Retina 2014
Reaching New Heights

Program Directors
Peter K Kaiser MD and Pravin U Dugel MD

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

McCormick Place
Chicago, Illinois

Friday–Saturday, Oct. 17–18, 2014

Presented by:
The American Academy of Ophthalmology

Sponsored by an unrestricted educational grant from Regeneron Pharmaceuticals, Inc.

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2014 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 Chicago and Retina 2014: Reaching New Heights.

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Allegro: C
ArcticDx: C
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Pfizer, Inc.: C
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Second Sight Medical Products, Inc.: S
ThromboGenics, Inc: C,S
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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.

2014 Retina Subspecialty Day Meeting Learning Objectives
Upon completion of this activity, participants should be able to:

■ Explain the current management of macular edema secondary to retinal occlusive disease and diabetic retinopathy
■ Explain the pathobiology and management of atrophic and exudative AMD and other causes of CNV
■ Identify 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
■ Summarize current and new clinical trial data for retinal diseases such as AMD, diabetic retinopathy, and retinal vein occlusion

2014 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.

2014 Retina Subspecialty Day CME Credit
The American Academy of Ophthalmology is accredited by the Accreditation Council for Continuing Medical Education to provide CME 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.

Self-Assessment Credit
This activity meets the Self-Assessment CME requirements defined by the American Board of Ophthalmology (ABO). Please be advised that the ABO is not an accrediting body for purposes of any CME program. The ABO does not sponsor this or any outside activity, and the ABO does not endorse any particular CME activity. Complete information regarding the ABO Self-Assessment CME Maintenance of Certification requirements is available at http://abop.org/maintain-certification/part-2-lifelong-learning-self-assessment/cme.

NOTE: Credit designated as “self-assessment” is AMA PRA Category 1 Credit™ and is also preapproved by the ABO for the Maintenance of Certification (MOC) Part II CME requirements.

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. Please contact the AMA to obtain an application form 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.

Attendance Verification for CME Reporting
Before processing your requests for CME credit, the Academy must verify your attendance at Subspecialty Day and/or at AAO 2014. 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 Final Program and/or Subspecialty Day Syllabus exchange voucher(s) onsite;
■ Register in advance and pick up your badge onsite if materials did not arrive before you traveled to the meeting; or
■ Register onsite.

CME Credit Reporting
South, Level 2.5; Academy Resource Center, Booth 508
Attendees whose attendance has been verified (see above) at AAO 2014 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 2014 at the CME Credit Reporting booth.

Academy Members: The CME credit reporting receipt is not a CME transcript. CME transcripts that include AAO 2014 credits entered onsite will be available to Academy members on the Academy’s website beginning Nov. 13, 2014.
NOTE: CME credits must be reported by Jan. 15, 2015. After AAO 2014, 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 2014.

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 2014 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 Form
- Instruction Course Verification Form

Visit the Academy’s website for detailed CME reporting information.
The Charles L Schepens MD Lecture
Management of Posterior Uveal Melanoma: Past, Present and Future

Friday, October 17, 2014
10:15 AM – 10:35 AM

Jerry A Shields MD

Jerry A. Shields, M.D. is director of the Oncology Service at Wills Eye Hospital and Professor of Ophthalmology Thomas Jefferson University in Philadelphia. He was a resident at Wills Eye Hospital and completed fellowships in ophthalmic pathology and retinal surgery. For more than 40 years, he has been active in the care of patients with ocular tumors and in clinical research related to tumors of the eyelids, conjunctiva, intraocular structures, and orbit.

He has authored or co-authored more than 1300 articles in scientific journals and more than 548 textbook chapters for a total of more than 1756 scientific publications. He has authored or co-authored 13 major textbooks and has given 1531 national and international lectures, including 77 named lectures. He has also received 30 national and international academic awards for his contributions. In March 2013 he received the prestigious National Physician of the year award (named top doctor in America) for Clinical Excellence by Castle Connolly Medical LTD, NY, NY.

Dr. Shields has served on the editorial boards of 13 journals. He was the organizer and first president of the International Society of Ocular Oncology, president of the Ophthalmic Club of Philadelphia, and president of the Wills Eye Medical Staff, and president of the Macula Society in 2009. Dr. Shields is married to Dr. Carol Shields also practices on the Oncology Service of Wills Eye Hospital and has made many similar contributions. They have 7 children ranging from ages 25 to 13 years of age.
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College of Physicians and Surgeons
Columbia University Medical School

Leandro C Zacharias MD
Sao Paulo, Brazil

Marco A Zarbin MD PhD FACS
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Institute of Ophthalmology and Visual Science
Rutgers-New Jersey Medical School
How To Text in Your Questions for Panels

From your mobile device, compose a text to 41411. In the message field type aprsr insert a space and then type your question and hit send.

Or to connect via Wi-Fi on your Smartphone, tablet or laptop, scan the QR Code in the syllabus to go to the question page; or open your browser and go to http://ai.acuport.org, then select the Room: North Hall B and follow the instructions to submit a question to the panel.

Participating Panels:

- Pediatric Surgery Case Discussion
- Retinal Vein Occlusion
- How I Treat Exudative AMD
- How to Treat Uveitis
- Fact or Fiction
- Surgical Complications
# Retina 2014: Reaching New Heights

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

## FRIDAY, OCT. 17, 2014

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<tr>
<th>Time</th>
<th>Event</th>
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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>Peter K Kaiser MD*</td>
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<td>Pravin U Dugel MD*</td>
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### Section I: Vitreoretinal Surgery, Part I
Moderators: David R Chow MD, Kourous Rezaei MD*

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<tr>
<td>8:05 AM</td>
<td>Introduction and Self-assessment</td>
<td>David R Chow MD*</td>
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**Fact or Fiction: Current and Emerging Vitrectomy Systems**
Moderator: David R Chow MD

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<th>Time</th>
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<tr>
<td>8:07 AM</td>
<td>Faster Cut Rates Are Better and Safer: Fact</td>
<td>Carl C Claes MD*</td>
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<tr>
<td>8:10 AM</td>
<td>Faster Cut Rates Are Better and Safer: Fiction</td>
<td>William E Smiddy MD</td>
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<tr>
<td>8:14 AM</td>
<td>Smaller Gauge Is Better and Safer: Fact</td>
<td>Maria H Berrocal MD*</td>
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<tr>
<td>8:17 AM</td>
<td>Smaller Gauge Is Better and Safer: Fiction</td>
<td>David F Williams MD</td>
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<tr>
<td>8:21 AM</td>
<td>Duty Cycle Control Is Necessary: Fact</td>
<td>Kirk H Packo MD*</td>
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<tr>
<td>8:24 AM</td>
<td>Duty Cycle Control Is Necessary: Fiction</td>
<td>Carl C Awh MD*</td>
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<tr>
<td>8:28 AM</td>
<td>Endoscopic Vitrectomy Is a Needed Skill: Fact</td>
<td>Victor H Gonzalez MD*</td>
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<tr>
<td>8:31 AM</td>
<td>Endoscopic Vitrectomy Is a Needed Skill: Fiction</td>
<td>Dean Eliott MD</td>
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<tr>
<td>8:35 AM</td>
<td>Peristaltic Pumps Are Better Than Venturi: Fact</td>
<td>Peter W Stalmans MD PhD*</td>
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<tr>
<td>8:38 AM</td>
<td>Peristaltic Pumps Are Better Than Venturi: Fiction</td>
<td>Steven T Charles MD*</td>
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**Surgical Debates**
Moderator: Kourous Rezaei MD*

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<tr>
<td>8:42 AM</td>
<td>Fixated IOL Is Better Than Anterior Chamber IOL: Pro</td>
<td>Jonathan L Prenner MD*</td>
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<tr>
<td>8:45 AM</td>
<td>Fixated IOL Is Better Than Anterior Chamber IOL: Con</td>
<td>Richard S Kaiser MD*</td>
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<tr>
<td>8:49 AM</td>
<td>Perfluoro-n-Octane Is Better Than Retinotomy in Rhegmatogenous Retinal Detachment Repair: Pro</td>
<td>Stanley Chang MD*</td>
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<tr>
<td>8:52 AM</td>
<td>Perfluoro-n-Octane Is Better Than Retinotomy in Rhegmatogenous Retinal Detachment Repair: Con</td>
<td>John W Kitchens MD</td>
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<th>Time</th>
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<tr>
<td>8:56 AM</td>
<td>Disposable Instruments Are Cost-effective and as Good as Reusable: Pro</td>
<td>Sunil Gupta MD*</td>
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<tr>
<td>8:59 AM</td>
<td>Disposable Instruments Are Cost-effective and as Good as Reusable: Con</td>
<td>Manish Nagpal MD*</td>
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<td>9:02 AM</td>
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<tr>
<td>9:03 AM</td>
<td>Pars Plana Vitrectomy With Scleral Buckle for Primary Retinal Detachment Repair Is Better: Pro</td>
<td>Gaurav K Shah MD*</td>
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<td>9:06 AM</td>
<td>Pars Plana Vitrectomy With Scleral Buckle for Primary Retinal Detachment Repair Is Better: Con</td>
<td>Paul E Tornambe MD*</td>
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<td>9:09 AM</td>
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<tr>
<td>9:10 AM</td>
<td>Combination Macular Surgery and Cataract Extraction Is Better for the Patient: Pro</td>
<td>Timothy G Murray MD MBA*</td>
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<tr>
<td>9:13 AM</td>
<td>Combination Macular Surgery and Cataract Extraction Is Better for the Patient: Con</td>
<td>Nancy M Holekamp MD*</td>
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<td>9:16 AM</td>
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<td>9:17 AM</td>
<td>Conclusion and Self-assessment</td>
<td>Kourous Rezaei MD*</td>
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</table>

