Save the Date:

2015
38th Annual Macula Society Meeting
Montelucia Resort and Spa
Scottsdale, Arizona
February 25 – 28, 2015
The Macula Society

37th Annual Scientific Program

Ocean Reef Club
Key Largo, Florida
February 19 - 22, 2014

The Macula Society
3401 Enterprise Parkway, Suite 310, Cleveland, Ohio 44122
(216) 839-4949 Fax: (216) 831-8221
Email: maculasociety@aol.com
Website: maculasociety.org
Accreditation

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the Medical College of Wisconsin and the Macula Society. The Medical College of Wisconsin is accredited by the ACCME to provide continuing medical education for physicians.

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International Member Representative
Anat Loewenstein, MD

Young Member Representative
Rajendra S. Apte, MD, PhD
Meeting Registration Desk

Wednesday, February 19, 2014
10:00 a.m.-7:00 p.m.
Thursday, February 20, 2014
6:15 a.m.-1:30 p.m.
Friday, February 21, 2014
6:30 a.m.-1:30 p.m.
Saturday, February 22, 2014
6:30 a.m.-1:00 p.m.

Speaker Ready Room is located in
Town Hall

Wednesday, February 19, 2014
10:00 a.m.-7:00 p.m.
Thursday, February 20, 2014
6:15 a.m.-1:30 p.m.
Friday, February 21, 2014
6:30 a.m.-1:30 p.m.
Saturday, February 22, 2014
6:30 a.m.-1:00 p.m.

Meetings

Executive Committee
Wednesday, February 19, 2014
1:00 p.m.-3:00 p.m.
Carysfort Hearth

Annual Business Meeting (Members Only)
Friday, February 21, 2014
6:45 a.m.-7:30 a.m.
Town Hall

Young Member Mentor Lecture

Introduction: Rajendra S. Apte, MD, PhD
Guest Speaker: Daniel F. Martin, MD
Thursday, February 20, 2014
6:45 a.m.-7:30 a.m.
Reef Conference Center
Scientific Program
(all presentations will be in Town Hall)

Case Conference
Wednesday, February 19, 2014
3:30 p.m.-6:40 p.m.

General Sessions
Thursday, February 20, 2014
7:30 a.m.-1:12 p.m.

Friday, February 21, 2014
7:30 a.m.- 1:03 p.m.

Saturday, February 22, 2014
7:30 a.m.-1:03 p.m.

Social Program
Wednesday, February 19, 2014
Welcome Buffet Dinner
Palm Court
7:00 p.m.-10:00 p.m.

Thursday, Friday, Saturday
Breakfast Buffet for all registered attendees
Reef Conference Center
Thursday – 7:00 a.m.-10:00 a.m.
Friday – 6:30 a.m.-10:00 a.m.
Saturday – 7:00 a.m.-10:00 a.m.

Friday, February 21, 2014
37th Annual Macula Society Gala
Cocktails
6:45 p.m.
Lagoon/Beach
Gala Dinner Reception
7:30 p.m.
Lagoon/Beach
*Dressy attire, beach appropriate shoes for women
2014 Awards

Presentation of 2014 Green Lecture and Award
Thursday, February 20, 2014 9:36 a.m. Page 64
“Macular Degeneration: From Mechanism to Therapy”
Recipient: Hendrik P.N. Scholl, MD, MA
Presenter: Morton F. Goldberg, MD

Presentation of 2014 J. Donald M. Gass Medal
Thursday, February 20, 2014 1:03 p.m. Page 108
Recipient: Anita Agarwal, MD
Presenter: Paul Sternberg, Jr., MD

The 2014 Young Investigator Award and Lecture
Friday, February 21, 2014 9:54 a.m. Page 142
“Microglia in the Retina: A Therapeutic Target for Age-Related Retinal Disease”
Recipient: Wai T. Wong, MD, PhD
Presenter: Alexander J. Brucker, MD

The 2014 Arnall Patz Medal
Friday, February 21, 2014 12:54 p.m. Page 180
Recipient: Tien Y. Wong, MD, PhD
Presenter: Lloyd Paul Aiello, MD, PhD

The 2014 Paul Henkind Memorial Lecture and Award
Saturday, February 22, 2014 9:36 a.m. Page 210
“Uveal Melanoma – The Present and The Future”
Recipient: J. William Harbour, MD
Presenter: Rajendra S. Apte, MD, PhD

The 2014 Evangelos S. Gragoudas Award
Saturday, February 22, 2014 11:42 a.m. Page 230
Recipient: Glenn C. Yiu, MD, PhD
Presenter: Cynthia Töth, MD
The Macula Society gratefully acknowledges the support of The Mills and Margaret Cox Macula Society Research Project sponsored by Retina Research Foundation from an RRF endowment established by the Cox Estate Alice R. McPherson, MD President Retina Research Foundation Houston, Texas
The Macula Society would like to thank Larry Yannuzzi, MD and the Macula Foundation for their continuing support of the Paul Henkind Memorial Lecture
The Macula Society

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**Macula Society**  
**2014 Case Conference**  
**WEDNESDAY, FEBRUARY 19, 2014**  
**SESSION I**  
**Imaging and Case Study Conference**

3:30 - 4:15 p.m.  
**Moderators:** Lee Jampol  
Carol Shields  

3:30  
Carol Shields  
Retina Wipeout

3:35  
Shlomit Schaal  
Acute Retinal Necrosis (ARN) Caused by the Epstein Barr Virus (EBV): Immunohistopathologic Confirmation

3:40  
Stephen Schwartz  
“Not Well Defined”

3:45  
R Theodore Smith  
AMD, Hemorrhage, Glaucoma and CNV

3:50  
Andrew Lotery  
Orange is the Colour

3:55  
Alan Cruess  
Choroidal Hemangioma with Overlying Choroidal Neovascularization

4:00  
Sai Chavala  
Life Beneath the Retina

4:05  
Nan-Kai Wang  
Bilateral Foveoschisis and Flecks in Boy and Girl Twins

4:10  
Lee Jampol  
Unknown

4:15 - 5:05 p.m.  
**Moderators:** Anita Agarwal  
Larry Yannuzzi

4:15  
Salomon Cohen  
An Intraretinal Hyperreflective Narrow Line

4:20  
Lawrence Yannuzzi  
Severe CSC

4:25  
Jerry Shields  
Retinal Detachment in a 10-Year-Old

4:30  
J. Fernando Arevalo  
Unknown

~20~
Macula Society
2014 Case Conference
Wednesday, February 19, 2014
continued

4:35     Anita Agarwal
        Bilateral Yellow Ring

4:40     Ayala Pollack
        Unusual Foveal Manifestations on OCT

4:45     Leonidas Zografos
        Presumed Ectopic Choroid

4:50     Craig Greven
        Traction Retinal Detachment with Proliferative
        Vitreoretinopathy Following Transpupillary Thermotherapy

4:55     José Pulido
        What You See is What You Get

5:00     Michaella Goldstein
        Too High to See it Clear

Session II
5:05 - 5:55 p.m.  Moderators:  Mark Johnson
                  Sophie Bakri

5:05     Mark Johnson
        Unknown

5:10     Shree Kurup
        Value of a Single Retinal Evaluation in a Juvenile with Multiple
        Invasive Procedures Over 8M

5:15     J. William Harbour
        Young Woman with Multiple Bilateral Choroidal Tumors

5:20     Sophie Bakri
        Ehrlichia Uveitis

5:25     Quan Nguyen
        Yet . . . Another Patient with White Dots in the Retina

5:30     Michael Elman
        Regression of Retinal Neovascularization in Proliferative
        Diabetic Retinopathy Using Topical Squalamine Lactate Drops
Macula Society
2014 Case Conference
WEDNESDAY, FEBRUARY 19, 2014
continued

5:35 Martine Mauget-Faysse
Dark Without Pressure:
Multimodal Imaging Analysis of a Case

5:40 Philip Rosenfeld
Bilateral Macular Edema in a 63-Year-old Woman

5:45 Oh Kwon
Clinical Course of Significantly Active Leaking
Microaneurysm on Oct (Salmo) in Diabetic Macular Edema

5:50 - 6:40 p.m.  Moderators: Caroline Baumal
Naresh Mandava

5:50 Caroline Baumal
Mystery Maculopathy

5:55 Thomas Ciulla
Ranibizumab in Diabetic Macular Edema Refractory to
Multiple Prior Treatments

6:00 Clement Chan
Gas Relief of Vitreomacular Traction and Closure of Macular
Hole in the Era of Pharmacologic Vitreolysis

6:05 Ron Adelman
Retinal Arterial Occlusion

6:10 Francis Munier
Mystery Case: A Benign Retinal Lesion in a Child

6:15 Helen Li
Decreased Vision in a Patient with Leukemia

6:20 Naresh Mandava
Acute Retinal Necrosis Presenting with Ischemic Optic
Neuropathy and Retinal Vascular Occlusive Disease

6:25 Janet Sunness
Inner Retinal Ischemia Versus Glaucoma

6:30 Gaetano Barile
Unilateral Visual Loss in a Young Woman

6:35 Itay Chowers
The Odyssey of the Iron Women
2014

Scientific Program

Wednesday through Saturday

February 19 – 22, 2014
Key Largo, Florida

The nine minutes allotted for each presentation consists of seven minutes for presentation and two minutes for discussion with the audience.
THURSDAY, FEBRUARY 20, 2014

SESSION I
Dry AMD

Moderator: Jordi Monés  Moderator: Cynthia Toth

7:30 a.m.  Following Disease Progression Using Visual Function Changes at 1 and 2 Years in Patients with Bilateral Geographic Atrophy
Janet Sunness

7:39 a.m.  Impact of a Lesion Size-Derived Classification of Geographic Atrophy in Progression Rate
Jordi Monés

7:48 a.m.  Comparison of Standardized Color Photography Grading to SDOCT Volume Analysis for Quantitative Assessment of Intermediate Age-Related Macular Degeneration and Prediction of Outcomes
Cynthia Toth

7:57 a.m.  Analysis of Drusen and Disease Progression in Age-Related Macular Degeneration
Ursula Schmidt-Erfurth

8:06 a.m.  Intravitreal Autologous Bone Marrow-derived CD34+ Stem Cell Therapy for Degenerative Macular Disease
Susanna Park

8:15 a.m.  Intravitreal Erythropoietin in Eyes with Geographic Atrophy Secondary to Age-Related Macular Degeneration
Stephen Sinclair

8:24 a.m.  The MAHALO Phase II Results: Lampalizumab (Anti-factor D) in Patients with Geographic Atrophy
Dante Pieramici

SESSION II
Neovascular AMD I

Moderator: Emily Chew  Moderator: Glenn Jaffe

8:33 a.m.  A New Rare Variant in the C3 Gene Predicts Progression to Advanced Stages of Macular Degeneration and New Predictive Models
Johanna Seddon

8:42 a.m.  Metabolic Pathways Altered in Neovascular Age-Related Macular Degeneration
Milam Brantley
8:51 a.m.  Elevation of Specific Vitreous Protein Biomarkers of Fibrosis and Proliferation in a Large Cohort of Eyes with Vision Loss During the Initiation Phase of anti-VEGF Therapy for Wet AMD
   Bert Glaser

9:00 a.m.  Multimodal Imaging Findings and Multimodal Vision Testing in Neovascular Age-Related Macular Degeneration
   Richard Spaide

9:09 a.m.  Effect of Baseline Retinal Pigment Epithelial Elevation Status on Visual Outcomes in the VIEW 1 and VIEW 2 Studies
   Glenn Jaffe

9:18 a.m.  Grey Hyper-Reflective Subretinal Lesions in Exudative Age-Related Macular Degeneration
   Giuseppe Querques

9:27 a.m.  Effect of Aspirin Use on Progression of Age-Related Macular Degeneration
   Emily Chew

9:36 a.m.  Presentation of the Green Lecture and Award
   “Macular Degeneration: From Mechanism to Therapy”
   Recipient: Hendrik P.N. Scholl, MD, MA
   Presenter: Morton F. Goldberg, MD

SESSION III
Neovascular AMD II

Moderator: Dave Brown  Moderator: Usha Chakravarthy

9:54 a.m  The Home Monitoring of the Eye (HOME) Study: Primary Findings
   Michael Elman

10:03 a.m.  The HOME Study: Lesion Characteristics of Early CNV
   David Brown

10:12 a.m.  What Does Early Exudative AMD Look Like?
   Nancy Hokekamp

10:21 a.m.  The Pattern of Anti-VEGF Use in Neovascular Macular Degeneration: A U.S. Claims Analysis
   Pravin Dugel

10:30 a.m.  Switch-over from PRN to Treat and Extend in Exudative AMD: 1 year Results from a Clinical Case Series
   Christian Prüente
10:39 a.m. Early vs. Delayed 20/40 Visual Acuity Achievers with Ranibizumab Treatment in the 24-month HARBOR Study
Charles Wykoff

10:48 a.m. Predictors of Visual Acuity Outcome and Time to Lesion Reactivation when Using Anti-VEGF Drugs to Treat Wet AMD
Usba Chakravarthy

10:57 a.m. Intravitreal Aflibercept in Eyes with Neovascular AMD Requiring Frequent Retreatment with Intravitreal Bevacizumab or Ranibizumab
Philip Rosenfeld

11:06 a.m. Short Term Outcomes of Aflibercept Conversion Therapy for Exudative Age-Related Macular Degeneration in Eyes Previously Treated with Bevacizumab, Ranibizumab or both
Anat Loewenstein

11:15 a.m. Systematic Review of Safety Across the Phase II and III Clinical Trials of Intravitreal Aflibercept Injection
Peter Kaiser

11:24 a.m. Pharmacokinetic Profile of Intraocular Aflibercept in Patients Receiving Intravitreal Aflibercept Therapy for Neovascular Age-Related Macular Degeneration
Clement Chun

11:33 a.m. Systemic Pharmacokinetics Following Intravitreal Injections of Ranibizumab, Bevacizumab or Aflibercept in Patients with Neovascular AMD or DME
Robert Avery

11:42 a.m. The Societal Costs Associated with Neovascular Macular Degeneration in the United States
Gary Brown

11:51 a.m. Lean Transformation of an Intravitreal Injection Clinic: Increasing Access and Enhancing Patient Experience
Dennis Han

SESSION IV
Other CNV, CSR

Moderator: Raj Apte

12:00 p.m. Five-Year Results of Combined Treatment for Polypoidal Choroidal Vasculopathy: Verteporfin PDT and Intravitreal Anti-VEGF
Hyung Woo Kwak
12:09 p.m. Extramacular Findings in Age-Related Macular Degeneration in Japanese Patients
Yasuo Yanagi

12:18 p.m. Predictors of Visual Outcome in Ranibizumab Treated Myopic Choroidal Neovascularisation – Exploratory Analysis of the Repair Study
Sobba Sivaprasad

12:27 p.m. Flat Irregular Pigment Epithelium Detachment in Chronic Central Serous Chorioretinopathy
Alain Gaudric

12:36 p.m. Visual Cycle Suppression via Patching in Central Serous Retinopathy
Rajendra Apte

12:45 p.m. Advantages and Limitations for Diagnosis and Assessment of Therapy Outcome in Central Serous Chorioretinopathy – Clinical Application of Spectral Domain Optical Coherence Tomography in Combination with Functional Diagnostics
Felix Sabates, Sr.

12:54 p.m. Effect of Spironolactone on Central Chronic Serous Chorioretinopathy: A Randomized Controlled Study (CSR)
Francine Behar-Cohen

1:03 p.m. Presentation of the 2014 J. Donald M. Gass Medal
Recipient: Anita Agarwal, MD
Presenter: Paul Sternberg, Jr., MD

1:12 p.m. End of Session

FRIDAY, FEBRUARY 21, 2014

SESSION V
Imaging

Moderator: Stephen Russell

7:30 a.m. How Colleagues Influence our Representation of Retinal Abnormalities
Stephen Russell

7:39 a.m. Analyses of Posterior Staphyloma by a Combination of 3D MRI and Ultra-Wide Field Fundus Imaging
Kyoko Obno-Matsui
7:48 a.m. Multimodal Imaging of Ghosts in Geographic Atrophy Areas  
_Eric Souied_

7:57 a.m. Fundus Autofluorescence Patterns in Central Serous  
Chorioretinopathy  
_Seung-Young Yu_

8:06 a.m. A Pilot Quantitative Study of Topographic Correlation Between  
Reticular Pseudodrusen and the Choroidal Vasculature Using En Face Optical Coherence Tomography  
_Amani Fawzi_

8:15 a.m. New Insights in Macular Microvasculature using Quantitative  
Adaptive Optics Scanning Light Ophthalmoscopy  
_Richard Rosen_

**SESSION VI**  
_Diabetic Retinopathy_

**Moderator: Lloyd Paul Aiello**  
**Moderator: Diana Do**

8:24 a.m. Microaneurysm Features on Adaptive Optics Scanning Laser  
Ophthalmoscopy are Associated with Fluorescein Leakage and  
Surrounding Retinal Neural Pathology in Diabetes  
_Jennifer Sun_

8:33 a.m. Increased Vitreous Placental Growth Factor Levels Associated  
with Retinal Ischemia  
_Jorge Arroyo_

8:42 a.m. Diabetic Retinopathy (DR) Lesions Located Predominantly  
Peripheral to ETDRS Photographic Field Coverage on  
Ultrawide Field Images Predict Markedly Increased Risk of DR  
Progression  
_Lloyd Paul Aiello_

8:51 a.m. Intravitreal Ranibizumab Therapy Improves Resolution of Hard  
Exudate in Patients with Diabetic Macular Edema  
_Michael Ip_

9:00 a.m. Intravitreal Afiblercept for Diabetic Macular Edema: 12-Month  
Efficacy and Safety Results of Phase 3, Randomized, Controlled  
VISTA-DME and VIVID-DME Studies  
_Jeffrey Heier_

9:09 a.m. Visual and Anatomic Outcomes from the VISTA-DME and  
VIVID-DME Studies of Intravitreal Afiblercept Injection (IAI)  
in Diabetic Macular Edema (DME) Patients with and without  
Prior Treatment for DME  
_Diana Do_
9:18 a.m. Safety and Efficacy of Dexamethasone Intravitreal Implant in Patients with Diabetic Macular Edema: Phase III, 3-Year, Randomized, Sham-Controlled Study
SriniVas Sadda

9:27 a.m. Ranibizumab for Diabetic Macular Edema: Long-Term Open-Label Extension of the Phase III Ride and Rise Trials
Lawrence Morse

9:36 a.m. The Course of Eyes with Vitrectomy Prior to Enrollment in a Randomized Trial Evaluating Ranibizumab Plus Prompt or Deferred Laser for Diabetic Macular Edema
Craig Greven

9:45 a.m. Repeated Ranibizumab Injections and Incidence of Sustained IOP Elevation or Initiation of Ocular Anti-hypertensive Treatment in Eyes with Diabetic Macular Edema
Justin Gottlieb

9:54 a.m. Young Investigator Award and Lecture Presentation
“Microglia in the Retina: A Therapeutic Target for Age-Related Retinal Diseases”
Recipient: Wai T. Wong, MD, PhD
Presenter: Alexander J. Brucker, MD

SESSION VII
Vein Occlusion

Moderator: Julia Haller

10:12 a.m. Dexamethasone Intravitreal Implant used as Monotherapy or Combined with Other Treatment for Macular Edema Secondary to Retinal Vein Occlusion
Michael Singer

10:21 a.m. Evaluation of Multiple Dexamethasone Intravitreal Implants in Patients with Macular Edema Associated with Retinal Vein Occlusion
Sophie Bakri

10:30 a.m. Dexamethasone Implant for Macular Edema Secondary to Ischemic Retinal Vein Occlusions
Francesco Bandello

10:39 a.m. Intravitreal Triamcinolone Acetonide Improves Macular Edema: Evaluation of 5000 Injections to Determine Efficacy and Evaluate Complications
Timothy Murray
10:48 a.m. Intravitreal Afibbercept Injection (IAI) for Macular Edema Secondary to Branch Retinal Vein Occlusion (BRVO): 24-Week Results of the VIBRANT Study
*Julia Haller*

10:57 a.m. Effect of Alternate Ranibizumab Dosing Regimens on Visual and Anatomic Outcomes in Patients with Retinal Vein Occlusion: The SHORE Study
*Franco Recchia*

11:06 a.m. Assessment of the Inner Segment/Outer Segment Layer in Patients with Macular Edema due to Central Retinal Vein Occlusion
*Barbara Blodi*

11:15 a.m. Predictive Value of Early Response to VEGF Inhibition in Retinal Vein Occlusions Defined by Optical Coherence Tomography and Fundus Autofluorescence
*Francisco Rodriguez*

11:24 a.m. Detection of Acute Ischemic Damages in Retinal Vascular Occlusive Diseases using OCT; “Prominent Middle-limiting Membrane Sign”
*Oh Kwon*

**SESSION VIII**
**VMT/VR Surgery**

*Moderator: Rishi Singh*  
*Moderator: William Smiddy*

11:33 a.m. Anatomical and Visual Outcomes Following Ocriplasmin Treatment for Symptomatic Vitreomacular Traction Syndrome
*Rishi Singh*

11:42 a.m. Ocriplasmin for the Treatment of Vitreomacular Traction: Predictors of Success and Complications
*Daniel Roth*

11:51 a.m. Panretinal Dysfunction after Ocriplasmin Injection is Likely Caused by Enzymatic Cleavage of Intraretinal Laminin
*Mark Johnson*

12:00 p.m. Cost Effectiveness of Treatment Options for Vitreomacular Adhesions and Macular Holes
*William Smiddy*

12:09 p.m. Lamellar Hole Associated Epiretinal Proliferation (LHEP)
*K. Bailey Freund*
12:18 p.m. Strategy for the Management of Macular Holes: The European Vitreo-Retinal Society Macular Hole Study
Ron Adelman

12:27 p.m. Autologous Transplantation of the Internal Limiting Membrane for Refractory Macular Holes
Fumio Shiraga

12:36 p.m. Factors Involved in Persistent Subfoveal Fluid Development Following Macular Hole Surgery: An Intraoperative and Perioperative OCT Analysis from the PIONEER Study
Justis Ehlers

12:45 p.m. Surgical and Anatomic Outcomes of Combined Penetrating Keratoplasty and Pars Plana Vitrectomy Cases
William Mieler

12:54 p.m. Presentation of Arnall Patz Medal
Recipient: Tien Y. Wong, MD, PhD
Presenter: Lloyd Paul Aiello, MD, PhD

1:03 p.m. End of Session

SATURDAY, FEBRUARY 22, 2014

SESSION IX
Other Macular Diseases

Moderator: Frank Holz

7:30 a.m. Chorioretinal Folds: Associated Disorders and a Related Maculopathy
Timothy Olsen

7:39 a.m. Progression of Functional Loss in Macular Telangiectasia Type 2
Frank Holz

7:48 a.m. Visual and Anatomic Outcome in Eyes with Idiopathic Juxtafoveal Macular Telangiectasia (MacTel) and Full Thickness Macular Holes Undergoing Surgical Repair
Christina Flaxel

7:57 a.m. Biomarkers Lactate Dehydrogenase (LDH) and Hemoglobin (Hb) in Sickle Cell Ocular Microangiopathy
Anita Agarwal
8:06 a.m.  Assessment of Subjective and Objective Screening Parameters for the Detection of Functional Hydroxychloroquine Toxicity  
*Catherine Cukras*

8:15 a.m.  Integrated Genome- and Exome-wide Association Studies in East Asians Identifies Novel Coding Variants Associated with Age-Related Macular Degeneration  
*Tien Wong*

8:24 a.m.  Exomes and Stem Cells – Genetic Testing in the 21st Century  
*Edwin Stone*

**SESSION X**  
**Tumors**

*Moderator: Carol Shields*  
*Moderator: David Abramson*

8:33 a.m.  Autofluorescence of Intraocular Tumors  
*Carol Shields*

8:42 a.m.  Expanding Clinical and Histopathologic Spectrum of Ocular Melanocytomas  
*Jerry Shields*

8:51 a.m.  Comparison of the Diagnostic Contribution of Multiple Ocular Imaging Techniques in a Multimodal Diagnostic Approach of Small Pigmented Choroidal Tumors  
*Leonidas Zografos*

9:00 a.m.  Long-Term Visual Function after Proton Therapy in Patients with Uveal Melanomas at High Risk of Vision Loss  
*Evangelos Gragoudas*

9:09 a.m.  Histopathologic and Genomic Analysis of Biopsy Sites for New FNAB Technique in Uveal Melanoma  
*Amy Schefler*

9:18 a.m.  RAP, TAP, and TRAAP: Retinal Invasion by Uveal Melanoma Revisited using Multimodal Imaging and Current Concepts of Angiogenesis  
*Jose Pulido*

9:27 a.m.  Intravitreal Chemotherapy for Retinoblastoma: Local and Systemic Safety in 107 Injections  
*David Abramson*

9:36 a.m.  **Paul Henkind Memorial Lecture and Award Presentation**  
“Uveal Melanoma - The Present and The Future”  
*Recipient: J. William Harbour, MD*  
*Presenter: Rajendra S. Apte, MD, PhD*
9:54 a.m. On Line Presentation Discussion Session
   Moderators: Neil Bressler, Susan Bressler, Mark Johnson, Barbara Blodi, Dan Martin

SESSION XI
Uveitis/ROP

Moderator: Harry Flynn                Moderator: Lihteb Wu

10:21 a.m. Multiple Evanescent White Dot Syndrome: Multimodal Imaging
   Lawrence Yannuzzi

10:30 a.m. Macular Choroidal Blood Flow Velocity Increases with
   Regression of Multiple Evanescent White Dot Syndrome
   Susumu Ishida

10:39 a.m. Idiopathic Multifocal Choroiditis/Punctate Inner Choroidopathy
   with Acute Secondary Photoreceptor Loss
   Lee Jampol

10:48 a.m. Pathogenesis of Persistent Placoid Maculopathy: A Multimodal
   Imaging Analysis
   Grant Comer

10:57 a.m. Endophthalmitis Caused by Streptococcal Species: Clinical
   Settings, Microbiology, Management, and Outcomes
   Harry Flynn

11:06 a.m. Assessment of Changes in Quality of Life Among Patients in the
   SAVE Study – Sirolimus as Therapeutic Approach to Uveitis: A
   Randomized Study to Assess the Safety and Bioactivity of
   Intravitreal and Subconjunctival Sirolimus in Patients with
   Uveitis
   Quan Nguyen

11:15 a.m. Peripheral Cryoablation for Treatment of Pars Planitis
   James Folk

11:24 a.m. Outcomes of Treatment of Pediatric CNV with Intravitreal
   Anti-angiogenic Agents: The Results of The KKESH
   International Collaborative Retina Study Group
   J. Fernando Arevalo

11:33 a.m. Agressive Posterior Retinopathy of Prematurity in Costa Rica
   Lihteb Wu

11:42 a.m. Presentation of The 2014 Evangelos S. Gragoudas Award
   Recipient: Glenn C. Yiu, MD, PhD
   Presenter: Cynthia Tóth, MD
SESSION XII
Basic Science

Moderator: Jay Ambati

11:51 a.m. Safety, Pharmacokinetics, and Efficacy of Intraocular Celecoxib
Stephen Kim

12:00 p.m. Genetic and Environmental Factors in AMD
Stephen Tsang

12:09 p.m. Target-independent Suppression of Choroidal Neovascularization by Human IgG1 or IVIG
Jayakrishna Ambati

12:18 p.m. Retinal Angiogenesis Suppression Through Small Molecule Activation of P53
Sai Chavala

12:27 p.m. Targeted Knockdown of Overexpressed Vascular Endothelial Growth Factor (VEGF164 in Mueller Cells Safely Reduces Intravitreal Neovascularization in Model of Retinopathy of Prematurity
Mary Elizabeth Hartnett

12:36 p.m. Role of Nitric Oxide in Early Diabetic Retinopathy
Jennifer Kang-Mieler

12:45 p.m. What Causes Differences in Choroidal Thickness?
Robert Mullins

12:54 p.m. Cone Photoreceptor and Outer Segment Rescue/Regeneration After Cell-Based Therapy in RP
Henry Kaplan

1:03 p.m. End of Session and Meeting
Abstracts
Thursday – 7:30

FOLLOWING DISEASE PROGRESSION USING VISUAL FUNCTION CHANGES AT 1 AND 2 YEARS IN PATIENTS WITH BILATERAL GEOGRAPHIC ATROPHY

Janet Sunness, Greater Baltimore Medical Center
Carol A. Applegate, Greater Baltimore Medical Center

Purpose: For clinical trials for advanced dry AMD, visual function outcome measures may be affected by the patient’s adaptation to eccentric fixation. Prior work has shown that for the worse-seeing eyes of patients with bilateral GA, there may be spontaneous improvement in visual acuity, and this may confound the use of visual acuity as an outcome measure in GA. This study looks at contrast sensitivity and reading speed as other possible outcome measures.

Methods: In our prospective natural history study of GA, 53 patients with bilateral GA had both 1 and 2 year follow-up visits. Best-corrected VA, Pelli-Robson contrast sensitivity, and maximum reading rate were assessed at each visit. The results are broken down by visual acuity categories: group 1=VA 20/50 or better; group 2=VA from 20/51 to 20/199; group 3=VA 20/200 or worse.

Results: For contrast sensitivity, findings were similar in better and worse seeing eyes. The mean baseline log contrast sensitivity was reduced by 0.48 log units (10 letters) relative to normal for groups 1 and 2. For groups 1 and 2, 10% had a 0.3 further worsening in contrast sensitivity at 1 year, and 16% at 2 years relative to baseline. 5% of groups 1 and 2 improved by 0.3 at 1 year and at 2 years relative to baseline. For reading rate, findings were similar in better and worse seeing eyes for group 1, but different for group 2. For group 2, better-seeing eye baseline reading rate was 60 wpm, and there was a mean decline of 10 letters at one year and 13 at 2 years. Worse-seeing eye baseline reading rate was 36 wpm, and mean decline was 6 letters at 1 year and 1.5 letters at 2 years. At both 1 and 2 years, reading rate improved by >=10 wpm in 25% of worse-seeing eyes.
Conclusions: Contrast sensitivity does not change greatly over 2 years, and reading rate may improve from better eccentric fixation despite worsening of GA. Visual function measures are difficult to use as main outcome measures for GA.

Thursday – 7:30

NOTES:
Impact of a Lesion Size-Derived Classification of Geographic Atrophy in Progression Rate

Jordi Monés, Institut de la Macula i de la Retina and Barcelona Macula Foundation
Marc Biarnés, Institut de la màcula i de la retina
Hussein Muhtaseb, Institut de la màcula i de la retina

Purpose: Knowledge of enlargement rates in geographic atrophy (GA) secondary to age-related macular degeneration is required to characterize its natural history, the prognosis at an individual level, to optimally define eligibility criteria and to assess efficacy outcomes in clinical trials. Currently, FAF patterns are mostly accepted as prognostic predictors. However a latent class analysis in our patients pointed out that size was a major driver of progression. The purpose of this study is to explore a classification based on baseline lesion size (BLS) among other characteristics.

Methods: Patients of a prospective, natural history study of patients with pure GA (the GAIN study, NCT01694095) were eligible. All participants received a complete ophthalmologic exploration, and imaging was performed with Spectralis HRA+OCT ® (Heidelberg Engineering, Heidelberg, Germany). The classification involved a 4-step, consecutive process: 1) Increased FAF (yes/no); 2) Those with increased FAF were stratified in two groups, Focal increased FAF and Other (more widespread FAF): 3) Patients with widespread FAF were divided in 3 groups according to tertiles of BLS (1st, 0.1 to 3.76 mm²; 2nd, 3.82 to 9.72mm²; and 3rd, 9.94 to 37.83 mm²); and 4) These 3 groups were additionally stratified in uni or multifocal lesions. The rate of growth (in mm²/year, by percentage and by square root of growth -sqr-) was compared.

Results: We included 109 eyes of 82 patients. When progression was measured in absolute mm²/year, the larger the lesion the higher the progression (p=0.0003). These findings were observed also even after sqr transformation (p=0.0003).
RESULTS CONTINUED

However, when measured as proportion of growth they were inversely associated: the smaller the lesions, the higher the rate (p=0.0001). Widespread presence of soft drusen was also associated with decreased growth (p=0.05).

Conclusions: The proposed classification indicates that BLS may be a major driver of progression of GA. Determining which metrics are used in clinical trials may be crucial since absolute growth and proportional growth rates may show trends in opposite directions. In this study, the sqr transformation did not appear to correct this question.

Thursday – 7:39

NOTES:
COMPARISON OF STANDARDIZED COLOR PHOTOGRAPHY GRADING TO SDOCT VOLUME ANALYSIS FOR QUANTITATIVE ASSESSMENT OF INTERMEDIATE AGE-RELATED MACULAR DEGENERATION AND PREDICTION OF OUTCOMES

Cynthia Toth, Duke University Eye Center
Francisco Folgar, Duke University
Sina Farsiu

Purpose: To determine correlation of color fundus photography (CFP) grading of drusen and geographic atrophy (GA) with spectral domain optical coherence tomography (SDOCT) volume analysis of drusen and retinal pigment epithelium abnormal thinning (RAT) and their ability to predict outcomes.

Methods: Eyes with intermediate age-related macular degeneration (AMD) enrolled in the prospective Age-Related Eye Disease Study 2 (AREDS2) Ancillary SDOCT Study had both semi-automated SDOCT segmentation, macular volumes for drusen and RAT calculated based on a normative SDOCT database of 115 healthy age-controlled eyes. Baseline drusen and RAT volumes were correlated with same-visit AREDS2 CFP grading of drusen and GA by nonparametric Spearman rank correlation. Each baseline measurement was compared with 2-year outcome of choroidal neovascularization (CNV) by Wilcoxon rank sum test, odds ratio (OR), and receiver operating characteristic area the curve (AUC).

Results: 265 intermediate AMD eyes with baseline CFP and SDOCT analysis were included. On CFP, mean (± standard deviation) drusen score was 6.1 ± 1.1 and mean GA area was 0.11 ± 0.50 disc areas. On SDOCT analysis, mean drusen volume was 0.084 ± 0.160 mm³ and mean RAT volume was 0.8 ± 2.1x10⁻³ mm³. Greater CFP drusen score (scale 0-7) was associated with greater drusen volume (p<0.001, Kruskal-Wallis), although each score corresponded to a wide variance in SDOCT drusen volume. Of 239 eyes followed to year 2, 30
RESULTS CONTINUED

developed CNV (13%). CNV was associated with greater CFP drusen score (6.7 ± 0.5 vs. 6.1 ± 1.0, p=0.001, OR=2.55, AUC=0.64) and greater SDOCT drusen volume (Mean ± standard deviation volumes: 0.17 ± 0.28 mm³ vs. 0.06 ± 0.12 mm³, p<0.001, OR=20.97, AUC=0.68). CNV was not associated with baseline CFP GA area or SDOCT RAT volume.

