

# Monday, August 27

## 7:30 AM

### A Novel Collaborative Multicenter Telemedicine Diabetic Retinopathy Assessment Program

- Ingrid E. Zimmer-Galler, MD
- Julia A. Haller, MD
- David Lee
- Lisa Hark
- Cynthia Owsley
- David Friedman, MD, MPH, PhD

**OBJECTIVE** To determine barriers and enablers to the delivery of screening for diabetic retinopathy by telemedicine technology to prevent vision loss and promote eye health.

**PURPOSE** Approximately 50% of patients with diabetes do not undergo recommended eye evaluation and this burden is multiplied in underserved populations. The purpose of this study is to utilize a novel multi-center telemedicine approach to remotely screen patients with diabetes in outpatient clinic and pharmacy settings. Barriers and enablers to delivery of diabetic retinopathy screening will be evaluated.

**METHODS** The INSIGHT collaborative research group is screening participants with diabetes for retinopathy at 4 outpatient sites in Baltimore, Birmingham, Miami and Philadelphia using a non-invasive, non-mydriatic fundus camera. Visual acuity is tested with a vision screener. Retinal images and visual acuity data are uploaded via the Internet to a reading center and database. Following expert evaluation, results are reported to patients and their physicians. Rates of patients who screen positive for diabetic retinopathy, severity of disease, and the proportion who receive recommended follow-up examinations are being evaluated as are patient-reported responses to the screening process.

**RESULTS** Remote diabetic retinopathy evaluations began in December 2011. As of March 2012, 348 subjects were enrolled across 4 sites in community-based outpatient clinic and pharmacy settings. All patients had 3 images taken of each eye, two of the retina and one external image. Trained staff administered pre- and post-screening questionnaires related to eye care utilization and patient satisfaction. All costs associated with the remote evaluations are being monitored. Analysis of an initial subgroup of patients revealed an average age of 39 years, average self-reported hemoglobin A1c level of 9.2% and a self-reported rate of 32% of subjects without medical insurance.

**CONCLUSION** This collaborative research effort may provide an empirical basis for cost-effective screening and detection of diabetic retinopathy among persons with diabetes utilizing remote digital retinal imaging. Implementation of telemedicine technology as an adjunct technique may reduce disparity in eye care among socioeconomically disadvantaged groups and improve diabetic retinopathy assessment rates.

**TAKE HOME MESSAGE** Remote surveillance for diabetic retinopathy by telemedicine technology is a promising public health solution that may help reduce vision loss from diabetes.

7:34 AM

# Identification of Diabetic Retinopathy Genes Through a Genome-Wide Association Study Among Mexican-Americans

- Victor Hugo Gonzalez, MD

**OBJECTIVE** To identify genetic susceptibility loci for severe diabetic retinopathy among Mexican-Americans with type 2 diabetes from a South Texas population.

**PURPOSE** To identify genetic susceptibility loci which are involved in the development and the progression of diabetic retinopathy.

**METHODS** 286 Mexican-Americans with type 2 diabetes completed physical and ophthalmologic exams including photos for DR grading. Subjects with moderate to severe NPDR and PDR were defined as cases for this study. DNA samples were genotyped using the Affymetrix GeneChip HumanMapping100K. 104,572 genotyped SNPs from 285 subjects passed quality control criteria and were used to impute 1,326,990 SNPs available in HapMap Phase IIIMexican population in LA, California. Logistic regression under an additive genetic model was performed for each SNP adjusting for the effects of age, gender, diabetes duration, and serum glycosylated hemoglobin level to identify candidate region for the genetic risk of severe DR

**RESULTS** There were two directly genotyped markers associated with severe diabetic retinopathy at P-value less than .0001 level. The strongest signal (rs2300782,  $P = 6.04 \times 10^{-5}$ ) mapped to an intron region of CAMK4 (calcium/calmodulin-dependent protein kinase IV) on chromosome 5. SNP rs10519765 in chromosomal 15q13 had association with severe diabetic retinopathy with  $P = 6.21 \times 10^{-5}$  where the FMN1 (formin 1) gene is located. Using well-imputed markers based on the HapMap IIIMexican population, we identified an additional 32 SNPs located in 11 chromosomal regions with nominal association with severe diabetic retinopathy at P-value less than .0001 level.

**CONCLUSION** In this genome-wide association analysis for severe DR, several SNPs and associated genes with suggestive evidence were identified. The signals implicate genes involved in inflammation, oxidative stress, and cell adhesion for the development and progression of DR. Analyses using genes or pathways as the unit of investigation might more fully extract the genetic risk for DR

**TAKE HOME MESSAGE** There are genes which appear to be associated with the development of severe DR in the Mexican-American population in South Texas.

**7:38 AM**

# Navigated Macular Laser Therapy Results in Stabilizing Diabetic Macular Edema (DME)



- William R. Freeman, MD
- Igor Kozak, MD, PhD
- Jay Chhablani
- Giulio Barteselli, MD
- Sharif Y El Emam, MD
- Marco Cortes

**OBJECTIVE** To report initial data using a navigated laser to treat Diabetic Macular Edema after Anti-VEGF therapy.

**PURPOSE** To evaluate the effectiveness of navigated macular laser combined with anti-VEGF injections in a series of DME patients with varying levels of initial central retinal thickening and responses to anti-VEGF therapy. The goal was to evaluate the potential to use this image stabilized guided laser to provide a more durable treatment than anti-VEGF monotherapy alone.