**Section II: My Coolest Surgical Video**

Moderator: Tarek S Hassan MD*
Virtual Moderator: Donald J D'Amico MD*
Panelists: J Fernando Arevalo MD FACS*, Mark W Johnson MD*, Pauline T Merrill MD*, Virgilio Morales-Canton MD*, Steven D Schwartz MD*, Lihteh Wu MD*

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<tr>
<td>9:19 AM</td>
<td>Introduction and Self-assessment</td>
<td>Tarek S Hassan MD*</td>
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<td>9:21 AM</td>
<td>Persistent Optic Pit Maculopathy: Surgical Management with Autologous Fibrin</td>
<td>Sengul C Ozdek MD</td>
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<td>9:24 AM</td>
<td>Discussion</td>
<td>Grazia Pertile MD</td>
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<td>9:29 AM</td>
<td>Bilateral Gunshot Injury</td>
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<tr>
<td>9:37 AM</td>
<td>Novel OVDs Prior to PFO Injection Prevents Migration of PFO</td>
<td>Taiji Sakamoto MD PhD</td>
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<td>9:45 AM</td>
<td>Not New Technique: Coat’s Disease</td>
<td>Shunji Kusaka MD</td>
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<tr>
<td>9:48 AM</td>
<td>Discussion</td>
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<tr>
<td>9:53 AM</td>
<td>Heads Up: No Microscope Vitreoretinal Surgery</td>
<td>Claus Eckardt MD*</td>
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Vote for Coolest Surgical Video

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<td>10:03 AM</td>
<td>Advocating for Patients</td>
<td>Alan E Kimura MD MPH</td>
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<td>10:08 AM</td>
<td>Conclusion and Self-Assessment</td>
<td>Tarek S Hassan MD*</td>
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**The Charles L Schepens MD Lecture**

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<tr>
<td>10:10 AM</td>
<td>Introduction of the 2014 Charles L Schepens MD Lecture</td>
<td>David W Parke II MD*</td>
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<tr>
<td>10:15 AM</td>
<td>Management of Posterior Uveal Melanoma: Past, Present and Future</td>
<td>Jerry A Shields MD</td>
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<tr>
<td>10:35 AM</td>
<td>REFRESHMENT BREAK and RETINA EXHIBITS</td>
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</table>

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Section III: Business of Retina
Moderators: James F Vander MD, Lawrence S Halperin MD*

<table>
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<tr>
<td>11:22 AM</td>
<td>Introduction and Self-assessment</td>
<td>James F Vander MD</td>
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<tr>
<td>11:31 AM</td>
<td>The Affordable Care Act: The Sky Is Falling—Pro</td>
<td>George A Williams MD*</td>
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<tr>
<td>11:34 AM</td>
<td>The Affordable Care Act: The Sky Is Falling—Con</td>
<td>Paul Sternberg Jr MD</td>
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<tr>
<td>11:38 AM</td>
<td>The Future of Retina: A SWOT Analysis</td>
<td>David W Parke II MD*</td>
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Section IV: Pediatric Retina
Moderators: William S Tasman MD FACS, Michael T Trese MD*

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<td>Introduction and Self-assessment</td>
<td>William S Tasman MD FACS</td>
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<td>11:49 AM</td>
<td>Wide-Field Imaging in Pediatric Retinal Diseases</td>
<td>Antonio Capone Jr MD*</td>
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<tr>
<td>11:56 AM</td>
<td>Universal Screening for Pediatric Eye Disease</td>
<td>Darius M Moshfeghi MD</td>
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<tr>
<td>12:03 PM</td>
<td>Panel: Pediatric Surgery Case Discussion</td>
<td>Michael T Trese MD*</td>
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</table>

Panelists: Audina M Berrocal MD*, R V Paul Chan MD, Felix Y Chau MD, Kimberly A Drenser MD PhD, Philip J Ferrone MD*, Jonathan E Sears MD,

<table>
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<td>Conclusion and Self-Assessment</td>
<td>Michael T Trese MD*</td>
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<td>12:25 PM</td>
<td>LUNCH and RETINA EXHIBITS</td>
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Section V: Retinal Vein Occlusion
Moderators: James C Folk MD*, Sohan S Hayreh MD PhD DSc

<table>
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<td>1:40 PM</td>
<td>Introduction and Self-assessment</td>
<td>James C Folk MD*</td>
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<tr>
<td>1:42 PM</td>
<td>The Workup of the Retinal Vein Occlusion Patient—When Is it Necessary and What to Order?</td>
<td>J Michael Jumper MD*</td>
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<td>1:49 PM</td>
<td>Vein Occlusions: An Evidence-Based Approach to Initiation of Therapy—Clinical Trials and Subgroup Analysis</td>
<td>Julia A Haller MD*</td>
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<tr>
<td>1:56 PM</td>
<td>Panel: Retinal Vein Occlusion</td>
<td>David M Brown MD*</td>
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Panelists: Sharon Fekrat MD*, Seenu Hariprasad MD*, Derek Y Kunimoto MD JD*, Timothy W Olsen MD,* Ingrid U Scott MD MPH*, Adnan Tufail MD

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<td>What’s New on the Horizon From Retinal Vein Occlusion?</td>
<td>Joan W Miller MD*</td>
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<td>Conclusion and Self-assessment</td>
<td>Sohan S Hayreh MD PhD DSc</td>
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Section VI: Late Breaking Developments, Part I
Moderator: Evangelos S Gragoudas MD*, J Fernando Arevalo MD FACS*

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<td>Results of eROP Trial</td>
<td>Graham E Quinn 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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<td>Update of the Results of the Pan-American Collaborative Retina Study Group Studies</td>
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<td>A Retrospective Cohort Study in Patients with Tractional Diseases of the Vitreomacular Interface</td>
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<td>NEWTON Study: Intravitreal Aflibercept Injection for Previously Treated Macular Edema Associated With Central Retinal Vein Occlusions</td>
<td>Rahul Khurana MD*</td>
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**Break With the Experts**

3:04 PM – 3:42 PM  Moderators: M Gilbert Grand MD, Andrew J Packer MD

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<td>Wet AMD</td>
<td>Ivana K Kim MD*</td>
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<td>Business of Retina</td>
<td>Robert L Avery MD*</td>
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<td>Derek Y Kunimoto MD JD*</td>
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<td>Srinivas R Sadda MD*</td>
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<td>Mary Elizabeth Hartnett MD FACS*</td>
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<td>Sunir J Garg MD FACS*</td>
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<td>Vascular Occlusions</td>
<td>Ingrid U Scott MD MPH*</td>
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No asterisk indicates that the presenter has no financial interest.
### Section VII: First-time Results of Clinical Trials, Part I
Moderators: Suber S Huang MD MBA*, Marco A Zarbin MD PhD FACS*

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<td>iDEAL Phase 2 Study of Intravitreal iCo-007 for Diabetic Macular Edema</td>
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### Section VIII: Neovascular AMD
Moderators: Tien Yin Wong MBBS*, Masahito Ohji MD*

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<td>Development of Atrophy in Neovascular AMD Treated With Anti-VEGF Therapy: Results of the HARBOR Study</td>
<td>Srinivas R Sadda MD*</td>
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<td>Switching: Does It Improve Outcomes?</td>
<td>Rishi P Singh MD*</td>
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<td>Beyond Anti-VEGF: Is It Really a Choroidal Neovascular Membrane?</td>
<td>Pravin U Dugel MD*</td>
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<td>Sustained-Release Drug Delivery: Where Do We Stand?</td>
<td>Glenn J Jaffe MD*</td>
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**Rapid Fire: AMD Pipeline Update**