Conclusions: SDOCT measurements of drusen volume correlated with CFP drusen score. CFP drusen area and SDOCT drusen volume measurements both predict CNV at year 2. SDOCT drusen volume had greater sensitivity and specificity to predict CNV, based on greater AUC and OR per unit of measurement. SDOCT measurements of drusen and RAT volume in intermediate AMD may serve as early predictors of disease progression.

Thursday – 7:48

NOTES:
ANALYSIS OF DRUSEN AND DISEASE PROGRESSION IN AGE-RELATED MACULAR DEGENERATION

Ursula Schmidt-Erfurth, Medical University Vienna
Ferdinand Schlanitz, Medical University of Vienna
Bernhard Baumann, Medical University of Vienna
Alessio Montuoro
Ulrike Scheschy, Medical University of Vienna
Abtin Shahlaee, Medical University of Vienna
Magdalena Baratsits
Tamara Mittermüller, Medical University of Vienna
Katja Hatz, Vista Klinik
Michael Pircher, Medical University of Vienna
Christoph Hitzenberger, Medical University of Vienna

Purpose: To evaluate the progression of drusen volume over time and the associated development of advanced age-related macular degeneration (AMD).

Methods: Patients with early AMD were imaged using simultaneous spectral-domain (SD-OCT, Spectralis) and polarization-sensitive OCT (PS-OCT). All patients underwent continuous follow-up examinations every 6 months for three years. Data from PS-OCT were segmented for drusen volume automatically using an algorithm based on the RPE-based polarization-sensitive information, whereas SD-OCT data were segmented manually by expert graders using an OCT-reader software (OCTAVO).

Results: 396 volume-scans from 33 eyes were examined using SD-OCT and PS-OCT. In total, 19,206 individual B-scans were graded manually. The mean drusen volume per eye at baseline was 0.12mm³ for SD-OCT and 0.15mm³ for PS-OCT. The increase of drusen volume over time was shown to be approximately linear, with a regression equation of y=0.03x + 1.0 for SD-OCT and y=0.027x + 1.0 for PS-OCT (x = months), with a calculated doubling of drusen volume after 33.3 resp. 37.0 months. Drusen regression was observed in 24 eyes at least once over three years. Of this group, 8 eyes
developed choroidal neovascularisation (CNV) and 2 eyes geographic atrophy. Eyes without drusen regression showed no signs of progression towards advanced AMD.

Conclusions: Drusen present a linear increase in volume over time. Advanced AMD occurred only in eyes with regression. However, spontaneous regression without advanced AMD was also frequently observed. PS-OCT offers selective delineation of the RPE with fast automated segmentation, consistent with manual grading of standard SD-OCT. Further development including an eye-tracking modality will support investigating the natural history of drusen in AMD on a large scale.

*Thursday – 7:57*

**NOTES:**
Intravitreal Autoologous Bone Marrow-Derived CD34+ Stem Cell Therapy for Degenerative Macular Disease

Susanna Park, University of California Davis Eye Center
Gerhard Bauer, University of California Davis
Athanasios Panorgias, University of California Davis Eye Center
Mehrdad Abedi, University of California Davis Comprehensive Cancer Center
Ravi Jonnal, University of California Davis Eye Center
Robert Zawadzki, University of California Davis Eye Center
John Werner, University of California Davis Eye Center
Jan Nolta, University of California Davis

Purpose: Adult human bone marrow contains stem cells that play an important role in tissue repair and maintenance. A subpopulation of these stem cells, characterized as CD34+, has the ability to home into damaged tissue, including degenerating retina, where possible local trophic effects have been observed. This study explored the safety and feasibility of intravitreal injection of autologous CD34+ cells from bone marrow as a potential therapy for degenerative macular disease.

Methods: Patients with hereditary or dry age-related macular degeneration (AMD) with best corrected visual acuity (BCVA) of 20/100 to 20/400 in the worse eye were enrolled. Bone marrow aspiration from the iliac crest was performed under local anesthesia. The CD34+ cells were isolated from the aspirate under GMP- (Good Manufacturing Practice)-conditions using a magnetic cell-sorter and injected intravitreally. Patients were followed for 6 months with serial eye examination, ETDRS BCVA, microperimetry, fluorescein angiography, multifocal and full-filed electroretinography (ERG), optical coherence tomography (OCT) and adaptive optics (AO)-OCT imaging.

Results: Three eyes (three subjects) were enrolled (one with dry atrophic age-related macular degeneration (AMD); two with Stargardt’s disease). The bone marrow aspiration was well-
tolerated and without any adverse effects. A total of 3 to 7 million CD34+ cells were isolated and injected intravitreally per eye. The injection was well-tolerated during the follow-up period. BCVA improved 1.5 to 4 lines in the study eye during the follow-up period. No funduscopic, angiographic or OCT changes were noted during the follow-up except for some mild progression of geographic atrophy extrafoveally in both eyes of the AMD subject. Multifocal ERG showed a trend toward stabilization in the study eye compared to the contralateral eye in the Stargardt’s subject. Full-field ERG showed stable or enhanced amplitude in the study eye. AO-OCT imaging of the treated eye with Stargardt’s disease showed new punctuate hyperreflectivity within the retinal layers suggestive of new intraretinal cellular incorporation.

Conclusions: In this initial exploratory study, intravitreal injection of autologous CD34+ stem cells from bone marrow appears feasible and well-tolerated in eyes with hereditary or age-related macular degeneration. A larger study with longer follow-up is planned to further explore this therapy.

Thursday – 8:06

NOTES:
INTRAVITREAL ERYTHROPOIETIN IN EYES WITH GEOGRAPHIC ATROPHY SECONDARY TO AGE-RELATED MACULAR DEGENERATION

Stephen Sinclair; Sinclair Retina Associates
Kelly Hurley
Britt Parvus
Peter Presti, Interactive Multi-media Technology Center, Georgia Technology Inst.

Purpose: To investigate the role of Procrit intravitreal injections in stabilizing vision and geographic atrophy (GA) in eyes with atrophic AMD and to characterize SDOCT and central visual field acuity perimetry (Omnifield) findings associated with GA.

Methods: A retrospective pilot study examined eyes treated off-label with Procrit 10U injected intravitreal every 6 weeks. Photographed GA areas (identified on autofluorescence and fluorescein angiograms) were manually outlined and the area converted to mm² using the OCT caliper. SDOCT images were analyzed for loss of PR ellipsoid-segment, loss of ONL, and RPE thickening. Primary outcomes were the effect of treatment on GA enlargement rate and Omnifield Fixation Acuity, Best acuity in 6 degrees of fixation and Global Macular Acuity (weighted average of threshold acuities within 10° of fixation). GA enlargement rate was also compared between treated eyes and fellow untreated eyes with similar GA.

Results: 32 eyes of 28 patients were treated for 1.6±0.8 yrs. with 12±6.2 injections. Eyes were followed for 0.75±0.36 yrs. prior to treatment with avg. initial GA area of 10.2±7.0mm². Treatment reduced the rate of GA enlargement by 0.67±0.2.0mm²/y (56%) from 2.55±3.8 mm²/y prior to treatment. In 24 untreated fellow eyes, GA enlargement was 2.25±0.89mm²/y, or 0.32±0.38mm²/y larger than in treated eyes. In the treated eyes visual acuity over the term improved by an average 0.1 logMAR +/-0.30 logMAR with no significant difference from the fellow untreated eyes. Omnifiled GMA improved 0.16±0.09logMAR during
treatment compared with a loss of 0.05 ± 0. prior to treatment. GA was described by OCT loss of PR ellipsoid segment junction and ONL. Indicators of future GA progression were loss of ONL and RPE thickening at the margins. Central acuity visual field scotomas corresponded with loss of PR ellipsoid segment.

Conclusions: In this off-label study, intravitreal Procrit® appears to slow progressive GA expansion and vision loss in AMD. Acuity perimetry and OCT are useful for mapping areas of preserved vision, monitoring disease progression, and predicting future GA enlargement.

Thursday – 8:15

NOTES:
**Thursday – 8:24**

**THE MAHALO PHASE II RESULTS: LAMPALIZUMAB (ANTI-FACTOR D) IN PATIENTS WITH GEOGRAPHIC ATROPHY**

*Dante Pieramici, California Retina Consultants*
*Brian Yaspan, Genentech, Inc.*
*Zhengrong Li, Genentech, Inc.*
*Amy Dressen, Genentech, Inc.*
*Menno van Lookeren Campagne, Genentech, Inc.*
*Robert Graham, Genentech, Inc.*
*Tatiana Beres, Genentech, Inc.*
*Kha Le, Genentech, Inc.*
*Erin Henry, Genentech, Inc.*
*Carole Ho, Genentech, Inc.*
*Erich Strauss, Genentech, Inc.*

**Purpose:** Genetic variations and complement hyperactivity are implicated in the pathogenesis of age-related macular degeneration (AMD). Lampalizumab (formerly identified as FCFD4514S and anti-factor D) is an antigen-binding fragment that targets complement factor D, a rate-limiting enzyme in the alternative complement pathway and potential therapeutic target for geographic atrophy (GA) secondary to AMD. The MAHALO Phase II study assessed the safety, tolerability and evidence of activity of lampalizumab in patients with GA.

**Methods:** No dose-limiting toxicities were identified following intravitreal lampalizumab 10 mg in a Phase Ib open-label safety run-in. The Phase II component enrolled 129 patients aged 60–89 years with GA secondary to AMD in the absence of choroidal neovascularization. Patients were randomized 2:1:2:1 to lampalizumab 10 mg or sham, administered monthly or every other month. The sham arms were pooled for the analyses. The primary endpoint was change in GA area from baseline to month 18 on fundus autofluorescence. We also evaluated the relationship between specific genetic polymorphisms linked with GA characteristics and lampalizumab treatment response in an exploratory analysis.
Results: One hundred twenty-three patients received at least 1 sham or lampalizumab treatment and had at least 1 post-baseline primary efficacy measurement (sham pooled, n=40; lampalizumab monthly, n=42; lampalizumab every other month, n=41). A 20.4% reduction in GA progression was reported in the lampalizumab monthly arm relative to the pooled sham arm. This positive treatment effect was observed at month 6 through month 18. Furthermore, a 44% reduction in GA progression was observed in a subpopulation positive for the complement factor I (CFI) biomarker; 57% of the collected samples in MAHALO were CFI biomarker-positive. A relatively low incidence of serious adverse events (SAEs) was reported, with no deaths or ocular serious adverse events suspected to be study drug-related.

Conclusions: MAHALO is the first study to show a positive treatment effect in reducing GA progression through complement inhibition. The positive effect observed following monthly lampalizumab was further magnified in the CFI biomarker-defined subpopulation. Our data suggest that CFI is prognostic for GA progression and predictive for lampalizumab treatment response.

Thursday – 8:24

NOTES:
A NEW RARE VARIANT IN THE C3 GENE PREDICTS PROGRESSION TO ADVANCED STAGES OF MACULAR DEGENERATION AND NEW PREDICTIVE MODELS

Johanna Seddon, Tufts Medical Center; Tufts University School of Medicine

Purpose: We discovered new rare genetic variants in CFH, C3, CFI and C9, which were strongly associated with advanced age-related macular degeneration (AMD) in case-control association studies – Nature Genetics 2011; 43:1232-1236; Nature Genetics 2013; 45:1366-1370. In this study, we determined the independent effects of the new rare C3 variant on conversion from the early and intermediate forms to the advanced stages of AMD, and the impact on our algorithms for predictive modeling.

Methods: Participants included 2,137 non-progressors and 840 progressors followed over 12 years. New rare genetic loci including a mutation in C3 were assessed for their independent effects on progression to neovascular disease or geographic atrophy using Cox proportional hazards model, controlling for established common genetic loci and demographic, behavioral and macular characteristics. The contribution of genes to risk models was assessed using AUC statistics and reclassification analyses.

Results: The rare C3 variant was independently associated with conversion to advanced stages of AMD, controlling for age, gender, education, body mass index, smoking, baseline AMD severity, macular drusen status and common AMD genetic loci with a hazards ration (HR) of 1.7, P=.002. A model with the new rare genetic loci in CFH and C3 along with established genetic loci had an AUC of .911 for progression at 10 years. Reclassification analyses suggested an improvement in the model for individuals in the higher risk groups.

Conclusions: The rare C3 genetic variant is independently related to AMD progression. Additional genetic loci enhance accuracy of our predictive models.
**Metabolic Pathways Altered in Neovascular Age-Related Macular Degeneration**

Milam Brantley, Vanderbilt Eye Institute  
Karan Uppal, Department of Medicine, Emory University  
Samantha Williamson, Vanderbilt Eye Institute  
L. Goodwin Burgess, Vanderbilt Eye Institute  
Anita Agarwal, Vanderbilt Eye Institute  
Margaret Pericak-Vance, Hussman Institute of Human Genomics, Miller School of Medicine, University of Miami  
Jonathan Haines, Department of Epidemiology and Biostatistics, Case Western Reserve University  
Dean P. Jones, Department of Medicine, Emory University

**Purpose:** To identify metabolic pathways that are altered in neovascular age-related macular degeneration (NVAMD).

**Methods:** We performed metabolomic analysis using C18 liquid chromatography-Fourier-transform mass spectrometry (LC-FTMS) on frozen plasma samples from 60 NVAMD patients and 117 controls. Data were collected from mass/charge ratio (m/z) 85-2000 on a Thermo LTQ-Orbitrap Velos mass spectrometer, and metabolic features were extracted using an adaptive processing software package with xMSeAnalyzer. Log2 fold change filtering based on k-fold cross-validation accuracy criteria was used to maximize true positives and minimize false positives. The Limma package in R was used to identify differentially expressed metabolites (DEMs). P-values were corrected using Benjamini and Hochberg False Discovery Rate (FDR) to account for multiple testing. Metabolome-wide Spearman correlation was performed for the DEMs using an absolute correlation threshold of 0.4 at FDR of 0.1 to identify top correlated features. DEMs and top correlated features were matched to the Metlin metabolomics database and further analyzed with MetaboAnalyst to identify metabolic pathways most significantly altered in NVAMD.
Results: After data filtering, 8563 m/z features were analyzed. A total of 101 m/z features were found to significantly differ between NVAMD cases and controls using FDR $q=0.1$. Pathway analysis with MetaboAnalyst showed the primary bile acid biosynthesis pathway to be significantly altered in NVAMD ($p=4.73 \times 10^{-12}$), with approximately seven times the number of expected hits seen for this pathway. Many of these hits were putatively matched to molecules in the sterol biosynthesis pathway, the initial phase of primary bile acid synthesis.

Conclusions: Metabolomic analysis can be used to identify individual metabolites that discriminate NVAMD cases from controls, and subsequent pathway analysis can identify the metabolic pathways that are most altered in disease. This analysis corroborates the difference in bile acid levels between NVAMD patients and controls found in our previous study of an independent cohort, and it advances this knowledge by identifying primary bile acid biosynthesis as involved in AMD pathophysiology.

**Thursday – 8:42**

NOTES:
ELEVATION OF SPECIFIC VITREOUS PROTEIN BIOMARKERS OF FIBROSIS AND PROLIFERATION IN A LARGE COHORT OF EYES WITH VISION LOSS DURING THE INITIATION PHASE OF ANTI-VEGF THERAPY FOR WET AMD

Bert Glaser, Bert M. Glaser National Retina Institute

Purpose: The purpose of this study was to assess the difference in the vitreous proteome of wet AMD (wAMD) in eyes that experience vision loss during the initial 3 months of anti-VEGF therapy versus those that gain 5 or more BCVA ETDRS letters.

Methods: A total of 199 eyes with wAMD were followed for at least 12 months. Each patient was evaluated and grouped based on their BCVA ETDRS response to the initial 3 months of anti-VEGF therapy. Two groups were formed for this study, those who lost any ETDRS letters of vision following the first three months of therapy, and those who gained 5 more letters. A total of 943 vitreous aspirates were screened for the presence and abundance of 40 proteins using reverse phase protein microarray technology; 66 patients gained $\geq 5$ letters (number of vitreous samples = 407) and 133 patients lost letters (number of vitreous samples = 536). The 40 pathway proteins screened were picked based on their importance in the key biochemical processes in AMD, including: angiogenesis, proliferation, invasion, apoptosis, inflammation, hypoxia and oxidative stress.

Results: Of the 40 screened proteins, 5 showed a significantly higher mean level of expression in eyes with vision loss secondary to wAMD during the initial 3 months of Anti-VEGF therapy compared to eyes with visual improvement. The proteins that showed significance were TGF-Beta ($P = 0.0005$), VEGFR2 Tyr996 ($P = 0.0020$), PEDF ($P = 0.0052$), ER alpha Ser167 ($P = 0.0059$) and MMP-2 ($P = 0.0250$).
Conclusions: This study demonstrates significant elevation of vitreous protein biomarkers of fibrosis, proliferation, and tissue invasion in eyes that experience vision loss during the initial phase of anti-VEGF treatment compared to those that experience a gain in vision. These results may help to enhance our understanding of why vision loss occurs in patients with wAMD with the potential of developing new vision saving therapies.

Thursday – 8:51
Purpose: To investigate the interactions among multimodal imaging findings and multimodal vision testing in neovascular age-related macular degeneration (AMD).

Methods: Design: Prospective Cross-Sectional Study. Participants: There were 82 eyes of 57 consecutive patients with neovascular AMD examined in a retinal practice. Methods: Each patient underwent multimodal fundus imaging including spectral domain optical coherence tomography (OCT) and fundus autofluorescence imaging, each of which was graded by 2 masked readers. Multimodal vision testing included visual acuity using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol refraction, contrast sensitivity, reading speed, and microperimetry. Main Outcome Measures: Predictors of each modality of vision testing as modeled using generalized estimating equations (GEE).

Results: The mean visual acuity was 61 ETDRS letters (20/63 Snellen equivalent, median 68.5, IRQ 52.8 – 73). GEE modeling showed the significant independent predictors of visual acuity were the area of confluent hypoautofluorescence (P<0.001) and the presence of Type 2 CNV (P<0.001). The significant predictors of reading speed were the area of confluent hypoautofluorescence (P=0.005), the presence of Type 2 CNV (P<0.001), and the size of the defect in the interdigitation zone in the OCT image (P=0.001). The only significant predictor of contrast sensitivity was the size of confluent hypoautofluorescence (P<0.001), which showed an inverse
correlation. A history of smoking (P<0.001), subretinal drusenoid deposit (P=0.015), and the size in the defect in the ellipsoid zone (P<0.001) all were inversely correlated with the microperimetry score.

Conclusions: The data from the visual performance tests have potential impacts on visual rehabilitation strategies and also their predictors suggest possible research avenues for future treatment improvements. Confluent absence of autofluorescence was a highly significant predictor of several modalities of vision testing and serves as an easy parameter to obtain and measure in patients with neovascular AMD. Addressing inherent damage to the retinal pigment epithelium may improve vision outcomes in eyes with neovascular AMD.

*Thursday – 9:00*

NOTES:
Thursday – 9:09

**Effect of Baseline Retinal Pigment Epithelial Elevation Status on Visual Outcomes in the VIEW 1 and VIEW 2 Studies**

*Glenn Jaffe, Duke University Eye Center*

**Purpose:** To determine whether drug and regimen effect on visual acuity (VA) depends on baseline retinal pigment epithelial elevation (RPEE) in VIEW 1 and 2 studies.

**Methods:** 2,457 patients with treatment-naïve neovascular age-related macular degeneration (NVAMD) were randomized to four treatment groups: ranibizumab 0.5mg every 4 weeks (Rq4), intravitreal aflibercept (IAI) 2mg every 4 weeks (2q4), 0.5mg every 4 weeks (0.5q4), and 2mg every 8 weeks (2q8). The 0.5q4 group was not included in these analyses. RPEE definition included serous pigment epithelial detachment (PED) and those due to choroidal neovascular membrane complex or blood components.

**Results:** There were 1,349 patients with known RPEE at baseline: 435, 460, and 455 in Rq4, 2q4 and 2q8, respectively. At baseline, corresponding VA among eyes with RPEE was 54.6, 54.7 and 54.0, and among those without, it was 52.4, 52.4 and 53 ETDRS letters. Effect on VA change over week 52 was dependent on RPEE status at baseline and treatment group. In eyes given 2q4, by week 52, VA improvement and cumulative incidence of eyes gaining > 15 letters, was not significantly different, regardless of baseline RPEE (Relative risk (RR) = 0.96 (95% CI: 0.70, 1.33). In contrast, for both Rq4 and 2q8 groups, at week 52, mean improvement in VA in eyes without baseline RPEE was greater than for those with baseline RPEE, and this difference was statistically similar for Rq4 (4 letters) and 2q8 (2 letters) groups. Cumulative incidence of eyes gaining > 15 letters was also greater for eyes without baseline RPEE compared to those with baseline RPEE [Rq4: RR = 0.70 (95% CI: 0.52: 0.95); 2q8: RR = 0.66 (95% CI: 0.50, 0.90)].
Conclusions: Visual acuity at week 52 depended on presence of baseline RPEE and treatment regimen. IAI 2q4 effectively improved VA in eyes with or without baseline RPEE, while IAI 2q8 and Rq4 had more favorable effect on VA in eyes without baseline RPEE. These data may help inform clinician’s initial treatment regimen choice in eyes with NVAMD.

Thursday – 9:09

NOTES:
GREY HYPER-REFLECTIVE SUBRETINAL LESIONS IN EXUDATIVE AGE-RELATED MACULAR DEGENERATION

Giuseppe Querques, University Paris Est Creteil  
Raphaëlle Ores  
Nathalie Puche  
Rocio Blanco-Garavito  
Benedicte Merle  
Gabriel Coscas, Eye University Clinic, Hospital of Creteil  
Oudy Semoun  
Hassiba Oubraham  
Eric Souied

Purpose: To investigate the effects of ranibizumab on grey hyper-reflective subretinal lesions (GHSL) diagnosed by spectral-domain optical coherence tomography (SD-OCT) in patients with exudative age-related macular degeneration (AMD).

Methods: Retrospective interventional study. Data from 28 consecutive patients affected with exudative AMD that presented GHSL as visualized by SD-OCT were collected. GHSL characteristics were analyzed, before and after intravitreal ranibizumab injection.

Results: Thirty eyes of 28 patients (5 male, 23 female, aged 57-91 years) were included. At study entry, GHSL was associated with SD-OCT exudative features in 24/30 eyes (80%), including subretinal fluid (SRF) in 20/30 eyes (67%), and retinal cysts in 11/30 eyes (37%). Twenty-four eyes with SD-OCT exudative features at study entry received prompt treatment; 6 eyes without SD-OCT exudative features at study entry received deferred treatment (after one-month observation), when SD-OCT exudative signs emerged (SRF in 3/6 eyes, and retinal cysts in 5/6 eyes). Ninety-three percent of the GHSL responded to ranibizumab treatment. GHSL thickness was significantly reduced (from 482±116 µm to 367±102 µm, p<0.0001) after treatment.
Conclusions: Our findings suggest that GHSL might be considered as qualitative criteria for retreatment of exudative AMD. It may represent an early sign of CNV reactivation, and should prompt to early treatment.

NOTES:

Thursday – 9:18
Effect of Aspirin Use on Progression of Age-Related Macular Degeneration

Emily Chew, National Institute of Health
Traci Clemons
Elvira Agron
Michael Klein, Oregon Health & Science University
Frederick Ferris
Barbara Blodi

Purpose: To determine whether aspirin use is associated with the progression of age-related macular degeneration (AMD).

Methods: Participants aged 50 to 85 years, with no geographic atrophy or neovascularization at baseline (N = 2442) enrolled in the Age-Related Eye Disease Study 2 (AREDS2), a multicenter, phase 3, randomized, controlled clinical trial were analyzed. In order to reduce bias from confounding variables, propensity scoring was used to match aspirin users, defined as those individuals taking aspirin at least five times per week, to non-aspirin users. The propensity score for aspirin use was generated using a logistic regression model of baseline characteristics (age, sex, race, education, smoking history, hypertension, diabetes, and angina). Matching participants based upon propensity scores yielded 957 aspirin users and 957 non-aspirin users (N = 1914). Progression of AMD was defined as development of either any geographic atrophy or neovascularization during the study period (2006 – 2012). Proportional hazards regression, adjusted for propensity score and age, was used to evaluate the association between aspirin use and AMD progression.

Results: Aspirin propensity score adjusted for age was not associated with AMD progression (odds ratio [OR] =0.80, 95% confidence interval [CI] =0.41-1.56, P = 0.5076). When outcomes were analyzed individually, neither geographic atrophy (OR =1.31, 95% CI =0.52-3.32, P = 0.5688) nor neovascularization (OR =0.60, 95% CI = 0.23-1.58, P =0.3049) was associated with the aspirin propensity score.
Conclusions: Contrary to previous reports of association of aspirin use with advanced AMD, especially neovascular AMD, observational data from the AREDS2 suggest that the use of aspirin has no statistically significant association with AMD progression. We can reassure our patients with AMD that aspirin could be considered when medically indicated.

Thursday – 9:27

NOTES:
Presentation of the 2014 W. Richard Green Lecture and Award

Hendrik P.N. Scholl, MD, MA
Presented by Morton F. Goldberg, MD
Thursday, February 20, 2014 – 9:36 a.m.

Given for significant contributions to our understanding of the pathogenesis of retinal diseases

Mark O.M. Tso, MD, 2001
Daniel M. Albert, MD, 2002
J. Donald M. Gass, MD, 2004
Hans E. Grossniklaus, MD, 2005
Mark Blumenkranz, MD, 2006
Michael Marmor, MD, 2007
Sohan Hayreh, MD, 2008
Prof. Dr. Anselm Kampik, 2009
Ralph C. Eagle, Jr., MD, 2010
David N. Zacks, MD, 2011
David J. Wilson, MD, 2012
John Sarks, FRCS, FRANZCO 2013
Shirley Sarks, FRCS, FRANZCO, MD, 2013

Hendrik P.N. Scholl, MD, MA, is the Dr. Frieda Derdeyn Bambas Professor of Ophthalmology. He is the director of the Retinal Degenerations Clinic of the Retina Division, Wilmer Eye Institute, and the director of the Visual Neurophysiology Service of the Johns Hopkins Hospital. He is also the co-director of Wilmer’s newly founded Center for STem cells and Ophthalmic Regenerative Medicine (STORM). He received his MD from the Eberhard Karls University of Tuebingen, Germany, and did his residency at the Centre for Ophthalmology, University of Tuebingen. He did his clinical research fellowship at Moorfields Eye Hospital, London, UK. In 2004, he was awarded the Heisenberg-Fellowship of the German Research Foundation for his achievements in the field of macular degeneration and subsequently joined the faculty at the Dept. of Ophthalmology, University of Bonn for five years until he was recruited to the Wilmer Eye Institute in 2010.
Dr. Scholl specializes in medical and surgical management of retinal diseases such as age-related macular degeneration (AMD) and diabetic retinopathy. He has a specific expertise in inherited retinal degenerations and uses the latest diagnostic technology such as electroretinography, microperimetry and high-resolution imaging. Dr. Scholl’s primary research interest relates to visual loss in retinal degenerations and to therapeutic measures in order to rescue vision. In his leadership role of large multi-center clinical studies, he aims to develop better tools to prove therapeutic efficacy for upcoming clinical trials.

Dr. Hendrik Scholl’s work represents an extraordinary advancement in retinal research. He has a specific expertise in inherited retinal and macular degenerations and has published more than 100 peer-reviewed original and review articles, inside and outside the eye literature including Nature, Nature Genetics, Journal of Immunology, PLoS ONE and Progress in Retinal and Eye Research.

Dr. Scholl’s group was the first to show systemic complement activation in AMD and contributed to find that complement-factor-H binds malondialdehyde-epitopes and protects from oxidative stress. Those findings have already contributed to ongoing clinical trials in AMD targeting the complement system and may well result in further preventive and therapeutic strategies. Dr. Scholl is internationally recognized for his innovative work as a clinician scientist.
THE HOME MONITORING OF THE EYE (HOME) STUDY: PRIMARY FINDINGS

Michael Elman, Elman Retina Group, P.A.

Purpose: To determine whether home monitoring with the ForeseeHome device (Notal Vision Ltd, Tel Aviv, Israel), using macular visual field testing with hyperacuity techniques and telemonitoring, results in earlier detection of age-related macular degeneration–associated choroidal neovascularization (CNV), reflected in better visual acuity, when compared with standard care. The main predictor of treatment outcome from anti-vascular endothelial growth factor (VEGF) agents is the visual acuity at the time of CNV treatment.

Methods: 1,970 participants age 53 to 90 years at high risk of CNV developing were screened. Of these, 1520 participants with a mean age of 72.5 years were enrolled in the HOME study at 44 AREDS 2 clinical centers. In the standard care and device arms arm, investigator-specific instructions were provided for self-monitoring vision at home followed by report of new symptoms to the clinic. In the device arm, the device was provided with recommendations for daily testing. The device monitoring center received test results and reported changes to the clinical centers, which contacted participants for examination. The main outcome measure was the difference in best-corrected visual acuity scores between baseline and detection of CNV as determined by investigators clinically.

Results: 763 participants were randomized to device monitoring and 757 to standard care and were followed up for a mean of 1.4 years between July 2010 and December 2013. At the prespecified interim analysis, 82 participants progressed to CNV, 51 in the device arm and 31 in the standard care arm. The primary analysis achieved statistical significance, with the participants in the device arm demonstrating a smaller decline in visual acuity with fewer letters lost from baseline to CNV detection (median, -4 letters; interquartile range [IQR], -11.0 to -1.0 letters) compared with standard care (median, -9
RESULTS CONTINUED

letters; IQR, -14.0 to -4.0 letters; P = 0.021), resulting in better visual acuity at CNV detection in the device arm. The Data and Safety Monitoring Committee recommended early study termination for efficacy.

Conclusions: Persons at high risk for CNV developing benefit from the home monitoring strategy for earlier detection of CNV development, which increases the likelihood of better visual acuity results after intravitreal anti-VEGF therapy.

Thursday – 9:54

NOTES:
Thursday – 10:03

**The HOME Study: Lesion Characteristics of Early CNV**

*David Brown, Retina Consultants of Houston*

**Purpose:** Use of the ForeseeHome plus standard care monitoring in people at high risk of AMD progression has been demonstrated to detect choroidal neovascularization (CNV) earlier than standard care monitoring alone. The purpose of this presentation is to describe clinical features of early (CNV) as determined by a reading center based on fluorescein angiography (FA) and optical coherence tomography (OCT).

**Methods:** A comparative analysis of FA and OCT images graded by masked readers centrally in all CNV events (study endpoint as determined by the clinical investigators) diagnosed during the HOME study was performed. Comparisons were made for 3 categories: 1) all CNV cases as determined by the investigator, 2) cases confirmed by FA and/or OCT and 3) cases confirmed by FA only.

**Results:** The investigators diagnosed 82 CNV events as of April 2, 2013. For the first category, median and mean (SD) lesion size (disc areas [DA]) were 0.0 and 0.53 (0.97), (n=47) in the device arm compared to 0.7, 1.46 (2.53), (n=23) in the control arm, (p=0.01), with median change in VA from baseline of -4 and -9 letters respectively (p=0.021). For the second category, median and mean (SD) lesion size were 0.23 and 0.64 (1.04), (n=39) in the device arm compared to 0.7, 1.46 (2.53), (n=23) in the control arm (p=0.05), with median change in VA from baseline of -4 and -10 letters respectively (p=0.008). For the third category, the median and mean lesion size were 0.69 and 1.09 (1.16), (n=23) in the device arm compared to 0.99, 1.77 (2.69), (n=19) in the control arm, (p=0.31), with median reduction in VA from baseline of 4 and 12 letters, respectively (p=0.006).
Conclusions: More favorable vision outcomes following anti-VEGF therapy of CNV lesions have been associated with small CNV lesions relative to larger lesions. The ForeseeHome enables the detection of CNV when lesion size is very small and with good VA thus increasing the likelihood of better visual outcomes following treatment.

Thursday – 10:03

NOTES:
WHAT DOES EARLY EXUDATIVE AMD LOOK LIKE?

Nancy Holekamp, Barnes Retina Institute
Michael Elman, Elman Retina Group, P.A.
Howard Fine, Robert Wood Johnson Medical School

Purpose: The ForeseeHome device has been validated in a prospective clinical trial for early detection of exudative age-related macular degeneration (AMD). The purpose of this presentation is to examine and describe clinical features of early choroidal neovascularization (CNV) as detected by the ForeseeHome device.

Methods: A retrospective review of cases in which exudative AMD was detected by the ForeseeHome device.

Results: Four cases in which early CNV in AMD was detected by the ForeseeHome device were examined. In all four cases visual acuity was excellent, ranging from 20/16 to 20/30. In 3 of the 4 cases, patients were asymptomatic. In all four cases, OCT showed no evidence of fluid. In 3 of 4 cases, there was evidence of mild leakage on fluorescein angiography (FA). In two of the patients, after the ForeseeHome alert no treatment was given initially. Two-week follow-up confirmed progressive clinical evidence of CNV and anti-VEGF treatment was started. In two cases, anti-VEGF treatment was given at the time of the ForeseeHome alert. Both patients required only 3 anti-VEGF injections to stop the exudation. All patients retained excellent visual acuity.

Conclusions: The ForeseeHome device detects exudative AMD at an extremely early stage. After closely examining a small number of cases of CNV detected by the ForeseeHome device, the following observations were made: Early exudative AMD may be asymptomatic. Early exudative AMD may not be apparent on OCT. Early exudative AMD may be subtle on FA. Early exudative AMD may respond well to a limited number of injections with preservation of excellent vision. Analysis of a larger number of cases of early CNV detected by the ForeseeHome device is warranted.
THE PATTERN OF ANTI-VEGF USE IN NEOVASCULAR MACULAR DEGENERATION: A U.S. CLAIMS ANALYSIS

Pravin Dugel, Retinal Consultants of AZ, Ltd.
Szilard Kiss, Weill Cornell Medical College
Kathleen Wilson, Truven Health Analytics
Alice Huang, Truven Health Analytics
David Smith, Truven Health Analytics
Helen Varker, Truven Health Analytics
Stephen Johnston, Truven Health Analytics
Adam Turpcu, Genentech, Inc.

Purpose: To compare the number of first-line intravitreal (ITV) anti-VEGF injections and associated costs in patients treated with aflibercept (AFB) or ranibizumab (RBZ) for neovascular age-related macular degeneration (AMD).

