi-automated treatment which advances the target aiming beam from pre-planned location to the next sequentially while still applied by the physician using a foot pedal under visual observation on the screen. A new toggling feature permits the physician to align and aim the laser using a comfortable infrared imaging modality, and after laser is performed, switching briefly to a full color imaging mode in order to evaluate treatment intensity and titrate the laser lesions on the retina in real time. We performed all treatments without topical anesthesia. These improvements have shortened the combined angiogram and treatment time with more than 150 precisely targeted bilateral treatments in diabetic patients to under 20 minutes. The additional marking of areas not to be treated on in the fovea or optic nerve proved to be successful. Patients report an extremely high degree of comfort. The semiautomatic advancement of treatment locations of the preplanned treatment allows photocoagulation to be performed under four minutes per eye with more than 150 laser positions. Lesion accuracy is 86%. This was compared to a series of eyes treated using a standard 532 nm slit lamp mounted laser and treated while viewing a mounted frame.
of a fluorescein angiogram. The direct hit rate using slit lamp based delivery was lower (67%). Thus, the microaneurysm treatment with the Navilas® system is more accurate than with the slit lamp, p=0.014. Documentation software integrated into the device permits a report to be printed or electronically stored which includes pre-op angiograms, post-op color images of burns and locations as well as laser treatment parameters and the treatment plan. Preliminary results using a contact lens for wide field photocoagulation show that Navilas® treatments may be extended for use in the periphery.

**CONCLUSIONS:** The Navilas® system allows for photocoagulation of the human fundus using angiographic guidance and permits more accurate treatment than slit lamp delivery systems. It may change management of eyes with macular edema and proliferative disease by allowing precise angiographic-guided treatment only of desired pathology. The Navilas® system makes this possible for treatment of macular edema, and certain variants of CNV and may also allow selective ablation of ischemic areas in proliferative diabetic retinopathy.
Robert Machemer’s Teachings: From Vitrectomy to Controlled Drug Release

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PURPOSE: To describe the impact Robert Machemer had on the development of vitreoretinal technology and controlled drug release systems

METHODS: 1969 to 2009 historical data, archives and the author’s memory were used to show the impact Machemer had on the development of two new fields of research and the impact he had on his fellows toward research and patient care.

RESULTS: Vitreous Aspiration Irrigation Cutter, secondary instruments to cut vitreous bands, diathermy, endophotocoagulation, endocryo, trocar systems, automated forceps and scissors as well as the first endofiber optic illumination and a motorized operation microscope were developed in three years. As the fight against PVR couldn’t be mustered using instrumentation alone, a biodegradable controlled drug release system was developed and clinically tested against fibrosis. These advances lead to a succession of events that multiplied efforts made by research teams all around the world, leading to better patient care.

CONCLUSIONS: Thanks to a great teacher, vitreoretinal surgery is now main stream. Controlled drug release is bound to further change the approach to retinal diseases, including AMD.
Prevalence and Significance of Subretinal Drusenoid Deposits (Reticular Pseudodrusen) in Age-related Macular Degeneration

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Sandrine Zweifel, MD, Yutaka Imamura, MD, Theodore Spaide, BS, Takamitsu Fujiwara, MD

PURPOSE: To determine the prevalence and significance of subretinal drusenoid deposits (reticular pseudodrusen) among patients with age-related macular degeneration (AMD).

METHODS: A prospective study with a nested case-control study was done of consecutive patients with AMD seen in a referral retinal practice. Late AMD was defined as either central geographic atrophy or choroidal neovascularization. The control group consisted of patients who did not have AMD as their primary diagnosis, central serous chorioretinopathy, high myopia, retinal detachment or laser treatment in the macular area. The presence of subretinal drusenoid deposits was determined by two methods, using the blue channel of color fundus photograph and the spectral domain optical coherence tomography (SD-OCT) sections. Soft drusen were determined from color fundus photographs and confirmed by SD-OCT. The main outcome measures were the prevalence of ocular risk factors and subretinal drusenoid deposits in eyes with AMD and their association with late AMD.

RESULTS: There were 153 patients who had any form of AMD, with a mean age of 80.3 years and 131 had at least 1 eye with late AMD. There were 101 controls. Subretinal drusenoid deposits were diagnosed in the case group in 13 (8.7%) of right and 18 (12.0%) of left eyes using the blue channel of the color photograph and in 58 (38.4%) of right and 54 (35.8%) of left eyes using SD-OCT. Soft drusen and subretinal drusenoid deposits detected by SD-OCT were found to be independently correlated with late AMD (soft drusen odds ratio = 16.66 P <0.001, subretinal drusenoid deposits as detected by OCT odds ratio: = 2.64 P=0.034). In the control group subretinal drusenoid deposits were diagnosed in 6 (6.5%) of right and 6 (6.3%) of left eyes using SD-OCT.