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<td>Update on Gene Therapy for AMD</td>
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<td>Update on Encapsulated Cell Technology</td>
<td>David S Boyer MD*</td>
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<td>Squalamine Eye Drops for Retinal Disease</td>
<td>Thomas A Ciulla MD</td>
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<td>Update on Integrin Antagonists</td>
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<td>Update on Anti-PDGF Drugs for AMD</td>
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<td>Peter K Kaiser MD*</td>
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SATURDAY, OCT. 18, 2014

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**Section IX: Imaging**
Moderators: Taiji Sakamoto MD PhD*, Richard F Spaide MD*

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<td>Ultrahigh-Resolution OCT Jay S Duker MD*</td>
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<td>8:19 AM</td>
<td>Adaptive Optics Mina Chung MD*</td>
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<td>8:23 AM</td>
<td>Wide Field Imaging Szilard Kiss MD*</td>
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<td>What’s Next in Fluorescein Angiography Richard B Rosen MD*</td>
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<td>8:31 AM</td>
<td>Fundus Autofluorescence: What Are We Looking At? Christine Curcio PhD</td>
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<td>Difficult Retinal Diagnosis With Multimodal Imaging Giovanni Staurenghi MD*</td>
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<td>The Real Meaning of Biomarker Assessment in Clinical Trials: Useful or Useless? Jason S Slakter MD*</td>
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<td>Introduction and Self-assessment Mark S Humayun MD PhD*</td>
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<td>8:56 AM</td>
<td>OCT Angiography – New Insights into Macular Telangiectasis Type 2 Richard F Spaide MD*</td>
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<td>9:02 AM</td>
<td>Artificial Retina: Beyond the Functional Benefits Stanislao Rizzo MD</td>
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<td>9:08 AM</td>
<td>Genotype Group Determines Beneficial or Harmful Response to AREDS Components: Analysis of Data from AREDS Report Number 38 Carl C Awh MD*</td>
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<td>Does RPED Size Determine Ranibizumab Treatment Success? A New Sub-Analysis of the HARBOR Study Pravin U Dugel MD*</td>
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<td>Conclusion and Self-assessment Mark S Humayun MD PhD*</td>
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**Section XI: Late Breaking Developments, Part III**
Moderators: Frederick L Ferris MD*, Judy E Kim MD*

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<td>A Randomized Clinical Trial of Intravitreal Bevacizumab vs. Intravitreal Dexamethasone for Diabetic Macular Edema: BEVORDEX Mark C Gillies MD PhD</td>
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<td>10:19 AM</td>
<td>Latest Treatments for Central Serous Chorioretinopathy Francine Behar-Cohen MD</td>
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<td>Phase Ib/Ia Study of AKB-9778, a Novel Tie2 Activator, in Diabetic Macular Edema Daniel Matthew Miller MD PhD</td>
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<td>Interim Phase 2 Results of Squalamine Lactate Ophthalmic Solution 0.2% (OHR -102) in Neovascular Age-Related Macular Degeneration</td>
<td>Prema Abraham, MD*</td>
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<td>Implantable MicroPump for Drug Delivery in Patients with Diabetic Macular Edema</td>
<td>Arturo Santos MD*</td>
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<td>Conclusion and Self-assessment</td>
<td>Judy E Kim MD*</td>
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**Section XII: Diabetes**
Moderators: Travis A Meredith MD*, Lawrence J Singerman MD*

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<td>Anti-VEGF Therapy Is a Sustainable Treatment Model for Diabetic Macular Edema: Pro</td>
<td>Lloyd P Aiello MD PhD* 92</td>
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<td>Anti-VEGF Therapy Is a Sustainable Treatment Model for Diabetic Macular Edema: Con</td>
<td>Harry W Flynn Jr MD 93</td>
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<td>Audience Vote: Final and Next Baseline</td>
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<td>There Are Systemic Safety Concerns With Anti-VEGF Therapy: Pro</td>
<td>Robert L Avery MD* 94</td>
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<tr>
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<td>Usha Chakravarthy MBBS PhD* 95</td>
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<td>Update on the DRCR Studies</td>
<td>Lee M Jampol MD* 100</td>
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<td>Update on Anti-VEGF Trials for Diabetic Macular Edema</td>
<td>Dante Pieramici MD* 101</td>
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<td>Subthreshold Laser for Diabetic Macular Edema</td>
<td>N H Victor Chong MD* 104</td>
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<td>Sustained-Release Steroids for Diabetic Macular Edema: Ozurdex</td>
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<td>Baruch D Kuppermann MD PhD* 109</td>
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<td>What’s Next in the Treatment of Diabetic Macular Edema?</td>
<td>Peter A Campochiaro MD* 111</td>
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<td>Lawrence J Singerman MD*</td>
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**Section XIII: First-time Results of Clinical Trials, Part II**
Moderators: Alexander J Brucker MD*, Gary C Brown MD*

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<td>Conbercept Clinical Trials</td>
<td>Peter K Kaiser MD* 112</td>
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<td>COMRADE-B Retinal Vein Occlusion Trial</td>
<td>Simon RJ Taylor MA PhD 113</td>
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<td>MEAD: Diabetic Macular Edema Trial Subanalysis</td>
<td>Anat Loewenstein MD* 115</td>
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<td>Lucentis Compared to Avastin Study: Two-Year Results</td>
<td>Karina Berg MD* 117</td>
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<td>VIVID/VISTA for DME: Two-Year Results</td>
<td>Diana V Do MD* 118</td>
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<td>Study Assessing Double-Masked Uveitis Treatment (SAKURA) Phase 3 Trial</td>
<td>Sunil K Srivastava MD* 119</td>
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### Section XV: Non-neovascular AMD

Moderators: Michel Eid Farah MD, Young Hee Yoon MD*

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<td>Natural History of Geographic Atrophy—What Do I Tell My Patient?</td>
<td>Philip J Rosenfeld MD PhD</td>
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<td>Notal Preferential Hyperacuity Perimeter</td>
<td>Susan B Bressler MD*</td>
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<td>Smartphone-Based Home Monitoring</td>
<td>Anne E Fung MD*</td>
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<td>Genetics and Risk of AMD</td>
<td>Emily Y Chew MD</td>
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**Rapid Fire: Dry AMD Trial Update**

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<td>Carl D Regillo MD FACS*</td>
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<td>Retinal Pigment Epithelial Transplantation</td>
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<td>Stem Cell Trials</td>
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<td>Visual Cycle Modulation</td>
<td>Jennifer Irene Lim MD*</td>
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<td>Dry AMD Trial Endpoints</td>
<td>Karl G Csaky MD*</td>
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<td>Conclusion and Self-Assessment</td>
<td>Young Hee Yoon MD*</td>
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### Section XVI: Vitreoretinal Surgery, Part II

Moderators: Mark S Blumenkranz MD*, Donald J D’Amico MD*

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<td>Jonathan L Prenner MD*</td>
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<td>What Did You Do?</td>
<td>Jonathan L Prenner MD*</td>
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<td>4:49 PM</td>
<td>The Lead Doesn’t Spare Anyone</td>
<td>Cesare Forlini 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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<td>Mauricio Maia MD*</td>
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<td>Malhar Soni MD MS PNB FRCS</td>
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<td>Leonardo Zacharias MD</td>
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<td>Conclusion and Self-assessment</td>
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Faster Cut Rates Are Better and Safer: Fact

Carl Claes MD

Citius, Altius, Fortius has always been the dream of humanity, and it has often become reality. Thirty years ago vitrectomies were performed with 20-gauge cutters that performed maximally at 600 cuts/min. Our senior colleagues might remember the lack of control and the spectacular iatrogenic complications connected to these “dinosaur” instruments. In order to acquire some degree of control, the aspiration rate had to be reduced maximally and the single-cut mode used. These settings are not compatible with efficient and safe vitreous removal. Fortunately, we don’t live in this pioneer era anymore, and vitreous can be safely removed in a matter of minutes. Ultrahigh-speed vitrectomy (10,000 cuts/min) removes extremely small bites of vitreous in a delicate way and causes less spatial perturbance than large, ripped off chunks, and in this way reduces fluid and gel turbulence. The result is a safer, more controlled vitrectomy in a stable environment. The real atraumatic shaving of the vitreous base and membranes becomes reality and changes our surgical approach.