Methods: Retrospective cohort study based on US claims data. Included patients had initiated first-line ITV anti-VEGF treatment with RBZ or AFB (index date) from November 18, 2011 to July 31, 2013, were aged ≥18 y on the index date, had ≥12 mo continuous insurance prior to index date (baseline period), were diagnosed with AMD during the baseline period or on the index date (ICD-9-CM 362.52), and had at least 6 or 12 mo of follow-up enrollment post index date without switching to a different anti-VEGF agent. Outcomes assessed within the 6- and 12-mo follow-ups included the number of anti-VEGF injections and their associated costs. Multivariable regressions compared outcomes for AFB vs RBZ, adjusting for patient demographics, baseline comorbidities, treatments, and general health status indices.

Results: In total, 486 AFB patients and 1,329 RBZ patients had at least 6-mo of follow-up data (134 vs 571, respectively, in 12-mo analyses). Mean [SD] number of injections was similar for AFB and RBZ recipients at 6 mo (3.8 [1.5] vs 3.9 [1.9], respectively) and 12 mo (5.4 [2.9] vs 5.7 [3.7], respectively). Similarly, mean anti-VEGF therapy-related costs were comparable for
RESULTS CONTINUED

AFB and RBZ recipients at 6 mo ($7244 [$4208] vs $7858 [$4805], respectively) and 12 mo ($11,046 [$6853] vs $11,417.81 [$8731], respectively). Multivariable regression determined that, over the first 6- and 12-mo post index date, neither the number or costs of injections differed significantly between AFB and RBZ patients (treating RBZ as reference: Incidence Rate Ratio [IRR]=0.97, 95% confidence interval [CI]=0.92-1.02, P=0.224 [6 mo]; IRR=0.93, 95% CI=0.82-1.05, P=0.224 [12 mo]; Cost Ratio [CR]=0.96, 95% CI=0.90-1.02, P=0.212 [6 mo]; CR=0.91, 95% CI=0.80-1.05, P=0.182 [12 mo]). The overall mean days between injections differed by 2.9 days between the AFB and RBZ patients (44.8 and 41.9, respectively).

Conclusions: In this claims analysis of AMD patients initiating first-line anti-VEGF treatment, injection frequency, days between injections, and healthcare costs over 6 and 12 mo did not differ significantly between AFB and RBZ treatments. Although further follow-up is warranted, this initial analysis suggests AMD treatment patterns for AFB and RBZ in a real-world setting are similar.

Thursday – 10:21

NOTES:
Switch-Over from PRN to Treat and Extend in Exudative AMD: 1 Year Results from a Clinical Case Series

Christian Prüente
Bianca Gerendas, Medical University of Vienna
Katja Hatz, Vista Klinik

Purpose: To evaluate the differences of a pro re nata (PRN) treatment regimen and a treat and extend (T&E) regimen with intravitreal ranibizumab in neovascular age-related macular degeneration (AMD) in a clinical routine setting.

Methods: In a retrospective, consecutive, interventional case series results of 146 eyes switched from a PRN regimen to a T&E regimen with intravitreal ranibizumab for neovascular AMD were analyzed. PRN treatment was based on monthly BCVA and optical coherence tomography (OCT) evaluation. Retreatment was applied in case of reoccurrence of intra- or subretinal fluid, hemorrhages or loss of vision due to lesion activity. In 2012 all eyes with disease activity were consecutively transferred to a T&E regimen. Visit intervals were sequentially lengthened by 2 weeks when no lesion activity was present. Injections were given at each visit. If lesion activity recurred the interval was reduced. Evaluation was performed with respect to visual outcome, course of BCVA and frequency of injections and visits.

Results: After changing from PRN to T&E mean Snellen VA continuously improved from 20/42 (0.47±0.22) at baseline to 20/36 (0.55±0.23) at 1 year follow-up. The proportion of eyes that lost any VA during T&E was 1.6%. During the PRN maintenance phase (after 3 monthly loading doses) mean VA dropped from 20/36 (month 3; 0.56±0.21) to 20/42 (0.47±0.22) at last PRN follow-up (baseline T&E). Mean fluctuation of BCVA during the maintenance phase was significantly higher for the PRN regimen (0.30±0.17) compared to T&E (0.10±0.09). The mean number of injections/month was 0.47 (PRN) and 0.76 (T&E),
RESULTS CONTINUED

respectively. The mean visit and thus treatment interval for the T&E regimen 7.07±2.28 weeks. The mean number of visits was 1.10±0.10 vs. 0.76±0.17 (including baseline and exit visit) respectively.

Conclusions:  In a switch-over group from a PRN to a T&E regimen in eyes with neovascular AMD visual stabilization during the maintenance phase was significantly better for the T&E period resulting in more better visual outcome and less visits but more injections.

Thursday – 10:30

NOTES:
Purpose: To characterize patients who achieved a Snellen visual acuity (VA) equivalent of 20/40 or better within the phase III HARBOR trial of wet age-related macular degeneration (AMD) and to compare the differences among patients who achieved this important milestone earlier vs later during treatment with ranibizumab 0.5 mg or 2.0 mg administered monthly or as-needed (PRN) for 24 months. To evaluate baseline visual and anatomic predictors of delayed 20/40 achievers.

Methods: Within the HARBOR trial, patients who attained 20/40 or better VA at month (M) 3 (early 20/40 achievers; n=334, 36.7%) and those who did not achieve 20/40 VA at M3 but did at M12 (delayed 20/40 achievers; n=102, 12.1%) were identified. Patients with 20/40 or better VA at baseline (n=151) were excluded from this analysis. The 20/40 Snellen threshold identified a patient population that differed compared to ≥15-letter gainers, especially in the delayed 20/40 achievers (overlap: early, ~68%; delayed, ~30%). Baseline characteristics including VA (ETDRS Best-Corrected VA) and anatomic outcomes through M24 were evaluated.

Results: The proportion of early 20/40 achievers in each arm of HARBOR was 40.5% (0.5 mg monthly), 36.5% (0.5 mg PRN), 35.3% (2.0 mg monthly), and 34.5% (2.0 mg PRN); the proportion of delayed 20/40 achievers was 12.3%, 12.0%, 12.6%, and 11.3%, respectively. Early 20/40 achievers experienced mean VA gains (letters) from baseline that plateaued at M3 (+16.4) and were maintained through M12 (+16.9) and M24 (+16.1). Delayed 20/40 achievers experienced slower initial mean VA gains (letters) through M3 (+8.1) and
mean VA improvement did not peak or plateau until M12 (+20.0) and were subsequently maintained through M24 (+18.0). Compared with early achievers, delayed 20/40 achievers had, on average, significantly lower baseline VA (58.9 vs 53.4 letters, respectively; P<0.0001), significantly larger baseline total choroidal neovascular (CNV) area (2.72 vs 3.47 disc areas [DA], respectively; P=0.0007), and significantly larger baseline total lesion area (2.82 vs 3.60 DA, respectively; P=0.0006).

Conclusions: Within HARBOR, 12.1% of wet AMD patients who did not achieve 20/40 VA at M3 did achieve this milestone at M12. These delayed 20/40 achievers are more likely to have worse baseline VA and larger CNV lesions compared to early 20/40 achievers. In delayed 20/40 achievers, mean VA gain plateaued at M12, and VA gains for both early and delayed 20/40 achievers were sustained through M24.

Thursday – 10:39

NOTES:
Purpose: Among 297 participants with wet AMD assigned to discontinuous anti-VEGF treatment using ranibizumab or bevacizumab in the IVAN trial, we sought to quantify associations between (1) lesion area and activity with baseline visual function, and lesion characteristics and visual function with (2) reading 68 ETDRS or more at the last visit, (3) time to lesion reactivation after initial 3 injections and (4) the need for 3 or fewer injections/year.

Methods: Wet AMD lesions at baseline line were classified as more (presence of haemorrhage or classic CNV) or less active and by quartile of lesion area. Predictors investigated (all available after initial 3 injections) were: lesion characteristics and ETDRS distance acuity, logMAR near visual acuity (NVA) and Pelli-Robson contrast sensitivity (CS) at baseline and 3 months. Data were analysed by multiple linear, logistic or Cox regression, using the likelihood ratio test to optimize model fit.

Results: More active (-9.4 letters, 95%CI -12.7 to -6.1, p<0.0001) and larger lesions (-1.6 letter per quartile, 95%CI -3.0 to -0.1, p=0.03) were independently associated with reading fewer ETDRS letters at baseline; similar associations were observed for NVA and CS. ETDRS letters read at baseline and 3 months independently predicted reading 68 ETDRS or more at the last visit (pseudo r² = 0.34, p<0.0001). Median (95% CI 44% to 56%) time to lesion reactivation was 78 days. Larger lesion area (but not activity) and worst quartile of ETDRS letters at baseline predicted longer time to lesion reactivation (p<0.002). Lesion area and NVA at baseline were the best independent predictors of needing 3 or fewer injections/year.
but the model fitted poorly (pseudo $r^2 = 0.04$, p=0.04) and neither association was linear.

Conclusions: Participants presenting with larger and more active lesions had worse baseline visual function. ETDRS letters read at baseline and 3 months, but not lesion characteristics, predicted good ETDRS outcome. The factors investigated were unable to predict the need for few injections.

Thursday – 10:48

NOTES:
Purpose: To evaluate the effects of switching from bevacizumab or ranibizumab to aflibercept in eyes with neovascular AMD requiring frequent retreatment every 4 to 6 weeks.

Methods: A retrospective review was performed on patients with neovascular AMD undergoing anti-VEGF therapy for at least one year with persistent or recurrent macular fluid requiring retreatment every 4 to 6 weeks with intravitreal bevacizumab or ranibizumab prior to the switch to intravitreal aflibercept. Patients were followed for a minimum of 6 months after the switch. All patients were treated using a treat-and-extend strategy, and the treatment interval immediately after the switch was the same as the interval immediately before the switch. Best-corrected visual acuity (BCVA), number of injections, and SDOCT imaging measurements were collected.

Results: A total of 73 eyes of 65 patients with neovascular AMD met the inclusion criteria during the study period. The mean duration of anti-VEGF therapy prior to the first aflibercept injection was 44.9 months (range 13.8-104.7). The mean number of total injections was 30.7 for the entire treatment period prior to the switch and 9.8 for the 12 months prior to the switch. The average number of anti-VEGF injections was reduced by 0.59 during the 6 months after the first aflibercept injection compared with the 6 months prior to the first
RESULTS CONTINUED

Aflibercept injection (p<0.001). BCVA increased by 0.5 letters during the 6 months after the switch to aflibercept, which was not statistically different from the 0.9 letter increase during the 6 months before the switch to aflibercept (p=0.78). Central retinal thickness did improve from 257.6 microns to 239.0 microns during the 6 months after the switch to aflibercept (p<0.001). Sixty-nine of the 73 eyes had vascularized retinal pigment epithelial detachments (PEDs). The change in PED cube-root volume 6 months after the switch to aflibercept was statistically significant (-0.08 mm, p<0.001) compared with the change in PED volume 6 months before the switch (-0.02 mm, p=0.19).

Conclusions: The mean number of injections, PED volume, and central retinal thickness measurement decreased significantly following the switch to aflibercept in eyes undergoing frequent reinjection using a treat-and-extend treatment strategy, but the BCVA did not change.

Thursday – 10:57

NOTES:
SHORT TERM OUTCOMES OF AFlIBERCEPT CONVERSION THERAPY FOR EXUDATIVE AGE-RELATED MACULAR DEGENERATION IN EYES PREVIOUSLY TREATED WITH BEVACIZUMAB, RANIBIZUMAB OR BOTH

Anat Loewenstein, Tel Aviv Medical Center
Michaella Goldstein, Tel Aviv Medical Center
Eyal Cohen

Purpose: Preliminary evaluation of intravitreal aflibercept treatment for refractory or recurrent exudative age-related macular degeneration (AMD) in patients previously treated with bevacizumab/ranibizumab.

Methods: A retrospective chart review included patients with exudative AMD and choroidal neovascularization (CNV) who had been previously treated with bevacizumab, ranibizumab or both, and were converted to aflibercept therapy due to refractory or recurrent disease. Demographic data, treatment history, visual acuity (VA), central macular thickness (CMT) on spectral-domain optical coherence tomography (SD OCT) and complications were collected.

Results: Thirteen eyes (12 patients, 4 male, 8 female, mean age 70 years [range 50-88]) were included in the study. All eyes received a mean of 24.3 bevacizumab/ranibizumab injections previously and 4.7 aflibercept injections (range 3-6) following the switch. Mean follow up from first aflibercept injection was 28.7 weeks. Mean VA was 20/100-3 prior to conversion, and was unchanged at the end of the follow up. Subgroup analysis showed that patients with shorter disease duration (less than 12 months prior to conversion) had an improvement in vision following the conversion from a mean of 20/63 before conversion, to 20/40 at the end of follow up post conversion. Mean CMT was 458 µm before the first aflibercept injection improving significantly to 371µm (P=0.034) at last follow up. An increase in blood pressure occurred in 1 patient 1 day later.
following the first aflibercept injection. This increase in blood pressure was a one time event and did not recur following repeated injections.

Conclusions: Conversion to aflibercept in cases of neovascular AMD, either recurrent or non-responsive to bevacizumab/ranibizumab may result in stabilization of visual acuity stabilization and improving the anatomic outcome, especially in patients with shorter disease duration.

Thursday – 11:06

NOTES:
**SYSTEMATIC REVIEW OF SAFETY ACROSS THE PHASE II AND III CLINICAL TRIALS OF INTRAVITREAL AFLIBERCEPT INJECTION**

*Peter Kaiser, Cole Eye Clinic, Cleveland Clinic*

**Purpose:** To perform a systematic review of selected ocular and systemic adverse events pooled from randomized, controlled, multicenter clinical trials of intravitreal aflibercept injection (IAI) across three indications (neovascular age-related macular degeneration (AMD), macular edema following central retinal vein occlusion (CRVO), and diabetic macular edema (DME)).

**Methods:** The safety analysis included patients from eight clinical trials across three retinal diseases: AMD (CLEAR-IT 2, VIEW 1, VIEW 2); CRVO (COPERNICUS, GALILEO); DME (DAVINCI, VIVID, VISTA). Rates (number of events/person-years at risk) for ocular and systemic events of interest were analyzed. Different time periods are analyzed to account for the variability in dosing and comparators in the different trials.

**Results:** Over 3900 patients were included in the analyses. Overall, the rates of adverse events studied were low. Findings for both ocular and systemic adverse events were consistent for all three indications (AMD, CRVO and DME). For ocular events of intraocular inflammation and endophthalmitis, there were no significant differences between rates for IAI and comparators or between fixed and alternative dosing. Similarly, for systemic safety events such as death, adjudicated Antiplatelet Trialists’ Collaboration-defined arterial thromboembolic events, and wound-healing complication adverse events, no significant differences were observed in the different comparators or treatment groups.
RESULTS CONTINUED

Conclusions: This systematic review indicates that the selected ocular and systemic adverse events of interest were low, and suggests that IAI was generally well tolerated in a large population of patients with various retinal diseases.

Thursday – 11:15

NOTES:
Pharmacokinetic Profile of Intraocular Aflibercept in Patients Receiving Intravitreal Aflibercept Therapy for Neovascular Age-Related Macular Degeneration

Clement Chan, Southern California Desert Retina Consultants and Inland Retina Consultants
Carsten Meyer, Pallas Klinik
Zengping Liu, Universitäts-Augenklinik Bonn
Tim Krohne, University of Bonn

Purpose: There is a lack of studies on intraocular pharmacokinetics of aflibercept in human eyes. This study investigates the pharmacokinetics after intravitreal injections of 2.0 mg aflibercept for treatment of patients with neovascular age-related macular degeneration.

Methods: A short 27-gauge needle connected to a tuberculin syringe with a plunger was used to retrieve 0.10 to 0.25 mL of aqueous via a limbal paracentesis immediately prior to each intravitreal 2.0 mg aflibercept injection for treatment of neovascular AMD. A syringe with specimen was immediately capped, taped, and stored in a freezer at -80-degree Celsius. Batches of specimens frozen in dry ice were shipped to the University of Bonn for analysis. Each specimen was diluted in phosphate buffered saline (PBS) for enzyme-link immunosorbent assay (ELISA) for analysis of vascular endothelial growth factor (VEGF) and free-aflibercept levels, after appropriate calibration.

Results: Twenty-nine specimens were retrieved from 11 patients (8 women, 3 men). Ages ranged from 76 to 89 (mean: 83.1). The best-spectacle corrected visual acuity ranged from 20/25 to 20/500 (median: 20/60). All but one eye had PCIOL. The interval from last injection to specimen retrieval ranged from 0 to 69 days (median: 37.5 days). Only 3 naïve eyes had VEGF levels ≥ 9 pg/mL (9.26, and 74 pg/mL). Marked VEGF
suppression was noted for all non-naïve eyes up til 69 days from last injection, with VEGF levels ≤ 10 pg/mL in 23 specimens, and between 10 and 20 pg/ml in 3 specimens (obtained ≥ 50 days). Results are consistent with mathematical model predicting suppression of intraocular VEGF level for 72 days after a single aflibercept injection (M Stewart). This is in contrast to 27-38 days for bevacizumab and 36.4 days for ranibizumab (Muether et al) in VEGF-binding after a single injection. There were very low unbound aflibercept levels at all time points tested, consistent with a relatively short intraocular half-life predicted by the mathematical model (7.1 days).

Conclusions: A single Intravitreal injection of 2.0 mg aflibercept results in marked VEGF suppression for at least 70 days. Further investigation will detect the upper boundary in duration of suppression. This information is highly relevant for clinicians treating patients with neovascular AMD.

Thursday – 11:24

NOTES:
**SYSTEMIC PHARMACOKINETICS FOLLOWING INTRAVITREAL INJECTIONS OF RANIBIZUMAB, BEVACIZUMAB OR AFLIBERCEPT IN PATIENTS WITH NEOVASCULAR AMD OR DME**

*Robert Avery, California Retina Consultants*

*Alessandro Castellarin*

*Nathan Steinle*

*Dilsher Dhoot*

*Dante Pieramici, California Retina Consultants*

*Robert See*

*Stephen Couvillion*

*Ma’an Nasir*

*Melvin Rabena*

*Kha Le, Genentech, Inc.*

*Jennifer Visich*

*Mauricio Maia*

**Purpose:** The objective of this study was to compare the systemic pharmacokinetics (PK) of the anti-vascular endothelial growth factor (VEGF) therapies, intravitreal (IVT) ranibizumab (RBZ), IVT bevacizumab (BEV) and IVT aflibercept (AFB), and evaluate differences in plasma free-VEGF concentrations in patients with neovascular age-related macular degeneration (AMD) or diabetic macula edema (DME).

**Methods:** Study included 45 patients with neovascular AMD and 45 patients with DME, with 15 patients receiving each anti-VEGF agent per disease state (n=90). All patients were naïve to anti-VEGF therapy or had not received anti-VEGF therapy during previous 4 months. Each participant received 3 monthly IVT injections of RBZ 0.5 mg or 0.3 mg, BEV 1.25 mg, or AFB 2.0 mg. Enzyme-linked immunosorbent assays (ELISA) were used to measure anti-VEGF agent concentrations in serum samples collected at screening, 3 hours, 1, 3, 7 and 28 days following the first and third doses. Outcome measures also included systemic plasma free-VEGF.
Results: In AMD patients, systemic exposure of RBZ was similar between doses 1 and 3, while that of BEV and AFB following dose 3 increased, compared to dose 1, by 63% and 40%, respectively. Also, systemic exposure of BEV and AFB were significantly higher than that of RBZ (AUC in AFT-treated and in BEV-treated patients ranged 10-13x higher, and 38-62x higher, respectively, compared to the AUC in RBZ-treated patients. While systemic concentration of RBZ in AMD patients remained below its IC50 (0.06 nM) at most observed time points, systemic levels of AFB were above its IC50 (0.068 nM) at most time points tested, and systemic levels of BEV were above its IC50 (0.668 nM) at most time points following dose 3. In agreement with the systemic concentrations of the three anti-VEGF agents, levels of free systemic VEGF showed only a minor drop in plasma free-VEGF throughout the treatment period with RBZ IVT injections, while measured plasma free-VEGF was substantially lower than baseline following IVT BEV or AFB injections. The systemic exposure of BEV and RBZ in DME patients was found to be similar to that observed for AMD patients. Systemic exposure data for AFB in DME patients will also be presented.

Conclusions: In AMD patients, systemic drug concentrations of BEV and AFB, following IVT injection, reached levels greater than their reported IC50 values for VEGF inhibition, and resulted in higher systemic exposure and lower systemic free VEGF levels than observed with IVT RBZ. These observations may provide a rationale for the differences in systemic serious adverse events reported between anti-VEGF agents in certain comparative studies.

Thursday – 11:33

NOTES:
Purpose: To ascertain the annual, societal, costs associated with neovascular, age-related macular degeneration (AMD).

Methods: Two hundred consecutive patients with neovascular AMD from a multi-state vitreoretinal practice underwent a cross-sectional, prevalence-based, medical economic survey. The direct interview survey quantified the incremental, annual, societal healthcare costs attributable only to vision loss from neovascular AMD. Included were: 1) direct ophthalmic medical, 2) direct non-ophthalmic medical, 3) direct non-medical, and 4) indirect medical costs. A Control Cohort consisted of patients with good vision in the better-seeing eye (20/20-20/25). The Study Cohorts were comprised of four vision-based cohorts – Cohort 1: 20/30-20/50, Cohort 2: 20/60-20/100, Cohort 3: 20/200-20/400, and Cohort 4: 20/800 – no light perception. Vision in the better-seeing eye (vision) was the primary clinical outcome, as were costs measured in U.S. 2009 real dollars. Direct ophthalmic medical costs included those for: providers, facilities, drugs, spectacle/low-vision correction, and medical/surgical interventions. Direct non-ophthalmic medical costs included depression/trauma costs. Direct non-medical costs (caregiver costs), included those for: 1) transportation, 2) activities of daily living, and 3) residence changes. Indirect medical costs included: 1) lost wages and 2) the inability to volunteer.

Results: The mean, incremental, annual, societal, cost for the Control Cohort was $6,116, and in the Study Cohorts 1-4 averaged $39,910 (p=0.000). Study Cohort 1 mean costs were $20,339, while Cohort 4 mean costs averaged $82,984 (p=0.000). Direct, ophthalmic medical costs comprised 17.9% of societal
RESULTS CONTINUED

costs in the Study Cohorts, versus 74.1% in the Control Cohort (p=0.0001). Direct non-medical costs comprised 67.1% of societal costs for Study Cohorts 1-4 and 20.7% for the Control Cohort (p=0.000). Indirect medical costs, respectively, comprised 11.3% and 0.8% of societal costs (p=0.002). Among Study Cohorts 1-4, 27.9% of direct non-medical (caregiver) costs were paid, and 72.1% were unpaid (provided by family or friends), while in the Control Cohort, 3.9% were paid and 96.1% unpaid (p = 0.0001).

Conclusions: The societal healthcare costs associated with neovascular AMD increase dramatically as vision in the better-seeing eye decreases.

Thursday – 11:42

NOTES:
LEAN TRANSFORMATION OF AN INTRAVITREAL INJECTION CLINIC: INCREASING ACCESS AND ENHANCING PATIENT EXPERIENCE

Dennis Han, Medical College of Wisconsin
Ravi Singh, Retina Associates, Kansas City
Kay Mareno
Kay Kastner
Joseph Beringer
Stephen Alper
Aneesh Suneja, FlowOne Lean Consulting, LLC

Purpose: Increased adoption of anti-VEGF therapy for retinal disease has led to a need for greater efficiency in providing intravitreal injections. To this end, we determined if application of Lean principles could improve access and reduce patient total visit length in an academic retina outpatient clinic structured to provide intravitreal injection therapy. The Lean approach, applied originally in the manufacturing realm, attempts to identify and eliminate various forms of waste in a process while preserving value-added steps. It has more recently been applied in healthcare, often focused on improving process flow and decreasing patient wait time, a known correlate of patient satisfaction.

Methods: Personnel resources for the injection clinic consisted of a core team of a receptionist, one physician, two technician-scribes and a photographer (1.0 FTE of each of above). Space/equipment resources consisted of three multifunctional exam rooms and an OCT room. To control for variation in visit length, extended patient consultation visits were scheduled outside the 3.5 hour injection clinic interval prior to process intervention. We mapped the flow of 30 patients. Current state value stream mapping quantified patient wait time, technician cycle time, walking distance and imaging cycle time. From this, a future state value stream map was formulated a priori that predicted a 40-50% reduction in total visit length. Value-added time of brief history taking, VA measurement, IOP check, and physician face-to-face counseling time was preserved. Primary outcome measure was total visit length reduction; secondary outcome measure was capacity for injection visits per 3.5 hour injection clinic interval.
Results: Value stream mapping identified at least 4 major categories of waste: overprocessing (e.g., repetitive data entry and informed consent documentation), waiting (by both staff and patients), motion (patients moving to different activity stations), and underutilization of human resources. Interventions consisted of (1) reduced handoffs (2) reduced walking of patients and staff, (3) rapid access to OCT instrumentation, (4) reduced dependency of process steps, and (5) reduced technician and physician cycle time. A multifunctional device, (the RAVI-Guide, a hybrid caliper-speculum) was designed to increase the speed and comfort of the injection procedure, with a concurrent increase in the amount of time available for physician-patient counseling. After intervention, we observed mean total visit length reduction from 88 minutes to 44 minutes (50%) for patients undergoing OCT and from 45 minutes to 29 minutes (35%) for patients not undergoing OCT. Capacity for injection visits increased from 16 to 21 per 3.5 hour clinic session with preservation of physician-patient face-to-face counseling time. In conjunction with other Lean-transformed standard clinics, the injection clinic was associated with an overall Avatar satisfaction top-box rating of 94% (“strongly agree to recommend this doctor to others”), exceeding the average for our institution.

Conclusions: Application of Lean principles in an intravitreal injection clinic resulted in an increase in patient access, reduced total visit length with preservation of value-added time, and a high level of patient satisfaction, without increased resource expenditure. The forms of waste we identified are universally encountered, indicating widespread potential for benefit of Lean in a variety of retina practice settings.


Thursday – 11:51

NOTES:
FIVE-YEAR RESULTS OF COMBINED TREATMENT FOR POLYPOIDAL CHOROIDAL VASCULOPATHY: VERTEPORFIN PDT AND INTRAVITREAL ANTI-VEGF

Hyung Woo Kwak, Kyung Hee University
Seung-Young Yu, Kyung Hee University Hospital

Purpose: To evaluate the 5-year efficacy of photodynamic therapy (PDT) combined with intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) in patients with polypoidal choroidal vasculopathy (PCV).

Methods: Twenty-seven eyes of 27 patients with symptomatic PCV in treatment naïve eyes followed up for ≥60 months after PDT and anti-VEGF combination therapy were retrospectively reviewed. The patients received intravitreal anti-VEGF (1.25 mg bevacizumab or 0.5 mg ranibizumab) within 7 days after PDT. All clinical data, including baseline characteristics; imaging data from fluorescein angiography, indocyanine green angiography, and optical coherence tomography; presence of recurrence; and best-corrected visual acuity (BCVA) were investigated.

Results: The mean baseline BCVA was 0.67±0.36 logMAR, 0.34±0.28 logMAR at 12 months (p=0.000 vs. baseline) and 0.59±0.49 at 60 months (p=0.197). On the final evaluation at 60 months, the mean BCVA was improved in 11 eyes (40.74%), stable in 8 eyes (29.6%), and decreased in 8 eyes (29.6%). Mean BCVA was significantly improved up to 12 months and then improvement slowly decreased over 60 months. Significant improvement maintained until 36 months (p=0.004). The mean CFT was 346±47.6 at baseline and significantly decreased to 193.4±19.0 at 12 months and the final CFT at 60 months was 231.2±25.1. PDT was administered 2.30±0.71 times and anti-VEGF injected 9.45±1.21 times over the 60-month period. The baseline PED volume showed positive correlation with BCVA change at final visit (p=0.034, r=1.051).
Conclusions: Significant visual improvement by combined PDT and anti-VEGF injection was maintained up to the third year of initial treatment; however, utmost improvement decreased after the first year. After 60 months, 70.4% of PCV patients showed stable or improved BCVA. The baseline PED volume was significantly correlated with long-term visual outcome.

Thursday – 12:00

NOTES:
EXTRAMACULAR FINDINGS IN AGE-RELATED MACULAR DEGENERATION IN JAPANESE PATIENTS

Purpose: To describe the extramacular choroidal and retinal abnormalities in age-related macular degeneration (AMD) in Japanese patients and identify the difference in the two major types of exudative AMD, i.e., typical AMD (tAMD) and polypoidal choroidal vasculopathy (PCV).

Methods: Fifty-two eyes with exudative AMD and twenty-nine control eyes were enrolled in this retrospective observational case series. Swept-Source OCT (SS-OCT) was performed with a TOPCON DRI-OCT (Topcon, Tokyo, Japan) using a custom scan acquisition protocol. The choroidal thickness from 5 regions: 4 mid-peripheral regions, i.e., superior, inferior, nasal and temporal region, each of which are 4.5-papilla-diameter distant from the fovea and the foveal center, was evaluated by manual segmentation. Ultrawidefield pseudocolor retinal imaging and fundus autofluorescence (FAF) was acquired with Optos 200Tx (Optos PLC, Dunfermline, United Kingdom). All color images and FAF were inspected by two independent investigators and the extrafoveal abnormalities were identified in respect to their location.

Results: Foveal choroidal thickness in eyes with PCV, but not in eyes with tAMD, tended to be thicker than that in normal eyes. In eyes with tAMD, the choroidal thickness was not different from the normal eyes. Interestingly, in eyes with PCV, superior and temporal choroid was significantly thicker than normal eyes. The prevalence of pseudocolor and FAF abnormality in AMD was 68 and 75%, compared to 59 and 48% in normal eyes (P>0.05 and P=0.033). Pseudocolor and FAF abnormalities were detected both in the far-periphery and mid-periphery, but mainly located in the midperipheral region both in AMD and normal eyes. There was no difference in the
prevalence of pseudocolor and FAF abnormality between eyes with tAMD and PCV. There was no association of foveal choroidal thickness and the presence of retinal abnormalities.

Conclusions: Imaging of peripheral retina and choroid enables precise assessment of exudative AMD. PCV is associated with widespread thickening of choroid more than was previously considered, and the prevalence of peripheral retinal abnormalities was high in eyes with exudative AMD but was not different between tAMD and PCV.

*Thursday – 12:09*

NOTES:
Purpose: To identify factors associated with the visual acuity outcomes in the study eye after ranibizumab therapy for myopic choroidal neovascularization (CNV) in the REPAIR study.

Methods: This Phase II, prospective, open-label, single arm, multicentre, 12-month study included 65 patients with active primary or recurrent subfoveal or juxtafoveal myopic CNV, with a best-corrected visual acuity (BCVA) score of 24-78 Early Treatment Diabetic Retinopathy Study (ETDRS) letters in the study eye and a diagnosis of high myopia of at least -6 dioptres. They received 0.5 mg ranibizumab administered intravitreally, followed by monthly injections given as needed (based on a predefined algorithm) for up to 11 months. An initial univariate analysis of variance was used to individually evaluate the associations of demographic, baseline visual acuity and macular thickness variables with change from baseline in visual acuity at 12 months in the study eye. Any variable whose univariable F-test has a p-value of <0.20 was considered a potential predictor and entered into a multivariate linear model.

Results: At 12 months the mean change in visual acuity from baseline is 13.8 letters (SD=14.02) with patients receiving a median of 3 injections (IQR 2-5) out of a possible 12. 52.4% of the patients reported a 10 letter gain or more. A univariate ANOVA identified gender (p-value = 0.0829) and baseline visual acuity categorised as < 53 or >= 53 letters (p-value = < 0.0001) as potential predictors of change from baseline in visual acuity at 12 months. The results of fitting the
RESULTS CONTINUED

multivariable model indicate a weaker association for gender when controlling for baseline visual acuity. Therefore, visual acuity at baseline is the only statistically significant (p-value < 0.05) predictor of change in visual acuity at 12 months with worse baseline visual acuity defined as <53 ETDRS letters associated with higher mean visual acuity improvement (23.47; 95% CI (17.88, 29.07) versus 9.68; 95% CI (5.23, 14.14)) (p-value = 0.0003). Baseline macular thickness did not influence visual outcome. However, patients with thinner baseline central retinal thickness defined as <300µm required lesser average number of injections (2.5 vs 4.0) and a higher proportion attained a dry macula at 12 months (85.7% vs 53.2%) than patients with baseline central retinal thickness defined as >=300 µm.

Conclusions: This analysis suggests that baseline visual acuity is a predictor of change in visual acuity at 12 months.

Thursday – 12:18

NOTES:
FLAT IRREGULAR PIGMENT EPITHELIUM DETACHMENT IN CHRONIC CENTRAL SEROUS CHORIORETINOPATHY

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Rabih Hage, Hôpital Lariboisière, Paris
Sarah Mrejen-Uretska
Pascale Massin, Hospital Lariboisière

Purpose: The aim of this study was to determine the incidence of Flat Irregular Pigment Epithelium Detachment (FI PED) in patients with Chronic Central Serous Choroidopathy (CSC) and its possible association with Type 1 Choroidal New vessels (CNV)

Methods: Retrospective study of 110 patients with chronic CSC, examined using Fundus Autofluorescence (FAF), Indocyanine Green Angiography (ICGA) and Spectral domain OCT (SD-OCT) at least once during their follow-up. The records of the 39 patients who presented a FI PED (54 eyes) were analyzed. The diagnosis of CNV or polypoidal choroidal vasculopathy (PCV) was based on the presence of sub or intraretinal hemorrhages, hard exudation, and multimodal macular imaging including early and late frames of SLO ICGA,

Results: The mean patient age was 58.3 years, 74.4% were males, a serous retinal detachment (SRD) was present in the 54 eyes and the choroidal thickness was increased in all cases. FI PED was bilateral in 38.5% of eyes. In 42/54 eyes, FI PED was subfoveal, and it was extrafoveal in 12 cases. In 43/54 eyes, FI PED remained stable for many years without lesion extent (mean symptom duration: 15 years) or was not complicated or did not respond to a trial of anti-VEGF treatment. Eleven eyes with FI PED presented with additional characteristic findings or were highly suspected of type 1 CNV (8) or PCV (3) during their follow-up. In 8/11 cases, early frames of SLO ICGA showed the abnormal pattern of the CNV network. On
ICGA, the late hyperfluorescence was less specific of CNV since it was also present in FI PED not suspected of neovascularization.