CONCLUSIONS: Both soft drusen and subretinal drusenoid deposits occur in patients with AMD and both are significantly associated with late AMD. These findings suggest that detection and classification of drusen and consequently assignment of risk should be based on a methodology that includes SD-OCT.
Photodynamic Therapy for Chronic or Recurrent Steroid Associated Central Serous Chorioretinopathy

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PURPOSE: To evaluate the short term efficacy of photodynamic therapy (PDT) for steroid associated chronic or recurrent central serous chorioretinopathy (CSC).

DESIGN: Interventional case series.

METHODS: Retrospective review of nine consecutive cases of steroid associated CSC treated with PDT using half-fluence for fovea involving treatments (n=4) and full-fluence for extrafoveal treatments (n=5). The main outcome measures included anatomic changes measured on optical coherence tomography (OCT) and changes in best-corrected visual acuity (BCVA) after PDT.

RESULTS: All eyes had fovea involving serous retinal detachment on OCT and 6 (67%) eyes had history of 3 or more recurrences. The mean duration of current episode of CSC prior to PDT was 45 months (range: 3-131 months). The mean follow-up after PDT was 8 months (range: 3-18 months). Serous retinal detachment disappeared in all cases following PDT without any complications. Compared to baseline mean BCVA of 20/83, mean BCVA was 20/43 at 3 months (p=0.018), and 20/47 at last follow-up (p=0.075). Visual acuity improved by 2 lines in 3 (33%) eyes.

CONCLUSIONS: Despite chronicity and recurrences seen in steroid associated CSC, serous retinal detachment resolved in all cases and modest improvement of visual acuity was observed following PDT at least for short term. Given the difficulty of managing these cases, PDT as applied in this study may be an effective and safe treatment.
Impact of Vitrectomy on Non-Exudative Age-related Macular Degeneration

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PURPOSE: To determine whether incidental vitrectomy surgery alters the progression of non-exudative age-related macular degeneration (AMD) or conversion to exudative AMD.

METHODS: Forty-four eyes of 22 patients with AMD who had unilateral vitrectomy for unrelated cause were included in the study. The progression and/or conversion of non-exudative AMD on follow-up was compared between the two eyes: one following vitrectomy vs. one without vitrectomy for each of the 22 subjects. Inclusion criteria included subjects with bilateral non-exudative AMD of AREDS (Age-Related Eye Disease Study) category 3 AMD, uniocular vitrectomy for incidental cause (epiretinal membrane or macular hole), a pre-operative best corrected visual acuity of 20/320 or better in each eye. Subjects were excluded if they had had bilateral vitrectomy, had less than 2 years of follow-up, or previous choroidal neovascularization (CNV), retinal detachment, diabetic retinopathy, angioid streaks, high myopia, vascular occlusions, or extensive macular scarring or atrophy precluding acuity comparisons following vitrectomy. Two vitreoretinal specialists independently graded pre- and post-vitrectomy fundus photographs of all eyes in a masked fashion.

RESULTS: For the twenty-two subjects, the average follow up duration was 5.5 years with a range of 2-15 years. CNV developed in five control eyes and in two vitrectomized eyes, and geographic atrophy developed in seven control and four vitrectomized eyes. The difference between vitrectomized eyes and fellow eyes for the combined endpoints of geographic RPE atrophy or CNV was statistically significant (p=0.02).

CONCLUSIONS: In this pilot study we did not find that vitrectomy surgery increased the progression of non-exudative AMD or increased conversion to exudative AMD. Although conclusions are limited by sample size, an association was found between incidental vitrectomy and reduced progression of non-exudative AMD and conversion to exudative AMD. Additional studies are needed to confirm or refute this association.
A Phase Ia Study in Geographic Atrophy with FCFD4514S, a Novel Humanized Monoclonal Antibody Directed Against Complement Factor D

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PURPOSE: Genetic and environmental factors have been implicated in the pathogenesis of age-related macular degeneration (AMD). In addition, the alternative complement pathway (ACP) may play a pivotal role in the development of AMD. Select genetic polymorphisms associated with complement components appear to have a strong correlation with the susceptibility to AMD, and complement Factor D has been detected in drusen of patients with geographic atrophy (GA), an advanced form of AMD. FCFD4514S (anti-fD) targets Factor D, a rate-limiting enzyme of the ACP. Inhibiting the ACP with anti-fD may slow or arrest the progression of GA and subsequent vision loss. The Phase Ia study is investigating ocular and systemic safety and tolerability of anti-fD in GA patients following intravitreal injection.

METHODS: The Phase Ia study with anti-fD is an open-label, multicenter, single-dose, dose-escalation study in patients with GA. The study is being conducted in GA patients with best-corrected visual acuity in the range of 20/125-20/400. At each dose, an initial screening period is followed by a one-time intravitreal injection in which anti-fD is administered. Six cohorts are being evaluated that include study drug dose levels of 0.1mg, 0.5mg, 1mg, 2mg, 5mg, and 10mg. Following study drug administration, each patient is monitored at multiple visits over the subsequent 14 day dose limiting toxicity period. Additional assessments are performed during the 90-day study period. The objectives of this study are to investigate the ocular and systemic safety and tolerability, serum pharmacokinetics and immunogenicity, and determine the maximum tolerated dose (MTD) of anti-fD in patients with GA.