**METHODS** This was a retrospective review of 45 eyes with DME. Patients underwent ETDRS vision testing, ophthalmoscopic examination, SD-OCT and fluorescein

angiography (FA) at baseline and follow up visits. Eyes with baseline CRT > 440 microns (Spectralis OCT) (Group I), were treated with up to 4 intravitreal injections of anti-VEGF agent. Eyes underwent navigated focal laser (Navilas Laser, OD-OS, Teltow Germany). When central retinal thickness (CRT) was reduced below < 440 microns. Eyes with initial CRT < 440 microns (Group II) were treated with navigated focal laser monotherapy. After laser, eyes were followed monthly.

**RESULTS** Mean baseline acuity was  $56 \pm 20$  letters. This improved to  $62 \pm 17$  letters at the time of laser and remained stable as of the last follow up ( $62 \pm 20$  letters). Baseline CRT was mean  $378 \pm \text{SD}128$  microns, after navigated laser, it was mean  $294 \pm 82$  microns. Post-laser, CRT remained stable at 3-6 months follow up, with a mean of  $297 \pm 123$  microns, with no further anti-VEGF injections. Two-thirds of Group I eyes ( $n=27$ ) demonstrated more than a 20% decrease in CRT after 2-3 injections. In this subgroup, navigated laser maintained visual gain without additional anti-VEGF therapy. One third of Group I eyes did not demonstrate a significant response to anti-VEGF injections. In this subgroup, navigated laser has maintained visual stability. In eyes with mild retinal thickening at baseline (Group II;  $n=18$ ), navigated laser therapy resulted in stable acuity and CRT, without additional treatment with up to 6 months follow-up.

**CONCLUSION** A standardized approach to DME involving initial anti-VEGF injections for eyes with significant retinal thickening and navigated laser therapy applied to retinas with CRT <440 microns appears to offer an effective and durable treatment result. Additional follow-up and direct comparison to current treatment paradigms are planned.

**TAKE HOME MESSAGE** Laser treatment has the potential to reduce the number of intravitreal injections in combination therapy for DME.

**7:48 AM**

# Intravitreal Bevacizumab for Recurrent Vitreous Hemorrhage After Vitrectomy for Diabetic Retinopathy



- Mathew W. MacCumber, MD, PhD
- Renaud Duval, MD, FRCS(C)
- Jack A. Cohen, MD
- Kevin Ferencak, BS

**OBJECTIVE** To describe our experience using intravitreal bevacizumab for recurrent vitreous hemorrhage (VH) after vitrectomy for proliferative diabetic retinopathy (PDR).

**PURPOSE** Of the several ways of managing recurrent VH following vitrectomy for PDR, the role of intravitreal bevacizumab has yet to be clarified in the literature. We describe our experience using intravitreal bevacizumab for these eyes.

**METHODS** Retrospective chart review of patients treated with intravitreal bevacizumab for recurrent VH following vitrectomy for PDR between 2007 and 2012. Patients who had less than 6 months follow-up after vitrectomy were excluded. Patients with recurrent VH were typically examined monthly and given bevacizumab until clearance. Snellen visual acuity measurements were converted to logMAR visual acuity for analysis.

and then converted back to report results. The main outcomes were number of injections given, number of eyes with complete resolution of the VH and the number of eyes that required additional procedures such as outpatient fluid-air exchange or repeat vitrectomy.

**RESULTS** There were 12 eyes of 9 patients that were included in the study. Follow-up after primary vitrectomy had mean of 24.5 months (median 18.5 months, range of 8 to 52.5 months). Two eyes with severe vitreous hemorrhages had a second vitrectomy and one of these also had an outpatient fluid-air exchange early in the post-operative period. A mean of 8.75 bevacizumab injections (median 7, range 1 to 19 injections) were given in the post-operative period for recurrent VH. During the post-operative period the mean number of recurrent VHs was 4 (median 3, range 2-8). Of the 12 eyes, 10 had total resolution of the VH by the last post-operative visit. The visual acuity before the first bevacizumab injection had mean of counting fingers (median CF, range 20/100 to hand motions). Final visual acuity had mean of 20/80 (median 20/60 and range 20/20 to CF).

**CONCLUSION** Intravitreal bevacizumab is a useful adjunct for the management of recurrent VH after vitrectomy for PDR. Eyes often had multiple injections and had recurrent VHs after injections were discontinued, however, recurrences tended to decrease over time. Repeat vitrectomy or fluid-air exchange was only required in the early post-operative period for the most severe cases.

**TAKE HOME MESSAGE** Intravitreal bevacizumab is a useful adjunct for the management of recurrent vitreous hemorrhage in eyes that had undergone vitrectomy for diabetic retinopathy.



**7:52 AM**

# Rapid Progression of Proliferative Retinopathy Despite Extensive Panretinal Photocoagulation: Could Early Vitrectomy Have Saved the Eye?



- Anina Abraham, MD

**OBJECTIVE** Early vitrectomy may be sight-saving in young diabetics with aggressive proliferative diabetic retinopathy.