Conclusions: Flat irregular PED was frequently observed in a series of chronic CSC patients. It was caused by type 1 CNV, associated or not with PCV in only 20% of cases. The remaining 80% of cases had no complication during the follow-up. We can assume that these cases were not CNV or at least not active CNV and that they did not need a specific treatment. However, we cannot rule out a possible future evolution towards CNV with such a clinical picture.

*Thursday – 12:27*

**NOTES:**
Purpose: To determine whether suppression of the visual cycle is beneficial for macular photoreceptor function in patients with neurosensory detachment from central serous retinopathy (CSR).

Methods: We performed a prospective, single-arm clinical trial of 8 treatment-naïve participants with neurosensory retinal detachments from CSR. A complete eye exam, including visual acuity, optical coherence tomography (OCT), and multifocal electroretinography (mfERG) was performed on day one of the study. The CSR eye was then patched for 24 hours and then dilated and un-patched just prior to repeat mfERG on day two. A repeat OCT and complete eye exam were also performed on day two. The primary outcome measure was the change in mfERG after 24 hours of patching. We analyzed the averaged response density (ARD, measured in nanovolts per square degree of visual field: nV/deg²) for the foveal, peri-foveal, and macular rings. Secondary outcome measures include the change in visual acuity, and OCT central thickness and volume.

Results: The mean ARD for the foveal, peri-foveal, and macular rings were 19.8 nV/deg², 14.9 nV/deg², and 11.73 nV/deg² respectively on day one and 21.63 nV/deg², 13.29 nV/deg², and 9.48 nV/deg² respectively on day two. Although these were not statistically significant by paired t-test analysis (p = 0.78, 0.79, and 0.90 respectively), there was high inter-patient variability in response to patching. The mean best corrected visual acuity was 20/30 on both day one and two. The mean
Results continued

central macular volume was 9.25 mm3 on day one and 9.14 mm3 on day two (p= 0.98). The mean maximum central thickness on OCT was 425 μm on day one and 419 μm on day two (p=0.91).

Conclusions: While the averaged data in this small prospective clinical trial are unable to show a statistically significant improvement in mfERG after 24hrs of patching, four of the eight participants did experience a substantial improvement in their individual mfERGs. This improvement seen in half of the participants suggests that photoreceptor function may benefit from suppression of the visual cycle during 24hrs of patching. Given the availability of visual cycle modulators, a larger prospective trial may help address this potential benefit.

Thursday – 12:36

NOTES:
ADVANTAGES AND LIMITATIONS FOR DIAGNOSIS AND ASSESSMENT OF THERAPY OUTCOME IN CENTRAL SEROUS CHORIORETINOPATHY – CLINICAL APPLICATION OF SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY IN COMBINATION WITH FUNCTIONAL DIAGNOSTICS

Felix Sabates, Sr., University of Missouri Kansas City School of Medicine
Peter Koulen, Vision Research Center
Nelson Sabates, UMKC Vision Research Center
Gary Gallimore, UMKC Vision Research Center
Josh Schliesser
Nancy Kunju

Purpose: Identifying functional and structural parameters of the retina in central serous chorioretinopathy (CSCR) patients the study determined whether a Spectral Domain – Optical Coherence Tomography (SD-OCT) -based diagnosis can be significantly supplemented with functional diagnostic tools, and to what degree the determination of disease severity and therapy outcome can benefit from diagnostics complementary to OCT.

Methods: CSCR patients were evaluated prospectively with microperimetry and SD-OCT to determine retinal sensitivity function, and retinal thickness as outcome measures along with measures of visual acuity. Patients received clinical care that involved pharmacotherapy targeting inflammation or focal laser photocoagulation. Using standard descriptive statistical methods correlative analyses of clinical parameters were performed.

Results: Correlation of clinical parameters with a focus on functional parameters, specifically visual acuity and mean retinal sensitivity, as well as on the structural parameter, mean retinal thickness, showed that functional measures were similar in diagnostic power. A moderate correlation of OCT data with the standard functional assessment of visual acuity, but a
RESULTS CONTINUED

strong correlation of OCT and microperimetry data, however, show that diagnostic measures cannot always be used interchangeably, but that complementary use is of higher clinical value.

Conclusions: The study indicates that integrating SD-OCT with microperimetry provides a more complete diagnosis with high clinical relevance for complex and difficult to quantify diseases such as CSCR.

Thursday – 12:45

NOTES:
Effect of Spironolactone on Central Chronic Serous Chorioretinopathy: A Randomized Controlled Study (CSR)

Francine Bebar-Cohen, Hôpital Ophtalmique Jules Gonin
Min Zabo, Inserm U598
Tâal beydouB, Hotel-Dieu of Paris
Elodie Bousquet, Hotel-Dieu of Paris
Pierre Raphael Rothschild, Inserm U598
Alain Gaudric, Hospital Lariboisiere, University Paris 7
François Chast, Hotel-Dieu of Paris

Purpose: We have shown that retina and choroid are mineralocorticoid targets. Mineralocorticoid receptors (MR) activation by high doses glucocorticoids induced choroid vessels dilatation and leakage in rats, that was prevented by specific MR antagonists. We have hypothesized that MR activation could intervene in chronic central serous chorioretinopathy (CSR).

Methods: Sixteen patients with chronic CSR (> 4 months) were randomized to oral spironolactone (50mg/d) or placebo for 30 days. After 8 days wash-out period, patients were switched to the other treatment (placebo or spironolactone) for 30 days and followed up to 90 days. The primary endpoint was the reduction of sub-macular fluid, measured by thickness and volume from ELM to bruch, or ILM to bruch using segmentation methods. The secondary endpoint was the reduction of macular choroidal thickness using EDI-OCT. Crossover data were analyzed using the linear mixed effects model framework; Since a strong and asymmetric carry-over effect was present, analysis was made on the first period results only. This analysis was made on the absolute and relative difference between inclusion and day 30. These differences were compared using Student’s T-test or Mann-Whitney test, according to the results of the normality tests for the crossover analysis. Difference between the two groups was considered significant for p < 0.05.
Results: The differences of geometrical parameters (width, volume of whole, intern or extern retina) were very strongly correlated (> 0.98). Reduction of subretinal fluid was significantly higher in the spironolactone treated group as compared to the placebo treated group, either when measuring the ELM / bruch thickness or volume; and also when comparing the central macular volume. Moreover, the macular choroidal thickness was significantly reduced after spironolactone treatment but not after placebo treatment.

Conclusions: In this prospective randomized controlled study, even if the number of patients is low, the results clearly show a significant effect of spironolactone after 30 days of treatment on macular and choroidal thickness validating the hypothesis that MR is involved in CSR physiopathogenesis. Further larger studies are required to precise the optimal conditions of MR antagonists use in chronic CSCR.

*Thursday – 12:54*

NOTES:
**Presentation of the 2014 J. Donald M. Gass Medal**

*Anita Agarwal, MD*

*Presented by Paul Sternberg, Jr., MD*

*Thursday, February 20, 2014 – 1:03 p.m.*

The J. Donald M. Gass Medal is presented for outstanding contributions in the study of macular diseases

J. Donald M. Gass, MD
W. Richard Green, MD
Stuart Fine, MD, 1995
Gabriel J. Coscas, MD, 1996
Alan Bird, MD, 1997
Lawrence A. Yannuzzi, MD, 1998
Lawrence J. Singerman, MD, 1999
Harvey A. Lincoff, MD, 2001
Evangelos S. Gragoudas, MD, 2002
Neil M. Bressler, MD, 2003
Lee M. Jampol, MD, 2004
Gisèle Soubran, MD, 2005
Emily Y. Chew, MD, 2006
Jerry Shields, MD, 2007
Carmen A. Puliafito, MD 2008
Joan W. Miller, MD, 2009
Alexander J. Brucker, MD, 2010
Janet S. Sunness, 2011
Frederick L. Ferris III, MD, 2012
William F. Mieler, MD, 2013

Dr. Anita Agarwal is an associate professor of ophthalmology at the Vanderbilt Eye Institute. She received ophthalmology residency training at the Postgraduate Institute in Chandigarh, India under the mentorship of Dr. Amod Gupta, and at the University of Florida, Gainesville. This was followed by a medical retina fellowship at Vanderbilt under Dr. J. Donald M. Gass and a vitreoretinal surgical fellowship at West Virginia University under the mentorship of Dr. Lionel Chisholm. She returned to Vanderbilt University as an assistant professor in 1999. There, she worked alongside Dr. Gass, an
opportunity that further enhanced their interaction, and thereby her learning, ultimately taking over his clinical practice.

She is the author of the Fifth Edition of the Gass’ Atlas of Macular Disease, and has co-authored landmark research papers on the genetics of macular degeneration. Her clinical interests include a variety of infectious, inflammatory, degenerative and dystrophic medical retinal disorders. Her research in genetics of AMD is supported by a NEI grant titled ‘Unifying Genetics Epidemiology of Macular Degeneration’, continuously funded since 2000. She is a member of the Macula Society and Retina Society and has been recognized as one of America’s best doctors and top ophthalmologists. She has also received honor awards from the American Academy of Ophthalmology and the American Society of Retina Specialists. She serves on the editorial board of Ophthalmology and Retina Cases and Brief Reports.
HOW COLLEAGUES INFLUENCE OUR REPRESENTATION OF RETINAL ABNORMALITIES

Stephen Russell, The University of Iowa
LuAnn Dvorak, University of Iowa

Purpose: To demonstrate the relationship of variety, beauty and artistic progression of retinal drawings over a three decade span.

Methods: Following IRB approval, over 12,000 fundus drawings made by residents, retina fellows and faculty at the University of Iowa from 1958 to 1990 were evaluated. Of these, 126 were chosen for further analysis based upon representative similarities and differences in artistic character, attractiveness and time period. Images were qualitatively analyzed for style, drawing technique and common stylistic features.

Results: Over multi-year intervals, retinal drawings demonstrated some commonality of overall style, although artists showed numerous differences in individual feature representation. The style of retinal drawings demonstrated a progression from realistic (1950’s and 60’s) to iconic (1970’s) to simplistic/caricature (1980’s).

Conclusions: Despite great differences in the representation of individual fundus features, contemporaneous clusters of faculty and trainees share recognizable artistic styles. Retinal drawings that differ from their period style often demonstrate unique representations of fundus structures that remain rapidly comprehensible and esthetically pleasing.
NOTES:
ANALYSES OF POSTERIOR STAPHYLOMA BY A COMBINATION OF 3D MRI AND ULTRA-WIDE FIELD FUNDUS IMAGING

Kyoko Ohno-Matsui, Tokyo Medical and Dental University
Muka Moriyama

Purpose: Posterior staphyloma is an outpouching of the wall of the eye that has a radius of less than the surrounding curvature of the wall of the eye. Curtin classified the staphyloma into 10 types, however, the classification appears subjective because it is based solely on ophthalmoscopic examination. Thus, we performed 3D MRI analyses of eye shape and determined the presence and types of staphyloma. Morphologic features of the entire fundus obtained by Optos were also evaluated.

Methods: 198 eyes (105 patients) with pathologic myopia were examined both by Optos and 3D MRI. The presence and types of staphyloma were first determined in 3D MRI images of the globe, and then the fundus features by Optos images were analyzed.

Results: The mean axial length of the 198 eyes was 30.0 ± 2.3 mm. 98 eyes (49.5%, 56 patients) had no evident staphyloma by 3D MRI, and the globe had ‘barrel shape.’ In the remaining 100 eyes with staphyloma, the most prevalent type was wide, macular staphyloma (Curtin Type I), and was found in 74 eyes. 3D MRI images showed a protrusion of wide area of the posterior segment, and the most protruded point existed lower to the central axis. The border of the staphyloma showed pigmental abnormalities in Optos images. The second frequent type was narrow, macular staphyloma (Curtin Type II) and it was found in 14 eyes by 3D MRI. 3D MRI images showed a ‘cylinder shape’ and the most protruded point existed along the central axis. Optos images showed pigmentary abnormalities along the edge of staphyloma, however, they were less severe than in the eyes with wide, macular staphyloma. 3D MRI images of other staphylomas were also analyzed.
Conclusions: Even in the severely myopic eyes (mean axial length > 30.0mm), around a half of the eyes did not have evident staphyloma, and the globe was barrel-shaped. Wider staphyloma tended to be deeper, and when the staphyloma became wide, the area lower to the central axis tended to be protruded.

NOTES:
Multimodal Imaging of Ghosts in Geographic Atrophy Areas

Eric Souied, Hospital Intercommunal, University Paris Est
Clemence Bonnet
Hassiba Oubraham
Gabriel Coscas, Eye University Clinic, Hospital of Creteil
Giuseppe Querques, University Paris Est Creteil

Purpose: To describe the multimodal imaging features of lesions identified in areas of geographic atrophy (GA) in age-related macular degeneration (AMD) patients.

Methods: This is a retrospective case series of GA patients harboring lesions in atrophic areas. Multimodal imaging examination including infrared (IR) reflectance, fundus autofluorescence (FAF) and spectral-domain optical coherence tomography (SD-OCT) was performed for each patient. IR and FAF appearance and mean SD-OCT height of the structures in GA were analyzed.

Results: A total of 36 eyes of 25 patients (20 women; mean age 82.3±5.9 years, range 73-92 years) with GA were included. In all eyes, on IR reflectance images, drusen in GA appeared as hyporeflective lesions surrounded by hyporeflective halos, within an area of background hyporeflectivity due to GA. On FAF, drusen in GA appeared as hypoautofluorescent in most cases in 20/36 eyes (55.5%). On SD-OCT, drusen in GA appeared as hyporeflective pyramidal structures (HPS). In 35/36 eyes (97.2%) the center was heterogeneously hyporeflective, whereas the peripheral part of the HPS was hyporeflective in all eyes (100%).

Conclusions: We describe a multimodal imaging of distinctive lesions. Because these HPS appear in GA areas, and because of their pyramidal or dome-shaped aspect on SD-OCT, we suggest the term of “ghosts.”
Fundus Autofluorescence Patterns in Central Serous Chorioretinopathy

Seung-Young Yu, Kyung Hee University Hospital
Hyung Woo Kwak, Kyung Hee University

Purpose: To investigate the patterns and frequency of fundus autofluorescence (FAF) abnormalities in patients with central serous chorioretinopathy (CSC) and evaluate correlation with spectral domain OCT (SD-OCT) findings and BCVA

Methods: Cross-sectional observational study, in which 127 eyes of 119 patients with CSC underwent fundus photography, FAF imaging, fluorescein angiography, indocyanine green angiography, and SD-OCT

Results: Alterations in FAF were classified into 5 patterns: blocked, mottled, hyper, hyper/hypo, and descending tract in order by the length of duration of symptom (P = 0.000). The visual acuity was the best in the blocked AF group (P = .045). Intact inner/outer segment junction on SD-OCT were most common in the blocked AF group (P = 0.000).

Conclusions: The FAF abnormalities in CSC showed multiple distinct patterns and seem to correlate with duration of symptom and BCVA.
A PILOT QUANTITATIVE STUDY OF TOPOGRAPHIC CORRELATION BETWEEN RETICULAR PSEUDODRUSEN AND THE CHOROIDAL VASCULATURE USING EN-FACE OPTICAL COHERENCE TOMOGRAPHY

Amani Fawzi, Northwestern University, Feinberg School of Medicine
Jonathan Chou, Northwestern University
Dilraj Grewal, Northwestern University

Purpose: To analyze the topographic correlation between reticular pseudodrusen (RPD) visualized on infrared reflectance (IR) and choroidal vasculature using en-face volumetric spectral-domain optical coherence tomography (SD-OCT).

Methods: A masked observer marked individual RPD on IR images using ImageJ (NIH, Bethesda, MD). Using the macular volume scan (Cirrus, Carl Zeiss Meditec Inc, Dublin, CA), the RPE slab function was used to generate a C-scan of the most superficial choroidal vasculature. An independent masked grader created a topographic binary map of the choroidal vasculature by thresholding the en-face image, which was overlaid onto the IR map of RPD. For each IR image, ImageJ was used to generate a random set of dots as “control lesions”.

Results: 17 eyes of 11 patients (78 ± 13.7 years) with RPD were analyzed. The average number of RPD lesions identified on IR images was 414 ± 71.5, of which 49.6 ± 4.3% were located overlying the choroidal vasculature, compared to 45.4 ± 4.0% in controls (p=0.014). 50.4 ± 4.3% of lesions overlay the choroidal stroma, of which 76.5 ± 3.1% were ≤3 pixels from the choroidal vessels. The percentage of RPD lesions located within ≤3 pixels from the choroidal vasculature was significantly greater than the percentage located ≥7 pixels away (p<0.0001). Compared to “controls lesions” (71.6 ± 3.8%), RPD were more likely to be located ≤3 pixels away...
from choroidal vessels (p=0.014). In contrast, control lesions were more likely to be > 7 pixels away from choroidal vessels than RPD (9.1 ± 1.9% vs. 4.8 ± 1.2%, respectively, p=0.002).

Conclusions: Our analysis shows that RPD lesions follow the underlying choroidal vasculature. Approximately half the RPD directly overlay the choroidal vessels and the majority of the remaining lesions were ≤3 pixels from the vessel edge, supporting the hypothesis that RPD may be related to pathologic changes at the choroidal level.

Friday – 8:06

NOTES:
New Insights in Macular Microvascularity using Quantitative Adaptive Optics Scanning Light Ophthalmoscopy

Richard Rosen, New York Eye and Ear Infirmary
Richard Weitz, New York Eye and Ear Infirmary
Moataz Razeen, New York Eye and Ear Infirmary
Alexander Gan, New York Eye and Ear Infirmary
Richard Bavier, New York Eye and Ear Infirmary
Nisbit Shah, New York Eye and Ear Infirmary
Eric Cheang, New York Eye and Ear Infirmary
Chun Liu, New York Eye and Ear Infirmary
Joseph Carroll, Medical College of Wisconsin
Alfredo Dubra, Medical College of Wisconsin
Toco Chui, New York Eye and Ear Infirmary

Purpose: Adaptive Optics Scanning Light Ophthalmoscopy (AOSLO), coupled with fluorescein angiography (FA), is able to resolve dynamic cellular details of human retinal microvasculature in healthy and diseased eyes. Using quantitative image analysis, AOSLO provides a platform for characterizing retinal microvascular changes due to age, onset of disease or response to treatment. Here, we show how foveal avascular zone (FAZ), capillary density and lumen in diabetes (DR), central retinal vein occlusion (CRVO), and sickle cell retinopathy (SCR) are different from those in fellow eyes and/or normal eyes.

Methods: During AOSLO FA imaging, simultaneous reflectance (790 nm) and fluorescence (488 nm) image sequences with 1.75° field of view were stitched together to create microvascular maps of a 6° square region centered on the fovea. AOSLO FA maps were skeletonized and divided into regions of interest (ROIs). Vessel length (mm) and density (mm-1) were then calculated per ROI. For FAZ attribute quantification, the FAZ was delineated manually creating an FAZ layer mask. Based on the masks, FAZ area (mm2), effective diameter (µm, diameter of a uniform circle derived from FAZ area), perimeter (µm) and tortuosity index (TI) were computed.
Results: Comparison of FAZ parameters of area, diameter, and perimeter in normal and vasculopathic eyes showed large variations, with CRVO eyes having highest values followed by SCR, DR, and controls. Tortuosity Index (TI), however, was highest in DR eyes followed by SCR, CRVO and controls. All 3 CRVO fellow eyes showed capillary dropout near the FAZ with significant decrease in vessel length and density compared to control eyes. FAZ mean capillary lumen diameter for early diabetic subjects was found to be 35% larger than that of the control subjects.

Conclusions: Quantification of the microvascular geometry utilizing AOSLO in vivo microscopy shows significant potential for studying complex clinical questions involving retinal vascular diseases. This approach may help direct therapeutic interventions based upon fine numerical distinctions as opposed to clinical impressions derived from conventional clinical imaging modalities.

Friday – 8:15

NOTES:
**Microaneurysm Features on Adaptive Optics Scanning Laser Ophthalmoscopy are Associated with Fluorescein Leakage and Surrounding Retinal Neural Pathology in Diabetes**

*Jennifer Sun, Joslin Diabetes Center*  
*Jan Lammer, Joslin Diabetes Center*  
*Paolo Silva, Joslin Diabetes Center*  
*Lloyd Paul Aiello, Beetham Eye Institute*

**Purpose:** To utilize adaptive optics scanning laser ophthalmoscopy (AOSLO) to define characteristics of microaneurysms (MAs) in diabetic eyes that are highly associated with fluorescein leakage and surrounding local retinal neural pathology.

**Methods:** Images of macular MAs in diabetic eyes were acquired by AOSLO confocal and pinhole aperture offset techniques in blocks of 50 frames (30 frames/sec). Dewarping, image averaging and automatic registration/alignment were performed. MA dimension, wall reflectivity and deformability, and perfusion pattern were assessed on dynamic and static images. Some eyes also underwent spectral domain optical coherence tomography (SDOCT) with substacks of 5 B-scans graded within a 500µm box centered on each MA for neural pathology including inner layer disorganization, outer layer disruption, cysts, hyperreflective foci and subretinal fluid. Fluorescein angiography (FA) evaluated MA leakage in a small subset.

**Results:** Images of macular MAs in diabetic eyes were acquired by AOSLO confocal and pinhole aperture offset techniques in blocks of 50 frames (30 frames/sec). Dewarping, image averaging and automatic registration/alignment were performed. MA dimension, wall reflectivity and deformability, and perfusion pattern were assessed on dynamic and static images. Some eyes also underwent spectral domain optical coherence tomography (SDOCT) with substacks of 5 B-scans.
RESULTS CONTINUED

graded within a 500µm box centered on each MA for neural pathology including inner layer disorganization, outer layer disruption, cysts, hyperreflective foci and subretinal fluid. Fluorescein angiography (FA) evaluated MA leakage in a small subset.

Conclusions: Ultrahigh resolution AOSLO imaging identifies MA wall parameters such as deformability and hyperreflectivity that are associated with diabetic vascular permeability and local neural pathology. Future AOSLO studies may elucidate why some MAs adversely affect local neuroanatomy and subsequent visual outcomes while others do not. Such findings might help assess risk, guide treatment, and serve as biomarkers of therapeutic response in the diabetic eye.

Friday – 8:24

NOTES:
Purpose: To characterize the vitreous cytokine, chemokine, and growth factor profiles in patients with increasing retinal ischemia.

Methods: This IRB-approved study retrospectively analyzed 81 undiluted vitreous samples. The specimens underwent a Bio-Plex Pro Human Cytokine Assay to determine the levels of 34 proteins including chemokines, cytokines, non-inflammatory proteins, and growth factors. Specimens were divided into the following four groups based whether the patient underwent: 1) vitrectomy for epiretinal membrane peeling and/or macular hole with no history of diabetes (control group), 2) vitrectomy for epiretinal membrane peeling and/or macular hole with a history of diabetes (DM group), 3) vitrectomy for proliferative diabetic retinopathy (PDR group), and 4) vitrectomy for neovascular glaucoma (NVG group). Parametric and non-parametric analyses were performed using SPSS software comparing demographics, as well as protein levels between each group.

Results: There was no significant difference in age and gender between groups. Numerous proteins were noted to be significantly elevated comparing the control and DM group (G-CSF, sCD40L, Endoglin, IL-6, PlGF, VEGF-D), the DM and PDR group (leptin, IL-8, PlGF, VEGF-A), as well as the DM to NVG group (G-CSF, leptin, TIE-2, sCD40L, EGF, HB-EGF, IL-6, IL-8, PlGF, TNF-alpha). Of note, placental growth factor (PlGF) exhibited a significant increase in all the aforementioned comparisons. Most proteins elevated in the PDR and NVG groups were significantly elevated compared to the control group as well.
Conclusions: Both angioproliferative growth factors as well as inflammatory proteins are elevated in eyes with severe retinal ischemia. We found that vitreous levels of PI GF increase significantly in patients with worsening retinal ischemia.

NOTES:
DIABETIC RETINOPATHY (DR) LESIONS LOCATED PREDOMINANTLY PERIPHERAL TO ETDRS PHOTOGRAPHIC FIELD COVERAGE ON ULTRAWIDE FIELD IMAGES PREDICT MARKEDLY INCREASED RISK OF DR PROGRESSION

Lloyd Paul Aiello, Beetham Eye Institute
Paolo Silva, Joslin Diabetes Center
Jennifer Sun, Joslin Diabetes Center

Purpose: To determine if distribution of diabetic retinopathy (DR) lesions outside versus within the ETDRS standard photographic field area, as identified using ultrawide field (UWF) imaging, predicts DR progression.

Methods: Mydriatic 7-standard field ETDRS photos and UWF images (UWFI, Optos200MA) were obtained at the same visit in 200 eyes (100 participants) at baseline. ETDRS photos and UWFI were independently evaluated by two masked graders with differences adjudicated by a third grader. ETDRS photo DR distribution: absent 12.5% eyes; mild NPDR 22.5%; moderate NPDR 30%; severe NPDR 6.5%; very severe NPDR 1.6% and PDR 27%. UWFI were evaluated for DR lesion distribution and assessed as having either predominantly peripheral lesions (PPL) outside the ETDRS field coverage or not having a predominance of lesions peripheral to the ETDRS photo area. All participants were invited for follow up ETDRS photos which were obtained after 4.12±0.28 years (range 3.0-4.6 years).

Results: Of 91 (91%) participants alive at followup, 71 (140 eyes) were re-imaged (77% of eyes, 78% of participants). There were no significant differences in age, DM duration, 2-year prior HbA1c or DR severity between eyes that did or did not complete followup. In eyes with NPDR (N=112) at baseline, 84 (75%) were re-imaged at followup, PPL were present in 44 (52%) and DR progression occurred in 34 (40%). Baseline DR severity was not different between eyes with or without PPL.
RESULTS CONTINUED

(p=0.86). Compared to eyes without PPL, eyes with PPL had an 86% increased risk of >1 step of clinical DR progression [28% (11 eyes) vs 52% (23), p=0.03] and a 4-fold increased risk of >2 step DR progression [8% (3) vs 32% (14), p=0.007]. The increased risk remained significant after adjusting for baseline DR severity and DM duration.

Conclusions: In patients with baseline NPDR, DR lesions predominantly peripheral to the area imaged by ETDRS standard field photography are associated with markedly increased risk of DR progression over 4 years, independent of baseline DR severity. If these findings are confirmed, peripheral retinal evaluation may potentially become essential in both clinical and research settings to more accurately determine the risk of DR progression in eyes with NPDR.

Friday – 8:42

NOTES:
Intravitreal Ranibizumab Therapy Improves Resolution of Hard Exudate in Patients with Diabetic Macular Edema

Michael Ip, University of Wisconsin Medical School
Amitba Domalpally, University of Wisconsin-Madison
Jason Ehrlich, Genentech

Purpose: In patients with diabetic macular edema (DME), the formation of lipid-rich extravascular deposits known as hard exudate (HE) are commonly observed in the retina. The presence and growth of HE, particularly near the fovea, is thought to be associated with an increased risk of visual impairment. We evaluated the effect of monthly intravitreal ranibizumab on HE area, and the impact of HE on visual acuity outcomes in patients with DME using data from two phase 3 clinical trials (RIDE, NCT00473382; RISE, NCT00473330).

Methods: Between the two studies, 759 patients with DME were randomized to receive monthly 0.3 mg or 0.5 mg intravitreal ranibizumab, or sham injections. HE area was assessed from color photographs both on an ordinal scale and using continuous estimates of areas within the Early Treatment Diabetic Retinopathy Study (ETDRS) grid.

Results: Data from 739 eyes were available for analysis. Mean baseline HE area was similar in the three arms, ranging from 0.65 to 0.82 mm2. Through 24 months of treatment, the percentage of eyes without HE increased from 20.9% to 36.3% in the sham group, from 22.1% to 61.3% in eyes treated with 0.3 mg ranibizumab, and from 23.6% to 62.0% in the ranibizumab 0.5 mg group. A difference between treatment groups in resolution of HE became evident at month 12. At baseline, there was no correlation between visual acuity (VA) and presence of HE in the central subfield in any treatment arm. Post-baseline, there was also no consistent correlation between presence of HE in the central subfield and VA change over time.
Conclusions: In this exploratory analysis, monthly intravitreal ranibizumab resulted in significantly greater resolution of HE compared to sham. In contrast to the rapid effects of ranibizumab on macular edema, changes in HE area were more gradual. Contrary to prior expectations, the presence and area of HE did not increase as DME resolved (either in the ranibizumab or sham groups). Importantly, baseline VA was not correlated with the presence of HE, nor was the therapeutic benefit of ranibizumab on visual acuity affected by the presence of HE. These data suggest that in the context of intravitreal anti-VEGF therapy, the presence of HE is not a prognostic indicator of poor visual outcomes.

Friday – 8:51

NOTES:
Intravitreal Aflibercept for Diabetic Macular Edema: 12-Month Efficacy and Safety Results of Phase 3, Randomized, Controlled VISTA-DME and VIVID-DME Studies

Jeffrey Heier, Ophthalmic Consultants of Boston

Purpose: To compare the efficacy and safety of intravitreal aflibercept injection (IAI) with conventional macular laser photocoagulation for treatment of diabetic macular edema (DME).

Methods: Two similarly designed, double-masked, active-controlled, phase 3 studies, VISTA-DME and VIVID-DME, randomized 466 and 406 DME patients, respectively, in a 1:1:1 ratio to receive either IAI 2 mg every 4 weeks (2q4), IAI 2 mg every 8 weeks (2q8, following 5 initial monthly doses), or laser. The primary efficacy endpoint was the mean change from baseline in best corrected visual acuity (BCVA) at week 52. A secondary efficacy endpoint was the proportion of patients who gained ≥15 letters from baseline to week 52.

Results: The mean improvement in BCVA from baseline to week 52 in the 2q4 and 2q8 groups vs the laser group was 12.5 and 10.7 letters vs 0.2 letters (P<.0001) in VISTA-DME, and 10.5 and 10.7 letters vs 1.2 letters (P<.0001) in VIVID-DME, respectively. The proportion of patients who gained ≥15 letters from baseline to week 52 in the 2q4 and 2q8 groups vs the laser group was 41.6% and 31.1% vs 7.8% (P<.0001) in VISTA-DME and 32.4% and 33.3% vs 9.1% (P<.0001) in VIVID-DME, respectively. The most frequent ocular adverse events (AEs) included conjunctival hemorrhage, eye pain, and vitreous floaters. The most frequent non-ocular AEs included hypertension and nasopharyngitis, which occurred with similar frequency across treatment groups. The overall incidence of ocular and non-ocular AEs and serious AEs in the IAI groups was similar to the laser group. The overall
RESULTS CONTINUED

Incidence of the Anti-Platelet Trialists’ Collaboration-defined arterial thromboembolic events was similar across treatment groups.

Conclusions: In both VISTA-DME and VIVID-DME, intravitreal aflibercept groups demonstrated significant and robust superiority of BCVA endpoints over laser at week 52, with similar efficacy in the 2q4 and 2q8 treatment groups. IAI was generally well tolerated with no systemic safety signals evident through week 52, and no overall difference between treatment groups in serious systemic adverse events, including APTC events.

Friday – 9:00

NOTES:
Purpose: To evaluate visual and anatomic outcomes following treatment with IAI and laser in subgroups of DME patients with and without prior anti-VEGF therapy for DME.

Methods: Two similarly designed phase 3 studies, VISTA-DME and VIVID-DME, randomized 872 DME patients to receive either IAI 2 mg every 4 weeks (2q4), IAI 2 mg every 8 weeks (2q8, following 5 initial monthly doses), or laser. The primary efficacy endpoint was the mean change from baseline in best-corrected visual acuity (BCVA) at week 52. An exploratory analysis examined the improvements in BCVA and central retinal thickness (CRT) at week 52 in patients with and without prior anti-VEGF therapy.

Results: Overall, 27.0% of patients had prior anti-VEGF therapy for DME at baseline. The adjusted treatment difference (IAI minus laser [97.5% confidence interval]) in mean BCVA change from baseline to week 52 in the 2q4 and 2q8 groups was 10.8 (8.8, 12.8) and 9.8 (7.9, 11.8) letters in the total patients population, 11.8 (7.6, 15.9) and 11.7 (8.1, 15.4) letters in a subgroup of patients with prior anti-VEGF therapy, and 10.5 (8.2, 12.8) and 9.2 (6.9, 11.4) letters in a subgroup of patients without prior anti-VEGF therapy, respectively. The corresponding adjusted treatment difference for mean change in CRT was -132.7 (-155.4, -109.9) and -127.1 (-150.8, -103.4) mm in the total patient population, -108.9 (-154.1, -63.8) and -116.5 (-161.4, -71.6) mm in a subgroup of patients with prior anti-VEGF therapy, and -142.3 (-168.9, 115.6) and -131.8 (-160.1, -103.6) mm in a subgroup of patients without prior anti-VEGF therapy, respectively. The overall incidence of
RESULTS CONTINUED

ocular and non-ocular adverse events and serious adverse events, including the Anti-Platelet Trialists’ Collaboration-defined arterial thromboembolic events, was similar across treatment groups in the total patient population.

Conclusions: Visual and anatomic improvements over laser with both IAI regimens in subgroups of patients with and without prior anti-VEGF therapy were similar.

Friday – 9:09

NOTES:
Purpose: To evaluate the safety and efficacy of dexamethasone intravitreal implant (Ozurdex, DEX implant) 0.7 mg and 0.35 mg for treatment of diabetic macular edema (DME).

Methods: Pooled data analysis of results from two 3-year, randomized, multicenter, masked, sham-controlled, phase III clinical trials with identical protocols. Patients (n=1048) with DME, best-corrected visual acuity (BCVA) between 34 and 68 ETDRS letters, and central subfield retinal thickness (CRT) ≥300 µm by optical coherence tomography (OCT) were randomized in a 1:1:1 ratio to treatment with DEX implant 0.7 mg, DEX implant 0.35 mg, or sham procedure. Patients who met retreatment eligibility criteria could be retreated no more often than every 6 months. The primary endpoint for the United States FDA was achievement of ≥15-letter improvement in BCVA from baseline at study end in the intent-to-treat population with last-observation-carried-forward for missing values. Safety measures included adverse events (AEs) and intraocular pressure (IOP).
Results: Mean number of treatments received over 3 years was 4.1 for DEX implant 0.7 mg, 4.4 for DEX implant 0.35 mg, and 3.3 for sham. At study end, the percentage of patients with ≥15-letter improvement in BCVA from baseline was 22.2% with DEX implant 0.7 mg, 18.4% with DEX implant 0.35 mg, and 12.0% with sham (P≤0.018 for DEX implant 0.7 mg and 0.35 mg vs sham); mean reduction in CRT from baseline was greater with DEX implant 0.7 mg (−117.3 µm) and DEX implant 0.35 mg (−127.8 µm) than sham (−62.1 µm) (P<0.001). Rates of cataract-related AEs in phakic eyes were 67.9%, 64.1%, and 20.4% in the DEX implant 0.7 mg, DEX implant 0.35 mg, and sham groups, respectively. IOP increases were usually controlled with medication or no therapy; only 1 (0.3%) patient treated with DEX implant 0.7 mg and 1 (0.3%) treated with DEX implant 0.35 mg underwent glaucoma incisional surgery for steroid-induced IOP elevations.

