Retina 2017
Retinal Mardi Gras

Program Directors
Carl D Regillo MD and Richard F Spaide MD

In conjunction with the American Society of Retina Specialists, the Macula Society, the Retina Society, and Club Jules Gonin

Ernest N Morial Convention Center
New Orleans, Louisiana
Friday–Saturday, Nov. 10–11, 2017

Presented by:
The American Academy of Ophthalmology

Supported in part by an unrestricted educational grant from Genentech

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Program Director
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2017 Retina Subspecialty Day Planning Group

On behalf of the American Academy of Ophthalmology and the American Society of Retina Specialists, the Macula Society, the Retina Society, and Club Jules Gonin, it is our pleasure to welcome you to New Orleans and Retina 2017: Retinal Mardi Gras.

Carl D Regillo MD FACS
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Acucela: S | Aerpio: C
Alcon Laboratories Inc.: C,S
Allergan: C,S | Bausch + Lomb: C
Bayer Healthcare Pharmaceuticals: C
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Regeneron Pharmaceuticals Inc.: C,S
ThromboGenics Inc.: S

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Eyemedix: C,O,P,S
Iridex: P
John Hopkins University: P
oProbe: C,O,P
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Opticent Inc.: O

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Dr. Ferris started his career at the National Eye Institute (NEI), National Institutes of Health, in 1973. He has been the director of the Division of Epidemiology and Clinical Applications at NEI since 1994 and was the clinical director at NEI from 2000 to 2017.

He received an A.B. degree from Princeton University in 1968 and completed his medical training and internship at Johns Hopkins in 1973. Following this initial medical training, he joined the Public Health Service and started his 44-year career at NEI.

During this career, Dr. Ferris became a board-certified ophthalmologist in 1978, when he completed his ophthalmology residency training at the Wilmer Institute, Johns Hopkins Hospital, and he is also a board-certified epidemiologist. Through a joint appointment with NEI, he continued his association with Johns Hopkins as an associate professor of ophthalmology until 1995.

Dr. Ferris has participated in many clinical trials during his NEI career. Notably, he was project officer of the Diabetic Retinopathy Study, co-chairman of the Early Treatment Diabetic Study, and chairman of the Age-Related Eye Disease Study. He has published 295 manuscripts in peer-reviewed journals and is currently actively involved in AREDS2, CATT, and DRCR.net studies and multiple intramural clinical studies at NEI, as well as being a senior editor of JAMA-Ophthalmology.

Dr. Ferris has been president of the Association for Research in Vision and Ophthalmology (ARVO) in 2006 and has received numerous honors, including a U.S. Public Health Service Commendation Medal, multiple awards from the Macula and Retina Society, the Jackson Memorial Lectureship, the Alcon Research Institute Award, and the Helen Keller Prize for Vision Research; he has been named an ARVO Gold Fellow and a Fellow of the Society for Clinical Trials, as well as recently being named a Johns Hopkins University Scholar.
CME Credit

Academy's CME Mission Statement

The purpose of the American Academy of Ophthalmology’s Continuing Medical Education (CME) program is to present ophthalmologists with the highest quality lifelong learning opportunities that promote improvement and change in physician practices, performance, or competence, thus enabling such physicians to maintain or improve the competence and professional performance needed to provide the best possible eye care for their patients.

2017 Retina Subspecialty Day Meeting Learning Objectives

Upon completion of this activity, participants should be able to:

- Present established and innovative approaches to the management of retinal vascular and surgical retinal conditions
- Explain the current management of macular edema secondary to retinal occlusive disease and diabetic retinopathy as well as the newly proven therapies for proliferative diabetic retinopathies
- Explain the pathobiology and management of atrophic and exudative AMD and other causes of ocular neovascularization
- Identify imaging tests most helpful in the diagnosis and management of retinal conditions and discuss emerging developments in retinal imaging
- Describe new vitreoretinal surgical techniques and instrumentation
- Identify new developments in hereditary retinal degenerations, pediatric retinal diseases, and ocular oncology
- Discuss effective treatments to manage complications from medical and surgical interventions
- Summarize current and new clinical trial data for retinal diseases such as AMD, diabetic retinopathy, hereditary retinal conditions, and retinal vein occlusion

2017 Retina Subspecialty Day Meeting Target Audience

The intended target audience for this program is vitreoretinal specialists, members in fellowship training, and general ophthalmologists who are engaged in the diagnosis and treatment of vitreoretinal diseases.

2017 Retina Subspecialty Day CME Credit

The American Academy of Ophthalmology is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The American Academy of Ophthalmology designates this live activity for a maximum of 14 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Teaching at a Live Activity

Teaching instruction courses or delivering a scientific paper or poster is not an AMA PRA Category 1 Credit™ activity and should not be included when calculating your total AMA PRA Category 1 Credits™. Presenters may claim AMA PRA Category 1 Credits™ through the American Medical Association. To obtain an application form, please contact the AMA at www.ama-assn.org.

Scientific Integrity and Disclosure of Financial Interest

The American Academy of Ophthalmology is committed to ensuring that all CME information is based on the application of research findings and the implementation of evidence-based medicine. It seeks to promote balance, objectivity, and absence of commercial bias in its content. All persons in a position to control the content of this activity must disclose any and all financial interests. The Academy has mechanisms in place to resolve all conflicts of interest prior to an educational activity being delivered to the learners.

The Academy requires all presenters to disclose on their first slide whether they have any financial interests from the past 12 months. Presenters are required to verbally disclose any financial interests that specifically pertain to their presentation.

Control of Content

The American Academy of Ophthalmology considers presenting authors, not coauthors, to be in control of the educational content. It is Academy policy and traditional scientific publishing and professional courtesy to acknowledge all people contributing to the research, regardless of CME control of the live presentation of that content. This acknowledgment is made in a similar way in other Academy CME activities. Though they are acknowledged, coauthors do not have control of the CME content, and their disclosures are not published or resolved.

Attendance Verification for CME Reporting

Before processing your requests for CME credit, the American Academy of Ophthalmology must verify your attendance at Subspecialty Day and/or the AAO 2017. In order to be verified for CME or auditing purposes, you must either:

- Register in advance, receive materials in the mail, and turn in the Subspecialty Day Syllabi exchange voucher(s) onsite;
- Register in advance and pick up your badge onsite if materials did not arrive before you traveled to the meeting;
- Register onsite; or
- Scan the barcode on your badge as you enter an AAO 2017 course or session room.
CME Credit Reporting

Lobby E and Lobby II and Academy Resource Center, Hall G – Booth 3140

Attendees whose attendance has been verified (see above) at AAO 2017 can claim their CME credit online during the meeting. Registrants will receive an email during the meeting with the link and instructions on how to claim credit.

Onsite, you may report credits earned during Subspecialty Day and/or AAO 2017 at the CME Credit Reporting booth.

Academy Members: The CME credit reporting receipt is not a CME transcript. CME transcripts that include AAO 2017 credits entered onsite will be available to Academy members on the Academy’s website beginning Dec. 7, 2017.

After AAO 2017, credits can be claimed at www.aao.org. The Academy transcript cannot list individual course attendance. It will list only the overall credits spent in educational activities at Subspecialty Day and/or AAO 2017.

Nonmembers: The Academy will provide nonmembers with verification of credits earned and reported for a single Academy-sponsored CME activity, but it does not provide CME credit transcripts. To obtain a printed record of your credits, you must report your CME credits onsite at the CME Credit Reporting booths.

Proof of Attendance

The following types of attendance verification will be available during AAO 2017 and Subspecialty Day for those who need it for reimbursement or hospital privileges, or for nonmembers who need it to report CME credit:

- CME credit reporting/proof-of-attendance letters
- Onsite registration receipt
- Instruction course and session verification

Visit www.aao.org/cme for detailed CME reporting information.
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Steven Yeh MD
Atlanta, GA
Vote on Each Debate!

Cast your vote for the winner of each debate. Pull out your mobile device or laptop and go to join.fxptouch.com/retina and vote on the following debates:

**Friday, November 10, Section IV: Debates – Part I**
11:10-11:37 AM
- Subthreshold Laser for Diabetic Macular Edema: Pro or Con
- OCT Angiography Is Ready for Mainstream Clinical Use: Pro or Con
- Heads-up 3-D Digital Surgery Viewing Is Now for Vitrectomy: Pro or Con
- Use of Intraoperative OCT Improves Surgical Outcomes: Pro or Con

**Saturday, November 11, Section XIV: Debates – Part II**
9:23-9:57 AM
- Displacement of Submacular Hemorrhage in AMD Improves Visual Outcomes: Pro or Con
- Widefield Imaging is Necessary in Practice: Pro or Con
- Chandelier Scleral Buckling is Better Than Conventional SB: Pro or Con
- Internal Limiting Membrane Flaps are Needed to Optimize Macular Hole Closure: Pro or Con
- 27-gauge Vitrectomy is an Essential Platform: Pro or Con
# Retina 2017: Retinal Mardi Gras

In conjunction with the American Society of Retina Specialists, the Macula Society, the Retina Society, and Club Jules Gonin

## FRIDAY, NOV. 10

<table>
<thead>
<tr>
<th>Time</th>
<th>Session/Topic</th>
<th>Presenter(s)</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>7:00 AM</td>
<td>CONTINENTAL BREAKFAST</td>
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<tr>
<td>8:00 AM</td>
<td>Opening Remarks</td>
<td>Carl D Regillo MD FACS* Richard F Spaide MD*</td>
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<tr>
<td>8:05 AM</td>
<td>Section I: Masters of Surgery</td>
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<td></td>
<td>Moderator: Susanne Binder MD*</td>
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<tr>
<td>8:05 AM</td>
<td>Intraocular Foreign Body Removal: Tips and Tricks</td>
<td>Grazia Pertile MD</td>
<td>1</td>
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<tr>
<td>8:11 AM</td>
<td>Retinectomy: When and How</td>
<td>Steven T Charles MD*</td>
<td>2</td>
</tr>
<tr>
<td>8:17 AM</td>
<td>Concurrent Pars Plana Vitrectomy / Cataract Extraction vs. Sequential Surgery: Is There a Difference in Outcomes?</td>
<td>William F Mieler MD</td>
<td>3</td>
</tr>
<tr>
<td>8:23 AM</td>
<td>When and How to Treat Myopic Traction Maculopathy</td>
<td>Hiroko Terasaki MD*</td>
<td>5</td>
</tr>
<tr>
<td>8:29 AM</td>
<td>Are There 2 Types of Lamellar Macular Holes? Diagnosis and Management</td>
<td>John T Thompson MD*</td>
<td>8</td>
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<tr>
<td>8:35 AM</td>
<td>Section II: Vitreoretinal Surgery, Part I</td>
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<tr>
<td></td>
<td>Moderators: Timothy G Murray MD MBA* and Suber S Huang MD MBA*</td>
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<tr>
<td>8:35 AM</td>
<td>What’s New in Vitreoretinal Surgery Equipment</td>
<td>David R Chow MD*</td>
<td>10</td>
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<tr>
<td>8:41 AM</td>
<td>Retinal Detachment Outcomes in IRIS</td>
<td>George A Williams MD*</td>
<td>11</td>
</tr>
<tr>
<td>8:47 AM</td>
<td>Complex Retinal Detachments: Best Approaches and What to Expect</td>
<td>Richard S Kaiser MD*</td>
<td>12</td>
</tr>
<tr>
<td>8:53 AM</td>
<td>Results of Vitrectomy for Eyes following Failure of Surgery for Proliferative Vitreoretinopathy</td>
<td>Gary W Abrams MD*</td>
<td>14</td>
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<tr>
<td>8:59 AM</td>
<td>The Management of Recurrent Macular Holes</td>
<td>Tarek S Hassan MD*</td>
<td>16</td>
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<tr>
<td>9:05 AM</td>
<td>Strategies in Trauma Surgery</td>
<td>Carl C Claes MD*</td>
<td>19</td>
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<tr>
<td>9:11 AM</td>
<td>Management of Combined Schisis Retinal Detachment</td>
<td>Gaurav K Shah MD*</td>
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<tr>
<td>9:17 AM</td>
<td>Treatment of Optic Pit Maculopathy</td>
<td>Mark W Johnson MD*</td>
<td>21</td>
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<tr>
<td>9:23 AM</td>
<td>Combined Keratoprosthesis and Vitrectomy Surgery Outcomes</td>
<td>Jennifer Irene Lim MD*</td>
<td>23</td>
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<tr>
<td>9:29 AM</td>
<td>The Charles L Schepens MD Lecture</td>
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<tr>
<td>9:29 AM</td>
<td>Introduction of the 2017 Charles L Schepens MD Lecture</td>
<td>David W Parke II MD*</td>
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<tr>
<td>9:35 AM</td>
<td>Clinical Trials in Ophthalmology: Past, Present, and Future</td>
<td>Frederick L Ferris III MD*</td>
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<td>9:55 AM</td>
<td>REFRESHMENT BREAK and RETINA EXHIBITS, Hall B</td>
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<td>10:45 AM</td>
<td>Section III: The Business of Retina</td>
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<td>Moderator: James F Vander MD</td>
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<td>10:45 AM</td>
<td>ASC Update</td>
<td>Derek Y Kunimoto MD JD*</td>
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<td>10:50 AM</td>
<td>Changes in Health-Care Reimbursements</td>
<td>David W Parke II MD*</td>
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* Indicates that the presenter has financial interest. No asterisk indicates that the presenter has no financial interest.
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<tr>
<td>11:00 AM</td>
<td>How Is AAO Helping Retina Specialists?</td>
<td>Cynthia Ann Bradford MD</td>
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<td>Should I Sell My Practice?</td>
<td>Reginald J Sanders MD</td>
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<td>Subthreshold Laser for Diabetic Macular Edema: Pro</td>
<td>Paulo E Stanga MD*</td>
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<td>Subthreshold Laser for Diabetic Macular Edema: Con</td>
<td>Andrew A Moshfeghi MD*</td>
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<td>11:20 AM</td>
<td>OCT Angiography Is Ready for Mainstream Clinical Use: Pro</td>
<td>Caroline R Baunal MD*</td>
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<td>Heads-up 3-D Digital Surgery Viewing Is Now for Vitrectomy: Pro</td>
<td>John W Kitchens MD*</td>
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<tr>
<td>11:27 AM</td>
<td>Heads-up 3-D Digital Surgery Viewing Is Now for Vitrectomy: Con</td>
<td>Julia A Haller MD*</td>
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<td>Update on Intraocular Sustained Drug Delivery: Are We Making Progress?</td>
<td>Glenn J Jaffe MD*</td>
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<td>11:44 AM</td>
<td>The Spectrum of Central Serous Retinopathy: Clinical Characteristics</td>
<td>Giuseppe Querques MD</td>
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<td>11:50 AM</td>
<td>The Latest on Central Serous Retinopathy Management</td>
<td>Francine Behar-Cohen MD*</td>
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<td>11:56 AM</td>
<td>Gene Therapy for AMD: Where Do We Stand?</td>
<td>Szilard Kiss MD*</td>
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<td>Treatment Options for Vitreomacular Traction</td>
<td>Robert L Avery MD*</td>
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<td>Screening for Hydroxychloroquine Retinopathy: Latest Guidelines</td>
<td>David J Browning MD PhD*</td>
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<td>Update on Clinical Trials for Retinal Degeneration</td>
<td>Byron L Lam MD*</td>
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<td>Update on Hemorrhagic Occlusive Retinal Vasculitis after Cataract Surgery</td>
<td>Dean Eliott MD</td>
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<td>Advocating for Patients</td>
<td>Sohail J Hasan MD PhD</td>
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<td>1:50 PM</td>
<td>Uveitis Panel, Part I</td>
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<td>Moderator: Daniel F Martin MD</td>
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</tbody>
</table>
### Section VII: My Coolest Surgical Video

**Moderator:** Donald J D’Amico MD*

**Panelists:** Raymond Iezzi MD, Mathew W MacCumber MD PhD*, Mauricio Maia MD*, Flavio A Rezende MD PhD*

**Virtual Moderator:** Yannek I Leiderman MD PhD*

**2:10 PM** Autologous Retinal Transplant for Chronic Retinal Detachment with Proliferative Vitreoretinopathy Without Macular Hole / Autologous Retinal Transplantation in Recurrent Retinal Detachment Complicated with PVR and Giant Macular Hole

Akshay S Thomas MD, 57
Giuseppe Lo Giudice MD

**2:14 PM** Panel Discussion

**2:17 PM** Removal of a Large Intraocular Foreign Body Using a Modified Flute Needle from an Eye with 20/20 Vision

Kenneth K W Li MBCHB 57

**2:19 PM** Panel Discussion

**2:22 PM** Management of Subretinal Cysticercosis

Simar R Singh MBBS 58

**2:24 PM** Panel Discussion

**2:27 PM** Early Vitrectomy Restored Dragging Macula in Infant Eyes with Familial Exudative Vitreoretinopathy

Shunji Kusaka MD* 58

**2:29 PM** Panel Discussion

**2:32 PM** Endoresection of Retinal Capillary Hemangioblastoma in a Patient with Von-Hippel Lindau Syndrome

Antonio Capone Jr MD* 58

**2:34 PM** Panel Discussion

### Section VIII: Pediatric Retina

**Moderator:** Thomas C Lee MD

**2:37 PM** Persistent Fetal Vasculature Syndrome: A Review and a New Presentation

Michael T Trese MD* 59

**2:43 PM** Use of Anti-VEGF Therapy for ROP: When and How

R V Paul Chan MD* 60

**2:49 PM** Telemedicine for ROP: When, Why, and How?

Antonio Capone Jr MD* 62

**2:55 PM** Neonatal Birth Hemorrhage: Incidence, Systemic Findings, and Visual Impact

Darius M Moshfeghi MD* 63

**3:01 PM** Pediatric Retina Panel Discussion

**Panel Moderator:** G Baker Hubbard MD

**Panelists:** Audina M Berrocal MD*, Kimberly A Drenser MD PhD*, Philip J Ferrone MD*, Mary Elizabeth Hartnett MD FACS* 64

### REFRESHERMENT BREAK With the Experts and RETINA EXHIBITS, Hall B

**Moderators:** M Gilbert Grand MD and Andrew J Packer MD

**3:21 PM** AMD (Dry)

Philip J Rosenfeld MD PhD* 59
Marco A Zarbin MD PhD FACS*

**AMD (Wet)**

David S Boyer MD* 60
Jeffrey S Heier MD*

**Business of Retina**

George A Williams MD*

**Diabetic Retinopathy**

Suber S Huang MD MBA* 61
Jennifer K Sun MD* 62
Lihteh Wu MD*

* Indicates that the presenter has financial interest. No asterisk indicates that the presenter has no financial interest.
### Gene Therapy
- **Steven D Schwartz MD***

### Intraocular Tumors
- **Ivana K Kim MD***

### Macular Holes
- **Tarek S Hassan MD***
- **John T Thompson MD***

### New Instrumentation
- **David R Chow MD***

### Ocular Imaging
- **Amani Fawzi MD**
- **K Bailey Freund MD***
- **David Sarraf MD***

### Pediatric Retinal Disease
- **Audina M Berrocal MD***
- **Philip J Ferrone MD***

### Retinal Detachment
- **Gary W Abrams MD***
- **Timothy G Murray MD MBA***
- **Hiroko Terasaki MD***

### Vascular Occlusions
- **Michael S Ip MD***
- **Ingrid U Scott MD MPH***

### Vitreolysis
- **Robert L Avery MD***

### Section IX: Late Breaking Developments, Part I
**Moderator:** Andrew P Schachat MD***
**Panelists:** Judy E Kim MD*, Baruch D Kuppermann MD PhD*, and Michael A Singer MD*

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<td>4:01 PM</td>
<td>Three-Year Update for Phase 3 Voretigene Neparvovec Study in Biallelic RPE65-Mediated Inherited Retinal Disease</td>
<td>Albert M Maguire MD</td>
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<td>4:06 PM</td>
<td>DRCR Network Comparison of ETDRS and Ultrawide Field Imaging for Diabetic Retinopathy Severity Evaluation</td>
<td>Lloyd P Aiello MD PhD</td>
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<td>4:11 PM</td>
<td>SCORE2 Month 6 to 12 Results: Monthly vs Treat-and-extend Anti-VEGF Injection Schedules among Good Responders at Month 6</td>
<td>Ingrid U Scott MD MPH</td>
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<td>4:16 PM</td>
<td>Twelve Month Safety and Efficacy Outcomes from a Phase 2 Study of APL-2 in Patients with Geographic Atrophy</td>
<td>David S Boyer MD</td>
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<td>Lampalizumab Phase III Trial for Geographic Atrophy Secondary to AMD, the Spectri Topline Results</td>
<td>Jeffrey S Heier, MD</td>
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<td>4:26 PM</td>
<td>Panel Discussion</td>
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### Section X: First-time Results of Clinical Trials
**Moderator:** Alexander J Brucker MD

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<tr>
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<td>Phase 2 Trial of Ciliary Neurotrophic Factor for Macular Telangiectasia</td>
<td>Emily Y Chew MD</td>
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<td>4:41 PM</td>
<td>Suprachoroidal Triamcinolone Acetonide with and without Intravitreal Aflibercept for Diabetic Macular Edema: Results of the 6-Month Prospective, Phase 1/2 HULK Study</td>
<td>Charles C Wykoff MD PhD</td>
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<td>4:46 PM</td>
<td>TREC-DME Trial: Two-Year Outcomes</td>
<td>David M Brown MD</td>
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<td>4:51 PM</td>
<td>Hawk &amp; Harrier: 48-week Results of Two Multi-centered, Randomized, Double-masked Trials of Brolucizumab vs. Aflibercept for Neovascular AMD</td>
<td>Pravin U Dugel MD</td>
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### Section XI: Neovascular AMD

**Moderator:** Jason S Slakter MD

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<td>Histologic Correlates for OCT Findings in AMD</td>
<td>K Bailey Freund MD*</td>
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<td>5:02 PM</td>
<td>The Pharmacokinetics of Anti-VEGF Agents</td>
<td>Diana V Do MD*</td>
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<tr>
<td>5:08 PM</td>
<td>Treatment Patterns and Visual Outcomes for AMD</td>
<td>Mark C Gillies MD PhD*</td>
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<td>5:14 PM</td>
<td>Anti-VEGF Monotherapy vs. Combination Therapy with Photodynamic</td>
<td>Tien Yin Wong MBBS*</td>
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<td>Therapy for Treatment of Polypoidal Choroidal Vasculopathy</td>
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<td>5:20 PM</td>
<td>Combined Ang2 and VEGF Blockade for Wet AMD: What to Expect</td>
<td>Jeffrey S Heier MD*</td>
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<td>5:26 PM</td>
<td>Update on Emerging Treatments for Neovascular AMD</td>
<td>Peter K Kaiser MD*</td>
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<td>5:32 PM</td>
<td>Closing Remarks</td>
<td>Carl D Regillo MD FACS*</td>
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<td>Richard F Spaide MD*</td>
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### SATURDAY, NOV. 11

7:00 AM CONTINENTAL BREAKFAST

8:00 AM Opening Remarks Carl D Regillo MD FACS* Richard F Spaide MD*

### Section XII: Imaging

**Moderators:** Amani Fawzi MD and Giovanni Staurenghi MD*

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<tr>
<td>8:05 AM</td>
<td>New Biomarkers of Angiogenesis in AMD Using OCT Angiography</td>
<td>David Sarraf MD*</td>
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<td>8:11 AM</td>
<td>Swept-Source OCT: Current Status</td>
<td>Jay S Duker MD*</td>
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<td>8:17 AM</td>
<td>Widefield OCT and OCT Angiography Imaging</td>
<td>Nadia Khalida Waheed MD*</td>
<td>82</td>
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<tr>
<td>8:23 AM</td>
<td>Subclinical Diabetic Macular Changes Revealed by OCT Angiography:</td>
<td>Richard B Rosen MD*</td>
<td>83</td>
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<td>Why It Matters</td>
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<tr>
<td>8:29 AM</td>
<td>OCT Angiography in the Management of AMD and Polypoidal</td>
<td>Philip J Rosenfeld MD PhD*</td>
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<td>Choroidal Vasculopathy</td>
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<td>8:35 AM</td>
<td>Redefining Atrophy in the Era of OCT and Multimodal Imaging</td>
<td>Srinivas R Sadda MD*</td>
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<td>8:41 AM</td>
<td>Disease Expression in AMD Is Correlated with Choroidal Thickness</td>
<td>Richard F Spaide MD*</td>
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<td>8:47 AM</td>
<td>New Imaging Findings in Pathologic Myopia</td>
<td>Kyoko Ohno-Matsui MD</td>
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### Section XIII: Late Breaking Developments, Part II

**Moderator:** Joan W Miller MD*

**Panelists:** J Fernando Arevalo MD FACS*, Mark S Humayun MD PhD*, Elias Reichel MD*, Demetrios Vavvas MD

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<td>8:53 AM</td>
<td>Systemic vs. Fluocinolone Acetonide Implant Therapy for Intermediate,</td>
<td>John H Kempen MD</td>
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<td>Posterior and Panuveitis: 7 Year Results of the MUST Trial and Follow-up</td>
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<td>8:58 AM</td>
<td>Clinical evaluation of eSight—A Head Borne Video System for</td>
<td>Robert G Devenyi, MD, FACS,</td>
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<td>Maculopathy Induced Low Vision</td>
<td>FRCSc, MBA</td>
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<td>9:03 AM</td>
<td>A Phase Ib Clinical Safety Study of a Novel Tumor Targeted Therapy</td>
<td>Carol L Shields MD</td>
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<td>Protocol U: Short-Term Evaluation of Combination Dexamethasone + Ranibizumab vs. Ranibizumab Alone for Persistent Central-Involved DME Following Anti-VEGF Therapy</td>
<td>Raj K Maturi MD</td>
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<td>Panel Discussion</td>
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**Section XIV: Debates, Part II**
Moderator: Gregg T Kokame MD*

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<td>Displacement of Submacular Hemorrhage in AMD Improves Visual Outcomes: Pro</td>
<td>Sunir J Garg MD FACS*</td>
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<td>Displacement of Submacular Hemorrhage in AMD Improves Visual Outcomes: Con</td>
<td>Jeffrey G Gross MD*</td>
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<td>9:30 AM</td>
<td>Widefield Imaging Is Necessary in Practice: Pro</td>
<td>Steven D Schwartz MD*</td>
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<tr>
<td>9:33 AM</td>
<td>Widefield Imaging Is Necessary in Practice: Con</td>
<td>Rajendra S Apte MD PhD*</td>
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<td>Chandelier Scleral Buckling Is Better than Conventional SB: Pro</td>
<td>Jason Hsu MD*</td>
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<tr>
<td>9:40 AM</td>
<td>Chandelier Scleral Buckling Is Better than Conventional SB: Con</td>
<td>Edwin Hurlbut Ryan Jr MD*</td>
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<td>Internal Limiting Membrane Flaps Are Needed to Optimize Macular Hole Closure: Pro</td>
<td>Jerzy Nawrocki MD PhD</td>
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<tr>
<td>9:47 AM</td>
<td>Internal Limiting Membrane Flaps Are Needed to Optimize Macular Hole Closure: Con</td>
<td>William E Smiddy MD</td>
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<td>27-gauge Vitrectomy Is an Essential Platform: Pro</td>
<td>Maria H Berrocal MD*</td>
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<tr>
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<td>27-gauge Vitrectomy Is an Essential Platform: Con</td>
<td>John S Pollack MD*</td>
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**Section XV: Oncology**
Moderators: Evangelos S Gragoudas MD* and Ivana K Kim MD*

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<td>Expanding Clinical Spectrum of Uveal Melanocytomas</td>
<td>Jerry A Shields MD</td>
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<td>Advances in Prognostic Biopsy for Uveal Melanoma</td>
<td>Tara A McCannel MD</td>
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<td>10:56 AM</td>
<td>Paraneoplastic Retinal Conditions</td>
<td>Anita Agarwal MD*</td>
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<td>Cutting-Edge Discoveries in the Genetics of Uveal Melanoma</td>
<td>J William Harbour MD</td>
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<td>Intraocular Lymphoma for Dummies</td>
<td>Jose S Pulido MD MS</td>
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**Section XVI: Diabetes**
Moderators: Jennifer K Sun MD* and Lloyd P Aiello MD PhD*

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<td>Retinal Nonperfusion and Anti-VEGF Therapy in Diabetic Retinopathy: What We Know and What We Don't Know</td>
<td>Dante Pieramici MD*</td>
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<td>11:20 AM</td>
<td>Factors Associated with Worsening Proliferative Diabetic Retinopathy in Eyes Treated with Panretinal Photocoagulation or Ranibizumab</td>
<td>Susan B Bressler MD*</td>
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<tr>
<td>11:26 AM</td>
<td>Persistent Macular Thickening following Intravitreous Aflibercept, Bevacizumab, or Ranibizumab for Center-Involved Diabetic Macular Edema with Vision Impairment</td>
<td>John A Wells III MD*</td>
<td>119</td>
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<td>Plasma VEGF Concentrations after Intravitreous Anti-VEGF Therapy for Diabetic Macular Edema</td>
<td>Lee M Jampol MD</td>
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<td>11:38 AM</td>
<td>Treating Proliferative Diabetic Retinopathy with Diabetic Macular Edema: Anti-VEGF Alone or with Panretinal Photocoagulation?</td>
<td>Neil M Bressler MD*</td>
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<td>11:44 AM</td>
<td>Novel Treatment Strategies for Diabetic Retinopathy and Diabetic Macular Edema: Impactful, or Impossible?</td>
<td>Pravin U Dugel MD*</td>
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<td>11:50 AM</td>
<td>The Role of Steroids in Diabetic Macular Edema</td>
<td>Anat Loewenstein MD*</td>
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**Section XVII: Innovative Retinal Interventions**
Moderator: Mark S Blumenkranz MD*

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<td>Cannulation of Central Retinal Artery Occlusion with a Microneedle</td>
<td>Kazuaki Kadonosono MD</td>
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<td>12:01 PM</td>
<td>Scleral Inlay for Treatment of Optic Disc Pit Maculopathy</td>
<td>Claus Eckardt MD*</td>
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<td>Hypersonic Vitrectomy: Initial Clinical Experience</td>
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**Section XVIII: Uveitis, Part II**
Moderator: Sonia Mehta MD

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**Section XIX: Non-neovascular AMD**
Moderator: Paisan Ruamviboonsuk MD*

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* Indicates that the presenter has financial interest. No asterisk indicates that the presenter has no financial interest.
### Section XX: Vitreoretinal Surgery, Part II

Moderators: Ron Afshari Adelman MD MPH and Mauricio Maia MD*  

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### Section XXI: Retinal Vein Occlusion Panel Discussion

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<td>Panelists: Sophie J Bakri MD*, Colin A McCannel MD*, Ingrid U Scott MD MPH*</td>
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### Section XXII: Video Surgical Complications: What Would You Do?

Moderator: Kourous Rezaei MD*  

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* Indicates that the presenter has financial interest. No asterisk indicates that the presenter has no financial interest.
Intraocular Foreign Body Removal: Tips and Tricks
Basic Rules for Foreign Body Removal

Grazia Pertile MD

I. Study the Situation
   A. Where is the foreign body (FB)?
   B. Is it visible by ophthalmoscopic examination? Do we need additional investigations like CT or ultrasound?
   C. How large is it?
   D. Does it have a round or an irregular shape?

II. Choose the Right Instrument to Approach the FB
   A. A FB may slip out of the instrument and hit the retina. Round FBs and irregular glass splinters require great attention during removal.
   B. Apart from the special FB forceps, larger instruments borrowed from other subspecialties can be useful to firmly grasp large or irregular FB.

III. Remove Any Obstacle That May Bother on Your Way Out of the Eye
    Perform a careful peripheral vitrectomy to avoid vitreous traction and consequent retinal damage while removing the FB.

IV. Make Sure the Exit Is Sufficiently Wide
    Make the sclerotomy large enough to prevent the FB from slipping out and injuring the retina and/or choroid during the removal.

V. Don’t Damage the Surrounding Area during the FB Removal
    Pay special attention to the corneal endothelium and the lens, if present.
Retinectomy: When and How

Steve Charles MD

Retinectomy (Charles 1978) is defined as removing all retina, vitreous, and epiretinal membrane anterior to a circumferential so-called relaxing retinotomy (Machemer 1978). Retinectomy produces less hypotony than relaxing retinotomy, probably because it involves debulking of proliferating retinal pigment epithelium (RPE) and glial cells as well as elimination of substrate (scaffold), extending from the posterior edge of the vitreous base anteriorly to the ciliary body. If lensectomy is required, rather than leaving the capsule so a sulcus IOL can be implanted at a later date, a total capsulectomy should be performed using end-grasping forceps. Leaving capsule results in adherence to the iris, concave iris, epipupillary membranes and hypotony, and closure of inferior peripheral iridectomy by fibrous proliferation. Residual lens epithelial cells associated with remaining capsule can be highly reactive and cause inflammation, which leads to ciliary body membranes and resultant hypotony and concave iris. Debulking of proliferating RPE and glial cells also reduces recurrent proliferative vitreoretinopathy (PVR). All silicone oil reoperations should be performed under oil; forceps membrane peeling, subretinal surgery, and retinectomy work very well under oil. There is no need to remove oil and use liquid perfluorocarbons and then replace the oil at the end of the case in PVR reoperations with oil present. These additional unnecessary steps add time and cost as well as increasing inflammation. Liquid perfluorocarbons often become subfoveal in PVR cases. Further, there is no need for buckles in PVR cases. Buckles cause, on average, a 2.75 D myopic shift—they damage the conjunctiva and episclera, making glaucoma surgery less effective; cause strabismus, pain, slight ptosis, and ocular surface disorder; and increase operating time and cost.

Many surgeons currently perform retinectomy under BSS or, even worse, under liquid perfluorocarbons. Retinectomy should be performed under air as a final step in the reattachment experiment as a subset of interface vitrectomy. The steps in the reattachment experiment are as follows: (1) remove all apparent vitreous traction, including anterior loop traction, (2) perform inside-out forceps membrane peeling for all apparent, peelable epiretinal membranes, (3) remove or segment subretinal bands causing retinal elevation using punch-through retinotomy without using diathermy or cutter retinotomy, (4) initiate drainage of subretinal fluid through existing retinal breaks or a posterior drainage retinotomy if needed, (5) start fluid–air exchange when the height of the retinal detachment stops decreasing, (6) perform simultaneous drainage of subretinal fluid and fluid–air exchange until the retina reattaches, subretinal air appears, or the reattachment process stalls, (7) perform vitrectomy under air if residual vitreous traction is identified, (8) perform forceps peeling of epiretinal membrane under air if additional membrane is identified, (9) use punch-through retinotomy and end-grasping forceps to remove subretinal bands under air if bands are preventing reattachment, and (10) if the retina remains partially detached, use incremental retinectomy under air, using diathermy or endolaser hemostasis only to large vessels. If 270-degree retinectomy is needed, extend to 360 degrees because experience has shown the remaining 90 degrees will typically contract later.
Concurrent Pars Plana Vitrectomy / Cataract Extraction vs. Sequential Surgery: Is There a Difference in Outcomes?

William F Mieler MD, Ivy Zhu MD, Elmer Tu MD

I. Background

A. Many patients undergoing pars plana vitrectomy (PPV) surgery have varying degrees of pre-existing cataract.

B. Holekamp (2005) has reported that PPV surgery hastens cataract formation, especially in patients < 50 years of age.1

1. Increased oxygen level / gradients play a key role in the development of nuclear sclerotic cataract (less so in ischemic diabetic patients).

2. Cataract formation may be further exacerbated by use of intraoperative surgical adjuncts (air / gas / silicone oil).

II. Surgical Techniques

A. Surgery may be performed entirely by the vitrectomy surgeon, or with an anterior segment surgeon.

B. Generally place an infusion cannula, and then the anterior segment surgeon performs the phacoemulsification surgery with placement of a posterior chamber IOL.

C. No limitation of PPV surgery following cataract surgery, and no short-term complications

III. Previous Studies


1. No anterior segment or postoperative complications: mild recurrent vitreous hemorrhage in 3 patients, though none requiring further surgery, YAG capsulotomy in 5 patients

2. VA improved from a mean of 20/80 to 20/40.

B. More recent concurrent small-gauge surgery has been reported by Hohn (2016) and Pavlidis (2016), with successful anatomic and visual results.3,4

C. Small-gauge surgery still induces cataract as reported by Almony (2012).5

IV. Current Study

112 consecutive cases of current phacovitrectomy surgery, with a minimum of 6 months follow-up

A. Indications included macular abnormalities (holes, adhesions, epiretinal membranes) in 31 patients, and complications of diabetes in 54 patients. Other causes included retinal detachment (RD), periph-
eral exudative hemorrhagic chorioretinopathy, radiation retinopathy, etc.

B. Outcomes were highly favorable for macular indications, with significant visual improvement (mean of 20/80 to 20/40); only 1 patient required further surgery for a reopening macular hole.

C. Outcomes were highly favorable in diabetic VH cases, though not as favorable in the diabetic tractional RD patients, as improvement was limited by macular ischemia and/or pigment atrophy.

D. No short-term complications, though 5 diabetic patients required further PPV following development of recurrent RD.

V. Concerns

A. Ability to accurately judge refractive power of the IOL is a concern, though generally not a problem.6

B. Depending on the insurance carrier, there may be less reimbursement when 2 surgeons are involved in a single operation.

C. From the patient standpoint, expenses are generally 17% to 20% less than in sequential surgery.7

VI. Summary

A. Concurrent phacovitrectomy surgery provides the patient with a single operation, it is cost effective, and there is rapid visual recovery and good unaided visual return.

B. Excellent results can be obtained, depending upon the underlying diagnosis.

References and Selected Readings


When and How to Treat Myopic Traction Maculopathy

Hiroko Terasaki MD

I. Introduction

Macular retinal detachment without macular hole (MH) in a highly myopic eye was reported over 20 years ago (Phillips, BJO, 1958). After the development of OCT, Takano and Kishi (AJO, 1999) demonstrated retinoschisis-like structural changes and tractional retinal detachment in highly myopic eyes with posterior staphyloma. These are believed to represent prodromal stages of retinal detachment with macular hole (MHRD) (see Kobayashi and Kishi, Ophthalmology, 2003, and many other reports). The term “myopic traction maculopathy” has been proposed to encompass these pathologic conditions as prodromal stages of MHRD (Panozzo et al., Arch Ophthalmol, 2004).

Vitrectomy with or without internal limiting membrane peeling is a common treatment modality for these prodromal stages in the attempt to prevent the development of MHRD (summarized in Ohno-Matsui et al, Prog Retin Eye Res, 2016). However, the development of MH after surgery has been reported in about 15%-30% (Shimada et al., 2012; Gao et al., 2013; Ho et al., 2014) and in 5% in our series with standard vitrectomy with internal limiting membrane (ILM) peeling. Recently, the foveola-nonpeeling technique (Ho, Retina, 2012; Ho et al., 2014) or the fovea-sparing technique (Shimada et al. 2012) has been reported for myopic schisis. However, exact indications and most suitable methods for this technique should be discussed.

Unfortunately, many patients have already developed MH and MHRD. These MHRD eyes are usually immediately indicated for surgery. In both MH and MHRD, the most common concern is the closure rate of MH. In the MH, the reported closure rate varies from about 60% to 100%, and 95% in our series. To improve the anatomical results, inverted ILM flap technique (Michalewska et al., Ophthalmology, 2010) has been indicated for myopic MH and MHRD (Kuriyama et al., 2013; Hayashi et al., 2014; Michalewska et al., 2014).

MH closure rate has been reported to be much less in MHRD than in myopic MH without RD, which in many articles was about up to 60% using the standard procedure of vitrectomy with ILM peeling and gas or silicone tamponade. For preventing flat, open MH, which is the cause of poor postoperative visual acuity or may cause the recurrence of RD, inverted ILM flap technique might be indicated as a common technique. However, the eyes with functional advantage by this technique have yet to be determined.

II. Myopic Traction Maculopathy (MTM)

A. Representative MTM conditions from a surgical point of view (see Figure 1) and surgical results

1. We analyzed 79 eyes of 76 patients who underwent vitrectomy for MTM and were divided into 4 types as mentioned above: retinoschisis, lamellar MH, foveal retinal detachment (FRD), and FRD + lamellar MH.

Figure 1. Classification for considering timing of surgery for myopic schisis.
2. All the 4 types except retinoschisis showed increased BCVA after surgery and positive correlation between pre- and postoperative BCVA. Both pre- and postoperative BCVA in eyes with FRD were significantly worse than those in eyes without FRD ($P = .029$ and $P = .031$, respectively). Postoperative full-thickness MH developed in 4.9% of cases in all types except retinoschisis.