RESULTS: Enrollment and dose limiting toxicity evaluation have been completed in each of the 0.1mg, 0.5mg, 1mg, 2mg and 5mg single-dose cohorts, and no dose limiting toxicities were observed in these cohorts. Enrollment is ongoing in the 10mg cohort. To date, anti-fD has been well tolerated, and no study drug related ocular events, systemic adverse events or serious adverse events have been observed.

CONCLUSIONS: Anti-fD is a potential treatment for AMD. The ocular and systemic safety and tolerability, serum pharmacokinetics, immunogenicity and MTD of anti-fD are being evaluated in patients with GA. The results from the completed phase Ia study will be presented.
Inhibition of Alpha 5 Beta 1 Integron in Neovascular Age-related Macular Degeneration (AMD): A Phase 1 Study

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For the Ophthotech Integrin Antagonist in AMD Study Group

PURPOSE: To assess the safety and pharmacokinetic profile of intravitreal volociximab, an Alpha 5 Beta 1 integrin antagonist, in combination with ranibizumab in wet age-related macular degeneration (AMD). Alpha5 Beta1 integrins are transmembrane receptors which bind to fibronectin in the extracellular matrix. This leads to intracellular signal transduction controlling critical events involved in angiogenesis such as cell proliferation, survival and migration. These Alpha 5 Beta 1 integrin mediated activities are downstream to VEGF and other activators of angiogenesis. Alpha 5 Beta1 integrin antagonism has demonstrated potent anti-angiogenic effects in preclinical oncologic and ophthalmic models.

METHODS: Phase 1, open label, multicenter, dose escalation study of eyes with all subtypes of choroidal neovascularization secondary to AMD. Patients receive three monthly intravitreal injections of the combination of volociximab, an anti-Alpha 5 Beta 1 integrin monoclonal antibody (0.5, 1.25 or 2.5 mg) and ranibizumab (0.5 mg). Both anti-VEGF treatment-naïve eyes (n=37) and anti-VEGF experienced eyes (n=11) were treated with the experimental regimen. Treatment-experienced eyes were investigator determined to be unresponsive to previous anti-VEGF monotherapy (lack of visual and anatomic response).

RESULTS: To date, all 37 treatment-naïve eyes received three doses of volociximab in combination with ranibizumab for wet AMD. Baseline visual acuity and OCT center point thickness (CPT) were 52.4 letters and 344 µm respectively. After three doses of combination therapy (week 12) the mean change in VA was +10.4 letters. Thirty five percent of patients gained >3 lines (15 letters) of vision. The mean change in OCT CPT thickness was -125 µm. To date, 11 treatment-experienced eyes received 3 doses of volociximab in combination with ranibizumab for wet AMD. Baseline visual acuity and OCT CPT were 56.5 letters and 333 µm respectively. After three doses of combination therapy (week 12) the mean change in VA was +7.4 letters. Thirty percent of patients gained >3 lines (15 letters) of vision. The mean change in OCT CPT was -106 µm. Dose escalation was completed without evidence of dose-limiting toxicity.

CONCLUSIONS: Preliminary results of this phase 1 study of volociximab combined with ranibizumab suggest a favorable safety profile.
Macular EpiRetinal Brachytherapy in Treated Age-related Macular Degeneration Patients (MERITAgE): Interim Results

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Tim Jackson, MD

Purpose: To assess the safety and efficacy of epimacular brachytherapy for previously treated neovascular age-related macular degeneration (nAMD).

Methods: Fifty subjects with classic, minimally classic and occult lesions were enrolled. Entry criteria included a loading phase of 3 consecutive anti-VEGF injections and a minimum of 3 intravitreal anti-VEGF retreatment injections in the 6 months preceding enrolment, or 5 injections in 12 months preceding enrolment. Subjects had received a mean of 12 injections prior to enrolment. Subjects underwent pars plana vitrectomy and 24 Gray beta irradiation for 4-5 minutes, using a retractable Strontium-90 source in an endoscopic probe (NeoVista, Freemont, CA). Anti-VEGF injections were administered if there was a 5 ETDRS letter loss, >50 micron central retinal thickness increase on optical coherence tomography (OCT), new macular haemorrhage, or new activity visible with fundus fluorescein angiography (FFA). Subjects were retreated with the same anti-VEGF agent they were receiving prior to enrolment (bevacizumab 1.25 mg or ranibizumab 0.5 mg). Monthly OCTs and regular FFAs (0, 1, 6, 12 months) were read centrally. Co-primary outcome measures were mean ETDRS visual acuity and mean number of anti-VEGF retreatment injections.

Results: To date, 27 subjects have reached the 6 month milestone. Subjects received a mean of 1.9 retreatment injections including the mandated injection at baseline for active leakage. Mean visual acuity was maintained over time at baseline VA (+1.6 letters in pseudophakes). There was a favourable safety profile with no retinal breaks, detachments or radiation retinopathy.