Conclusions: DEX implant 0.7 mg and 0.35 mg provided statistically and clinically significant improvement in BCVA and reduction in CRT with an average of only 4–5 injections over 3 years. The safety profile was favorable.

Friday – 9:18

NOTES:
RANIBIZUMAB FOR DIABETIC MACULAR EDEMA: LONG-TERM OPEN-LABEL EXTENSION OF THE PHASE III RIDE AND RISE TRIALS

Lawrence Morse, UC Davis
Jiameng Zhang, Genentech
Jason Ehrlich, Genentech

Purpose: The RIDE and RISE Phase III studies established the efficacy and safety of up to 3 years treatment with monthly ranibizumab (RBZ) in patients with diabetic macular edema (DME). In the open-label extension phase of these studies we evaluated if the efficacy and safety achieved with monthly RBZ was maintained with less-than-monthly treatment using a protocol-based regimen that allowed for more.

Methods: In the core studies, patients with DME (n=759) were randomized to monthly 0.5 mg or 0.3 mg RBZ injected intravitreally or sham injection for 2 years. In year 3, patients in the sham group were eligible for crossover to monthly 0.5 mg RBZ. After month 36, patients (n=500) who enrolled in the optional extension received open-label 0.5 mg RBZ regardless of prior randomization. Treatment was criteria-based: patients received RBZ only if experiencing a ≥5 letter decrease in visual acuity (VA) from Month 36, or if DME was observed on optical coherence tomography. The visit interval could be extended from 30 days to 60 or 90 days for patients who did not require treatment based on these criteria.

Results: Overall, VA outcomes were excellent, with VA gains achieved after 36 or 12 months of monthly RBZ maintained using less than monthly dosing. An average of 4.5 injections were administered over a mean 14.1 months follow-up. ~25% of patients did not require further RBZ treatment to maintain VA. Of the ~75% who received additional treatment, vision outcomes were also maintained. Less than 10% received continued monthly RBZ. The types and incidence of ocular
and non-ocular adverse events in the extension phase appeared generally similar to the known safety profile of ranibizumab as observed in the core DME studies.

Conclusions: The results of the RIDE and RISE extension studies demonstrate the long-term durability of ranibizumab’s efficacy in DME. In roughly 25% of patients exiting the 3 year core studies, mean VA outcomes were maintained for more than a year without the need for further treatment. In those requiring further treatment, these data demonstrate that less-than-monthly treatment can be sufficient to maintain vision for the majority of patients. The safety profile of RBZ appeared similar to that observed in the controlled core studies.

Friday – 9:27

NOTES:
THE COURSE OF EYES WITH VITRECTOMY PRIOR TO ENROLLMENT IN A RANDOMIZED TRIAL EVALUATING RANIBIZUMAB PLUS PROMPT OR DEFERRED LASER FOR DIABETIC MACULAR EDEMA

Craig Greven, Wake Forest University Eye Center

Purpose: To present and compare the visual and anatomic outcomes in eyes with and without previous vitrectomy receiving anti-Vascular Endothelial Growth Factor (VEGF) therapy with Ranibizumab for center involved diabetic macular edema (DME).

Methods: An exploratory post hoc assessment of eyes enrolled in Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol receiving intravitreal Ranibizumab plus prompt or deferred laser for DME was performed. Visual acuity, and ocular coherence tomography (OCT) metrics were compared in eyes with previous vitrectomy (N = 25) and eyes without previous vitrectomy (N = 336).

Results: At baseline eyes with prior vitrectomy had worse visual acuity, less macular edema and were more apt to have severe retinopathy and prior cataract surgery than eyes without a history of vitrectomy. Analyses were adjusted for these covariates and outcomes of visual acuity, OCT central subfield thickness and volume were assessed at each annual visit through 3 years. No statistically significant differences in these outcomes were seen comparing those eyes with and without vitrectomy at baseline.

Friday – 9:36
Conclusions: These results do not support the clinical impression that intravitreal anti-VEGF injections are less effective in eyes that have had a vitrectomy.

Contrary to perceptions and previous publications, there is no evidence in our data that eyes with center involving DME and a history of prior vitrectomy have a clinically important difference in outcome using anti-VEGF and laser from those with no vitrectomy.

Friday – 9:36

NOTES:
REPEATED RANIBIZUMAB INJECTIONS AND INCIDENCE OF SUSTAINED IOP ELEVATION OR INITIATION OF OCULAR ANTI-HYPERTENSIVE TREATMENT IN EYES WITH DIABETIC MACULAR EDEMA

Justin Gottlieb, University of Wisconsin

Purpose: To assess the risk of persistent intraocular pressure (IOP) elevation in eyes with diabetic macular edema (DME) receiving repeated ranibizumab injections through 3 years, compared with eyes receiving focal/grid laser.

Methods: In a phase III clinical trial conducted by the Diabetic Retinopathy Clinical Research Network (DRCR.net), eyes with baseline DME and IOP ≤ 24 mmHg were randomly assigned to sham+prompt laser (N = 260) and ranibizumab+prompt or deferred laser (N = 322). Pre-dilation IOP was assessed every 4 weeks through 1-year, and every 16 weeks through 3-year visits. Cumulative probability of persistent IOP elevation (defined as IOP of ≥22 mmHg + ≥6 mmHg increase from baseline at 2 consecutive visits) or initiation of ocular anti-hypertensive medication or procedure anytime, was calculated using the Kaplan–Meier method. Data were censored if ocular or systemic steroids were received, if vitrectomy was performed, or eye developed IOP elevation due to neovascularization or ghost cell glaucoma. Sham eye data were censored if a vascular endothelial growth factor inhibitor was received.

Results: Mean baseline IOP was 16±3 mmHg in both groups. Four and 5% of sham and ranibizumab eyes, respectively, had a baseline IOP of 22-24 mmHg. In each group, 3% had a history of glaucoma or used IOP-lowering medicine prior to randomization. On average, 8 and 13 intravitreal injections were performed in the ranibizumab groups through year 1 and
RESULTS CONTINUED

3 respectively. Cumulative probability of persistent IOP elevation or initiation of ocular anti-hypertensive medications or procedure by the 1-year and 3-year visits will be presented at the meeting.

Conclusions: Conclusions will follow from the final results and be presented at the meeting.

Friday – 9:45

NOTES:
The 2014 Macula Society Young Investigator Award
(previously the Richard and Hinda Rosenthal Award)

Wai T. Wong, MD, PhD
Presented by Alexander J. Brucker, MD
Friday, February 21, 2014 – 9:54 a.m.

“To that individual or group of individuals under 50 years of age whose work gives promise of notable advance in the clinical treatment of disorders of the eye.”

Bert M. Glaser, MD, 1991
Mark S. Blumenkranz, MD, 1992
Thaddeus P. Dryja, MD, 1993
Carman A. Puliafito, MD, 1994
Matthew A. Thomas, MD, 1995
Peter A. Campochiaro, MD, 1996
Niel M. Bessler, MD, 1997
Edwin M. Stone, MD, 1998
Joan W. Miller, MD, 1999
William E. Smiddy, MD, 2000
Richard F. Spaide, MD, 2001
Susan B. Bessler, MD, 2002
Carol L. Shields, MD, 2002
Lloyd Paul Aiello, MD, PhD, 2003
Jason S. Slakter, MD, 2003
Daniel F. Martin, MD, 2004
Ursula Schmidt-Erfurth, MD, 2005
Timothy G. Murray, MD, MBA, 2005
Anat Loewenstein, MD, 2006
Philip J. Rosenfeld, MD, PhD, 2007
Glenn J. Jaffe, MD, 2007
J. William Harbour, MD, 2008
Timothy W. Olsen, MD, 2010
K. Bailey Freund, MD, 2011
SriniVas R. Sadda, MD, 2012
Rajendra S. Apte, MD, PhD, 2013
Dr. Wai T. Wong is Chief of the Unit on Neuron-Glia Interactions in Retinal Disease at the National Eye Institute, National Institutes of Health, in Bethesda, Maryland. He received engineering and biology degrees at the Massachusetts Institute of Technology and MD and PhD (Neuroscience) degrees at the Washington University in St. Louis. He performed postdoctoral research and completed his Ophthalmology residency at the University of Pennsylvania, which was followed by fellowship training in Medical Retina at the National Eye Institute.

Dr. Wong's translational research group at the NEI focuses on chronic neuroinflammatory mechanisms underlying retinal diseases, particularly in regard to microglia, the primary resident immune cell in the retina. His research focus has been to understand the mechanisms by which retinal immune cells drive neuroinflammatory changes in age-related macular degeneration, diabetic retinopathy, and retinitis pigmentosa, and to target these mechanisms in interventional clinical studies. His work has been supported by the NEI Intramural Program, as well as by grants from the American Health Assistance Foundation/BrightFocus Foundation and the Prevention of Blindness Society of Metropolitan Washington. His research has been described in over 70 peer-reviewed publications and book chapters.
Purpose: Evaluate the safety and efficacy of ≥2 dexamethasone intravitreal implants (DEX implants) used as monotherapy or in combination with other therapy for macular edema associated with retinal vein occlusion (RVO).

Methods: A multicenter, retrospective, open-label chart review study (SHASTA study) evaluated the safety and efficacy of DEX implant in 289 patients with branch or central RVO who were treated with ≥2 DEX implants and followed for 3–6 months after the last implant. Subgroup analysis compared results in patients who received DEX implant as monotherapy versus in combination with other RVO treatments.

Results: DEX implant was used as monotherapy in 84 (29.1%) patients and combined with other RVO therapy, most commonly intravitreal anti-vascular endothelial growth factor, in 205 (70.9%) patients. Mean number of DEX implant treatments was ~3 in each group; mean days to reinjection was 151 and 177 in monotherapy and combination therapy groups, respectively (P<.001). Mean change in best-corrected visual acuity (BCVA) from baseline after the first through sixth DEX implant injections ranged from +0.6–+3.4 lines in
monotherapy group and +1.3–+2.8 lines in combination therapy group; 52.4% of patients treated with monotherapy and 46.3% treated with combination therapy gained ≥3 lines in BCVA. Mean decreases in central retinal thickness (CRT) from baseline after the first through sixth DEX implant injections ranged from 165–230 µm in the monotherapy group and 136–175 µm in the combination therapy group; 63.1% of patients treated with monotherapy and 65.9% treated with combination therapy achieved CRT ≤250 µm. The most common adverse event was increased intraocular pressure (IOP). During the study, 25.0% of patients treated with monotherapy and 37.1% treated with combination therapy had IOP ≥25 mm Hg (P=0.048). One (1.2%) patient treated with monotherapy and 3 (1.5%) treated with combination therapy underwent glaucoma laser surgery; 5 (2.4%) patients treated with combination therapy underwent glaucoma incisional surgery.

Conclusions: Use of ≥2 DEX implants alone or in combination with other RVO treatments is safe and effective for reducing CRT and improving BCVA. Gains in BCVA and reduction in CRT were similar in patients treated with ≥2 DEX implants alone and with adjunctive RVO treatments.

NOTES:

Friday – 10:12
EVALUATION OF MULTIPLE DEXAMETHASONE INTRAVITREAL IMPLANTS IN PATIENTS WITH MACULAR EDEMA ASSOCIATED WITH RETINAL VEIN OCCLUSION

Sophie Bakri, Mayo Clinic
Ahmed Omar, Mayo Clinic
Kapil Kapoor, Mayo Clinic
Raymond Iezzi, Mayo Clinic

Purpose: The dexamethasone 700 mcg implant (DEX) (Ozurdex®; Allergan, Inc., Irvine, CA) has been used increasingly for cystoid macular edema (CME) secondary to retinal vein occlusion (RVO). The purpose of this study is to evaluate the safety, efficacy and reinjection intervals of patients receiving multiple DEX injections.

Methods: This was a retrospective study of patients treated for CME associated with RVO. Each patient had initial complete ophthalmologic evaluation with optical coherence tomography (OCT), with follow up 4-6 weeks after each injection. Retreatment criteria included persistent or increased intraretinal or subretinal fluid on OCT. Outcome measures included best corrected visual acuity, intraocular pressure (IOP), central macular thickness on OCT, extent of fluid resolution on OCT, and required treatment for elevated IOP and cataract.

Results: 31 patients had 82 DEX injections, with 19 patients having 2 injections, 12 having 3 injections, 10 having 4 injections, 6 having 5 injections, and 4 having 6 injections. 14 patients (45%) developed ocular hypertension, and 40% of phakic patients required cataract surgery. No patients required glaucoma surgery or developed endophthalmitis. The average time to complete resolution of fluid on OCT for all DEX injections was 52 days (range = 28 to 245, SD ±8 days) (Tables 2 and 3). There were 35 (43%) events of incomplete resolution of fluid on OCT. The average time to appearance of new fluid...
RESULTS CONTINUED

on OCT for all DEX injections was 113 days (range = 28-258 days, SD ±9 days). The average time to the use of additional treatment for new fluid for all patients receiving DEX injections was 119 days (range 42-309 SD ±9 days).

Conclusions: This study suggests that repeated, as needed, injections of the dexamethasone implant for the treatment of CME associated with RVO may be used. Patients should be monitored and treated for ocular hypertension and the development of visually significant cataract.

Friday – 10:21

NOTES:
DE XAM ETHA SO N E IM PLANT FO R M ACULAR EDEMA SEC ONDA RY TO ISCHEMIC RETINAL VE IN OCCLUSIO NS

Francesco Bandello, University Vita-Salute, Scientific Institute San Raffaele
Pierluigi Iacono, Fondazione GB Bietti, Roma
Maurizio Parodi

Purpose: To evaluate the effects of dexamethasone implant for the treatment of macular edema (ME) secondary to ischemic retinal vein occlusions over a 12-month follow-up.

Methods: The design of the study is a prospective, open-label, interventional, case series. Patients affected by ME related to ischemic central retinal vein occlusion (CRVO) and ischemic branch retinal vein occlusion (BRVO) were prospectively recruited. Following a comprehensive ophthalmological examination including best-corrected visual acuity (BCVA) assessment on ETDRS chart, fluorescein angiography, and optical coherence tomography, each patient received a first dexamethasone implant. Further retreatment were performed on the basis of the detection of ME from the fourth month on.

Primary outcome measure was the mean changes in the ETDRS letter score at the 12-month examination.

Secondary outcome measures included the mean change in central macular thickness (CMT), and the number of injections at the end of the follow-up.

Results: Overall, twenty-four patients were enrolled (11 patients with ME secondary to ischemic CRVO and 13 patients with ME related to ischemic BRVO). Mean ETDRS letter score was 44,3 at baseline, and 60,8 at the 12 month examination in the subgroup with ischemic CRVO. Mean ETDRS letter score in the subgroup with ischemic BRVO changed from the baseline value of 75,3 to the 91,6 at the end of the follow-up. Baseline CMT was 776µm and 544µm in CRVO and BRVO, respectively, and improved to 444µm and 321µm at the 12-
RESULTS CONTINUED

month examination. The mean number of dexamethasone injections was 1.8 in the CRVO subgroup and 1.7 in the BRVO subgroup.

Conclusions: Dexamethasone implant can reduce ME in eyes affected by ischemic CRVO and ischemic BRVO, leading to a slight visual acuity improvement.

Friday – 10:30

NOTES:
Intravitreal Triamcinolone Acetonide Improves Macular Edema: Evaluation of 5,000 Injections to Determine Efficacy and Evaluate Complications

Timothy Murray, Murray Ocular Oncology and Retina
Victor Villegas, MOOR
Aaron Gold, MOOR

Purpose: To evaluate the impact of intravitreal triamcinolone acetonide treatment on macular edema with specific focus on sdOCT indications for treatment and outcomes. To determine the complication profile of single, and repetitive, intravitreal injection focused on incidence of endophthalmitis, pseudoendophthalmitis, elevated intraocular pressure, and cataract progression in a defined delivery treatment.

Methods: IRB approved, retrospective review of 4,574 intravitreal triamcinolone acetonide injections within a single vitreo-retinal surgical practice. All patients consented and treated between July, 2007 and December 2013 were identified by electronic record review. Demographics were abstracted and individual charts were reviewed for indication of treatment, best corrected visual acuity, pre-treatment IOP, baseline sdOCT findings, post-treatment outcomes abstracted included visual acuity, IOP, sd-OCT findings, glaucoma medications, cataract progression or surgery and findings of inflammatory/infectious endophthalmitis.

Results: 4,574 intravitreal triamcinolone acetonide injections were performed in 2,267 patients over this 6 year period. Mean followup was 34 months (range 6-74 months). Intravitreal triamcinolone acetonide injections were performed at approximately 500 injections per year until 2012 when injection volume markedly increased to 898 and 1,140 injections in 2012 and 2013 respectively. Baseline VA was 20/200 improving to 20/50 at 6 months (p < .05). Baseline CPT sdOCT was 547 microns decreasing to 317 microns at
6 months (p < .005). No cases of culture positive endophthalmitis were seen (0/4,574, 0%). Pseudo-endophthalmitis was seen in 5 intravitreal Kenalog injections (5/1235, 0.40%), 5 intravitreal compounded triamcinolone acetonide, 0.86%), and 2 intravitreal Triescence (2/2,567, 0.07%) [p <.01]. IOP elevation requiring glaucoma medication therapy occurred in 194 patients (194/2,267, 8.55%) at any time during followup. No patient required glaucoma surgery during the treatment window. Of 1,036 phakic patients, cataract progression was noted in 440 patients (440/1036, 42.4%). No patient developed injection related retinal tear/detachment. No patient required enucleation.

Conclusions: Intravitreal injection of triamcinolone acetonide for treatment of complex macular edema is associated with decreased intra-retinal edema and improved visual acuity. Elevated intraocular pressure is infrequent and responsive to topical glaucoma medications without requiring glaucoma surgery. Cataract progression is common in this older patient population and surgical intervention is not associated with an increased complication profile. Intravitreal Triescence is associated with the lowest profile of elevated intraocular pressure and pseudoendophthalmitis.

Friday – 10:39

NOTES:
Intravitreal Aflibercept Injection (IAI) for Macular Edema Secondary to Branch Retinal Vein Occlusion (BRVO): 24-Week Results of the VIBRANT Study

Julia Haller, Wills Eye Hospital

Purpose: To compare the efficacy and safety of IAI with laser photocoagulation for the treatment of macular edema secondary to BRVO.

Methods: A phase 3, multicenter, double-masked, active-controlled study, VIBRANT randomized treatment-naïve patients with unilateral macular edema secondary to BRVO who were diagnosed within 12 months and had a BCVA between 73 and 24 letters (20/40 to 20/320 Snellen equivalent) to receive either IAI 2 mg every 4 weeks (n = 91) or laser (n = 92) from baseline to week 20. The primary efficacy endpoint was the proportion of patients who gained ≥15 letters in best-corrected visual acuity (BCVA) from baseline to week 24. The secondary efficacy endpoints included the mean change from baseline in BCVA and central retinal thickness (CRT) at week 24.

Results: The proportion of patients who gained ≥15 letters from baseline to week 24 was 53% in the IAI group compared with 27% in the laser group (P < .001). The mean improvement in BCVA from baseline to week 24 was 17.0 letters in the IAI group and 6.9 letters in the laser group (P < .0001). The mean reduction in CRT from baseline to week 24 was 280.5 mm in the IAI group and 128.8 mm in the laser group (P < .0001). The most common ocular adverse events in IAI patients were conjunctival hemorrhage (19.8%) and eye pain (4.4%). Over the 24 weeks of the study, traumatic cataract in an IAI patient was the only ocular serious adverse event (SAE) that occurred. The incidence of non-ocular SAEs was 8.8% in the IAI group and 9.8% in the laser group. One death due to pneumonia and one Anti-Platelet Trialists’ Collaboration-defined event of
RESULTS CONTINUED

non-fatal cerebrovascular accident occurred during the 24 weeks of the study, both in patients in the laser group. There were no cases of intraocular inflammation or endophthalmitis.

Conclusions: Monthly injections of intravitreal aflibercept were well tolerated and significantly improved visual acuity at week 24 in patients with macular edema secondary to BRVO.

Friday – 10:48

NOTES:
**Effect of Alternate Ranibizumab Dosing Regimens on Visual and Anatomic Outcomes in Patients with Retinal Vein Occlusion: The SHORE Study**

*Franco Recchia, Tennessee Retina  
Linda Yau  
Gary Sternberg*

**Purpose:** The SHORE study evaluated whether PRN treatment with ranibizumab in patients with retinal vein occlusion (RVO), after reaching a stable disease state, provides visual acuity (VA) gains comparable to monthly dosing over 15 months.

**Methods:** This 15-month, phase IV, randomized study enrolled a total of 202 eligible patients with branch RVO (BRVO, N=115) and central RVO (CRVO, N=87). From Months (M) 0-6, patients received 7 monthly ranibizumab 0.5 mg injections, and, between M7 and M14, continued to receive monthly ranibizumab injections until the first month at which pre-specified VA and spectral-domain OCT (SD-OCT) stability criteria were met. Patients were then randomized (1:1) to continue ranibizumab monthly (N=85) or switch to PRN ranibizumab (N=86). Non-randomized patients (N=31; i.e., those who completed the study but did not meet stability criteria at any visits from M7 to M14, or those who discontinued either prior to M7 or prior to achieving disease stability) continued to receive monthly injections. The primary efficacy analysis was a longitudinal analysis modeling the change in BCVA from baseline over the timepoints M7 to M15. The slopes of the BCVA curves for the PRN and monthly treatment groups were compared.

**Results:** Approximately 80% of patients were randomized by M8. There was no significant difference in the slopes of the BCVA change from baseline between M7 to M15 between the monthly and PRN arms. The mean BCVA change from baseline at M15 was +21.0 letters (PRN arm) and +18.7 letters
RESULTS CONTINUED

(monthly arm). At M15, 70.7% and 66.3% of PRN- and monthly-treated patients gained ≥15 letters from baseline, respectively, and 76.8% and 71.3% of PRN- and monthly-treated patients achieved a Snellen equivalent of 20/40 or better, respectively. Average VA gains were 20.6 letters in BRVO patients and 18.0 letters in CRVO patients. Mean CFT change from baseline at M15 was -247.8 µm (PRN arm) and -289.9 µm (monthly arm). The PRN group received a mean of 3.7 injections between M7 and M14. Ocular and systemic safety profiles over 15 months were generally balanced between the PRN and monthly arms, with no dose exposure trends observed.

Conclusions: In SHORE, PRN treatment with ranibizumab in RVO (BRVO and CRVO patients), after reaching a stable disease state, provided VA gains comparable to monthly dosing. Both the PRN and monthly groups demonstrated rapid and clinically meaningful reductions in CFT on SD-OCT throughout the study. Safety was consistent with previous ranibizumab studies in RVO.

Friday – 10:57

NOTES:
ASSESSMENT OF THE INNER SEGMENT/OUTER SEGMENT LAYER IN PATIENTS WITH MACULAR EDEMA DUE TO CENTRAL RETINAL VEIN OCCLUSION

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Yijun Huang, Fundus Photograph Reading Center
Jeong Pak, Fundus Photograph Reading Center
Amita Domalpally, University of Wisconsin-Madison

Purpose: To evaluate the inner segment/outer segment (IS/OS) layer seen on spectral domain optical coherence tomography (SD-OCT) in eyes with macular edema due to central retinal vein occlusion (CRVO).

Methods: In 6 patients with macular edema from CRVO, we compared the IS/OS layer (or ellipsoid zone) using spectral domain OCT (SD-OCT) to the IS/OS layer in the normal fellow eyes. At the University of Wisconsin Fundus Photograph Reading Center (FPRC), we used a computer-aided manual segmentation protocol for the SD-OCT images and measured two separate features: 1) the area of absent IS/OS within the raster using an “en face” view and 2) the IS/OS thickness (height) in the central subfield.

Results: A total of 10 eyes of 6 patients were graded using the FPRC segmentation protocol. Of the six CRVO eyes with macular edema, four eyes had OCT scans of the normal fellow eye. In the CRVO eyes, mean OCT central retinal thickness was 538 microns (401 – 754um); in the normal eyes, mean central retinal thickness was 250 microns (224 – 270um). In the CRVO eyes, 5 out of 6 eyes had at least one area of absent IS/OS. In some CRVO eyes, the area of absent IS/OS was multifocal. Using the en face view, the mean area of absent IS/OS was 3.2 mm2 (SD of 3.1mm2); in all normal eyes, the IS/OS was completely intact. In the central subfield of eyes with edema, the mean IS/OS thickness was 18.2um; in the normal eyes, the mean central subfield thickness was 35.3um.
Conclusions: We report the area of IS/OS defects seen “en face” using reading center OCT segmentation software in CRVO eyes with significant macular edema. The IS/OS defects in the eyes with edema were not found in the normal eyes and may represent a valuable means of assessing photoreceptor damage. In addition, the IS/OS central subfield thickness in these CRVO eyes was significantly thinner than the IS/OS thickness of the normal eyes. Monitoring both area of IS/OS defects and height of the IS/OS layer will be tested in upcoming CRVO clinical trials.

NOTES:
**Predictive Value of Early Response to VEGF Inhibition in Retinal Vein Occlusions Defined by Optical Coherence Tomography and Fundus Autofluorescence**

Francisco Rodriguez, Fundacion Oftalmologica Nacional
Hector Hernandez, Fundacion Oftalmologica Nacional

**Purpose:** To evaluate the baseline spectral domain optical coherence tomography (SD-OCT) characteristics of macular edema (ME) due to retinal vein occlusion (RVO) for visual outcome after intravitreal anti-VEGF injection.

**Methods:** Sixty patients treated in one eye with either intravitreal bevacizumab or ranibizumab for ME due to RVO were retrospectively reviewed. Multivariate analysis was used to evaluate the relative contribution of several variables at baseline and three months, including SD-OCT characteristics such as inner segment/outer segment (IS/OS) junction integrity, central retinal thickness (CRT), presence of sub-retinal fluid (SRF), presence of vitreo-macular adhesion (VMA), sub-foveal fundus auto-fluorescence (FAF), macular ischemia (MI) and best-corrected visual acuity (BCVA) with final visual outcome.

**Results:** There was a significant decrease in baseline CRT 388 ± 128.54 compared to 326 ± 175.24 at 3 months (p <0.001, Wilcoxon test). In assessing visual acuity (logMAR) in patients, statistically significant differences were found between the baseline and the 3, 6 and 12 months (p < 0.001, Friedman test). Significant decrease (logMAR) was found between baseline and 3 months (p <0.001), 6 months (p <0.001) and 12 months (p <0.001). The strongest individual predictor of final BCVA among patients with ME due to RVO was the integrity of photoreceptor IS/OS/ELM layer on SD-OCT. Significant association was found between the presence at three months with changes in visual acuity at 6 months (r² = .232, p <0.001) and 12 months (r² = .506, p <0.001). Taking the values of
visual acuity at 3, 6 and 12 months and initial VA as a covariate significant association was found between three months (r² = 0.697, p < 0.001), 6 months (r² = 0.745, p < 0.001) and 12 months (r² = 0.786, p < 0.001).

Conclusions: Our results suggest that baseline SD-OCT characteristics, the status of inner segment/outer segment (IS/OS) junction integrity, can be helpful in predicting the final visual outcome after intravitreal anti-VEGF injection for the management of macular edema secondary to retinal vein occlusion in these patients.

Friday – 11:15

NOTES:
DETECTION OF ACUTE ISCHEMIC DAMAGES IN RETINAL VASCULAR OCCLUSIVE DISEASES USING OCT; “PROMINENT MIDDLE-LIMITING MEMBRANE SIGN”

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Suk Ho Byeon, Yonsei University College of Medicine
Yong Sung You, Nune Eye Hospital

Purpose: To describe characteristic OCT findings of acute ischemic damages in retinal artery occlusion (RAO) and investigate clinical features and follow up results of central retinal vein occlusion (CRVO) showing the acute ischemic damages at presentation.

Methods: Retrospectively, 18 RAO cases and 50 consecutive eyes of 50 patients with acute CRVO less than 1 month of disease duration with acceptable fluorescein angiography (FA) and OCT were reviewed. A hyperreflective line located in the inner synaptic portion of the retinal outer plexiform layer (“prominent middle-limiting membrane [p-MLM] sign”) in OCT was used as an acute ischemic damage signs. P-MLM sign was consistently noticed up to 1 month showing regional correlation with the retinal opaque areas in RAO. In acute CRVO cases, retinal ischemic sign in OCT at presentation were determined by the concurrence of two independent experienced researchers. CRVO cases with prominent definitive MLM sign were grouped and compared with the group of eyes with no MLM sign and equivocal MLM sign (non-MLM group), for clinical features including initial and final visual acuity, central fovea thickness (CFT), CRVO type, and neovascular glaucoma development.

Results: In RAO cases, the degree of retinal opacity was variable according to each case and area decreasing intensity as time passed. Increased reflectivity of the inner retina and a p-MLM in OCT were consistently noticed up to 1 month showing regional correlation with the retinal opaque areas. In
RESULTS CONTINUED

50 CRVO eyes, the mean age was 57.9±16.7 years and 14 eyes (28%) had prominent MLM sign, 21 eyes (42%) had no MLM sign, and 15 eyes (30%) had equivocal findings. Mean follow-up duration was 10.0±8.3 months. Eyes with prominent MLM sign presented worse initial and final BCVA in comparison with combined non-MLM group (logarithm of the minimum angle of resolution, LogMAR, 1.10±0.72 versus 0.47±0.49 in the MLM group, P=0.007; and LogMAR 1.19±0.91 versus 0.43 ± 0.49 in the non-MLM group, P=0.012). The MLM group eyes presented more ischemic-type CRVO (57.1% versus 4.8%, P=0.001), and developed more neovascular glaucoma (two eyes versus none), than the combined non-MLM group. Eyes with equivocal MLM had larger CFTs when compared with either the no-MLM or the prominent MLM group. (775.3±291.3 versus 426.4±239.1 and 409.9 ± 179.3 µm, respectively; P=0.001 for both comparisons with the equivocal MLM group).

Conclusions: A ‘Prominent MLM sign’ is a useful imaging indicator of acute ischemic retinal damage. CRVO showing p-MLM on OCT had worse visual outcome with higher incidence of being classified into ischemic type CRVO.

Friday – 11:24

NOTES:
ANATOMICAL AND VISUAL OUTCOMES FOLLOWING OCRIPLASMIN TREATMENT FOR SYMPTOMATIC VITREOMACULAR TRACTION SYNDROME

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Sunil Srivastava
Jonathan E. Sears, Cole Eye Institute
Andrew Schachat, Cleveland Clinic
Peter Kaiser, Cole Eye Institute

Purpose: To evaluate the anatomic and visual outcomes of patients treated with ocriplasmin for the treatment of symptomatic vitreomacular adhesion including vitreomacular traction syndrome and macular holes.

Methods: This was a retrospective, interventional, single center, case series of patients with symptomatic vitreomacular adhesion (sVMA). Patients were treated with a single intravitreal injection of 0.125mg ocriplasmin (Jetrea, Thrombogenics Inc. USA, Alcon/Novartis EU) with the reconstitution technique recommended by the manufacturer. The primary study endpoint was the resolution of sVMA by spectral domain OCT (SDOCT) at day 28. Secondary outcome measures included time to vitreous release, visual acuity, changes in the OCT thickness and structure, and macular hole closure rate.

Results: Seventeen patients were included in the study and resolution of VMA was verified by SDOCT in 8 patients by day 28 (overall response rate of 47.1%, 8/17 eyes) with most patients experiencing vitreomacular adhesion release by 7 days (41.2%, 7/17 eyes). Those who did not have VMA resolution showed no statistically significant change in VMA diameter as measured by horizontal and vertical 5-line raster scans at final follow-up (p=0.82 and p=0.75, respectively). The mean baseline Snellen visual acuity was 20/49 and at final follow up was 20/46 (p=0.59). The average central subfield thickness was 371 microns prior to treatment and 324 microns at final follow up (range 191-767 microns, p=0.25). Patients meeting
three of four positive predictors criteria (eg. no ERM at baseline, VMA diameter ≤ 1500 µm, and phakic lens status) showed a response rate of 50.0% (7 of 14 patients) those meeting all four criteria (eg. younger than 65, no ERM at baseline, VMA diameter ≤ 1500 µm, and phakic lens status) showed a response rate of 75.0% (3 of 4 eyes). Transient outer segment ellipsoid zone loss was documented in 7 patients and subretinal fluid presence following injection was noted in 5 patients. Four of the five patients with macular holes at baseline experienced resolution of their macular hole after injection.

Conclusions: This is the first study to quantify the extent of outer retinal changes seen in patients receiving ocriplasmin. Our initial experience with ocriplasmin shows a significant anatomic effect and is accompanied by transient changes in the outer retinal structures visualized by SDOCT.

Friday – 11:33

NOTES:
Ocriplasmin for the Treatment of Vitreomacular Traction: Predictors of Success and Complications

Daniel Roth, Robert Wood Johnson Medical School  
Kunjal Modi, NJ Retina  
Henry Feng, Robert Wood Johnson Medical School  
William Feuer, Bascom Palmer Eye Institute  
Howard Fine, Robert Wood Johnson Medical School  
H. Matthew Wheatley, Robert Wood Johnson Medical School

Purpose: Ocriplasmin is a proteolytic enzyme for the treatment of symptomatic vitreomacular adhesion (VMA). Our study evaluates the features of our initial series of eyes treated with intravitreal ocriplasmin, in order to determine predictors of success and potential complications with this agent.

Methods: A retrospective review of 62 eyes with symptomatic VMA, associated with vision loss and anatomic distortion of the macula, was performed. Each eye was treated with a single pars plana injection of ocriplasmin (125 mcg in 0.1 cc). Associated conditions included macular hole, cystoid macular edema, myopic schisis, epiretinal membrane, dry AMD and diabetic macular edema.