B. Indications for vitrectomy for MTM without MH and MHRD

Since no postoperative MH developed in eyes with MTM without lamellar MH and FRD in our data, this stage may be an indication for surgery if the patient is symptomatic with decreased vision. On the other hand, if patients are closely followed, surgery can be performed once the progression of foveal detachment is confirmed. However, when MTM eyes demonstrate a champagne glass foveal configuration with decreased visual acuity, surgery should probably be performed before the development of FRD, since this condition may evolve into an impending MH soon after foveal detachment.

C. Surgical complications

1. Development of MH with or without retinal detachment during or after surgery
2. Paravascular hole formation with or without retinal detachment during surgery
3. Damage to the nerve fiber layer with or without increased IOP

D. Foveola nonpeeling technique or fovea-sparing ILM peeling (see Figure 2)

2. In these articles, all 8 eyes and all 15 eyes with foveal detachment attributed by high myopia had no postoperative MHs.

III. MH Surgery for a Highly Myopic Eye

After adapting ILM peeling technique, the closure rate of a myopic MH without RD might increase from 60%-80% to 62%-100% including with inverted ILM flap technique or autologous concentrated platelet (Summarized by Alkabes et al., 2014), and in our series, 94% closure rate after initial surgeries with standard ILM peeling.

Inverted ILM flap technique (Michalewska et al., 2010) has been tried to treat this condition. Using this method, the successful closure has been reported in 5 of 6 eyes (Kuriyama et al., 2013), and in 19 of 19 eyes (Michalewska et al., 2014).

Indication of this technique for high myopic MH surgery has to be decided. From our results of MH surgery (see Figure 3), minimum size of open MH after first surgery was greater than 500 μm, which might be the indication for the inverted ILM flap technique.

Figure 2. Intraoperative OCT during foveal-sparing ILM peeling (arrows are trimmed ILM).

Figure 3. Macular hole closure rate in highly myopic eyes. Two of 33 eyes failed to close MH. If minimal diameter of MH was more than 500 μm, 28.6% of eyes did not obtain MH closure. If maximal diameter (basal diameter of MH) was more than 1200 μm, 40% of eyes did not obtain MH closure.
IV. MHRD

Vitrectomy for myopic MHRD was first reported by Gonvers and Machemer (AJO, 1982). Since then, the results of surgery for myopic MHRD have been reported in many articles (references are listed in Kinoshita, 2017). Compared to the rate of successful retinal reattachment, the MH closure rate has remained unsatisfactory. Some of these previous articles have not included OCT results. In the recent case series, or as controls of new technique, 60% (Arias et al., 2015) and 55% (Nishimura et al., AJO, 2011) of MHs have been reported to be closed after vitrectomy with ILM peeling and silicone oil, and 35% with ILM peeling with complete fluid–air exchange (Chen et al., 2016). In our series, 39% of MHs were closed after vitrectomy with or without ILM peeling with gas or silicone tamponade.

To improve the poorer rates of MH closure for myopic MHRD, inverted ILM flap technique was attempted and reported favorable results: 20 of 20 eyes (Chen et al., 2016; insertion of inverted ILM flap) and 5 of 5 eyes (Kinoshita et al., 2017) showed closed MH postoperatively. Thus, this new technique might be considered as one of the options to achieve MH closure in eyes with myopic MHRD (see Figure 4).

The pre- and postoperative visual acuities in MHRD were worst among the schisis, MH, and MHRD in highly myopic eyes even with anatomically closed MH, because of the photoreceptor degeneration after the long-standing anatomical change. Other new ideas and techniques to improve retinal function can be expected in the future.

References and Selected Readings

Are There 2 Types of Lamellar Macular Holes? Diagnosis and Management

John T Thompson MD

I. Diagnosis

Are macular pseudoholes distinct from lamellar macular holes?

A. Pseudoholes originally characterized by fundus appearance, predating OCT

1. Defined by International Vitreomacular Traction Study Group
   a. Invaginated or heaped foveal edges
   b. Concomitant ERM with central opening
   c. Steep macular contour to the central fovea with near-normal central foveal thickness
   d. No loss of foveal tissue

2. The limitation in this classification of pseudohole is that some eyes with biomicroscopic appearance of macular pseudohole don't fit OCT definition of pseudohole, and vice versa.

B. Lamellar macular holes were increasingly recognized by OCT; defined by International Vitreomacular Traction Study Group.

1. Irregular foveal contour
2. Defect in inner fovea
3. Intraretinal splitting (schisis) typically between the outer plexiform and outer nuclear layers
4. Maintenance of an intact photoreceptor layer

C. The pseudohole example given in the manuscript doesn’t fit the definition; the foveal contour of the pseudohole example is not steep and it doesn’t have near-normal central foveal thickness. Also, many lamellar macular holes don’t have intraretinal splitting.

D. We need a revised definition of macular pseudohole and lamellar macular hole.

E. Proposed pseudohole definition

A macular pseudohole is a slitlamp biomicroscopic diagnosis. The macula looks like a macular hole, but isn’t on OCT. Almost all eyes with macular pseudohole have an epiretinal membrane causing this appearance. The OCT may resemble a typical epiretinal membrane or fit the definition of a lamellar macular hole.

F. Proposed OCT definition of lamellar macular hole

1. Steep, often irregular foveal contour with increased or decreased foveal thickness
2. May have intraretinal splitting (schisis) of variable depth
3. Epiretinal membranes virtually always present and some eyes demonstrate lamellar hole epiretinal proliferation (LHEP)
4. Most lamellar macular holes are secondary to an epiretinal membrane, but there is a small subgroup of lamellar macular holes that are secondary to cystoid macular edema, macular telangiectasia, myopic macular schisis, or vitreomacular traction syndrome.

II. Treatment

A. Vitrectomy for vision loss associated with macular pseudoholes associated with vision loss is well established, with good visual results overall. Massin and colleagues: 50 eyes with macular pseudoholes treated with vitrectomy and epiretinal membrane removal (ILM not intentionally removed).

1. Median preoperative visual acuity was 20/63 and median postoperative visual acuity improved to 20/40.
2. Visual acuity improved 2 or more lines in 62% of eyes.

B. Vitrectomy for lamellar macular holes is a newer indication, with fewer published studies.

1. Witkin and colleagues reported improvement in 1 of 4 eyes and recommended against treatment.
2. Case reports by Kokame (1 eye), Hirakawa (2 eyes), and Spaide (1 eye) found improved visual acuity.
3. Garretson and colleagues: 27 eyes with lamellar macular holes confirmed by OCT
   a. Visual acuity improved in 93% eyes (> 0 lines)
   b. The mean improvement in visual acuity was 3.2 lines.
5. Sato and colleagues\textsuperscript{9}
   a. Forty-two eyes compared vitrectomy with and without air tamponade
   b. Mean acuity improved significantly in both groups, with no difference.
6. Ko and colleagues\textsuperscript{10}
   a. Seventy-three eyes with lamellar macular hole
   b. Visual acuity improved significantly only in eyes without LHEP to 20/25.

III. Conclusion
Vitrectomy is indicated for eyes with visual acuity loss secondary to lamellar macular holes, but visual improvements are generally not as favorable as in eyes with epiretinal membranes and without lamellar macular holes.

References
What’s New in Vitreoretinal Surgery Equipment

David R Chow MD
Retinal Detachment Outcomes in IRIS

George A Williams MD

The IRIS Registry is a qualified clinical data registry (QCDR) as defined by the Centers for Medicare and Medicaid Services that began enrolling patient data in April 2014. IRIS is operative with over 40 EHR systems. As of January 1, 2017, IRIS held data on 119 million unique patient visits from 32 million individual patients representing the practice data of 11,274 integrated ophthalmologists. IRIS is now the largest QCDR in the world. These data provide an unprecedented and unique opportunity to evaluate disease patterns and treatment outcomes across a large population. This paper will present treatment outcomes of primary, noncomplex retinal detachment surgery in IRIS.

From 2013 to 2016, 80,869 unique patients received at least 1 noncomplex retinal detachment operation, defined as CPT code 67107 (repair of retinal detachment: scleral buckling) or CPT code 67108 (repair of retinal detachment: with vitrectomy, any method, with or without air or gas tamponade, focal endolaser photocoagulation, cryotherapy, drainage of subretinal fluid, scleral buckling, and/or removal of lens by the same technique). A total of 82,069 eyes were analyzed, indicating an incidence of 3.4% bilateral involvement over the study period.

Primary operation success was determined by the need for subsequent operation(s) as defined by CPT codes 67107, 67108, or 67113 within 3 months or 6 months of the initial surgery. Preoperative visual acuity was used as a surrogate for macular status. A BCVA of 20/40 or better was used for a macula-on detachment.

There were 10,310 patients (13% of total patients) with 10,510 eyes (13% of total eyes) receiving a scleral buckle as the first operation. There were 70,559 patients (87% of total patients) with 71,559 eyes (87% of total eyes) treated with vitrectomy at the initial operation.

Single-operation surgical success rates at 3 months and 6 months for CPT codes 67107 and 67108 will be presented. Final BCVA will be correlated with type of primary operation and need for reoperation.
Rhegmatogenous retinal detachments (RRD) can be surgically treated with scleral buckling (SB), pars plana vitrectomy (PPV), or a combination of the two procedures. The American Society of Retina Surgeons’ Preferences and Trends Survey has shown a declining use of the scleral buckle over the last decade. With decreasing utilization of the scleral buckle, an important question arises: are there certain situations in which the additional of a scleral buckle provides superior outcomes for retinal detachment repairs? In recent years, a number of randomized controlled trials and retrospective reviews have evaluated scleral buckling with or without PPV vs. PPV alone for patients with retinal detachment. In general, these studies have found no significant difference in outcomes. However, the majority of previous trials and reviews have focused on simple to moderately complex cases and excluded patients with high-risk characteristics.

In one particular published study in the journal *Retina*, the authors evaluated surgical outcomes of eyes with high-risk retinal detachments (early PVR, large retinal tears, hemorrhage, trauma-induced detachments). They performed a retrospective study of 678 patients with retinal detachment treated with a combination of PPV and SB or PPV alone at 1 large retina practice. Patients were excluded if they lacked high-risk features or had previous retina surgery.

Of the 678 patients reviewed, 65 (9.6%) qualified as high-risk and were included in the study. A group of 13 surgeons performed PPV-SB on 36 patients and PPV alone on 29 patients. The overall success rate for the 65 high-risk patients, regardless of surgical procedure, was 63.1%. This success rate is consistent with previously reported rates of high-risk cases, which go on to develop PVR at a much higher frequency than typical eyes. They found that the addition of the scleral buckle was associated with significantly higher success rates compared to vitrectomy alone. For patients treated with the combination vitrectomy and scleral buckle, surgical success was 75.0% (27/36) compared to 48.3% (14/29) for patients treated with vitrectomy alone, giving an odds ratio of 3.24 (95% CI, 1.12-9.17; \( P = .029 \)). They also evaluated baseline characteristics and found that the benefit of a buckle with vitrectomy was only shown for individuals 65 years and younger. For patients over 65 years, there was no difference in anatomical outcomes between the surgical approaches. Interestingly, this study found that lens status did not have an impact on surgical outcomes in the high-risk cohort; there was no benefit or detriment to using a scleral buckle in phakic patients vs. pseudophakic eyes.

A further review of the literature reveals an array of clinical outcomes when comparing scleral buckles to vitrectomy plus buckle. A number of randomized controlled trials have explored surgical management for patients with uncomplicated rhegmatogenous retinal detachments with variable conclusions. Some randomized trials found no difference in single-surgery anatomical success between scleral buckle alone and vitrectomy, while 1 study found that vitrectomy had significantly higher attachment rates than scleral buckle alone. However, other papers from the literature reveal no benefit between the 2 procedures for detachments in general. Heimann et al found that there was no benefit in the single operation reattachment rate for phakic eyes and better reattachment rate with PPV (±SB) for pseudophakic eyes.

The European Vitreo-Retinal Society accumulated data from 176 surgeons in 48 countries. The eyes had complex retinal detachments including Grade B or C PVR, choroidal or hypotony or large retinal tears. The results showed that in Grade C-1 PVR, there was not a statistically significant difference in the failure rate between those treated with vitrectomy ± buckle and those treated with scleral buckle alone (\( P = .7 \)). Vitrectomies with a buckle had an higher failure rate than those who did not receive a buckle (\( P = .007 \)). Large or giant retinal tears treated with vitrectomy also had a significantly lower failure rate than those treated with scleral buckle (\( P = 7\times10^{-8} \)). The authors concluded that in patients with retinal detachment, when a large tear or a giant tear is present, vitrectomy is the procedure of choice. If a vitrectomy is to be performed, these data suggest that a supplemental buckle may not be helpful.

Ultimately, the only way to determine the success rates for detachments in general and by procedure of choice is to prospectively analyze the data. The closest approximation to a clinical trial is to analyze the IRIS Registry. The AAO IRIS Registry is the first United States-based national comprehensive eye disease database. The IRIS Registry’s electronic health record (EHR) base consists of approximately 1790 ophthalmologist-based practices with 7791 participating physicians as of September 30, 2016. While not truly a prospective trial, the number of cases in the IRIS Registry is remarkable, and thus it provides us with the largest data set available for analysis to date.

Using the IRIS Registry, we obtained all eyes who underwent a primary retinal detachment repair procedure (CPT code 67107, 67018, or 67113) between January 1, 2013, and September 30, 2016, with at least 6 months of follow-up. Of those eyes that underwent a primary repair (102,503 eyes from 97,746 patients), we evaluated the rate of a second retinal detachment repair procedure (67107, 67108, or 67113) within 3 months and 6 months of the initial repair, respectively.

We analyzed the IRIS Registry to determine the overall success rate for a primary retinal detachment repair, compared primary success rates for scleral buckle vs. vitrectomy, and finally determined success rates for complex retinal detachments. The complex RD study cohort was constructed based on ICD-9 and ICD-10 diagnostic codes from the IRIS Registry population. Aggregated data from the IRIS Registry are de-identified and do not require patient level consent. The final results for these analyses will be presented at the AAO meeting.
References


Results of Vitrectomy for Eyes following Failure of Surgery for Proliferative Vitreoretinopathy

Gary W Abrams MD

Introduction
Approximately 5%-15% of first operations for retinal detachment fail, and proliferative vitreoretinopathy (PVR) is reported to occur in 7%-10% following primary retinal detachment. The incidence of failure of the first vitrectomy for PVR is variable, but most reports are in the 25%-30% range. We have studied the results of repeat vitrectomy after failure of vitrectomy for PVR.

Patients
This is a retrospective series of cases from 2000 through 2015 with all cases done by a single surgeon (GWA). Included were eyes that had a failed prior vitrectomy for PVR. We excluded diabetic retinal detachment or other vascular retinopathies, penetrating injuries, acute blunt trauma, and children under the age of 8. The study included 51 eyes of 50 patients, with 25 females and 25 males. The age range was 8-81 years, with an average age of 56.2 years. All cases had at least 1 failed vitrectomy for PVR. Five cases were my failed cases, and 46 were referred from other retina surgeons. Thirty-one patients lived in Michigan and 19 in other states. Twenty-two patients came referred from other retina surgeons. Thirty-one patients lived within 100 miles of Detroit, with the farthest distance being 1032 miles. Eyes had an average of 2.22 prior vitrectomies for PVR; 46/51 had a prior scleral buckle. There was retained silicone oil in 25 eyes, and 26 had residual gas or were fluid filled. The majority of eyes had both anterior and posterior PVR. The cornea was clear in 34 and had mild to moderate changes in 17. Four eyes were phakic, 14 were aphakic, and 33 were pseudophakic.

Surgery
The lens was removed in phakic eyes, and 4 of 33 pseudophakic eyes had removal of the IOL. Epiretinal membranes were removed in 50 of 51 eyes; and subretinal membranes, in 17. A retinectomy was done in 44 eyes (86%), with the retinectomy ranging from 1 to 12 clock hours, with an average of 5.8 clock hours. Three eyes had 360-degree retinectomies. Silicone oil was used in 49 eyes; and gas, in 2 eyes.

Results
Follow-up was 6 months or more in 51 eyes, 12 months or more in 47 eyes, and more than 12 months in 37 eyes. The retina was attached at the last follow-up in 43 of 51 eyes (84%). If corneal opacity prevented visualization of the retina (2 eyes), the retina was considered detached. Success was defined as the following: retina attached, silicone oil removed, and visual acuity of 5/200 or better. Silicone oil was removed from 23 of 49 eyes that received silicone oil, and 17 of those eyes met the criteria for success. The visual acuity was 20/400 or better in all successful eyes, and 3 of those eyes had 20/50 visual acuity. Silicone oil was retained in 26 eyes. The reason for silicone oil retention was relative hypotony in 15 eyes, patient choice in 1, referring physician choice in 7, and unknown in 3. Visual acuity was 5/200 or more in 74% of eyes when silicone oil was removed and only 19% when silicone oil was retained.

Successful eyes (vs. unsuccessful eyes) generally had better preoperative visual acuity (P = .0001), were more likely to come from within 100 miles of Detroit (P = .0094), had less postoperative hypotony (0% vs. 35%; P = .0051), and had postoperative visual acuity ≥ 5/200 (100% vs. only 15% in unsuccessful eyes; P < .001). Unsuccessful eyes were more likely to have 2+ or more preoperative flare (P = .0037) and to have postoperative hypotony (IOP of ≤ 5 mmHg) (P = .0051). Factors found not significant were age, previous number of surgeries for PVR, number of surgeries we did, removal of epiretinal membranes, size of retinectomy, preoperative cells in anterior chamber, preoperative and postoperative corneal clarity, and preoperative hypotony. Other factors found not significant were preoperative lens status, preoperative PVR classification (anterior only vs. posterior only vs. mixed anterior / posterior), preoperative hypotony (0% vs. 35%; P = .0051). Factors found not significant were age, previous number of surgeries for PVR, number of surgeries we did, removal of epi- and subretinal membranes, size of retinectomy, preoperative cells in anterior chamber, preoperative and postoperative corneal clarity, and preoperative hypotony. Other factors found not significant were preoperative lens status, preoperative PVR classification (anterior only vs. posterior only vs. mixed anterior / posterior), preoperative scleral buckle present, preoperative silicone oil, and 23- vs. 20-gauge vitrectomy. We found no difference in outcome between eyes operated more than 8 years ago and eyes operated 8 years ago or less.

Lessons Learned

- We can reattach most eyes with failed PVR surgery.
- Visual results are modest, but some eyes have good ambulatory vision.
- Eyes with better preoperative visual acuity have best outcome.
- Hypotony is a significant problem postoperatively.
- It is difficult to remove silicone oil in PVR reoperation patients.
- Hypotony is a significant problem: 12/47 eyes with IOP reported at 6 or more months follow-up had IOP ≤ 5 mmHg.
- Hesitation of referring physicians to remove silicone oil even in patients with better prognosis
- Hesitation of some patients to remove silicone oil
- Corneal complications are frequent in both successful and unsuccessful eyes.
- Some are severe.
- Often at least mild preoperative corneal abnormalities
- Excessive associated with retained silicone oil and/or hypotony
- Intraoperative complications may be more frequent than in general vitrectomy cases.
- Two cases of intraoperative choroidal hemorrhage
- Is it worthwhile to do reoperations for failed PVR surgery?
- Success means attached retina, ambulatory vision, adequate IOP, and removal of silicone oil from the eye.
- Some eyes do quite well.
- Even in eyes with poor visual acuity, we should push for silicone oil removal when possible.
Selected Readings


The Management of Recurrent Macular Holes

Tarek S Hassan MD

I. Recurrent Macular Hole (MH): Introduction
   A. Fortunately – rare
   B. Fortunately – excellent outcomes with repeat vitrectomy
      1. Renewed interest given new techniques to repair recurrent, chronic, and/or large, full-thickness MHs
      2. Need to determine which surgical maneuvers are needed for which difficult MH cases

II. MH Repair: History of Success
   A. Described in 1991 (Kelly & Wendel)¹
   B. Consistent improvement in closure rates and visual acuity (VA) improvement since
      1. Now expected closure rate is > 90% for acute and subacute MHs—nearly curable.²⁻⁴
      2. Success rates have been stable over past 7-10 years.
   3. Reasons for improvement
      a. MH patients present earlier for surgery.
         i. Earlier diagnosis (OCT is everywhere)
         ii. Earlier surgery done on smaller MHs = better outcomes
      b. Surgical fellows are better and more consistently trained to successfully perform this repair, including internal limiting membrane (ILM) peeling.
      c. Better surgical visualization with improved dyes, lenses, viewing systems

III. Most MHs Close—Some Do Not
   A. Surgical success with vitrectomy, posterior hyaloid removal, membrane peeling (± ILM peeling – mostly stained with indocyanine green or brilliant blue). Fairly standard technique.
      1. Relief of traction from MH: Histologic changes
         b. Otherwise normal retinal pigment epithelium
         c. No significant tissue inflammatory response
         d. Resolution of cystoid macular edema (CME) with MH closure
      2. Possible increase in cytokines that aid healing²⁵
   B. Timing of MH closure
      1. Most eyes: < 1 day to 7 days
      2. With more time – gliotic plug matures
   C. Timing of MH surgery failure
      1. Primary failure: MH never closes.
      2. Early reopening: Failure to form initial solid gliotic plug and MH reopens.
      3. Late reopening: After gliotic plug forms – MH reopens after at least several weeks.
   D. Terminology of MH surgery failure
      1. Persistently open or incompletely closed
         a. MH never closes.
         b. MH reopens within first several days / weeks postoperatively.
         c. (Incomplete) repair: Flat edges but open central MH
      2. Recurrent
         a. MH reopens after immediate postop period.
         b. Usually > 1 month
   E. Incidence of MH reopening
      2. Mean time to reopening: 12-15 months⁶⁻⁹
         a. Series entirely or mostly from pre–small gauge vitrectomy era
         b. At a time with poorer visualization, training, and availability of OCT

IV. Impact of Small-Gauge Vitrectomy on MH Repair
   A. Not well described; no proven advantages
   B. Theoretical advantages
      1. Less invasive = less inflammation?
      2. Less inflammation = less postoperative CME?
   C. Anatomic results appear the same as before small-gauge vitrectomy era.
   D. Impact of small-gauge vitrectomy on MH reopening: Unknown

V. Recurrent MHs, Current Series: Associated Retinal Consultants, Royal Oak, Michigan
   A. First look at recurrent MHs treated entirely with small-gauge vitrectomy techniques
B. Retrospective review: 392 eyes (8 surgeons)

1. All with successful closure of idiopathic full-thickness MHs following initial 23- or 25-gauge vitrectomy

2. Study Group: All eyes that had reopening of MH after documented closure, at least 1 month after initial vitrectomy: \( n = 13 \) eyes (3.3%)

a. Initial MH repair: All holes initially closed successfully.
   i. All had ILM peeling: 6/13 with indocyanine green assistance, 7 without stain
   ii. All with gas tamponade: 6/13 with C3F8, 7/13 with SF6
   iii. VA improved from 20/137 to 20/61

b. All MHs reopened
   i. Time to reopening
      (a) Mean: 28 months
      (b) Range: 5 weeks to 10 years
   ii. Epiretinal membrane (ERM) identified around reopened MH in 85%
   iii. Cataract extraction (CE) performed in 38% prior to MH reopening
   iv. CME developed prior to MH reopening in 15%.

c. All MHs underwent reoperation—second vitrectomy
   i. ERM peeled in 70%
   ii. More ILM peeling attempted in 100%
      (a) Surgeons felt ILM remnants removed in 9/13 eyes
      (b) All eyes with gas tamponade (12/13 with C3F8)
      (c) All MHs closed again > 1 month
      (d) Mean VA improved from 20/148 to 20/115

d. 3/13 MHs reopened again …
   i. Time to reopening: 5, 5, and 49 months
   ii. Management
      (a) Two chose no more surgery.
      (b) One eye had third vitrectomy with ERM peeling.
         (i) MH currently remains closed after 2 years.
         (ii) VA improved from 20/400 to 20/60.

VI. Recurrent MHs, Current Series: Considerations

A. At most recent follow-up: MHs closed in all eyes that had all surgeries.

B. Mean VA improvement: 20/148 to 20/89

C. Other eye: 10/13 patients (77%) had, or later developed, a full-thickness MH in the other eye.

   1. Greater intrinsic ILM contraction? Higher likelihood of significant late ERM formation?
   2. High incidence of contralateral MH seen in another major series of recurrent MHs after 20-gauge vitrectomy.
      a. Thompson et al (2000) = 69%
      b. General incidence of bilateral MHs = 10%-15%

VII. Why MHs Reopen

A. ERM

1. High rate of ERM formation in reopened MHs (57%-73%)8,11
2. Found to have Müller cells with myoblastic features, fibrous astrocytes with contractile elements12,13

3. Causative in MH reopening?
   a. Likely ERM is extension of normal postop healing; seen in 64%-73% of closed MHs14,15
   b. Maybe ERM does not need to be peeled?

B. Residual vitreous ± ILM remnants at MH edge – split hyaloid, ILM on downward slope of MH edge, etc.

C. CME

1. After CE
   a. Four-fold increase in MH reopening in eyes with CE after vitrectomy vs. eyes with vitrectomy alone or with combined CE, vitrectomy11
   b. Seven-fold increase in MH reopening in eyes with CME after CE11

2. After other inflammatory events: retinal detachment, trauma, iritis, YAG capsulotomy, etc.

VIII. Recurrent MHs after Small-Gauge Vitrectomy, Current Series: Conclusions

A. Low incidence

B. Generally happens many months later

C. Associated with new ERM tissue

D. High likelihood of successful closure after reoperation with repeat vitrectomy, further membrane peeling, and fluid-gas exchange
   1. 77%-100% in multiple reports
   2. Good visual outcomes after repeat vitrectomy(ies)

E. Majority of patients associated with full-thickness MH in the other eye
IX. Current Strategies: Repairing Recurrent MHs

A. All reported to be successful
   1. Repeat vitrectomy, membrane peel, fluid–gas exchange
   2. Vitrectomy with ILM flap techniques
   3. Vitrectomy with autologous tissue implantation / transplantation
   4. Vitrectomy with creation of submacular fluid bleb to free edges, fluid–gas exchange

B. Not all recurrent MHs are created equal.
   1. Best technique for repair likely determined by the size and chronicity of recurrent MH as well as other confounding anatomic features.
      a. Large holes (> 750 microns) may do better with more than repeating the original procedure.
      b. ERM ± ILM remnants allows for further membrane peeling to succeed.
   2. Controlled comparative trials would help us to determine which procedure to use for which case, particularly with the advent of newer techniques that involve placing a scaffolding of tissue within the recurrent MH.

References

Strategies in Trauma Surgery
Trauma Essentials: TENERE ViESC

Carl Claes MD

- **T:** Trauma
- **E:** Evaluate
  - History (+ bystanders)
  - Slitlamp
  - Ultrasound
  - CT scan
  - MRI (CAVE metal)
- **NE:** Negotiate
  - Inform
  - Birmingham Eye Trauma Terminology / Ocular Trauma Score
  - Individual prognosis impossible
  - Functional recovery vs. anatomic / aesthetic recovery
- **R:** Reconstruct
  - Integrity of the globe / watertight
  - Repair cornea, sclera leaks
  - Suture iriscolobomas
  - Drain choroidals
- **E:** Explore / navigate
  - Identification of the different structures
  - Blood clot / fibrine / scarring / retina / choroid / ciliary processes
- **Vi:** Visualize
  - Major obstacle in trauma surgery
  - Hemostasis: diathermy, heavy liquids, silicone oil, viscoelastics
  - Opaque media: temporary kerathoprosthesis: open sky
  - Opening virtual space: silicone oil / viscoelastics / heavy liquids
- **E:** Excise
  - Scar tissue, blood clots, fibrosis, necrotic tissues
  - Free up incarcerated tissues
  - Retina-choroidectomy in posterior perforation sites
  - Selectively separate / clean recoverable structures
  - *Never* eliminate unidentified tissues
- **S:** Save
  - Vital tissues / avoid iatrogenic damage
  - Iris (optional)
  - Ciliary body (clean, traction relief)
  - Posterior pole retina
  - Optic nerve
- **C:** Consolidate
  - Flatten retina / retinal massage / endolaser
  - Silicone oil is indispensable.
  - Multiple treatment sessions
  - Graft: cornea / sclera / conjunctiva
Management of Combined Schisis Retinal Detachment

Gaurav K Shah MD and Abdallah Jeroudi MD

I. Introduction to Retinoschisis (RS) Terminology
   A. Degenerative RS
   B. Schisis detachment
   C. Retinal detachment (RD) complicating RS

II. RS Basics

III. RD Complicating RS Management
   A. Different surgical approaches
      1. Barricade laser / cryotherapy
      2. Scleral buckling
      3. Pars plana vitrectomy
   B. Reported outcomes of surgery with different surgical approaches

IV. Review of RS with Outer Wall Breaks and the Development of RD Complicating RS in a Large, Tertiary-Center Referral Practice
   A. Observation group: 28.6% of initially observed RS patients with outer wall breaks progressed to symptomatic RS complicating RD at a mean of 20.6 months.
   B. Laser / cryotherapy barricade group
   C. Vitreoretinal surgery group
      Symptoms of RD with visual field loss: Factors associated with RS associated with RD were presence of symptoms (100% of patients) and posterior extension to the arcades / macula (93% of patients).
      1. 2.4% of all patients with RS over a 15-year period
      2. 86%, single procedure success rate; 100%, final success rate

V. Widefield Infrared Imaging in RD and RS
   A. RD
      1. Subretinal fluid appears “dark.”
      2. Exposed retinal pigment epithelium (RPE) of a tear appears “light.”
   B. RS
      Light / translucent appearance with prominent vascular appearance
   C. RD complicating RS
      Mixed appearance

VI. Conclusions
   A. RD complicating RS seen in 2.4% of all RS patients.
   B. About 25% of RS with outer wall breaks may progress to symptomatic RD complicating RS.
   C. Consider widefield infrared imaging for surveillance of RS patients; it can assist in distinguishing between RD and RS.

Selected Readings

Treatment of Optic Pit Maculopathy

Mark W Johnson MD

I. Cavitary Optic Disc Anomalies Associated with Macular Fluid / Detachment
   A. Typical optic disc coloboma
   B. Optic pit and atypical coloboma
   C. Morning glory disc anomaly

II. Pathogenic Mechanism
   A. Fluctuating pressure gradients along anomalous communications within disc cavitation induce migration of fluid into adjacent retinal tissue.
      1. Schisis-like intraretinal fluid connecting with the optic disc is a nearly universal feature.
      2. Fluid eventually percolates into subretinal space in most eyes.
      3. Rare patients exhibit subretinal fluid alone.
   B. Evidence for fluctuating pressure gradients
      1. Subretinal migration of vitreous substitutes (gas, silicone oil, heavy liquid)
      2. Vitreous gel incarceration into disc cavitation
      3. Spontaneous waxing and waning of macular fluid
      4. Observation of vitreous debris moving in and out of cavitation with digital pressure on globe
   C. Source of macular fluid
      1. Depending on pathoanatomy of congenital disc anomaly, macular fluid may be vitreous fluid, cerebrospinal fluid, or possibly admixture of both.
      2. Age of patient may be clue (eg, extensive retinal detachment in 1-year-old child unlikely represents liquid vitreous).

III. Therapeutic Implications of Pathogenesis / Pathoanatomy
   A. Factors that alter pressure gradients may affect macular fluid (eg, carbonic anhydrase inhibitors).
   B. Permanent cure likely requires barrier to intraretinal (as well as subretinal) fluid migration from the disc cavitation.

IV. Surgical Approaches
   A. Macular buckling
      1. Posterior scleral indentation may close intraretinal fluid channels.
      2. Experienced groups have reported excellent results.
   B. Vitrectomy alone
      1. Hirakata and colleagues reported resolution of macular fluid in 90% of eyes.
      2. Therapeutic mechanism unclear
      3. Long-term recurrence rate unknown
      4. Real-world failures and recurrences are common.
   C. Titrated juxtapapillary laser photocoagulation followed by vitrectomy and gas tamponade
      1. Technique (see Kiang and Johnson)
         a. Laser performed at slitlamp immediately prior to vitrectomy
            i. Red wavelength laser and contact lens stereopsis for maximum safety
            ii. Careful titration of power for thermal spread into middle retinal layers, but avoiding nerve fiber layer
         b. Vitrectomy with peeling of posterior hyaloid (no internal limiting membrane [ILM] peeling)
         c. Gas tamponade with 7-10 days of reading position postoperatively
      2. Results (Kiang and Johnson)
         a. Complete resolution of macular fluid in 11/11 eyes (100%)
         b. Recurrence in 1 eye over mean follow-up of 48 months
         c. Mean VA improved from 20/125 to 20/57 (∆P = .0072).
         d. Possible laser-induced cecocentral scotoma in only 1 patient with extensive prior laser treatments
      3. This approach can be used as primary procedure or following unsuccessful vitrectomy alone.
   D. Vitrectomy and plugging of cavitation with autologous sclera
      1. Several case reports suggest efficacy in select eyes with medium-sized cavitations.
      2. Safety and long-term outcomes unknown
E. Proposed vitrectomy adjuncts of questionable value

1. ILM peeling
   a. No plausible rationale
   b. Increases risk of macular hole

2. Inner retinal fenestration
   a. Likely heals spontaneously in early postoperative period
   b. Benefit likely derives from vitrectomy alone

3. Vitrectomy with tissue adhesive or ILM flap over disc cavitation
   a. No theoretical role in eyes with cerebrospinal fluid source
   b. Long-term benefit unclear compared with vitrectomy alone

Selected Readings


Combined Keratoprosthesis and Vitrectomy Surgery Outcomes

Jennifer I Lim M

I. Indication for Keratoprosthesis and Vitrectomy
   A. Opacification of cornea with history of multiple failed grafts
   B. Concomitant retinal condition requiring vitrectomy
   C. Placement of pars plana glaucoma drainage device

II. Rationale for Combination Surgery
   A. High rates of post-keratoprosthesis glaucoma
   B. Concomitant management of posterior segment disease
   C. Allows for removal of membranes anteriorly in eyes with severe scarring from prior penetrating keratoplasties

III. Results with Combination Surgery
   A. Lim et al (UIC data)
      1. Complications rates with and without concomitant vitrectomy
      2. Lower rate of de novo glaucoma
      3. Lower rates of subsequent vitrectomy for posterior segment complications
      4. Lower rates of secondary procedures for complications
   B. Perez et al data
      1. Complete pars plana vitrectomy (PPV) vs. partial or anterior PPV
      2. Lowered rates of retroprosthetic membranes and uncontrolled glaucoma
      3. Visual acuities similar for both groups

IV. Visual Acuity Outcomes
   A. UIC data: Comparison of outcomes for PPV with keratoprosthesis vs. keratoprosthesis alone
      1. > 75% of eyes improved 3 or more lines of visual acuity at 1 year for both groups.
      2. Lowered rates of secondary procedures ($P < .001$) and de novo glaucoma
   B. Limitations due to underlying conditions, especially glaucoma

V. Complications
   A. Retroprosthetic membranes
      1. Most common complication post-keratoprosthesis
      2. Requires PPV if too thick or YAG laser
      3. Frequently recurrent and may require PPV
   B. Endophthalmitis
      1. Prophylaxis required; lack of biointegration increases risk for infection.
      2. Bacterial, fungal causes
      3. Rates vary in series as time dependent: 2.7% per year
      4. Antibiotic prophylaxis is helpful.
      5. Wagoner et al showed 54% lost more than 2 lines of visual acuity.
      6. Management with and without vitrectomy
         a. Vigilance required with low threshold for PPV
         b. Tap and injection in prior PPV eyes was successful.
   C. Posterior segment complications
      1. Proliferative vitreoretinopathy (PVR) and rhegmatogenous retinal detachment (RRD)
         a. Decreased with concomitant total vitrectomy
         b. Petrou: Serous elevation followed by PVR; series had 22% PVR RRD.
      2. Choroidals
      3. Hypotony
      4. Cystoid macular edema
      5. Epiretinal membrane

Selected Readings


Clinical Trials in Ophthalmology: Past, Present, and Future

Frederick L Ferris III MD

I. Past Clinical Trials
A. First clinical trial: The Book of Daniel
B. Centuries pass until next major trial: Lind—Citrus for scurvy
C. First nonrandomized major eye clinical trial: Patz—Oxygen and retrolental fibroplasia

II. Diabetic Retinopathy
A. Airlie House symposium
B. Photocoagulation development
   1. Gerd Meyer-Schwikerath
      a. Sun as a light source for photocoagulation
      b. Xenon arc photocoagulator
   2. William Beetham and Lloyd M Aiello: Scatter photocoagulation as a treatment for proliferative diabetic retinopathy
C. Clinical trials and randomization thought to be impossible for a diabetic retinopathy study
   1. Diabetic retinopathy patients are too diverse.
   2. Physicians know what is best for individual patients.
   3. Patients will not accept randomization.
   4. Diabetic retinopathy cannot be categorized.
   5. Photocoagulation is dangerous.
D. First major randomized clinical trial in ophthalmology: Diabetic Retinopathy Study (DRS)
   1. Eligibility criteria
      a. Patients with proliferative diabetic retinopathy in 1 or both eyes
      b. Bilateral severe nonproliferative diabetic retinopathy
   2. Site visits necessary to develop the new procedures for multicenter study
E. DRS trial stopped early because of 50% reduction in blindness after 2 years.¹
F. ETDRS addressed unanswered questions from DRS.
   1. Early and Deferred Scatter Photocoagulation: equivalent efficacy and safety²
   2. Focal/grid photocoagulation reduced vision loss from diabetic macular edema (DME) by 50%.³

III. Diabetic Retinopathy Clinical Research Network (DRCRnet)
A. Initiated in 2003
B. Clinical research efficiency enhanced and costs reduced
C. Multiple concurrent and consecutive studies with shortened start-up and collaboration with industry and foundations supporting half the total cost of studies in the last decade. Twenty-six protocols to date.⁵

IV. New Era in Diabetic Retinopathy Care
B. DRCRnet: Protocols B and I demonstrate laser superior to corticosteroids for DME.
C. Protocol T: Ranibizumab, afibercept, bevacizumab all safe and effective treatments for DME⁶
   1. No difference in efficacy seen in eyes with 20/30-20/40 visual acuity
   2. Afibercept more effective in improving visual acuity in persons with visual acuity of 20/50 or worse
D. Protocol S: Ranibizumab an effective alternative to scatter photocoagulation for PDR⁷

V. Future Directions in Clinical Trials
A. Use of EMR systems such as the Academy’s IRIS® Registry for observation studies
B. Eventual ability to download clinical trial data from EMR could be possible; migrate from local EMR to central database as currently done at National Eye Institute Clinical Center.
C. Considerable work will be necessary prior to use of EMR in clinical trials.
   1. Develop EMRs that can talk to each other or at least to a central site
   2. Developing “common data elements” is a major hurdle.

VI. Clinical Trials Will Remain the “Gold Standard” and the “Indispensable Ordeal”
They have evolved dramatically and have the potential for community-wide involvement.
References


ASC Update
Out of Network Billing

Derek Kunimoto MD JD

I. Out of Network (OON) Billing
   A. What is it?
   B. Spectrum of OON
   C. Is it uncommon?
   D. Medicare patient facility fee vs. OON facility fee
   E. Claims process and collection
   F. Financial impact
   G. Sounds great, but payers have taken an active stance against OON (eg, litigation by Cigna and Aetna).
   H. Landmines
      1. If any Medicare patients slip through
      2. If financial disclosure does not get signed

II. Cigna v Humble (2016)
   A. Cigna claimed Humble was submitting claims in exceedingly large dollar amounts.
   B. Cigna claimed Humble was “fee forgiving” by consistently waiving the patient cost-share of the billed charges.
   C. Court held that Humble did not “fee forgive,” since this only occurs when no effort is made to collect from patients.
   D. Humble was awarded underpayments of > $11,000,000 and penalties of > $2,000,000.

III. Aetna v Humble (2016)
   A. Focused on referral fees paid to doctors
   B. Sued for money had and received, fraud, negligent representation, and ERISA (Employee Retirement Income Security Act) relief
   C. Court found hospitals may not bill patients one way and the plan another way. Awarded Aetna more than $20,000,000.
   D. Court awarded Aetna > $41,000,000 for payments made between 2010 and 2013.
   E. Court awarded Aetna > $12,000,000 for kickbacks paid by Humble.
Changes in Health-Care Reimbursements

David W Parke II MD

Introduction
Changes in health-care reimbursement are driven by a host of factors. At the macro level, they are driven by over-arching policy considerations that in recent years have been characterized by (1) the move “from Volume to Value,” (2) a policy imperative to modulate the rate of rise of health-care costs, and (3) the objective of increasing payment for primary care services. This constitutes the framework within which all changes, at both the federal and the commercial level, are considered. At the macro level, access to care—while not generally a “direct” driver of reimbursement change—can play a role in differential reimbursement based on geography, area payer mix, facility payments, and attempts to rectify disparities in care.