Conclusions: These interim results suggest that epimacular brachytherapy may reduce the need for anti-VEGF retreatment, whilst maintaining and/or improving vision, however further follow-up is needed. Epimacular brachytherapy has the potential to reduce the treatment burden that patients face, and the financial cost to healthcare providers. A large (n=363) multicentre UK RCT (MERLOT) is now underway.
Radiation Therapy for Exudative Age-related Macular Degeneration: One Year Results of a Non-Invasive Approach

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PURPOSE: Phase I study to evaluate the safety and tolerability of IRay(TM) stereotactic radiosurgery system in subjects with choroidal neovascularization secondary to age-related macular degeneration.

METHODS: Patients were enrolled who met the following inclusion criteria: age ≥ 50, subfoveal CNV due to AMD, ETDRS BCVA 69-24 letters. Two cohorts were treated: treatment naïve (TN), previously treated (PT) requiring on-going therapy (leakage on fluorescein, increased fluid or persistent CME on OCT). Treatment protocol consisted of: 1) ranibizumab at time zero, 16 Gy IRay within 14 days, ranibizumab at day 30. Monthly evaluation: ETDRS protocol refraction, OCT, quarterly FA. Ranibizumab retreatment criteria: increase >100 microns on Zeiss Cirrus OCT central subfield, new macular hemorrhage, new classic CNV on FA, ≥ 10 ETDRS letter decrease from previous examination with fluid on OCT.

RESULTS: Twenty-eight patients were enrolled and all have completed at least 12 months of follow-up. Safety results demonstrated no device-related serious adverse events: myocardial infarct leading to death (n=1), unrelated malignancy (n=2, including one death), respiratory arrest leading to death (n=1). No radiation-related ocular side effects: no retinopathy, no cataract progression, no IOP increase. Device-related adverse effects: transient asymptomatic superficial keratopathy after I-Guide application, spontaneously resolved. Visual acuity results at 12 months: 96% losing ≤ 15 letters, 74% gaining ≥ 0 letters, 48% gaining ≥ 15 letters. Visual acuity results were similar in TN (n=16) and PT (n=11) cohorts at 12 months: losing ≤ 15 letters (100% TN, 91% PT), gaining ≥ 0 letters (75% TN, 73% PT), and gaining ≥ 15 letters (44% TN, 55% PT). In this group, a total of 38 injections were performed between months 3 and 12, for a mean of 0.9 injections per patient in the PRN phase. 52% of patients required no additional injections.

CONCLUSIONS: IRay non-invasive radiotherapy demonstrated excellent safety at 12 months with no evidence of radiation-induced ocular events. There is a biologic effect in both treatment naïve and previously treated AMD populations and all lesion types. The data show that IRay radiotherapy in conjunction with ranibizumab extends the durability of anti-VEGF effect and decreases the need for ranibizumab injections, while demonstrating VA results at least equal to those typically seen with monthly anti-VEGF regimen.
Angiographic and Optical Coherence Tomography Outcomes Following X-ray Irradiation for Treatment of Wet Age-related Macular Degeneration

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PURPOSE: To describe the anatomic results following external X-ray irradiation for treatment of age-related macular degeneration (AMD) as evaluated by fluorescein angiography (FA) and optical coherence tomography (OCT).

METHODS: A phase I non-randomized, open-label, uncontrolled safety trial of orthovoltage X-ray irradiation for treatment of wet AMD. There were three groups of radiation evaluated:
1) 16 Gy with 2 mandatory ranibizumab injections, followed by prn ranibizumab monthly;
2) 24 Gy with 2 mandatory ranibizumab injections, followed by prn ranibizumab monthly; and,
3) 16 Gy with prn ranibizumab monthly. Patients received FA at baseline, month 1, and every 3 months thereafter. Additionally, OCT were obtained at baseline, and monthly thereafter. The FA were independently, retrospectively reviewed for evidence of radiation retinopathy, total lesion size, choroidal neovascular (CNV) membrane size, and greatest liner dimension (GLD). The OCT were independently, retrospectively reviewed for change in central subfield thickness and total macular volume change.

RESULTS: At 12 month follow-up, complete results were available for the 16 Gy plus 2 mandatory ranibizumab injections group. The following FA parameters demonstrated a median decrease: 62% decrease in total CNV size, 29% decrease in GLD, and 15% decrease in total lesion size. On OCT, there was a mean decrease of 117 microns on central subfield thickness and a mean decrease of 0.67 cubic mm in central macular volume.

CONCLUSIONS: The effects of orthovoltage irradiation in combination with ranibizumab upon the CNV secondary to AMD are to decrease the amount of leakage, decrease the extent of leakage, and decrease the size of the lesion, which is substantially different from either the natural history or the recorded history of monotherapy with either vascular endothelial growth factor inhibitors or photodynamic therapy.
A Novel Strategy for Identifying and Quantitating Geographic Atrophy in Dry Age-related Macular Degeneration Using Spectral Domain Optical Coherence Tomography

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PURPOSE: The area and progression of geographic atrophy (GA) in patients with non-exudative AMD was assessed using the spectral-domain optical coherence tomography (SDOCT) fundus image and a novel square root transformation strategy was used to determine the enlargement rates.