**PURPOSE** To describe six cases of proliferative diabetic retinopathy, which rapidly worsened 1-3 months following tight panretinal photocoagulation.

**METHODS** 6 eyes of 6 patients in the age group 35 - 45 years, whose blood sugar was well controlled with insulin, were assessed retrospectively. All 6 patients had best corrected visual acuity of 20/20 in the assessed eye when they were diagnosed to have proliferative diabetic retinopathy. All underwent 3 sittings of panretinal photocoagulation, each sitting one week apart.

**RESULTS** All six eyes had a drop in visual acuity in the range of 20/80 to counting fingers at 1 foot, due to a taut posterior hyaloid and associated tractional retinal detachment, 1 - 3 months following panretinal photocoagulation. None of the patients had associated risk factors like renal disease or uncontrolled hypertension or diabetes.

**CONCLUSION** Early vitrectomy may be indicated in young diabetics with aggressive proliferative retinopathy. Panretinal photocoagulation alone may only aggravate the disease and cause increased traction on the retina.

**TAKE HOME MESSAGE** Early vitrectomy may save the eye of a young diabetic with aggressive lasered proliferative diabetic retinopathy.

**7:56 AM**

# Transvitreal Fibrinoid Pseudo-endophthalmitis After Diabetic Vitrectomy



- Caesar K. Luo, MD
- Alan J. Ruby, MD
- George A. Williams, MD
- Melissa D. Neuwelt, MD

**OBJECTIVE** Describe the presentation and clinical course of non-infectious transvitreal fibrinoid response following vitrectomy for diabetic retinopathy.

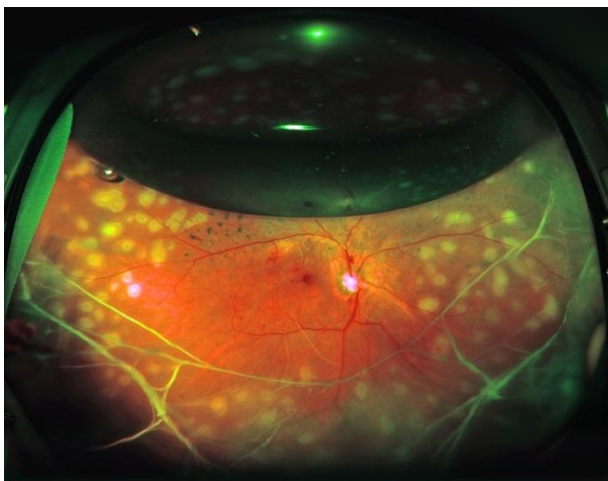
**PURPOSE** This series of patients manifested a brisk fibrinoid response following vitrectomy for diabetic retinopathy. The purpose of this series was to differentiate this unique phenomenon from true infectious endophthalmitis, and to describe the clinical postoperative course.

**METHODS** This is a retrospective chart review series. 8 eyes of 7 patients were included. Data collected from charts included age, gender, surgical indication, preoperative and serial visual acuities, phakic status, vitrectomy procedures, and postoperative clinical characteristics of involved eye.

**RESULTS** Patients had a mean age of 65.6 years (51-82 years) with 5 females and 2 males. Patients had a range of diabetes duration from 4-27 years and a mean HgbA1C of 9.1 (5.8-14.1). Surgical indications included nonclearing vitreous hemorrhage (5), tractional retinal detachment (3), and clinically significant macular edema (1). All eyes underwent 23 gauge vitrectomy with endolaser. All patients manifested transvitreal bands on postoperative day 1 without anterior chamber reaction. Mean time to resolution of transvitreal fibrinoid bands was 8.8 days (4-15 days), on standard postoperative topical medications alone.

**CONCLUSION** Transvitreal fibrinoid response after diabetic vitrectomy is a dramatic phenomenon that can occur in a wide variety of patients with diabetic retinopathy. It is important to differentiate this from infectious endophthalmitis, as this series of cases resolved spontaneously on topical medications alone.

**TAKE HOME MESSAGE** Differentiation between true post-vitrectomy infectious endophthalmitis vs. sterile transvitreal fibrinoid response.



**8:06 AM**

# 36-Month Efficacy and Safety Results of RISE and RIDE, 2 Phase III Randomized Controlled Clinical Trials of Ranibizumab for Diabetic Macular Edema

- David M. Brown, MD
- Amy C Rundle, MS
- Jiameng Zhang, PhD
- J. Jill Hopkins, MD
- Jason S Ehrlich, MD, PhD

**OBJECTIVE** To evaluate the long-term efficacy and safety of ranibizumab in patients with diabetic macular edema (DME), as measured by changes in visual acuity, retinal anatomy and incidence of adverse events.

**PURPOSE** Following the 24-month controlled treatment period, patients originally randomized to ranibizumab (RBZ) continued treatment while those randomized to sham were eligible to cross over to monthly 0.5 mg RBZ. Analysis of the 36-month data addresses two important questions: 1) Are 24-month outcomes maintained through month 36?, and 2) What, if any, are the consequences of delaying treatment with RBZ?