Overview
On the surface, ophthalmology as a specialty has the highest percentage of Medicare patients of any specialty except geriatrics. Retina, as a subspecialty of ophthalmology, is no different. Therefore, ophthalmologists are dramatically impacted by what goes on within Medicare. However, Medicare is similarly impacted by ophthalmology. In professional fees, ophthalmology has two of the “Top Twenty” diseases on total cost basis for Medicare—cataract and glaucoma. If Part B drug costs are included, AMD and diabetic retinopathy also move into the Top Twenty. We estimate that total Medicare payments to ophthalmologists for professional services approaches $100 billion per 10-year period.

Medicare payments per unit of professional service to ophthalmologists in general have remained essentially flat over the past 8 years (measured by the Medicare Physician Fee Schedule), while others, such as vascular surgery, urology, cardiology, radiation oncology, and radiology, have seen double-digit substantive increases.

Advocacy to reverse these decreases in payments faces a tough challenge. In 2016, according to the U.S. Department of Labor Bureau of Labor Statistics, 9 of the 10 top occupation titles by annual mean wage were physicians. Orthodontists were the tenth. According to the 2017 Medscape Physician Compensation Report, ophthalmologists rank 11th of 27 specialties, with an average annual compensation of $345,000. The average physician salary has increased 42% over the past 6 years. Again, using Medscape statistics, the average ophthalmologist salary increased 12% in 2016 compared to the prior year—the fourth highest among specialties.

While the rate of increase in total health-care costs has slowed compared to a decade ago, it still continues to rise at a greater rate than the general economy. And while physician compensation is only about 20% of all health-cost expenditures, the ophthalmologist controls the vast majority of eye care costs—including Part B drug costs, site of surgical service, imaging studies, etc.

Economists, health policy wonks, employer groups, integrated systems, commercial payers, and the federal government have focused on linking the higher U.S. physician payment more to the quality of outcomes of care than to a strict per-service system. This is the so-called “Volume to Value” payment transition. While used most often to describe changes within the Medicare program, it is being pushed at least as actively in the commercial insurance space—in part due to the higher levels of physician compensation (relative to Medicare) in the vast majority of commercial plans.

How is this impacting physician reimbursement and compensation? Relative to nearly every other physician specialty, few ophthalmologists are salaried by hospital systems—but about 10%-15% are compensated by academic and nonacademic integrated systems. Some (like Geisinger Health Systems, with 1,600 employed physicians) are abandoning performance bonuses and moving to 100% straight salary. But most systems see value-based reimbursement as almost requiring a reward-and-penalty compensation system based on a mix of quality, patient experience, and productivity factors.

Reimbursement within Medicare falls into 2 buckets: fee-for-service (FFS) Medicare and Medicare Advantage (MA). While most attention is focused on FFS Medicare reimbursement changes, it is important to note that as of January 2017 about one-third of the 56 million Medicare beneficiaries were enrolled in the Medicare Advantage program. This is highest in Minnesota (56%) and lowest in Alaska, Wyoming, Vermont, New Hampshire, Delaware, and Maryland (all under 10%). Of large metro areas, the highest penetration rate is Miami-Dade at 64%.

FFS Medicare reimbursement remains based on a relative value unit (RVU) methodology but is now modified by participation in the Quality Payment Program (QPP). The QPP has 2 major components: the Merit-Based Incentive Payment System (MIPS) and the Advanced Alternative Payment Model (APM) for clinicians in certain types of accountable care organizations. Since ophthalmologist participation in APMs will initially be limited, most attention should be paid to MIPS. Under MIPS there is a potential range in 2019 payments between −4% of Medicare payments to a bonus, which will be based on your MIPS “score,” the number of providers eligible for bonuses, and the size of the bonus pool. It is anticipated that cost and quality will become increasingly heavily weighted.

For all physicians, key elements then become the clinical relevance and utility of quality measurements, managing evolution in performance (such as dealing with “topped out” measures), and adequate risk adjustment to neutralize differentials in disease mix, severity, and comorbidities. When cost enters the equation, the algorithms must ensure that only the right costs are attributed to the correct physicians. Currently, the cost algorithms are far from perfect in this regard, which is one reason for the delayed inclusion in reimbursement schema.

It is our responsibility as a profession to actively work with refinement in reimbursement methodologies, since we are in the best position to judge their clinical relevance, their inaccuracies, and their unintended consequences.
References


What Is IRIS Up To Lately?

William L Rich III MD FACS

First, some history. In 1985 the Academy, along with the American College of Cardiology and the American Society of Chest Physicians, was the first to publish evidence-based guidelines, or preferred practice patterns. Most specialties followed suit. In 1996, in order to measure the impact of guidelines on outcomes, the Academy launched a surgical registry, the National Eye Outcomes Network (NEON). It was paper based and disruptive of practice workflow, and the public and payers weren’t interested in the data. It was discontinued within a few years.

With the widespread U.S. adoption of EHR and a new technology to extract data from EHRs to calculate quality measures and outcomes, the Academy launched the IRIS (Intelligent Research in Sight) Registry in April of 2014 with a goal of involving 2200 ophthalmologists and 8 million patients by 2017. As of June of 2017 IRIS is contracted with 16,294 docs (from 4990)—approximately 86% of U.S. ophthalmologists. It has collected data on 34 million eye patients and 134 million records and is now the world’s largest medical clinical registry.

To what end? The IRIS Registry has resulted in several advances that will be discussed in the presentation. These seminal changes impacting U.S. ophthalmologists and their patients include the following:

- Enabling ophthalmologists to meet federal quality reporting mandates, thus avoiding penalties and earning Medicare bonuses
- Calculation of ophthalmic disease prevalence
- Generation of new science
- Maintenance of certification and state licensure
- Informing public policy
- Evaluation of current practice patterns and population research
How Is AAO Helping Retina Specialists?

Cynthia A Bradford MD

The American Academy of Ophthalmology works to support all members in their ability to deliver patient care. Through the Academy’s Federal Affairs Secretariat and its committees tremendous work is done.

The Health Policy Committee works on Medicare, third-party reimbursement, Physician Quality Reporting System (PQRS) / value-based payment modifier, and health information technology / Meaningful Use programs, the new physician payment program Medicare Access and CHIP Reauthorization Act (MACRA) / Merit-based Incentive Payment System (MIPS), and alternative payment models (APMs). The committee manages our Current Procedural Terminology (CPT) initiatives as well as ICD-10 changes. Also on this committee are our RVS Update Committee (RUC) representatives, who work to ensure that ophthalmology services are fairly valued for patient care. In 2016 when the Centers for Medicare and Medicaid Services (CMS) had a flawed methodology that was used to cut retina and glaucoma payments, the Academy led a collaborative coalition that induced CMS to abandon the flawed methodology for 2017.

The Academy fights for you on coverage policy. For example, Academy input helped ensure that there was patient access to the important OCT testing services to help manage a wide range of retinal diseases.

The announced Medicare’s Part B Drug demonstration would have been destructive to retinal practices and was one of the key issues for the Academy’s Congressional Advocacy Day in 2016. It was very rewarding to go back on the Hill in 2017 and thank Congress for its intervention in scuttling this project.

The Research, Regulatory and External Scientific Relations committee interfaces with the FDA on many issues, most importantly the ongoing issue of drug compounding. The Academy staffs a working group on compounding with representatives from glaucoma, retina, cornea, and oculoplastics. Our initiative is supported by congressional letters, which once again were a focus of the 2017 Congressional Advocacy Day. This committee is also involved in research issues and drug pricing.

The OPHTHPAC Committee not only is a fundraising committee but also maintains contact with key members of Congress who can be counted on to sign onto letters, propose legislation, and undertake other interventions for ophthalmology. This is a key committee for supporting the work of other committees. OPHTHPAC relationships were key to our success in derailing oversized payment cuts.

The IRIS Registry allows members to track their outcomes, and with the pooled data on treatments, retina may be one of the first subspecialties to have the ability to evaluate the outcomes of new treatments for AMD and diabetes without lengthy, expensive trials and recognize problems with new treatments earlier too.

The Academy has partnered with the retinal societies to help secure new taxonomy codes that may help subspecialists in quality measurement. The Academy first approached the subspecialty groups with the idea of taxonomy two years ago, when physicians were faced with the prospect of being evaluated by Medicare based on resource use. To ensure that CMS fairly defines the “peers” to which it compares ophthalmologists, the Academy wanted to ensure that subspecialists have the ability to distinguish themselves from other ophthalmologists in their Medicare enrollment data.

The presentation will include up-to-date information on issues pertinent to the practice of retina.
Should I Sell My Practice?

Reginald J Sanders MD

- Do you want to sell your practice?
- My Misconception
- In Actuality
- Private Equity vs. Venture Capital
- Venture Capital (VC)
- Private Equity (PE)
- Recent PE Purchases
- How does PE make a company more valuable?
- Didn’t we see this in the 1990s?
- 1990s Private Equity Strategy
- Why did they fail?
- Why is this on the table again?
- What is different now?
- How might PE make this work?
- EBITDA
- What is the deal
- Example: Initial Terms
- Company Goes Public IPO
- The Basic Math
- Potential Outcomes
- Due Diligence
- Why Talk to Private Equity
- Can we do the same without PE
Subthreshold Laser for Diabetic Macular Edema: Pro

Paulo E Stanga MD
Subthreshold Laser for Diabetic Macular Edema: Con

Andrew A Moshfeghi MD MBA

I. The Treatment of Diabetic Macular Edema (DME): Historical Context
   A. Early Treatment Diabetic Retinopathy Study: thermal focal / grid laser photocoagulation
      1. Gold-standard treatment for 3 decades
      2. Realistic goal: Preserve vision, but not improve it, for the average DME patient
   B. Off-label intravitreal corticosteroids
      1. Undesirable side-effect profile despite moderate likelihood of improvement in vision
      2. Not a first-line therapy due to side-effect profile and efficacy that is not as good as intravitreal anti-VEGF agents

II. Current State of the Art and Its Rationale
   A. Intravitreal anti-VEGF therapy with or without focal / grid laser photocoagulation for center-involved DME
      1. An abundance of rigorous data demonstrating unprecedented efficacy and safety guides our frequent use of these drugs.
      2. New gold-standard treatment for DME
      3. Realistic goal: Improve and preserve vision for the average DME patient
   B. Second-line therapy includes intravitreal corticosteroid therapy as monotherapy or as an anti-VEGF adjuvant.
      1. An abundance of rigorous data demonstrating efficacy and safety guides our selective use of these drugs.
      2. Realistic goal: Eradicate recalcitrant edema when anti-VEGF monotherapy and/or laser cannot in an attempt to preserve and improve vision
      3. May not be appropriate for some patients due to IOP issues and cataract aversion
   C. Potential application of subthreshold laser photocoagulation: See Section III
   D. Future integration of novel DME treatment strategies

III. Why Subthreshold Laser for DME Does Not Make Sense
   A. Lack of rigorous data demonstrating observable treatment effect
   B. Lack of rigorous data demonstrating the safety of subthreshold laser for the target patient population
   C. Need for new capital equipment acquisition in an environment of declining reimbursement for office-based laser therapies

IV. Conclusions
OCT Angiography Is Ready for Mainstream Clinical Use: Pro

Caroline Baumal MD

I. What Is OCT Angiography (OCT-A)?

OCT-A is a dye-free, noncontact modality to image the retinal and choroidal circulation. Images are high resolution and depth resolved. A variety of devices are commercially available, with others pending approval. One common principle for OCT-A devices is that detection of motion contrast is used to acquire images.

II. Clinical Utility of OCT-A

Clinical utility has been demonstrated in multiple disorders, most notably AMD, choroidal neovascularization (CNV), diabetic retinopathy, macular telangiectasia, retinal vascular occlusion, and others.

III. The Science: Clinical Studies

There have been over 1000 papers a year since 2010 with the key word “OCT angiography.”

2010: 1022
2011: 1039
2012: 1010
2013: 1230
2014: 1184
2015: 1348
2016: 1350

OCT-A has uniquely thus far demonstrated the following:
- Changes in retinal vessels before clinically detectable retinopathy
- Unsuspected CNV in eyes with dry AMD / geographic atrophy
- Confirmed CNV in equivocal cases
- Demonstrated longitudinal anatomic response in CNV after anti-VEGF therapy
- Precise quantifiable foveal avascular zone (FAZ) dimensions that may better define the FAZ-to-visual acuity relationship
Section IV: Debates, Part I

IV. Practical Issues
How will I incorporate OCT-A into my clinical practice?

V. Economics
Cost of the device, relationship to cost for fluorescein angiography, time considerations, utility to improve patient care

VI. The Final Word
OCT-A is the next stage of innovation in retinal imaging, supported by science and clinical studies to improve patient management and uncover the pathogenesis of retinal disease.

Selected Readings
Due to space limitations, this is only a minute fraction of the important publications on OCT angiography.


Table 1. How Does OCT-A Compare with Fluorescein Angiography?

<table>
<thead>
<tr>
<th>Fluorescein Angiography</th>
<th>OCT-A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive</td>
<td>Noninvasive</td>
</tr>
<tr>
<td>Dye based, intravenous injection</td>
<td>No dye used</td>
</tr>
<tr>
<td>Potential systemic side effects including anaphylaxis</td>
<td>No systemic side effects</td>
</tr>
<tr>
<td>Imaging time: 5-30 minutes</td>
<td>Imaging time: under 5 minutes</td>
</tr>
<tr>
<td>Lower resolution, limited details of retinal and choroidal vasculature</td>
<td>Higher resolution, more detail</td>
</tr>
<tr>
<td>Two-dimensional image</td>
<td>Three-dimensional image, segmentation possible, amenable to data manipulation</td>
</tr>
<tr>
<td>Images superficial retinal vascular plexus</td>
<td>Images superficial and deep retinal vascular plexus, choroidal</td>
</tr>
<tr>
<td>Dynamic blood flow information</td>
<td>Static blood flow information</td>
</tr>
<tr>
<td>Blood flow information</td>
<td>Structural and blood flow information</td>
</tr>
</tbody>
</table>
OCT Angiography Is Ready for Mainstream Clinical Use: Con

Karl G Csaky MD

I. Background
OCT angiography (OCT-A) is a novel imaging modality that utilizes movement disparities on the OCT to identify vascular structures that exhibit sufficient blood flow characteristics. While this imaging tool has the potential to image retina and choroidal vessels without the need for intravenous dyes, several aspects limit its utility in day-to-day retinal clinics. However, as the technology evolves and improves it is anticipated that many if not all of these limitations will be overcome and OCT-A will find its place in the routine evaluation of retinal patients.

II. Challenging Image Interpretation and Analysis
A. Difficult to resolve choroidal neovascularization from overlying retinal vasculature projection artifacts
B. Other issues

III. Time Management Issues
A. Need to spend time at the machine to fully analyze the images
B. Difficult for a photographer to do
C. Not compatible with a busy clinic

IV. Limited or No Prospective Clinical Trial Data on the Utility of OCT-A in the Management of Retinal Diseases
A. Difficult to understand the meaning of various findings on OCT-A
B. Not clear how to utilize in the context of anti-VEGF therapy
C. Examples

V. Limited Histopathologic Correlations to OCT-A Imaging
A. New data are available for retinal vasculature.
B. Limited data on most other OCT-A findings
C. Difficult to interpret the clinical significance

VI. Poor or No Insurance Reimbursement
A. No unique code for OCT-A vs. OCT
B. Difficult to justify the costs of the machine
Heads-up 3-D Digital Surgery Viewing Is Now for Vitrectomy: Pro

John W Kitchens MD

It is without remorse that retinal surgeons should embrace heads-up surgical viewing. In order to avoid the clear and present danger of light toxicity, this system allows vitrectomy at lower light levels. In addition, surgeons can now perform macular procedures without encountering the sum of all fears—iatrogenic injury during macular peeling—due to the greater depth of focus. This system allows surgeons to stay locked on in order to search and destroy retinal pathology thanks to greater peripheral awareness. For training institutions, like Wills Eye Hospital, this system improves the training of the next generation of surgeons, better enabling them to support and defend the vision of their patients. Despite the fact that medicine seems to be constantly under fire from decreasing reimbursements, adopting heads-up surgical viewing is a debt of honor we owe our patients.
Heads-up 3-D Digital Surgery Viewing
Is Now for Vitrectomy: Con
Julia A Haller MD

Key Issues
- Worth the price?
- Need for constant technical help?
- Need for change?
- Complicated to run
- Get used to looking at a screen while operating on the eye in front
- Retraining

Not ready for prime time.

Live 3-D digital imaging was introduced for cornea and cataract procedures with the TrueVision 3D Surgical system (TrueVision Systems) in 2008. The original design for neurosurgery and ophthalmology used a rear projection system with dual stacked projectors and a retractable screen, but it has evolved to a high-definition (HD) video monitor placed in front of the surgeon so as to be viewable as a “heads-up display” with passive polarization 3-D glasses. Tremendous strides have been made in image quality, computational processing speed, and 3-D monitor. This technology converts an operating room microscope into a digital imaging system. In 2014, the Leica M844 and Leica M822 ophthalmology microscopes (Leica Microsystems) were made globally available with TrueVision 3D visualization, recording, and editing technology. Combined with TrueVision’s fifth-generation ICM5 camera platform, the 3K display provides a new level of image quality and utility.

The improvement in image resolution and color quality has been a key factor in the adoption of 3-D digital imaging for heads-up live retina surgery. Additionally, 3-D camera improvements have provided a greater sense of depth, and faster computer processing has reduced latency between image capture and video output so that retinal procedures can now be routinely performed in a heads-up fashion working off the 3-D screen. In an experimental study, Eckardt and Paulo found the method to be well suited for heads-up surgery in vitreoretinal procedures. In their survey of 20 surgeons and a retrospective analysis of more than 400 vitreectomy cases, the authors noted that nearly 92% of the volunteers preferred the ergonomics of the heads-up technique. They deemed the hands-up technique and the traditional method to be similar as far as speed, ease of microscopic manipulations, and image sharpness. However, they noted that surgeons made significantly fewer mistakes with the heads-up method.

The next opportunity for enhancing 3-D retinal surgery lies in digital image manipulation capabilities, which may allow surgeons to significantly reduce microscope illumination levels. In early use, the TrueVision 3D ICM5 camera’s high dynamic range function has allowed retinal surgeons to reduce microscope illumination by 80% or more while still producing excellent image quality for live surgery. This could be key in reducing retinal phototoxicity risk for patients.

Although there are significant advantages, there are some challenges that must be considered. First, the image obtained from the microscope is projected to the monitor, thus necessitating the presence of both the microscope and the TrueVision system (both of which have large footprints) in the OR. While the image obtained through the 3-D glasses offers adequate depth perception to safely facilitate membrane peeling and complex surgical maneuvers, image quality continues to be refined to reproduce colors and stereo information maximally.

References and Selected Readings


Use of Intraoperative OCT Improves Surgical Outcomes: Pro

Justis P Ehlers MD

In the last 10-15 years, OCT has transformed the clinical management of vitreoretinal diseases. The high-resolution anatomic information provided by OCT is a natural complement to the operating room. OCT has given clinicians the ability to visualize vitreomacular traction, macular holes, or epiretinal membranes in ways not previously possible. In that same way, applying intraoperative OCT to ophthalmic surgery has the potential to transform the surgical approach to macular surgery through the visualization of residual membranes, confirmation of surgical objectives, and identification of architectural alterations resulting from surgical manipulations. Multiple studies have now demonstrated that intraoperative OCT impacts surgical decision making. This enhanced surgical approach provides unique opportunities for improving surgical safety and maximizing outcomes.

Selected Readings


Use of Intraoperative OCT Improves Surgical Outcomes: Con

Omesh P Gupta MD

OCT is a powerful diagnostic tool in the office setting. However, the practical utility of intraoperative OCT remains unclear. In particular, surgical cases that utilize intraoperative OCT must demonstrate superior results in order for this technology to gain widespread acceptance. An argument will be presented that outlines why intraoperative OCT does not improve clinical outcomes.
Update on Intraocular Sustained Drug Delivery: Are We Making Progress?

Glenn J Jaffe MD

I. Sustained Delivery Systems
A. Transscleral delivery
B. Intravitreal implant
C. Intravitreal injection
D. Suprachoroidal infusion
E. Subretinal implant
F. Refillable reservoir

II. FDA-Approved Intravitreal Implants
A. FDA-approved nonbiodegradable implants
   1. Implant administration
      a. Surgically implanted fluocinolone acetonide implant
         i. Approved in 2005 for uveitis affecting posterior segment
         ii. Releases over 2.5-3 years
      b. Injectable fluocinolone acetonide implant
         i. Approved for chronic diabetic macular edema
         ii. Releases over 2.5-3 years
   2. Implant characteristics
      a. Polymeric drug reservoir
      b. Drug core
      c. Drug released across semipermeable membrane
      d. Zero order release kinetics
      e. Placement techniques
         i. Secured to eye wall (surgical procedure)
         ii. Injected into vitreous cavity (office-based procedure)
   3. Advantages
      a. Linear drug delivery
      b. Implant nontoxic
      c. Suitable for very sustained delivery (years)
   4. Disadvantage: Implant retained in eye after drug depleted

B. FDA-approved biodegradable implant
   1. Injectable dexamethasone delivery system
      a. Approved in 2010 for macular edema, uveitis
      b. Releases over 2.5-3 years
   2. Implant characteristics
      a. Polymeric matrix
      b. Drug in matrix
      c. Drug released as matrix erodes
      d. Placement technique: Injected into vitreous cavity (office-based procedure)
   3. Advantages
      a. No remaining implant once matrix erodes
      b. Office-based delivery
   4. Disadvantages
      a. May be difficult to match drug release, implant erosion
      b. Delivery duration limited

III. Novel Implants in Development
A. Unmet needs from current implants
   1. Need to broaden disease applicability
   2. Need to minimize side effects
   3. Need to maximize efficacy
   4. Need to prolong delivery duration

B. Examples of novel implants in development
   1. Cell-based
      a. Encapsulated cell technology
      b. Genetically engineered cells that overproduce protein of interest
      c. Encapsulated in polymeric delivery system
      d. Designed to minimize immune response
      e. Scleral fixated, surgical procedure
      f. Useful to deliver proteins
      g. Can deliver over years
         i. Multiple posterior segment indications
         ii. Feasible to deliver multiple proteins simultaneously (combination therapy)
      h. Phase 2/3A trial for neovascular AMD not successful; likely inadequate drug levels
         i. In development for MacTel 2
   2. Refillable implants
      a. Posterior micropump
         i. Can deliver small molecules, proteins
ii. Multiple ocular indications

iii. Several components
   (a) Electronics and battery
   (b) Extrascleral drug reservoir
   (c) Refill port
   (d) Electrolysis chamber and check valve
   (e) Intraocular cannula

iv. Tested in Phase 1 diabetic macular edema study
   (a) Promising efficacy
   (b) Surgical technique evolved to cause less chance of implant damage

b. Port delivery system
   i. Placed through pars plana
   ii. Surgical procedure, no scleral sutures
   iii. Minimally invasive office refill
   iv. Sustained release between refills
   v. Tested in Phase 1 neovascular AMD study: Favorable results
   vi. Now in Phase 2 neovascular AMD study (LADDER study)

c. Injectable fluocinolone acetonide implant
   i. Office-based injection procedure
   ii. Tested for intermediate, posterior, panuveitis
      (a) Individual investigator trial (Glenn Jaffe): Favorable 2-year results
      (b) Tested in two Phase 3 studies: Results favorable to date

3. Suprachoroidal delivery
   a. Office-based injection procedure
   b. Can deliver small molecules
   c. Tested triamcinolone delivery for uveitis, macular edema in eyes with retinal vein occlusion
   d. Favorable results in Phase 1/2 studies
Central serous chorioretinopathy (CSR) was originally described as a condition of young men with a benign natural history, with most of those affected experiencing complete resolution of symptoms and pathology. However, it is now recognized that CSR can be chronic, progressive, and unremitting; varying between races and occurring in females and in older age groups. CSR is also associated with vision loss, which in some cases can be severe and bilateral.

In a multimodal imaging approach in which we examined 100 patients with a diagnosis of CSR, 3 patterns of leak were observed, from a single hot spot, to multiple distinct spots with healthy retinal pigment epithelium (RPE) intervening, to widespread pigment epithelial disturbance with extensive gravitational tracks. When hot spots were small, distinct, and few (< 3), hyperautofluorescence was localized. Extensive involvement of the RPE with diffuse leak was associated with widespread autofluorescence changes that included both increased and decreased autofluorescence. Small distinct focal pigment epithelial detachments occurred in 70% of eyes, and choroidal thickening was almost universal. Around one-third of evaluated eyes had individually recognizable large choroidal vessels, and in these eyes, choroidal vessels were easily distinguished in the central macula on indocyanine green angiography. In two-thirds the outer choroid was occupied by regions of sinusoidal vascular caverns and individual vessel contours could not be distinguished. In these eyes indocyanine green angiography showed diffuse hypercyanescence in the early frames, thus precluding visualization of the choroidal vasculature.

Correlations between autofluorescence, fluorescein angiography, indocyanine green, and OCT in the presenting eye and fellow eyes of these cases will be shown, along with the relationships with other pachychoroid phenotypes (pigment epitheliopathy, neovascularopathy, and polypoidal choroidal vasculopathy).

Selected Readings

The Latest on Central Serous Retinopathy Management

Francine Behar-Cohen MD
Gene Therapy for AMD: Where Do We Stand?

Szilard Kiss MD
Treatment Options for Vitreomacular Traction

Robert L Avery MD

I. Vitrectomy
   A. Standard of care for years
   B. Success rates
   C. Complications
   D. Meta-analysis
II. Pharmacologic Vitreolysis
   A. Ocriplasmin
      1. Randomized clinical trials
      2. Better success with case selection
      3. Safety concerns
   B. Integrin antagonists
III. Pneumatic Vitreolysis
   A. Success rates
   B. Complications
   C. Gas choice
   D. Meta-analysis
   E. Cost analysis
IV. Observation
   A. Large observational studies
   B. Release rates by grade of vitreomacular traction
V. Individualize Treatment Relative to Baseline Characteristics
   A. Good visual acuity, minimal symptoms: Observe
   B. Very extensive adhesion: Vitrectomy
   C. Consider offering staged procedure for others.

Selected Readings

Screening for Hydroxychloroquine Retinopathy: Latest Guidelines

David J Browning MD PhD

In 2016 the third iteration of the Academy’s guidelines for screening of hydroxychloroquine retinopathy (HCR) was published.1-3 To summarize, the following are termed major risk factors: daily dose > 5.0 mg/kg actual body weight (ABW), duration of use > 5 years, subnormal glomerular filtration rate (GFR), concomitant use of tamoxifen, and pre-existing macular disease. Daily dose is the most important risk factor. If none of these are present, the guidelines advise a baseline fundus examination within the first year of starting HC. Baseline standard automated perimetry with testing protocol based on the patient’s race and spectral domain OCT (SD-OCT) are termed “always useful” but “not critical.” If any major risk factors are present, the guidelines recommend that these tests be done at baseline and then annually from the start. If no major risk factors are present, it recommends that annual screening begin after 5 years of HC use. The guidelines do not recommend that ophthalmologists advocate for dosing reduction when patients are above the 5.0 mg/kg ABW threshold, but only that we take note of the fact as a major risk factor. If changes consistent with retinopathy are detected on standard automated perimetry and/or SD-OCT and are confirmed by repeat testing or supplemental testing with fundus autofluorescence (FAF) or multifocal electroretinogram (mERG), cessation of HC “should be made in conjunction with the patient and the prescribing medical physician.”

The 2016 guidelines differ from the 2011 guidelines in 6 ways:

1. In the 2011 guidelines, the major risk factors differed. The following were present in 2011 but not 2016: a cumulative dose of HC of 1000 g, daily dose for short persons > 6.5 mg/kg ideal body weight (IBW)/day, elderly (threshold not stated), liver dysfunction, renal dysfunction (not stated in terms of GFR).
2. In the 2011 guidelines, daily dose was not the most important risk factor, and it was an important risk factor only for short, obese patients for whom daily dose was recommended to be < 6.5 mg/kg IBW/day.
3. In the 2011 guidelines, baseline 10-2 visual field (VF) plus one of the following—SD-OCT, FAF, or mfERG—were recommended.
4. In the 2011 guidelines, it was recommended that all patients, regardless of race, receive the 10-2 VF, and not 24-2 or 30-2 VF.
5. In the 2011 guidelines, FAF and mfERG were given equal weight to SD-OCT.
6. In the 2011 guidelines, tamoxifen was not a risk factor.

The Academy guidelines carry legal weight in the United States and are influential across the world. Given the changes in the guidelines from 2011 to 2016, a closer look at the evidential basis for the changes is worthwhile.

- In 2011, the recommendation to base daily dosing on IBW in short persons was based on a level III retrospective, unreplicated survey with selection bias.4 The recommendation failed to consider that daily dosing in short persons based on IBW would lead to overdosing in short, asthenic (rather than obese) persons.5 The 2016 daily dosing guidelines were based on a level III, retrospective, unreplicated study with selection bias and nonstandardized grading of ancillary studies with unspecified masking.6 The 2016 guidelines remedied the 2011 guidelines’ flaw for short, asthenic persons, but substituted a new flaw, not present in the 2011 guidelines, for the short, obese patient. Daily dosing based on the 5.0 mg/kg/ABW threshold is safer for the short, asthenic patient, but it is dangerous in the short, obese patient.7 Figures 2B and C from the same study actually make the point (in the figure, check the predicted risk at high BMI for B compared to C).
- The 2016 guidelines discard the 2011 guideline on daily dosing by IBW for short, obese patients based on an area-under-the-curve analysis of a receiver-operating-characteristic curve (figure 2A).8 However, the study did not compare results to daily dosing using the lesser of ABW and IBW as recommended earlier.9 When this comparison is done, using an independent sample, using the lesser of ABW and IBW provides a better predictor of retinal toxicity than ABW.8
- The importance of tamoxifen is based on a level III, retrospective, unreplicated study with selection bias and nonstandardized grading of ancillary studies with unspecified masking.6 Twelve of 177 cases of HCR were taking tamoxifen compared to 26 of 2184 patients taking HC without retinopathy. The only other study in an independent sample, also a retrospective chart review, did not find an association.8

Given the weight that Academy guidelines have as a standard of care, the clinician must consider carefully whether to depart from them. Nevertheless, the evidence suggests that an alternative perspective is rational, specifically on the following points:

1. In daily dosing, it is rational to choose a daily dose that is the lesser by the ABW and IBW methods. It is simple to execute using a freely downloadable application, DoseChecker, which calculates the toxic dose using both methods and then preferentially selects the method that recommends the lower dose. This eliminates the 2011 guidelines’ flaw in short, asthenic patients and the 2016 guidelines’ flaw in short, obese patients. DoseChecker also provides a weekly dosing schedule, combining 200-mg and 400-mg daily doses to achieve a safe dosing regimen.
2. Tamoxifen as a major risk factor is a hypothesis, not a replicated fact.
3. There is rationale to obtaining baseline SD-OCT and 10-2 VFs in all patients.
4. There is rationale to abandoning the 5-year hiatus in screening for patients without a major risk factor and instead to screen all patients yearly. A high percentage of patients will have a major risk factor in any case. Yearly testing provides training to the patient in taking the 10-2 VF, a concept familiar to clinicians who rely on VF testing in glaucoma. It provides a chance to review dosing when it matters most, and an opportunity to check for renal status changes, which can occur in systemic lupus erythematosus. In multiple studies, clinicians have shown that they ignore the guidelines’ recommendation for a 5-year hiatus in screening.

5. There is rationale for abandoning the mindset that toxic dosing is just a risk factor. If the prescribed dosing is in a toxic range, which occurs in 12.8%-74.7% of persons taking HC in various series, there is a rationale for consulting with the prescribing physician about changing it to a safer level.

6. There is rationale for avoiding reliance on the 24-2 and 30-2 VFs for Asian patients. There are too few test points centrally. Instead, there is rationale for focusing attention on the 8-10 degree annulus of the 10-2 and to supplement, but not replace, the 10-2 VF with a 24-2 and/or 30-2 VF. A good way to screen Asian patients is with broader length SD-OCT line scans, and placing added weight on FAF imaging, which covers the perifovea as well as the parafovea.

There is no controversy over several issues:

1. Asian patients have a higher rate of pericentral rather than paracentral retinopathy.

2. 10-2 white VF and SD-OCT tests used together will pick up almost all patients early enough to avoid sight-threatening retinopathy.

3. Renal disease is a major risk factor.

4. Skills in interpreting necessary ancillary testing need to be honed. For the 10-2 VF, a cluster of scotoma points in the high-risk zone 2 to 8 degrees from fixation for white and black patients or 8 to 10 degrees from fixation in Asian and black patients; a scotoma that persists and grows in breadth or depth; and the appearance of new scotomas should lead to further investigation. The 10-2 VF with a white test object has less noise than the version using a red test object and the advantage of the pattern standard deviation display. For the SD-OCT, be aware that a decrease in reflectivity of the parafoveal or perifoveal ellipsoid zone and/or external limiting membrane relative to the foveal reflectivity is an early sign of retinopathy. Complete absence of the ellipsoid zone and/or external limiting membrane (the flying saucer sign) is a sign of more advanced disease. Thinning of the outer nuclear layer over a succession of SD-OCTs should be looked for (“spread of the red” on the ETDRS display of comparisons to population norms).

References


Update on Clinical Trials for Retinal Degeneration

Byron L Lam MD

I. Gene Therapy Clinical Trials

A. Adeno-associated virus (AAV) vectors, subretinal
   1. Leber congenital amaurosis
      a. RPE65
      b. Phase 3 completed
      c. FDA considering approval
   2. Choroideremia
      a. Phase 2 ongoing
      b. Phase 3 planned
   3. Achromatopsia
      a. CNGB3 and CNGA3 subtypes
      b. Phase 1-2 ongoing
   4. X-linked retinitis pigmentosa
      a. Phase 1 ongoing
   B. AAV vector, intravitreal
      1. X-linked retinoschisis; Phase 1-2 ongoing
   C. Lentivirus vectors, subretinal
      1. Stargardt maculopathy
         a. ABCA4
         b. Phase 1-2 ongoing
      2. Usher syndrome type 1B; Phase 1-2 ongoing
   D. Optogenetic
      1. Channelrhodopsin 2; Phase 1 ongoing

II. Oral Agents

A. Leber congenital amaurosis
   1. RPE65 and LRAT
   2. 9-cis-retinal
   3. Phase 1 and 2 completed
   4. Phase 3 planned

B. Stargardt maculopathy
   1. ABCA4
      a. Deuterated vitamin A (C20-D3-vitamin A); Phase 2 ongoing
      b. RPE65 inhibitor; Phase 2 ongoing

III. Stem Cell Preliminary Treatments Overview

Selected Readings


Update on Hemorrhagic Occlusive Retinal Vasculitis after Cataract Surgery

Dean Elliott MD

I. General Features of Hemorrhagic Occlusive Retinal Vasculitis (HORV)
   A. Extremely rare condition
   B. Can occur after any intraocular procedure, usually cataract surgery
   C. Delayed presentation of sudden, painless, severe visual loss; mean onset of symptoms 1 week after the procedure (range: 1 day to 1 month)
   D. Strong association with intraocular vancomycin
      1. Intracameral bolus
      2. Anterior chamber irrigation solution
      3. Intravitreal injection

II. Timing
   A. If HORV occurs after 1 eye undergoes cataract surgery, it can also occur in the second eye after the second eye undergoes surgery, even if the second surgery is performed years later (if vancomycin is used). There is evidence that if vancomycin is not used in the second eye, then HORV does not develop in the second eye.
   B. In bilateral sequential cataract surgery separated by a few weeks, the first eye can be normal until the second eye undergoes surgery, and then HORV can occur simultaneously in both eyes very soon after the second surgery (if vancomycin is used).

III. Clinical Findings on Presentation
   A. Visual acuity
      1. Usually severely reduced
      2. May be normal in mild cases
   B. Cornea: Normal or mild corneal edema
   C. Anterior chamber
      1. Mild to moderate inflammation
      2. No hypopyon
   D. Vitreous: Mild to moderate inflammation
   E. Retina
      1. Peripheral retinal involvement in all cases
         a. Large patches of intraretinal hemorrhages, often along venules
         b. Small dot / blot hemorrhages
         c. Sectoral or widespread retinal vasculitis
      2. Macular involvement in severe cases: macular whitening

IV. Fluorescein Angiography
   A. Severe peripheral nonperfusion; sectoral or widespread
   B. Peripheral retinal vasculitis
   C. Macular ischemia in advanced cases
   D. Intraretinal hemorrhages correspond to areas of vasculitis and nonperfusion.

V. Differential Diagnosis
   A. Acute postoperative endophthalmitis: Pain, hypopyon, and severe vitritis are not present in HORV.
   B. Viral retinitis
      1. White areas of retinitis are not present in HORV.
      2. Viral retinitis is not associated with a recent surgical procedure.
   C. Central retinal vein occlusion (CRVO) or combined central retinal artery occlusion (CRAO) / CRVO
      1. May be associated with cataract surgery
      2. Findings present on postoperative day 1, unlike HORV which typically has a normal exam at this time
      3. Severe venous dilation and tortuosity are not characteristic of HORV.
   D. Medication toxicity
      1. Toxic anterior segment syndrome (TASS): TASS has severe corneal edema and findings on postoperative day 1, unlike HORV.
      2. Aminoglycoside toxicity: Aminoglycoside toxicity has macular infarction with minimal or no peripheral vascular occlusion, while HORV has severe peripheral vascular occlusion and vasculitis.
      3. Cefuroxime toxicity: Intracameral injection of overdoses have associated TASS and retinal hemorrhages.

VI. Clinical Course
   A. There are some cases of presumed endophthalmitis (cases with retinal findings out of proportion to inflammation and without hypopyon) that in retrospect were probably HORV.
      1. These cases were treated with intravitreal vancomycin and had progression of retinal ischemia
documented on fluorescein angiography performed before and after vancomycin treatment.

2. These cases that had received vancomycin twice, once during cataract surgery and again for presumed endophthalmitis, and had particularly poor outcomes, with most eyes progressing to no light perception.

B. Visual outcomes are often poor.

1. The majority of eyes are worse than 20/200.
2. Approximately one-quarter of eyes progress to no light perception.
3. A few asymptomatic cases are 20/20. HORV may be under-recognized due to mild involvement in some cases of uniocular or first eye administration.

C. Neovascular glaucoma is common, occurring in approximately 50% of eyes.

D. Eyes that received certain treatments appear to have more favorable outcomes.

1. Steroids (topical, periocular, intraocular, and/or systemic)
2. Early anti-VEGF treatment
3. Early panretinal photocoagulation

VII. Etiology

Immunology experts were consulted. They hypothesize that this may represent a rare type III hypersensitivity reaction to vancomycin. Presumed similar mechanism to leukocytoclastic vasculitis and Henoch-Schonlein purpura, which are type III hypersensitivity reactions in the skin that have rarely been associated with vancomycin.

VIII. ASRS-ASCRS Task Force

A. HORV registry developed at www.asrs.org

B. 36 eyes of 23 patients were identified with HORV. All cases received intraocular vancomycin.

C. 2014 ASCRS member survey

1. 50% of respondents were using intracameral antibiotics for endophthalmitis prophylaxis during cataract surgery. Among those using prophylactic antibiotics, 52% of American surgeons were using vancomycin.
2. Many high-volume cataract surgeons using intracameral vancomycin have never knowingly experienced HORV, and the task force believes it to be extremely rare.

D. A Clinical Alert was sent to all ASCRS and ASRS members in an effort to publicize the association between HORV and intraocular vancomycin.

E. Although new cases of HORV are still being reported, the incidence appears to have considerably decreased.


Selected Readings

2017 Advocating for Patients

Sohail J Hasan MD PhD

Ophthalmology’s goal of protecting sight and empowering lives requires active participation in and commitment to advocacy from every ophthalmologist. Contributions to the following three critical funds are a part of that commitment:

- OPHTHPAC® Fund
- Surgical Scope Fund (SSF)
- State Eye PAC

Please join the dedicated community of ophthalmologists who are contributing to protect quality patient eye care for everybody. The OPHTHPAC Committee is identifying Congressional Advocates in each state to maintain close relationships with federal legislators in order to advance ophthalmology and patient causes. At Mid-Year Forum 2017, we honored nine of those legislators with the Academy’s Visionary Award. This served to recognize them for addressing issues important to us and to our patients. The Secretariat for State Affairs is collaborating closely with state ophthalmology society leaders to protect Surgery by Surgeons at the state level. This year has seen an unprecedented effort by optometry to advance its scope of practice via legislation rather than education. Our mission of protecting sight and empowering lives requires robust funding of both the Surgical Scope Fund and the OPHTHPAC Fund. Each of us has a responsibility to ensure that these funds are strong.