DESIGN: Prospective longitudinal natural history study.

PARTICIPANTS: Eighty-six eyes of 64 patients with at least 6 months follow-up.

METHODS: Patients with GA secondary to AMD were enrolled in this study. Areas of GA were identified and quantified using the SDOCT fundus image. At least five fundus images were obtained on all patients. Reproducibility of these measurements using a digitizing tablet was assessed. The enlargement rates for the areas of GA were calculated using standard area measurements and measurements obtained following square root transformation of the data. Additional longitudinal data were obtained from other studies investigating the progression of GA to test the square root transformation strategy.

RESULTS: The mean total area at baseline was 4.59 mm² (1.8 disc areas (DA); range [0.12 - 16.635 mm²]). The mean follow up time was 1.24 years. Measurements were highly reproducible (intraclass correlation coefficient=0.996). On average, the enlargement rate was 1.2 mm² (0.47 DA; range [0.01 - 3.61 mm²/year] and was correlated with the baseline lesion area (r=0.45, p<0.001). Square root transformation of the lesion area measurements yielded an enlargement rate of 0.28 mm/yr which was independent of baseline lesion size (r=-0.09, p=0.40). The square root transformation of the data yielded a single pooled test-retest standard deviation (SD) for the area measurements (SD=0.03mm) which was independent of baseline lesion size. This observation was confirmed using larger datasets obtained from other clinical trials.

CONCLUSIONS: The SDOCT fundus image proved to be useful for identifying and reproducibly quantitating GA in AMD. Square root transformation of area measurements resulted in test-retest standard deviations and enlargement rates which were independent of baseline lesion size. This strategy was applicable to GA measurements obtained from different trials using different imaging modalities. This independence from baseline lesion size permits the use of smaller sample sizes and shorter clinical trials to explore novel therapies for GA.
E-ETDRS Visual Acuity Testing After Autorefraction versus Manual Refraction in Eyes with Diabetic Macular Edema

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PURPOSE: To compare visual acuity (VA) scores obtained after autorefraction to those obtained after manual refraction in eyes with a wide range of VA in patients with diabetes.

METHODS: Electronic Early Treatment Diabetic Retinopathy Study Visual Acuity Test© (E-ETDRS) letter score (EVA) was measured after autorefraction (AR-EVA) and after a Diabetic Retinopathy Clinical Research Network (DRCR.net) protocol manual refraction (MR-EVA). A variety of autorefractor models were utilized in this study. The order of testing was randomized and subjects and VA examiners were masked to refraction source when possible. A second EVA measurement, utilizing an identical DRCR.net manual refraction (MR-EVAsupl), was performed in order to establish test-retest variability for comparison purposes.

RESULTS: In 564 eyes of 300 subjects, the median MR-EVA was 73 (Snellen equivalent 20/40). MR-EVA was slightly better than AR-EVA, with a median difference (AR-EVA – MR-EVA) of -2 letters (interquartile range -6 to +1 letters). The median difference between the 2 EVAs obtained with manual refraction (MR-EVAsupl – MR-EVA) was 0 (interquartile range -2 to +2 letters). Variability between AR-EVA and MR-EVA was significantly greater than the test-retest variability of MR-EVA (P<0.001), although the degree of variability appeared related to autorefractor type (P<0.001). Autorefraction spherical equivalent was similar to manual refraction spherical equivalent (median difference: 0.00, interquartile range -0.63 to +0.25 D).

CONCLUSIONS: In a cohort of eyes with a wide range of VA and across a broad range of sites with a large variety of autorefractors, visual acuity measurements are slightly worse when obtained using spectacle correction obtained from an autorefractor than from a manual refraction. This disparity may be device dependent as there may be substantial differences in performance between autorefractor models. Estimates of variability in VA testing could be used to plan future trials for patients with diabetic retinopathy. Substituting autorefraction for manual refraction may afford cost and time savings.

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Relationship of Optical Coherence Tomography-measured Central Retinal Thickness, Visual Acuity and Level of Diabetic Retinopathy in a Pooled Analysis of Diabetic Retinopathy Clinical Research Network Studies

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PURPOSE: To assess the relationship between optical coherence tomography (OCT)-measured retinal thickness, visual acuity and level of diabetic retinopathy in a pooled analysis of eyes with center involved diabetic macular edema (DME) among study participants enrolled in three Diabetic Retinopathy Clinical Research Network randomized clinical trials.

METHODS: Cross-sectional study of 2,058 eyes among 1,717 study participants enrolled in 3 randomized clinical trials (Protocols B, I, and J) evaluating treatments for DME. At baseline, retinal thickness was measured with a time domain (Stratus™, Carl Zeiss Meditec, Dublin, CA) OCT and visual acuity was measured with the Electronic-Early Treatment Diabetic Retinopathy Study (E-ETDRS Visual Acuity Test©) procedure.