**METHODS** RISE and RIDE are double-masked, phase III sham-controlled clinical trials. A total of 759 adults with DME (Best Corrected Visual Acuity [BCVA] 20/40-20/320 Snellen equivalent and central foveal thickness [CFT]  $\geq 275\mu\text{m}$  on optical coherence tomography) were randomized (1 eye per patient) 1:1:1 to monthly 0.5 mg or 0.3 mg RBZ or sham injection. In year 3 patients originally randomized to sham were eligible to cross over to monthly 0.5 mg RBZ. Macular laser was available to all, starting at month 3. The primary efficacy outcome was the proportion of patients gaining  $\geq 15$  ETDRS letters in BCVA from baseline at month 24. Safety was assessed based on ocular and systemic adverse events (AEs).

**RESULTS** Approximately 74% of the sham patients crossed over to 0.5 mg RBZ. At Month 36 73.2% of the patients originally randomized to sham, and >78% of RBZ patients remained on study. Visual acuity benefits of ranibizumab were generally maintained at Month 36. The proportions of patients gaining  $\geq 15$  letters from baseline, in the pooled RIDE/ RISE populations, was 20.6% in the sham/crossover, 44.0% in the RBZ 0.3 mg, and 40.9% in the RBZ 0.5 mg group. 98.0% in the RBZ 0.3 mg and 96.8% in the RBZ 0.5 mg group lost <15 letters, versus 91.8% in the sham/crossover group. Mean CFT decrease was maintained through Month 36 in patients originally randomized to RBZ. Sham/crossover patients experienced improvements in OCT in year 3. Ocular and systemic AEs were generally consistent with the controlled Month 24 data. APTC events (deaths of unknown or vascular cause, non-fatal myocardial infarctions, and non-fatal strokes) occurred in 10.8% and 10.4% of 0.3 mg and 0.5 mg RBZ patients through Month 36.

**CONCLUSION** BCVA gains at month 24 with both doses of ranibizumab were sustained through month 36. Vision was maintained through month 36 in 96.8 -98% of the patients randomized to RBZ at baseline. Delayed treatment did not result in the same extent of VA improvement seen in patients originally randomized to RBZ. Ocular and systemic safety was generally consistent with the results seen at Month 24.

**TAKE HOME MESSAGE** Ranibizumab treatment offers sustained long-term visual acuity and retinal anatomy benefits for patients with diabetic macular edema.

<b>Outcome Measure</b>	<b>Sham/0.5mg (n=257)</b>	<b>RBZ 0.3 mg (n=250)</b>	<b>RBZ 0.5mg (n=252)</b>
Gaining $\geq 15$ Letters, % (95% CI)	20.6% (15.7%, 25.6%)	44.0% (37.8%, 50.2%)	40.9% (34.8%, 46.9%)
Mean $\Delta$ BCVA from Baseline (SD)	4.5 (14.1)	12.4 (13.0)	11.2 (14.7)
Loss of <15 Letters, % (95% CI)	91.8% (88.5%, 95.2%)	98.0% (96.3%, 99.7%)	96.8% (94.7%, 99.0%)

**8:14 AM**

# A Prospective Randomized Trial of Intravitreal Bevacizumab Versus Ranibizumab for the Management of Diabetic Macular Edema

- Rodrigo Jorge, MD  
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Erika Takaki, MD  
Jefferson A S Ribeiro, MD  
Renato Peroni, MD  
Ingrid U. Scott, MD, MPH  
José Cardillo, MD  
André Messias, MD

**OBJECTIVE** Comparatively evaluate the effect of intravitreal bevacizumab versus ranibizumab on central macular thickness and best-corrected visual acuity of DME patients.

**PURPOSE** To compare anatomic and visual acuity outcomes associated with intravitreal bevacizumab (IVB) versus ranibizumab (IVR) for the management of diabetic macular edema (DME).

**METHODS** Forty-eight patients (63 eyes) with center-involving DME were randomly assigned to receive either 1.5 mg/0.06 cc IVB or 0.5 mg/0.06 cc IVR. Intravitreal injections were performed at baseline and monthly if central subfield thickness (CSFT) measured by spectral domain optical coherence tomography (SDOCT) > 275  $\mu$ m. Comprehensive ophthalmological examination was performed monthly, including

**SDOCT and Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) measurement.**

**RESULTS** To date, 96% and 70% of the patients completed 24 and 48 weeks of follow-up, respectively. A statistically significant reduction in mean CSFT was observed for the IVB and IVR groups at all study visits compared to baseline ( $p < 0.05$ ). Mean  $\pm$  SE CSFT ( $\mu\text{m}$ ) was  $451.7 \pm 22.3$  and  $312.1 \pm 14.6$ , for IVB, and  $421.9 \pm 23.1$  and  $282.9 \pm 15.5$  for IVR, at baseline and week 48, respectively. There was no significant difference in CSFT reduction between the IVB and IVR groups at any study visit. A significant improvement in mean BCVA was observed within each of the two study groups at all study visits compared to baseline ( $p < 0.05$ ); mean  $\pm$  SE BCVA (logMAR) was  $0.60 \pm 0.05$  and  $0.41 \pm 0.06$  for IVB, and  $0.63 \pm 0.05$  and  $0.39 \pm 0.05$  for IVR, at baseline and week 48, respectively. There was no significant difference in BCVA improvement between the IVB and IVR groups at any study visit. One patient developed endophthalmitis after his first ranibizumab injection.