Results: Visual acuity (VA) ranged from 20/40 to 20/400 with a mean Snellen VA equivalent of 20/92. Ocriplasmin induced VMA resolution in 35% of patients (67% macular hole (MH) eyes, 4% of non-MH eyes). 13% experienced VMA release if other macular disease was also present vs. 56% if no other disease present (p=0.003). Higher rate of VMA release seen in younger patients (p=0.05). 38% VMA release if VMA diameter < 750 μm vs. 0% if VMA diameter > 750 μm (p=0.015). For every additional 100 μm of VMA diameter, 20% increased likelihood of VMA not releasing. Only 1 of the 11 eyes (9.1%) with epiretinal membrane had VMA release. Factors that did NOT predict VMA release include photopsia, dyschromatopsia, subjective visual loss, decreased VA at one week, pre-treatment VA, presence of DM, and prior
treatments. MH closed in 32% of eyes with MH and MH closure was associated better pre-injection VA (p=0.014). Mean VMA diameter was 206 μm in MH eyes that closed, vs. 569 μm in those that did not close. MH closure was not associated with MH diameter itself in these eyes, but most eyes in this cohort had smaller MHs. In 56% of eyes with MH, the MH width enlarged initially after ocriplasmin. Additionally, 29% of eyes developed new subretinal fluid after ocriplasmin injection, which usually resolved spontaneously over a mean of 80 days. No eyes in our series experienced an obliteration of the ellipsoid layer. Subjective worsening of vision was reported during the initial 2 days after injection in 44% of eyes, with objective VA decline in 20% and 33% at 1 week and 6 weeks, respectively. Photopsia and dyschromatopsia was reported in 50% and 10% of eyes, respectively. 50% of eyes in this cohort eventually underwent vitreoretinal surgery.

Conclusions: Ocriplasmin, a recently approved intravitreal injection for the treatment of symptomatic VMA, may effectively accomplish vitreomacular separation in eyes with pathology associated with vitreomacular traction. However, case selection and appropriate patient expectations are important in the management of symptomatic VMA with ocriplasmin.

Friday – 11:42

NOTES:
Purpose: To describe the structural and functional characteristics of ocriplasmin-induced vision loss and propose a hypothesis regarding the mechanism of ocriplasmin retinal toxicity.

Methods: We evaluated a 63-year-old woman reporting acute vision loss following intravitreal ocriplasmin injection with complete ophthalmologic examination, Goldmann visual field testing, autofluorescence photography, spectral domain optical coherence tomography (SD-OCT), and full-field electroretinography (ERG). The findings were compared with data from the literature regarding localization of laminin in the retina and pathological consequences of laminin deficiency in animal and human eyes.

Results: Findings suggesting panretinal dysfunction in our patient 9 days after ocriplasmin injection included visual acuity loss, visual field constriction, pupillary abnormalities, attenuated retinal arteries, loss of outer retinal signals on SD-OCT, and severely reduced ERG responses. B-waves were reduced more than A-waves suggesting post-receptoral dysfunction in addition to decreased photoreceptor activity. Laminin is present throughout the retina, including the interphotoreceptor matrix and synapses in the outer plexiform layer (OPL). Laminin deficient mice demonstrate shortened photoreceptor inner and outer segments, disorganized synapses in the OPL, and severely reduced ERG B-waves. Patients with mutations in the laminin B2 gene (Pierson syndrome) are prone to retinal detachment attributed to reduced retinal adhesion.
Conclusions: Retinal dysfunction associated with intravitreal ocriplasmin injection is not limited to the macular region and appears to involve the entire retina. Enzymatic cleavage of intraretinal laminin is a biologically plausible mechanism for acute ocriplasmin retinal toxicity.

NOTES:
Purpose: To evaluate cost-effectiveness and utility for pharmaceutical and surgical treatment of vitreomacular adhesions (VMA) and full thickness macular holes (MH).

Methods: Outcomes of published clinical trials (index studies) of surgical treatment of VMA and MH, and a prospective, multicenter clinical trial of pharmaceutical vitreolysis with intravitreal ocriplasmin with saline control were used to generate a model for costs of treatment and visual benefits. Markov analysis, with cost data from the Center of Medicare and Medicaid Services (CMS), was used to calculate imputed costs for each primary treatment modality in a facility setting with surgery performed in a hospital or ambulatory surgery center (ASC). The main outcome measures were imputed costs of therapy, cost per line saved, cost per line-year saved, cost per quality-adjusted life years (QALY) saved.

Results: When PPV was selected as the primary procedure, the overall imputed cost ranged from $5,905-$8,073. The cost per line was $2,365-$3,229, the cost per line-year saved was $163-$223 and the cost per QALY saved was $5,430-$7,423. If intravitreal injection of ocriplasmin (IVO) was the primary procedure, the overall imputed cost was $8,828-$11,080. The cost per line ranged from $3,531-$4,432, the cost per line-year saved was $244-$306, and the cost per QALY saved was between $8,118-$10,189. If intravitreal saline injection (IVS) were used as a primary procedure, the overall imputed cost was between $5,921 and $10,686. The cost per line was $2,368-$4,274, the cost per line-year saved ranged from $163-$295 and the cost per QALY saved ranged from $5,444-$9,826.
Conclusions: PPV as a primary procedure was the most cost effective therapy in this model. The other treatments had similar costs per QALY saved, and compare favorably to costs of therapy for other retinal diseases.

Friday – 12:00

NOTES:
LAMELLAR HOLE ASSOCIATED EPIRETINAL PROLIFERATION (LHEP)

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Richard Spaide
Claudine Pang, Vitreous Retina Macula Consultants of New York

Purpose: To describe a novel type of epiretinal proliferation found predominantly in association with a lamellar macular hole (LMH), termed as lamellar hole associated epiretinal proliferation (LHEP).

Methods: This was a retrospective observational case review of 2,030 eyes of 1,104 patients with diagnoses including LMH, full-thickness macular hole (FTMH) and epiretinal membrane (ERM) imaged with spectral-domain optical coherence tomography (SD-OCT) from 2008 to 2013. SD-OCT scans of all eyes were examined and the epiretinal proliferation was categorized using SD-OCT criteria. LHEP was defined on SD-OCT imaging as an epiretinal material of homogenous, medium reflectivity which differed from the thin, highly reflective line of conventional ERM. The subset of eyes found to have LHEP was studied and qualitatively compared to a comparable group of eyes with conventional ERM using the SD-OCT data.

Results: LHEP was detected only in eyes with inner retinal defects. LHEP was found in 68 of 2,030 (3.3%) eyes, of which 88.2% had LMH and 11.8% had FTMH. LHEP was not seen in 1,734 eyes that had ERM without inner retinal defects. LHEP was found in 60 of 197 (30.5%) eyes with LMH and 8 of 99 (8.0%) eyes with FTMH. Using SD-OCT, LHEP appeared to originate from within the retinal defect, showed a homogenous medium reflectivity on the epiretinal surface, and conformed to the adjacent retinal anatomy. In contrast to ERM, LHEP did not induce distortion or edema of the underlying normal retinal tissue. In 2 eyes, cystic-like spaces were detected within the LHEP. In the area immediately around the full- or partial-thickness hole, there was a splitting
of the retina in the region of Henle’s fiber layer in 98.2% of
eyes with LMH and LHEP, and 87.7% had visible connecting
tissue on SD-OCT from the base of the lamellar hole to the
proliferating epiretinal tissue.

Conclusions: SD-OCT imaging showed a subset of patients, particularly
those with LMH, had a proliferation of epiretinal tissue with
medium reflectivity, with no evidence of contractile properties
that appeared to proliferate from injured layers of the mid-
etina. This phenotype differs from conventionally described
ERMs in appearance and induced changes of the underlying
retina. Given these distinct anatomic relationships, the
presence of LHEP could affect surgical outcomes.

Friday – 12:09

NOTES:
STRATEGY FOR THE MANAGEMENT OF MACULAR HOLES: THE EUROPEAN VITREO-RETINAL SOCIETY MACULAR HOLE STUDY

Ron Adelman, Yale University School of Medicine
Barbara Parolini
Zosia Michalewska
Didier Ducournau, EVRS

Purpose: To study factors associated with success or failure of macular hole repair.

Methods: International collaborative multi-center non-randomized clinical study spanning 4 continents. Clinical manifestations, techniques, dyes, tamponade agents, post-operative positioning, success rate and complications were studied.

Results: 140 retina specialists from 28 countries enrolled 4,207 cases of idiopathic macular hole. 85.7% of holes closed following vitrectomy and 59% gained at least 3 lines of visual acuity. After multivariate logistic regression, predictors for hole closure include earlier stage, shorter duration of hole and staining (p<0.001). There was no statistically significant difference among dyes including ICG, trypan blue, brilliant blue and other dyes. Staining improved anatomical outcome, but it did not affect visual outcome. There was no statistically significant difference in success rate among a variety of tamponades. Factors associated with better visual outcome include: hole closure, better baseline visual acuity, earlier stage and shorter duration of hole (p<0.001). 6% of cases had Inverted ILM flap technique that was associated with good anatomical and visual outcome. Retinal tear was noted in 3.2% of cases.

Conclusions: Vitrectomy for early macular hole is associated with better visual outcome. Staining improves anatomical success but not visual success. There was no statistically significant difference among tamponades. Inverted ILM flap technique may be a promising technique for large macular holes.
NOTES:
AUTLOGOUS TRANSPLANTATION OF THE INTERNAL LIMITING MEMBRANE FOR REFRACTORY MACULAR HOLES

Fumio Shiraga, Okayama University Graduate School
Yuki Morizane, Okayama University Graduate School

Purpose: To determine the effectiveness of autologous transplantation of the internal limiting membrane (ATI) for refractory macular holes.

Methods: Ten eyes of 10 consecutive patients who underwent ATI for the treatment of refractory macular holes were studied. The primary diseases in these patients were large idiopathic macular hole (disease duration longer than one year) (4 eyes), traumatic macular hole (1 eye), myopic foveoschisis (2 eyes), pit-macular syndrome (2 eyes) and proliferative diabetic retinopathy (1 eye). Except 5 eyes with idiopathic or traumatic macular holes, the other five eyes had developed macular holes after the initial vitrectomy with internal limiting membrane (ILM) removal. In all eyes, the regular macular hole surgery had failed in macular hole closure. The main outcome measures were the macular hole closure and the best-corrected visual acuity (BCVA).

Results: Macular holes were successfully closed in 9 eyes (90%) after ATI. The postoperative BCVAs were significantly better than the preoperative BCVAs (p = 0.007, paired t-test). Postoperative BCVAs improved by more than 0.2 logMAR in 8 eyes (80%) and were unchanged in 2 eyes (20%). In 9 eyes with successful closure of macular holes after ATI, transplanted ILM flaps were visible as a high reflective area on spectral domain optical coherence tomography within seven days after ATI. This high reflective area disappeared within 3 months.

Conclusions: ATI contributed to improved anatomical and visual outcomes in the treatment of refractory macular holes.
NOTES:
**FACTORS INVOLVED IN PERSISTENT SUBFOVEAL FLUID DEVELOPMENT FOLLOWING MACULAR HOLE SURGERY: AN INTRAOPERATIVE AND PERIOPERATIVE OCT ANALYSIS FROM THE PIONEER STUDY**

*Justis Ehlers, Cleveland Clinic*
*Yuji Ito, Cole Eye Institute*
*Peter Kaiser, Cole Eye Institute*
*Rishi Singh, Cole Eye Institute, Cleveland Clinic*
*Jamie Reese*
*Sunil Srivastava*

**Purpose:** To evaluate the variables associated with persistent subfoveal fluid formation following macular hole (MH) surgery utilizing intraoperative optical coherence tomography (iOCT) and perioperative OCT.

**Methods:** A prospective consecutive case series of eyes from the PIONEER iOCT study that underwent MH surgery were analyzed for postoperative persistent subfoveal fluid. Thirty-eight eyes of 37 patients with MH that underwent pars plana vitrectomy (PPV) and successful MH closure were included. The incidence and area of subfoveal fluid was assessed at 2 weeks postoperative on OCT. Clinical characteristics, preoperative OCT, and iOCT findings were analyzed relative to the subfoveal fluid area at 2 weeks following surgical repair. Preoperative OCT assessment included MH area and width. iOCT MH analysis involved architectural alterations analysis following internal limiting membrane (ILM) peeling, including the length of the subretinal hyporeflectivity; expansion of ellipsoid zone (EZ) [inner segment / outer segment (IS/OS)] to retinal pigment epithelium (RPE) (EZ-RPE height) and the length of lateral subretinal hyporeflectance expansion (SRHR) following ILM peeling. The correlation between the subfoveal fluid area and visual outcomes was also investigated.
Results: Two weeks following surgical repair, subfoveal fluid was identified in 59.3% of eyes. The mean subfoveal fluid area at postoperative 2 weeks was 10318.4 mm². No preoperative variables, including MH area and MH width were associated with the development/size of persistent subfoveal fluid. Following ILM peeling, the EZ-RPE height and length of SRHR significantly increased following ILM peeling [50.3 mm vs 41.8 mm, 3.43 mm vs 1.36 mm; respectively (p < 0.01)]. Architectural alterations following ILM peeling were the primary variables associated with subfoveal fluid incidence and size. Increased EZ-RPE height and increased SRHR were correlated with decreased subfoveal fluid size (p < 0.03). The presence of persistent subfoveal fluid significantly delayed vision recovery, though not the final visual acuity (p = 0.037).

Conclusions: The pathogenesis of persistent subfoveal fluid following MH surgery has been unknown. Architectural alterations to the outer retina identified with iOCT following ILM peeling are significantly associated with subfoveal fluid formation. The physical impact of ILM peeling on the RPE/outer retinal relationship may result in increased retinal tissue mobility, which may increase tissue apposition decreasing subfoveal fluid formation.

Friday – 12:36

NOTES:
Surgical and Anatomic Outcomes of Combined Penetrating Keratoplasty and Pars Plana Vitrectomy Cases

William Mieler, University of Illinois at Chicago
Randee Miller, University of Illinois at Chicago
Yannek Leiderman, University of Illinois at Chicago

Purpose: To report the visual and anatomic outcomes of combined pars plana vitrectomy (PPV) and penetrating keratoplasty (PKP) surgical cases (PPV-PKP cases).

Methods: The medical records of all patients who underwent combined PPV-PKP surgery at the Illinois Eye and Ear Infirmary from 01-2001 though 05-2013 were retrospectively reviewed. Patient demographics, ocular history, surgical procedures performed, pre- and postoperative visual acuities, presence of surgical complications, and final anatomic outcomes were recorded.

Results: Ninety patients were identified as having underwent a combined PPV-PKP procedure during the 12-year period. Eleven patients were excluded because of insufficient medical records. Of the remaining 79 patients (61% male, 39% female), 65 underwent a single combined PPV-PKP, 11 had two combined surgeries, and 3 required a third operation. The mean age at first surgery was 48 years. The most common indications for PPV surgery were retinal detachment (43%) and proliferative vitreoretinopathy (30%). The most common indications for corneal transplantation were corneal decompensation (43%), traumatic corneal scar (20%), and failed corneal graft (19%). Forty-two patients (53%) had a history of ocular trauma; thirty-six (86%) of these eyes had a history of an open-globe injury. Eighty percent of surgeries utilized a temporary keratoprosthesis (TKP). The average preoperative visual acuity was hand motions (LogMAR 2.4), while the average final visual acuity was slightly improved to a LogMAR value of 2.3 (p=0.05). Average follow-up time was 26 months. At final follow up, 54% of retinas remained
attached and 56% of corneal grafts were clear. Eighty-two percent of patients had at least one postoperative complication with the most frequent being some degree of corneal graft failure (62%), recurrent retinal detachment (34%), and hypotony (31%). Thirty-one patients (40%) had at least one subsequent surgical procedure.

Conclusions: Few large series examining the outcomes of combined PPV-PKP procedures exist in the current literature. In this report, a small, statistically significant improvement in final visual acuity was documented, yet the amount of improvement was limited by a significant number of complications. Combined PPV-PKP surgery is an option for eyes with complicated pathology, however patients should be educated regarding realistic outcomes and potential for postoperative complications.

Friday – 12:45

NOTES:
The 2014 Arnall Patz Medal Recipient

Tien Y. Wong, MD, PhD
Presented by Lloyd Paul Aiello, MD, PhD
Friday, February 21, 2014 – 12:54 p.m.

The Arnall Patz Medal is presented for outstanding contributions in retinal vascular and macular diseases

Arnall Patz, MD
Matthew Davis, MD
John Clarkson, MD, 1995
Daniel Finkelstein, MD, 1995
Ronald Klein, MD, 1996
Rosario Brancato, MD, 1997
Koichi Shimizu, MD, 1998
Morton F. Goldberg, MD, 1999
W. Richard Green, MD, 2000
Sohan S. Hayreh, MD, 2001
Eva M. Kohner, MD, FRCP, 2002
Gary C. Brown, MD, MBA, 2003
Evangelos Gragoudas, MD, 2004
Harvey Lincoff, MD, 2005
Michael L. Klein, MD, 2006
Jean-Jacques De Laey, MD, 2007
Yuval Yassur, MD, 2007
Napoleone Ferrara, MD, 2008
Lawrence J. Singerman, MD, FACS, 2009
Lawrence A. Yannuzzi, MD, 2010
Leonidas Zografos, MD, 2011
Gabriel J. Coscas, MD, 2012
Peter A. Campochiaro, MD, 2013

Dr. Wong completed medical school from the National University of Singapore, residency training ophthalmology at the Singapore National Eye Center, and graduate degrees (MPH and PhD) from the Johns Hopkins University. SERI is internationally recognized for vision and eye research, and has produced more than 1,000 scientific articles since 1997. Prior to his
current position, Dr. Wong was previously Professor and Chairman of the Department of Ophthalmology at the University of Melbourne.

Dr. Wong balances a clinical practice in macular and retinal diseases with a broad-based research program focused on the epidemiology of retinal diseases, particularly in the fields of diabetic retinopathy and age-related macular degeneration. He has made significant contribution in the development and application of retinal vascular imaging technology to understand early pathways in retinal and systemic diseases. He has published more than 800 peer-reviewed papers, including papers in the New England Journal of Medicine, the Lancet, the Journal of the American Medical Association (JAMA), and Nature. He has given more than 200 invited plenary, symposium and named lectures around the world, and received >US$40 million in peer-reviewed grant funding.

Dr. Wong is the Executive Editor of the American Journal of Ophthalmology, and on the Editorial Board of Investigative Ophthalmology and Visual Sciences, and Ophthalmic Epidemiology, having served terms on the Boards of British Journal of Ophthalmology and Diabetes Care. For his academic service and research, Dr. Wong has been recognized internationally with numerous awards, including the Sandra Doherty Award from the American Heart Association, the Alcon Research Institute Award, the Novartis Prize in Diabetes, the Commonwealth Health Minister’s Award for Excellence in Health and Medical Research, the Australian Society of Medical Research Medical Research of the Year Award and the President’s Science Award in Singapore.
**CHORIORETINAL FOLDS: ASSOCIATED DISORDERS AND A RELATED MACULOPATHY**

*Timothy Olsen, Emory Eye Center*

*Neal Palejwala, Emory University*

*Lyndon Lee*

*Steven Yeh*

*Chris Bergstrom*

**Purpose:** Chorioretinal folds (CRFs) represent a clinical sign that may be associated with multiple systemic, orbital and ophthalmologic disorders. We have reviewed forty patients and 57 eyes that have CRFs. We report both the associations with systemic disease and describe a CRF-related maculopathy.

**Methods:** Observational, retrospective case series. Methods: We reviewed fifty-seven affected eyes from 40 patients with the clinical sign of CRF from one of two academic institutions. Imaging studies were variable and included color fundus photographs, fundus autofluorescence, fluorescein (FA) and indocyanine green angiography, and ocular coherence tomography.

**Results:** The mean age at diagnosis was 63 years. We followed patients for a mean of 19 months. CRFs were most commonly associated with hyperopia (13). Systemic autoimmune disease was found in 11 (28%) patients. CRFs are commonly circumlinear along the temporal vascular arcades. The mean presenting Snellen visual acuity was 20/50, declining slightly to 20/60 at final follow-up. Twenty-two patients had FA with 36% demonstrating late leakage similar in appearance to that seen angiographically as occult CNV (late leakage of undetermined source). Of these, 4 did not receive treatment while 4 were treated, 2 with anti-vascular endothelial growth factor (VEGF) agents.
Conclusions: We propose that chronic CRFs, regardless of the etiology, are associated with a unique CRF-related maculopathy that has a FA appearance similar to occult choroidal neovascularization and occurs primarily in older individuals with chronic CRFs. This maculopathy has a slow evolution that leads to progressive, atrophic vision loss.

Saturday – 7:30

NOTES:
**Progression of Functional Loss in Macular Telangiectasia Type 2**

**Frank Holz, University of Bonn**  
*Tjebo Heeren*  
**Traci Clemens, EMMES**  
**Hendrik Scholl, Wilmer Eye Institute**  
**Alan Bird, Moorfields Eye Hospital**  
**Peter Charbel Issa**

**Purpose:** To investigate progressive functional loss in patients with macular telangiectasia (MacTel) type 2 and to compare the ability to detect functional decline between microperimetry and visual acuity testing.

**Methods:** In a prospective longitudinal observational study, 40 patients with MacTel type 2 underwent microperimetry testing (MP1, Nidek) to topographically map macular retinal sensitivity. A customized uniform test grid with a one degree interval between test points was used within the central visual field. Distance best corrected visual acuity (BCVA) was determined for comparison. The main outcome measure was the change of cumulative defect size (number of test points with absolute scotoma) on microperimetry testing and change in distance BCVA. All patients were phenotyped by various imaging modalities including SD-OCT and cSLO fundus autofluorescence.

**Results:** Mean review period was 55.3 months (SD=17.3 months; range: 24-87 months). In 58% of all 71 eyes included for analysis, microperimetry revealed spread (n=31) or new development (n=10) of an absolute scotoma. At the same time, BCVA decreased >2 lines in only 17%. Twenty-five (35%) eyes showed no change in visual function. Presence of an absolute scotoma at baseline, but not baseline BCVA, was predictive for functional decline on longitudinal microperimetry testing. Eyes with an absolute scotoma at
RESULTS CONTINUED

baseline showed further growth of the scotoma in 94%. In contrast, only 26% of eyes without an absolute scotoma at baseline developed an absolute scotoma de novo.

Conclusions: The results indicate a progressive visual field loss over time in MacTel type 2. Such loss of focal retinal sensitivity typically is more sensitive to detect functional decline and may precede significant loss of central visual acuity. Therefore, microperimetry may provide considerably more power when being used as a functional outcome parameter in future interventional clinical trials that aim to halt or slow the progression of MacTel type 2.

Saturday – 7:39

NOTES:
Purpose: To report visual and anatomic outcomes in eyes with idiopathic juxtafoveal macular telangiectasia (MacTel) undergoing small gauge vitrectomy surgery with gas tamponade for full thickness macular holes (FTMH)

Methods: Medical records of all adult patients with the diagnoses of both MacTel and FTMH who were diagnosed and had surgery between 2003-2013 at Casey Eye Institute were reviewed. Preoperative and postoperative data were obtained including visual acuity and OCT imaging to evaluate the overall visual acuity changes and the macular hole closure rates. These cases were then compared with historical controls that also underwent surgical repair as well as those undergoing observation only.

Results: Over a 10- year period, 3 cases that met the search criteria were identified. Hole closure was obtained in 2 of the 3 cases, with 2 cases requiring multiple procedures. Overall, final visual acuity was unchanged in these cases. Six prior cases undergoing surgical repair have been reported in the literature. In 3 of these cases, the holes closed while in 3 cases the hole remained open. In addition, 3 cases had improved vision while 2 had no vision changes and the 3rd had reduced vision post-operatively. In those cases undergoing observation only, visual acuity tends to remain stable over time.

Conclusions: Surgical intervention for MacTel and FTMH may not provide visual acuity benefit. Eyes with MacTel tend to have stable visual acuity even with the development of a FTMH without intervention. Unless visual acuity decreases dramatically, surgical intervention may not be warranted.
NOTES:
Biomarkers Lactate Dehydrogenase (LDH) and Hemoglobin (Hb) in Sickle Cell Ocular Microangiopathy

Anita Agarwal, Vanderbilt Eye Institute
Joshua Warren, Univ. of Pennsylvania Medical School
Vina Manjunath, Royal Victoria Infirmary
Josephine McGrath, Vanderbilt Eye Institute
Jaclyn Kovach, Bascom Palmer Eye Institute
Adetola Kassim, Hematology at Vanderbilt University Medical Center

Purpose: To evaluate biomarkers of hyperviscosity (hemoglobin levels, Hb) and hemolysis (lactate dehydrogenase, LDH levels) and correlate their role in ocular microangiopathy (conjunctival telangiectasia, non-proliferative and proliferative retinopathy).

Methods: A retrospective review of 201 patients with Sickle cell disease (SCD) examined and followed at the Vanderbilt Eye Institute was conducted. Institutional review board (IRB) approval was obtained. Their ages ranged from 8 to 60 years. One-hundred and twenty-one (121) were homozygous sickle cell (SS), 27 were sickle beta-thalassemia (SB+, SB0), 46 were heterozygous sickle cell (SC) and 7 were minor heterozygous genotypes (S-Arab, S-hereditary spherocytosis & others). Total hemoglobin and fetal hemoglobin levels, LDH Levels and use of hydroxyurea, were compared against ocular findings that included conjunctival telangiectasia, non-proliferative and proliferative retinopathy (ocular microangiopathy).

Results: Total hemoglobin levels (Hb levels) ranged from 10.12 to 14.02 gm/dL in the SC group, from 8.75 to 10.88 in SB group and from 6.79 to 10.52 in SS group. The ocular microangiopathy was most severe in the SC group that had the higher total hemoglobin levels. The median of mean LDH levels of all patients was 334. In the SS sub group, the mean LDH level was 593.95 in the retinopathy group versus 378.80 in the no-retinopathy group, the difference was significant. In the SB sub group, the mean LDH level was 417.50 in the retinopathy group and 362.32 in the no-retinopathy group.
RESULTS CONTINUED

The LDH levels in the SC subgroup were comparable between the retinopathy and no-retinopathy groups. Among the 64 patients who were receiving hydroxyurea, the mean fetal Hb was 11.60% while those not receiving hydroxyurea had a mean fetal Hb of 6.67%.

Conclusions: Higher Fetal Hb was seen in patients receiving hydroxyurea, which tended to protect against ocular microangiopathy. Higher LDH levels correlated with more severe retinopathy, suggesting a role for hemolysis in causing microangiopathy. Patients with SC genotype had higher total Hb, resulting in higher viscosity that is likely contributing to the angiopathy.

Saturday – 7:57

NOTES:
**Assessment of Subjective and Objective Screening Parameters for the Detection of Functional Hydroxychloroquine Toxicity**

*Catherine Cukras*

*Nancy Huynh*

*Susan Vitale, NIH*

*Wai Wong, National Eye Institute, NIH*

*Paul Sieving*

**Purpose:** To evaluate the association between parameters derived from subjective and objective screening tests for hydroxychloroquine (HCQ) retinal toxicity and the presence of functional HCQ toxicity.

**Methods:** Participants with a previous or current history of HCQ treatment of duration > 5 years were enrolled in a prospective, single-center study and evaluated with a detailed medical history, dilated ophthalmological examination, color fundus photography, fundus autofluorescence (FAF) imaging, spectral domain optical coherence tomography (SD-OCT), automated Humphrey visual field (HVF) testing (10-2), and multifocal electroretinography (mfERG). Participants were defined as either (1) affected or (2) unaffected by HCQ-induced retinal toxicity using mfERG R1/R2 ring ratios and absolute R1 amplitudes. Associations of affected status with participant features and with the following test parameters were assessed: OCT retinal thickness in macular subfields, HVF mean deviation (MD), and manual grading of fundus and OCT images.

**Results:** Participants (n=57; 91.2% female, age 55.7±10.4 years, HCQ treatment duration 15±7.5 years; mean±SD) were divided into affected (n=19) and unaffected (n=38) groups using mfERG parameters. Mean age and duration of HCQ use were not statistically different between groups. Mean OCT subfield macular thicknesses in all 9 subfields and mean HVF MDs in the affected group were significantly lower (p<0.01 for all comparisons) than in the unaffected group. Mean OCT
RESULTS CONTINUED

macular thicknesses in inner subfields and mean HVF MDs were significantly correlated with the magnitude of mfERG R1/R2 ratio across all participants (r=-0.45, p=0.0007). Masked grading of retinal images for the presence of features indicative of retinal toxicity were positive in the (1) affected and (2) unaffected groups respectively at the following rates: 68.4% and 0% on color fundus photographs, 73.3% and 9.1% on FAF fundus images, 84.2% and 0% on SD-OCT grading for perifoveal loss of the photoreceptor inner segment/outer segment junction. Using a polynomial modeling approach, OCT retinal thicknesses in the inner subfields and HVF MDs were identified among testing variables as being most closely associated with affected status.

Conclusions: Inner retinal subfield OCT thickness and 10-2 HVF MD are quantitative objective measures that correlate well with an mfERG-based identification of HCQ toxicity. These measures may have utility as accessible screening parameters for the detection of HCQ toxicity.

Saturday – 8:06

NOTES:
INTEGRATED GENOME- AND EXOME-WIDE ASSOCIATION STUDIES IN EAST ASIANS IDENTIFIES NOVEL CODING VARIANTS ASSOCIATED WITH AGE-RELATED MACULAR DEGENERATION

Tien Wong, Singapore Eye Research Institute
Ching-Yu Cheng
Kenji Yamashiro, Kyoto University Graduate School of Medicine
Li Jia Chen, Chinese University of Hong Kong
Jeeyun Ahn, Seoul Metropolitan Government Seoul National University Boramae Medical Center
Lulin Huang, The Institute of Laboratory Medicine, Sichuan Academy of Medical Sciences & Sichuan Provincial People’s Hospital
Luzhen Huang, Ministry of Education of China
Gemmy Cheung, Singapore National Eye Centre
Xiao Li, Ministry of Education of China
Zhenglin Yang, The Institute of Laboratory Medicine, Sichuan Academy of Medical Sciences & Sichuan
Kyu-Hyung Park, Seoul National University Bundang Hospital, Gyeonggi, Korea
Chi Pang, Chinese University of Hong Kong
Chiea Khor, Genome Institute of Singapore
Ngabisa Yoshimura, Kyoto University Graduate School of Medicine

Purpose: There are very significant differences in the clinical presentation and treatment response of age-related macular degeneration (AMD) between European ancestry populations and Asians. Currently, our knowledge of the mechanism and genetic architecture of AMD in Asians is extremely limited.

Methods: The Genetics of AMD in Asians (GAMA) consortium performed an integrated genome-wide and exome-wide association study on a total of 2,119 East Asian patients with exudative AMD and 5,691 controls recruited from Hong Kong, South Korea, Japan, and Singapore, with replication in further independently collected 4,226 AMD cases and 10,289 controls, all of East Asian descent.
Results: We found genome-wide significant associations with novel variation within the coding frame of four loci in 6p21.1 (odds ratio [OR] = 0.78, p = 6.19x10-18), 6p21.33 (OR = 1.27, p = 1.32 x 10-11) and 12q22 (OR = 0.87, p = 2.85 x 10-8) and 16q13 (OR = 1.70, p = 5.60 x 10-22), with increased susceptibility to exudative AMD. The amino acid substitution in 16q13 is an East-Asian-specific mutation and was previously shown to influence cardiovascular-related traits. In addition, we confirmed the previously identified associations in CFH (rs10737680, OR = 0.59, p=7.54x10-38) and ARMS2/HTRA1 (rs10490924, OR = 2.42, p =1.20x10-103).

Conclusions: We identify novel susceptibility genes for AMD in East Asians. Our findings suggest that Asian AMD not only shares common genetic variants with European forms of AMD, but also has its distinct genetic signature.

Saturday – 8:15

NOTES:
EXOMES AND STEM CELLS – GENETIC TESTING IN THE 21ST CENTURY

Edwin Stone, University of Iowa Carver College of Medicine
Adam DeLuca, Wynn Institute for Vision Research
Budd Tucker, The University of Iowa
Robert Mullins, University of Iowa
Todd Scheetz, Wynn Institute for Vision Research
Terry Braun, Wynn Institute for Vision Research

Purpose: The extreme sensitivity of whole exome sequencing has dramatically increased clinicians’ ability to identify disease-causing mutations in their patients with rare inherited retinal diseases; but, this sensitivity is accompanied by several significant costs including: increased turnaround time, increased complexity of the results, and reduced statistical significance. We hypothesized that these challenges could be largely overcome by 1) prescreening patients with simpler, more focused genetic tests and 2) using patient derived cell lines to confirm novel findings in selected individuals.

Methods: One thousand consecutive families with the clinical diagnosis of inherited retinal disease were subjected to a tiered testing strategy composed of one or more of the following steps: microfluidic allele-specific testing, conventional automated DNA sequencing, and plasmid cloning of candidate exons. Two-hundred fifty-six of these individuals also had whole exome sequencing performed, and of these, patient-derived cell lines were established from two hundred.

Results: Plausible disease-causing mutations were identified in 48% of the families using one or more of the pre-exome tests. This included 34 individuals with non-exomic mutations in ABCA4, USH2A and CEP290 and 78 individuals with mutations in the highly repetitive portion of RPGR — none of which would have been detected with conventional exome sequencing. Each of the exome sequences revealed approximately 130,000 departures from the consensus human sequence but more than 99% of these variants could be excluded as disease-causing on...
RESULTS CONTINUED

the basis of their population frequency, their predicted effect on the encoded proteins or both. After this filtering, 300-400 plausible disease-causing variants remained for further consideration in each patient. A third of the patients studied with exome sequencing were found to harbor a plausible disease-causing genotype in a known retinal disease gene. For twenty individuals, patient-derived cell lines were used to demonstrate the pathogenicity of rare or novel variants.

Conclusions: Clinically focused allele- and gene-specific tests have the advantage of low cost, quick turnaround, and high statistical significance. However, many disease-causing genes and mutations have not yet been discovered and thus cannot be detected with these methods. Whole exome sequencing coupled in selected cases with in vitro analysis of patient-derived cells can be used to find these novel variants in a substantial fraction of patients.

Saturday – 8:24

NOTES:
**Purpose:** Fundus autofluorescence (AF) is a noninvasive technique for evaluation of intrinsic autofluorescence of the tissues within the eye. In recent years, AF has become an important diagnostic tool for the assessment of age-related macular degeneration and retinal dystrophies. In this presentation, we review the recent literature on AF of intraocular tumors.