RESULTS: The correlation coefficient for visual acuity versus OCT central subfield was -0.36. The slope of the best fit line to the baseline data was approximately -3.3 letters (99% confidence interval, -3.8 to -2.8) of lower visual acuity for every 100 µm increase in central subfield thickness. No association was found between OCT-measured central subfield thickness and level of diabetic retinopathy severity or between visual acuity and diabetic retinopathy severity. There were no obvious differences in correlation coefficients noted for subgroups based on prior treatment for DME or hemoglobin A1c levels.

CONCLUSIONS: There is a modest correlation between OCT-measured central subfield thickness and visual acuity. This pooled analysis from a broad cohort of OCT retinal thickness is a confirmation of similar conclusions obtained from smaller data sets and provides an even greater confidence that OCT measurements of retinal thickness obtained on time domain OCT, while critical to provide an objective, reproducible and reliable measurement of retinal thickness, cannot substitute reliably as a surrogate for visual acuity in an individual.

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Panretinal Photocoagulation or Anti-VEGF Drugs as a Pretreatment Before Vitrectomy for Proliferative Diabetic Retinopathy

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PURPOSE: To compare the effects of panretinal photocoagulation (PRPC) to those of intravitreal anti-VEGF drugs on biochemical parameters in the vitreous body of patients suffering from proliferative diabetic retinopathy (PDR).

METHODS: The vitreous body of patients vitrectomized in different centers for PDR was biochemically analyzed for alarm molecules (oxidative metabolites, inflammatory markers and VEGF. Ninetysix patients have received anti-VEGF drugs (ranibizumab or bevacizumab) one week to four weeks before surgery. The results were compared to each other and to a previous patient’s group which received an adequate PRPC before surgery.

RESULTS: Anti-VEGF drugs have led to a slight insignificant reduction of VEGF-values. In addition, all other values were not affected. In contrast, PRPC had led to a significant reduction of all values.

CONCLUSIONS: PRPC results in a more pronounced and sustained reduction of alarm molecules which are responsible for consecutive inflammation and VEGF upregulation. Thus, adequate coagulation appears to be the still the adequate treatment to reduce intra- and postoperative complications in patients suffering from PDR. This effect may be augmented by the additional application of both, intravitreal steroids and/or anti-VEGF drugs.
**DA VINCI: DME and VEGF Trap-Eye: Investigation of Clinical Impact: Phase 2 Study in Patients with Diabetic Macular Edema (DME)**

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**PURPOSE:** VEGF Trap-Eye (VTE) is a recombinant fusion protein consisting of VEGF binding domains of human VEGF receptors 1 and 2 fused to the Fc domain of human IgG1. This phase 2 study assesses the efficacy and safety of intravitreal VTE vs. laser photocoagulation in DME at the 24-week primary endpoint.

**METHODS:** DA VINCI is a multi-center, randomized, active-controlled Phase 2 clinical study, designed to assess safety and efficacy of 4 dose/dose intervals of VTE in comparison to laser photocoagulation. 221 patients were randomized (219 treated) to 1 of the following treatment arms: 0.5mg q4wks, 2mg q4wks, 2mg q8wks, 2mg prn or laser photocoagulation. The primary endpoint is the mean change from baseline in BCVA at week 24. Secondary endpoints include changes in retinal thickness (CRT) on OCT.

**RESULTS:** At 6 months, the mean change in BCVA for each VTE arm ranged from +8.5 to +11.4 letters and was statistically significantly better than the mean change in BCVA in the laser arm (+2.5 letters; p<0.01). No significant difference was noted among the VTE arms. Anatomical effects (mean change in CRT) for each VTE arm ranged from -127 µm. to -195 µm. and were significantly greater than the mean change in CRT for the laser arm (-68 µm.; p<0.01). VTE was generally well-tolerated, and adverse events (AEs) reported were those typically associated with intravitreal injections or underlying disease. There were two cases of endophthalmitis, one culture negative and one positive for Staphylococcus epidermidis. The most frequent AEs reported in the VTE arm include conjunctival hemorrhage, eye pain, floaters, ocular hyperemia, and increased IOP.

**CONCLUSIONS:** In this patient population at the 24-week primary endpoint, intravitreal VTE was generally well tolerated and produced significant improvements from baseline in visual acuity and retinal thickness as compared to laser photocoagulation.
Profile of Growth Factors in Vitreous Samples of Diabetic Patients

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Purpose: To describe the growth factor profile found in the vitreous samples of patients with diabetic retinopathy and to determine if there is a difference in the expression of transforming growth factor beta-1 and -2 (TGF-b-1 and -b-2), insulin-like growth factor-1 (IGF-1), and hepatocyte growth factor (HGF) between the diabetic and non-diabetic profiles.

Methods: Seventy-five samples were collected from 75 patients at the time of surgical intervention. The levels of TGF-b-1 and b-2, IGF-1, and HGF were analyzed and compared between the diabetic and non-diabetic groups. Further comparisons were made within the diabetic group between those with proliferative versus non-proliferative disease, as well as between those with active versus inactive disease.