**CONCLUSION** These data indicate that IVB and IVR are associated with similar effects on CSFT and BCVA at 1 year in patients with DME.

**TAKE HOME MESSAGE** These preliminary results suggest similar effects of intravitreal bevacizumab and ranibizumab on central subfield thickness reduction and visual acuity improvement



**8:22 AM**

# 0.5 mg and 2 mg Ranibizumab in Patients Unresponsive or With Incomplete Response to Bevacizumab for the Treatment of Diabetic Macular Edema

- Dante Joseph Pieramici, MD
- Melvin D Rabena, BS
- Ma'an A. Nasir, MD
- Alessandro A Castellarin, MD
- Robert See, MD
- Stephen Couvillion, MD, MD
- Nathan C. Steinle, MD
- Dilsher S. Dhoot, MD
- Michael D. Bennett, MD
- Jessica C Basefsky, BS
- Jack M Giust
- Lisha Wan, BA
- Robert L. Avery, MD

**OBJECTIVE** To report our experience with 0.5mg & 2.0mg ranibizumab in individuals with center involved DME previously treated with bevacizumab and demonstrating no response or incomplete response.

**PURPOSE** To evaluate the efficacy and safety of various doses of ranibizumab in patients with diabetic macular edema previously treated with bevacizumab.

**METHODS** Interim analysis of a prospective, nonrandomized, single center, interventional investigator sponsored study. Individuals with residual center involved DME following bevacizumab treatment were enrolled into this 12-month clinical trial. All enrolled subjects received at least 2 consecutive bevacizumab injections administered less than 7 weeks apart. Upon enrollment, all patients received 3 consecutive monthly injections of 0.5mg ranibizumab. At Month 3, all subjects with residual DME were switched to 3

consecutive monthly injections of 2.0 mg ranibizumab. Monthly evaluations include standardized VA, SD-OCT and complete ophthalmic evaluation. Fundus photos and FA were obtained quarterly.

**RESULTS** Twenty-six subjects with at least 6 months of follow-up were included in this analysis. Previous bevacizumab was adequate and consecutive prior to enrollment at an average of 35.3 days between bevacizumab injections. Mean VA was 59 letters at baseline; improved by +4.9 letters at Month 3 and +8.2 letters at Month 6. Mean central 1mm subfield thickness (CST) was 498 $\mu$ m at baseline; decreased by -131 $\mu$ m at Month 3 and -166 $\mu$ m at Month 6. Mean retinal volume decreased from 9.92mm<sup>3</sup> at baseline to 8.85mm<sup>3</sup> at Month 3 and 8.57mm<sup>3</sup> at Month 6. After 3 consecutive 0.5 mg ranibizumab injections, reduction in CST to below 300 $\mu$ m on SD-OCT was achieved in 19.2% (5/26) of subjects & CST decreased by >25% from baseline in 34.6% (9/26) of subjects. After 3 consecutive 2.0 mg ranibizumab injections, an additional 19.0% (4/21) of subjects achieved CST of  $\leq$ 300 $\mu$ m & CST decreased by >25% from Month 3 in 19% (4/21) of subjects. No serious adverse events were observed during the first six months of the study.

**CONCLUSION** Visual and anatomical improvement following ranibizumab can occur in some patients with minimal or no response to previous bevacizumab therapy. Incomplete or nonresponse to bevacizumab should not be a contraindication to considering ranibizumab therapy in patients with diabetic macular edema.

**TAKE HOME MESSAGE** Ranibizumab therapy may have a possible role in individuals with center-involved diabetic macular edema previously treated with bevacizumab and demonstrating no response or incomplete response.

**8:36 AM**

# Estimate of Vision Impairment or Legal Blindness Avoided in the US With Ranibizumab for Central-Involved Diabetic Macular Edema with Vision Loss

- Neil M. Bressler, MD
- Rohit Varma, MD, MPH
- Quan Doan, PharmD
- Paul Lee, MD, JD
- Mark Danese, MHS, PhD
- Chantal Dolan, PhD, MPH
- Adam Turpcu, PhD
- Abraham Lee, BA
- Jennifer Fine, Sc.D.
- Jason S Ehrlich, MD, PhD
- Shoshana Colman, PhD

**OBJECTIVE** Estimate vision impairment or legal blindness avoided in the U.S. using ranibizumab to treat patients with central-involved diabetic macular edema (DME) and vision impairment.

**PURPOSE** Estimate cases of visual impairment (visual acuity (VA) letter score less than 68 [20/40 or worse] in the better-seeing eye) or legal blindness (VA letter score less than 38 [20/200 or worse] in the better-seeing eye) avoided over 2 years in the U.S. with availability of ranibizumab for non-Hispanic white and Hispanic patients at least 45 years old with central-involved DME in 2011.