Teamwork is essential for optimizing results:

- Ultrahigh-speed cutting (small chunks of vitreous)
- Duty cycle control (ratio open / closed port)
- Small-gauge cutters (handheld instrument)
- Strong cutting capacity (closing force, sharpness)
- Valved trocars (tissue protection, stability)
- Intraocular pressure control (stability)

Payoff: Increased noise and handpiece vibration

Gain: More control, safer, faster, more complete vitreous removal, less iatrogenic damage

A modern vitrectomy setting can offer you these options, making 3-D vitrectomy and peristaltic pumps look like obsolete techniques.
Since the initial inception of vitrectomy, technical advances have yielded increased capabilities, resulting in more diseases being amenable to treatment with improved safety. A recently improved feature is faster cut rate capabilities. Faster cut rates might be beneficial for certain specific situations, but they offer no advantage or may even be counterproductive in others. Vitrectomy surgeons should evaluate this and other capabilities for themselves, objectively assessing the value added to overall performance and avoid being unduly influenced by promotional hype.

Selected Readings


Smaller Gauge Is Better and Safer: Fact

Maria H Berrocal MD

There has been a trend toward using smaller gauges for vitrectomy surgery during the past decade. Initially, small-gauge vitrectomy with trocar/cannulas was deemed ideal for simple cases, and its main advantage was presumed to be its sutureless capability. Technological evolutions have shown that smaller instruments provide distinctive advantages in a number of pathologies. The smallest probes, namely 27-gauge vitrectors, are able to perform maneuvers not possible with larger vitrectomy probes.
Smaller Gauge Is Better and Safer: Fiction

David F Williams MD

The development of sub-20-gauge vitrectomy instrumentation and techniques has been heralded as a major advance in the armamentarium of the vitreoretinal surgeon. Proponents of small-gauge vitrectomy cite many advantages relative to traditional 20-gauge surgery. These purported advantages will be listed and analyzed sequentially below.

This analysis is presented in light of the author’s modified 20-gauge vitrectomy technique, which will be shown in a surgical video accompanying this presentation. Modified 20-gauge vitrectomy is characterized by a single superior limbal conjunctival incision from the 10:30–1:30 o’clock meridians with a 3-mm radial relaxing incision at the 10:30 o’clock meridian. Sclerotomies are created at the 11, 12, and 1 o’clock meridians, and the infusion cannula is placed through the 12 o’clock sclerotomy and secured with a preplaced figure-of-8 suture. At the completion of the vitrectomy, the working sclerotomies at 11 and 1 o’clock are closed with a single-suture pass, and the 12 o’clock sclerotomy is closed with the preplaced suture simultaneous with removal of the infusion cannula. The conjunctiva is closed with a single buried suture at the site of the 10:30 o’clock conjunctival relaxing incision. This technique places all surgical incisions inconspicuously under the upper eyelid, minimizes conjunctival incisions and visible postoperative ocular redness, and eliminates postoperative suture irritation.

Less Conjunctival Disruption and Scarring

In most cases, small-gauge surgery does not require large conjunctival incisions and associated sutures. This benefit is offset in cases in which a wound leak requires opening of the conjunctiva for placement of a scleral suture to prevent postoperative hypotony. Scleral depression for peripheral retina examination may also cause conjunctival tears, particularly in older patients with delicate conjunctiva, thus requiring conjunctival sutures. Relatively minor modifications in 20-gauge technique, as described above and seen in the surgical video accompanying this presentation, offset this purported advantage.

Faster Healing of the External Eye

When small-gauge surgery can be accomplished without the need for a conjunctival suture, healing of the external ocular tissues can indeed occur faster than with modified 20-gauge surgery. However, the occurrence of subconjunctival hemorrhages and occasional need for conjunctival sutures in small-gauge surgery offset this minor advantage.

Less Postoperative Discomfort

Postvitrectomy discomfort is due almost exclusively to the presence of exposed conjunctival sutures. A single buried conjunctival suture in my modified 20-gauge technique eliminates this small-gauge advantage.

Faster Visual Recovery

This purported advantage of small-gauge surgery is due exclusively to the absence of scleral suture-induced postoperative astigmatism. However, the majority of vitrectomies are done in individuals with macular pathology, for which macular function and associated visual recovery occur slowly over several months. In these cases, the transient presence of suture-induced astigmatism is immaterial with regard to visual recovery.

Fewer Intraoperative Complications

There is no consistent evidence that there are fewer intraoperative complications in small-gauge than in 20-gauge vitrectomy. The smaller port of a small-gauge vitrectomy instrument, in association with high-speed cutting, may theoretically allow for shaving of the vitreous close to the mobile retina, with less potential for retinal incarceration in the port and iatrogenic retinal breaks. However, retinal breaks can still easily occur with small-gauge vitrectomy and a careful surgeon can minimize iatrogenic breaks irrespective of instrumentation. Small-gauge surgery does have an advantage in select cases of diabetic vitrectomy, in which the small port close to the instrument tip can allow shaving of fibrotic and proliferative membranes from the retinal surface, with fewer instrument exchanges compared with 20-gauge surgery. Small-gauge surgery may be associated with higher risks of select intraoperative complications, such as intra- and postoperative choroidal detachment and unwanted anterior chamber air infusion during fluid-air exchange. Careful attention to cannula placement and management and further improvements in instrumentation may mitigate these increased risks of small-gauge surgery.

Fewer Postoperative Complications

In early experience with small-gauge vitrectomy, there were reports of an increased risk of postoperative complications such as hypotony and endophthalmitis. Improvements in surgical technique and instrumentation appear to have mitigated much of this increased risk. However, the weight of evidence suggests that, at best, the incidence of postoperative complications is similar for small-gauge and 20-gauge surgery. The incidence of postoperative retinal tears and detachment appears to be similar between gauge techniques.

Faster Surgery

Faster surgery is predicated upon lack of need for scleral and conjunctival sutures, and in select cases the need for fewer instrument exchanges. The need to carefully assess the cannula wounds and the occasional need for conjunctival and scleral sutures partially offsets this possible advantage. The modified 20-gauge technique completely offsets any potential speed advantage for small-gauge surgery. Surgical speed and efficiency are highly surgeon dependent, and it is possible that surgeon variation in these factors outweighs gauge variation.
The cost of surgery often receives less attention than other metrics. However, 20-gauge vitrectomy is materially less expensive than small-gauge surgery. In our open-access, nonsurgeon-owned, specialty surgical hospital ophthalmology facility, the cost of a 20-gauge surgery pak is $225, compared to $344 and $379 for 23-gauge and 25-gauge paks. Twenty-three-gauge and 25-gauge paks are 53% and 68% more expensive than 20-gauge paks, respectively.

Traditional 20-gauge vitrectomy has a long track record of effectiveness and safety in the treatment of a wide variety of vitreoretinal pathologies. While small-gauge vitrectomy may offer marginal advantages in select cases, an experienced surgeon and minor adjustments in 20-gauge technique can offset the majority of its purported advantages.

*In calendar year 2013 my personal procedure time average was 24 minutes in 270 consecutive 20-gauge vitrectomies for indications exclusive of retinal detachment. The average time for 12 other retinal surgeons was 36 minutes and 29 minutes for 23- and 25-gauge surgery, respectively. See Table 1.*

### Table 1. Phillips Eye Institute, Ongoing Professional Performance Evaluation (OPPE), January 1, 2013, through June 30, 2013. David F Williams, Ophthalmology

<table>
<thead>
<tr>
<th>INDICATOR</th>
<th>Number</th>
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<th>PEI Procedure Time Average</th>
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### References

Duty Cycle Control Is Necessary: Fact

Kirk H Packo MD

I. Duty Cycle: The Science

A. Definition of vitrectomy probe duty cycle: The proportion of time the vitrectomy port is open rather than closed.

\[ \% \text{ duty cycle} = \frac{\text{open time}}{\text{open time} + \text{closed time}}. \]

B. Bias

Duty cycle can be biased, either open or closed. In an open bias system, the cutter remains open between the cutting cycles, allowing flow between the individual cuts. With an open cycle, flow will decrease in a linear fashion. In a closed bias system, the cutter is closed between cuts, and flow is thus decreased. As the cut rate increases, the duty cycle of open time increases, and flow thus increases.

II. Requirements of Safe and Efficient Vitreous Removal

A. Control flow

There obviously must be some flow into the probe for vitreous and other tissues to be removed. Ideally a surgeon must be able to select the amount of flow desired at that point in the operation, but also do so with minimum unwanted vitreous traction. There are multiple ways in which flow can be controlled as partially defined by Poiseuille’s Law and determined by the design of the probe. Surgeon-controlled duty cycle optimizes cutting and aspiration control. For example, the following parameters will increase flow into the probe:

1. Increasing the vacuum applied to the probe
2. Increasing the infusion pressure into the eye
3. Increasing the duty cycle (in an open bias system)
4. Decreasing the cutting rate (in an open bias system)
5. Decreasing the duty cycle (in a closed bias system)
6. Increasing the cutting rate (in a closed bias system)
7. Decreasing the gauge (diameter) of the probe
8. Rotating the port toward the target tissue

Flow can be controlled with either an open bias or closed bias system. The same amount of flow can be obtained by manipulated the parameters in both systems.