Results: The concentrations of TGF-b-1 and TGF-b-2 were significantly higher in the diabetic group versus the control group (TGF-b-1, p=0.006 and TGF-b-2, p=0.002). The levels of IGF-1 and HGF were also higher in the diabetic group, but the difference seen was only statistically significant for the HGF concentrations (IGF-1, p=0.9 and HGF, p<0.001).

Conclusions: TGF-b-1 and TGF-b-2 were found to be elevated in the diabetic samples, though less so in the inactive PDR and NPDR samples, as compared to the controls. HGF was also found to be elevated in the diabetic samples. Knowing these differences may be useful in determining the management of these patients, as, for example, some current medical therapies in the presence of elevated TGF-b may be more detrimental (diabetic crunch) and surgical therapy a more appropriate intervention. This data may also be used in the development and assessment of future targeted therapies in order to prevent progression before interventions are necessary.
Number of Retreatments Given in a Randomized Trial Comparing Intravitreal Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser with Sham Injection Plus Prompt Laser for Diabetic Macular Edema

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PURPOSE: To evaluate the number of intravitreal study drug or sham injections and laser retreatments given in a randomized trial comparing intravitreal ranibizumab combined with prompt or deferred laser or triamcinolone combined with prompt laser with sham injection combined with prompt laser for diabetic macular edema.

METHODS: Eight hundred and fifty four study eyes of 691 participants with center-involved DME and visual acuity (approximate snellen equivalent) 20/32 to 20/320 were enrolled in a multi-center randomized clinical trial. Eyes were randomized to sham+prompt laser (n = 293), 0.5-mg ranibizumab+prompt laser (n = 187), 0.5-mg ranibizumab+deferred laser (n = 188), or 4-mg triamcinolone+prompt laser (n = 186). Intravitreal study drug or sham injection was given at baseline and every 4 weeks through the 12-week visit. From the 16-week visit and thereafter, retreatment could be deferred if an eye was a success (defined as visual acuity letter score > 84 or optical coherence tomography (OCT) central subfield thickness (CSF) < 250, or both). Starting at the 24-week visit retreatment was given if improvement criteria was met (defined as either visual acuity improved by > 5 letters or OCT CSF improved by > 10% since the last non-sham injection or since baseline for the sham+prompt laser group). If success or no improvement, study treatment could be given at investigator discretion. Laser retreatment was given if there was edema involving the center of the macula (defined as OCT CSF > 250 microns) or edema threatening the center of the macula (defined as edema on clinical exam within 500 microns of the foveal center or edema associated with lipid within 500 microns of the foveal center or 1 disc area of edema within 1 disc area of the foveal center), and if complete laser (defined as direct treatment to all microaneurysms within areas of macular edema and grid treatment to all other areas of macular edema) had not been given, provided at least 13 weeks had transpired since last laser application. Retreatment followed a detailed algorithm facilitated by a web-based real-time data entry system. The ranibizumab groups could receive ranibizumab as often as every 4 weeks; the triamcinolone group could receive triamcinolone as often as every 16 weeks with sham injections as often as every 4 weeks in between; the sham+prompt laser could receive sham injections as often as every 4 weeks.

RESULTS: The follow-up retreatment results of this clinical trial will be presented; however because of the potential public health impact of these results, the Diabetic Retinopathy Clinical Research Network requests that the results be presented only after the 1-year primary manuscript is published, likely by May of 2010.
CONCLUSIONS: Conclusions will follow from the results presented.
Supported through a cooperative agreement from the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services EY14231, EY14229, EY018817.
Randomized Trial Comparing Ranibizumab Combined with Prompt or Deferred Focal/Grid Laser or Triamcinolone Combined with Prompt Focal/Grid Laser with a Sham Injection Combined with Focal/Grid Laser for Diabetic Macular Edema

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PURPOSE: To evaluate the efficacy and safety of 0.5-mg intravitreal ranibizumab combined with prompt or deferred focal/grid laser or 4-mg intravitreal triamcinolone combined with prompt focal/grid laser in comparison with focal/grid laser alone as treatments for diabetic macular edema (DME).

METHODS: Six hundred and ninety one study participants (mean age 63±10 years; 44% women) from 854 eyes with center-involved DME and visual acuity 20/32 to 20/320 were enrolled in a multi-center randomized clinical trial; NCT00445003. Eyes were randomized to sham injection plus prompt (within 3 to 10 days after injection) laser (sham+prompt laser group, n = 293), 0.5-mg ranibizumab plus prompt laser (ranibizumab+prompt laser group, n = 187), 0.5-mg ranibizumab plus deferred (>24 weeks) laser (ranibizumab+deferred laser group, n = 188), or 4-mg triamcinolone plus prompt laser (triamcinolone+prompt laser group, n = 186). The main outcome measures were best corrected electronic Early Treatment Diabetic Retinopathy Study visual acuity and safety at 1-year. A secondary outcome of interest was Optical Coherence Tomography (OCT) measured central subfield thickness (CSF) at 1-year. The primary analysis consisted of 3 pairwise comparisons of the mean change in visual acuity, adjusted for baseline visual acuity, in the sham+prompt laser group compared with each of the other 3 injection groups.