**METHODS** A model simulated VA outcomes over 2 years following diagnosis and treatment of central-involved DME with every 4 week ranibizumab 0.5mg intravitreal injection in patients with health insurance. Estimates were based on: 2011 U.S. population, prevalence of diagnosed diabetes, and 1-year incidence rate of central-involved DME from WESDR and LALES. Baseline VA of eyes treated with ranibizumab

was based on DRCR Network data. VA changes for patients with VA loss from DME at diagnosis in the incident eye and fellow eye incidence of DME were based on RIDE and RISE data. For patients with DME but without VA loss at diagnosis, VA changes with laser and no ranibizumab were based on ETDRS data.

**RESULTS** The model predicted 15,265 incident cases of central-involved DME with visual impairment at diagnosis in 2011 which could access treatment. Without ranibizumab, 3,944 cases of visual impairment were predicted. Ranibizumab reduced the cases by 33% (95% simulation interval (SI): 31% to 35%) to 2,632. Without ranibizumab, 193 cases of legal blindness were expected. Ranibizumab reduced cases of legal blindness by 78% (95% SI: 73% to 83%) to 42 cases. The model predicted 139,070 incident cases of central-involved DME without vision impairment at diagnosis with healthcare access. Without ranibizumab, 14,520 cases of vision impairment were predicted in 2 yrs. No cases of legal blindness were predicted over 2 years for patients with central-involved DME without vision impairment at diagnosis.

**CONCLUSION** This model suggests that every 4 week use of ranibizumab substantially reduces the incidence of vision impairment and blindness 2 years after diagnosis and treatment of central-involved DME with vision loss in both non-Hispanic white and Hispanic patients in the United States.

**TAKE HOME MESSAGE** Every 4 week use of ranibizumab substantially reduces the incidence of vision impairment and blindness 2 years after diagnosis and treatment of central-involved DME with vision impairment.

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**8:44 AM**

# Exploratory Analysis of Diabetic Retinopathy Progression Through 3 Years in a Randomized Clinical Trial Evaluating Ranibizumab and Triamcinolone

- Carl W. Baker, MD

**OBJECTIVE** Evaluate effect of intravitreal ranibizumab or intravitreal triamcinolone acetate on worsening (progression) of diabetic retinopathy.

**PURPOSE** Determine worsening of diabetic retinopathy up to 3 years among participants in a randomized clinical trial which compared treatments for diabetic macular edema (DRCRnet protocol I).

**METHODS** Exploratory analysis performed on eyes with diabetic macular edema randomly assigned to prompt focal/grid laser, intravitreal 0.5-mg ranibizumab+prompt or deferred (>24 weeks) laser, or 4-mg intravitreal triamcinolone+prompt laser. Worsening of retinopathy in eyes with non-PDR at baseline was defined as progression from non-proliferative diabetic retinopathy (non-PDR) to proliferative diabetic retinopathy (PDR) or worsening of 2 or more severity levels on reading center assessment of 7-field fundus photographs or receipt of scatter photocoagulation (PRP) or occurrence of vitreous hemorrhage or vitrectomy for PDR; in eyes with PDR at baseline, only the last 3 criteria were used.

**RESULTS** For eyes without PDR at baseline, the 3-year cumulative probabilities of worsening of retinopathy (and P value comparison with sham+prompt laser) were 28% in the sham+prompt laser group, 21% in the ranibizumab+prompt laser group ( $P = 0.03$ ), 13% in the ranibizumab+deferred laser group ( $P = 0.007$ ), and 38% in the triamcinolone+prompt laser group ( $P = 0.66$ ). For eyes with PDR at baseline, the 3-year cumulative probabilities of worsening of retinopathy were 41%, 21% ( $P = 0.05$ ), 21% ( $P$

= 0.06), and 23% ( $P = 0.003$ ), respectively. A median of 5 or fewer injections were given annually during the second and third year of follow-up in each group assigned to intravitreal injections.

**CONCLUSION** Intravitreal ranibizumab or intravitreal triamcinolone appears to reduce the risk of worsening of diabetic retinopathy in eyes with PDR; intravitreal ranibizumab also appears to reduce the risk of worsening in eyes without PDR. However, use of these treatments to reduce the rates of worsening of diabetic retinopathy is not yet warranted given the exploratory nature of these analyses.

**TAKE HOME MESSAGE** Intravitreal ranibizumab appears to reduce the risk of worsening of diabetic retinopathy in eyes with or without PDR.

**8:56 AM**

# Integrin Peptide Therapy: The Human Experience in DME

- Hugo Quiroz-Mercado, MD
- David S. Boyer, MD
- Baruch D. Kuppermann, MD, PhD

**OBJECTIVE** The objective was to evaluate the safety and efficacy of intravitreal ALG-1001 in humans with end stage DME with a primary endpoint of observing dose limiting toxicity.