**Methods:** Review of personal experience and published reports.

**Results:** The autofluorescence (AF) features of intraocular tumors range from bright hyper-AF to dark hypo-AF. The fundus AF generally represents the status of the overlying retinal pigment epithelium (RPE). Choroidal nevi typically have overlying hypo-AF from chronic RPE atrophy as opposed to choroidal melanoma that exhibits hyper-AF from overlying lipofuscin within RPE (orange pigment) and free fluorophores within fresh subretinal fluid. Choroidal metastases demonstrate overlying hyper-AF that correlate with focal RPE accumulation of lipofuscin as well as subretinal fluid, on the fresh advancing tumor margin. Choroidal hemangioma displays overlying hyper-AF from lipofuscin within RPE and fresh subretinal fluid, and when when fluid is resolved hemangioma appears hypo-AF from RPE atrophy. Congenital hypertrophy of the retinal pigment epithelium displays by marked hypo-AF of the RPE lesion and trace hyper-AF within the lacunae.

**Conclusions:** Autofluorescence is a valuable diagnostic tool for assessment of intraocular tumors. Some findings are strongly characteristic of certain tumors, particularly the bright hyper-AF overlying small choroidal melanoma and the dark hypo-AF of congenital hypertrophy of the RPE.
EXPANDING CLINICAL AND HISTOPATHOLOGIC SPECTRUM OF OCULAR MELANOCYTOMAS

Jerry Shields, Wills Eye Hospital-Oncology Service  
Ralph Eagle, Jr, Wills Eye Hospital  
Carol Shields, Wills Eye Hospital

Purpose: In 1962 and 1965, Zimmerman published two classic papers on optic nerve melanocytoma and stressed the benign nature of this lesion that had often been misdiagnosed previously as malignant melanoma. Subsequent publications have shown that there several clinical variations of optic nerve melanocytomas and tumors with identical histopathologic features but different clinical expressions can also occur in the iris, ciliary body and choroid. The purpose of this presentation is to review the expanding clinical spectrum of ocular melanocytomas.

Methods: Review of personal clinical and histopathologic observations on intraocular melanocytomas and review of the literature on this condition.

Results: Since Zimmerman’s publications, clinical and histopathologic observations have expanded our knowledge of intraocular melanocytomas. Unlike choroidal melanoma, only 65% of patients are Caucasian. Visual symptoms are present in 25%. The melanocytoma was dark brown to black in 100%. Associated findings include choroidal component (50%), retinal component (30%), optic disc edema (25%), vitreous seeds (5%), and retinal vein and retinal artery obstruction (2%). Optic nerve melanocytoma can undergo spontaneous necrosis, resulting in pain and severe visual loss. About 15% show subtle enlargement over several years. Malignant transformation occurs in 1-2% but these tumors apparently have little, if any, metastatic potential. It has been found that tumors with identical histopathologic features can also occur in the iris, ciliary body and choroid where they have typical clinical features that differ from uveal melanoma.
Conclusions: Since Zimmerman’s original reports, much has been learned about the clinical features of intraocular melanocytomas.

NOTES:
COMPARISON OF THE DIAGNOSTIC CONTRIBUTION OF MULTIPLE OCULAR IMAGING TECHNIQUES IN A MULTIMODAL DIAGNOSTIC APPROACH OF SMALL PIGMENTED CHOROIDAL TUMORS

Leonidas Zografos, Hospital Ophtalmique Jules Gonin
Irmela Mantel, University Eye Hospital Jules Gonin
Ann Schalenbourg, University Eye Hospital Jules Gonin

Purpose: The aim of the present study was to evaluate the diagnostic contribution of multiple ocular imaging techniques, including color fundus photography, fluorescein angiography (FA), indocyanine green angiography (ICGA), fundus autofluorescence (FAF) and optical coherence tomography (OCT) for evaluation of diagnostic elements, valuable for the differentiation between a small choroidal melanoma and a thick choroidal nevus.

Methods: The diagnostic contribution of color fundus photography, FA, ICGA, FAF and OCT was analyzed in 85 patients (85 eyes) with a small pigmented choroidal tumor, measuring 2-10mm in diameter and 0.8-2.5mm in thickness. The presumed diagnosis was a large choroidal nevus in 60 cases (71%), and a small choroidal melanoma in 25 cases (29%). The following parameters were analyzed on each imaging technique: identification of the tumor border, the presence of any retinal detachment on the tumor surface and beyond the tumor borders, the presence of orange pigment, the presence of drusen, pigment epithelium changes, and the pin point phenomenon. Thus, each imaging technique received a score of its sensitivity for each diagnostic element.

Results: The highest score for the identification of the tumor borders was reached by color fundus photography and to a lesser degree by ICGA. An associated retinal detachment was best identified on OCT, followed by FA for any retinal detachment overlying the tumor, and FAF for any retinal detachment outside the tumor borders. Orange pigment was equally
RESULTS CONTINUED

depicted by fundus color photography and by FAF. Drusen identification reached the same score on fundus color photography and FA. The pin point appearance was exclusively identified on FA. Pigment epithelium changes showed the best score on FAF, followed by FA and fundus color photography.

Conclusions: The majority of the investigated ocular imaging technique played an important role in the identification of the diagnostic elements which contribute to the distinction between a small choroidal melanoma and a thick nevus: Fundus color photography was the most appropriate imaging technique for 3 differencing elements, and FAF, AF, and OCT for 2 differencing elements each. These results emphasize the value of multimodal imaging in the differential diagnosis of small pigmented choroidal tumors.

Saturday – 8:51

NOTES:
Purpose: We previously evaluated patients with tumors located within 1 disc diameter (dd) of the optic nerve to determine ocular outcomes after proton beam therapy. However, the effects of tumor size and location on long-term visual function were not assessed. We evaluated patients at high risk of visual loss (small and medium tumors located near the optic nerve and large tumors) to determine long-term visual prognosis after proton therapy.

Methods: One hundred sixty-seven patients with small or medium tumors (<5 mm in height and <15 mm in diameter) located within 1 dd of the optic nerve and 313 patients with large tumors (>5 mm in height and/or >15 mm in basal diameter) were included in the analysis. All patients selected for inclusion had pre-treatment visual acuity of 20/200 or better in the affected eye and at least 5 years of follow-up after treatment. Two endpoints were evaluated: vision retention of 20/200 or better and vision of counting fingers (CF) or better. Rates of vision loss were calculated using the Kaplan-Meier method.

Results: Vision remained 20/200 or better in 27% of patients with large tumors 5 years after radiation therapy and 49% had vision of counting fingers or better. Visual acuity of 20/200 or better was observed in 24% of patients with small and medium tumors located near the disc, and 68% had visual acuity of CF at 5 years. Large tumors located near the optic nerve fared poorly, with 11% having vision of 20/200 or better.
Conclusions: Long-term follow-up of patients with unfavorable tumor characteristics showed that a small number of patients maintain vision (5 years rates were 26% and 56% for visual acuities 20/200 or better and CF or better respectively). However, loss of all visual function is not inevitable. Even in the group of patients at greatest risk (large tumors within 1 disc diameter of the optic nerve) 33% retained vision of CF or better at 5 years.

NOTES:

Saturday – 9:00
Historopathologic and Genomic Analysis of Biopsy Sites for New FNAB Technique in Uveal Melanoma

Amy Schefler, Retina Consultants of Houston
James Major, Retina Consultants of Houston
Tien Wong, Retina Consultants of Houston
Patricia Chevez Barrios, Houston Methodist Hospital

Purpose: 1) To demonstrate a new technique for fine needle aspiration biopsy which increases surgeon ease and accuracy of sampling, and 2) To assess the presence or absence of tumor cells in the needle track with histopathologic confirmation.

Methods: This was a prospective, single-arm, observational case series of twelve patients who were scheduled to undergo enucleation and genomic analysis of a choroidal or ciliochoroidal uveal melanoma. After informed consent was obtained, patients underwent a fine needle aspiration biopsy using retinal instrumentation, standard retina wide-field viewing lenses, and chandelier lighting which facilitated an upright view and the ability to video the procedure as well as protect the scleral bed from extraocular extension of tumor cells. Extensive histopathology was performed of the biopsy sites with 25-50 serial sections through the area of the trocar insertion. Genomic analysis was performed on cells that were extracted as well as any present in the anterior vitreous.

Results: Fine needle aspiration produced a successful yield for genomic analysis in all cases. Intraocular pressure was maintained throughout the procedure and no infusion lines or injections of BSS were needed. No enucleation specimens demonstrated any tumor cells within the sclera, pars plana, or pars plicata. One specimen demonstrated a small collection of tumor cells within the anterior vitreous in the quadrant of the biopsy site. No patient developed orbital recurrence. One patient developed metastatic uveal melanoma during the study period.
Conclusions: Using this technique, fine needle aspiration biopsy for posterior tumors can be performed easily and safely with upright rather than inverted viewing requiring a minimally skilled assistant. Excellent cellular yield can be obtained. Detailed histopathologic analysis indicates that the tracking of tumor cells into the scleral bed using this technique does not occur. This is the first study to perform such an analysis after fine needle biopsy in vivo rather than in vivo and, along with recent clinical survey data, should put to rest the debate about this rare complication.

Saturday – 9:09

NOTES:

Jose Pulido, Mayo Clinic
Gene Chen, Mayo Clinic
Anthony Daniels, Vanderbilt Eye Institute
Robert Mittra
Sundeep Dev, VitreoRetinal Surgery, PA-Minn Center

Purpose: In 1984, Augsberger, Golden and Shields showed that cases of uveal melanoma that had fluorescein angiographic (FA) evidence of obliteration of retinal vessels or tumoral retinal anastomoses were indicators of retinal invasion. We evaluated the multimodal findings in cases of retinal invasion by uveal melanoma.

Methods: Cases of uveal melanoma diagnosed by clinical examination and ultrasound underwent multimodal imaging with OCT, FA, and ICG angiography.

Results: In cases of retinal invasion, OCT showed extension of the hyper-reflective melanoma into the retina causing loss of the normal retinal architecture. ICG and FA angiography showed that cases with retinal invasion could show tumoral angiomatous proliferations (TAP) or tumoral retinal anastomoses and angiomatous proliferations (TRAAP) and overlying abnormal retinal capillaries. ICG was helpful to show that the tumoral invasive vessels received were fed by the retinal vasculature.
Conclusions: OCT is the method of choice to demonstrate retinal invasion.

One of the co-authors (Pulido) and others have previously shown the presence of VEGF in melanomas. With invasion of the overlying retina, there is new vessel growth and remodeling of the pre-existing vascularity within the tumor and the retina probably because of the relative hypoxia in the elevated retina and the underlying tumor. The pathophysiology and anatomy of tumoral-retinal anastomoses and angiomatous proliferations (TRAAPs) therefore resembles that of advanced RAP.

Saturday – 9:18

NOTES:
INTRAVITREAL CHEMOTHERAPY FOR RETINOBLASTOMA: LOCAL AND SYSTEMIC SAFETY IN 107 INJECTIONS

David Abramson, Memorial Sloan-Kettering Cancer Center
Jasmine Francis, MSKCC
Brian Marr
Scott Brodie

Purpose: To review ocular and systemic safety of intravitreal injections for children with retinoblastoma from a single center (Memorial Sloan-Kettering Cancer Center, New York) using a standardized technique and dose.

Methods: Retrospective review of single center (Memorial Sloan-Kettering Cancer Center, New York) experience in 107 consecutive intravitreal injections using a standardized technique employing sterile technique, digital massage lowering intraocular pressure, 33 gauge needle delivery of 30 micrograms of filtered Melphalan via the pars plana. Toxicity measured by electoretinography (ERG) before and after each injection, complete blood counts (CBC), cytological analysis of needle washings and cytology of fluid collected from distilled water washing of the surface of the eyes.

Results: There was no effect on CBC’s and no adverse systemic effects. All needle washings and effluent were negative for retinoblastoma cells. ERG did show significant degregation which was not specific for the inner or outer retina. Following each injection a 5.8 microvolt degregation in response was found (p=0.0001) so that the mean degregation per patient was 34 microvolts (approximately 30% decrease from pretreatment levels). Age of the child, weight of the child and concurrent ophthalmic artery chemotherapy were not correlated with this response. There has been no improvement with time in these affected eyes. Two eyes demonstrated tethering of vitreous seeds suggesting vitreous loss from the injection.
Conclusions: 30 micrograms of Melphalan injected via the pars plana with a 33 gauge needle for children with retinoblastoma adversely affects ERG recordings. The decrease is seen following each injection, averaging 5.8 microvolts and totals 34 microvolts after all injections are given. The effect is not specific for the inner or outer retina and to date has not improved when treatments stops. The response does not correlate with the age of the child, weight of the child or whether the child is receiving concurrent ophthalmic artery chemotherapy. CBC’s were not affected and no malignant cells were detected in needle washings or surface effluent. Tethered vitreous seeds suggest that vitreous may be lost during the procedure.

Saturday – 9:27

NOTES:
The 2014 Paul Henkind Memorial Lecture and Award Presentation

J. William Harbour, MD
Presented by Rajendra S. Apte, MD, PhD
Saturday, February 22, 2014 – 9:36 a.m.

John Marshall, MD, 1987
Morton F. Goldberg, MD, 1988
Arnall Patz, MD, 1989
Lloyd M. Aiello, MD, 1990
Alan Bird, MD, 1991
Jerry A. Shields, MD, 1992
Lawrence A. Yannuzzi, MD, 1993
Howard Schatz, MD, 1994
J. Donald M. Gass, MD, 1995
Mark O. M. Tso, MD, 1996
Lee M. Jampol, MD, 1997
Jose Cunha-Vaz, MD, PhD, 1998
Curtis Meinert, PhD, 1999
Gerald A. Fishman, MD, 2000
Thomas M. Aaberg, Sr., MD, 2001
Frederick L. Ferris III, MD, 2002
Gerard Lutty, PhD, 2003
Gholam Peyman, MD, 2004
Robert N. Frank, MD, 2005
Peter Hamilton, MD, 2006
Paul Sternberg, MD, 2007
Lloyd P. Aiello, MD, PhD, 2009
Anthony P. Adamis, MD, 2010
Joan W. Miller, 2011
Usha Chakravarthy, MD, 2012
Richard F. Spaide, MD, 2013

J. William Harbour, MD, professor of ophthalmology and holder of the Mark J. Daily Endowed Chair in ophthalmology of the Bascom Palmer Eye Institute of the University of Miami, is known for his clinical, surgical and research expertise in ocular oncology.

One of the few physicians in the country that specializes exclusively in the diagnosis and treatment of eye cancer in adults and children, Harbour serves
as vice chair for translational research and director of the Bascom Palmer Eye Institute ocular oncology service.

Harbour received a bachelor of science degree in biochemistry, summa cum laude, from Texas A&M University, and medical degree from Johns Hopkins University School of Medicine in Baltimore, Maryland. Following a three-year residency in ophthalmology at the Wills Eye Hospital in Philadelphia, Pennsylvania, he completed clinical fellowships in vitreoretinal diseases and surgery at the Bascom Palmer Eye Institute, and ocular oncology at the University of California in San Francisco. Harbour also completed a fellowship in molecular genetics of retinoblastoma as a Howard Hughes/National Institutes of Health (NIH) research scholar at the National Cancer Institute of the NIH in Bethesda, Maryland, and completed a postdoctoral research fellowship in molecular oncology at Washington University in St. Louis, Missouri.

Prior to joining the faculty of Bascom Palmer Eye Institute, Harbour served as the Paul A. Cibis Distinguished Professor of Ophthalmology and Visual Sciences at Washington University. He is listed in America’s Top Doctors and Best Doctors in America.

An academic leader, Harbour has received as American Academy of Ophthalmology Achievement Award, the Association for Research in Vision and Ophthalmology’s prestigious Cogan Award and the Macula Society’s Rosenthal Award. He serves as associate editor of Melanoma Research and BMC Cancer, and peer or external reviewer for numerous scientific journals. He has authored more than 90 articles and 26 book chapters for publication and has served as invited lecturer or visiting professor on more than 150 occasions. Harbour has received research support totaling more than $3.4M and holds two patents; including one for a genetic test he developed to predict outcomes in patients with melanoma in the eye.

At the University of Miami, Harbour has a joint appointment at the Sylvester Comprehensive Cancer Center and oversees a multi-disciplinary team of physicians and scientists studying the genetics and genomics of major eye cancers.

Harbour has two daughters and lives in Key Biscayne, Florida.
Purpose: Multiple Evanescent White Dot Syndrome (MEWDS) has been a perplexing, idiopathic chorioretinal disease since its first description by Jampol and co-authors more than 25 years ago. It is believed to be an immune-mediated inflammatory disease seen in genetically predisposed individuals....a vague description at best. The typical presentation is in young, female adults with a mild degree of myopia and a sudden disturbance in the central vision of one eye. The clinical presentation varies, usually with a few to numerous “white spots” noted in the fundus, enlargement of the blind spot and a granular disturbance of the foveal area. There is a gradual, spontaneous recovery period of a few to several weeks and a few lasting chorioretinal spots may persist, along with foveal abnormality. Occasionally, there may be a recurrence in the same eye.

Methods: Retrospective Case Series with Multimodal Imaging of 17 newly diagnosed patients examined with multimodal imaging.

Results: New observations on the nature and distribution of the spots and the clinical course were observed clinically with Fundus Autofluorescence (FAF), SD-Optical Coherence Tomography (OCT) Imaging and Indocyanine Green (ICG) angiography.
Conclusions: With the advent of new technological imaging systems, particularly OCT, FAF, and ICG angiography, it is easier to make a specific diagnosis, since these diagnostic adjuncts show specific manifestations in MEWDS . . . but not always. In some patients, there may be difficulty in differentiating MEWDS from other “white spot syndromes,” most specifically idiopathic multifocal choroiditis. This presentation describes new observations in MEWDS that will assist in its diagnosis and also add to its clinical spectrum in quest of further knowledge on its pathogenesis, and hopefully its treatment.

Saturday – 10:21

NOTES:
**Saturday – 10:30**

**Macular Choroidal Blood Flow Velocity Increases with Regression of Multiple Evanescent White Dot Syndrome**

Susumu Ishida, Hokkaido University

**Purpose:** To quantitatively evaluate changes in choroidal circulation hemodynamics using laser speckle flowgraphy (LSFG) in patients with multiple evanescent white dot syndrome (MEWDS).

**Methods:** This study is a retrospective observational case series including 8 eyes of 8 patients with MEWDS and 8 fellow eyes as controls. All patients received indocyanine green angiography (ICGA). The mean blur rate (MBR), an index of quantitative relative blood flow velocity, at the macula was measured by LSFG. The changes of the average MBR, best-corrected visual acuity (BCVA), and the mean deviation (MD) values on Humphrey perimetry were analysed between the affected eyes and the fellow eyes during 12-week follow-up.

**Results:** White dots resolved in all eyes 3 months after initial visit together with significant improvement of visual functions (i.e., BCVA and MD values) and substantial reduction of hypofluorescent spots on ICGA. When compared with the baseline measurements, the average MBR significantly (P = 0.03 for both) increased by 20.0% and 15.8% in the affected eyes at 1 and 3 months, respectively, whereas no significant change was detected in the fellow eyes.

**Conclusions:** These results suggest that choroidal circulation impairment may play a role in the pathogenesis of MEWDS.
Saturday – 10:30

NOTES:
Idiopathic Multifocal Choroiditis/Punctate Inner Choroidopathy with Acute Secondary Photoreceptor Loss

Lee Jampol, Northwestern University
Marion Munk, Northwestern University
Amani Fawzi, Northwestern University
Jesse Jung
Ursula Schmidt-Erfurth, Medical University Vienna
Kristin Biggee, Casey Eye Institute

Purpose: To report 6 cases (7 eyes) of idiopathic multifocal choroiditis (MFC)/PIC with small discrete chorioretinal lesions but extended acute photoreceptor (PR) irregularity and loss.

Methods: A retrospective multimodal imaging case series

Results: Five females and 1 male were included (mean age at disease-onset 31±6.4, range 23-42 years). Visual acuity at presentation was as severe as hand-motion with the central visual loss not explained by ophthalmoscopically visible lesions. No vitreous cells were present. SD-OCT showed extensive loss/irregularity of the ellipsoid zone, interdigitation zone and the external limiting membrane (ELM) not limited to the immediate location of the MFC lesions. The corresponding areas of PR-loss were hyperautofluorescent with FAF, the MFC lesion were hypoautofluorescent. ICG and FA showed only the MFC lesions. Scotomata detected in visual field corresponded to the areas of PR-loss. In 4 cases an ERG was performed, which showed a markedly reduced flat cone response and a markedly reduced rod-response. Four patients were treated with oral corticosteroids, 1 patient with additional intravitreal Avastin injections. Only in a single case was photoreceptor integrity restored.
Conclusions: MFC/PIC can present with a dramatic secondary permanent or transient PR-loss. Severity and extension of these MFC-associated changes are best evaluated using a multimodal imaging approach. It seems likely this rare presentation is a variant of MFC with chorioretinal atrophy, recently described by Jung et al.

Saturday – 10:39

NOTES:
PATHOGENESIS OF PERSISTENT PLACOID MACULOPATHY: A MULTIMODAL IMAGING ANALYSIS

Grant Comer, University of Michigan
Kanishka Jayasundera, University of Michigan
Melisa Nika, University of Michigan

Purpose: Persistent placoid maculopathy (PPM) is a rare, idiopathic, maculopathy affecting the choroid and outer retinal layers of both eyes. This report provides structural and functional evidence of PPM pathogenesis and justifies immunosuppression for short-term management.

Methods: This longitudinal case series follows three individuals with PPM for up to two years. Spectral domain optical coherence tomography, fundus autofluorescence, indocyanine green angiography, and microperimetry abnormalities were analyzed at baseline and again at various times after a treatment course of high-dose systemic corticosteroids.

Results: Multimodal imaging suggests that PPM affects the choriocapillaris and sub-retinal pigment epithelium space with secondary involvement of the outer retinal layers. Furthermore, imaging provides compelling evidence that PPM results from an inflammatory infiltrate that abates shortly after initiating high-dose systemic corticosteroids.

Conclusions: High-dose systemic corticosteroids may be necessary to limit sequelae from PPM. Natural history and controlled interventional studies are needed to support these findings and establish optimal long-term management.
ENDOPHTHALMITIS CAUSED BY STREPTOCOCCAL SPECIES: CLINICAL SETTINGS, MICROBIOLOGY, MANAGEMENT, AND OUTCOMES

Harry Flynn, Bascom Palmer Eye Institute
Ajay Kuriyan
William Smiddy, Bascom Palmer Institute
Audina Berrocal
Thomas Albini, Bascom Palmer Eye Institute
Darlene Miller, Bascom Palmer Eye Institute

Purpose: To report the clinical settings, antibiotic susceptibilities, and outcomes of endophthalmitis caused by Streptococcus species.

Methods: Single-center, retrospective, observational case series evaluating all patients with culture-positive endophthalmitis caused by Streptococcus species between January 1, 2000 and December 31, 2011.

Results: Study criteria were met by 63 patients. The most common clinical settings were bleb-associated (17, 27%), post-intravitreal injection (16, 25%), and post-cataract surgery (13, 21%). The isolates were S. viridans (47, 71%), S. pneumoniae (13, 21%), and β-hemolytic Streptococci (5, 8%). Sixty (95%) of 63 isolates were susceptible to vancomycin, 47 (98%) of 48 to ceftriaxone (third generation cephalosporin), and 57 (93%) of 61 to levofloxacin (third generation fluoroquinolone). Between the first and second half of the study period, the minimal inhibitory concentration (MIC) of antibiotics required to inhibit 90% of isolates increased by 1.5-fold for ceftriaxone and 2-fold for levofloxacin, and remained the same for vancomycin. Initial treatment was vitreous tap (49, 78%) or pars plana vitrectomy (14, 22%); all received intravitreal antibiotics. Visual acuity outcomes were variable; best corrected visual acuity (BCVA) was ≥20/400 in 16 (25%) patients and <20/400 in 47 (75%) patients. Evisceration/enucleation was performed in 16 (25%) patients.
Conclusions: Streptococcus isolates generally had high susceptibility rates. There were higher MICs required to inhibit 90% of isolates in vitro in the second half of the study period compared to the first half. Despite prompt treatment, the majority of patients had poor outcomes.

Saturday – 10:57

NOTES:
Assessment of Changes in Quality of Life Among Patients in the SAVE Study – Sirolimus as Therapeutic Approach to Uveitis: A Randomized Study to Assess the Safety and Bioactivity of Intravitreal and Subconjunctival Sirolimus in Patients with Uveitis

Quan Nguyen, Truhlsen Eye Institute, University of Nebraska Medical Center
Erin Vigil, Johns Hopkins University
Yasir Sepah, University of Nebraska Medical Center
Mohamed Ibrahim, Truhlsen Eye Institute, University of Nebraska Medical Center
Diana Do, Truhlsen Eye Institute, University of Nebraska Medical Center

Purpose: To assess the change in quality of life (QOL) in patients with non-infectious posterior, intermediate, or panuveitis, treated with subconjunctival (SCJ) or intravitreal (IVT) sirolimus as an immunomodulatory therapeutic (IMT) agent, delivered subconjunctivally (SCJ) or intravitreally (IVT) in the SAVE Study.

Methods: The 25-question Visual Function Questionnaire (VFQ-25) was administered at baseline, month 6, and month 12 visits. The survey measures self-reported vision health status for patients with chronic eye disease. The questionnaire assesses the effects of visual impairment on both task-oriented visual function and general health domains such as emotional well-being and social functioning. Each patient's questionnaire was converted to a scaled score between 0 (worst) and 100 (best). Individual question scores were combined into 12 different subcategories.

Results: Thirty subjects were randomized in the SAVE study (SCJ:IVT, 1:1). Among the 24 subjects who finished month 12, 18 completed all questions of the VFQ-25 at all three time points. Mean and median scores were calculated for each of
the subcategories and for overall composite score at baseline, month 6, and month 12, using Stata 12. Wilcoxon signed-rank test was performed. Overall, patients showed a significant improvement in composite scores between BL and month 6 as well as BL and month 12. From BL to month 6, patients showed significant improvements in the subcategories of general vision, distance activities, vision-specific mental health, and vision-specific role difficulties. From BL to month 12 patients improved significantly in the subcategories of vision specific mental health and vision-specific role difficulties.

Conclusions: Patients with uveitis who have been treated with local delivery of sirolimus demonstrated significant improvement in their QOL during the 12-month course of therapy. Specifically, subjects have gained in vision health and function. Larger randomized control trials with sirolimus are indicated to validate this gain in QOL.

Saturday – 11:06

NOTES:
**PERIPHERAL CRYOABLATION FOR TREATMENT OF PARS PLANITIS**

*James Folk, University of Iowa Hospitals & Clinics*

*Elliott Sohn, University of Iowa*

*Ben Chaon*

**Purpose:** To compare the outcomes of patients with active pars planitis who were treated with cryoablation to active snowbanks to patients who did not receive cryo.

**Methods:** A retrospective review of patients with pars planitis treated at the University of Iowa from 1973-2013 was conducted. Patients who underwent cryotherapy met inclusion criteria if they demonstrated evidence of intraocular inflammation with snowbanking and had a negative serologic workup for other causes of inflammation. Data collected at the initial and follow-up visits included: visual acuity, inflammatory activity (anterior chamber and vitreous cell), cystoid macular edema, treatment with cryoablation to peripheral snowbanks, use of topical, peri- or intraocular and/or systemic corticosteroids and immunosuppressive agents. Outcomes were analyzed using Kaplan-Meier survival estimates. Eyes that did not receive cryoablation were termed control eyes.

**Results:** 186 eyes (50 cryo-treated and 136 control) from 95 patients met eligibility criteria. Mean follow-up was 55.7 months. Cryoablation eyes had resolution of CME more often than control eyes, (p=0.006). Vitreous cell was significantly improved in the cryoablation eyes compared to the control eyes (p=0.005). AC cell significantly improved in the cryo group compared to controls (p=0.003). Overall, there was a trend toward better visual acuity in the cryo group compared to controls (p=0.068). The proportion of patients treated with systemic steroids increased during follow up among the control group, but tended to remain stable in the cryo-treated group (p=0.057). Visual acuity improved or remained stable in the majority of patients treated with cryotherapy.
Conclusions: Cryotherapy was associated with resolution of CME and significantly improved inflammatory activity compared to standard therapy. These results suggest a role for cryoablation in the treatment of patients with active pars planitis.

Saturday – 11:15

NOTES:
OUTCOMES OF TREATMENT OF PEDIATRIC CNV WITH INTRAVITREAL ANTI-ANGIOGENIC AGENTS: THE RESULTS OF THE KKESH INTERNATIONAL COLLABORATIVE RETINA STUDY GROUP

J. Fernando Arevalo, King Khaled Eye Specialist Hospital
Igor Kozak
Ahmad Mansour
Rocio Diaz
Jorge Calzada
Francesco Pichi
Vanessa Cruz-Villegas
Manuel Diaz-Llopis
Roberto Gallego-Pinazo, University and Polytechnic
Jay Chhablani, L V Prasad Eye Institute
Mauricio Martinez Cartier
Martin Meerhoff
William Mieler, University of Illinois at Chicago

Purpose: To evaluate safety and clinical results after the use of intravitreal anti-angiogenic agents for the treatment of choroidal neovascularization (CNV) in pediatric patients.

Methods: Retrospective multicenter study of a total of 45 eyes of 39 pediatric patients with CNV who were treated with intravitreal injection of anti-angiogenic agents (1.25 mg/0.05 ml bevacizumab [40 eyes] or 0.5 mg/0.05 ml ranibizumab [5 eyes]). Choroidal neovascularization due to various causes was clinically diagnosed and confirmed with imaging studies.

Results: There were 24 girls and 15 boys with group median age 13 years (range 3-17 years). Mean follow-up period was 12.8 months (range 3-60 months). The etiology of the CNV included idiopathic, uveitic, myopic CNV, and CNV associated with various macular dystrophies. Median logMAR visual acuity at presentation and last follow-up was 0.87 (Snellen equivalent 20/150) and 0.7 (Snellen equivalent 20/100), respectively which was statistically significant.
RESULTS CONTINUED

(p=0.0003). Mean and median number of injections received over the follow-up period was 2.2 and 1, respectively. At the last follow-up, 22 eyes of this group (48%) gained more than 3 lines of vision and 27 eyes (60%) had final visual acuity 20/50 or better. Nine eyes (20%) did not improve and had severe vision loss (20/200 or worse).

Conclusions: Intravitreal anti-angiogenic therapy for CNV in pediatric patients seems temporarily safe and effective in the majority of affected eyes. Due to the rarity and character of this condition, it is unlikely that any clinical trials will soon take place to study this or other treatment options.

Saturday – 11:24

NOTES:
AGGRESSIVE POSTERIOR RETINOPATHY OF PREMATURITY IN COSTA RICA

Libeth Wu, Instituto de Cirugía Ocular
Ana Catalina Tabarez-Carvajal, Hospital Nacional de Niños
Deyanira Mora-Solano, Hospital Nacional de Niños
Carlos Paniagua-Cascante, Hospital Nacional de Niños
R.V. Paul Chan, Weill Cornell Medical College

Purpose: To describe the incidence, management and outcomes of patients with aggressive posterior retinopathy of prematurity (AP-ROP) in Costa Rica during 2005-2012.

Methods: Retrospective study of 32 patients that were diagnosed with AP-ROP. In Costa Rica, all premature babies born with a birth weight of ≤ 1500 g or with a gestational age of ≤ 34 weeks are screened for ROP.

Results: During the study period, 4,390 neonates were screened for retinopathy of prematurity (ROP). Of these, 993 (22.6%) were diagnosed with ROP including 32 (0.73%) with AP-ROP. The mean gestational age at birth of patients with AP-ROP was 27.4 weeks with a range of 24 to 33 weeks. The mean birth weight was 868.2 g with a range of 665 to 1680 g. All 64 eyes with AP-ROP were treated with laser ablation of the avascular retina, 22 (34%) eyes required 2 laser sessions, 6 (9.3%) eyes required 3 sessions and the remaining 36 eyes (56%) were treated in one session. Despite adequate treatment, 2 (3.1%) eyes went on to a Stage 4A retinal detachment and 3 (4.7%) eyes developed a total retinal detachment.

Conclusions: Most eyes with AP-ROP in this study had a favorable outcome following laser ablation. However, approximately 8% of eyes progressed to retinal detachment despite adequate laser photocoagulation.
NOTES:
The 2014 Evangelos S. Gragoudas Award

Glenn C. Yiu, MD, PhD
Presented by Cynthia Toth, MD
Saturday, February 22, 2014 – 11:42 a.m.

Presented to the Vitreo Retinal fellow, sponsored by an active Macula Society member, who has the most highly regarded paper either published or in press as determined by the Awards Committee members ranking

Mark Kleinman, MD, 2012
Ruwlan Amila Silva, MD, 2013

Glenn C. Yiu, MD, PhD

Glenn C. Yiu, MD, PhD was born in Hong Kong and grew up in Brooklyn, NY. He completed his undergraduate studies at Columbia University, graduating summa cum laude with a double major in Biochemistry and Psychology. In 2000, he moved to Boston to pursue a combined MD-PhD degree at Harvard Medical School, obtaining his PhD in Neurobiology in 2006, and an MD with honors in 2008. His graduate thesis explored mechanisms of axon regeneration in the central nervous system. After completing a medical internship at Brigham & Women’s Hospital, he underwent residency training in ophthalmology at the Massachusetts Eye & Ear Infirmary. Currently, he is a clinical fellow in vitreoretinal surgery at Duke University, where he is involved in research examining the choroid’s role in ocular disease using enhanced-depth optical coherence tomography. Dr. Yiu has been the recipient of numerous awards, including the Heed Ophthalmic Foundation Fellowship Award, the Retina Society Fellowship Research Award, and the Ronald G. Michels Foundation Fellowship Award. After training, he wishes to pursue an academic career as a clinician-scientist. He is happily married to his wife Melody, and takes care of two pet rats with her.
Safety, Pharmacokinetics, and Efficacy of Intraocular Celecoxib

Stephen Kim, Vanderbilt Eye Institute
Jinsong Sheng, Vanderbilt University
Rohan Shah, Vanderbilt
Sunil Vooturi, University of Colorado Denver
Uday Kompella, University of Colorado Denver

Purpose: To determine the safety, pharmacokinetics, and anti-inflammatory effects of intraocular celecoxib in rabbits.