OPHTHPAC® Fund

OPHTHPAC is a crucial part of the Academy’s strategy to protect and advance ophthalmology’s interests in key areas, including physician payments from Medicare and protecting ophthalmology from federal scope of practice threats. Established in 1985, OPHTHPAC is one of the oldest, largest, and most successful political action committees in the physician community. We are very successful in representing your profession to the U.S. Congress.

As one election cycle ends, a new one starts, yet the pressure to remain vocal on our issues remains. Advocating for our congressional issues is a continuous battle, and OPHTHPAC is always under financial pressure to support our incumbent friends as well as to make new friends with candidates. These relationships allow us to have a seat at the table with legislators willing to work on issues important to us and our patients.

The relationships OPHTHPAC builds with members of Congress is contingent on the financial support we receive from Academy members. Academy member support of OPHTHPAC allows us to advance ophthalmology’s federal issues. We need to increase the number of our colleagues who contribute to OPHTHPAC and the other funds. Right now, major transformations are taking place in health care. To ensure that our federal efforts and our PAC remain strong, we need the support of every ophthalmologist to better our profession and ensure quality eye care for our patients.

The significant impacts that OPHTHPAC has made include the following:

- Derailed the onerous global surgery data collection proposal
- Preserved global surgical payments
- Halted the Part B Drug Demonstration
- Continued efforts in collaboration with subspecialty societies to preserve access to compounded and repackaged drugs such as Avastin

Contributions to OPHTHPAC can be made here at AAO 2017 or online at www.aao.org/ophtpac by clicking “Join.”

Leaders of the three retina societies—the American Society of Retina Specialists (ASRS), the Macula Society, and the Retina Society—are part of the Academy’s Ophthalmic Advocacy Leadership Group (OALG), which meets every January in the Washington, D.C., area to provide critical input and to discuss and collaborate on the Academy’s advocacy agenda. The topics discussed at the 2017 OALG agenda included panel discussions on the Merit Based Incentive Payment System (MIPS) and APM implementation, as well as Academy analysis initiatives related to the IRIS® registry. In addition, meeting participants discussed the changing paradigm for optometric scope battles, held a roundtable to discuss challenges for surgical subspecialties, and considered opportunities to ensure physician and patient choice regarding access to pharmaceuticals.

At Mid-Year Forum 2017, the Academy and the three retina societies ensured a strong presence of retina specialists to support ophthalmology’s priorities, and a record number of ophthalmologists visited members of Congress and their key health staff to discuss ophthalmology priorities as part of Congressional Advocacy Day. The ASRS, the Macula Society, and the Retina Society remain crucial partners with the Academy in its ongoing federal and state advocacy initiatives.

Surgical Scope Fund

The Surgical Scope Fund (SSF) provides grants to state ophthalmology societies to support their efforts to derail optometric surgery proposals that pose a threat to patient safety. Since its inception, the Surgery by Surgeons campaign and the SSF, in partnership with state ophthalmology societies, has helped 32 state / territorial ophthalmology societies reject optometric scope of practice expansion into surgery.

In 2017, your colleagues serving on the Academy’s Secretariat for State Affairs, along with State Governmental Affairs staff and the leaders of state ophthalmology societies, have been put to the task while dealing with an unprecedented number of simultaneous legislative battles. Eleven states have been affected so far this year:

- Alaska
- California
- Florida
- Georgia
- Illinois
- Iowa
- Maryland
- Massachusetts
- Nebraska
- North Carolina
- Pennsylvania
Patient safety setbacks as well as victories will be reviewed during the presentation, but do know that in each of these legislative battles, the benefits from SSF distributions are abundantly clear. The best lobbyists and public relations consultants are contracted as necessary, and media campaigns (including TV, radio, and social media) to educate the voting public are launched when needed to secure success and stop optometry from expanding its scope of practice to include surgery. Each of these endeavors is very expensive, and no one state has the resources to wage one of these battles on its own. Ophthalmologists must join together and donate to the SSF to fight for patient safety when a state faces a scope battle over optometric surgery.

The Academy relies not only on the financial contributions to the SSF from individual ophthalmologists and their practices, but also on the contributions made by ophthalmic state, subspecialty, and specialized interest societies. The ASRS, the Macula Society, and the Retina Society each contributed to the SSF in 2016, and we thank them and look forward to their contributions in 2017. Contributions to the SSF can be made here at AAO 2017 or online at www.aao.org/ssf.

**State Eye PAC**

It is also extremely important for all ophthalmologists to support their respective State Eye PACs because campaign contributions to legislators at the state level must come from individual ophthalmologists and cannot come from the Academy, OPHTHPAC, or the SSF. The presence of a strong State Eye PAC providing financial support for campaign contributions and legislative education to elect ophthalmology-friendly candidates to the state legislature is critical, as scope of practice battles and many regulatory issues are all fought on the state level.

**Action Requested: ADVOCATE FOR YOUR PATIENTS**

Academy SSF contributions are used to support the infrastructure necessary in state legislative / regulatory battles and for public education. PAC contributions are necessary at the state and federal level to help elect officials who will support the interests of our patients. Contributions to each of these three funds are necessary and help us protect sight and empower lives. SSF contributions are completely confidential and may be made with corporate checks or credit cards, unlike PAC contributions, which must be made by individuals and are subject to reporting requirements.

Please respond to your Academy colleagues and be part of the community that contributes to OPHTHPAC, the SSF, and your State Eye PAC. Please be part of the community advocating for your patients now.

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Uveitis Panel, Part I

Moderator: Daniel F Martin MD

Panelists: Janet Louise Davis MD, Debra A Goldstein MD, Pauline T Merrill MD, Annabelle A Okada MD, Sunil K Srivastava MD, Russell N Van Gelder MD PhD

NOTES
My Coolest Surgical Video

Autologous Retinal Transplant for Chronic Retinal Detachment with Proliferative Vitreoretinopathy without Macular Hole

Akshay S Thomas MD and Tamer H Mahmoud MD

Autologous Retinal Transplantation in Recurrent Retinal Detachment Complicated with Proliferative Vitreoretinopathy and Giant Macular Hole

Giuseppe Lo Giudice MD, Anton Giulio Catania MD, and Alessandro Galan MD

Removal of a Large Intraocular Foreign Body Using a Modified Flute Needle from an Eye With 20/20 Vision

Kenneth K W Li MBCHB and Yee Yan Chan MRCOphth
Management of Subretinal Cysticercosis

Simar R Singh MBBS and Vishali Gupta MBBS

Early Vitrectomy Restored Dragging Macula in Infant Eyes with Familial Exudative Vitreoretinopathy

Shunji Kusaka MD, Mayumi Ishimaru MD, Akiko Iwata MD, Kazuki Kuniyoshi MD, and Yoshikazu Shimomura MD

Endoresection of Retinal Capillary Hemangioblastoma in a Patient with Von-Hippel Lindau Syndrome

Antonio Capone Jr MD and Aristomenis Thanos MD
Persistent Fetal Vasculature Syndrome: A Review and a New Presentation

Classic, Eccentric Stalk, Multifocal, and Management

Michael Trese MD, Irina De la Huerta MD PhD, Prethy Rao MD, Kimberly Drenser MD PhD, and Antonio Capone MD

The name “persistent fetal vasculature syndrome” (PFVS) was suggested by Morton Goldberg in his Jackson Lecture almost 20 years ago. It replaced an incomplete name, “persistent hyperplastic primary vitreous.” The new name, PFVS, addressed all the vascular elements involved in the errors of assembly.

This talk will address three different presentations of PFVS.

Classic PFVS presents at birth with a lack of a red reflex instead a white fibrotic membrane replacing the posterior capsule of the lens. It is usually unilateral, with a smaller eye and elongated ciliary process.

The eccentric stalk has a different presentation. It presents at about 8 months of age with strabismus and a clear lens, except where the stalk adheres to the posterior lens, which often does not involve the visual axis. Posteriorly there is a tractional retinal detachment that surrounds the stalk, and as it progresses it moves the fovea, causing strabismus. Strabismus can be resolved by vitreous surgery dividing the stalk without strabismus surgery.

The third presentation, the rarest, is usually found on routine exam at a later age. It has multiple areas of persistent vessels along the retinal surface, which are best seen with fluorescein angiography. We refer to this as multifocal PFVS. Like the other two forms, it has areas of avascular peripheral retina.

These areas of avascular peripheral retina create a VEGF drive, which overcomes the genetic drive for the vessels to involute by apoptosis.

Management of each form, as well as the cellular features of retinal dysplasia, will be discussed.

Selected Readings


Use of Anti-VEGF Therapy for ROP: When and How

RV Paul Chan MD, Ruik Chee MD, J Peter Campbell MD MPH

Intravitreal anti-VEGF has shown promise in the treatment of retinopathy of prematurity (ROP) and retinal disorders in pediatric patients. However, there is still much to be determined about the long-term effects and implications of its use in patients with ROP.

I. Why Consider Anti-VEGF
   A. Treatment for ROP with cryotherapy and/or laser photocoagulation has been based on the Cryo-ROP and ETROP studies.1,2 Certain more aggressive forms of treatment-requiring ROP (eg, aggressive posterior ROP [APROP]) may progress despite laser or cryotherapy.
   B. ROP is a retinal vascular disorder, and VEGF has been shown to have an important role in its pathogenesis.
   C. Intravitreal anti-VEGF therapy has revolutionized retinal vascular disorders in adults. Since 2006 the number of published reports demonstrating the use of intravitreal anti-VEGF for ROP has increased significantly.

II. 2017 Ophthalmic Technology Assessment Committee (OTAC) Report of Evidence on Anti-VEGF for ROP, Compared to Laser Photocoagulation3
   A. No Level I evidence available
   B. Level II evidence: 6 studies4-9
   C. Level III evidence: 7 studies10-16

III. Support for the Use of Anti-VEGF in ROP
   A. Overall short-term efficacy and ocular safety
   B. Rapid regression of plus disease; effective for treatment of zone I ROP, posterior zone II ROP, and APROP.10,15,16
   C. Studies have demonstrated a lower likelihood of myopia, high myopia, and astigmatism.5,12,13

IV. Concerns about the Use of Anti-VEGF in ROP
   A. Variable recurrence rates with anti-VEGF therapy, with majority of studies reporting higher recurrence rates11,13,14
   B. Delayed and incomplete retinal vascularization, with prolongation of follow-up period17-20
   C. Detection of bevacizumab and ranibizumab in serum, and corresponding lower systemic VEGF levels of up to 8-12 weeks (bevacizumab) and 1 week (ranibizumab), with unclear long-term systemic adverse events21-24
   D. Need for understanding about the best timing for treatment, the best drug to use, and the lowest effective dose of anti-VEGF therapy
   E. There is a lack of knowledge regarding the potential long-term systemic effects of intravitreal anti-VEGF used in this patient population.

V. Clinical Trials Investigating the Use of Anti-VEGF for ROP
   A. Ongoing Phase 1 multicenter trial to determine lowest effective dose for bevacizumab (clinicaltrials.gov identifier NCT02390531)
   B. Ranibizumab vs. bevacizumab: Studies showing higher recurrence with ranibizumab compared to bevacizumab13
   C. The use of ranibizumab is being investigated in prospective multicenter trials.
      1. CARE-ROP study (Germany): Comparing Alternative Ranibizumab Dosages for Safety and Efficacy in Retinopathy of Prematurity (clinicaltrials.gov identifier NCT02134457).

VI. Summary
   A. Anti-VEGF for ROP has been shown to be effective in promoting regression of treatment-requiring ROP.
   B. Anti-VEGF for ROP may be particularly useful in certain cases (Zone I, posterior Zone II, APROP).
   C. Anti-VEGF for ROP is associated with need for prolonged follow-up.
   D. Unknown long-term risks should be communicated with patient families.
   E. The need for diligent follow-up should be communicated with patient families.

References


Telemedicine for ROP: When, Why and How?

*Antonio Capone Jr MD*

**I. Introduction**

**II. Problem Statement**

**III. Literature Review**

A. Background
B. Description of the technique
C. Resource requirements
D. Question for assessment
E. Description of evidence
F. Conclusions
G. Future research

**IV. Practical Considerations**

A. Resource requirements
B. Information technology considerations
C. Core components of an ROP telemedicine-based remote digital fundus imaging (RDFI-TM) evaluation program
   1. Personnel: The TM team
   2. Definition of roles
   3. Training
   4. Imaging
   5. Equipment maintenance
   6. Information management
   7. Image transfer and interpretation

**V. Risk Management Considerations for RDFI with TM for ROP**

A. Professional liability risk
B. Duty
C. Pitfalls in continuing care
D. Competency and credentialing
E. Consent for TM
F. Need for BIO before discharge
G. Outcomes

**VI. The “ROP Safety Net” Paradigm**

**VII. Summary**

**Selected Reading**

Neonatal Birth Hemorrhage: Incidence, Systemic Findings, and Visual Impact

Darius M Moshfeghi MD

The neonatal birth hemorrhage has been reported since shortly after the introduction of the direct ophthalmoscope over 150 years ago. It can range in appearance from a subtle flame hemorrhage in one eye to a catastrophic-appearing bilateral blood-and-thunder picture. Due to its transient nature, it is frequently dismissed as a comorbidity of birth in certain infants, of no visual consequence. To date, no prospective long-term evaluations have been performed to validate this hypothesis. The literature is replete with the enduring fascination of this phenomenon.

The purpose of this talk is to define the neonatal birth hemorrhage and discuss implications. Specifically, we will discuss the following:

- Original description
- Incidence
- Relative risks with delivery type
- Associations with complications of delivery
- Documentation techniques
- Grading scales
- Photographic evaluation
- Follow-up
- Relationship and potential associations with systemic findings
- Mechanism
- Visual acuity implications

Figure 1. Minimal hemorrhages, right eye.

Figure 2. Diffuse multilaminar hemorrhages in right eye.
Pediatric Retina Panel Discussion

Panel Moderator: G Baker Hubbard MD

Panelists: Audina M Berrocal MD, Kimberly A Drenser MD PhD, Philip J Ferrone MD, Mary Elizabeth Hartnett MD FACS
Late Breaking Developments, Part I

Moderator: Andrew P Schachat MD

Panelists: Judy E Kim MD, Baruch D Kuppermann MD PhD, Michael A Singer MD

Three-Year Update for Phase 3 Voretigene Neparvovec Study in Biallelic RPE65-Mediated Inherited Retinal Disease
Albert M Maguire MD

DRCR Network Comparison of ETDRS and Ultrawide Field Imaging for Diabetic Retinopathy Severity Evaluation
Lloyd P Aiello MD PhD

SCORE2 Month 6 to 12 Results: Monthly vs Treat-and-extend Anti-VEGF Injection Schedules among Good Responders at Month 6
Ingrid U Scott MD MPH

Twelve Month Safety and Efficacy Outcomes from a Phase 2 Study of APL-2 in Patients with Geographic Atrophy
David S Boyer MD

Lampalizumab Phase III Trial for Geographic Atrophy Secondary to AMD, the Spectri Topline Results
Jeffrey S Heier, MD
Phase 2 Trial of Ciliary Neurotrophic Factor for Macular Telangiectasia Type 2

Emily Y Chew MD; The Mac Tel Project Research Group

Introduction

Macular telangiectasia type 2 (MacTel type 2) is a bilateral degenerative disease characterized by perifoveal telangiectatic vessels and neurosensory atrophy.1,2 The affected eye may show the loss of retinal transparency, crystalline deposits, decrease or absence of macular pigment, and hyperplasia of the retinal pigment epithelium. Although the natural course of visual loss is gradual, at approximately 1 letter lost per year,3 affected individuals experience profound reduced visual function, especially for reading.4 There are no current proven therapies for this condition.

Objectives

To evaluate the effect of ciliary neurotrophic factor (CNTF) delivered in a device (NT-501) on the change from baseline area of the ellipsoid zone (EZ) loss at 24 months, as measured by en face imaging by spectral domain OCT

Method

This multicenter, single-masked, sham-controlled study in 11 clinical sites in the United States and Australia enrolled participants with MacTel type 2. If both eyes were eligible for the study, one eye was randomized to the implant or sham while the fellow received the other treatment. Unilateral eyes were randomized to treatment or sham. The primary outcome was the change in area of EZ loss at 24 months compared with the baseline. Functional changes include microperimetry, reading speed (words per minute [wpm]), and the National Eye Institute Visual Function Questionnaire.

Results

Sixty-seven participants (99 eyes) were enrolled in the study. The study population was mostly white, 61% were women, and the median age was 62 years (range: 44-79 years). The cohort had 35 participants eligible in one eye only, and 32 with both eyes enrolled in the study. The mean BCVA at baseline was 20/30. The baseline reading speed was reduced at 109 wpm (sham, 107.2 wpm; NT501 CNTF implant, 94.3 wpm; normal, approximately 160 wpm).

Two deaths occurred during the course of the study. No participants were otherwise lost to follow-up, and all surviving participants were followed to the final 24-month study visit. The CNTF implant reduced the risk of progression of the area of the EZ break at 24 months (P = .039). As expected, there was no change in visual acuity between the treatment groups. However, there was a stabilization of the reading speed in the treated eyes, while the sham eyes continued to experience reduced reading speed (P = .016) at Month 24 compared with baseline. The treated eyes showed retinal thickening in the macular area measured by the ETDRS grid, while the sham eyes continued to display retinal thinning. Other secondary analyses on visual acuity and microperimetry will be presented.

Safety Concerns

Consistent with previous studies of the NT501 CNTF implant in other ocular conditions, such as retinitis pigmentosa and geographic atrophy associated with AMD, the device was well tolerated. No study participant had the implant removed. Short-term adverse effects related to surgery resolved without any sequelae. Miosis, a previously known effect of CNTF implant, was noted in 18% of the study eyes. Electroretinographic changes, similar to those of Phase 1, showed an initial reduction the scotopic b-wave that returned to baseline levels by 1 year.

Conclusion

CNTF treatment delivered by NT501 was safe and well tolerated. CNTF had a beneficial effect and reduced the progressive loss of photoreceptors, compared to untreated eyes. The reading speed appeared to continue to deteriorate in untreated eyes, while it stabilized in the treated eyes. These results are sufficiently encouraging to support future Phase 3 studies in MacTel type 2.

References

Suprachoroidal Triamcinolone Acetonide with and without Intravitreal Aflibercept for Diabetic Macular Edema: Results of the 6-Month Prospective, Phase 1/2 HULK Study

Charles C Wykoff MD PhD, Rahul N Khurana MD, Shaun I R Lampen BS, and William C Ou BS

Purpose
To evaluate the safety and efficacy of suprachoroidal triamcinolone acetonide (CLS-TA) alone or in combination with intravitreal aflibercept for center-involving diabetic macular edema (DME)

Methods
HULK is a prospective, 6-month, open label, Phase 1/2 trial involving 20 subjects, assigned to 1 of 2 arms (IND 115683; NCT02949024). All subjects were ≥ 18 years of age with type 1 or type 2 diabetes mellitus with center-involving DME. Subjects had a central subfield thickness (CST) of ≥ 320 µm measured using spectral domain OCT. Subjects were required to have an Early Treatment Diabetic Retinopathy Study best corrected visual acuity (ETDRS BCVA) letter score of 83 to 14 (Snellen equivalent of 20/25 to 20/500). A diagnosis of uncontrolled glaucoma in the study eye was exclusionary. Treatment-naïve subjects had not received prior ocular-specific treatment for DME or had received treatment more than 1 year prior to enrollment (Tx-Naïve arm; n = 10). Previously treated subjects had persistent or recurrent DME despite prior treatment and had not received treatment within at least 90 days prior to screening (Previous-Tx arm; n = 10). Tx-Naïve eyes received 2 mg intravitreal aflibercept and 4 mg suprachoroidal CLS-TA at baseline, while Previous-Tx eyes received 4 mg suprachoroidal CLS-TA alone at baseline. Retreatment if necessary in either arm of the study was only with CLS-TA and was assessed monthly, starting at Month 2. Subjects meeting the following criteria were retreated with 4-mg CLS-TA: CST > 320 µm and not improved by at least 20% from either of the previous 2 visits (10% for CST > 500 µm), or loss of 10 or more letters, due to DME, from either of the previous 2 visits. Outcome measures included mean change in BCVA, CST, IOP, number of CLS-TA retreatments, and incidence of treatment emergent adverse events.

Results
At baseline, mean age was 62.5 years (range: 46-73), mean IOP was 13.8 mmHg (range: 9-22), mean BCVA was 67.2 ETDRS letters (range: 52-83), and mean CST was 447 µm (range: 328-691). Among Tx-Naïve eyes, mean BCVA was 67.2 ETDRS letters and mean CST was 422 µm. Among Previous-Tx eyes, mean BCVA was 67.2 ETDRS letters and mean CST was 473 µm. Previous-Tx eyes had received a mean of 21.8 prior intravitreal pharmaceutical injections for the management of DME. At baseline, 1 subject in the Previous-Tx arm had a prior diagnosis of open-angle glaucoma managed with timolol. All eyes have completed Month 3. At Month 3, mean changes in BCVA were +6.9 and +2.6 ETDRS letters in the Tx-Naïve and Previous-Tx arms, respectively. At Month 3, mean CST decreased by 88.2 µm and 94.3 µm to an absolute mean CST of 341 µm and 378 µm in the Tx-Naïve and Previous-Tx arms, respectively. In this 3-month evaluation time-frame, IOP increased 10 mmHg or more above baseline in 1 eye, and no eye had an IOP greater than 29 mmHg. One eye was prescribed latanoprost to manage increased IOP. In general, multiple suprachoroidal injections with CLS-TA as often as monthly did not appear to elevate IOP in this small study population. CLS-TA retreatment criteria were met for 5 of 10 Tx-Naïve subjects and 8 of 10 Previous-Tx subjects in the 3-month evaluation period. No serious adverse events were observed, and 1 episode of inadvertent intravitreal triamcinolone injection was observed.

Conclusions
In the current prospective, 6-month, open label, Phase 1/2 trial involving 20 total subjects, suprachoroidal triamcinolone acetonide alone or with intravitreal aflibercept appeared safe and efficacious for the treatment of DME, through 3 months of follow-up.
TREX-DME Trial: Two-Year Outcomes
Treat and Extend with and without Navigated Focal Laser vs. Monthly Dosing for Diabetic Macula Edema

David M Brown MD, Shaun I R Lampen BS, Charles C Wykoff MD PhD, John F Payne MD, W Lloyd Clark MD, Beau B Bruce MD PhD, and David S Boyer MD on behalf of the TREX-DME Study Group

Purpose
To compare the efficacy of a treat and extend (TREX) dosing algorithm of ranibizumab 0.3 mg with and without angiography-guided macular laser photocoagulation (GILA) to monthly dosing for center-involving diabetic macular edema (DME).

Methods
TREX-DME is a prospective, 2-year, open-label trial involving 150 eyes randomized to 1 of 3 arms (IND 119146, NCT01934556). All subjects had center-involved DME with a BCVA between 79 and 24 letters (20/25-20/320 Snellen equivalent). The Monthly cohort (n = 30) received ranibizumab treatments every 4 weeks for 2 years. The TREX (n = 60) and GILA (n = 60) arms received an injection every 4 weeks for the first 4 months. At Week 12, eyes in the TREX and GILA cohorts with a central retinal thickness (CRT) ≤ 325 µm began a treat and extend dosing regimen based on the percentage change in CRT. At each subsequent visit the treatment interval was extended, maintained, or reduced depending the change in CRT compared with Week 12. The GILA arm received angiography-guided focal laser on the 532-mm Navilas laser starting at Week 4. Subjects were re-evaluated every 3 months and retreated if microaneurysm leakage was present on fluorescein angiography.

Results
At baseline, mean age was 59.4 years, mean BCVA was 64.7 letters, and mean CRT was 468 µm. Among Monthly eyes, mean age was 58.7 years, mean BCVA was 65.1 letters, and mean CRT was 434 µm. In the TREX cohort, mean age was 59.4 years, mean BCVA was 64.1 letters, and mean CRT was 475 µm. The GILA arm had a mean age of 59.9 years, a mean BCVA of 59.9 letters, and a mean CRT of 479 µm. Among eyes that reached the 2-year endpoint, mean BCVA improved by 7.5, 9.6, and 9.0 letters in the Monthly, TREX, and GILA cohorts, respectively (P = .75). Additionally, 13 Monthly eyes (52%), 28 TREX eyes (64%), and 32 GILA eyes (64%) gained at least 1 line of vision. No eyes lost 3 lines of vision or more at Month 24. Mean CRT decreased by 139, 140, and 175 µm in the Monthly, TREX, and GILA cohorts, respectively (P = .09). At the 2-year endpoint, 49 TREX eyes (82%) and 53 GILA eyes (88%) were eligible for treatment extension. At Month 24, the mean number of intravitreal injections administered was 13.1, 10.7, and 10.1 in the Monthly, TREX, and GILA cohorts, respectively (P < .001 for TREX or GILA vs. Monthly; P = .27 for TREX / GILA). Mean treatment interval was 4.3, 6.2, and 6.7 weeks in the Monthly, TREX, and GILA cohorts, respectively (P < .001 for TREX or GILA vs. Monthly; P = .31 for TREX / GILA). Eyes in the GILA cohort received a mean of 3.1 and 1.9 navigated focal laser treatments in the first and second year of the study, respectively. No new safety signals were identified in Year 2.

Conclusions
In the current prospective, randomized trial, an individualized treat and extend regimen utilizing ranibizumab 0.3 mg with and without angiography-guided macular photocoagulation resulted in significantly fewer injections and yielded visual and anatomic gains comparable to subjects treated with monthly dosing at 2 years.
Hawk & Harrier: 48-week Results of Two Multi-centered, Randomized, Double-masked Trials of Brolucizumab vs. Aflibercept for Neovascular AMD

Pravin U Dugel MD
“Type 3 neovascularization” (NV) is a term used to describe NV found within the retina. “Type 3” is a natural extension of the anatomically based classification of NV described by J Donald M Gass MD, who called sub–retinal pigment epithelium (RPE) NV “type 1”; and subretinal NV, “type 2.” The term “type 3 NV” does not specify the vascular origin of this lesion but instead emphasizes its intraretinal location.

Type 3 NV was first described by Harnett et al in 1992 as a finding observed in patients with AMD. They termed this lesion “retinal vascular abnormalities associated with pigment epithelial detachment.” Subsequently, “deep retinal vascular anomalous complex” was used to describe this finding. In 2001, Yannuzzi et al proposed “retinal angiomatous proliferation” (RAP) for type 3 NV. They proposed a 3-stage classification of type 3 NV based on the imaging technology available at that time, in which the NV was believed to originate from the retinal circulation and later could become associated with the development of a chorioretinal anastomosis.

In 2003, Gass et al hypothesized that the origin of type 3 NV was from preclinical type 1 NV forming an “occult chorioretinal anastomosis.”

Recent reports relying on newer imaging technology, including spectral domain OCT, real-time angiography, and OCT angiography, appear to show that most type 3 lesions originate from the deep retinal circulation. An OCT-based classification was recently introduced that presumes the origin of type 3 NV to be from the deep vascular plexus, followed by a disruption of outer retinal layers and penetration through the RPE. However, there are likely some eyes in which type 1 lesions develop a type 3 component, and other cases in which type 3 lesions originate over areas of pre-existing type 1 NV. These lesions would be best classified as “mixed type 1,3 NV.”

Type 3 NV occurs almost exclusively in AMD and is far more common than previously recognized. In a consecutive series of newly diagnosed treatment-naïve AMD eyes, Jung et al identified type 3 NV as the predominant lesion component in 34.2% of their cases. Initially, early type 3 NV typically responds well to intravitreal anti-angiogenic therapy, but long-term visual outcomes may be poor due to the occurrence of macular atrophy.

Several clinicopathologic correlations of type 3 NV examining submacular surgery specimens and intact post-mortem eyes have largely supported a retinal rather than a choroidal source of early type 3 lesions by failing to demonstrate vascular connections through defects in the Bruch membrane. Only one of these reports evaluated an eye imaged with OCT during its course, but in this case, OCT was first performed years after the initiation of treatment.

This presentation will describe a clinicopathologic correlation of type 3 NV associated with a mixed serous-drusenoid pigment epithelial detachment imaged with serial eye-tracked spectral domain OCT simultaneously with intravitreal bevacizumab treatment over a 6-month period. The findings support the concept that type 3 NV originates from the retina without choroidal contributions and implants in the sub-RPE–basal lamina space. Further, intraretinal hyper-reflective foci represent migrated RPE and lipid-filled cells presumed to be microglia, participating in this process.
The Pharmacokinetics of Anti-VEGF Agents
Pharmacokinetic Study of Intravitreal Aflibercept in Humans with Neovascular AMD

Diana V Do MD, William Rhoades MD, Quan Dong Nguyen MD MSc

**Purpose**
To investigate the ocular pharmacokinetics of aflibercept after a single intravitreal injection in humans with neovascular AMD

**Design**
Prospective, noncomparative, interventional case series

**Methods**
Five eyes from 5 individuals with new-onset neovascular AMD and no history of vitrectomy surgery were enrolled. At baseline, aqueous humor and blood plasma samples were taken from all participants. Immediately after the samples were obtained, all study eyes received a single intravitreal injection of aflibercept, and this time point was designated as Day 0. Study eyes underwent sampling of aqueous humor and blood plasma at 6 additional study time points: 4 hours after injection and Days 1, 3, 7, 14, and 28. Concentrations of free and bound aflibercept were quantified using enzyme-linked immunosorbent assay.

**Results**
The average half-life of free aflibercept measured in the aqueous after intravitreal injection was found to be ~9 days. Individual patients exhibited a range of half-lives. Plasma levels of free aflibercept were low to undetectable during the first week following injection, and undetectable in all patients at time points beyond 7 days.

**Conclusions**
The directly measured half-life of intravitreal aflibercept is consistent with previous indirect estimates. The range of half-lives in individual patients may contribute to the differential duration of action observed clinically.
Treatment Patterns and Visual Outcomes for AMD

Mark C Gillies MD PhD

We studied the treatment patterns, disease activity, and visual outcomes of eyes from an observational database that were in the maintenance phase of treatment of neovascular AMD (nAMD) in order to guide management decisions for a treat-and-extend regimen. We also compared the behavior of eyes that had shorter induction phases (3 injections) with that of eyes with longer induction phases. Eyes with nAMD that were receiving vascular endothelial growth factor inhibitors using a treat-and-extend protocol were included. Persistently active eyes were excluded, as were eyes with < 12 months follow-up during the maintenance phase. The maintenance phase was defined as starting at the first visit when the practitioner graded the neovascular lesion as inactive.

Main Outcome Measures

- For analyses by eye
  - Treatment interval at first reactivation
  - Time to first reactivation
  - Visual acuity change during the study period
- For analyses by visit
  - Choroidal neovascular membrane activity graded by the treating physician
  - Time since previous injection
  - Visual acuity loss since previous injection (> 0 letters and > 5 letters)

The mean change in visual acuity during the maintenance phase was +1.0 letters at 12 months, +0.6 letters at 24 months, and −1.5 letters at 36 months. The median treatment interval increased from 35 days at the start of the maintenance phase to 63 days at 12 months and 60 days at 36 months. Thirty-nine percent of eyes remained inactive at all observed visits during the maintenance phase (minimum 1 year follow-up; mean: 945 days). The most common treatment interval at first reactivation was 8 weeks. Treatment intervals beyond 12 weeks seemed to be associated with increased risk of disease reactivation, with risk of reactivation reaching 37% at treatment intervals of > 20 weeks (see Table 1). Eyes with a longer induction phase had worse visual outcomes in the maintenance phase, and earlier and more frequent disease reactivation, although they received injections less frequently.

Visual acuity was generally maintained well during the study period. The most common interval at which reactivation first occurred was 8 weeks. Extension of treatment intervals from 3 to 4 months was associated with a substantially increased risk of reactivation. Longer induction phases were associated with worse visual acuity outcomes and earlier disease reactivation, perhaps because of undertreatment.

Table 1. Frequency and Adjusted Marginal Risk of First Reactivation of CNV at Each Treatment Interval, by Treatment Interval

<table>
<thead>
<tr>
<th>Interval of First Reactivation</th>
<th>Opportunities for Reactivationa</th>
<th>Frequency (n)</th>
<th>% Risk per Visit (95% CI)</th>
<th>Change in Risk from Previous Level (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 weeks</td>
<td>1157</td>
<td>128</td>
<td>9.9 (8.0, 12.3)</td>
<td>0</td>
</tr>
<tr>
<td>6 weeks</td>
<td>2100</td>
<td>262</td>
<td>12.1 (10.4, 14.1)</td>
<td>2.2</td>
</tr>
<tr>
<td>8 weeks</td>
<td>3019</td>
<td>365</td>
<td>14.5 (12.8, 16.4)</td>
<td>2.4</td>
</tr>
<tr>
<td>12 weeks</td>
<td>2650</td>
<td>299</td>
<td>15.3 (13.3, 17.5)</td>
<td>0.8</td>
</tr>
<tr>
<td>16 weeks</td>
<td>744</td>
<td>109</td>
<td>20.9 (16.9, 25.5)</td>
<td>5.6</td>
</tr>
<tr>
<td>20 weeks</td>
<td>467</td>
<td>126</td>
<td>36.5 (30.5, 43.0)</td>
<td>15.6</td>
</tr>
</tbody>
</table>

a Opportunities for reactivation includes visits for all eyes prior to the first reactivation.
Anti-VEGF Monotherapy vs. Combination Therapy with Photodynamic Therapy for Treatment of Polypoidal Choroidal Vasculopathy

Tien Y Wong MD MBBS

Polypoidal choroidal vasculopathy (PCV) is a subtype of exudative AMD, now considered to be a type 1 CNV. PCV is more common in blacks and Asians. While the standard of care for traditional classic exudative AMD is anti-vascular endothelial growth factor (anti-VEGF) monotherapy, the optimal treatment of PCV remains unclear in “real-world” settings.

Currently, the two main modalities of PCV treatment are anti-VEGF therapy with aflibercept, bevacizumab, or ranibizumab with and without combination with verteporfin photodynamic therapy (PDT). In recent years, several randomized trials have evaluated the various anti-VEGF agents in combination with PDT, which can be given at baseline or deferred later, sometimes as a “rescue” therapy in eyes unresponsive to anti-VEGF therapy.

Two larger randomized trials with more than 300 patients each have provided much clearer evidence on the use of anti-VEGF therapy and combination therapy for the treatment of PCV: the EVEREST-2 study and the PLANET study. EVEREST-2 compared intravitreal ranibizumab 0.5-mg monotherapy with combination therapy, comprising ranibizumab plus PDT at baseline; whereas the PLANET study compared intravitreal aflibercept 2-mg monotherapy with aflibercept combined with rescue PDT, given to patients who need this at 3 months onward.

**Anti-VEGF Monotherapy**

Regarding anti-VEGF monotherapy, both EVEREST-2 and PLANET reported significant visual acuity gain in the monotherapy arms at 1 year. This was +5.1 letters in EVEREST-2, and +10.8 letters in PLANET. Polyp closure rate was 34.7% in EVEREST-2 and 38.9% in PLANET, and the mean number of injections was 7.3 in EVEREST-2 and 8.1 in PLANET (Koh A, AAO 2016; Iida T, APVRS 2016).

These results were further corroborated by the DRAGON study, a Phase 4, randomized, double-masked, multicenter study based in China that compared the efficacy of ranibizumab monotherapy using monthly fixed dosing regimen with a p.r.n. regimen (Zhu Emretina 2016). Significant improvement in BCVA was achieved in both PCV and non-PCV patients in the monthly arm (+12.3 vs. 10.6 letters) and the p.r.n. arm (9.7 vs. 8.7 letters) at 24 months. Based on these clinical trial data, monotherapy with either ranibizumab or aflibercept can achieve visual improvement and reduction in disease activity and should be considered as first-line treatment in patients with PCV.

**Aflibercept or ranibizumab?**

Direct comparison between EVEREST-2, PLANET, and DRAGON, based on absolute number of letters gained, may suggest some advantage using aflibercept compared to ranibizumab when used as monotherapy. However, differences in baseline BCVA should be taken into account, as eyes with lower baseline BCVA are generally expected to achieve a larger magnitude of improvement. Differences in dosing regimens should also be considered a potential factor underlying any differences in BCVA change reported.

**Combination Therapy with PDT**

Combination therapy with PDT at baseline

Combination therapy including PDT and anti-VEGF therapy has been reported to achieve significantly better visual outcomes than PDT alone, and to reduce the rate of development of PDT-related hemorrhages. In the EVEREST-1 trial, combination therapy achieved slightly higher polyp closure rate than did PDT monotherapy, but the difference was not statistically significant. Patients in the combination arm also achieved the highest BCVA gain numerically (10.9 letters) compared to patients in the ranibizumab monotherapy arm (9.2 letters) or the PDT monotherapy arm (7.5 letters) at Month 6, but the difference was not statistically significant.

In the EVEREST-2 study, combination therapy of ranibizumab with PDT at baseline achieved superior BCVA gain (8.3 vs. 5.1 letters; \( P = .013 \)), higher proportion of patients with BCVA ≥ 69 letters (69.0% vs. 58.8%), higher polyp closure rate (69.3% vs. 34.7%, \( P < .01 \)), and higher proportion with absence of disease activity at Month 12 (79.5% vs. 50.0%) compared to ranibizumab monotherapy (Koh A, AAO, 2016). The combination arm also required fewer injections (mean: 5.2 vs. 7.3 injections over 12 months), with 50.6% of patients in the combination arm requiring only 3-4 injections over 12 months, which is significantly lower than that in the monotherapy arm (26.2%). However, currently there are no clear criteria to identify the subgroup that will benefit with few injections at baseline. These results suggest that while ranibizumab monotherapy is safe and achieves moderate BCVA gains in PCV, combination therapy is superior in terms of BCVA gain and polyp closure and can reduce the number of ranibizumab injections required up to 1 year.

**Deferred combination therapy with PDT at 3 months**

In addition to combination at baseline, deferred combination has also been evaluated in the FUJISAN study, which compared the outcome of initial or deferred PDT combined with intravitreal ranibizumab. In this study, patients were evaluated after 3 monthly intravitreal ranibizumab injections. In patients who met the retreatment criteria, deferred combination treatment was given. The study reported similar BCVA outcomes at 1 year between patients with baseline PDT and those with deferred PDT. However, with this approach, more than half of the patients in the deferred arm (17 out of 31 patients) did not require PDT.
Deferred combination therapy with rescue PDT at 3 months

The PLANET study evaluated deferred, rescue PDT combination therapy. Qualification for rescue PDT was strict and was based upon insufficient gain in BCVA and evidence of leakage from active polyps. The vast majority of patients did not meet the rescue criteria after 3 initial monthly aflibercept injections (87.9% and 85.7% in the aflibercept monotherapy arm and combination arm, respectively; \(P = .84\)). In fact, < 15% of patients needed rescue PDT. Both treatment arms achieved similar BCVA gain (10.7 vs. 10.9 letters, respectively) and polyp regression rates (38.9% vs. 44.8%, respectively; \(P = .32\)). Over 80% of patients had no signs of polyp activity at Week 52. The PLANET study thus concluded that aflibercept monotherapy achieved significant BCVA gains in over 85% of patients with PCV, and no significant additional benefit was demonstrated by adding rescue PDT in the small group of patients that required it.

Conclusion

The goal of PCV treatment, as in neovascular AMD, is to achieve the best possible visual outcome with the fewest number of treatments. Results of both EVEREST-2 and PLANET show that anti-VEGF monotherapy, with either ranibizumab (EVEREST-2) or aflibercept (PLANET), as well as combination therapy with PDT either at baseline (EVEREST-2) or as a rescue therapy at 3 months (PLANET), give excellent functional visual outcomes at 1 year, and are acceptable initial treatment options in patients presenting with symptomatic macular PCV. The therapy of choice depends on individual settings, access to PDT, and patient characteristics when deciding on the best treatment option.

References

Combined Ang2 and VEGF Blockade for Wet AMD: What to Expect

Anti-VEGF and Ang2 Inhibition Studies

Jeffrey S Heier MD

I. Introduction
   A. There is opportunity to investigate the improvement of outcomes for patients with neovascular AMD and diabetic macular edema (DME) by combining anti–vascular endothelial growth factor (anti-VEGF) treatment with inhibitors of agents such as angiopoietin 2 (Ang2) and thereby potentially providing synergistic mechanisms of action to anti-VEGF agents.
   B. A Phase 1 study was conducted to investigate the safety and tolerability of combination therapy with nesvacumab, a fully human monoclonal antibody against Ang2, and aflibercept, an anti-VEGF agent.

II. Methods
   A. Nesvacumab / aflibercept (REGN910-3) is a coformulation of nesvacumab and aflibercept, providing both agents in a single intravitreal injection.
   B. The first-in-human study of nesvacumab / aflibercept was an open-label, dose-escalation study of the safety and tolerability of intravitreal nesvacumab / aflibercept and nesvacumab alone in patients with neovascular AMD and clinically significant DME.