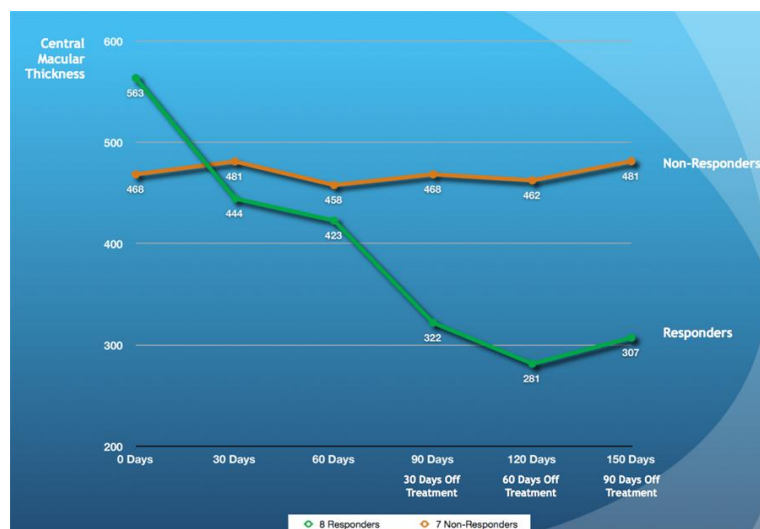
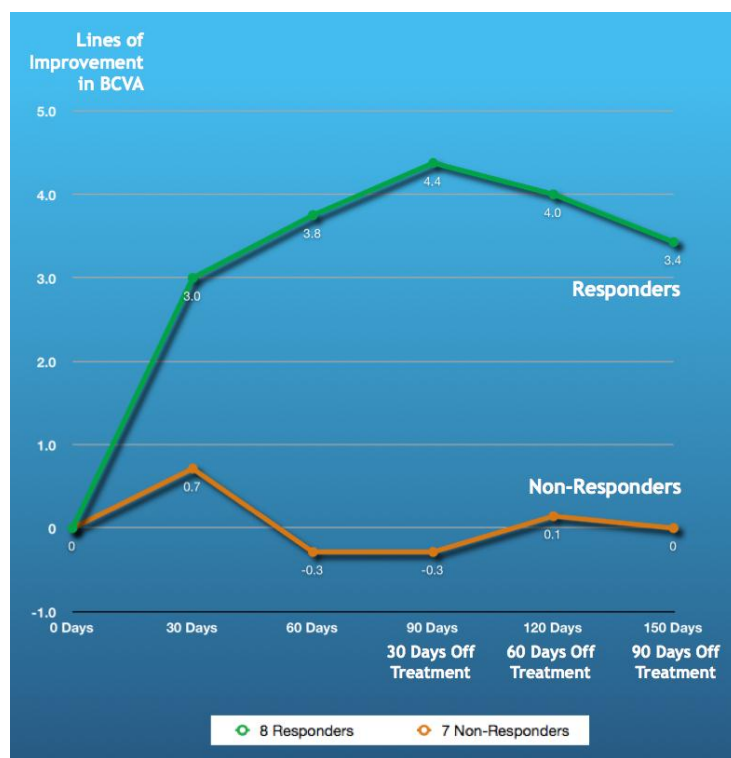
**PURPOSE** ALG-1001 inhibits integrin receptors *in vitro* and arrests aberrant blood vessel growth *in vivo* mediated by  $\alpha v\beta 3$ ,  $\alpha v\beta 5$  as well as  $\alpha 5\beta 1$  - integrin sites that are expressed in NV ocular tissue in both wet AMD and diabetic retinopathy. ALG-1001 demonstrated a statistically significant reduction in CNV and pre-retinal neovascularization in mouse models conducted by Dr. Peter Campochiaro.

**METHODS** 15 human subjects with end-stage DME completed this open label study. Baseline BCVA was  $\geq 20/100$  & patients had not undergone anti-VEGF treatment or focal laser within 90 days -- many refractory to Avastin and previous photocoagulation. 3 monthly intravitreal injections of 2.5mg ALG-1001 were given, following subjects for an additional 3 months. Safety measurements included BCVA, slit lamp evaluation, fundus exam, IOP measurements, OCT, FA, fundus photos, B-scan, and ERG.

**RESULTS** There were no Serious Adverse Events or significant Adverse Events with no inflammatory reactions or sustained elevations in IOP. 8 of 15 subjects reported a 3 line or more increase in BCVA after receiving 3 monthly injections with up to a corresponding 79% reduction in central macular thickness on OCT. Interestingly these clinical benefits in BCVA and OCT CMT persisted in nearly all responders for 90 days off treatment. The non-responders did not experience any loss in BCVA from baseline or an increase in OCT central macular thickness over 5 months.

**CONCLUSION** There was consistency in the lack of toxicity across all study metrics. ALG-1001 was very well tolerated. Despite the small study size, there was a clinically significant indicator of efficacy with improvements in BCVA tracking anatomic improvements in OCT central macular thickness. These improvements endured at least 90 days past the last intravitreal treatment in nearly all responders.

**TAKE HOME MESSAGE** This abstract describes the first human clinical trial (in DME) with the anti-integrin compound ALG-1001. This is a first in class anti-angiogenic compound for the treatment of vascular eye disease.





**9:04 AM**

# Visual Acuity and OCT Outcomes Following Cataract Extraction in Eyes With Diabetic Macular Edema

- Michael H. Scott, MD

**OBJECTIVE** Attendees will learn that the existence of central-involved diabetic macular edema should not automatically preclude cataract surgery in eyes scheduled to undergo cataract surgery.

**PURPOSE** To report visual acuity (VA) and optical coherence tomography (OCT) central subfield thickness (CSF) outcomes, 16 weeks following cataract surgery in eyes with central involved diabetic macular edema (CI-DME).