B. Minimize vitreous traction.

A key goal is to remove only the intended tissue and not to inadvertently move unwanted tissue into the port, or to create distant traction that may result in retinal tears or other complications.

III. Designs of Vitrectomy Probes

The design of a vitrectomy probe determines the fluidic control available to the surgeon. Although new probe designs are being developed, such as constant flow (100% duty cycle) probes, there are 3 commonly available commercial designs:

A. Spring-return probe

A commonly used probe is a pneumatically actuated, spring return probe. Commercial examples include the Alcon Accurus and the Bausch + Lomb Stellaris. In this probe style, the guillotine blade is driven down across the distal open port, compressing a spring in the handle. The blade returns to the open position with release of the stored energy in the spring. Spring return probes are designed only to operate in the open bias configuration. The duty cycle is variable and will decrease as the cutting rate increases, with a concurrent decrease in flow. Traditional spring-driven probes have duty cycle limitations at high cut speeds, causing flow limitations.

B. Electric driven probe

This probe design, now less often employed, includes examples such as the Bausch + Lomb Millennium Lightening. The blade is driven by an electric solenoid motor and operates with a fixed 50% duty cycle, and flow is always constant. In this design, increasing or decreasing the cut rate has no impact on the flow. Flow is manipulated by other parameters, such as the line vacuum.

C. Dual-pneumatic probe

This design removes the spring and utilizes a pneumatic pulse to both drive open and drive closed the blade. This design allows the choice of the duty cycle bias. A commercial example of this design is the Alcon Constellation UltraVit. This system allows selection between 3 different modes: open bias (“core”), equal bias (“50-50”), and closed bias (“shave”).

IV. The Advantages of High Cutting Rate

Since the majority of commercial systems operate exclusively or offer a selection of an open bias duty cycle cutter, high cut rates offer the most control of tissue removal.

A. Slower movement of tissue into port at a given flow; slower movement reduces tissue movement and minimizes vitreous traction.

B. Removal of tissue in smaller pieces, reducing vitreous traction along the fibers. Higher cut speeds create smaller bites and reduced resistance to flow, which decreases pulsatile traction on the retina.
V. Why the Control of Duty Cycle Is the Key

Since flow can be controlled with both open bias and closed bias systems to the same level, it is often erroneously argued that “duty cycle control is unnecessary and only complicates the machine.” Also, since high-speed cutting has the advantage of minimizing traction and high-speed cutting has its advantages seen in open bias systems, why even bother to create a machine that offers duty cycle control? The answer is that such a system offers the optimum control of all duty cycles regardless of whether it is open or closed bias, and this cannot be achieved to this level with a spring return probe.

A. The laws of physics

1. Spring-return probes

When a spring-return probe is compressed by an air pulse, potential energy is stored in the spring. The Law of Conservation of Energy states that energy is neither created or destroyed in any reaction. When the spring releases its potential energy, allowing the reopening of the port, energy is used to overcome friction and other forces, so that the reopening of the port is always slower than the closing. This will add to the “closed time” of the port, thereby reducing flow.

2. Dual-pneumatic probes

When the spring is removed from the probe design, the application of air pulse energy to both close and reopen the port is direct and needs only to overcome friction. No “potential energy” is created that will be lost during the reaction. Thus, the speed of the opening and closing can be controlled to its maximum. A dual pneumatic probe produces increased port-open time vs. a spring-return system, which allows increased flow at higher cut rates.

B. What “duty cycle control” really means

The debate is not whether or not you have the ability to select an open or closed bias system during a vitrectomy. The debate is all about truly controlling the duty cycle parameters regardless of the bias. Most surgeons select an open bias system for most all work, either by choice or due to the fact that their commercial machine only offers an open bias cutter. Most surgeons also select high cut rates with an open bias system in order to minimize traction and maximize fluidic control. Spring-return probes can’t break the laws of physics and will always operate less efficiently at high cut rates than dual-pneumatic probes. Dual-pneumatic probes truly “control” the duty cycle inherent in all vitrectomy probes. Because a dual-pneumatic probe maintains efficient flow at very high cut rates, they will always outperform a spring-return design. Dual-pneumatic probes operating at 7500 cpm with surgeon-controlled duty cycle reduce iatrogenic tears and postop complications.

There is no debate! You can’t change the laws of physics. You have to be able to control duty cycle for the safest and most efficient vitrectomy.

Figure 1. Spring-return probes (Accurus) and dual-pneumatic probes (UltraVit) are compared, assessing duty cycle changes vs. cut rate. Spring-return probes at all gauges have significantly lower duty cycles and related flow rates at a given cut rate than a dual-pneumatic probe operating in an open bias cycle.

References

Duty Cycle Control Is Necessary: FICTION!

Carl C Awh MD

Consider the definition of necessary:

nec-es-sar-y [nes-uh-ser-ee] adjective
1. Absolutely essential, indispensable, or requisite
2. Needed to achieve a certain result or effect

Results of a recent poll of practicing vitreoretinal surgeons (to be reviewed during my presentation) confirm that fewer than 10% use duty cycle control during vitreoretinal surgery. Flow and traction are the major determinants of vitreous cutter efficiency and safety. Poiseuille’s Law calculation:

\[
\text{Volume flow} = \frac{(\text{pressure difference}) \times (\text{radius}^4)}{(8/\pi) \times (\text{viscosity}) \times (\text{length})}
\]

Traction during VR surgery is related to the tendency of tissues under stress to transmit unwanted forces to adjacent or remote parts of the eye. Traction during vitrectomy is minimized by higher cut rate and smaller port size. High cut rate both reduces traction and increases flow (because cutting vitreous into smaller pieces reduces its viscosity).

Duty cycle control can influence flow by varying the percentage of time the vitrectomy cutter port is open. However, flow can be easily and delicately controlled by adjusting vacuum (pressure difference), a method that is more intuitive and direct. Duty cycle control is an appealing concept with theoretical advantages in select situations, but is certainly not necessary for effective and safe vitreous surgery.
Endoscopic Vitrectomy Is a Needed Skill: Fact

Victor H Gonzalez MD

I. Current Dilemma: You cannot fix what you cannot see or treat.
Current visualization systems:
A. Microscope
B. Indirect ophthalmoscopy
C. Contact lenses
D. Wide-angle viewing lenses

II. Endoscopy in Ophthalmology: Historical Perspective
A. First used by Thorpe in 1934 for intraocular foreign body removal
B. This was followed by Norris and Cleasby in 1978 with a 1.7-mm shaft endoscope.
C. M Uram in 1991 introduced a 20-gauge endoscope that contained the fibers for the light, camera, and laser in one probe.

III. Technology: E2 Laser and Endoscopy unit (Endoptics)
A. Light: 175 watt xenon
B. Laser
   1. 810-nm diode
   2. 2 watts power output
   3. 640-nm diode laser aiming beam
C. Image
   1. High-resolution Toshiba camera
   2. 480 lines of horizontal resolution
   3. 90-140 degree field of view
   4. Probes
      a. Semidisposable
      b. 20- and 23-gauge diameter
      c. Wide cone of light, 110 degrees

IV. Applications
A. Overcoming anterior segment opacities
   1. Corneal scarring
   2. Corneal edema
B. Endocyclophotocoagulation
C. Panretinal photocoagulation
D. Removal of cyclitic membranes in hypotony
E. Identification of retinal breaks during retinal detachment surgery
F. Visualization during open globe repair involving the anterior segment
G. Intraocular foreign body identification and removal
H. Visualization of posterior segment in cases of severe endophthalmitis
I. Pediatric surgery

V. Surgical Pearls
A. Learning curve
B. Proper position of monitor
C. Proper hand position of surgeon
D. Awareness of instrument position
E. Familiarize and limit constant changing perspective of endoscopy

VI. Limitations
A. No bimanual capability with current technology
B. Current instrumentation under development
C. Postop monitoring is limited in cases with corneal opacity.