III. Results
   A. A total of 20 patients (10 with neovascular AMD and 10 with DME) participated in the study.
   B. In the AMD cohort, the mean age was 76 years, 40% of patients were female, and the mean baseline BCVA and central retinal thickness (CRT) were 61.7 letters and 414.7 µm, respectively.
   C. In the DME cohort, the mean age was 61 years, 70% of patients were female, and the mean baseline BCVA and CRT were 59.7 letters and 472.0 µm, respectively.
   D. The most common ocular adverse event was reduced visual acuity (2 patients [10%]). Neither of these events was related to the study drug or the study procedure.
   E. No adverse event considered dose-limiting toxicity, and no ocular serious adverse events were reported.
   F. Visual and anatomic improvements were seen with intravitreal nesvacumab / aflibercept at all dose levels.

IV. Conclusions
   Nesvacumab / aflibercept did not result in dose-limiting toxicity at any dose level studied in either neovascular AMD or DME patients, and visual and anatomic improvements were seen at all dose levels in this Phase 1 study.

V. Ongoing Trials
   A. Based on these results, 2 randomized, double-masked, active-controlled, Phase 2 studies, ONYX and RUBY, were initiated to evaluate the efficacy, safety, and tolerability of repeated doses of intravitreal nesvacumab / aflibercept in patients with neovascular AMD and DME, respectively.
   B. Both studies compare 2 dosing regimens of nesvacumab / aflibercept with intravitreal aflibercept alone through Week 36.
   C. The primary endpoint of ONYX and RUBY is the change from baseline in BCVA measured by the Early Treatment Diabetic Retinopathy Study letter score at Weeks 12 through 36.
Update on Emerging Treatments for Neovascular AMD

Peter K Kaiser MD

Extracellular VEGF Pathways

Platelet derived growth factor (PDGF) Pathway
**Tyrosine Kinase Pathways**

**Endothelial Cell**

- VEGF-A
- VEGF-B
- VEGF-C
- VEGF-D
- OTX-TKI
- RTKI-MPP *drop*
- GB-102
- PAN 90066 *drop*
- SK 1011 *oral*
- Sutene (X82) *oral*
- DE-120 *oral*

**Pericyte**

- PDGF-AA
- PDGF-AB
- PDGF-CC
- PDGF-DD

Tyrosine kinase cascade

Figure 3

**Multiple Pathways**

**Endothelial Cell**

- VEGF-A
- VEGF-B
- VEGF-C
- VEGF-D
- Calmodulin (CaM)
- OHR-102 *drop*

**Pericyte**

- PDGF-AA
- PDGF-AB
- PDGF-CC
- PDGF-DD

Calmodulin (CaM) activates tyrosine kinase pathways even in absence of ligand

Selective uptake by activated endothelial cells

Inhibits Calmodulin (CaM)
Intracellular dephosphorylation of VEGF, PDGF, bFGF receptors
Inhibits integrin expression
Inhibits Na+/H+ exchanger (NHE3)
Inhibits actin filament formation (Alters shape and volume of EC)

Figure 4
**Tie2 Pathway**

Figure 5

**Integrin Pathways**

Figure 6
New Biomarkers of Angiogenesis in AMD Using OCT Angiography

David Sarraf MD

NOTES
Swept-Source OCT: Current Status

Jay S Duker MD and Carl Rebhun BA

I. Fourier Domain OCT: Two Types
   A. Spectral domain OCT (SD-OCT):
      With SD-OCT, the low-coherence light source has a broad band wavelength and the reflection is depth-encoded by frequency.
   B. Swept source OCT (SS-OCT)
      1. With SS-OCT, the wavelength of the light source is rapidly changed via a tunable laser.
      2. SS-OCT requires narrow linewidth, high-speed, frequency-swept lasers that are very expensive.
      3. Light reflections are depth encoded and are detected with photodetectors (as opposed to a charge-coupled device camera as in SD-OCT). After detection, the reflections are rapidly decoded with Fourier transform.
      4. In general, SS-OCT devices use a longer wavelength than SD-OCT. Both 1000-nm and 1300-nm wavelengths have been utilized.

II. Clinical Advantages of SS-OCT
   A. Faster acquisition speed (100,000 A-scans per second or greater): Some prototype devices have imaged at speeds of up to 1,000,000 A-scans per second.
   B. Wider scanning range: 12-mm to 16-mm scan length (see Figure 1H)
   C. Less sensitivity roll-off than SD-OCT: Possible to image vitreous and choroid well simultaneously
   D. Longer wavelength: Better ability to penetrate choroid, lens opacity, vitreous debris, pigmented epithelial detachments

III. Disadvantages of SS-OCT
   A. Increased cost of light source
   B. Lower axial resolution (4-5 microns vs. 6-8 microns)
   C. Worse signal-to-noise ratio
   D. Worse motion artifact

IV. Current Commercial Status of SS-OCT
   A. Topcon: DRI (Deep Range Imaging) OCT Triton1
      1. Specs
         a. 100,000 A-scans per second
         b. 1050-nm wavelength: No visible line for patient while scanning, which allows for better patient fixation
         c. Tracking is available to help reduce motion artifacts.
      2. Multimodal imaging: Built-in color fundus photo, red free, fundus autofluorescence, fluorescein angiography, OCT, and OCT angiography (OCT-A) (see Figure 1)

Figure 1. OCT angiography (OCT-A) and line scan. Right eye of a 28-year-old healthy white male using a SS-OCT. (A) Full-thickness (internal limiting membrane to Bruch membrane) 3x3-mm OCT-A. (B) 3x3-mm OCT-A of the superficial capillary plexus. (C) 3x3-mm OCT-A of the deep capillary plexus. (D) 3x3-mm OCT-A of the avascular outer retina. In this image, white spots represent noise. (E) 3x3-mm OCT-A of the choriocapillaris. (F) Full-thickness 6x6-mm OCT-A. (G) Red-free fundus image. Arrow corresponds to B-scan in (H). (H) Highly sampled structural OCT B-scan.
3. Commercially available outside of the United States
4. Available for research purposes in the United States

B. Zeiss: Plex Elite 9000
1. Specs
   a. 100,000 to 200,000 A-scans per second
   b. 1060-nm wavelength: No visible line for patient while scanning, which allows for better patient fixation
   c. Tracking is available to help reduce motion artifacts.
2. Available for research purposes only; FDA approved in United States for this reason
3. OCT and OCT-A capability
   a. “Wide field” imaging with 12x12-mm structural OCT cube scan and 12x12-mm OCT-A
   b. Future iterations of software will allow for automatic montaging of multiple 12x12-mm OCT-As.

V. Summary
A. SS-OCT has theoretical advantages (increased speed, deeper penetration, better ability to image through opaque media) and disadvantages (worse axial resolution, worse signal-to-noise ratio, and more expensive) compared to SD-OCT.
B. SS-OCT will allow for increased field of view with “wide field” imaging. In addition, with increased A-scan acquisition speed there will be better resolution of larger scans.
C. Data suggest that perhaps there is a better delineation of CNV on SS OCT-A than on SD OCT-A.\textsuperscript{2,3}

References
Widefield OCT and OCT Angiography Imaging

Nadia K Waheed MD

Widefield imaging is gaining increasing clinical importance. It enables us to view pathology that may not be seen with traditional imaging, especially in the setting of retinal vascular disorders and in diabetic retinopathy. OCT and OCT angiography have traditionally been limited to the central macula. However, with the availability of better eye-tracking technology, it is now possible to obtain wider and wider fields of view on OCT angiography which were not available previously. Moreover, the high resolution of the vascular images on OCT angiography allows for the visualization of much finer detail than is seen with dye-based angiography.

This presentation will review wide-field OCT angiography and its application in retinal vascular disease. Qualitative evaluation of wide-field imaging on OCT will be compared to traditional dye-based wide-field imaging, and the results will be presented.
Subclinical Diabetic Macular Changes Revealed by OCT Angiography: Why It Matters

Richard B Rosen MD

The emergence of laser and fluorescein angiography in the early 1960s ushered in modern management of diabetic retinopathy. Previously, pituitary ablation, a high-risk, high-morbidity procedure, was the only therapy available. By 1980, 5 million Americans were known to suffer from diabetes mellitus (>26 million today), and diabetic retinopathy was responsible for about 20% of new cases of blindness between the ages of 45 and 74. Nearly half of the 1 million patients who developed severe diabetic retinopathy went blind within 5 years of diagnosis. The critical role of intensive glucose and blood pressure control to delay or prevent the complications of diabetes was not established.1

Laser treatment to suppress neovascularization quickly gained popularity, but methodology and indications were unclear until the Diabetic Retinopathy Study defined panretinal photocoagulation (PRP) and demonstrated its ability to reduce severe visual loss by 50%. Due to the morbidity of the procedure, treatment was reserved until threshold high-risk characteristics were observed. The Early Treatment Diabetic Retinopathy Study similarly helped define the indications for focal laser to the macula, limiting treatment to areas of confirmed retinal thickening to minimize macular injury and optimize retention of visual acuity.1

Controversy regarding the role of tight blood glucose control remained a major barrier to retinopathy management until the Diabetes Control and Complications Trial demonstrated definitively that blood glucose control delays or prevents retinopathy and other complications in people with type I diabetes. Subsequent studies showed a similar effect was seen in type II diabetes with control of blood glucose and blood pressure levels. More recently, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) eye study found that intensive control of blood glucose levels with combination lipid therapy (statin and fibrate) reduced diabetic retinopathy disease progression in patients with type II diabetes.1

The discovery of vascular endothelial growth factor (VEGF) and subsequent development of anti-VEGF drugs, combined with the development of high-resolution spectral domain OCT, greatly improved the prospects for vision preservation and restoration in diabetic eyes. With advances in laser treatment and improved vitrectomy techniques, blindness has been reduced by 90% in patients with severe diabetic retinopathy. Still there are substantial limitations to our current rescue strategy for controlling diabetic retinopathy.

OCT angiography (OCT-A), a recent advance, offers noninvasive imaging of the retinal vasculature, with higher resolution than conventional fluorescein studies, approaching adaptive optics.2 While OCT-A currently doesn’t reveal leakage, it can reveal the full spectrum of microvascular retinopathy in multiple capillary beds and detect the loss of even single capillary segments (see Figure 1).

Figure 1.

Compared to fundus photography, OCT-A is much more sensitive to early detection of retinopathy without the morbidity, time, and expense of dye-based studies.2 Its consistent detail and resolution make it ideal for quantitative analysis, such as multilayer perfused capillary density mapping and foveal avascular zone size and configuration (see Figure 2).3-6 Perfused capillary density maps and averages can be used to scale degree of diabetic retinopathy, which may be used for longitudinal follow-up.5
The ability to noninvasively detect the earliest lesions of diabetic retinopathy prior to visible hemorrhages and microaneurysms will result in a paradigm shift in our thinking about the timing of onset and progression of the disease. Earlier recognition offers the opportunity to reduce damage and maximize reversibility through encouragement of more aggressive medical management, as well as judicious application of VEGF-neutralizing treatment. Current anti-VEGF agents have been shown to slow down and even reverse capillary nonperfusion. Newer agents specifically designed to reverse early capillary closure are currently in early stages of testing.

By revealing silent disease, OCT-A anticipates the next generation of therapeutics for diabetic retinopathy. Oral medications or nondestructive light therapies may eventually become important adjunctive tools for early treatment, initiated at the first evidence of disease instead of waiting for damage severe enough to justify the morbidity of laser or even intraocular injection.

References
Introduction

OCT angiography (OCT-A) is a revolutionary imaging technique that can rapidly and noninvasively image the retinal and choroidal vasculature. The strategy uses repeated OCT B-scans at the same position and identifies signal differences between the repeated B-scans to generate images that correlate with flow or movement. When these difference B-scans are compiled into a volumetric dataset and viewed using an en face approach, the aggregate image looks similar to the retinal and choroidal vasculature seen when viewing dye-based angiograms resulting from fluorescein or indocyanine green angiography. OCT-A has many advantages over conventional dye-based angiography. No exogenous dyes are needed, so OCT-A is much safer than conventional angiography. OCT-A is also much faster, more comfortable for the patients since no venipuncture or bright flashes of light are needed, and less expensive. It can be performed through an undilated pupil and can be repeated frequently to help with the management of macular diseases.

A disadvantage of OCT-A imaging is that it cannot identify dynamic vascular leakage. But an advantage of OCT-A imaging is that both structural and flow information can be extracted from the same scan, so the results of leakage—which includes fluid in the retina, under the retina, and under the retinal pigment epithelium (RPE)—can be readily appreciated. After all, in most macular diseases, vascular leakage is associated with macular fluid.

OCT-A can be performed using spectral domain OCT (SD-OCT) or swept source OCT (SS-OCT) instruments. While most of us are familiar with SD-OCT imaging, SS-OCT is a newer technology with certain advantages for imaging choroidal neovascularization (CNV) and polypoidal choroidal vasculopathy (PCV). Compared with SD-OCT, which uses a laser wavelength of about 840 nm, SS-OCT is another Fourier domain technology that results in less sensitivity roll-off of the signal into the choroid, and its longer wavelength (~1050 nm) allows for less attenuation of the light by the RPE and for a higher laser power to be used, resulting in a better penetration into the choroid with a higher signal to noise from tissues under the RPE compared with SD-OCT imaging. Not surprisingly, SS-OCT-A imaging has been shown by several groups to be better than existing SD-OCT-A technology for imaging neovascularization under the RPE. Thus, SS-OCT-A is the preferred OCT-A imaging strategy for visualizing type 1 neovascularization (NV) in AMD, PCV, and any macular diseases complicated by CNV.

OCT-A Imaging Strategies for CNV and PCV

Unlike traditional dye-based angiography, in which the NV is viewed using a standard en face approach as the dye fills and drains from the retinal and choroidal circulations and multiple images are acquired over a time period ranging from 5 to thirty minutes, OCT-A scans are acquired in under 10 seconds. Image processing requires additional time, ranging from under a minute to several minutes, depending on the instrument. While dye-based angiography provides 2-dimensional viewing of the vasculature, OCT-A provides a 3-dimensional dataset that can be manipulated to extract images based on the location of the NV. This depth-resolved information is a distinct advantage of OCT-A over conventional dye-based angiography, which requires stereoscopic viewing.

Different en face and cross-sectional imaging strategies are used in OCT-A to optimize the visualization of CNV and PCV. The earliest strategies were segmentation strategies that involved slabs with parallel boundaries and variable spacing between these boundaries. These slabs sliced through the NV without regard to natural tissue layers such as the RPE, and different en face images were obtained depending on whether neovascular lesions were captured within the entire slab.

In addition, to be able to appropriately interpret the en face flow images, it became apparent that the corresponding en face structural image derived from the same slab needed to be viewed at the same time in order to identify any variation in signal strength that may confound the interpretation of the en face flow images. After all, if there’s a decrease in the signal strength, then the flow images may be interpreted erroneously to have regions of decreased flow, but the correct interpretation would be that the decrease in the flow signal was the result of a decrease in the signal. The converse of this argument is that an increase in the flow in the presence of an increase in the structural signal may represent a projection artifact arising from the overlying retinal circulation. This is why it is essential to visualize the B-scans with and without the superimposed flow signals to ensure the correct position of the slab boundaries and identify any potential artifacts including the retinal vascular projections. These retinal vessel projection artifacts are always a potential problem whenever the hyper-reflective RPE is included in a particular slab, which is almost always the case when imaging CNV and PCV. For this reason, several groups have developed algorithms for the automatic removal of these retinal projection artifacts from the OCT-A images.

We’ve developed a novel slab that is useful for screening eyes for the presence of macular NV, and this slab is used in conjunction with an algorithm to remove the retinal vessel projection artifacts. This slab should identify all type of CNV and PCV, as well as type 3 NV, known as retinal angiomatous proliferation. The boundaries of this slab extend from the outer border of the outer plexiform layer in the retina to the inner portion of the choroid known as the choriocapillaris (CC). This outer-retina-to-choriocapillaris slab is referred to as the ORCC slab.

Once the NV is identified using the ORCC slab, choosing slabs that further localize the position of the NV can further refine the image. To refine visualization of type 2 or type 3 NV, it is possible to segment a slab from the outer border of the outer plexiform layer to the RPE, and for viewing type 1 NV and PCV, it’s then possible to pick a slab that extends from the RPE to the CC. This simple strategy allows for the identification of all macular NV while also locating the NV to the appropriate macular compartment.
Detection and Management of Subclinical CNV in Nonexudative AMD

Since the histopathological studies of Sarks and Green in the 1970s, we’ve known that eyes with drusen could harbor nonexudative NV. In the 1990s, two groups using indocyanine green (ICG) angiography validated these observations and identified plaques and hot spots in eyes with assumed nonexudative AMD. In these studies, the fellow eyes of these patients had established exudative disease. During follow-up, these investigators showed that the nonexudative eyes containing ICG abnormalities were at a higher risk for active exudation than eyes without these ICG findings. Now OCT-A can identify these subclinical neovascular lesions.

Recently, we expanded on our original observation and followed 160 eyes with nonexudative AMD and showed that eyes with subclinical neovascular disease are at a 15-fold higher risk for exudation over 12 months than eyes without these subclinical lesions. We do not recommend treatment of these subclinical lesions with inhibitors of vascular endothelial growth factor (VEGF), since the majority of these eyes have excellent vision and may not necessarily develop exudation even though these lesions grow. After all, if anti-VEGF therapy is started for lesions in the absence of exudation, when would the treatment ever stop? While treatment is not recommended, we do recommend close follow-up every 2-3 months and daily home monitoring.

The Role of OCT-A in the Active Management of CNV and PCV

OCT-A has been very useful in diagnosing, characterizing, and following the changes that occur to macular NV while undergoing anti-VEGF therapy. Several groups have developed nomenclatures to help characterize the changes that occur to NV during the course of therapy. The hope was that these descriptive characteristics might be helpful in determining the need for retreatment. However, there haven’t been any studies showing that the OCT-A appearance of NV alone can be used to determine the need for retreatment.
Until these studies are done, we will continue to depend on the structural OCT information, such as the retinal thickness and RPE maps, in addition to the cross-sectional B-scans, to determine retreatment when using either a p.r.n. or treat-and-extend regimen. However, when the clinician is uncertain whether retreatment is needed after reviewing the structural OCT information, then OCT-A may prove useful in assessing the growth of NV in the absence of exudation, and if the growth of NV is shown to serve as a harbinger of recurrent exudation, then OCT-A may be useful in guiding retreatment.

Another valuable use of OCT-A is in identifying whether NV is even present when macular fluid is present. Conditions that may masquerade as macular NV include large nonvascularized serous pigment epithelial detachments in AMD, drusen with associated subretinal fluid, chronic central serous chorioretinopathy, vitelliform maculopathies, and choroidal nevi with subretinal fluid, just to name a few. Treatment may depend on whether OCT-A can identify a neovascular lesion.

Summary

OCT-A is a powerful, noninvasive imaging strategy for the diagnosis of macular NV. SS-OCT-A appears to be superior to SD-OCT-A for the visualization of neovascular lesions under the RPE. Different en face imaging strategies and retinal vessel projection artifact removal algorithms have been developed to help facilitate the diagnosis and characterization of macular NV. While the ORCC slab is an ideal screening strategy for determining the presence of NV, more refined segmentation strategies are useful to further locate the NV as being above or below the RPE. Currently, OCT-A has proven very useful in assessing whether macular NV is present, but it remains unclear whether the en face flow images from OCT-A provide any additional value over the OCT structural images when determining retreatment with anti-VEGF therapy. The combination of en face flow and structural images, along with the different segmentation strategies used to visualize macular NV and macular fluid, clearly demonstrate that OCT-A provides multimodal imaging from a single imaging modality, and all these images are provided from a single OCT scan.

References

Redefining Atrophy in the Era of OCT and Multimodal Imaging

Srinivas R Sadda MD

I. Rationale for Redefining Atrophy
   A. Multiple pathways of atrophy are now known to exist.
      1. Drusen-associated atrophy
      2. CNV-associated atrophy
      3. Pseudodrusen-associated atrophy
   B. Multimodal imaging technologies are now broadly available, and OCT has become of primary importance.
   C. Need for recognition of earlier stages: Current trials may be targeting a point which is too late.

II. Process for Developing a New OCT / Multimodal Definition

   Organization of Classification of Atrophy Meeting (CAM) consensus group
   A. International panel of experts in imaging, histopathology, reading centers, AMD
   B. Pre-meeting exercises to assess level of agreement / disagreement
   C. Cases with longitudinal multimodal imaging to allow determination of the first point at which atrophy became evident
   D. Three end-points required to be defined by CAM investigators:
      1. Complete / end-state atrophy
      2. Incomplete / partial atrophy
      3. No atrophy but high-risk features
   E. Consensus discussions over the course of 3 meetings in a 1-year period
   F. Advantages and disadvantages of various imaging technologies were reviewed.

III. Consensus Results

   A. Fundamental principles
      1. Atrophy to be defined by the layers involved: photoreceptors and/or retinal pigment epithelium (RPE)
      2. Atrophy to be defined based on the level of completeness: complete or incomplete
      3. OCT to serve as base or reference modality to define atrophy, with other modalities used for confirmation
   B. Four new terms were introduced:
      1. Complete RPE + outer retinal atrophy, defined by the following (all criteria required):
         a. Presence of hypertransmission of ≥ 250 micrometers
         b. Presence of a zone of attenuation / disruption of RPE ± basal laminar (BL) complex of ≥ 250 micrometers
         c. Evidence of overlying photoreceptor degeneration whose features include all of the following: outer nuclear layer thinning, external limiting membrane loss, ellipsoid zone / interdigitation zone loss
         d. Absence of signs of an RPE tear
      2. Incomplete RPE + outer retinal atrophy, defined by the following (all criteria required):
         a. Some hypertransmission must be present, but often discontinuous
         b. Some irregularity of RPE ± BL complex
         c. Detectable photoreceptor degeneration, signs of which can include “wedge,” “subsidence”
         d. Absence of signs of an RPE tear
      3. Complete outer retinal atrophy defined by the following (all criteria required):
         a. Continuous loss of ellipsoid zone
         b. Severe thinning of outer retina
         c. Intact RPE band
      4. Incomplete outer retinal atrophy defined by the following (all criteria required):
         a. Subretinal drusenoid deposits with detectable ellipsoid zone
         b. Detectable thinning of the outer retina
Disease Expression in AMD Is Correlated with Choroidal Thickness

Richard F Spaide MD

Drusen are focal accumulations of extracellular material in the posterior pole of the eye between the basal lamina of the retinal pigment epithelium (RPE) and the rest of the Bruch membrane. Descriptive terms have been used to help differentiate various phenotypes of drusen: “hard” and “soft” are examples. Determination of hard and soft is a subjective matter, but it was recognized that hard drusen are small and soft drusen are larger, so the size of the drusen became an attribute used to grade levels of severity of AMD. Accumulations of medium drusen (63-125 µm) or the appearance of a single large drusen (> 125 µm) constituted the threshold to diagnose AMD in the Age-Related Eye Disease Study (AREDS). In analyzing data from AREDS, Klein and associates found that focal hyperpigmentation developed in some patients after the appearance of drusen. Focal hyperpigmentation was an independent risk factor, along with drusen, for the development of late AMD, which they defined as either geographic atrophy (GA) or choroidal neovascularization (CNV). This formed a model of AMD as presented by investigators of the AREDS.

Although this model was quickly accepted as doctrine, several preceding concepts of disease were not integrated into this construct. In 1990 Mimoun, Soubrane, and Coscas described patients with pseudodrusen that were best seen in blue light. The authors thought pseudodrusen were not actual drusen, but rather constituted an appearance that arose from the choroid. In the Wisconsin Reading Center classification, used in the Beaver Dam studies and in the AREDS, a similar appearing manifestation was thought to be a severe form of soft drusen. In the grading done for AREDS, the designation of “soft drusen” could really mean the patient might have soft drusen, soft drusen with pseudodrusen, or pure pseudodrusen. The risk attributed to soft drusen in that study was an indeterminate amalgamation of risk from soft drusen and pseudodrusen combined. Later OCT imaging and histopathology both showed pseudodrusen were collections of material under the retina (not under the RPE), called “subretinal drusenoid deposits” (SDD), a term preferable to “pseudodrusen.” “Pseudo” plus “drusen” means “false drusen,” which signifies that the collections are not drusen but does not indicate what the collections are. SDD were found to be associated with thin choroids, while soft drusen were associated with normal-thickness choroids.

Also in 1990, an unusual pattern of branching vessels with discrete saccular enlargements leading to serous and hemorrhagic detachments of the RPE was described. At first it appeared that idiopathic polypoidal choroidal vasculopathy, as it was called, was a rare condition, but soon it was determined that the disease accounted for half of the cases of CNV in Asia. In 1992 and 1996 Hartnett and coworkers described a deep retinal neovascularization seen in older eyes that originated from the retina. This was later called “retinal angiomatous proliferation” and even later was known as “type 3 neovascularization.” These cases do not necessarily have choroidal contributions to the neovascularization, particularly in early disease.

Thus the 2008 model requires several important caveats. Soft drusen were not necessarily that, as SDD in any mixture with soft drusen were graded as soft drusen. Type 3 neovascularization does not necessarily have a choroidal component, and thus cannot accurately be characterized as CNV. Finally, in a histopathologic study Sarks showed that in a series of 46 eyes with GA, 15 had unsuspected CNV. Thus the 2008 model is grossly incomplete; consequently, it has limited capability to explain or predict later stages of disease. The hallmark of a sound theoretical construct is that it not only explains disease but also has prognostic capabilities.

Gass originally established that drusen and CNV were parts of AMD, but none of these newer conditions were recognized when he wrote his seminal papers. Since then many new and powerful forms of ophthalmic imaging have been developed. Genetic testing, not possible in the time of Gass, has discovered risk alleles for AMD. Information gleaned from patient series, case-control, and follow-up studies have helped quantify risk. These newer factors have raised important questions about how AMD should be defined. One approach would be to conclude that SDD, type 3 neovascularization, and potentially polypoidal choroidal vasculopathy are not part of a larger spectrum of AMD. This is an easy way out, since there would be no need for changes in the old definition of AMD. The downside is having to use an incomplete classification system that lacks consistency with observed facts, as will be discussed in the following sections, examining each in turn.

Pachydrusen

More recently a new type of drusen form has been delineated. The name for this type of drusen was a portmanteau of “pachychoroid” and “drusen,” yielding “pachydrusen.” This type of drusen has notable differences from conventional soft drusen. They are generally greater than 63 µm in diameter, are irregular in shape, have a sharply defined border, and are scattered across the posterior pole. Soft drusen typically are round or ovoid, have poorly defined borders, and aggregate in the central macula. Soft drusen can have pigmentation on their upper contour, while pachydrusen have pigmentary changes between. The choroid in-between drusen shows vascular markings, while in eyes with pachydrusen the fundus has a reddish-orange hue with little in the way of vascular markings. Both soft drusen and pachydrusen are found under the RPE.

Choroidal Thickness and Nonexudative AMD

The nonexudative manifestations of AMD can be thought of as accumulations of specific extracellular deposits in the neighborhood of the RPE. More precisely, drusen and pachydrusen are accumulations of extracellular material below the RPE, while pseudodrusen are deposits on top of the RPE, and thus the name “subretinal drusenoid deposits.” SDD are more commonly found in eyes with thinner choroids. Soft drusen are
typically found in eyes with normal choroidal thicknesses, and pachydrusen are found in eyes with thicker choroids.

Although these are different manifestations, there are no large differences in the risk alleles between eyes with SDD and those with soft drusen.23-26 Thus it would be difficult to predict the presence of SDD vs. soft drusen based only on risk alleles. Knowing the choroidal thickness would help improve the predictive capability. The presence of SDD is highly associated with the development of outer retinal atrophy, GA, and type 3 neovascularization, and each of these has been associated with a thinner choroid.

Eyes with thicker choroids may develop macular neovascularization with aging. The risk alleles in a group of these patients did not differ from those seen in typical AMD.23 Polypoidal choroidal vasculopathy has a different phenotypic manifestation than conventional macular neovascularization, and is typically found in eyes with thicker choroids.24-26 Polypoidal choroidal vasculopathy shares similar risk allele profiles with neovascularization in AMD. Thus the differences in phenotypic manifestation do not appear to hinge on the risk alleles but on other factors, including choroidal thickness and race.

These considerations raise the possibility that there are risk alleles that alter the propensity to develop AMD and that perhaps separate genes may influence how the disease is manifest once it appears. These disease-modifying genes would not appear to be significant or apparent if all groups of AMD are lumped together, but if the subtypes were analyzed, their significance could become more clear.

### References


New Imaging Findings in Pathologic Myopia

Kyoko Ohno-Matsui MD PhD

Pathologic myopia (PM) is a major cause of visual impairments worldwide and especially in east Asian countries. The visual impairments are located in the macula and optic nerve, and they are specific to PM. The main cause of these complications is the eye deformity represented by posterior staphylomas.1

Recent advances in ocular imaging have contributed significantly to the clinical management of PM. OCT, especially enhanced-depth imaging OCT and swept source OCT, has allowed clinicians to make accurate diagnoses and to monitor the effectiveness of treatments for eyes with macular complications, such as myopic CNVs and myopic traction maculopathy. In addition, new pathologies such as dome-shaped maculas have been identified by the newer OCT devices.2 The ability to examine the alterations in the deeper structures, such as intrachoroidal cavitation and disc pits / conus pits in the papillary and peripapillary regions, has allowed clinicians to determine whether these lesions can account for the visual field defects in eyes with PM.

The information obtained by wide-field fundus imaging has provided important insights on PM because the affected areas in these eyes are not necessarily restricted to the posterior segment. Wide-field angiography has clarified the changes occurring in the retinal and choroidal circulation spanning the entire fundus, such as the presence of retinal avascularity at 360 degrees3 and choroidal vascular remodeling, including the formation of macular vortex veins.4 Such circulatory alterations in the retina and choroid could predispose the eyes with PM to develop vision-threatening complications.

Imaging of Eyes with Posterior Staphylomas

Posterior staphyloma, a hallmark alteration of eyes with PM, has been defined by Spaide1 as an outpouching of the ocular wall with a radius of curvature shorter than that of the surrounding ocular wall. Highly myopic eyes with posterior staphylomas have significantly worse visual and anatomical consequences than highly myopic eyes without staphylomas. Despite their importance, the description of posterior staphylomas has been based mostly on 2-dimensional ophthalmoscopic examinations. Recently, Moriyama and colleagues applied 3-dimensional MRI (3D-MRI) to examine and classify posterior staphylomas.5 3D-MRI has the advantage of being able to view the shape of the entire eye, including the anterior segment. However, 3D-MRI has a relatively low spatial resolution and is not feasible as a screening technique.

OCT has been used to analyze the curvature of the sclera in eyes with PM. Due to the limited scan length and depth of penetration of the imaging light, the earlier OCT devices were limited in their usefulness in viewing the posterior staphylomas. A new prototype of a wide-field swept source OCT device allows the 3-dimensional reconstruction of a posterior staphyloma image in the region of interest with a size of 20 mm × 14 mm and a depth of 5 mm. With the wide-field OCT, it is possible to examine images of posterior staphylomas in highly myopic eyes in their full three-dimensional extent. The data obtained by such imaging may be an important first step for future therapies targeting staphylomas before vision-threatening complications develop.

Swept Source OCT Imaging of Macular Complications due to PM

Swept-source OCT imaging has allowed clinicians to characterize each type of lesion in eyes with myopic maculopathy. These lesions include diffuse chorioretinal atrophy, patchy chorioretinal atrophy, lacquer cracks, myopic CNV, CNV-related macular atrophy, and a relatively new pathology called dome-shaped macula. Diffuse atrophy is characterized by an extreme thinning, almost an absence, of the choroid. In addition, such imaging has shown that patchy atrophy and CNV-related macular atrophy are not simply atrophies of the retina-choroid but also have defects of the Bruch membrane.

Wide-Field Imaging of Retinal and Choroidal Circulation

Images of 360 degrees of the peripheral retinal avascular area have been obtained by wide-field fluorescein angiography. These images have shown choroidal vascular remodeling in eyes with PM, the presence of vortex veins in the macula, and a downsizing of the perfused area by the usual vortex veins in the equator.

Imaging Eye Deformities in Eyes with a Posterior Staphyloma

A 3D MRI technique to observe the shape of the eye as a whole.

Figure 1.
Wide-field OCT can obtain images of posterior staphylomas in highly myopic eyes in a resolution and size unachievable so far, and it may replace 3D-MRI in assessing posterior staphylomas. Wide-field OCT is expected to become an important tool to examine staphylomas objectively and quantitatively for many patients as a screening device.

References
Late Breaking Developments, Part II

Moderator: Joan W Miller MD

Panelists: J Fernando Arevalo MD FACS, Mark Humayun MD PhD, Elias Reichel MD, Demetrios Vavvas MD

Systemic vs. Fluocinolone Acetonide Implant Therapy for Intermediate, Posterior and Panuveitis: 7 Year Results of the MUST Trial and Follow-up Study

John H Kempen MD

Clinical Evaluation of eSight—A Head Borne Video System for Maculopathy Induced Low Vision

Robert G Devenyi, MD, FACS, FRCSC, MBA

A Phase 1b Clinical Safety Study of a Novel Tumor Targeted Therapy (AU-011) for the Treatment of Primary Choroidal Melanoma

Carol L Shields MD

Protocol U: Short-Term Evaluation of Combination Dexamethasone + Ranibizumab vs. Ranibizumab Alone for Persistent Central-Involved DME Following Anti-VEGF Therapy

Raj K Maturi MD
Displacement of Submacular Hemorrhage in AMD Improves Visual Outcomes: Pro

Sunir J Garg MD FACS

Thick submacular hemorrhage causes significant vision loss in some eyes with exudative AMD. Surgical displacement can improve vision in a number of these cases. Administration of post-vitrectomy anti-VEGF injections helps maintain the visual acuity gains.
Displacement of Submacular Hemorrhage in AMD Improves Visual Outcomes: Con

Jeffrey G Gross MD

The natural course of untreated submacular hemorrhage (SMH) secondary to neovascular age-related macular degeneration (nAMD) is typically severe vision loss and disciform scarring. Larger and thicker SMHs are historically associated with worse visual outcomes. Observational studies demonstrate that patients not receiving treatment have a mean final visual acuity of 20/1250.1

Nonsurgical pneumatic displacement procedures were developed to manage SMH by displacing the hemorrhage away from the macula with the goal of improving visual outcomes. These procedures involve intravitreal gas injection, with or without intravitreal tissue plasminogen activator (tPA).2,3 Although anatomic displacement is successful in many cases, incomplete displacement is common and this technique may not be advised for SMH in a supramacular location. Average final visual results at 1 year were lower than immediate postprocedure results in nearly all studies. Nonsurgical displacement techniques are associated with severe complications. The most common are vitreous hemorrhage and retinal detachment. Surgical procedures include pars plana vitrectomy (PPV) with direct evacuation of the hemorrhage, PPV with partial gas–fluid exchange (GFX) and intravitreal tPA, PPV with GFX and subretinal tPA, and more recently PPV with subretinal air, subretinal tPA, and GFX. Although successful in rapidly displacing the SMH, the long-term vision results without supplemental anti-VEGF have been disappointing.4-6 A recent study of 101 eyes showed visual acuity improving from 20/2250 to only 20/1150 and 3-line improvement in only 20% of eyes.5 Surgical techniques are associated with severe complications such as vitreous hemorrhage, retinal detachment, recurrent thick SMH, and macular hole formation.5,6

A less invasive and successful management uses anti-VEGF monotherapy to treat SMH by inhibiting the underlying pathology and facilitating reabsorption of the SMH. Small as well as large and thick SMHs can be managed safely, resulting in resolution of the subfoveal component within 3-4 months.7,9 Visual outcomes in several observational studies requiring a 3-line difference demonstrated an average of 37% with a 3-line improvement; 54%, stable; and only 9% worse than 3 lines.8 Recent studies demonstrate 3-line improvement in 60% of eyes and mean vision of 20/125 to 20/156 at 12 months.7,9 Most studies have not reported any serious adverse effects. Of those that did, the most common complication was VH requiring PPV in 4% of eyes. Anti-VEGF monotherapy may be a preferred treatment for SMH secondary to AMD because it is convenient, effective, and associated with considerably fewer complications than pneumatic or surgical displacement intervention while achieving similar visual outcomes.10

References

Widefield Imaging Is Necessary in Practice: Pro

*Steven D Schwartz MD*

Advances in retinal imaging technology over the last 50 years have enabled transformative shifts in the diagnosis and management of retinal disease. With each successive improvement in scanning laser ophthalmoscopy, angiography, autofluorescence, and OCT, our understanding of retinal and choroidal pathology has become increasingly rich and textured with the additional information each imaging modality provides.

Ultrawide-field imaging has become an essential tool for the identification of peripheral retinal and vascular pathology. The high resolution and multimodal capabilities of this device are also providing new insights into a variety of disorders, even those that primarily involve the posterior pole. Ultrawide-field is evolving to become the standard-of-care imaging modality for many diseases and is finding new clinical and research applications such as screening and telemedicine.

**Selected Reading**

Widefield Imaging Is Necessary in Practice: Con

Rajendra S Apte MD PhD

Although widefield imaging has revolutionized the ability of physicians to better diagnose, quantify, and treat retinal disease, it does not replace the granularity and the art of a comprehensive funduscopic examination. Fundamental discovery and progress in understanding the pathobiology of retinal disease was achieved by forward-thinking retinal specialists using their clinical observations to make rational hypotheses that were then tested with novel therapeutic approaches. Excessive reliance on technology to make clinical diagnoses and decisions will hamper this process of intelligent discovery, which has led to tremendous advances in molecular medicine, precision medicine, and surgical technology in our field. Descartes said “I think, therefore I am.” As surgeon scientists, the moment we forget this axiom and rely on technology to do the thinking for us, we will lose the creativity that is a defining characteristic of retinologists, ultimately leading to lack of innovation. In addition, cost considerations will make it imperative that we limit indiscriminate utilization of ever-expanding imaging technologies in clinical care.
Chandelier Scleral Buckling Is Better than Conventional SB: Pro

Jason Hsu MD

Primary scleral buckling (SB) has changed little since the 1960s, while vitrectomy has rapidly evolved. Between 2005 and 2013, the routine recommendation to perform SB alone for retinal detachment fell from 27% to 9%. Despite this shift to vitrectomy, we have not seen a significant improvement in outcomes. Furthermore, SB may be the better choice in some cases, such as young patients without a posterior vitreous detachment. However, few fellows are receiving enough training to feel comfortable with performing primary SB. How can we prevent the extinction of this tried and true technique? It must evolve. Imagine performing a vitrectomy for retinal detachment using a 20 D lens and indirect ophthalmoscope. Why do we continue to do this with buckles? Chandelier illumination with wide-angle viewing is the first critical step toward preserving and further enhancing primary SB.

Reference
1. American Society of Retina Specialists Preferences and Trends (PAT) Survey.
Chandelier Scleral Buckling Is Better than Conventional SB: Con

Edwin Hurlbut Ryan Jr MD

Chandelier scleral buckling is not better than conventional scleral buckling, for several reasons. First, it is an additional, unnecessary step that poses the risk of lens trauma as well as vitreous loss. Second, it adds more expense, unnecessary use of equipment, and time. Third, it is an acknowledgment of inadequate indirect ophthalmoscopic skill acquisition in the current generation of trainees. If they can’t see pathology in the OR, what are they missing in the office?
Macular hole became a curable disease after the publication of a paper by Kelly and Wendel in 1991. Different adjuvants were investigated to improve the anatomical and functional results, without any final consensus. By the beginning of the 21st century, the benefit of vitrectomy, circumferential internal limiting membrane (ILM) peeling around the macular hole, and gas injection were established as a method of choice for macular hole. This classical approach is widely accepted in current ophthalmology.

The inverted internal limiting membrane flap technique (flap technique) was first performed by one of the authors (JN) in 2006 and first presented by us in a video in 2009 (by which time we had already operated on a few hundred macular hole cases), and then as a paper in 2010. The aim of developing the new technique was to prevent the flat open appearance of macular hole postoperatively. The initial method was vitrectomy, peeling of the ILM around the macular hole up the margins of the hole without detaching the ILM. Then ILM flaps were trimmed and put in an inverted fashion on the top of the macular hole. This position was secured with fluid–air exchange. The first video was awarded Best of Show at major international meetings (American Society of Retina Specialists, European VitreoRetinal Society, German Ophthalmological Society).

Our first paper presented a prospective comparative study comparing the flap technique to the classical approach in large macular holes. We found statistically significantly higher closure rate (98% vs. 88%), less “flat open” closure type (2% vs. 19%), and better functional outcome 1 year after flap technique (0.28 vs. 0.17).