Methods: The right eye of animals received a single 0.1 ml injection of celecoxib (1.5mg, 3mg, or 6mg) prepared in dimethyl sulfoxide (DMSO). Left eyes served as controls and received 0.1ml DMSO. Dark- and light-adapted electroretinograms (ERG) were obtained at baseline and at 1, 4, and 12 weeks after injection. After 12 weeks, eyes were enucleated for histopathological analysis. For intraocular pharmacokinetics, 3mg of celecoxib was injected into both eyes of each animal. Drug levels in vitreous and retina/choroid were analyzed by high-performance liquid chromatography and tandem mass spectrometry at the following time points after injection: 0.25 hr (15 min), 1, 4, 24, and 72 hours and at 1, 2, 4, and 8 weeks. For efficacy experiments, 1µg lipopolysaccharide (LPS) in 50µl saline was injected into the vitreous of both eyes to induce inflammation. The right eye of each animal was then injected immediately afterwards with either 3mg celecoxib (6 eyes) or 2mg triamcinolone acetonide (6 eyes). The left eye served as a control and was injected with equal volume (50µl) saline. Twenty-four hours later, 200 µl of aqueous fluid was removed and total leukocyte concentration was determined by a masked observer using a hemocytometer. Remaining aqueous fluid was immediately diluted 1:1 in chilled stabilization buffer and prostaglandin E2 (PGE2) concentration was later determined by enzyme-linked immunoassay.
Results: Serial ophthalmic examinations showed no signs of intraocular inflammation or increased intraocular pressure in celecoxib-injected eyes, but cataract formation was observed at higher concentrations. Histologic and ERG studies demonstrated no signs of retinal or optic nerve toxicity. After a single injection of 3mg celecoxib, both vitreous (28.5 ng/ml) and retina/choroid (26.1 µg/ml) drug concentration at 8 weeks exceeded the minimum inhibitory concentration 50 (MIC50) of its target enzyme cyclooxygenase-2. Treatment with celecoxib and triamcinolone significantly reduced total leukocyte count by 40% (P = 0.02) and 31% (P= 0.01) respectively. Mean leukocyte count was 13,400 ± 7052 cells/µl in control eyes (LPS and saline) and 8094 ± 6400 cells/µl and 9222 ± 5100 cells/µl in celecoxib- and triamcinolone-treated eyes respectively. Reduction in PGE2 levels paralleled reduction in leukocyte counts. Mean PGE2 was 7140 pg/ml in control eyes and 2769 pg/ml (P = 0.04) and 1209 pg/ml (P < 0.01) in celecoxib- and triamcinolone-treated eyes respectively.

Conclusions: Intraocular injection of celecoxib was nontoxic to the retina and optic nerve. Pharmacokinetic analysis demonstrated excellent penetration into the retina/choroid and maintenance of drug levels that exceeded the MIC50 out to 8 weeks. Celecoxib demonstrated potent anti-inflammatory effects after intraocular injection but there was an association with cataract formation at higher concentrations.

Saturday – 11:51

NOTES:
GENETIC AND ENVIRONMENTAL FACTORS IN AMD

Stephen Tsang, Columbia University Medical Center
Jin Yang, Columbia University

Purpose: To explore the mechanisms of AMD with iPSC-derived RPE cells carrying an ARMS2/HTRA1 allele mutation.

Methods: The ARMS2/HTRA1 mutation was confirmed through gene sequencing. Patient-specific iPS was derived from fibroblasts and differentiated into RPE. Immunostaining and immunoblots confirmed RPE-specific marker expression. A high-risk group with mutant alleles and low-risk wild-type group were fed 5 times with 10uM A2E over 10 days. Fluorescent microscopy examined autofluorescence. After 10 minutes of blue light treatment, suspended fluorescent cells were compared between groups. Transmission electron microscopy (TEM) was used to compare morphology of iPSC-derived RPE cells, both pre- and post-treatment and with native cells from two monkeys (aged 1 and 24). Waters synapt G2 QTOF Mass Spectrometry analyzed label-free shotgun proteomics with identityE quantitation software (MS). Western blots further assayed proteins.

Results: Neither high-risk nor low-risk cells displayed changes in RPE-specific markers. HTRA1 was elevated among high risk groups. Pre-treatment iPSC-RPE cells resembled 1-year-old monkey RPE morphologically. After treatment, a mixture of phacosomes and lipofuscin appeared as in aged monkey cells. Higher SOD2 protein concentrations were pronounced in low risk cells. In low risk cells, SOD activity kit showed a combination of A2E with blue light stimulated SOD; there was almost no response in the high risk group.

Conclusions: iPSC-RPE cells treated with A2E and blue light appeared similar to AMD patient RPE cells, suggesting utility as a disease model. Changes in activity of SOD2 may reflect the disease mechanisms of ARMS2/HTRA1-related AMD.
TARGET-INDIRECT SUPPRESSION OF CHOROIDAL NEOVASCULARIZATION BY HUMAN IgG1 OR IVIG

Jayakrishna Ambati, University of Kentucky

Purpose: Bevacizumab, a humanized IgG1 (hIgG1) monoclonal antibody (mAb), is used in choroidal neovascularization (CNV). Although bevacizumab binds human VEGF but not mouse VEGF, it has been reported to suppress angiogenesis in mice. We hypothesized that an intrinsic characteristic of the IgG1 mAb, independent of its target, was responsible for its angioinhibitory effect.

Methods: We tested the effect of bevacizumab, ranibizumab (an anti-VEGF Fab fragment lacking the Fc portion), purified hIgG1, 7 other therapeutic human IgG1 or IgG2 mAbs, and intravenous immunoglobulin (IVIG) in the laser-induced CNV mouse model. Bevacizumab was also tested in humanized VEGF mice, mice lacking Fc RI, the high affinity receptor for the Fc portion of hIgG1, and in wild-type mice undergoing bone marrow transplantation (BMT) from Fc RI -/- mice. Tissue biopsies from patients treated with either IVIG or a hIgG1 mAb for non-ocular conditions were assessed for blood vessel density before and after treatment.

Results: Bevacizumab, 6 other therapeutic hIgG1 mAbs, and IVIG inhibited CNV when administered by intravitreously. IVIG was also effective when injected systemically. However, neither ranibizumab nor bevacizumab depleted of its Fc moiety nor a therapeutic hIgG2 mAb (which does not bind Fc RI) were angioinhibitory. In humanized VEGF mice, bevacizumab was more effective than ranibizumab. The anti-angiogenic effect of bevacizumab was abrogated by Fc blockade or Fc RI ablation. Bevacizumab reduced macrophage infiltration into CNV, and did not suppress angiogenesis in wild-type mice receiving Fc RI -/- bone marrow, implicating circulating...
macrophages. In kidney, muscle, and skin biopsies from humans treated with IVIG or a hIgG1 mAb, blood vessel density was reduced after treatment.

Conclusions: We have identified a novel target-independent, Fc RI-dependent anti-angiogenic class effect of hIgG1 antibodies and IVIG, which are used in millions worldwide. Our findings offer new, and potentially inexpensive, therapeutic opportunities for repurposing existing, approved drugs as angioinhibitors for neovascular diseases. Our data also provide a rationale for clinical testing of higher doses of bevacizumab to achieve an additive effect of VEGF inhibition and Fc RI activation, and of local or systemic IVIG. This work also strikes a cautionary note for greater vigilance in the use of therapeutic hIgG1 mAbs not intended to suppress angiogenesis.

Saturday – 12:09

NOTES:
Purpose: Neovascular age-related macular degeneration is a leading cause of irreversible vision loss in the Western world. Neovascular age-related macular degeneration (NV-ARMD) leads to irreversible vision loss as a consequence of pathologic angiogenesis. Intravitreal use of neutralizing antibodies to VEGF-A provides significant visual rehabilitation, but recalcitrant cases are emerging, with one study reporting 45% of NV-ARMD patients not having the desired response to anti-VEGF monotherapy. Also, the need for frequent, repeat treatments have clinicians and scientists searching for durable treatments that can reduce dependence on anti-VEGF. Cytokine-targeted therapies (such as anti-vascular endothelial growth factor) are effective in treating pathologic ocular angiogenesis, but have not led to a durable effect and often require indefinite treatment. The purpose of this study is to identify a durable method of inhibiting CNVM, and reduce patient, physician, and healthcare burden.

Methods: Cell based assays, flow cytometry, immunohistochemistry, immunofluorescence, western blot, quantitative PCR, matrigel tube assay, TUNEL assay, several rodent models of retinal angiogenesis, and hind limb ischemia were performed for this study.

Results: We show that Nutlin-3, a small molecule antagonist of the E3 ubiquitin protein ligase MDM2, inhibited angiogenesis in several model systems. We found that a functional p53 pathway was essential for Nutlin-3–mediated retinal antiangiogenesis and disruption of the p53 transcriptional network abolished the antiangiogenic activity of Nutlin-3. Nutlin-3 did not inhibit established, mature blood vessels in the adult mouse retina, suggesting that only proliferating
retinal vessels are sensitive to Nutlin-3. Furthermore, Nutlin-3 inhibited angiogenesis in nonretinal models such as the hind limb ischemia model.

Conclusions: Our work demonstrates that Nutlin-3 functions through an antiproliferative pathway with conceivable advantages over existing cytokine-targeted antiangiogenesis therapies. Epimacular and juxtascleral brachytherapy are being evaluated in clinical trials with mixed success. MDM2 inhibitors may have a more attractive side effect profile, since they do not elicit DNA damage and, with repeat administration, may even be more robust than a single radiation treatment. Our in vivo results suggest that MDM2 inhibitors, such as Nutlin-3, offer a new therapeutic strategy for inhibiting retinal angiogenesis and may be complementary to existing treatments. Optimization or investigation of other MDM2 inhibitors is attractive for the treatment of NV-ARMD.

Saturday – 12:18

NOTES:
TARGETED KNOCKDOWN OF OVEREXPRESSED VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF)164 IN MUELLER CELLS SAFELY REDUCES INTRAVITREAL NEOVASCULARIZATION IN MODEL OF RETINOPATHY OF PREMATURITY

Mary Elizabeth Hartnett, Moran Eye Center, University of Utah
Yanchao Jiang, Moran Eye Center
Haibo Wang, Moran Eye Center
Zhibong Yang, Moran Eye Center
Lori Fotheringham

Purpose: Compared to antibody against vascular endothelial growth factor (VEGF), targeted inhibition of VEGFA in Mueller cells (MCs) significantly reduced intravitreal neovascularization (IVNV) without reducing body weight gain and retinal thickness in a rat model of retinopathy of prematurity (ROP). Here, we assessed safety of targeted inhibition of overproduced MC-VEGFA compared to rat splice variant VEGF164 in the rat ROP model.

Methods: The rat ROP model was adapted to inhibit overproduced MC-VEGFA or MC-VEGF164 using a lentivector with a CD44 polymerase II promoter that permitted coexpression of GFP and shRNA. Efficient expression of shRNAs to VEGFA, VEGF164 or control luciferase occurred by embedding each within a microRNA. In vitro testing was performed on plasmids containing shRNAs for VEGF, VEGF164 or control for specificity and efficiency of knockdown. Purified viruses were delivered by subretinal injections to day 8 rat pups in the ROP model. GFP expression was assessed with Micron III imaging. At day 18 and 25, retinal lysates, sections or flat mounts were prepared for protein, apoptotic cells, avascular retinal area (AVA) and IVNV.

Results: shRNAs for VEGFA or VEGF164 were chosen based on the best knockdown of mRNA and protein in rat MCs. GFP was visualized at p18 and p25 in vivo. Knockdown of VEGF
RESULTS CONTINUED

occurred in retinal lysates. At p18, knockdown of MC-VEGFA or MC-VEGF164, compared to luciferase-shRNA control, significantly inhibited IVNV (P<0.001) without affecting AVA. At p25, all groups had less IVNV than at p18, and knockdown of MC-VEGF164 significantly inhibited IVNV compared to MC-VEGFA. TUNEL positive cells were greater in the outer nuclear layer at p18 in retinas treated with MC-VEGFA shRNA (P<0.001) compared to MC-VEGF164 shRNA or control. There was no difference in TUNEL positivity at p25 or in retinal thickness, body weight gain or serum VEGF at either time point or treatment.

Conclusions: Targeted reduction in overproduced VEGFA may provide a safe means to inhibit pathologic angiogenesis in conditions like ROP, in which ongoing development occurs. Knockdown of MC-VEGF164 may be safer than knockdown of MC-VEGFA. More study is warranted to determine potential effects on retinal function from MC-knockdown of VEGFA or MC-VEGF164.

Saturday – 12:27

NOTES:
ROLE OF NITRIC OXIDE IN EARLY DIABETIC RETINOPATHY

Jennifer Kang-Mieler, Illinois Institute of Technology
Micah Guthrie, Illinois Institute of Technology

Purpose: It is well known that nitric oxide (NO) production is altered in diabetic retina. Recently, we have developed a nitric oxide sensor that can measure the intraretinal NO concentration. The purpose of this study is to measure NO levels in early stage of diabetic retinopathy.

Methods: Long-Evans rats received an intraperitoneal injection of streptozotocin and the measurements were made three weeks after the injection. Diabetic rats were grouped into moderate blood glucose (MBG, 250-400 mg/dL) or high blood glucose (HGB, >500 mg/dL) groups. Retinal NO measurements were made using a custom-made double-barreled microelectrode that measured NO and recorded the electroretinogram (ERG). The intraretinal ERGs were used to determine retinal depth, allowing for the construction of a retinal NO profile. Diabetic NO measurements were compared to control NO measurement from healthy rats and healthy rats that received an intravitreal injection of L-NG-nitroarginine methyl ester (L-NAME, nitric oxide synthase inhibitor).

Results: NO concentration at the choroid/retina boundary was \(2.32 \pm 0.27 \, \mu M\) for controls. MBG diabetics had significantly higher NO concentration at \(3.73 \pm 0.39 \, \mu M\) (\(p=0.015\)). HGB diabetics and L-NAME profiles had significantly lower NO concentration at \(1.04 \pm 0.16 \, \mu M\) (\(p<0.001\)) and \(0.83 \pm 0.15 \, \mu M\) for L-NAME (\(p<0.001\)), respectively. NO concentration at the retina/vitreous boundary was \(1.18 \pm 0.11 \, \mu M\). MBG diabetics were not significantly different from control at \(1.54 \pm 0.19 \, \mu M\) (\(p=0.32\)). HGB and L-NAME profiles were significantly lower than control at \(0.20 \pm 0.09 \, \mu M\) (\(p=0.042\)) and \(0.12 \pm 0.06 \, \mu M\) (\(p=0.006\)), respectively.
Conclusions: To date, this study is the first to measure intraretinal NO levels in control and diabetic rats. High levels of NO in the MBG diabetics and low levels of NO in the HBG diabetics are unexpected and suggest a non-linear relationship of NO and blood glucose level. Our HBG diabetic NO profiles were similar to L-NAME profiles suggesting either inhibition of NOS activity or a depleted pool of L-arginine with uncontrolled high blood glucose. The differences between the MBG and HBG diabetics may explain the conflicting reports in literature about the changes in NO levels in early diabetic retinopathy.

Saturday – 12:36

NOTES:
WHAT CAUSES DIFFERENCES IN CHOROIDAL THICKNESS?

Robert Mullins, University of Iowa
Elliott Sohn
Budd Tucker, The University of Iowa
Edwin Stone, University of Iowa Carver College of Medicine

Purpose: Changes in choroidal thickness (either hypertrophy or atrophy) have been described in a number of macular diseases, including age-related macular degeneration. In spite of compelling anatomic data, very little is known about the cellular and molecular basis of the differences between thick and thin choroids. We performed a series of experiments using donor eyes to characterize the structural and biochemical factors that may contribute to choroidal thickness.

Methods: One hundred forty-one eyes from 104 donors (mean age + standard deviation, 81.5 ± 12.2) were studied. Choroidal thickness was determined on H&E stained macular sections by measuring the distance between Bruch’s membrane and the sclera. Selected examples were employed for immunofluorescence, Masson’s trichrome staining, ultrastructural analysis, or proteomic analyses. Validation of enriched proteins was performed on a minimum of 5 eyes of each category by Western blot and/or immunohistochemistry.

Results: Human eyes showed a normal distribution of choroidal thickness with lower values than generally reported clinically. The average thickness was 155µm with a standard deviation of 69µm. Eyes with geographic atrophy (n=12) showed significantly thinner choroids than seen in age matched controls (p<0.01). Preservation of collagen and decreased cellularity were observed histologically and ultrastructurally in thin choroids. Proteomic analyses revealed an increase in levels of SERPINA1 and SERPINA3 in thick choroids and increased abundance of TIMP3 in thin choroids.
Conclusions: In spite of recent interest in choroidal thickness, the genetic and biochemical factors responsible for this phenotype have not been described. This study suggests that alterations in different classes of protease inhibitors contribute to extremes of choroidal thickness in humans. Modification of these pathways may provide novel therapeutic targets for age-related macular degeneration.

**Saturday – 12:45**

**NOTES:**
CONE PHOTORECEPTOR AND OUTER SEGMENT RESCUE/REGENERATION AFTER CELL-BASED THERAPY IN RP

Henry Kaplan, University of Louisville

Purpose: The major cause of hereditary retinal degeneration in North America is Retinitis Pigmentosa (RP). The most frequent cause of RP is a Pro23His (P23H) mutation in rhodopsin (RHO) (~ 8.5% of cases). One of our goals with cell-based retinal therapy is to halt disease progression by cone photoreceptor rescue/regeneration following transplantation of iPSC or retinal progenitor cells in our swine model of P23H retinopathy.

Methods: We produced a transgenic miniature pig model of RP with a P23H RHO mutation using somatic cell nuclear transfer. The tempo of rod photoreceptor degeneration is aggressive so that at P120 there is only a single layer of nuclei in the outer nuclear layer (ONL). Swine GFP+ rod-derived iPSC or GFP+ retinal progenitor cells (5 x 10^4 cells/µl in ~ 25 µl) were injected beneath the visual streak of the experimental OD in 5 transgenic pigs at ~ P14; the control OS received diluent only. One month later the recipients were euthanized and their enucleated eyes examined with immunohistology and multifocal ERG (mfERG).

Results: When transplanted beneath the visual streak both rod-derived iPSC and E57 retinal progenitor cells integrated into the ONL and rescued/regenerated adjacent cones and their OS. The effect of the transplanted cells extended for approximately 1000 µm for cones and 800 µm for cone OS. mfERG recordings revealed enhanced P1 recordings from hexagons in the retinal area with rescued/regenerated cone OS.
Conclusions: Swine rod-derived iPSC and E57 retinal progenitor cells can rescue/regenerate cone photoreceptors and their OS following subretinal transplantation in P23H retinopathy. The functional benefit of preserved cone function for patients with progressive RP from P23H retinopathy is unknown but may be significant.

Saturday – 12:54
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Grant Support      S  Grant support for the past one year (all sources) and all sources used for this project if this form is an update for a specific talk or manuscript with no time limitation

Planner and Speaker Disclosures

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Arevalo, J. Fernando ..............Second Sight LLC (C); Iridex, Optos, Inc., Novartis Pharmaceuticals Corp., Second Sight LLC (L);
Springer SBM LLC (P); King Khaled Eye Specialist Hospital (S)
Augustin, Albert ....................Allergan (C); Allergan (L)
Averbukh, Edward ...................Ad hoc advisor to Bayer (C)
Avery, Robert ......................Alcon, Allergan, Bausch and Lomb, Genentech, Notal Vision, Novartis, QLT, Regeneron, Replenish (C); Alcon, Allergan, Bausch and Lomb, Genentech, Notal Vision, Novartis, QLT, Regeneron, Replenish (L); Novartis, Regeneron, Replenish (O); Replenish (P); Allergan, Genentech, QLT, Regeneron (S)
Bakri, Sophie ......................Allergan Genentech Regeneron Valeant (C)
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Behar-Cohen, Francine ........................................ (P)
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Bressler, Neil ........................................... Grant support from Genentech, Novartis, Bayer, Regeneron to my institution (Johns Hopkins University) for research in which I am the principal investigator (S)
Brown, David ............................................... Notal Vision, Genentech/Roche, Regeneron/Bayer, Novartis, Alcon, Allergan, Clearside Biomedical, Acucela, Allegro Ophthalmics, Envisia Therapeutics, Heidelberg Engineering, Carl Zeiss Meditech, Optos, Pfizer, Quantel, Sanofi (C); Alcon/Novartis (L)
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Center for Value-Based Medicine (O); Genentech ArcticDx (S)
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Chan, Clement ........................................ Allergan, Regeneron, ThromboGenics, Valeant (C); Acucela, Genentech, National Eye Institute, Regeneron, Sequenom (S)
Chavala, Sai ............................................ Serrata, LLC Regeneron Pharmaceuticals, Inc.
Ophthotec Corporation Inc. (O); Serrata, LLC (P); NIH K-08 Award Research to Prevent Blindness (unrestricted grant and early career development award) (S)
Cheung, Gemmy .................................................. Bayer (C); Bayer (L);
Bayer, Roche, GlaxoSmithKline (S)
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Heidelberg (L); Novartis, Alcon, Quantel (S)
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PLANNER AND SPEAKER DISCLOSURES CONTINUED

Ciulla, Thomas .......................... Ohr Pharmaceuticals Inc (C); Ohr Pharmaceuticals Inc (O); Ohr Pharmaceuticals Inc (S)
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Dubra, Alfredo ......................... Canon USA Inc. (C); US Patent 8,226,236. (P); Burroughs Wellcome Fund, Research to Prevent Blindness, Glaucoma Research Foundation. (S)
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Duker, Jay ............................... Alcon/Novartis Pharmaceuticals Corporation, EMD Serono, Thrombogenics, Optos, Allergan (C); Carl Zeiss, Meditec, Optovue (S)
Ehlers, Justis ............................. Thrombogenics (C); Thrombogenics (L); Bioptigen (P)
Ehrlich, Jason ............................ Genentech (E); Roche (O)
Farzui, Sina ............................... Duke University (P)
Fawzi, Amani ............................. Macula Society 2013 Research award and NIH/NEI (R01-EY01995, R01-EY021470) (S)
Fine, Howard ........................... Allergan, Genentech, Regeneron (C); Genentech, Regeneron (L); Auris Surgical Robotics Inc (O); Auris Surgical Robotics Inc (P)
Freund, K. Bailey ...................... Regeneron SAB Honorarium Genentech, SAB Honorarium Heidelberg, SAB Honorarium (C)
Fujimoto, James ........................ J. Fujimoto has stock options in Optovue. (O); J. Fujimoto receives royalties from intellectual property owned by MIT and licensed to Carl Zeiss and Optovue. (P)
PLANNER AND SPEAKER DISCLOSURES CONTINUED

Gaudric, Alain ..........................Novartis, Pharma, Thrombogenics, Bayer (C)
Glaser, Bert ..............................Ocular Proteomics, LLC (E); NIE/NIH SBIR Phase II 2R44EY021082-02A1 (S)

Goldstein, Michaella ........................Allergan, Bayer, Novartis (C)
Gragoudas, Evangelos ........................QLT Pharmaceuticals (P)
Graham, Robert .................................Genentech (E)
Greven, Craig ..............................Consultant – Thrombogenics (C)
Haller, Julia ..............................An advisory board member for Kal Vista and LPath, and a consultant to Advanced Cell Technologies, Merck, Regeneron Pharmaceuticals, Second Sight, and ThromboGenics. (C)

Han, Dennis .................................FlowOne (C); RAVI-Guide (P); Genentech Regeneron (S)
Harbour, J. William ..........................Castle Biosciences, Inc. (C); Castle Biosciences, Inc. (P)
Haritoglou, Christos ..........................Allergan, Novartis, Alimera (L); Novartis (S)
Hatz, Katja ..............................Novartis Switzerland Allergan (C)
Heier, Jeffrey ..............................Consultant to Acucela, Aerpio, Alimera, Allergan, Bausch & Lomb, Bayer, Dutch Ophthalmic, Endo Optiks, Forsight, Genzyme, Heidelberg Engineering, Kala Pharmaceuticals, Kanghong, LPath, Nicox, Notal Vision, Ohr Pharmaceutical, Ophthotech, Oraya, QLT, Regeneron Pharmaceuticals, Roche, Sequenom, Thrombogenics, Vertex, and Xcovery (C); Research funding from Acucela, Aerpio, Alcon, Alimera, Allergan, Bayer, Fovea, Genentech, Genzyme, GlaxoSmithKline, LPath, Neovista, Neurotech, Notal Vision, Novartis, Ohr Pharmaceutical, Ophthotech, Paloma, and Regeneron Pharmaceuticals (S)

Henry, Erin ..............................Employee of Genentech, Inc., with Roche stock/stock options (E)

Hitzenberger, Christoph ............................Canon Inc. (C); Canon Inc. (S)
Hollander, David ............................Allergan, Inc (E); Stock options, Allergan, Inc. (O)
Holz, Frank ..............................Heidelberg Engineering, Zeiss, Optos (C); Heidelberg Engineering (L); Heidelberg Engineering, Zeiss, Optos (S)
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Ip, Michael ............................Eye Technology, Ltd. Genentech Neurionetics Valeant (C); Allergan, Inc (S)

Ishida, Susumu .............................Alcon, Novartis, Pfizer, Bayer, Saten, Senju, Otsuka, Wakamoto (L)
Jaffe, Glenn ..................................Heidelberg Engineering Alcon Neurotech (C)
Jampol, Lee ..............................Baxter International, Janssen/Quintiles (C)
Jonnal, Ravi ................. Co-inventor of adaptive optics optical coherence tomography. U.S. Patent 7,364,296. “Method and apparatus for improving both lateral and axial resolution in ophthalmoscopy” (P)

Kaiser, Peter ............ Alcon, Bayer, Genentech, Regeneron, Changd Kanghong, Ophthotech, ArcticDx, Allegro, Novartis, SKS Ocular (C); SKS Ocular (O)

Kiss, Szilard ............. Allergan, Alimera, Alcon, Genentech/Roche, Optos, Regeneron/Bayer (C); Allergan, Alimera, Alcon, Genentech/Roche, Optos, Regeneron/Bayer (L); Allergan, Genentech/Roche, Optos, Regeneron/Bayer (S)

Kitchens, John .......... Allergan, Genentech, Regeneron, Synergetics (C); Genentech, Regeneron (L)

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Mauget-Faysse, Martine ................................. Bayer Novartis (C);
                                      Bayer Novartis Thea Heidelberg (L)
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                                      Fédération des aveugles et handicapés visuels de France,
                                      Fondation Nestlé France. (S)
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                                      Allergan, Bayer, Novartis (L)
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                                      Novartis, Bayer, Allergan, Clancootech and Roche were paid
                                      to the research foundation at the City Hospital Triemli, Zurich (C);
                                      Honoraria for lectures invited by Bayer and Novartis were paid
                                      to the research foundation at the City Hospital Triemli, Zurich (L);
                                      The research foundation at the City Hospital Triemli,
                                      Zurich has obtained research grants by Bayer and Novartis (S)
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                                      Biotech, Inc. ONL Therapeutics, LLC Maculogix, Inc. (C);
                                      European Association for Vision and Ophthalmology, Alcon,
                                      Chilean Society of Ophthalmology, Korean Ophthalmological Society,
                                      STEM – Bishop Strachan School, Heed Ophthalmic Foundation, Centre
                                      for Eye Research Australia, Royal Australian and New Zealand College of
                                      Ophthalmologists (L); The Massachusetts Eye and Ear Infirmary (P); Lowy
                                      Medical Research (S)
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                                      Ophthotech, Notalvision (C); Novartis, Bayer,
                                      Alcon, Allergan, Ophthotech (L); Ophthotech (O)
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                                      Advisory Board (C); Genentech, Inc: Speakers Bureau (L);
                                      Genentech, Inc: Grant support (S)
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                                      studies being sponsored by Santen, XOMA, AbbVie, Genentech, and
                                      Regeneron (C); JDRF, Genentech, Regeneron, XOMA, Santen (S)
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Perry, Hugh ....................................... University of Southampton (E); Novartis (L);
                                      MS Society, Wellcome Trust, ARUK, MRC,
                                      Alzheimer Society, Wellcome Trust Strategic Award (S)
PLANNER AND SPEAKER DISCLOSURES CONTINUED

Pieramici, Dante ........................................ Genentech (C); Genentech (S)
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(payed to the institution) (L); Novartis, Alcon,
Bayer (payed to the institution) (S)
Rabena, Melvin .................................................. Genentech (L)
Recchia, Franco .......................... Genentech (C); Genentech (S)
Reeves, Barnaby .............................................. Janssen-Cilag, teaching fee (C)
Rodriguez, Francisco .......................... Alcon Bayer Novartis Allergan (C);
Alcon Bayer Novartis Allergan (L)
Rosen, Richard .................. OD-OS Clarity Optovue OcuSciences Opticology (C);
Opticology (P); Zeavision Genentech (S)
Rosenfeld, Philip .......................... Carl Zeiss Meditec (S)
Roth, Daniel .......................... Allergan, Regeneron, Ohr Pharmaceuiticals (C);
Bayer Health (L); Forsight Labs, Ohr Pharmaceuiticals (O); Allergan (S)
Russell, Stephen .......................... I am the publisher of the book,
The Lost Art of Retinal Drawing,
from which the data is taken for this presentation (O)
Sadda, SriniVas .......................... Allergan, Regeneron, Genentech (C);
Allergan, Genentech (S)
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Regeneron, Genentech, Allergan, Alcon, Valiant, DORC (S)
Sato, Taku .......................................................... Alcon Japan Inc. (S)
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Consultant for Allergan (C)
Schwartz, Stephen .......................... Alimera Bausch + Lomb Santen (C);
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Scott, Lanita .......................... Allergan, Inc. (E); Allergan, Inc. (O)
Seddon, Johanna .......................... Tufts Medical Center-P (P);
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Shiraga, Fumio .......................... Alcon, Japan Novartis, Pharma, Byer, Santen,
Pharma Bausch & Lomb (C)
Silva, Rufino .......................... I am member of Advisory Boards for Novartis,
Bayer, Allergan, Thea (C)
PLANNER AND SPEAKER DISCLOSURES CONTINUED

Sinclair, Stephen .......................... Sinclair Technologies, LLC
Intelligent Medical Imaging Technology, LLC (O);
Sinclair Technologies, LLC Intelligent Medical Imaging Technology, LLC (P)
Singer, Michael ............................ Allergan (C); Allergan (L)
Singh, Harinderjit .......................... grant for study (S)
Singh, Ravi ............................... Co-inventor on patent application of RAVI Guide (P)
Singh, Rishi ............................... Genentech, Alcon, Regeneron, Thrombogenics,
Bausch and Lomb (C); Regeneron, Genentech, Thrombogenics (L)
Sivaprasad, Sobha .......................... Novartis, Allergan, Bayer and Alimera Sciences (C);
Novartis, Allergan, Bayer (L); Novartis, Allergan, Bayer (S)
Slakter, Jason ............................... Acuела, Lpath, Ohr, Oraya, Regeneron,
XcoveryVision (C); Regeneron, Bayer (L); SKS Ocular, LLC (O);
Acuела, Alimera, Allergan, Bayer, Centocor, Corcept, Genentech,
Genzyme, GSK, Kanghong Biotech, Lpath, Novagali, Ohr, Oraya, Pfizer,
Regeneron, Sanofi-Aventis, Santen, XcoveryVision (S)
Smith, David ............................... I am an employee of Truven Health Analytics.
Truven Health Analytics was paid by
Genentech, Inc. to conduct this study. (E)
Smith, R Theodore .......................... NIH/NEI R01 015520 (S)
Soubrane, Gisèle ............................ Allergan Novartis Thea (C)
Souied, Eric ............................... Bauch+Lomb, Thea, Novartis, Bayer, Allergan (C);
Novartis, Heidelberg (L)
Spaide, Richard ............................ Topcon, Bausch and Lomb (C); Topcon (P)
Steinle, Nathan ............................. Regeneron (L)
Sternberg, Gary ............................ I am an employee of Genentech/Roche. (E);
I own options and/or stock in Roche (O)
Strauss, Erich .............................. Genentech, Inc (E); Stocks/Stock Options,
Roche (O); Patent Pending, Genentech, Inc (P)
Sun, Jennifer .............................. Boston Micromachines (equipment),
Optovue (equipment) (S)
Sunness, Janet .............................. Acuella, Acurian, Genentech, Roche, Cell Cure,
Alcon (C); ProgSTAR study site PI (funded by Dept of Defense through Foundation Fighting Blindness) (S)
Töth, Cynthia ............................. Royalties from Alcon.
Patents pending in OCT analysis, unlicensed. (P);
Genentech, Bioptigen, Physical Sciences Incorporated,
EMMES Corporation (S)
Tuomi, Lisa ..................................................Genentech, Inc. (E)
Turpcu, Adam .........................Adam Turpcu is an employee of Genentech (E)
van Lookeren Campagne, Menno ......................Genentech Inc. (E)
Varma, Rohit ....................................Allergan, AqueSys, Genentech,
                          Merck & Co., Replenish, Bausch + Lomb (C)
Visich, Jennifer .................................................................Genentech (E)
Walt, John .................................Allergan, Inc. (E); Allergan, Inc. (P)
Ward, James .....................I am a paid consultant to Genentech Inc. (C)
Whitcup, Scott ..........................Allergan (E); Allergan stock (O)
Wong, Tien .................................................................Alcon Allergan (C)
Wykoff, Charles .......Alimera, Bayer, Synergetics, and Thrombogenics (C);
                          Speaker Bureau: Genentech and Regeneron (L); Genentech, Regeneron,
                          Alimera, Pfizer, Xoma, Ampio, GSK, NEI, Xcovery,
                          Acucela, Quark, Santeen, Allergan, Novartis, Must,
                          OpthoTech, Thrombogenics, Genzyme (S);
Yaspan, Brian .........................Full time employee of Genentech (E)
Yau, Linda .................................Genentech, Inc. (E); Genentech, Inc. (O)
Ying, Howard .......Johns Hopkins University (P); National Eye Institute (S)
Yoshimura, Nagahisa ...........Canon, NIdek, Novartis, Bayer, Pfizer (C);
                          Canon, NIdek, Novartis, Bayer, Pfizer, Otsuka, MSD, Santen, Senju (L);
                          Canon, NIdek, Topcon, Novartis, Bayer, Pfizer, Otsuka,
                          MSD, Santen, Senju (S)
Zawadzki, Robert ...............Patent on AO-OCT (P); NEI (EY 014743) (S)
Zhang, Jiameng ......................Roche (E)
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<th>Planners and Authors With no Relevant Commercial Interest</th>
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<td>Abedi, Mehrdad</td>
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<td>Abramson, David</td>
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<td>Francais, Catherine</td>
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PLANNERS AND AUTHORS WITH NO RELEVANT COMMERCIAL INTEREST CONTINUED

Francis, Jasmine
Gaillard, Marie-Claire
Gallimore, Gary
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Midena, Edoardo
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Mittelmüller, Tamara
<table>
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<th>Planners and Authors With No Relevant Commercial Interest Continued</th>
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<tr>
<td>Mittra, Robert</td>
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