Selected Readings


Endoscopic Vitrectomy Is a Needed Skill: Fiction

Dean Eliott MD

I. Vitreoretinal Pathology in the Presence of Anterior Segment Opacities

A. The most common indication for endoscopic vitrectomy
   1. Case reports and small retrospective series indicate its use for the following:
      a. Rhegmatogenous retinal detachment repair
      b. Endophthalmitis treatment
      c. Intraocular foreign body removal
      d. Neovascular glaucoma treatment
      e. Subluxated/dislocated IOL management
      f. Retained lens fragment removal
      g. Proliferative diabetic retinopathy treatment
      h. Proliferative vitreoretinopathy treatment

B. Alternatives to endoscopic vitrectomy in the presence of anterior segment opacities
   1. Corneal opacity (presumed temporary): observation period for nonurgent conditions followed by vitrectomy
   2. Corneal opacity (presumed permanent): temporary keratoprosthesis followed by permanent keratoplasty or keratoprosthesis
   3. Hyphema/hypopyon/fibrin: anterior chamber washout and/or fibrin membrane removal
   4. Pupillary miosis: lysis of synechiae, sphincterotmy, iris hooks, or use of Avi wide-field viewing lens instead of BIOM
   5. Cataract: combined phacoemulsification/PCiol implantation/vitrectomy or pars plana lensectomy ± IOL implantation
   6. Iris-fixated IOL: iris hooks and/or use of Avi wide-field viewing lens instead of BIOM, or (rarely) explantation
   7. IOL surface opacities: removal of opacities or (rarely) explantation
   8. Capsular opacity: partial capsulectomy

II. Pathology Involving Retro-Iridal Structures

A. Endoscopic vitrectomy enables enhanced visualization.
   1. Case reports and small retrospective series indicate enhanced visualization of the following structures and/or pathology:
      a. Posterior iris surface
      b. Ciliary sulcus including IOL haptics and/or sutures
      c. Pars plicata including cyclitic membranes
      d. Pars plana including sclerotomy sites
      e. Ora serrata
      f. Peripheral retina including small retinal breaks

B. Alternatives to endoscopic vitrectomy for visualization of retro-iridal structures and/or pathology
   1. Scleral depression with:
      a. Wide-angle viewing: Avi wide-field lens provides 130 degrees; BIOM lens provides 120 degrees
      b. Endoillumination: using chandelier and/or endoillumination probe
   2. Scleral depression with external illumination:
      using operating microscope and/or endoillumination probe

III. Disadvantages of Endoscopic Vitrectomy

A. Cost of endoscopy system and probes
B. Learning curve: due to lack of stereopsis, difficulty with orientation, and dissociation between surgeon’s hand movement and intraoperative view as seen on the video monitor
C. Limited depth perception: lack of stereopsis; light and video ports are coaxial so no shadows are cast by instruments on the retinal surface.
D. Limited field of view: 23-gauge probe provides 90-degree field of view.
E. Limited image quality: images obtained by small-gauge endoscopy probes are inherently low resolution; 23-gauge probe provides 6,000 pixels.
F. No ability for bimanual surgery
G. Postoperative exams limited by anterior segment opacities, thus reliance on ultrasound to identify postoperative findings
H. Additional anterior segment surgery often required (for permanent media opacities)
I. Postoperative visual rehabilitation period lengthened due to additional procedures; may be important in pediatric patients at risk for amblyopia
Selected Readings


Peristaltic Pumps Are Better Than Venturi: Fact

Peter W Stalmans MD PhD

The Principles of Vacuum and Flow Control

Working within the eye requires specialist systems that observe fluid mechanics. Fluids continually deform under applied shear stress, but respond to pressure. Ophthalmic surgical devices employ various methods to create a vacuum and generate controllable pressure to induce flow and move fluids.1-5

A common and low-cost method of creating a vacuum is seen in the venturi pump. This leverages the venturi effect—the reduction in fluid pressure that results when a fluid flows through a constricted section of pipe—to reduce pressure within a cartridge located inside the ophthalmic device. The venturi pump is operated with compressed air. The speed at which the vacuum is created is mainly dependent on the volume of the cartridge. A large volume will result in slower vacuum response times. The efficiency depends on several factors, such as rise time, compressed air usages, noise, and costs. Typically, the efficiency is around 85%, and maximum vacuum is achievable at around 650 mmHg at sea level. Systems featuring this method of vacuum generation offer vacuum control.

Another method to create a vacuum is the displacement of fluid directly in the aspiration line. In ophthalmic devices, the most common method employs a peristaltic pump. By displacing the fluid at a point in the aspiration line, a pressure difference between the infusion pressure and this point is created in the aspiration line. Due to this pressure difference, an aspiration flow is created. Because this method uses the displacement of a fluid volume, the flow can be controlled by alternating the speed at which this volume is displaced. The pump rotation stops once the preset vacuum limit has been reached. Once the occlusion has been removed, the pump returns to the rotation speed to deliver the intended and preset flow volume.6-8 The faster the fluid is displaced, the faster the vacuum is created. Systems featuring this method of vacuum generation offer flow control.

Benefits of Vacuum and Flow Control

Vacuum control provides the opportunity to generate a vacuum and faster flow of fluids, which introduces the possibility to attract tissue, such as blood during vitrectomy or lens particles during phaco surgery.

Flow control provides a more constant flow, which provides enhanced safety when working in close proximity to delicate structures, such as (detached) retina or posterior lens capsule.

Limitations of Vacuum and Flow Control

Venturi pumps are inherently unable to provide precise, viscosity-independent flow control, whereas peristaltic systems characteristically produce mild flow fluctuations inherent to the rotary compression of flexible tubing. Concerns about the safety and precision of both systems, especially alongside recent advances in surgical “tools” and techniques—in particular, increases in peripheral vitrectomy, combined phaco-vitrectomy, and smaller gauge procedures—means that precise, viscosity-independent flow control is becoming even more critical.

A pivotal study published in 2013 by the European Vitreoretinal Society (EVRS) Retinal Detachment Study Group showed that vitrectomy for retinal detachment performed with vacuum-based venturi systems had a 2.9-times higher failure rate than the same surgery performed with flow-based peristaltic systems.9 A failure rate of 0.7% with 23-gauge and 1.1% with 20-gauge was achieved with peristaltic pumps, which rose to 1.4% with 23-gauge and 2.5% with 20-gauge when a venturi system was used.

The main limitation of the venturi pump is control of depression generated by the pump that affects aspiration control. The venturi pump can only create a depression of vacuum, increasing the gradient of pressure required to maintain flow. A typical vacuum pump has a minimum outflow, based on the pressure gradient and the instrumentation size, which rules out the possibility of controlling the aspiration flow below this. Venturi pumps cannot work with positive pressure at pump level, so to compensate, many surgeons set the cut rate as high as possible to provide a partial compensation for this issue. A lag time is caused due to the air volume of the often large (250 cc) cartridge that needs to be removed before the desired vacuum level is built. Recently, platforms have shown improvements in this regard, with the creation of smaller mini-chambers. However, this has not addressed the absence of true flow control, which is an inherent shortcoming of a venturi system. Peristaltic systems work with positive pressure at pump level, hence there is no minimum outflow, and the aspiration flow can be controlled between zero and any higher setting. Peristaltic systems generate a gradient of pressure, so that flow remains stable independent of the fluid’s viscosity, but characteristically produce mild flow fluctuations inherent to the rotary compression of a flexible tubing.

More recently, a new pump type became available to the ophthalmic surgeon: the VacuFlow Valve Timing intelligence (VTi®) system. This was developed to compensate for the weaknesses of both peristaltic and venturi systems. It consists of combined flow control and vacuum control in a single fluidics system, which combines a series of very precise computer-controlled operating pistons and closure valves working in very small flow chambers.

Commercially Available Systems

Traditional ophthalmic surgical devices feature a venturi pump (offering vacuum control only), or a peristaltic pump (offering flow control only). Since the introduction of intraocular ophthalmic surgery in the 1970s, these types of pump systems have been widely used by surgeons worldwide. However, later systems offer both vacuum and flow control, in response to the increasing proportion of clinical cases that require combined phacovitrectomy. This requires optimum versatility: vacuum mode for core vitrectomy with the opportunity to switch to flow mode for work in the periphery.

Systems currently commercially available include:

- The Alcon Constellation® Vision System is an ophthalmic microsurgical system for various types of eye surgery.
Launched in 2009, it features a venturi pump mechanism, which offers vacuum control only.

- Bausch + Lomb first launched its Stellaris system featuring a venturi pump and vacuum control in 2007. The Bausch + Lomb Stellaris PC (Procedural Choice) Vision Enhancement System—a subsequent combined vitrectomy and phacoemulsification system—was launched in 2010.
- DORC (The Dutch Ophthalmic Research Centre International B.V.) launched the DORC Associate platform in 2001. It also features dual venturi and peristaltic pumps to provide options for vacuum and flow control.
- DORC EVA was launched in 2013. It features a unique, new fluid control system—VacuFlow Valve Timing Intelligence (VTi)—which combines a series of very precise computer controlled operating pistons and closure valves working in very small flow chambers (6-ml volume). At present, this device was CE approved in 2013 but has not yet received FDA approval.

Vacuum vs. Flow Control

Vacuum control and flow control both have advantages and limitations. Generally, vacuum control can be useful during core vitrectomy when high vitreous removal speed is required, but flow control provides greater safety when working close to the (detached) retina. Better flow control allows for optimal surgical safety.