The first to show an interest in this technique were Japanese and Indian ophthalmologists who confirmed our results in large and myopic macular holes. In 2013, 3 papers were published; in 2014 there were 5 new papers; in 2015, 9; and in 2016, 18. All of the papers confirmed the efficacy of the flap technique in large and myopic macular holes with and without retinal detachment.

Subsequently, modifications of the technique were developed. Our group presented the temporal inverted ILM flap technique, where an ILM flap is peeled only from the temporal side of the macular hole and used to cover macular hole on the surface of retina. ILM was not peeled in the remaining area around the macular hole. Similar techniques were also developed in Japan and Korea. Chen and Yang demonstrated that the lens capsule may also be used to close the macular hole after failed surgery. Morizane et al developed a free flap technique, and Grewal and Mahmoud even proposed a free retina flap transplantation. Chakrabarti et al used autologous blood as a “glue” for ILM flap and did not use any tamponade for macular hole surgery.

Controversy continues about the necessity of incorporating the inverted ILM flap technique into conventional vitrectomy. Many ophthalmic surgeons have satisfactory results with the classical approach and thus do not see a reason to perform the inverted ILM flap technique. However, especially in more difficult cases, all published papers are in favor of this new technique.

The presenting author would like to offer arguments supporting the use of the inverted ILM flap technique in macular hole surgery.

References

Internal Limiting Membrane Flaps Are Needed to Optimize Macular Hole Closure: Con

William E Smiddy MD

The anatomic and visual results may not correlate in certain treatments. The discriminating physician and patient must weigh the functional benefits and the incumbent risks of this, or any, treatment intervention.
27-gauge vitrectomy provides significant advantages in the management of a number of pathologies. The benefits are more dramatic in traction and rhegmatogenous retinal detachments. Specific techniques to repair these detachments can only be performed with 27-gauge vitrectomy. Maneuvers that can be safely executed with 27-gauge vitrectomy probes include blunt dissection, shaving tissue from vessels, lift and shave techniques, and peeling epiretinal membranes and internal limiting membranes with the vitrector. The exquisite flow control that can be achieved with 27-gauge vitrectomy allows for increased safety during maneuvers on the surface of the retina. Recent publications underscore the reduced complications noted with 27-gauge vitrectomy, namely, reduced hypotony, postoperative bleeding, and iatrogenic breaks.1-3

References
27-gauge Vitrectomy Is an Essential Platform: Con

John S Pollack MD

While there is a place for 27-gauge vitrectomy in our surgical armamentarium, its role is limited. For most retina surgeries, the potential benefit of instrumentation over 25- or 23-gauge is limited. In many situations, 27-gauge instruments make surgery more difficult rather than easier. Therefore, 27-gauge vitrectomy is not an essential vitrectomy platform.
Retinoblastoma Genetic Testing: Who Needs It and Why?

Carol L Shields MD

I. Basic Facts about Retinoblastoma (Rb) Genetics

A. Classic Rb is caused by a mutation in the Rb gene on chromosome 13.
   1. Somatic Rb: If mutation occurs in tumor only (not blood), then it’s a somatic mutation; presume that there is no mutation elsewhere in the body. These patients are at risk for only 1 tumor in 1 eye and no other problems.
   2. Germline Rb: If mutation occurs in blood and tumor, then it’s a germline mutation; presume the mutation is in every cell of body.
      a. At risk for multiple, bilateral Rbs, pinealoblastoma of brain, and remote second cancers
      b. Survival with pinealoblastoma was 6% before 1995; 44% since 1995.

B. Odd mutations in some children
   1. Mosaic Rb: The Rb mutation arises after egg fertilization, so only a fraction of the patient’s cells are affected. This is not inherited from parents but can be passed to progeny if germ cells are affected.
   2. Low penetrant Rb: The Rb mutation is partially functional, so affected patients have fewer tumors, more unilateral disease, more unaffected carriers, more skip generations.
   3. MYCN Rb: It is estimated that 97% of Rb is caused by Rb1 mutation on chromosome 13 and that 1%-3% occur at MYCN mutation. These are usually very young patients with unilateral advanced Rb.

II. Who Needs Genetic Testing?

   All Rb Children
   A. We know bilateral and familial disease will have germline mutation in 100% of cases.
   B. Anticipate unilateral sporadic disease to have germline mutation in 15% of cases.

III. Where to Get Genetic Testing?

   Several centers (no financial interest)
   
   A. Browse www.genetests.org and search for “retinoblastoma gene testing”
   B. University of Pennsylvania Genetics Department
      1. website: www.med.upenn.edu/genetics/gdl/
      2. email: gdlab@mail.med.upenn.edu
   C. Impact Genetics: http://impactgenetics.com

IV. Why Do Genetic Testing?

   A. To understand patient risks for bilateral Rb, pinealoblastoma, and second cancers
   B. To engineer the Rb mutation out of family genome by preimplantation genetic diagnosis. This eliminates the mutation for future progeny.

Selected Readings

Expanding Clinical Spectrum of Ocular Melanocytomas

Jerry A Shields MD and Carol L Shields MD

One-Sentence Objective

Ocular melanocytoma was initially described by Zimmerman as a benign tumor that occurred on the optic disc and had typical clinical and histopathologic features.

Purpose

The purpose of this presentation is to highlight new observations on ocular melanocytomas that were seen in an ocular oncology service and to describe the expanding spectrum of these tumors based on further clinical and/or histopathologic observations.

Methods

We reviewed more than 400 patients coded with a diagnosis of melanocytoma. Most of them were also subclassified as a nevus for coding and retrieval purposes, because in reality melanocytoma is an atypical variant of melanocytic nevus. We reviewed charts of patients seen in our ocular oncology service and specifically identified those that had new findings that were not previously well known in the earlier literature.

Results

We identified cases of melanocytoma that involved the optic disc, choroid, ciliary body, and iris. Those in the choroid were dark brown to black in color, and none were amelanotic. They resembled a typical nevus or low-grade melanoma. Optic disc melanocytomas showed growth in about 20% of cases. In the early part of this review some eyes were enucleated and were diagnosed as melanocytoma or very low-grade melanoma, but none developed metastasis. The vision in optic disc and choroidal melanocytomas varied from 20/20 to no light perception, the latter being due to severe necrosis in the tumor. Secondary central retinal vein obstruction and central retinal artery obstruction developed in 2 separate cases.

Iris melanocytomas were found to have very typical clinical findings that are unlike those of other iris nevi. They usually have a uniform dark brown to black color. A very distinct feature in many cases is a granular multinodular surface that is highly characteristic and quite different from the typical iris nevus. Some iris melanocytomas showed enlargement but were believed to be benign despite slow growth, and some were confirmed histopathologically. In the early part of this study, iris tumors showing growth were treated with iridectomy or iridocyclectomy, but it was eventually found that they were benign pathologically despite the clinical enlargement.

A rare but impressive variant seen in some iris melanocytomas is an extremely large mass that sheds extensive pigment over the entire iris and into the angle. We have seen 3 such cases of this “giant” iris melanocytoma in children in the first decade of life, all of which were confirmed histopathologically.

Conclusion

Our knowledge of ocular melanocytoma has changed greatly in recent years since the original descriptions. It is now known that this tumor can occur not only in the optic nerve but also in the iris, ciliary body, and choroid, where they may have very typical features. The vast majority of melanocytomas are benign, and transformation into low-grade melanoma is extremely rare.

Selected Readings

Advances in Prognostic Biopsy for Uveal Melanoma

Tara A McCannel MD PhD

Molecular testing in uveal melanoma at the time of treatment can reveal whether there is a lower or higher risk of metastasis. Determining metastatic risk is valuable to both the patient and the health-care team. Studies assessing the desire to know molecular prognostic test results have shown that patients want as much information about their cancer as possible, and the oncologist may oversee a screening program for systemic surveillance or consider a clinical trial for a high-risk patient.

Information Provided by Biopsy

Cytopathology

The most common type of intraocular tumor of adults is a metastatic tumor to the choroid. Patients with choroidal melanoma may have a past medical history of cancer, such as breast, lung, colon, or prostate. It may be helpful to the patient’s general oncologist to confirm that the cancer in the eye does not represent metastatic recurrence of another primary malignancy. Furthermore, some metastatic tumors may have a similar clinical appearance to a primary choroidal melanoma.

Molecular prognosis

Biologic markers can be identified that help predict a patient’s risk for developing choroidal melanoma metastasis. The molecular risk factor most strongly associated with metastasis is monosomy 3, the loss of a whole copy of chromosome 3 in the tumor tissue. Additional chromosomal aberrations in uveal melanoma occur on chromosomes 6 and 8. Tests that assess chromosomal aberrations use DNA-based platforms. Both DNA and RNA can be analyzed from the tumor to determine prognosis.

In addition to institution-based DNA-based protocols, such as fluorescent in-situ hybridization (FISH), single nucleotide polymorphism (SNP) analysis, or next-generation sequencing (NGS), most ophthalmic oncology centers include commercially available testing platforms to provide prognostic information to patients. At this time, there are 2 available commercial tests, a multiplex-ligation probe amplification (MLPA) test, which is a DNA-based test by Impact Genetics (LabCorp, USA), and a gene expression profile (GEP) test, an RNA-based test by Castle Biosciences.

The MLPA test

Copy number testing using the MLPA technique is performed on chromosomes 1p, 3, 6, and 8 from a biopsy sample. Monosomy 3 portends a high risk for metastasis. Chromosome 8q gain combined with monosomy 3 portends a worse prognosis than monosomy 3 alone. In samples where no monosomy 3 is detected (ie, disomy 3), additional sequencing for a GNAQ or GNA11 mutation, SF3B1 mutation, and EIF1AX mutation are performed. These GNA mutations are related to tumor development and are found in over 90% of all uveal melanoma. They also confirm that actual melanoma tumor tissue was submitted for analysis. A mutation in SF3B1 without monosomy 3 indicates risk for late-onset metastasis, and an EIF1AX mutation is associated with good prognosis.

The GEP test

The expression of a panel of genes is analyzed in the tumor tissue submitted. The pattern of over- and/or underexpressed genes is matched to either a class 1 (good prognosis) or a class 2 (poor prognosis) profile. Class 1 is further divided into a class 1A and class 1B. Recently, Castle Biosciences added a test for PRAME1, a biomarker associated with metastatic risk, to help identify those at risk for late-onset metastasis.

BAP1 mutation testing

A mutation in the BRCA-associated protein-1 (BAP1) gene, located on chromosome 3, results in loss of expression of this tumor suppressor gene in choroidal melanoma tissue. BAP1 mutations are highly correlated with a poor prognosis for metastasis in choroidal melanoma. BAP1 testing can be performed by sequencing, or immunohistochemical staining for BAP1 protein can be evaluated on a cytopathology smear (author, unpublished data). BAP1 mutation, presence of monosomy 3, and class 2 in choroidal melanoma are often found together in a patient at high risk for metastasis.

Multiple prognostic tests may offer a more complete picture for the patient. A class 1A may underestimate metastatic risk in 20% of patients. A patient may want to know both the class and the monosomy 3 status, as both provide more risk information.

Methods for Performing Biopsy

Transscleral biopsy

Transscleral biopsy is a straightforward approach to obtaining tissue, and when possible we recommend that this approach be the first consideration when a fine-needle aspiration biopsy is planned. After the tumor is identified on the sclera with transillumination, the biopsy can be performed. If a sufficient sample yield results from the first pass, the surgeon can use the same site (or be in the near vicinity) for subsequent needle passes.

Transvitreal biopsy

Nonvitrectomy approach: This technique involves using a binocular indirect ophthalmoscopy to visualize the tumor, and passing a needle from a trans–pars plana location opposite to the tumor. The biopsy involves movements that are reversed and upside-down to one’s actual view.

Vitrectomy approach: Most ophthalmic oncologists who are vitreoretinal surgeons may be more comfortable with incorporating wide-field imaging from an operating room microscope and a standard small-gauge vitrectomy setup when considering a transvitreal biopsy. More variations in technique are possible with vitrectomy transvitreal biopsy, particularly when obtaining tissue may be challenging.
Summary

Fine-needle aspiration biopsy provides important information for patients regarding the metastatic potential of their choroidal melanoma. The most important reason to become skilled in performing tumor biopsy is to inform patients of their prognosis. Evolving vitrectomy techniques allow for biopsy in even very small tumors. We recommend that ophthalmic oncologists become familiar with various tumor biopsy techniques to improve the chances of obtaining sufficient material for prognostic testing.

References

Paraneoplastic Retinal Conditions

Anita Agarwal MD

I. Paraneoplastic Disorders
   A. Benign diffuse uveal melanocystic proliferation (BDUMP)
   B. Cancer-associated retinopathy
   C. Melanoma-associated retinopathy
   D. Paraneoplastic vitelliform maculopathy
   E. CRMP5-associated rod cone degeneration

II. Case: 78-Year-Old White Woman
   A. “Everything looks dark,” 4 months
      1. VA: 20/70 O.U.
      2. IOP: 15 and 16
      3. 1-2 + nuclear sclerosis O.U.
      4. Anterior chamber and vitreous clear O.U. (see Figures 1 and 2)
   B. Medical history
      1. Healthy except for hypertension
      2. No known cancer

C. Differential diagnosis
   1. Idiopathic uveal effusion syndrome (IUES)
   2. BDUMP
   3. Uveal lymphoma
   4. ? Other cause

D. Lymph node biopsy: cytokeratin-positive ovarian cancer
   1. USG: ovarian tumor
   2. PET scan: supraclavicular lymph node and right ovary positive

III. Cancer-Associated Retinopathy
   A. Often predates the diagnosis of cancer
   B. Presents with acute onset of photopsias and rapidly progressive night blindness evolving into day and night blindness, difficulty with central vision and color vision
   C. Associated antibodies
      1. Recoverin (23 kDa)
      2. Enolase (46 kDa)
      3. Arrestin (48 kDa)
      4. Carbonic anhydrase II (CAII, 30 kDa)
      5. Tubby-like protein 1 (TULP1, 78 kDa)
      6. Interphotoreceptor retinoid-binding protein (IRBP, 145 kDa)
7. Heat shock cognate protein 70 (hsc-70, 70 kDa)
8. Photoreceptor cell-specific nuclear receptor (PNR, 41 kDa)

D. Fundus
1. Normal initially
2. Later: retinal pigment epithelial mottling, vascular attenuation

E. Histology: loss of photoreceptors

IV. Melanoma-Associated Retinopathy
A. Often occurs after a known diagnosis of cutaneous melanoma
1. Average time: 18 months after melanoma diagnosis
2. Most often associated with cutaneous melanoma
3. Only 2 cases with uveal melanoma
4. One case with nasal mucosal melanoma
B. Affects bipolar cells
C. Antibodies against:
   1. 35-kDa Müller cell protein
   2. 22-kDa neuronal antigen found in both the retina and optic nerve
   3. A novel membrane-associated 33-kDa protein
   4. Transducin-a
   5. Transducin-b
   6. Arrestin
   7. Rhodopsin
D. Electroretinogram (see Figure 3)
   Characteristic finding: Electronegative electroretinogram on combined rod and cone response

E. Fundus and OCT normal initially (see Figure 4)
F. Visual fields mostly full

![Fundus & OCT normal initially](image1)

Figure 4.

V. Paraneoplastic Vitelliform Maculopathy
A. Metastatic cutaneous melanoma
B. Anti-bestrophin antibodies
C. Subretinal antibodies

![Figure 5.](image2)

Figure 5.
VI. Case: 66-Year-Old Woman

A. October 2012
1. Rapid decrease in vision after a fall
2. Colors appear washed out
3. VA dropped from 20/40 to count fingers over 1 month
4. Vitreous hemorrhage in O.S.
5. Vitrectomy O.S. in Dallas
6. VA did not improve in both eyes

B. May 2013
1. VA: 20/200 O.U.
2. Color vision: 0/14 O.U.
3. Autofluorescence: Unremarkable (see Figure 6)
4. Fluorescein angiogram (see Figure 7)
5. Central scotomas (see Figure 8)

6. ERG and auto-immune antibodies
   a. Diminished cone function O.U.
   b. Reduced rod function O.U.
   c. CRMP-5 IgG (collapsin-response-mediator protein) positive marker for lung cancer
   d. Diagnosis: Paraneoplastic retinopathy
   e. No improvement in symptoms on steroids

7. PET scan/CT chest
   a. Subcarinal lesion
   b. Biopsy: Small cell lung cancer

8. Chemotherapy, followed by radiation

9. Progressed: 2 years later (see Figure 9)
VII. CRMP5 Paraneoplastic Disorder
   A. Optic disc edema and vitritis (Pulido et al): paraneoplastic ocular association
   B. Cone rod retinopathy

VIII. Summary
   A. Important paraneoplastic disorders in adults
   B. High index of suspicion
   C. History and associated findings are helpful.
   D. Appropriate diagnostic tools

Figure 9.
Cutting-Edge Discoveries in the Genetics of Uveal Melanoma

J William Harbour MD

I. Introduction: Challenges to Improving Outcomes in Patients with Uveal Melanoma

II. The Molecular Landscape of Uveal Melanoma
   A. Gene expression profiling
      1. Class 1A, Class 1B, and PRAME
      2. Class 2
   B. G-alpha-q mutation cluster: nonprognostic initiating events
      1. GNAQ
      2. GNA11
      3. CYSLTR2
      4. PLCB4
   C. “BES” mutation cluster: prognostic progression events
      1. BAP1
      2. SF3B1
      3. EIF1AX
   D. Are monosomy 3 and other chromosomal markers obsolete?

III. Clinical Applications
   A. Diagnostic confirmation
   B. Prognostication and surveillance
   C. Therapeutic choice

IV. Conclusions: The Future of Precision Medicine in Uveal Melanoma
Intraocular Lymphoma for Dummies

Jose S Pulido MD MS

To describe the recent diagnostic and treatment options for the most predominant form of vitreoretinal lymphoma, namely diffuse large B cell lymphoma, this is a review of the literature and the experience at the Mayo Clinic.

MYD88 L265P mutation is seen in about 80% of cases; therefore, a PCR for this mutation helps in making the diagnosis, which has been notoriously difficult to make. Local therapy using intravitreal methotrexate and rituximab has been very helpful in the treatment of the local disease. Systemic high-dose intravenous methotrexate is helpful in treating bilateral disease, in conjunction with intravitreal therapy. Whether it is helpful in preventing or delaying the development of central nervous system lymphoma (CNSL) is still in dispute. If there is development of CNSL or recurrent ocular disease, alternatives to high-dose methotrexate include pomalidomide, stem cell transplantation, and ibrutinib, in conjunction with local therapy. Because of the risks of redevelopment of disease, local radiation should be given if other options are not possible. Aqueous levels of IL10 are helpful in following the redevelopment of local disease. Although PVRL is still a difficult disease to diagnose and treat, new advances are developing.
Retinal Nonperfusion and Anti-VEGF Therapy in Diabetic Retinopathy: What We Know and What We Don’t Know

Dante J Pieramici MD

“The greatest scientific discovery was the discovery of ignorance.” —Yuval Noah Harari

I. Retinal Nonperfusion Is a Pathophysiologic Process Common to Many Common Retinal Diseases.
   A. Diabetic retinopathy
   B. Retinal venous occlusive disease
   C. Retinal arterial occlusive disease
   D. Hypertensive retinopathy
   E. Sickle retinopathy
   F. Carotid insufficiency
   G. Retinal vasculitis

II. Pathophysiology of Retinal Microvascular Loss in Diabetic Retinopathy
   A. Polyol pathway
   B. Advanced glycation end products
   C. Protein kinase C activation
   D. Hemodynamic changes
   E. Inflammation
   F. Oxidative stress
   G. Renin-angiotensin-aldosterone system
   H. Pericyte loss
   I. Capillary basement membrane thickening
   J. Growth factors: VEGF

III. VEGF and Diabetic Retinopathy
   A. Upregulated by hypoxia
   B. Powerful permeability factor
   C. Present in supportive cells (Müller cells)
   D. Necessary for fetal development of retinal vasculature
   E. Neuroprotective? May depend on dose
   F. Stimulates endothelial cell proliferation, migration, survival, permeability, angiogenesis
   G. Antiapoptotic

IV. Concerns that Anti-VEGF Leads to Increased Retinal Nonperfusion
   A. Animal models suggest anti-VEGF is associated with reduction in retinal capillaries.
      1. Ultrastructural studies in primates: Changes seen within 24 hours
   B. Numerous case reports correlate increased retinal nonperfusion with the use of anti-VEGF agents in retinal vein occlusion (RVO) and diabetic macular edema (DME).
   C. Systemic use of anti-VEGF associated with increased cerebrovascular events and APTCs
      1. May result from reduction of VEGF and its promotion of endothelial cell proliferation and survival
      2. Anti-VEGF reduces nitric oxide and prostacyclin; this may predispose to thrombosis.

V. Evidence Suggesting that Anti-VEGF Does Not Promote Retinal Nonperfusion
   A. Elevated VEGF levels are associated with capillary nonperfusion. Eyes treated with anti-VEGF for RVO/DME had reduced rates of development of capillary nonperfusion.
   B. DME eyes with baseline macular nonperfusion can still realize visual improvements with anti-VEGF therapy. Data from RISE/RIDE (IP 2015, Pieramici 2017 unpublished)
   C. Positive effects of anti-VEGF therapy on the regression and reduced progression of diabetic retinopathy (DR) in Phase 3 clinical trials of ranibizumab, bevacizumab, aflibercept
   D. Peripheral reperfusion noted in diabetic and RVO/DME patients treated with anti-VEGF (also Pieramici 2017 unpublished)

VI. Future Directions
   A. Spectral domain OCT angiography, swept source OCT angiography
   B. Doppler OCT
   C. Other novel imaging modalities
References


Factors Associated with Worsening Proliferative Diabetic Retinopathy in Eyes Treated with Panretinal Photocoagulation or Ranibizumab

Susan B Bressler MD

I. Background

A. Protocol S of the Diabetic Retinopathy Clinical Research Network (DRCRnet) found that at 2 years the visual acuity (VA) in eyes randomly assigned to ranibizumab (Lucentis, Genentech) was no more than 5 letters worse than (noninferior to) eyes managed with panretinal photocoagulation (PRP).1

1. In an area-under-the-curve analysis, over the course of 2 years the ranibizumab group had superior VA compared with the PRP group (adjusted mean difference over 2 years = +4.2 letters; P-value < .001; 95% CI, +3.0 to +5.4).

2. Additional benefits were associated with ranibizumab, such as preservation of visual field, a lower incident rate of vision-impairing diabetic macular edema (DME), and fewer eyes progressing to vitrectomy.

B. The objective of this analysis was to compare rates, timing, and severity of events that represent worsening of diabetic retinopathy (DR) in each of the treatment arms of Protocol S and to evaluate predictive factors associated with proliferative diabetic retinopathy (PDR) worsening.

II. Methods

A. 394 study eyes (305 patients; mean age: 52 years), stratified by presence of vision-impairing DME at baseline, were assigned to ranibizumab (191 eyes) or PRP (203 eyes) and followed to 2 years.

B. The primary outcome was a composite outcome of adverse events that represent PDR worsening, including the first occurrence of vitreous hemorrhage (VH), retinal detachment (RD), anterior segment neovascularization, or neovascular glaucoma.

C. Nineteen baseline predictive factors were evaluated for a relationship with PDR worsening. This included person characteristics (demographics, medical history), study eye ocular examination features, variables derived from reading center interpretation of fundus photographs and OCT images, and attributes associated with the delivery of PRP (for the PRP group only).

III. Results

A. PDR worsening: Figure 1 shows the cumulative probability of PDR worsening as the composite outcome (1a), or as the first occurrence of VH (1b), RD (1c) or vitrectomy (1d) through 2 years.

1. Rates of the composite outcome were 42% in the PRP group vs. 34% (hazard ratio [HR] = 1.33; 99% CI, 0.90-1.98; P = .063).

a. The HR increased to 1.45 (P = .024) when the analysis was adjusted for baseline DR severity.

b. In the subgroup of participants without vision-impairing DME at entry (302 eyes, 77% of study eyes among which the PRP group was not required to receive ranibizumab at baseline to manage DME), the composite event rate was higher in the PRP group (43%; 99% CI, 35%-56%) compared with the ranibizumab group (31%; 99% CI, 22%-42%) (HR 1.62; 99% CI, 1.01-2.60; P = .008).

2. The 2-year cumulative probability of VH was 39% (99% CI, 30%-49%) in the PRP group and 30% in the ranibizumab group (99% CI, 22%-40%) (HR 1.38; 99% CI, 0.91-2.10; P = .048).

3. The 2-year cumulative probability of RD was 11% (99% CI, 6%-19%) in the PRP group and 5% in the ranibizumab group (99% CI, 2%-13%) (HR 2.13; 99% CI, 0.80-5.65; P = .046).

4. The 2-year cumulative probability of vitrectomy was 17% (99% CI, 11%-26%) in the PRP group and 5% in the ranibizumab group (99% CI, 2%-11%) (HR 3.81; 99% CI, 1.46-9.91; P < .001).

B. Predictive factors associated with PDR worsening

1. Ranibizumab or PRP group:

   a. One additional factor was associated with greater risk of the composite outcome, irrespective of treatment assignment: Early Treatment Diabetic Retinopathy Study DR severity level—64% high risk PDR (≥ level 71) vs. 23% moderate PDR or less (≤ level 65; HR 3.97; 99% CI, 2.48-6.36; P < .001).

2. PRP group only:

   a. One additional factor was associated with greater risk of the composite outcome: PRP laser delivery—60% pattern scan laser vs. 39% conventional single-spot laser (HR 2.04; 99% CI, 1.02-4.08; P = .008).

b. Important caveats: Nonrandom assignment to pattern vs. single-spot laser. Results maybe subject to bias and confounding.
C. Severity of PDR-worsening events

1. Change in VA between 2 visits straddling a VH event was $-19.2 \pm 24.9$ letters for the 69 eyes in the PRP group and $-14.8 \pm 28.3$ letters for the 52 eyes in the ranibizumab group with VH.

   a. Adjusted mean difference between the treatment groups (ranibizumab minus PRP) adjusted for VA before the VH was 5.0 letters worse in the PRP group than the ranibizumab group (99% CI, −7.2 to 17.2; $P = .29$).

   b. More eyes had a 10-letter decrease associated with VH in the PRP group than in the ranibizumab group (58% vs. 42%, respectively; $P = .076$).

2. Loss of VA associated with an RD event was 6.1 letters worse in the PRP group (CI: −19.6 to 31.7; $P = .48$).

IV. Conclusions

The more advanced the PDR level, the more likely eyes will experience PDR worsening; however, eyes managed with ranibizumab are less likely to progress than eyes treated with PRP. This provides additional evidence in support of ranibizumab as a treatment alternative to PRP for management of eyes with PDR.

References


Persistent Macular Thickening following Intravitreous Aflibercept, Bevacizumab, or Ranibizumab for Center-Involved Diabetic Macular Edema with Vision Impairment

John A Wells III MD for the Diabetic Retinopathy Clinical Research Network (DRCRnet)

I. Introduction

A. Despite anti-VEGF therapy, diabetic macular edema (DME) can persist in many eyes. In the DRCRnet’s Protocol I, 40% of eyes treated with ranibizumab for DME had persistent DME through 24 weeks (OCT central subfield thickness greater than machine-specific cutoffs).1

B. In the DRCRnet’s Protocol T, aflibercept, bevacizumab, and ranibizumab were compared for the treatment of DME. Understanding the prevalence of persistent DME and the subsequent visual and anatomic outcomes of eyes treated with 1 of 3 anti-VEGF agents may be relevant to management.

II. Methods

Exploratory analyses of 546 of 660 participants (83%) meeting inclusion criteria for this investigation based on a similar study from Protocol I

A. Persistent DME defined as follows: OCT-confirmed DME at baseline, receipt of at least 4 of 6 monthly intravitreous anti-VEGF injections through 24 weeks, no more than 2 missed visits between the 28-week and 1-year visits, and no alternative treatments received

B. After 24 weeks, eyes were considered to have chronic persistent DME until there were 2 consecutive visits with central subfield thickness < 250 µm (time-domain equivalent) and 10% thinner than the 24-week level.

III. Results

A. Through 24 weeks, persistent DME was less likely with aflibercept (32%) and ranibizumab (41%) than bevacizumab (66%) (aflibercept vs. bevacizumab, P < .001; ranibizumab vs. bevacizumab, P < .001, aflibercept vs. ranibizumab, P = .05).

B. Chronic persistent DME through 2 years was less likely with aflibercept (44%) than with bevacizumab (68%; P = .03) but not aflibercept vs. ranibizumab (54%; P = .41) or ranibizumab vs. bevacizumab (P = .16).

C. The percentage of eyes at 2 years with or without chronic persistent DME gaining ≥ 10 letters from baseline was 62% vs. 63% (P = .88) with aflibercept, 51% vs. 55% (P = .96) with bevacizumab, and 45% vs. 66% (P = .10) with ranibizumab.

D. Overall, only 3 eyes with chronic persistent DME lost ≥ 10 letters.

IV. Conclusions

A. Eyes assigned to aflibercept were less likely to have chronic persistent DME through 2 years than eyes assigned to bevacizumab, among eyes with persistent DME through 24 weeks.

B. Substantial visual acuity loss at 2 years is uncommon with any of these anti-VEGF agents using the DRCRnet retreatment algorithm, even when DME chronically persists.

Reference

Plasma VEGF Concentrations after Intravitreous Anti-VEGF Therapy for Diabetic Macular Edema

Lee M Jampol MD for the DRCRnet

I. Background

A. The Diabetic Retinopathy Clinical Research Network performed a comparative effectiveness trial of 3 anti-VEGF agents commonly used to treat diabetic macular edema—aflibercept, bevacizumab, and ranibizumab.

1. Reported systemic side effects of bevacizumab delivered intravenously to treat certain cancers include hypertension, proteinuria, and cardiovascular and gastrointestinal complications.1

2. Systemic drug levels after intravitreous injections and their potential impact on systemic VEGF levels could be associated with an increased risk of systemic side effects.1-4

B. In a preplanned ancillary study to the DRCRnet Protocol T, plasma samples were collected to assess the effects of anti-VEGF agents on systemic free-VEGF levels and the correlation of free-VEGF levels to systemic side effects.

II. Methods

A. Comparative effectiveness trial with participants randomly assigned to 2-mg aflibercept, 1.25-mg bevacizumab, or 0.3-mg ranibizumab following a retreatment algorithm.

B. Plasma samples were collected before injections at baseline, 4-week, 52-week, and 104-week study visits. 436 participants with available plasma samples were included in the analysis.

C. Systemic free-VEGF levels from an ELISA immunoassay were compared across anti-VEGF agents and correlated with systemic side effects.

D. The main outcome measure was change in the natural log \((\ln)\) of plasma VEGF levels.

III. Results

A. Baseline free-VEGF levels were similar across all 3 groups.

1. At 4 weeks, mean \(\ln(\text{VEGF})\) changes were \(-0.30 \pm 0.61\), \(-0.31 \pm 0.54\), and \(-0.02 \pm 0.44\) pg/ml for the aflibercept, bevacizumab, and ranibizumab groups, respectively.

2. The adjusted differences between treatment groups (adjusted CI; \(P\)-value) were \(-0.01 (-0.12, +0.10; P = .89)\), \(-0.31 (-0.44, -0.18; P < .001)\), and \(-0.30 (-0.43, -0.18; P < .001)\) for aflibercept-bevacizumab, aflibercept-ranibizumab, and bevacizumab-ranibizumab, respectively.

3. At 52 weeks, a difference in mean VEGF changes between bevacizumab and ranibizumab persisted \((-0.23 [-0.38, -0.09]; P < .001)\); the difference between aflibercept and ranibizumab was \(-0.12 (P = .07)\); and between aflibercept and bevacizumab, +0.11 \((P = .07)\).

4. Treatment group differences at 2 years were similar to 1 year.

B. No apparent treatment differences were detected at 52 or 104 weeks in the cohort of participants not receiving injections within 1 or 2 months before plasma collection.

C. Participants with \((n = 9)\) and without \((n = 251)\) a heart attack or stroke had VEGF levels that appeared similar at 104 weeks.

IV. Conclusions

At 4 weeks, plasma free-VEGF was lower in the aflibercept and bevacizumab groups than in the ranibizumab group. At 52- and 104-week visits the difference was statistically significant only for bevacizumab vs. ranibizumab. At 52- and 104-week visits, participants who had not had intravitreous injections for either 1 or 2 months prior to the visit had no differences in change in free-VEGF levels among any of the treatment groups. Thus by approximately 1 or 2 months after an injection, levels of plasma free-VEGF may be similar for each of the 3 treatments and close to normal. Investigators are uncertain whether the presence of anti-VEGF drug in the blood affects the plasma free-VEGF levels or accounts for some or all of the differences that were identified between changes in VEGF levels. Furthermore, the clinical importance of these findings is unknown.
Figure 1. Change in plasma ln(VEGF) concentrations (pg/ml) by treatment group assignment and visit—all participants at 4 weeks (n = 139/130/141 for aflibercept / bevacizumab / ranibizumab groups). P = .89 / < .001 / < .001 for aflibercept vs. bevacizumab / aflibercept vs. ranibizumab / bevacizumab vs. ranibizumab.

Figure 2. Change in plasma ln(VEGF) concentrations (pg/ml) by treatment group assignment and visit—all participants at 52 weeks (n = 132/115/130 for aflibercept / bevacizumab / ranibizumab groups). P = .07 / .07 / < .001 for aflibercept vs. bevacizumab / aflibercept vs. ranibizumab / bevacizumab vs. ranibizumab.

Figure 3. Change in plasma ln(VEGF) concentrations (pg/ml) by treatment group assignment and visit—all participants at 104 weeks (n = 98/84/78 for aflibercept / bevacizumab / ranibizumab groups). P = .07 / .13 / .002 for aflibercept vs. bevacizumab / aflibercept vs. ranibizumab / bevacizumab vs. ranibizumab.

References

Treating Proliferative Diabetic Retinopathy with Diabetic Macular Edema: Anti-VEGF Alone or with Panretinal Photocoagulation?

Neil M Bressler MD

I. Case Discussion

A white woman in her sixties with insulin-dependent diabetes for 35 years presents with visual acuity of 20/63 in her right eye (RE) and 20/50 in her left eye (LE) with correction. She had panretinal photocoagulation (PRP) for proliferative diabetic retinopathy (PDR) and macular laser treatment for diabetic macular edema (DME) in her RE 8 years ago, with stable-appearing PDR, some peripheral visual field loss from the PRP, and thinning of the macula in the RE. She had no iris or angle neovascularization in either eye and had an IOP of 15 mmHg in the RE and 12 mmHg in the LE. The LE also had neovascularization of the disc (NVD) greater than Diabetic Retinopathy Study (DRS) standard photography 10A, preretinal hemorrhage along the inferotemporal arcade, and thickening of the macula (OCT central subfield thickening [CST]) of 451 microns from DME that appeared to be accounting for the decreased visual acuity in the LE.

A. Management option 1: Treat PDR with PRP and treat DME with anti-VEGF therapy

B. Management option 2: Use anti-VEGF alone to treat both the PDR and the DME

II. Results from Protocol S1 of the Diabetic Retinopathy Clinical Research Network (DRCRnet) and Results from CLARITY2 in the UK Provide Some Level 1 Evidence (Randomized Clinical Trials) to Address This Situation.

A. Randomization: 394 eyes among 304 study participants

1. Ranibizumab Group
   a. n = 191
   b. 88% followed to 2-year visit (excluding deaths)
   c. Median (quartiles): 22 visits (18, 24 visits)
   d. 38% had high-risk PDR.
   e. 22% had central-involved DME with visual acuity (VA) loss of 20/32 or worse.

2. PRP Group
   a. n = 203
   b. 86% followed to 2-year visit (excluding deaths)
   c. Median (quartiles): 16 visits (9, 22 visits)
   d. 37% had high risk PDR.

B. Treatment: Ranibizumab Group

1. Six initial injections every 4 weeks (One exception: If no neovascularization [NV] at 4-month or 5-month visit, then injection withheld.)
2. Starting at 6-month visit
   a. Inject if NV improved compared with any previous 3 consecutive visits where injection given.
   b. Withhold injections if NV stable over previous 3 consecutive injections.
3. After injection withheld, resume injections if NV worsens until NV stable over previous 3 consecutive injections.
4. Starting at 12-month visit, when stable with no injection, double follow-up to 2 months and then to every 4 months until NV worsens.

C. Treatment: PRP Group

1. Prompt PRP: Initially ...
   a. 1 to 3 sittings within 8 weeks of randomization
   b. Standard laser full session = 1200 to 1600 burns
   c. Automated pattern full session = 1800 to 2400 burns
2. Ranibizumab required for eyes with central-involved DME causing vision loss at baseline—relevance to this case: Eyes in Protocol S with PDR and DME either got anti-VEGF alone, or anti-VEGF with PRP. Therefore, we can compare this subgroup result along with the overall results to consider management of cases with PDR and DME.
3. If the size or amount of NV increased following initial completion of PRP, then additional PRP could be given.

D. Injections for eyes with baseline DME in ranibizumab Group (n = 36)

1. Prior to 1-year visit, median: 9
2. Prior to 2-year visit, median: 14 (median of approximately 5 in second year)
E. Visual acuity results

1. Mean change in visual acuity letter score from baseline to 2 years, overall study: +2.8 in Ranibizumab Group; +0.2 in PRP Group; 2-year adjusted mean difference: +2.2; 95% CI, −0.5, +5.0. Meets prespecified noninferiority criterion: lower bounds of the 95% CI of −0.5 letters was greater than the noninferiority limit of −5.0 letters.

2. Mean change in visual acuity letter score area under-the-curve analysis from baseline over 2 years, overall study: +4.5 in Ranibizumab Group; −0.3 in PRP Group; adjusted mean difference over 2 years (AUC): +4.2; P-value < .001; 95% CI, +3.0, +5.4.

3. Among eyes with central-involved DME causing vision loss at baseline—relevance to this case: mean change in visual acuity letter score from baseline to 2 years: +7.9 Ranibizumab Group (n = 33); +1.9 PRP Group (n = 37). Note: Even though PRP Group also got anti-VEGF for DME: 2-year adjusted mean difference was +3.0 letters; 95% CI, −4.2, +10.3, suggesting superior visual acuity outcomes if treating PDR with DME with anti-VEGF alone rather than anti-VEGF for the DME and PRP for the PDR.

F. Other potential benefits of Ranibizumab Group compared with PRP Group (not specific to eyes with PDR and DME causing vision loss):

1. Less peripheral visual field loss
   a. Mean cumulative point score change from baseline on Humphrey Visual Field 30-2 Plus 60-4: −23 for Ranibizumab Group vs. −422 for PRP Group = −372 worse in PRP Group (P < .001).
   b. Mean deviation change from baseline: −0.08 for Ranibizumab Group vs. −2.50 for PRP Group = 2.4 (P < .001).
   c. There is no reason to believe these results should not be extrapolated to the subgroup with PDR and DME at baseline wherein both groups got anti-VEGF for DME and the PRP Group got PRP for the PDR, but the Ranibizumab Group only received anti-VEGF for both the PDR and the DME.

2. Fewer vitrectomies by 2 years: 4% for the Ranibizumab Group vs. 15% for the PRP Group: P < .001. Numbers are too small to determine if similar advantage for the Ranibizumab Group among subgroup with PDR and DME at baseline.

G. Other reports recently published with relevance to this case:

1. Recent analyses from the DRCRnet investigators show rates of a composite outcome of PDR-worsening (ie, vitreous hemorrhage, vitrectomy, any retinal detachment, neovascular glaucoma, or neovascularization of the iris) were lower in the Ranibizumab Group than in the PRP Group. Numbers are too small to determine if similar advantage for the Ranibizumab Group among subgroup with PDR and DME at baseline, although difference in rates appeared even greater among eyes not required to receive ranibizumab at baseline for vision-impairing DME.

2. Results from CLARITY, a randomized clinical trial of aflibercept vs. PRP for PDR, showed superior mean gain in visual acuity at 1 year, confirming results from Protocol S and strengthening confidence in conclusions from results. Note that no eyes in CLARITY had DME with vision loss at baseline, and if DME developed, eyes in the PRP group could receive macular laser for DME, but not anti-VEGF for DME through the 1-year primary outcome visit.

3. With both DCRRnet Protocol S and CLARITY results, ophthalmologists and patients with PDR must consider concerns regarding adherence to treatment. Ten percent loss at 1 year in CLARITY and 12% loss to follow-up at 2 years in the DRCRnet is likely the best-case scenario. Of course, compliance with follow-up after PRP is also critical: ~50% need at least 1 more session of PRP, typically between 6 and 12 months after the initial PRP; ~1/6 go on to vitrectomy, and effects beyond 2 years are not yet known.