RESULTS: The mean baseline visual acuity letter score in study eyes was 63±12 (approximate Snellen equivalent of 20/63) and the mean OCT CSF was 405±134 µm. The baseline characteristics of the 4 groups were similar. The follow-up results of this clinical trial will be presented; however because of the potential public health impact of these results, the Diabetic Retinopathy Clinical Research Network and sponsor (National Institutes of Health) have requested that the results be presented only after the manuscript on the primary visual acuity outcomes at 1 year is published, likely by May of 2010.

CONCLUSIONS: Conclusions will follow from the results presented. Supported through a cooperative agreement from the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services EY14231, EY018817, EY14229.
A Comparison of Ranibizumab Combined with Prompt or Deferred Laser or Triamcinolone Combined with Prompt Laser with Sham Injection Combined with Prompt Laser among Subgroups of Eyes with Diabetic Macular Edema

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PURPOSE: To evaluate potential differences among baseline subgroups in a randomized clinical trial comparing intravitreal ranibizumab combined with prompt or deferred laser or triamcinolone combined with prompt laser with sham injection combined with prompt laser for diabetic macular edema (DME).

METHODS: Six hundred and ninety one study participants (mean age 63±10 years; 44% women) contributing 854 study eyes with center-involved DME and visual acuity 20/32 to 20/320 were enrolled in a multi-center randomized clinical trial. Eyes were randomized to sham injection+prompt laser (n = 293), 0.5-mg ranibizumab+prompt laser (n = 187), 0.5-mg ranibizumab+deferred laser (n = 188), or 4-mg triamcinolone+prompt laser (n = 186). The mean change in visual acuity from baseline to the 1-year primary outcome visit was evaluated among the following subgroup determinations at baseline: evidence of pseudophakia, prior treatment for DME, visual acuity, optical coherence tomography (OCT)-measured central subfield thickness (CSF), level of diabetic retinopathy determined by reading center grading of fundus photographs, or description of edema by the treating ophthalmologist as predominantly focal or predominantly diffuse.

RESULTS: The mean baseline visual acuity letter score in study eyes was 63±12 and the mean OCT CSF was 405±134 µm. The baseline characteristics of the 4 intervention groups were similar. Approximately 30% of eyes in each of the 4 treatment groups were pseudophakic at baseline and 63% of eyes had a history of prior treatment for DME. The follow-up results of this clinical trial will be presented. Because of the potential public health impact of these results, the Diabetic Retinopathy Clinical Research Network and sponsor (National Institutes of Health) have requested that the results be presented only after the 1-year primary manuscript is published, likely by May of 2010.

CONCLUSIONS: Conclusions will follow from the results presented. Supported through a cooperative agreement from the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services EY14231, EY018817, EY14229.
Intravitreal Ranibizumab or Triamcinolone Compared with Focal/Grid Laser on Progression of Diabetic Retinopathy in Eyes Treated for Diabetic Macular Edema

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PURPOSE: To evaluate the effect of intravitreal ranibizumab or triamcinolone on progression of level of diabetic retinopathy in a randomized clinical trial comparing intravitreal ranibizumab combined with prompt or deferred laser or triamcinolone combined with prompt laser with sham injection combined with prompt laser for diabetic macular edema (DME).

METHODS: Six hundred and ninety one study participants (mean age 63±10 years; 44% women) from 854 eyes with center-involved DME and visual acuity 20/32 to 20/320 were enrolled in a multi-center randomized clinical trial. Eyes were randomized to sham injection+prompt laser (n = 293), 0.5-mg ranibizumab+prompt laser (n = 187), 0.5-mg ranibizumab+deferred laser (n = 188), or 4-mg triamcinolone+prompt laser (n = 186). The difference in the proportion of eyes with a 2 step progression of level of diabetic retinopathy, as graded on fundus photographs, from baseline to the 1-year primary outcome visit in the ranibizumab treated groups or the triamcinolone+prompt laser group were compared with the sham+prompt laser group. The proportion of eyes which developed a vitreous hemorrhage or received panretinal photocoagulation were also compared amongst treatment groups.

RESULTS: A wide range of baseline diabetic retinopathy severity levels were represented in this clinical trial, with approximately 60% of eyes having moderately severe non-proliferative diabetic retinopathy or less. The follow-up results of this clinical trial will be presented; however because of the potential public health impact of these results, the Diabetic Retinopathy Clinical Research Network and sponsor (National Institutes of Health) have requested that the results be presented only after the manuscript on the primary visual acuity outcomes at 1 year is published, likely by May of 2010.

CONCLUSIONS: Conclusions will follow from the results presented.

Supported through a cooperative agreement from the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services EY14231, EY14229, EY018817.