References

Peristaltic pumps are not optimal for vitrectomy for many reasons. Transorifice pressure (delta P) rises rapidly when dense epiretinal membrane, dense vitreous hemorrhage, scar tissue, lens material, or a dense subregion of peripheral vitreous occludes the port, resulting in aspiration surge when the highly viscous or dense material suddenly goes through the port. Aspiration surge causes acute vitreoretinal traction and retinal breaks. Peristaltic pumps directly control flow, not vacuum. Combining a flow-based peristaltic or piston pump system with vacuum sensors can only stop the pump when a preset vacuum level has occurred; it cannot proportionally control vacuum, especially if there is tissue, high viscosity material, or bubbles in the tubing.

Peristaltic pumps inherently produce low-frequency pulsatile vacuum as the rollers compress and decompress the tubing or membrane; they do not produce constant flow rates as some surgeons incorrectly state.

Peristaltic pump console-based flow control must interact through 2-way transmission of the fluidic signal through 84 inches of compliant tubing, with very slow response time driven automatically by sensors in the console or surgeon foot pedal command, while port-based flow limiting via small-diameter cutters and duty cycle control is instantaneous. Console sensor, pump-based flow control is limited by the compliance of the tubing, which causes high slew rate fluidic pulses to be smoothed out. In addition fluidics signals for sensing and control can only propagate at the speed of sound in fluid and must propagate from the cutter to the console and back to the cutter, a very slow process.

Peristaltic pumps and piston pumps are not effective at zeroing out the transorifice pressure gradient when the foot pedal is not depressed because they are not pressure controlled systems. Actively controlling both IOP and vacuum using a venturi pressure-based system enables the controller to eliminate dangerous residual vacuum or reflux when the surgeon lifts his or her foot to the nondepressed position. Simply stopping the peristaltic pump does not zero out transorifice pressure if there are any bubbles in the line, and it cannot compensate for tubing elasticity.

Peristaltic pumps suffer from another major disadvantage: they do not function well in an air-fluid mixture. A common and useful technique is to remove residual vitreoretinal traction after fluid-air exchange is performed—one type of interface vitrectomy. Air dampens and restricts retinal motion and the visible fluid-air exchange is performed—one type of interface vitrectomy; in fact the highest possible cutting rate is taught that cutting rates should be reduced when removing dense tissue through the port. In addition to producing port-based flow limiting, high cutting rates cyclically interrupt flow through the port, thereby increasing fluidic resistance, especially when using single actuation pneumatic cutters. High cutting rates are beneficial for all cases and all tasks because of increased fluidic stability, which in turn decreases pulsatile vitreoretinal traction on both detached and attached retina and thereby reduces the incidence of iatrogenic retinal breaks. The author refers to the amount of fluid that passes through the port during an open-close cycle as “pulse flow.” High cutting rates produce smaller pulses with much less pulsatile vitreoretinal traction than occurs with lower cutting rates. Small pulse flow means that the vitreous doesn’t have time to accelerate and produce remote effects because of the Force = Mass x Acceleration (F = MA) relationship. In addition, port-based flow limiting decreases surge and therefore iatrogenic retinal breaks after sudden elastic deformation of dense epiretinal membrane, lens material, or scar tissue through the port. In addition to producing port-based flow limiting, high cutting rates reduce the travel of uncut vitreous collagen fibers through the port. 25-gauge provides more resistance than 23-gauge because fluidic resistance is proportional to the fourth power of the diameter. It has long been incorrectly taught that cutting rates should be reduced when removing dense epiretinal membranes, scar tissue, and lens material, or performing core vitrectomy; in fact the highest possible cutting rate should be used for all tasks and all cases unless all the vitreous has been removed and very dense tissue must be addressed.

Selected Readings


Fixated IOL Is Better Than Anterior Chamber IOL: Pro

Jonathan L Prenner MD

The approach to IOL implantation in an eye with insufficient capsular support continues to present a unique surgical challenge. A report from the American Academy of Ophthalmology Ophthalmic Technology Assessment (OTA) group reviewed the standard approaches to this surgical problem—anterior chamber IOL (AC-IOL), scleral sutured posterior chamber IOL (PC-IOL), and iris fixated PC-IOL—and did not identify compelling data to recommend one technique over another. However, each approach has well-known liabilities. AC-IOL placement may increase the risk of developing glaucoma, intraocular inflammation, and corneal decompensation. Modern techniques including sutureless scleral fixation and transconjunctival IOL rescue allow one to avoid the complications of AC-IOL placement and reduce the complication rates seen with older approaches.

Selected Readings


Fixated IOL Is Better Than Anterior Chamber IOL: Con
Options in Selecting a Secondary IOL

Richard S Kaiser MD

Surgeons have multiple options when placing an IOL:
- Fixated in capsular bag
- Sulcus-fixated
- Fixated to the sclera
- Sutured to the peripheral iris
- Anterior chamber

If capsular support is adequate, placing an IOL in the bag or in the sulcus is the primary goal for surgeons. However, when there is no capsular support, the alternative approaches are limited to fixating the lens to the sclera or to the peripheral iris, or placing an anterior chamber IOL (AC-IOL). Techniques to secure the lens to the iris or sclera have gained popularity recently, but use of the modern, open-loop, flexible, “Kelman-style” AC-IOL remains an excellent choice and according to some published reports in the literature, may actually be the overall safer technique.

When choosing a technique for placing an IOL, a review of the literature supports the use of all 3 alternative methods; numerous reports demonstrate strong similarities in final visual results and complication rates for all 3 approaches. However, unusual yet serious complications, including retinal detachment, hemorrhagic choroidal detachment, and late onset IOL dislocation, can occur more frequently with scleral fixated IOLs.5,6

Old-style, closed-loop, rigid AC-IOLs are fraught with post-operative morbidity, most commonly ocular pain, decreasing endothelial cell counts, and corneal edema. These complications, however, do not occur with any regularity when using the modern-style, open-loop AC-IOL; in fact, there have been no studies linking these complications with the open-loop AC-IOL. Appreciating the differences between the two styles of AC-IOL is crucial when planning a surgical approach.

Putting the literature reports aside, individualizing the technique for the particular patient is crucial. Details of the clinical exam should guide the surgeon in selecting the proper approach. For example, an AC-IOL is a good option if the anterior segment is healthy—with a normal angle, minimal to no peripheral anterior synechiae, no significant glaucoma, and so on. Patient age and systemic health, such as the use of anticoagulants, should be considered as well. If there is no capsular support and the iris is disrupted or even absent, scleral fixation of the IOL is likely the best intraocular option. Surgeons should also self-assess their surgical skills and comfort with each technique in selecting an approach. Finally, surgeons should always keep in mind, when appropriate, that leaving the patient aphakic and using a contact lens may sometimes be the best option. At times, the best surgery may be no surgery.

References
Perfluoro-n-Octane Is Better Than Retinotomy in Rhegmatogenous Retinal Detachment Repair: Pro

Stanley Chang MD

It is preferable to avoid injury to the retina during vitrectomy for rhegmatogenous retinal detachment (RRD). Perfluorocarbon liquid (PFO) displaces subretinal fluid through the peripheral retinal breaks as it is injected into the posterior pole. Sometimes retinal breaks not seen preoperatively can be identified. The detached retina is more accurately repositioned and stabilized, and peripheral vitrectomy to remove traction around the retinal breaks can be done more safely. Application of endolaser photocoagulation is better visualized and with greater precision. Drainage retinotomies interrupt the retinal nerve fiber layer and result in larger visual field defects than the hole made. Most retinotomies are placed in the superior retina, resulting in defects in the inferior visual field, the most useful part of the visual field for most patients. Drainage retinotomies can also be a source of recurrent proliferation or bleeding. The most common complication of using PFO is subfoveal perfluorocarbon. This complication can be minimized by watching the interface of PFO in relationship to the retinal breaks, not elevating the retina break under PFO, using valved cannulas, and reducing the infusion flow as the eye is filled with more PFO. I have never had a case of subfoveal PFO, in thousands of cases.
Perfluoro-n-Octane Is Better Than Retinotomy in Rhegmatogenous Retinal Detachment Repair: Con
Perfluoron vs. Draining Retinotomy: The Case for Draining Retinotomy

John Kitchens MD

There is no question that Perfluoron (PFO) is a valuable tool, and retina surgeons all owe a great deal of gratitude to Dr. Chang for his help in developing it. However, it is not “labeled” for routine retinal detachment repair. According to the label for PFO:

Perfluoron® liquid is an intraoperative tool indicated for use during vitreoretinal surgery in patients with primary or recurrent retinal detachment complicated by penetrating ocular trauma, giant retinal tear(s), or proliferative vitreoretinopathy (PVR). (See www.myalcon.com/products/surgical/retinal-stabilizing-adjuncts/perfluoron.shtml)

Accordingly, PFO is not truly indicated for routine retinal repair. In addition, PFO has potential complications, including subretinal PFO, inflammation, elevated IOP, and corneal edema. The cost associated with PFO makes its routine use in surgery centers or fiscally responsible hospitals difficult.