4. Cost-effectiveness of Ranibizumab Group (assuming 0.5-mg dose) compared with PRP Group: for subgroup of 46 eyes with vision-impairing DME and PDR (only participants with 1 study eye could be evaluated for this analysis), the incremental cost-effectiveness ratio (ICER) was $53,568 per quality-adjusted-life-year (QALY) when treating the better-seeing eye. If considering the study eye in Protocol S, ICER is $191,653 per QALY. Cost-effectiveness for individuals with PDR without DME is unlikely ($662,978/QALY), highlighting challenges in that scenario when cost-effectiveness findings are at odds with clinical efficacy and safety results. It is unknown what costs or effectiveness would be with aflibercept or bevacizumab at this time to have confident cost-effectiveness outcomes using those agents.

III. Conclusions

When considering treatment of PDR with DME, data from Protocol S, as well as CLARITY, would suggest that anti-VEGF, if accessible, without PRP, following the DRCRnet anti-VEGF treatment regimen for PDR and for DME, is more likely to improve visual acuity, cause less visual field loss, and lead to fewer vitrectomies than combining PRP with anti-VEGF. Furthermore, anti-VEGF without PRP for such cases would be cost-effective within parameters considered cost-effective in the United States when treating the better-seeing eye.
References


Novel Treatment Strategies for Diabetic Retinopathy and Diabetic Macular Edema: Impactful, or Impossible?

Pravin U Dugel MD
The Role of Steroids in Diabetic Macular Edema

Anat Loewenstein MD and Michaela Goldstein MD

Introduction

The complex pathogenesis of diabetic macular edema (DME) includes the release of various cytokines in addition to VEGF. It has been shown that the levels of inflammatory factors in vitreous samples from patients with DME are increased as compared to normal eyes or to diabetics without macular edema. Steroids have been shown to significantly reduce the level of these cytokines—namely, to combat the inflammatory part of diabetic retinopathy. Triamcinolone was the first steroid to be investigated, and its effectiveness has been shown to be similar to that of anti-VEGF agents in pseudophakic patients. It does cause an increase in IOP and, in phakic patients, the development of cataract. Ozurdex, a slow-release biodegradable implant containing dexamethasone, has been shown to improve visual acuity and have long-term effects in diabetic patients. It has been shown to have similar efficacy to that of anti-VEGF agents in pseudophakic patients. It has also been shown to be beneficial in vitrectomized eyes. It also increases IOP, although in a smaller percentage of patients compared to triamcinolone, and in most cases this increase can be easily treated with antiglaucoma medication. Its efficacy has been shown to be of a duration of 4-5 months. Iluvien, a slow-release nonbiodegradable implant containing fluocinolone, has been shown to be effective mainly in eyes with chronic, long-standing macular edema. It causes cataract in most patients and a higher percentage of IOP increase, also easily treatable in most cases.

Background Observations

Treatment of DME with steroids is indicated as first line in patients who are noncompliant to monthly treatment and monitoring or who are not suited to anti-VEGF agents. Also, they can be used as second-line treatment in patients unresponsive to anti-VEGF agents.

In my experience...

There is room for the treatment of DME patients with steroids. The ocular side effects are usually easily manageable, and the treatment can be useful for patients not suited to or nonresponsive to anti-VEGF agents.
Cannulation of Central Retinal Artery Occlusion with a Microneedle

Kazuaki Kadonosono MD

Introduction

Central retinal artery occlusion (CRAO) is caused by a thrombus or embolism in the central retinal artery, mainly in the optic nerve head, and it is an ophthalmological emergency and a cause of blindness due to the resulting inner retinal ischemia.1 Standard treatment options for CRAO include conservative treatments, such as anterior chamber paracentesis, ocular massage, and IOP-lowering agents. Both intravenous thrombolysis and intra-arterial thrombolysis have been used to treat CRAO for the past decade.2,3 However, there haven’t been any approved treatments for CRAO yet.

Background Observations

CRAO must be treated by lysing the thrombus or dislodging the embolus in the central retinal artery as soon as possible.4 If there was an accepted retinal endovascular approach to treating a clot in a retinal arterial vessel, it would be a great help in treating CRAO. We recently developed an endovascular cannulation procedure that enables treatment of CRAO by injecting tissue plasminogen activator (tPA) into the central retinal artery with a microneedle setup.5 We conducted a study of endovascular cannulation of the central retinal artery in CRAO to evaluate the efficacy and safety of the surgical procedure. The intra-retinal-arterial cannulation involves an endovascular cannulation technique by which a 47-gauge microneedle is inserted into the central retinal artery to inject tPA (see Figure 1).

In my experience, our surgical procedure has several advantages. First the success rate is high, possibly because tPA comes into more direct contact with the clot than during previous fibrinolysis therapies. Second, there is a lower risk of systemic complications, such as cerebral infarction, because the total tPA dose, 200 μg, is too small to induce general complications. However, the surgery is still challenging. The learning curve may be steep for surgeons wishing to perform this technique, and special instruments may be needed to hold the microneedle during cannulation and facilitate performance of the procedure.

References

Scleral Inlay for Treatment of Optic Disc Pit Maculopathy

Claus Eckardt MD

Pars plana vitrectomy with additional procedures such as gas tamponade, peripapillary laser, internal limiting membrane (ILM) surgery, intraretinal fenestration, and radial neurotomy is often an effective treatment for optic disc pit maculopathy. However, it is not infrequent that the intraretinal and subretinal fluid resolution extends over several months.

A much faster regression of the serous maculopathy was reported after closure of the optic disc pit with an inverted ILM flap. We report on 2 patients who were treated with an autologous scleral transplant for closure of the optic disc pit. During vitrectomy the scleral transplant was inserted like an inlay deep in the optic pit.

The first patient had been repeatedly operated on without success, including stuffing an ILM flap into the pit. With the inlay, a complete regression of the maculopathy was observed within 6 days, and shortly afterward this was followed by a visual improvement to 20/20. The second patient, who previously had not undergone any laser or other surgery, only showed a gradual regression of the maculopathy, which may have been possible even without any manipulation in the optic disc pit.

Both cases show that using a scleral inlay, a fast regression of the serous maculopathy is possible, but not guaranteed.

References
Hypersonic Vitrectomy: Initial Clinical Experience

Carl C Awh MD

“Hypersonic vitrectomy” describes a method of vitreous removal in which ultrasonic power is used to drive the vitrectomy probe tip. The tip of the hypersonic vitrectomy handpiece oscillates at a frequency of approximately 1.7 million “cuts” per minute, creating a localized region of tissue disruption just within or at the surface of the port. This phenomenon is termed “hypersonic liquefaction.” The emulsified material is drawn through the probe and out of the eye by conventional vacuum/aspiration methods. However, there exists a phenomenon of low suction that can be induced at the port of the device simply through the action of the hypersonic oscillation.

In vitro studies in cadaver eyes and in vivo animal trials have demonstrated that the hypersonic vitrector is able to effectively remove vitreous. Comparative in vivo animal trials of hypersonic vitrectomy cutters and conventional guillotine-style pneumatic cutters found no identifiable differences in post-mortem retinal histopathology.

In July 2017, 3 surgeons (Stanga, Agarwal, Venkataraman) used the hypersonic vitrectomy device to perform 22 cases in 20 human subjects. These cases were performed in India, with appropriate oversight and consent.

Maneuvers successfully performed during these initial cases included the following:

- Induction of posterior vitreous detachment
- Core vitrectomy
- Peripheral vitrectomy with scleral depression
- Removal of dense vitreous hemorrhage
- Removal of retained lens cortex
- Posterior capsulotomy
- Aspiration of preretinal blood

An iatrogenic retinal break in an area of mobile detached retina was the sole reported intraoperative complication.

By the time of this presentation, additional cases should have been performed in the United States. Surgical video and further discussion of the capabilities and limitations of the hypersonic vitrectomy device will be presented.
Autologous Retinal Transplant for Macular Holes: Initial Experience

Tamer H Mahmoud MD

The last few years have witnessed an unprecedented revolution in surgical management of macular holes. Large, chronic, myopic, and traumatic macular holes have higher success rates of hole closure with internal limiting membrane (ILM) flaps. However, in many instances, the ILM has already been peeled during the initial vitrectomy.

The ultimate goal is to close the hole, and the autologous retinal transplant was first described in a case of myopic macular hole that failed to close after multiple attempts. The initial impression was the successful closure of the hole, but this was also followed by some functional visual improvement, with increased retinal sensitivity over the transplant and thickening of the flap. Initial technical challenges included keeping the donor retinal flap in place. Since then, significant improvement to the technique has been developed.

Main points to be discussed and presented in the form of videos:

1. Chronological change of technique of autologous retinal transplant (ART) since 2015
2. Bimanual vs. unimanual techniques
3. Positioning the transplant: preretinal vs. subretinal
4. Step-by-step approach for a successful ART
5. Tamponade: gas vs. oil
6. Morphological changes of ART over time
7. Combined choroidal and retinal transplant in geographic atrophy and other pathology
8. Special indications for ART; considerations and surgical tips
   a. Myopic macular holes with and without retinal detachment
   b. Giant macular holes in Alport syndrome
   c. Macular holes with juxtafoveal telangiectasis
   d. Combined macular holes with retinal detachment and proliferative vitreoretinopathy (PVR)
   e. Retinal detachment and PVR without macular holes
9. Complications and how to prevent them
10. Hypotheses about the ART
    a. Ectopic synaptogenesis
    b. Material transfer
    c. Müller cells
    d. Retinal plasticity
    e. Growth factors
11. Implications for macular diseases
12. Inverted ART for retinal detachment with PVR and other macular diseases
13. Future directions

Selected Readings

Retinal Pigment Epithelium Sheet Transplantation
Phase 1/2a Clinical Trial of Human Embryonic Stem Cell–Derived RPE for Treatment of Severe Vision Loss from Geographic Atrophy Associated with Advanced Non-neovascular AMD

Amir H Kashani MD PhD, J Lebkowski PhD, F Rahal MD, R Avery MD, H Salahi-Had MD PhD, W Dang PhD, C M Lin PhD, D Mitra PhD, D H Zhu MD PhD, L V Johnson PhD, D O Clegg PhD, D R Hinton MD, M S Humayun MD PhD

I. Selected Inclusion Criteria (please see clinicaltrials.gov for full list)
   A. Diagnosis of advanced dry AMD and age from 55 to 85
   B. Geographic atrophy and retinal pigment epithelium (RPE) loss observed by clinical and diagnostic testing
   C. Vision worse than 20/200 in the more affected eye
   D. Pseudophakia

II. Exclusion Criteria (please see clinicaltrials.gov for full list)
   A. No evidence or history of CNV
   B. No history of other vision-threatening disease (except mild nonproliferative diabetic retinopathy, early glaucoma controlled on only 1 topical medication, or mild dry eye)
   C. No history of immunodeficiency
   D. No history of immunosuppressive therapy
   E. No history of malignancy within past 5 years
   F. No history of HIV, HBV, or HCV

III. Treatment
   A. Single surgical procedure with subretinal placement of a composite implant containing a monolayer of approximately 100,000 stem cell–derived, mature, and polarized RPE on a synthetic substrate using a novel surgical delivery tool custom designed for this purpose
   B. Par plana vitrectomy
   C. Retinotomy and subretinal hydrodissection
   D. Intraocular endolaser
   E. Gas or oil tamponade

IV. Outcome Measures
   A. Primary outcome is safety assessed at 1 year.
   B. Secondary outcomes
      1. ETDRS visual acuity
      2. Microperimetry

V. Results
   The safety and early efficacy results of 5 subjects enrolled in the study will be presented.

VI. Conclusions
   Subretinal implantation of a stem cell–derived RPE monolayer is a safe and feasible method that may potentially have efficacy in the treatment of severe vision loss in subjects with geographic atrophy from non-neovascular AMD.
2017 Workup of Patients with Uveitis

James P Dunn Jr MD

I. Uveitis Workup: Key Point #1
There is no one standard workup for uveitis.

II. Uveitis Workup: Key Point #2
A. There is no one standard workup for uveitis.
B. Even on a Friday at 5 PM …

III. Uveitis Workup: Key Point #3
A. There is no one standard workup for uveitis.
B. But always consider sarcoid and syphilis.

IV. Why?
A. Uveitis is not a disease; it is a description.
B. There are many types of uveitis.
C. The specific diagnosis is made using a careful history, physical exam, and then a more focused history, supplemented by …
D. … the judicious use of laboratory tests and imaging studies, which are often supportive but not diagnostic.

V. Principles of the Workup
A. Distinguish infectious from noninfectious uveitis
B. Distinguish purely ocular disease from uveitis associated with systemic conditions
C. Obtain additional testing only if the results will influence your management (medical, surgical, referral, prognostic)

VI. Standardization of Uveitis Nomenclature (SUN) Dimensions
A. Course
   1. Onset: Sudden vs. insidious
   2. Duration
      a. Limited: < 3 months
      b. Persistent: ≥ 3 months
   3. Course
      a. Acute: Sudden onset, limited duration
      b. Recurrent: Flare-up > 3 months after stopping treatment
      c. Chronic: Persistent or flares in < 3 months after stopping meds (Am J Ophthalmol. 2005; 140:509-516.)
B. Laterality
   1. Unilateral
   2. Unilateral / alternating (bilateral, not simultaneous)
   3. Bilateral simultaneous
   4. Bilateral asynchronous
C. Anatomic location
   1. Anterior
   2. Intermediate
   3. Posterior
   4. Panuveitis
5. Note 1: Macular edema is a structural complication of uveitis and not, in and of itself, “posterior uveitis.”
6. Note 2: Intermediate uveitis with mild anterior chamber cells and macular edema is not “panuveitis.”

VII. Anterior Uveitis
A. Cells do not necessarily = flare.
B. Hypopyon
C. Keratic precipitates
   1. Granulomatous vs. nongranulomatous
   2. Diffuse vs. subjacent vs. Arlt’s triangle
D. Transillumination / atrophy
E. Hypopyon: color, surface appearance, mobility

VIII. Posterior Uveitis: Primary site of involvement
A. Retinitis
B. Choroiditis

IX. Retinal Vasculitis (Arterial, Venous)
A. Pattern
   1. Focal / paucifocal
   2. Multifocal
B. Description
   1. Placoid, punched-out, ameboid, ovoid, punctate
   2. Color
X. Other Descriptors
A. Ocular comorbidities
B. Response to treatment
C. Geography / travel
D. Ethnicity
E. Medical conditions
F. Family history

XI. Evolution of Chorioretinal Lesions over Time

XII. Laboratory Testing
A. “Meaningful Use”
B. Bayesian analysis
   1. Sensitivity and specificity
   2. Positive / negative predictive value
   3. Prior probability of disease
C. Cost

XIII. Example
A. TB accounts for 0.2%-0.5% of uveitis cases in the United States.
B. The sensitivity and specificity of derivative (PPD) are 75% and 85%, respectively.
C. If all patients with uveitis are screened for tuberculosis, the positive predictive value of a positive PPD is 1%.

XIV. What about Retinal Vasculitis?
“Patients with retinal vasculitis rarely suffer from systemic vasculitis. In fact, patients with retinal vasculitis are much more likely to suffer from an ocular infection, nonvasculitic systemic inflammatory diseases such as sarcoidosis, or an inflammatory syndrome restricted to the eye, such as birdshot choroidopathy, rather than systemic vasculitis.”

XV. Exceptions ...
A. Behçet disease
B. ANCA-positive vasculitis
C. Necrotizing scleritis

XVI. Lab Testing in Uveitis
A. “All” cases
   1. Chest x-ray (or chest CT) to rule out sarcoid
   2. Syphilis serology
B. In appropriate context
   1. HLA B27
   2. HLA A29
   3. Urinary beta-2 glycoprotein
   4. Lyme Ab screen
   5. IGRA/PPD skin test
   6. PCR testing (viral, toxo)
   7. CMP
   8. CBC (for monitoring)
   9. HIV

XVII. What Is “Idiopathic” Uveitis?
A. Everything except infectious uveitis!
B. Better to use the term “undifferentiated”
   1. Cannot be characterized as one of the known uveitic entities
   2. The term as applied to such an entity is fungible (think acute retinal necrosis, serpiginous TB, punctate inner choroidopathy).

Selected Readings
Don’t-Miss Diagnoses

Steven Yeh MD

I. Acute Retinal Necrosis
A. Clinical symptoms: pain, redness, photophobia, acute vision loss
B. Clinical features
   1. Necrotizing retinitis
   2. Occlusive arteritis
   3. Anterior chamber and vitreous inflammation
C. Other suggestive findings
   1. Keratitis in opposite eye (von Szily reaction)
   2. Hypertensive iritis
   3. Iris transillumination defects
   4. Pigmented scarring in patients with herpes simplex virus type 2
D. Increasing role of combination systemic and intra-vitreal antiviral agents
E. Systemic antiviral, administered either intravenously or orally, val esters of acyclovir or ganciclovir (ie, valacyclovir and valganciclovir)

II. Syphilis
A. Morbidity and Mortality Weekly Report of a cluster of ocular syphilis leading to blindness on the West Coast (King County, Washington, and San Francisco) featured in AAO bulletin 2014-2015.
B. Within 2007-2013, there was an increase in primary and secondary cases of syphilis disproportionately higher in men having sex with men (MSM).
C. Coinfection of HIV and syphilis is common; all patients diagnosed with ocular syphilis should also have HIV testing offered and performed.
D. Newer enzyme immunoassays and chemiluminescence assays offer increased sensitivity and specificity compared to traditional screening test of RPR followed by MHA-TP and FTA-ABS confirmatory assay (ie, reverse screening algorithm).

III. Toxoplasmosis
A. History: endemic area (Central, South America), cat exposure, history of eating undercooked pork
B. Immunosuppression: rheumatologic conditions requiring immunosuppression, solid organ or bone marrow transplantation on immunosuppression
C. Clinical features
   1. Retinal whitening
   2. With or without pigmented scarring
   3. May be atypical or bilateral in immunocompromised patients
   4. History of corticosteroid administration
D. Multiple regimens as combination or monotherapy (pyrimethamine / sulfadiazine, trimethoprim / sulfamethoxazole, azithromycin, clindamycin, atovaquone, spiramycin)
E. Lack of level 1 evidence to support routine use of antibiotic or corticosteroid treatments for acute toxoplasmosis retinochoroiditis in immunocompetent patients
F. Level 2 evidence suggests that long-term prophylactic treatment may reduce recurrences in chronic relapsing toxoplasmosis retinochoroiditis.

IV. Cytomegalovirus Retinitis (CMR)
A. History
   1. Immunocompromise: cancer patient on chemotherapy, solid organ or bone marrow transplant patient on immunosuppression, rheumatology patient on immunomodulatory therapy
   2. HIV patients with CD4+ count < 50 cells/μl: Not seen as often because of wide availability and success of antiretroviral therapy
   3. Symptoms: blurred vision, floaters, peripheral visual field loss
B. Clinical signs
   1. Smoldering, sometimes subtle retinitis and inflammation
   2. Peripheral retinitis > posterior pole: Both peripheral and posterior segment may be observed, particularly with aggressive or inadequately treated disease.
   3. Smoldering disease often observed if patient is on intermittent valganciclovir dosing (history of CMV RNA by polymerase chain reaction in blood).
C. Therapeutic considerations
   1. Intravenous antiviral (ganciclovir or foscarnet)
   2. Oral antiviral (ie, valganciclovir)
   3. Intravitreal antivirals (ie, foscarnet, ganciclovir)
   4. Ganciclovir implant no longer available
D. Chronic prophylactic therapy may predispose individuals to antiviral drug resistance (ie, CMV UL97 protein kinase and UL54 DNA polymerase mutations).
V. Ebola Virus Disease (EVD) / Zika (ZIKV) and Other Emerging Infectious Diseases (Dengue, Chikungunya, West Nile Virus)

A. EVD

1. History
   a. Demographic information: Liberia, Sierra Leone, or Guinean descent or health-care providers in Ebola outbreak
   b. Consider diagnosis in patients with possible exposure (ie, travel to West Africa, Democratic Republic of Congo; family members or friends hospitalized in an Ebola Treatment Unit).

2. No known risk of Ebola transmission through casual contact (ie, ophthalmic examination) with Ebola survivors

3. Spectrum of uveitis during EVD convalescence (anterior, intermediate, posterior, panuveitis)

4. Treatment
   a. Supportive therapy (ie, corticosteroids)
   b. Unknown role of antiviral therapies for this entity
   c. Extreme caution with invasive surgery (ie, cataract, vitreous opacity, others) due to viral persistence

B. ZIKV

1. History
   a. Infants of mothers with suspected or confirmed ZIKV infection
   b. Adults with recent travel to ZIKV-endemic areas

2. Clinical findings
   a. Infants with and without microcephaly may develop a spectrum of findings (retinal pigment mottling, iris coloboma, lens subluxation, optic nerve abnormalities) in the context of congenital Zika virus
   b. Adults: anterior uveitis, maculopathy, chorioretinal lesions reported

C. Other emerging infectious diseases associated with uveitis

1. Flavivirus: West Nile virus chorioretinitis, dengue maculopathy / foveolitis
2. Togavirus: Chikungunya
3. Bunyavirus: Rift Valley fever (Kenya)

VI. Intraocular Lymphoma

A. History and clinical symptoms: insidious onset, floaters, decreased vision, history of CNS lymphoma or systemic lymphoma

B. Classification

1. Primary vitreoretinal lymphoma (most commonly high-grade B-cell lymphoma)
2. Uveal lymphoma
   a. Primary neoplasms of iris, ciliary body, and choroid; most commonly low-grade B-cell lymphomas
   b. Secondary choroidal lymphomas derived from systemic metastases, usually confined to choroid

C. Clinical findings

1. Vitritis
2. Retinal or retinal pigment epithelial (RPE) infiltration
3. Subretinal lesions
4. Optic nerve edema with infiltrative disease

D. Diagnosis and treatment

1. Vitreous biopsy for cytopathology, flow cytometry, and gene rearrangement (ie, IgH gene rearrangement in B-cell lymphoma; T-cell receptor gene rearrangement in T-cell lymphoma)
2. Cytokine levels for interleukin-10 to interleukin-6 ratio (IL-10: IL-6 ratio > 1)
3. Management with neuro-oncologist, oncologist

VII. Birdshot Retinocochoroidopathy

A. Clinical symptoms: floaters, nyctalopia, decreased peripheral visual field

B. Differential diagnosis: Sarcoidosis

C. Clinical findings

1. Oval, cream-colored lesions nasal > temporal periphery
2. Vitritis
3. Cystoid macular edema
4. Segment periphlebitis (clinically and angiographically)

D. Workup

1. HLA-A29 testing
2. Evaluate for sarcoidosis, tuberculosis, and syphilis (ACE, PPD, or QuantiFERON-TB Gold, RPR, syphilis immunoglobulin G)
3. Electroretinography and visual field testing to document extent of peripheral visual field loss and rod / cone dysfunction at baseline

E. Early immunosuppression has been shown to prevent visual field and visual acuity loss at long-term follow-up.
VIII. Central Serous Retinopathy (CSR) vs. Vogt-Koyanagi-Harada Syndrome (VKH)

A. CSR can be difficult to distinguish from VKH, particularly in cases of multifocal CSR (sick retinal pigment epitheliopathy syndrome).

B. CSR

1. Historical information: neurosensory detachment (subretinal fluid) significantly worsening with corticosteroid, isolated pinpoint leak with pooling in neurosensory detachment by fluorescein angiography
2. Unilateral > bilateral
3. Vision mild to moderately impaired with hyperopic shift despite subretinal fluid (cf. moderate to severe vision impairment in VKH with subfoveal fluid)
4. No vitritis
5. OCT may show hyper-reflective material in patients with recurrent or chronic CSR but no subretinal septations observed (vs. VKH).
6. No optic disc edema by fluorescein angiography

C. VKH

1. Historical information: acute, bilateral vision loss
2. Bilateral > unilateral, asymmetric disease
3. Vitritis and optic disc edema
4. Vision poor with exudative retinal detachment
5. Fluorescein angiography shows optic disc leakage and pinpoint hyperfluorescent spots with pooling into multiple exudative detachments.
6. OCT may show subretinal septations and thickened choroid (also seen with CSR).
7. Diagnostic criteria
   a. Granulomatous panuveitis with exudative retinal detachment or RPE changes
   b. CNS signs: auditory, headache, meningismus
   c. Dermatologic signs: poliosis, vitiligo
   d. No history of trauma
   e. Negative workup for other infectious / autoimmune etiologies

IX. Chronic Retinal Detachment

A. History: gradual onset of vision loss

B. Clinical features

1. Decreased vision
2. Elevated IOP due to rhegmatogenous retinal detachment, thought to be due to clogging of trabecular meshwork by photoreceptors (Schwartz’s syndrome, 1972)
3. Pigmented cells in anterior chamber
4. Posterior synechiae may be observed.
5. Surgical repair of retinal detachment, management of IOP: Atovaquone

X. Endophthalmitis

A. Fungal

1. History of recent hospitalization, indwelling catheters, TPN, trauma (pediatric patients, poor historian), prior surgery (eg, overfiltering bleb)
2. May not have known risk factors for fungal endophthalmitis by history or protean uveitis symptoms
3. History of severely worsening uveitis on topical and systemic corticosteroids
4. Signs: mild vitreous inflammation, foveal yellow spot, subretinal lesions
5. Diagnosis may be challenging.
   a. Vitreous biopsy for gram stain, fungal stain, aerobic and anaerobic culture for bacteria, fungus, atypical organisms
   b. PCR testing for fungal DNA and sequencing (University of Washington)
6. Treatment
   a. Management with Infectious Disease for laboratory monitoring as related to systemic antifungals (ie, voriconazole, fluconazole) and time course of therapy
   b. Intravitreal voriconazole
   c. Intravitreal amphotericin

B. Bacterial

1. History: recent hospitalization, cardiac valvular disease, special endemic locations (eg, Asian males predisposed to endogenous Klebsiella pneumoniae endophthalmitis with a liver abscess), immunocompromise (leukemia / lymphoma), subtle complaints on review of systems (eg, fevers, bleeding gums, fatigue, weight loss)
2. History of ophthalmic surgery (ie, cataract surgery, glaucoma filtration surgery)
3. Clinical symptoms / signs
   a. May present initially as a unilateral anterior uveitis without posterior segment disease
   b. Worsening uveitis on corticosteroids
   c. Hypopyon uveitis without a clear etiology (ie, negative workup)
4. Diagnosis and treatment
   a. Consider anterior chamber paracentesis if disease is localized to the anterior segment
   b. Vitreous tap and inject or diagnostic vitrectomy
   c. Refer to uveitis or retina specialist
   d. Revisit history and review of systems if patient is worsening on therapy.
Selected Readings


Mosquito-Borne Uveitis: 2017 Update

Emmett T Cunningham Jr MD PhD MPH

I. Epidemiology
   A. Mosquito vectors
      1. Culex: West Nile virus (WNV)
      2. Aedes: dengue, chikungunya, Zika
   B. Global
      1. WNV: northern hemispheres
      2. Dengue, chikungunya, Zika: tropical and travel

II. Systemic Disease
   A. Incubation up to 2 weeks
      1. 80% asymptomatic
      2. 20% symptomatic: fever, headache, myalgia, arthralgia, malaise
   B. WNV: 5% of symptomatic have encephalopathy, most likely to have eye findings
   C. Dengue: Hemorrhage common, can be fatal
   D. Chikungunya: Arthritis common, severe and lasting
   E. Zika: mild, except in newborns / children

III. Ocular Manifestations
   A. Anterior inflammation, mild; vitreous inflammation, mild
   B. Multifocal retinochoroiditis / retinal vasculitis
      1. WNV: curvilinear pattern, signate lesions with dark center and pale surround
      2. Dengue: prominent vasculitis ± hemorrhage
      3. Chikungunya: prominent vasculitis / neuroretinitis
      4. Zika: retinal pigment epithelium (unilateral acute idiopathic maculopathy), focal chorioretinal scars, and RPE disruption

IV. Multimodal Imaging
   A. Wide-field color, fluorescein angiography (FA), fundus autofluorescence most useful: location and pattern of lesions
   B. OCT/OCT angiography: RPE and retinal vascular involvement
   C. FA: activity, ischemia

V. Complications
   A. Scars / atrophy
   B. Vascular occlusion / ischemia
   C. Cystoid macular edema

VI. Diagnosis: Serological Tests
   A. PCR early
   B. Antibody testing late (cross-reactive to other anti-flavivirus antibodies)

VII. Treatment: Supportive
   A. Fluids
   B. Pain control
   C. Corticosteroids

VIII. Prognosis
   A. Dependent upon site of lesions
   B. Generally good unless macular involvement

Selected Readings
mTOR Inhibition for Noninfectious Uveitis and Beyond: The Evolution of Intravitreal Sirolimus through Clinical Trials

Quan Dong Nguyen MD

I. Introduction to the Mechanistic Target of Rapamycin (mTOR) Pathway
   A. mTOR protein is an intracellular coordinator of ribosomal biogenesis, protein translation, and proper cell growth.
   B. Potential role of the mTOR pathway in the pathogenesis of ocular inflammation: Modulates cellular responses to insulin, insulin-like growth factors, nutrient levels, hypoxia, and redox status

II. Sirolimus
   Lipophilic microcyclic lactone that is isolated from the actinomycete Streptomyces hygroscopicus, a fungus discovered at Rapa Nui
   A. Mechanism of action
   B. Preclinical studies
   C. Clinical studies
      1. Early clinical studies

II. Sirolimus
   Lipophilic microcyclic lactone that is isolated from the actinomycete Streptomyces hygroscopicus, a fungus discovered at Rapa Nui
   A. Mechanism of action
   B. Preclinical studies
   C. Clinical studies
      1. Early clinical studies

2. Phase 1 and 2 clinical trials
   a. Sirolimus as a Therapeutic Approach for Uveitis (SAVE) study: subconjunctival and intravitreal sirolimus
   b. Sirolimus as a Therapeutic Approach for Uveitis: Protocol 2 with Comparison of Two Doses of Intravitreal Sirolimus (SAVE-2) study

3. Phase 3 clinical trials
   a. Sirolimus Study Assessing Double-Masked Uveitis Treatment-1 (SAKURA-1)
   b. Sirolimus Study Assessing Double-Masked Uveitis Treatment-2 (SAKURA-2)

III. Conclusion and Discussion
   A. Safety, tolerability, and efficacy profiles of intravitreal sirolimus
   B. Potential role of intravitreal sirolimus in the management of uveitis and ocular inflammatory diseases
New and Emerging Therapies for Uveitis

What’s on the Horizon in Uveitis in 2017

Thomas Albini MD

The lecture will summarize recent developments in the therapy of uveitis.

I. Local Steroids

A. Sutured fluocinolone: Seven-year update on the Multicenter Uveitis Steroid Treatment (MUST) study found that systemic therapy was better than local therapy in treating posterior segment uveitis; however, there was significant undertreatment in the local therapy arm in the second half of the study.

B. Injected fluocinolone: Two Phase 3 studies meet their primary endpoint.

C. Injected dexamethasone: Prospective comparative study of dexamethasone for uveitic cystoid macular edema

D. Suprachoroidal triamcinolone: Results of Phase 2 study demonstrate efficacy and minimal effect on IOP or cataract.

II. Local Nonsteroids

Intravitreal sirolimus: Integrated data from 2 Phase 3 studies meet their primary endpoint and demonstrate minimal effect on IOP or cataract.

III. Systemic Therapy

A. Anti-TNF-α: Adalimumab meets primary endpoints in 2 pivotal trials.

B. Anti-IL-6: Most recent data on sarilumab and tocilizumab will be reviewed.

IV. Gene Therapy

Soluble TNF-α receptor plasmid using electrotansfection begins Phase 1 study in posterior segment uveitis.

Selected Readings


How to Do Tap and Inject for Endophthalmitis

Harry W Flynn Jr MD and Nidhi Relhan MD

Introduction

Endophthalmitis is a vision-threatening condition that necessitates urgent evaluation and management. Treatment includes obtaining a vitreous sample for cultures and injection of intravitreal antimicrobials. By obtaining vitreous sample and using it to identify the causative micro-organisms, further management of the patient can be planned after the initial empiric treatment.

Traditional Approach for Vitreous Aspiration (Tap) as per Endophthalmitis Vitrectomy Study (EVS)

The Endophthalmitis Vitrectomy Study was a landmark multicenter, randomized clinical trial that enrolled 420 patients with clinical evidence of endophthalmitis within 6 weeks of cataract surgery or secondary IOL implantation. The EVS provided guidelines for the vitreous tap as well as pars plana vitrectomy (PPV). As per the EVS, 0.2 to 0.5 ml of vitreous sample was collected by way of the pars plana either by needle aspiration or by vitreous biopsy through a single sclerotomy using a vitrectomy cutter. After the tap, injections of intravitreal antibiotics were given in separate syringes. If an adequate sample could not be safely obtained, a vitreous biopsy using a vitrectomy instrument was performed. The EVS reported that in the subgroup of patients with presenting visual acuity of hand motions or better, there was no difference in the visual outcome (immediate PPV or tap). However, in the subgroup of patients with presenting visual acuity of light perception only, visual outcomes were better with immediate PPV than with tap.

Current-day Tap and Inject Options (see Figure 1)

The procedure can be performed in the outpatient clinic under local anesthesia (retro/ peribulbar block). The lids and conjunctiva are prepared with 5% povidone-iodine followed by placement of the speculum. A 23-gauge butterfly needle mounted on 10-cc syringe is inserted through pars plana and approximately 0.2 to 0.5 ml of vitreous is aspirated once the needle tip is at the center of the globe. Once the vitreous sample is removed, antimicrobials are injected into the vitreous cavity. The vitreous sample obtained is sent for the microbiology evaluation, including smear and culture. In case of growth on the culture media, antimicrobial susceptibility tests are further performed. A 25- or 27-gauge needle can also be used for vitreous aspiration.

Other Modifications

A modification of the vitreous tap procedure has been recently published. In this modified technique under subconjunctival anesthesia, a valved 25-gauge trocar cannula is inserted through pars plana, and subsequent aspiration of exudates/vitreous and antimicrobial injections are performed through the single port. In a prospective, randomized, single-center trial,

![Figure 1. Outpatient clinic tap and inject procedure: (A) Standard preoperative preparation with povidone-iodine. (B) Local anesthesia (retrobulbar or peribulbar block) with lidocaine solution. (C) Speculum placement. (D) Use 23-gauge butterfly needle on 10-cc syringe for tap. (E) Insert 23-gauge butterfly needle through pars plana. (F) Tap 0.2-0.5 ml of vitreous by slow suction followed by antibiotic injection through pars plana.](image-url)
Vahedi et al compared comfort and procedural facility using 25-gauge trocar cannula as a port to aspirate vitreous and inject intravitreal antibiotics to treat acute-onset endophthalmitis. Since there were no significant differences in the patient comfort, physician ease-of-use scores, vitreous sample volume, or successful vitreous taps and microbiological yield between the 2 groups, the study concluded that 25-gauge trocar technique is a viable option.

**Intravitreal Antimicrobial Injection**

Once the vitreous sample is obtained, empiric antimicrobials are injected intravitreally. The selection of antimicrobial agents is important, and the decision should be based on the type of endophthalmitis and suspected microbiological profile. Using a 30-gauge needle mounted on 1-cc syringe, antimicrobials are injected intravitreally:

- For presumed bacterial cases: Intravitreal vancomycin and ceftazidime via separate syringes. Intravitreal dexamethasone can be considered.
- For presumed fungal cases: Intravitreal amphotericin B or voriconazole without intravitreal steroids.

**Dose of Commonly Used Intravitreal Antimicrobial Agents**

The recommended doses of commonly used intravitreal antimicrobial agents are shown in Table 2.

- Amikacin may be substituted for ceftazidime (EVS proven efficacy).
- Ceftriaxone (2 mg/0.1 mL) may be substituted for ceftazidime if this is more readily available.
- Dexamethasone 4 mg/0.1 mL may be considered for acute-onset bacterial cases but should be avoided in suspected fungal endophthalmitis and delayed-onset (chronic) endophthalmitis until the organism is identified.

**References**

Drusenoid Detachment of the Retinal Pigment Epithelial: Life Cycle

Lawrence A Yannuzzi MD, Chandra Balaratnasingam MD, Christine Curcio PhD, K Bailey Freund MD, Rose Dolz-Marco MD, Orly Gal-Or MD

Purpose
Drusenoid pigment epithelial detachments (PEDs) are a well-defined lesion with a pathway to atrophy and AMD. We have analyzed relationships between retinal pigment epithelium (RPE) and drusen volume changes during the PED life cycle from genesis through resorption.

Methods
Cases of drusenoid PED were tracked using spectral domain OCT through periods of growth and collapse. Volumetric calculations and piece-wise linear regression analysis were used to determine the breakpoint between growth and collapse. Spectral domain OCT scans were independently evaluated for the appearance of internal hyper-reflective foci, acquired vitelliform lesions (AVLs), and thinning, as well as disruption of the RPE plus basal lamina band. The timing of these events with respect to the breakpoint was statistically evaluated. Morphometric characteristics of drusenoid PEDs were correlated with the PED collapse and the final visual acuity.

Results
Mean age of white patients with drusenoid PED in AMD was 75.3 years, and the mean period of follow-up was 4.1 years (median: 4.5 years; range: 0.6-6.6 years). The life cycle of drusenoid PEDs was asymmetric, in that the rate of collapse (0.199 mm³/month) was significantly faster ($P < .001$) than the rate of growth (0.022 mm³/month). The appearance of intraretinal hyper-reflective foci in the overlying neurosensory retina and AVLs preceded the breakpoint ($P < .001$). The timing of disruptions of the RPE plus basal lamina band did not differ from the breakpoint ($P = .510$). Maximal height, volume, and diameter of drusenoid PEDs were inversely correlated with final visual acuity (all $P < .001$) and positively correlated with a rate of PED collapse (all $P < .001$).

Conclusions
The life cycle of drusenoid PED is still poorly understood. However, our data suggest that spectral domain OCT signatures, including anterior migration, aggregation, and possibly cellular differentiation of RPE and even disintegration of the RPE layer into discontinuity with breaks or so-called “apertures,” in conjunction with changes in PED volume reduction as well as an AVL volume increase, may be markers for the onset of resorption in the lifecycle of these lesions.
Update on Cell-Based Therapies for Atrophic Maculopathy

Allen C Ho MD

I. Cell Therapy: Background

A. Retina has unique advantages as a target for cell-based therapies.1,2

1. The retina and retinal pigment epithelium (RPE) are accessible target tissues with vitreous surgery techniques for delivery of cell-based therapies.

2. Ocular immune privilege may reduce rejection of cell-based therapies delivered to the retina or subretinal space, and to date cell therapies appear well tolerated.

3. Diagnostic imaging techniques such as OCT, autofluorescent imaging, fluorescein angiography, adaptive optics, and microperimetry afford many unique structure-function correlations.

4. Because of these advantages, retinal diseases have moved to the forefront of clinical trials utilizing cell-based therapies.

B. Despite the advent of biological therapeutics, unmet medical needs persist for retinal diseases and retinal degenerations.

1. No effective treatment for geographic atrophy (GA) due to AMD

2. Nonresponders and partial responders in neovascular AMD and diabetic macular edema

3. No effective treatment for other retinal diseases—for example, macular (perifoveal) telangiectasia

4. Unmet medical needs can exploit vulnerable patients; complications were reported from an autologous adipose tissue–sourced “stem cell” program.3

II. Cell Therapy Sources: Stem Cells and Non-stem (Somatic) Cells (https://clinicaltrials.gov/ct2/results?term=cell+therapy+and+macular+degeneration &pg=1, assessed June 1, 2017)

A. Stem cells: two classic properties

1. Self-renewal: numerous cycles of cell division without differentiation

2. Potency: ability to differentiate into specialized cell types (totipotent, pluripotent, multipotent, unipotent)

B. Cell therapy sources

1. Embryonic stem cells: cell cultures derived from blastocyste or earlier stage embryo (Astellas, BioTime / Cell Cure OpRegen, Chinese Academy of Science Zhengzhou University, Federal University of Sao Paolo, Moorfield's Eye Hospital, Regenerative Patch Technologies, Stem Cells Inc., others)

2. Adult (somatic) stem and non-stem cells: Pluripotent adult stem cells are rare; although they can be found in umbilical cord blood,4 most adult stem cells are lineage restricted multipotent or unipotent5,6 (Janssen CNTO 2476 Palucorcel, MD Stem Cells Retina Associates of South Florida, others).