**METHODS** Prospective, observational study, in which 29 sites enrolled eyes with CI-DME (CSF  $250\mu\text{m}$  on time domain or  $310\mu\text{m}$  on spectral domain OCT) scheduled for cataract extraction within 28 days of enrollment. VA and OCT outcomes were assessed 16 weeks after cataract surgery. Treatment for DME before, at day of, or after surgery was at investigator discretion.

**RESULTS** Sixty (95%) eyes completed 16 weeks. Median participants' age was 64 years and 85% had type 2 diabetes with median duration of 19 years. Thirteen eyes (22%) had no prior DME treatment. Median pre-operative E-ETDRS VA letter score was 59 (20/63) and median CSF was  $309\mu\text{m}$ . Twenty one eyes (35%) did not receive pre-, peri-, or post-surgical DME treatment; 25 eyes (42%) received post-surgical treatment; intravitreal anti-VEGF injections (76%) were most common. At 16 weeks, the mean change in VA letter score was +12 (95 CI: +8 to +16) and 42% (95 CI: 29% to 55%) were 20/40 or better (letter score  $\geq 73$ ). Thirty-six eyes (60%, 95 CI: 47% to 73%) had  $\geq 10$  letters VA improvement ( $\sim$ Snellen equivalent  $\geq 2$  lines), 6 eyes (10%, 95 CI: 2% to 18%) lost  $\geq 10$  letters. Mean change in CSF from preoperative visit was  $+18\mu\text{m}$  (95 CI:

-18  $\mu\text{m}$  to +54  $\mu\text{m}$ ). Thickness increased  $\geq 1$  logOCT unit in 18% (95% CI: 8% to 28%), decreased  $\geq 1$  logOCT unit in 13% (95%CI: 4% to 22%), and resolved in 10% (95%CI: 2% to 18%)

**CONCLUSION** When pre-, peri-, and post-surgical management of macular edema was at investigator discretion most eyes with pre-operative DME did not exhibit meaningful increase (at least 1 log unit CSF increase) in macular edema, and VA appears to improve in majority of eyes 16 weeks after cataract surgery. Central-involved DME should not preclude cataract surgery in eyes scheduled to undergo cataract surgery.

**TAKE HOME MESSAGE** The existence of central-involved diabetic macular edema should not automatically preclude cataract surgery in eyes scheduled to undergo cataract surgery.

**9:12 AM**

## Risk of Endophthalmitis after Intravitreal Drug Injections With and Without Use of Topical Antibiotics in DRCR Randomized Clinical Trials



- Abdhish R. Bhavsar, MD

**OBJECTIVE** To compare endophthalmitis rates after intravitreal injection with and without use of topical antibiotics in four Diabetic Retinopathy Clinical Research Network (DRCR.net) trials.

**PURPOSE** To determine if applying topical antibiotics at the discretion of the investigator as part of a standardized DRCR.net injection procedure reduces the risk of endophthalmitis.

**METHODS** Data from all injections using single-use vials across four DRCR.net trials were included. The standardized procedure for these trials requires topical povidone-iodine, use of a sterile lid speculum, and topical anesthetic; however, use of topical antibiotics prior to, on the day of, or after injection is at the discretion of the treating ophthalmologist. Diagnosis of endophthalmitis was based on investigator's judgment.

**RESULTS** As of November 21, 2011, 8027 intravitreal injections involving single use vials among 1066 eyes had been administered in the DRCR.net trials. This includes 186 injections of bevacizumab in 108 eyes, 626 injections of masked study drug (saline or ranibizumab) in 260 eyes, and 7,215 injections of ranibizumab in 698 eyes. Among the 8027 total injections, topical antibiotics were given prior to the injection (on the day of injection) in 619 (8%), for several days after injection in 1,533 (19%), prior to and after injection in 2,542 (32%) and neither on the day of injection nor after injection in 3,333 (42%). Seven cases of endophthalmitis have occurred, including 6 (0.13%) out of 4694 using topical antibiotics, compared with 1 (0.03%) out of 3333 not using topical antibiotics ( $P$  value = 0.25).

**CONCLUSION** These prospectively accumulated results suggest that topical antibiotics before or after intravitreal injections, as given in the DRCR.net, are not likely reducing the risk of endophthalmitis and potentially could be increasing the risk due to additional manipulation of the ocular surface when applying antibiotics.

**TAKE HOME MESSAGE** Topical antibiotics do not appear necessary for a low rate of endophthalmitis with intravitreal injections and may possibly increase the risk of endophthalmitis.

Case	Intravitreal Drug Injected	Culture Results	Povidone-Iodine Use	Pre-op Antibiotics	Post-op Antibiotics
1	Bevacizumab	Coagulase negative staphylococcus	Yes	No	No
2	Ranibizumab	Coagulase negative staphylococcus	Yes	Yes	Yes
3	Ranibizumab	Culture negative	Yes	No	Yes
4	Ranibizumab	Coagulase negative staphylococcus	No*	Yes	Yes
5	Ranibizumab	Streptococcus viridans <sup>†</sup>	Yes	No	Yes
6	Ranibizumab	Coagulase negative staphylococcus	Yes	No	Yes
7	Masked drug (either saline or ranibizumab)	Culture negative	Yes	No	Yes