3. Induced pluripotent stem cells (iPSC): Can be derived directly from adult tissues such as skin fibroblasts and then differentiated into a variety of cell types. Recent work has provided evidence that both human photoreceptors and RPE can be derived from iPSC.6-8

C. Cell therapy

1. Somatic cells lack the ability to divide without differentiation.

2. Human adult umbilical cord cells (Janssen CNTO 2476 Palucorcel)

III. Cell Therapy Products Have the Potential to Meet Some of These Needs with 2 Potential Mechanisms of Action: Trophic and Regenerative

A. Secretion of supportive trophic factors in the pathological microenvironment (trophic tissue support)
1. Trophic cell therapy: Preclinical
   a. Adult umbilical cells CNTO 2476 (Centocor Janssen J&J) preserve retinal structure in the Royal College of Surgeons (RCS) rat retinal degeneration model.9

   ![Figure 2](image1)

   Figure 3.

   b. Adult umbilical cells CNTO 2476 (Centocor Janssen J&J) and their culture media alone induce RPE phagocytosis in cell culture (G Inana).

   ![CNTO 2476 Impact in RCS on RPE Phagocytosis](image2)

   Figure 4.

B. Replacement of diseased cells and tissue (tissue regeneration or cellular engraftment): Regenerative / replacement cell therapy studies10,11

   ![Regenerative](image3)

   Figure 5.

   C. Challenges exist in the development of cell-based products: ability to scale, predictability of animal models, surrogates for disease, allograft vs. xenograft, potential need for targeted cell delivery and new surgical techniques and instrumentation, measurable endpoints.

   ![Figure 6](image4)

IV. Janssen Cell Therapy Study12

Trophic mechanism of action: Phase 1/2a, multicenter, randomized, dose escalation, fellow-eye controlled study evaluating the safety and clinical response of a single, subretinal administration of human umbilical tissue–derived cells (CNTO 2476) in subjects with visual acuity impairment associated with geographic atrophy secondary to AMD10 (Janssen / Johnson & Johnson) at Wills Eye Hospital and Retina Institute of California. Note lack of subretinal pigmentation in this cell line.
V. Cell Cure / BioTime Cell Therapy Study

Replacement mechanism of action: Phase 1/2a clinical trial of human embryonic stem cell derived retinal pigment epithelium transplantation in advanced dry form of AMD: interim results (Cell Cure Neurosciences and BioTime) at Hadassah Hebrew University Medical Center. Note subretinal pigmentation in area of intra-operative subretinal bleb in Patients 1 and 2 but not in Patient 3.

VI. Astellas / Ocata Cell Therapy Study\textsuperscript{10,11}

Replacement mechanism of action: Phase 1/2 human embryonic stem cell-derived retinal pigment epithelium in patients with AMD and Stargardt macular dystrophy (Astellas Ocata) at Jules Stein Eye Institute, Wills Eye Hospital, Massachusetts Eye and Ear Institute, and Bascom Palmer Eye Institute. Note progressive subretinal pigmentation in these subjects.
VII. Potential Alternative Surgical Approaches for Subretinal Delivery: Janssen Ab Externo Subretinal Delivery and Subretinal Access System with No Retinotomy

Figure 11.

VIII. Summary

A. Cell-based therapy (stem cell and non-stem cell) are in clinical trials for atrophic AMD.

B. There are 2 mechanisms of action for cell therapies: trophic and regenerative

C. To date, cell therapies have been well tolerated in subjects with atrophic AMD. Clinical trials for trophic and regenerative studies are ongoing.

D. Improved surgical delivery of cell therapies is required for optimal safety and efficacy of these potential treatments.

References


Emerging Dry Macular Degeneration Treatments

David S Boyer MD

I. Risk Factors of Dry AMD
   A. Age
   B. Family history
   C. Gender
   D. Race
   E. Smoking
   F. Genetic factors
   G. High cholesterol
   H. Hypertension and cardiovascular disease
   I. Low intake of antioxidants / lutein

II. Age-Related Eye Disease Study (AREDS) Formula of Nutritional Supplement
   A. Proven to decrease risk of progression of dry AMD
   B. Did not prevent geographic atrophy (GA) from forming or progressing

III. Neuroprotection
   A. Ciliary neurotrophic factor (CNTF, Neurotech NT-501): Failed
   B. Intravitreal brimonidine tartrate (Alphagan P)
   C. Topical tandospirone (Alcon AL-8309B): Failed
   D. Topical OT-551 (Othera): Failed

IV. Reduce Toxic By-products
   A. Subcutaneous glatiramer acetate (Copaxone, TEVA Pharmaceuticals)
   B. Intravenous RN6G (anti-amyloid β antibody, Pfizer): Failed

V. Visual Cycle Modulators
   A. Oral ACU-4429 (Acucela): Failed; will be tested for Stargardt disease
   B. Fenretinide oral (Sirlon Therapeutics): Failed

VI. Other Mechanisms
   A. Increasing circulation
   B. Aldehyde trap
   C. Doxycycline (Actilate, Adoxa CK, Alodox, Doryx, Monodox, Oracea, Periostat, Vibramycin)
   D. Metformin (Fortamet, Glucophage, Glumetza, Riomet)
   E. Mitochondrial enhancement

VII. Complement Inhibition
   A. POT-4 (C3 inhibition, Potentia Pharmaceuticals)
   B. Eculizumab (C5 inhibition, Soliris / Alexion Pharmaceuticals)
   C. ARCI905 (C5 inhibition, Ophthotech)
   D. FCFD4514S (Lampalizumab, TNX-234; factor D inhibition, Genentech)
   E. rhCFHp (replacement of CFH, Ophtherion, Inc.)
   F. Factor B

VIII. Inflammatory Mechanisms
   A. Modulation of macrophages
   B. Inflammasomes inhibition
   C. Iluvien

Selected Readings
Identification of Markers for Disease Conversion in Early AMD

Ursula Schmidt-Erfurth MD

Impact of AMD Progression

Age-related macular degeneration (AMD) is still the leading cause of irreversible visual loss in the elderly population. Over time the disease progresses relentlessly towards late AMD. Late AMD can be broken down into 2 general forms, atrophic and neovascular; however, interindividual disease progression is variable and not all high-risk features in a macula progress to late AMD within an individual. The pathogenesis of AMD is still relatively unclear, and currently there is an effective treatment available only for the less common, neovascular form. Yet despite the availability of an efficient therapeutic strategy (ie, VEGF inhibition), most of the vision loss that has occurred during the initial phase of neovascular activity cannot be reversed and an early detection of disease conversion remains essential.

The introduction of OCT has had a profound impact on the assessment, early detection, and monitoring of AMD progression, by facilitating 3-D phenotyping of the retina and the neurosensory layers in fine detail. Thus, to expedite the search for therapies that could halt the progression of intermediate to late AMD it is essential to be able to identify early pathomorphological changes and predict individual AMD progression using adequate biomarkers that are accessible by OCT imaging.

Hallmarks of AMD Progression

A clinical hallmark of early AMD is the presence of drusen, which are focal deposits of cellular waste products that begin to accumulate between the retinal pigment epithelium (RPE) and Bruch membrane (BM). Excess drusen deposition can lead to damage of the RPE and an inflammatory or degenerative reaction that can result in retinal atrophy, the expression of vascular endothelial growth factor (VEGF) and subsequent neovascularization, or both. Drusen are dynamic structures that can increase in size, fuse, or regress. A drusen-related event of clinical interest is drusen regression—a naturally occurring phenomenon, where drusen spontaneously decrease in size or completely disappear. Although some eyes showed regression without subsequent late AMD onset, in many cases late AMD developed precisely at the location where drusen regressed; hence drusen regression is a potential surrogate anatomic endpoint of intermediate AMD.

We propose a data-driven predictive model of incoming drusen regression and disease conversion in early AMD using modern methods of machine learning. We developed an OCT-based drusen characterization using automated image analysis methods of the outer retina, with a focus on its shape and the local appearance of its structure and that of the overlying neurosensory layers, as well as its short-term longitudinal change. Using such characterization, we developed a machine learning method based on survival analysis to predict regression at the level of each individual druse.

Predictive Models Using Machine Learning

Machine learning is also the basis for automated segmentation of morphological layers or individual features associated with disease progression in AMD. The outer retinal layer segmentation (Figure 1) is based on the publicly available Iowa Reference Algorithms, which were first applied to obtain a segmentation of the outer nuclear layer (ONL). Then, we used the same graph-search segmentation approach with modified smoothness constraints, which define the allowed change in surface height when moving between neighboring surface points. The lower RPE surface is obtained as a surface positioned on the bright-to-dark intensity gradient, below the ONL, with a weak smoothness constraint to allow for the deformations introduced by drusen. This defines a layer consisting of the outer retinal hyperreflective bands (ORB) comprising outer photoreceptor segments and the RPE layer.

Hyperreflective foci (HRF) were identified as another major hallmark of early AMD activity. To segment HRF (Figure 2), a voxel classification method based on unsupervised representation and auto-context was developed. From a set of 2-D image patches at various scales (ranging from 2x2 to 40x40 px), a set of features was created using principal component analysis, where the first 15 eigenvectors were used as convolution kernels on the intensity scans. Then, from the convolutional features, a random forest classifier was trained to provide for every pixel of a B-scan, the probability that it belongs to HRF.

Figure 1. Example of outer retinal segmentation. Four surfaces are segmented, denoting 3 layers. ONL = outer nuclear layer, ORB = outer retinal band, comprising retinal pigment epithelium and outer photoreceptor segments.
Machine learning can be used to develop a data-driven interpretable predictive model of incoming drusen regression as a sign of disease activity and to identify OCT biomarkers associated with its risk in intermediate AMD. Patients with AMD were observed every 3 months, using Spectralis OCT imaging, for a minimum duration of 12 months and up to a period of 60 months. Segmentation of drusen and the overlying layers was obtained using a graph-theoretic method, and the HRF were segmented using a voxel classification method. Automated image analysis steps were then applied to identify and characterize individual drusen at baseline, and their development was monitored at every follow-up visit. Finally, a machine learning method based on a sparse Cox proportional hazard regression was developed to estimate a risk score and predict the incoming regression of individual drusen.

The predictive model was trained and evaluated on a longitudinal dataset of 61 eyes from 38 patients using cross-validation. The mean follow-up time was 37.8 ± 13.8 months. A total of 944 drusen were identified at baseline, out of which 249 (26%) regressed during follow-up. The prediction performance was evaluated as area under the curve (AUC) for different time points. Prediction within the first 2 years achieved an AUC better than 0.75. The predictive model proposed in this study represents a promising step toward image-guided prediction of AMD progression. Machine learning is expected to accelerate and contribute to the development of new therapeutics that delay the progression of AMD.
Machine Learning to Predict the Personalized Risk of AMD Progression from Imaging and Genetic Biomarkers

In patients with intermediate AMD, the risk and speed of progression to CNV or geographic atrophy (GA) are highly variable. Current risk assessment strategies rely on population-level associations rather than personalized approaches. We developed a fully automated machine learning method to individually predict AMD progression based on retinal imaging and genetics. Fellow eyes with intermediate AMD (n = 379) of patients enrolled in the HARBOR trial were included. For each eye, progression to CNV or GA was diagnosed based on standardized evaluation of monthly spectral domain OCT by 2 independent masked graders. As quantitative imaging biomarkers, we obtained a volumetric segmentation of retinal layers, drusen, reticular pseudodrusen, and HRF by fully automated image analysis at baseline and Months 1 to 4. We developed and validated a machine learning algorithm predicting the conversion to advanced AMD on an individual basis, using the extracted imaging biomarkers as well as known genetic risk factors of AMD (34 single-nucleotide polymorphisms) as input features. By Month 24, 88 eyes (23%) had converted. Of those, 68 eyes developed CNV and 20 eyes developed GA. The automated algorithm differentiated converting from nonconverting eyes with an area-under-the-receiver operating characteristic curve of 0.73. It was also feasible to differentiate a priori between GA and CNV with an accuracy of 0.80 for GA and 0.66 for CNV. The most critical features for progression were intraretinal HRF and reticular drusen. Including genetic markers did not further contribute to the prediction. Hence, we conclude that automated analysis of OCT biomarkers allows a personalized prediction of AMD progression. In our cohort of patients with unilateral CNV, genetic characterization did not add additional accuracy to the prediction of AMD conversion of the fellow eye.

Perspectives for Monitoring AMD Conversion

Intermediate AMD progresses in remarkably varied ways across patients and there are currently no known sensitive and specific biomarkers indicating type and timing of individual AMD progression. Detecting late AMD at the time of its onset is crucial for initiating effective therapy and preventing vision loss, but as the onset of late AMD has often already resulted in irreversible vision loss, therapeutic interventions need to ultimately target AMD at an intermediate stage when function is still intact. Efficient screening in millions of patients with early AMD can only be undertaken if the pathognomonic risk factors for progression/ conversion are recognized and targeted. Furthermore, the availability of robust biomarkers for disease progression is a crucial prerequisite for the development of innovative therapeutic strategies, particularly in a slowly and variably progressing disease such as intermediate AMD.

The pathways leading from intermediate to late AMD often have a preceding event of drusen regression in common. Therefore, we developed an interpretable predictive model of individual drusen regression in a data-driven way, in an effort to predict and identify markers of risk of imminent drusen regression. Furthermore, we suggest a predictive model for conversion of early AMD to active advanced AMD based on morphologic biomarkers such as alterations in the appearance of neurosensory layers and HRF, as well as age and genetic markers.

In summary, results of our pilot studies show that multidimensional patterns of OCT biomarkers are predictive of...
disease conversion in early AMD. Predictive and interpretable models of disease development are greatly needed to improve early patient management / screening for patients at risk and to increase our knowledge of pathophysiologic mechanisms of AMD progression. The proposed models allow personalized, objective, and reproducible prediction of AMD conversion, which develops within a predictable time frame. It is a promising step toward identification of innovative imaging biomarkers of imminent conversion from intermediate to late disease in AMD, and will aid in the development and evaluation of new interventions that target intermediate stages of AMD.

**Selected Readings**


External Drainage during Vitrectomy

J Michael Jumper MD

I. Introduction

A. Subretinal fluid drainage during scleral buckling procedures for rhegmatogenous retinal detachment (RRD) has been utilized for over 50 years.

B. Multiple drainage techniques have since been described to improve overall surgical outcomes and decrease the rate of complications. Several of these papers have described success with external drainage with a needle, including 2 recent reports of needle drainage utilizing chandelier illumination and contact or noncontact wide-field viewing systems.

C. None of these publications has discussed the use of this technique in anticipation of pars plana vitrectomy for repair of complex retinal detachment or retinoschisis.

D. We describe a technique of external drainage during vitrectomy in the treatment of progressive bulbar retinoschisis, severe exudative retinal detachment and RRD associated with retinoschisis.

II. Methods

A. Retrospective review of 4 eyes of 4 patients with bulbar subretinal fluid involving or threatening the macula, who underwent scleral buckling surgery with external drainage prior to pars plana vitrectomy and any other necessary procedures by one surgeon.

B. All patients had undergone a comprehensive ophthalmic examination by the same surgeon prior to surgical intervention.

C. Surgical technique

1. After performing a 360-degree conjunctival peritomy, the recti muscles were hooked and isolated with 2-0 silk sutures, and an encircling scleral band was placed.

2. The buckle was then affixed to the sclera with single interrupted 5-0 nylon horizontal mattress sutures in each of the 4 quadrants, and a Watzke sleeve was placed in the superonasal quadrant.

3. An infusion cannula was placed through the pars plana away from the bulbar retinal detachment or retinoschisis. A 25-gauge trocar-based chandelier light was then inserted 3.0-3.5 mm posterior to the limbus, opposite the area with the highest detachment or greatest schisis.

4. The scleral buckle was then tightened and the intraocular infusion pressure was raised. A wide-field noncontact viewing system attached to a microscope was used to visualize the fundus. A 25-gauge 0.5-inch needle on a tuberculin syringe with the plunger removed was positioned within the bed of the buckle, beveled away from the sclera, in the area of greatest bulbar detachment or retinoschisis.

5. With direct visualization through the operating microscope, the flat end of the needle was used to indent the sclera and anticipate location of entry of the needle. Once the drainage site was chosen, the needle was slowly inserted until the tip of the needle was visualized in the subretinal or intraschisis space. Drainage of fluid was continued until the detachment or schisis cavity had collapsed.

6. Elevated IOP (60 mmHg) was maintained during the drainage until after the needle was withdrawn. The puncture site was also monitored for any hemorrhage.

7. At this point, with the collapse of the large bulbar detachment or schisis cavity, surgery proceeded with standard pars plana vitrectomy with or without lensectomy, membrane peel, or intraocular gas tamponade.

III. Results

A. Four eyes of 4 patients who underwent scleral buckling with external drainage prior to vitrectomy by a single surgeon for a complex retinal detachment or retinoschisis were included in this series.

1. Two of the patients were men and 2 were women.

2. The average age at presentation was 50 years of age (range: 18 to 71).

3. Macular status

a. Two of the patients were macula-on at the time of surgery with vision of 20/40 or better.

b. Two of the patients were macula-off, with vision of hand motions or worse.

4. Average follow-up time was 25 months (range: 6-42).

5. All 4 patients were attached after a single surgical intervention.

a. One patient required a second surgery for removal of silicone oil and placement of anterior chamber IOL.

b. Another had the eye enucleated due to poor cosmetic appearance and pain.

6. No patients developed complications from the external drainage.
Selected Readings


Visual Recovery in Eyes with No Light Perception (NLP) after Open Globe Injury

Marco A Zarbin MD PhD FACS and Neelakshi Bhagat MD MPH

I. Background

A. Severe ocular trauma is a major cause of profound visual loss among young persons, who may be at higher risk for subsequent injury to their fellow eye.

B. Traditional practice has been to enucleate NLP eyes to reduce the risk of sympathetic ophthalmia or for cosmetic reasons, or simply to observe them.\textsuperscript{1,2} Loss of light perception after open globe injury, however, does not necessarily mean the patient will have permanent visual loss.\textsuperscript{1-10}

C. Reported visual recovery rates from NLP to LP or better after globe rupture range from 4\% to 33\%.\textsuperscript{3-12}

Soni et al:\textsuperscript{12} Of 73 NLP eyes (73 patients) with open globe injury that underwent primary repair, final VA was ≥ light perception (LP) in 17 eyes (23\%): 20/100 in 1 eye (1\%); counting fingers in 2 eyes (3\%); hand motion in 9 eyes (12\%); LP in 5 eyes (7\%); and NLP in 56 eyes (77\%).

II. Patient Selection

There is no set of findings (except optic nerve avulsion, optic nerve transection, profound loss of intraocular contents) that allows clinicians to be certain that NLP status is permanent after open globe injury.\textsuperscript{3-12}

III. Limitations of Clinical Exam

A. Assessment of LP with indirect ophthalmoscope is not always reliable.\textsuperscript{13} Influence of cognition:

1. Age: infant, child, adult, aged
2. Mental status: unconscious, incompetent, intoxicated

B. Influence of reversible anatomic changes that can create reversible loss of LP:

Choroidal or subretinal hemorrhage ± dense vitreous hemorrhage (VH), especially in presence of retinal detachment

IV. Focus on Anatomic Findings vs. Psychophysical Findings\textsuperscript{14}

A. Identify findings amenable to surgical repair. 
B-scan echography is best to identify:

1. Retinal detachment
2. Subretinal hemorrhage
3. Choroidal hemorrhage

B. Identify findings consistent with irreversible loss of vision. CT/MRI is best to identify:

1. Optic nerve avulsion / transection (identification difficult)
2. Profound loss of intraocular contents

V. Approach: Staged Surgery

A. First procedure

1. Repair ruptured globe if possible.
2. Remove foreign bodies.
3. Remove damaged tissue: extruded tissue, cataractous lens.
4. If possible, drain choroid hemorrhage.

B. Second procedure

1. Timing
   a. May be important to functional and anatomic success
   b. Usually determined by timing of liquefaction of suprachoroidal hemorrhage (echography)
   c. Plan for surgery within 2 weeks of injury.
2. Techniques
   a. Intraoperative keratoprosthesis if needed
   b. Drain suprachoroidal hemorrhage (6-mm cannula),
   c. Remove residual lens and/or foreign material if present.
   d. Remove vitreous and subretinal hemorrhage.
   e. Reattach retina (perfluorocarbon often used).
   f. Bimanual membrane dissection (especially for “napkin ring” subretinal fibrosis) ± 360° retinectomy.
   g. If extensive retina tear or retina incarceration in wound, consider silicone oil tamponade.

C. Potential benefit of pars plana vitrectomy: Example of Soni et al\textsuperscript{12}

Fifteen of 73 eyes (21\%) that presented with NLP after open globe injury underwent PPV to manage retinal detachment, VH, proliferative vitreoretinopathy, ± choroidal hemorrhage

1. Fourteen of the 15 (93\%) had final vision ≥ LP.
2. Fourteen of the 17 eyes (82\%) with final vision ≥ LP underwent PPV with mean follow-up of 18 months.
3. Eyes that underwent PPV were significantly more likely to achieve LP or better final vision than those that did not (odds ratio: 257; 95% CI, 25-2659).

4. Among 21 of 73 eyes (20%) that recovered LP on postoperative Day 1 (POD1) after open globe repair, final vision was LP or better in 13 (62%).

5. Among 52 of 73 eyes (71%) that did remain NLP on POD1 after open globe repair, 4 (8%) of 50 recovered LP or better vision.

VI. Summary

A. Consider enucleation for open globe injuries with NLP and major loss of retinal tissue or optic nerve avulsion / transection.

B. NLP eyes after open globe injury that undergo successful primary closure with intact optic nerve should be considered for additional surgery, particularly if there is:
   1. Recovery of LP on POD1 after primary repair
   2. Treatable pathology underlying NLP status: extensive choroidal hemorrhage, extremely dense VH, and/or subretinal hemorrhage
   3. NLP in fellow eye

C. Patients should be counseled that the chance of recovering ambulatory vision is very low (~5%).

References


A Novel Technique for Scleral Fixation of IOL

Motohiro Kamei MD and Takuya Kataoka MD PhD

I. Treatment Options for Implantation of an IOL in Eyes with Absent or Insufficient Capsule Support

A. Anterior chamber IOL (AC-IOL)
B. Iris-fixated IOL (suture or iris-claw)
C. Sutured scleral-fixated posterior chamber IOL (PC-IOL)
D. Sutureless scleral-fixated PC IOL

II. Complications of Each Technique

A. Closed-loop AC-IOL: pseudophakic bullous keratopathy, chronic iritis, pigment dispersion
B. Open-loop AC-IOL: endothelial cell loss, cystoid macular edema, pupillary block, hypotension
C. Iris-fixated IOL: chronic iritis, pigment dispersion, peripheral anterior synechia, pupillary distortion, suture degradation (possible risk)
D. Sutured scleral-fixated PC-IOL: suture erosion / breakage / exposure, endophthalmitis, lens tilting / decentration, iris capture, ocular hypertension, hypotony
E. Sutureless scleral-fixated PC-IOL: intraoperative haptic deformation / breakage, endophthalmitis, lens tilting / decentration, iris capture, ocular hypertension, hypotony

III. Sutureless Scleral-Fixated PC-IOL

A. Benefit: No suture-related complication and better centering and less tilting of the IOL
B. Various modified techniques: forceps-guided, fibrin glue-assisted, needle-guided, and sleeve-guided techniques have been reported.
C. Challenges remaining
   1. Difficulty of grasping the haptic tip, especially the tip of the second haptic
   2. Ciliary body detachment with introduction of the forceps through the sclerotomy
   3. Breaking or bending of the haptic when it is pulled out
   4. Leakage of intraocular fluid from the wound, which requires suturing
D. Even the most advanced technique, double-needle technique, requires controlling the position of the IOL in the eye when grasping the haptic with a forceps or introducing the haptic tip into a thin needle. Furthermore, stress on the wound from forceps applied forcibly to grasp the haptic, especially the second one, induces tissue damage.

IV. Novel Surgical Procedures

In this novel technique an extremely thin silicone tube (no. 244-1175-01, Hagitec Co., Ltd.; Chiba, Japan) is introduced into the posterior chamber through the corneoscleral wound and drawn out through a sclerotomy, and then the other end of the tube is connected to the tip of the IOL haptic outside the eye. Afterward, the haptics are drawn out of the eye from the posterior chamber by simply drawing the tube through the sclerotomy after inserting the IOL connected to the tube. This technique is easier because most maneuvers are performed outside the eye and less invasive because the silicone microtube is thin, thread-like, and soft.

Figure. 1. A radial, half-thickness scleral incision (1) about 1-mm long, 1.7 mm from the limbus is created. A second radial scleral incision (2) then is made in the same manner, parallel with and about 1.5 mm counterclockwise apart from the first incision. A scleral tunnel (3) is created between these 2 scleral incisions using a 27-gauge blade. A scleral pocket (4) about 0.5-mm long is made counterclockwise to the second radial incision as an extension of the first scleral tunnel. The same scleral incisions, tunnel, and pocket (5-8) are made in the same manner 180 degrees on the opposite side. A sclerocorneal incision 2.8-mm long (9) is made superiorly for later insertion of an IOL.
Figure. 2. A 30-gauge needle is inserted diagonally into the posterior chamber from the first scleral incision (1) bed 1.7 mm from the limbus.

Figure. 3. A straight 9-0 polypropylene needle is bent, inserted into the anterior chamber through the sclerocorneal incision (9), and connected to the 30-gauge needle.

Figure. 4. The 9-0 polypropylene needle is drawn out through the sclerotomy by pulling out the 30-gauge needle from the scleral incision (1). The 9-0 polypropylene filament is now passing from the sclerocorneal incision (9) through the anterior/posterior chamber to the first scleral incision (1).

Figure. 5. The end of a 9-0 polypropylene filament protruding from the sclerocorneal incision (9) is ligated to the end of silicone microtube about 10-cm long, and the end of the silicone microtube protruding from the ligation is trimmed.
Figure 6. The silicone microtube is drawn out from the posterior chamber through the sclerotomy to the outside of the first scleral incision (1) in an ab interno way by slowly pulling out the 9-0 polypropylene filament.

Figure 7. The silicone microtube is introduced through the scleral tunnel (3) by leading with the 9-0 polypropylene filament.

Figure 8. The same procedures are performed 180 degrees on the opposite side (5-7).

Figure 9. The other end of the silicone microtube is connected with the IOL haptic by inserting the haptic tip into the tube. A 3-piece acrylic IOL is used. The length of the overlap between the haptic and the silicone microtube is about 1 mm.

Figure 10. The IOL is inserted into the anterior chamber through the 2.8-mm long sclerocorneal incision (9). Both the antecedent and trailing haptics are connected to the end of the silicone microtube.
Figure. 11. Each haptic is drawn out from the posterior chamber through the sclerotomy to the outside of the first scleral incision (1) by slowly pulling out each silicone microtube and finally passed through the scleral tunnel (3) by leading with the silicone microtube.

Figure. 12. The tip of each haptic is disconnected from the silicone microtube and inserted into the scleral pocket (4).

References


To Peel or Not to Peel the Internal Limiting Membrane in Epiretinal Membrane Surgery

Lihteh Wu MD

I. Epiretinal membranes (ERMs) first described by Iwanoff in 1865.
Since then several names have been used to describe this condition:
A. Primary retinal folds
B. Cellophane maculopathy
C. Surface wrinkling retinopathy
D. Pre-retinal macular fibrosis
E. Macular pucker
F. Wrinkling of the internal retinal surface
G. Internoretinal fibrosis
H. Vitreoretinal interface changes

II. ERM: Introduction
A. ERMs are found in 9% of the population.
B. Many are asymptomatic.
C. A few cause metamorphopsia, decreased visual acuity, monocular diplopia, macropsia, and micropsia.
D. Possible to remove using vitreoretinal techniques
E. 6 patients (3 idiopathic ERM and 3 with ERM post rhegmatogenous retinal detachment)
1. Puckers removed via pars plana vitrectomy (PPV) and membrane peel (MP)
2. 5 patients with visual improvement
3. No recurrence of macular pucker
F. Early series reported favorable visual outcomes with 65% to 90% of patients undergoing PPV, improving their visual acuity.
G. Recurrence rate following PPV was 1% to 5%; however, no OCT at the time

III. To Peel or Not to Peel …
A. Increased tendency to stain and peel the internal limiting membrane in macular pucker removals
B. Development of chromovitrectomy made this easier.

IV. Internal Limiting Membrane (ILM)
A. The ILM constitutes the basement membrane of the Müller cells.
B. Composed of collagen fibers, glycosaminoglycans, laminin, and fibronectin
C. ILM plays an important role in the survival of retinal ganglion cells during embryogenesis.
D. No apparent harm induced in human adult eyes

V. ILM peeling during ERM removal does not have deleterious effects.
A. Little clinical attention paid to the ILM
B. ILM removal should be considered in all tractional maculopathies.

VI. Meta-analyses
A. Meta-analysis of 8 studies
B. Meta-analysis of 13 prior studies

VII. Why Not Peel the ILM?
A. Anatomical and ultrastructural changes within the macula have been described.
B. Unclear what the long-term effects are

VIII. Management
A. Laser?
B. PPV?
C. Observe?

IX. Paracentral Macular Holes
A. Reported to occur in 0.6% to 2.6% of macular surgeries with ILM peeling
B. Appear to occur at the site where ILM peeling was initiated or completed
C. ILM peeling may cause Müller cell damage, which in turn causes structural weakening of the retina, leading to macular hole formation.
D. ILM peeling may cause glial apoptosis and reduced retinal function.
E. Iatrogenic surgical trauma during grasping of the ILM with forceps may play a role.
F. Contraction of the remaining edge of the peeled ILM or ERM leads to continued traction and secondary hole formation.

X. Summary
A. Vitrectomy is the treatment of choice for symptomatic ERM.
B. ILM peeling does not offer any visual acuity improvement over no ILM peeling.
C. ILM peeling reduces the recurrence rate, but many recurrences are not clinically important.
D. Currently unclear if ILM peeling is detrimental to the eye.
E. Rare complications associated with ILM peeling have been reported (ie, eccentric MH, retinal thinning, and microscotomata).
Proliferative Diabetic Retinopathy Surgery: Scissor vs. Cutter

Andre V Gomes MD

I. Main Goals in Surgery for Proliferative Diabetic Retinopathy
   A. Clear the media
   B. Remove all fibrotic tissue and potential residual traction
   C. Reduce bleeding
   D. Avoid new breaks
   E. Reattach the retina
   F. Perform epiretinal membrane and or internal limiting membrane if needed
   G. Apply extensive panretinal photocoagulation
   H. Choose the appropriate tamponade when necessary

II. Recent Surgical Developments
   A. Wide selection of wide-angle viewing systems
   B. New light sources
   C. New machines
   D. Microincisional vitrectomy surgery with different gauge options
   E. The chromovitrectomy era
   F. Anti-VEGFs
   G. PFC liquids ...

III. What to Offer Our Patients?
   A. Segmentation / delamination
   B. “The probe only” technique
   C. Bimanual maneuvers
   D. 23, 25, 27 gauges ...

IV. Video Presentation
   Different complex cases using combined techniques in proliferative diabetic retinopathy surgery

V. Tips and Pearls

VI. A Simple Algorithm Is Proposed.

VII. Conclusion

Selected Readings


Panel: Fixing Retinal Detachments—Simple and Complex

Moderator: H Richard McDonald MD

Panelists: Susanne Binder MD, Ehab N El Rayes MD PhD, Yannek I Leiderman MD PhD, Young Hee Yoon MD
Retinal Vein Occlusion Case Panel Discussion

Moderator: Michael S Ip MD

Panelists: Sophie J Bakri MD, Colin A McCannel MD, Ingrid U Scott MD MPH

NOTES
Surgical Management of Massive Suprachoroidal Hemorrhage

Jose Garcia-Arumi MD

A 67-year-old woman with a high myopic eye developed a massive “kissing” hemorrhagich choroidal detachment during a trabeculectomy procedure. B-scan showed that 85% of the vitreous cavity was occupied by the choroidal detachment. We describe in the video the surgical approach.

With A- and dynamic B-scanning echography, the suprachoroidal hemorrhage was controlled until adequate clot lysis was observed (12 days).

A 25-gauge infusion cannula was introduced into the anterior chamber at the temporal quadrant and connected at 20-25 mm. A 4-mm radial sclerotomy was made in the quadrant with highest choroidal detachment. When the sclerotomy was almost full-thickness, we applied diathermy to close the choroidal vessels. With a 7/0 Vicryl needle, an incision was performed in the exposed choroid and the suprachoroidal hemorrhage was allowed to egress. While performing the 23-gauge microincisions at the pars plana, more drainage of the liquefied blood was observed. Anterior vitrectomy of the blood-stained vitreous was performed, and after some peripheral choroidal reattachment was obtained, a pars plana 6-mm infusion cannula was placed in the quadrant with less choroidal detachment. The pars plana infusion cannula was checked to be intravitreal, and the adjacent vitreous was cleaned with the help of a wide-field viewing system with a 160-degree precorneal lens, and a vitrectomy was performed. Then, once it was determined that vitreous and/or retina were not incarcerated in the anterior segment, perfluorocarbon liquid (PFCL) was injected, and the blood was pushed from the posterior choroid toward the anterior sclerotomies. As blood was removed, additional PFCL was injected up to the level of the sclerotomies, draining as much hemorrhage as possible. In this case, the hemorrhage drained through the sclerotomy out of the vitreous cavity, but also inward. Using the Chang cannula, while we were injecting the PFCL, the blood was drained inward, floating over the PFCL bubble, and was aspirated and removed with the cannula. Some clotted blood remained into the suprachoroidal space. Finally a PFCL–air exchange was performed, followed by a silicone oil exchange. Silicone oil was removed after 2 months. After total resorption of the hemorrhage, we can observe the retinal pigment epithelium changes induced by the blood.

Glaucoma surgery is one of the most common etiologies of massive suprachoroidal hemorrhage. Following this technique we have obtained satisfactory anatomic and visual results; the wide-field system facilitated the visualization of the whole massive suprachoroidal hemorrhage, and the PFCL allowed the drainage of the choroidal hemorrhage through the anterior sclerotomy.

Selected Readings
Bilateral Simultaneous Giant Retinal Tear Detachment

Remzi Avci MD

We present a case of a 58-year-old bilaterally pseudophakic male with nasal and temporal visual field loss in the left eye, and temporal visual field loss in the right eye. The BCVA was 0.4 and 0.5 in the right and left eye, respectively. On fundus examination, there was severe vitreous condensation in both eyes. A nasal giant retinal tear (GRT) of approximately 180° with macula-on nasal retinal detachment was observed in the left eye, and 130° temporal and 120° nasal giant tear with macula-on retinal detachment in the right eye.

Standard 23-gauge pars plana vitrectomy, removal of the anterior retinal flaps of giant tears, and perfluorocarbon liquid (PFCL)–silicone oil exchange was performed in both eyes. However, the anterior retinal flap of the very posteriorly located nasal GRT in the right eye was protected and reattached to prevent possible postoperative chronic hypotony complications secondary to large retinectomy after silicone oil removal. In the surgical technique, PFCL was injected as far as the posterior edge of the GRT, and subsequently the vitreous on the surface of the anterior retinal flap was shaved under air after partial fluid–air exchange. Then, the edge of the GRT was dried under air to prevent reverse slippage of the anterior retinal flap, and endolaser photocoagulation was performed to the edge of the tear under air before additional PFCL was injected to fill the vitreous completely. Finally PFCL–silicone oil exchange was applied. Two months after primary surgery, the silicone oil was removed from both eyes, and final visual acuity improved to 0.7 in the right eye and 0.8 in the left eye. The IOP was 16 and 17mmHg in the right and left eye, respectively.

In conclusion, we may prevent chronic postoperative hypotony complications secondary to large retinectomy in eyes with very posteriorly located GRT detachment, preserving the anterior retinal flap with a modified surgical technique.
Into the Deep with DSEK

Kevin J Blinder MD

This is a 40-year-old male with a history of trauma and past retinal detachment repair. The patient subsequently developed corneal decompensation and underwent a DSEK procedure. The video presentation will show a DSEK complication and its treatment.
Temporary Tamponade in Difficult Cases

Stanislao Rizzo MD

Treating recurrence of retinal detachment with proliferative vitreoretinopathy after silicone oil injection is always a difficult surgery. Different solutions have been proposed with different tamponades, but the results many times are not good.

The authors present surgical cases with a temporal tamponade of the lower retinal areas technique, which they also use in difficult cases of retinal and choroidal hemorrhagic detachment.
Retinal Detachment with PVR

Kouroos Rezaei MD

A young patient is presented with retinal detachment complicated with proliferative vitreoretinopathy. Patient undergoes vitrectomy surgery. Various surgical techniques with pearls and tricks are discussed during the video presentation.
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<td>None</td>
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<td>David M Brown MD</td>
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<td>Kazuaki Kadonosono MD</td>
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<td>Ivana K Kim MD</td>
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Apellis: C,O
Astellas Institute for Regenerative Medicine: S
Boehringer-Ingelheim: C
Carl Zeiss Meditec: C,S
Chengdu Kanghong Biotech: C
Digisight: O
Genentech: C,S
GlaxoSmithKline: S
Healios K.K.: C
Hemera Biosciences: C
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Ocunexus: C
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Unity Biotechnology: C

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Bayer Healthcare Pharmaceuticals: C
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Heidelberg Engineering: S
Novartis Pharmaceuticals Corp.: L
Optovue: C,L,S
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Adverum Biotechnologies: O
Astellas: S
Genentech: S

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Thrombogenics: C

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Allergan: S,C
Bausch+Lomb: L
Johnson & Johnson: L
QLT Phototherapeutics Inc.: C,L
Regeneron Pharmaceuticals Inc.: C,L

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Michael A Singer MD
Aerpio: C,S
Aestelis: S
Alimera Sciences Inc.: S
Amgen: C,L,S
Ampio: C,L,S
Bayer Healthcare Pharmaceuticals: L
Clearside: C,S
Genentech: C,S
Optos Inc.: S
Regeneron Pharmaceuticals Inc.: S,L
Santen Inc.: C

Rishi P Singh MD
Alcon Laboratories Inc.: C,S
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Ohr Pharma: E,O,S
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Regeneron Pharmaceuticals: C,S
Roche: S
SanoFi-Aventis: S
Santen Inc.: S
SKS Ocular LLC: O
ThromboGenics Inc.: S
Tyrogenex: C,S

William E Smiddy MD
None

Richard F Spaide MD
Topcon Medical Systems Inc.: C,P

Sunil K Srivastava MD
Allergan: C,S
Bausch+Lomb: C,S
Carl Zeiss Inc.: C
Optos Inc.: C
Regeneron Pharmaceuticals Inc.: C
Santen Inc.: C,S

Paulo E Stanga MD
Allergan: C,L
Bausch+Lomb: C,L,S
Bayer Healthcare Pharmaceuticals: C,L
Novartis Pharmaceuticals Corp.: C
Optos Inc.: C,L,S
Second Sight Medical Products Inc.: C,L,S
ThromboGenics Ltd.: C,L
Topcon Medical Systems Inc.: C,L,P,S

Giovanni Staurenghi MD
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Allergan: C
Bayer Healthcare Pharmaceuticals: C
Boehringer: C
Centervue: C,L,S
Genentech: C
Heidelberg Engineering: C,S,L
Hoffman La Roche Ltd.: C,L,S
Nidek Inc.: S
Novartis Pharmaceuticals Corp.: C,L,S
Ocular Instruments Inc.: P
Optos Inc.: C
Quantel Medical: C,S,L

Jennifer K Sun MD
Adaptive Sensory Technology: S
Boston Micromachines: S
Current Diabetes Reports: E
Genentech: S
JAMA Ophthalmology: E
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Merck & Co. Inc.: C
Novartis Pharmaceuticals Corp.: C
Optovue: S

Hiroko Terasaki MD
Alcon Laboratories Inc.: L,S,C
Bayer Healthcare Pharmaceuticals: L,S
Nidek: L,S
Novartis: L,S
Otsuka: L,S
Pfizer Inc.: L
Santen Inc.: S,L
Wakamoto: L,S
Zeiss: L

Akshay S Thomas MD
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John T Thompson MD
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Regeneron Pharmaceuticals Inc.: S

Michael T Trese MD
Digisight: O,C
Interview Medical Systems: O,P
Retinal Solutions: O,P

Russell N Van Gelder MD PhD
National Eye Institute: S
NovaBay: S

James F Vander MD
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Demetrios Vavvas MD
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Nadia Khalida Waheed MD
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John A Wells III MD
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Panoptica: C,S
Regeneron: S

George A Williams MD
Alcon Laboratories Inc.: C
OMIC-Ophthalmic Mutual Insurance Company: E

Tien Yin Wong MBBS
Allergan Singapore Pte Ltd.: C,L
Allergan Inc.: C,L
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Bayer Healthcare Pharmaceuticals Inc.: C,L,S
Novartis Pharma AG: C,L,S

Lihteh Wu MD
Bayer Health: C,L
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Novartis Pharmaceuticals Corp.: C
Quantel Medical: C,L

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