Draining retinotomy, on the other hand, requires no additional equipment or cost. Like PFO, a posterior retinotomy allows for reattachment of the macula efficiently. Although posterior retinotomy creates an iatrogenic “break” in the retina, it is a defect in an area with no vitreous traction, thus reducing the potential for reattachment secondary to the drainage site. The other major concern with drainage retinotomies is the potential for the development of epiretinal membrane formation. This can be minimized by careful placement of the drainage site (nasal, anterior to the equator).

In summary, PFO is a useful adjuvant for difficult cases. Its use for routine cases is less clearly obvious. Cost and potential complications associated with its use make draining retinotomy a better choice.
Disposables Instruments Are Cost-effective and as Good as Reusable: Pro

Sunil Gupta MD

I. Cost-Benefit Analysis
   A. Reliability
   B. Quality
   C. Fragility
   D. Sterility

II. Reliability, Quality, Fragility
   A. Progress has been made over the last decade in smaller gauge instruments for vitreo-retinal.
   B. 20-gauge to now introduction of 27-gauge coming into mainstream
   C. For best surgical outcomes, we need the focus of the surgeon to be on addressing the pathology and not problem-solving instrument’s inconsistencies.
   D. Perfection requires:
      1. Consistency of feel and function of handle
      2. Consistency of finish of tips
      3. Reliability of surface of apposition and tension at tips equality every time
         a. For example, internal limiting membrane (ILM) should be able to picked up cleanly without any trauma to the underlying nerve fiber layer (NFL) or vasculature.
         b. Grasp should be consistent to peel ILM slowly without undo traction on underlying NFL to reduce hemorrhages.
         c. Task is challenging enough without guessing if the tip is perfectly apposed and grasping vital vs. nonvital tissue.
   E. Reliability, Quality, Fragility
   F. Cleaning
      1. Was somewhat challenging with 20-gauge instruments
      2. 25- and 27-gauge instruments require watchmaker skills to keep clean of tissues while preserving the integrity of the shaft, forceps’ arms and most importantly the tips that grasp the tissue.
      3. Facility costs, training of appropriate staff needed
      4. In a multispecialty OR, we have found these skill sets to be challenging.

III. Cost-Benefit Analysis
   A. Factors to weigh: Tangible
      1. Cost of disposable instrument
      2. Cost of reusables
      3. Cost of inventory of nondisposables for appropriate level of sterilization given they are a tube instrument
      4. Cost of facilities
      5. Cost of employee, overhead
      6. Cost of repair of damaged instruments
   B. Factors to weigh: Intangible
      1. Surgical delay of poorly functioning instrument
      2. Stress on surgeon and staff of malfunctioning instrument
      3. Tissue trauma from irregular function of instruments
      4. Potential risk of lack of sterility. Although complete sterilization should eliminate fungus, bacteria, and viral contaminants, prions are known to be present in retinal tissue and not susceptible to traditional sterilization techniques used in the OR or surgical centers.

IV. Safety: Cross-infection
   A. Inability to clean and decontaminate due to design, especially of tubed instruments
   B. Prions may be resistant to decontamination techniques.
   C. Endotoxin reaction: Excessive bacterial breakdown products, not removed by cleaning
   D. Chemical burns or sensitization: Residues from chemical decontamination agents that can adsorb on surfaces
   E. Patient injury: Device failure from reuse fatigue, material alteration, or increased susceptibility to brittleness
Disposable Instruments Are Cost-effective and as Good as Reusable: Con

Manish Nagpal MD

Unlike buckling procedures, vitrectomy requires the use of specialized machines and instrumentation to perform the requisite procedure. The vitrectomy machine remains the main unit that drives all the components. Different companies make different models of the vitrectomy machine; some of them offer reusable tubings and other components, while some have totally disposable packs of the same. Cost becomes a major issue in consideration while deciding such factors. In a country like India, where we work, most of the patients are self-paying and hence there is a limit to the amount one could charge a patient. Hence most of us do reuse some of the components related to these procedures to make them economically viable for our patients.

The key is to be able to balance: to limit the reuse to a minimum so as not to compromise efficiency and sterility while still being able to provide good eye care to patients who otherwise may not be able to afford the surgery. Only 10%-15% of our patient population could pay the premium cost of vitrectomy—that is, enough to reimburse theater costs for us to be able to dispose of instruments after a single use. But the rest of our patients would not benefit from this at all and if untreated may lose vision in the due course of time. Hence, if we want to be able to provide surgical care to a majority of our patients using the finest and safest tools made by the industry, then we may need to reuse some of the equipment with due discretion.

However, if cost were not an issue, I don’t think there is any reason why one should ever reuse any disposable instrument.
Pars Plana Vitrectomy With Scleral Buckle for Retinal Detachment Repair Is Better: Pro

Gaurav K Shah MD, Harpreet S Walia MD

I. Goals of Surgery
A. The goal of retinal detachment repair is to find all breaks, close all breaks, and relieve all traction off breaks.
B. The addition of a scleral buckle to pars plana vitrectomy (PPV) in certain situations can better accomplish this goal.
C. The addition of a scleral buckle to pars plana vitrectomy:
   1. Relieves anterior traction by minimizing residual vitreous base contraction
   2. Provides permanent circumferential support
   3. Improves intraoperative visualization
   4. Carries minimum complication profile
   5. Has a proven excellent single operation success rate

II. Misconceptions About Adding Scleral Buckle
A. Lower success rate
B. Choice of initial treatment does not make a difference in outcome of failures.
C. Excessive incidence of complications and induced myopia

III. Excellent Single Operation Success Rates (SOSR)
A. Phakic patients
   1. Allows more meticulous peripheral shave
   2. Multi-surgeon series showed up to 97% SOSR for SB/PPV vs. 84% for PPV alone
B. Pseudophakic patients
   1. Improves visualization that can be compromised from capsular remnants and/or IOL optical aberration
   2. Supports any unseen and small pseudophakic breaks
   3. Large meta-analysis showed 93% SOSR for SB/PPV vs. 88% for PPV alone
C. High-risk patients
   1. Inferior detachments: 95% SOSR shown in retrospective series
   2. Tears > 1 hour, preop PVR grade b-c, VH > 5 hours, RD in 2 or more quadrants: 75% SOSR for SB/PPV vs. 48% for PPV alone
   3. Giant retinal tears: 97% final success rate after SB/PPB

IV. Why does single operation success matter?
A. Fewer subsequent reoperations: 8% after SB/PPV vs. 22% after PPV alone
B. Less postoperative PVR: 5% after SB/PPB vs 16% after PPV

V. Complications
A. Data regarding diplopia, strabismus, and extrusion is based on literature over 15 years old.
B. Induced myopia not extreme; mean myopia induced −1.38 D after SB vs. 0.85 after PPV.

VI. Conclusions
A. Primary pars plana vitrectomy for retinal detachment is a good procedure but may not be appropriate for all retinal detachments.
   1. Every vitrectomy is not standard: procedure can have multiple variables including surgeon technique and amount of vitreous removed.
   2. The indentation and support of a scleral buckle is less variable.
B. The addition of scleral buckle to pars plana vitrectomy provides excellent single operation success rate with minimal complications and is an effective strategy for retinal detachment repair.

References


Pars Plana Vitrectomy With Scleral Buckle for Primary Retinal Detachment Repair Is Better: Con

Paul E Tornambe MD

I. The Goal of Retinal Surgery: The Patient’s Perspective
   Restore predetachment vision!!!
   A. Patients spend considerable money (LASIK/premium IOLs) and have high expectations.
   B. Patients “tell” us all the time that:
      1. Vision consists of more than just visual acuity (VA).
      2. VA is how one reads a chart.
      3. Vision is how one perceives the environment with both eyes.
      4. An eye may have > 20/40 VA, but the vision may be “useless” if . . .
         a. Strabismus
         b. Diplopia
         c. Micropsia
         d. Metamorphopsia
         e. Photophobia
         f. Discomfort
         g. Epiphora
         h. Persistent macular edema (alters retinal blood flow)

II. The Purpose of Retinal Detachment Surgery: Surgeon’s Perspective
   To reattach the retina with one operation. Single-operation success is important, but overkill procedures may negatively affect vision.
   A. Less surgery is usually better than more.
   B. “Belt and suspender” operations may provide a higher single-operation success rate for the doctor but not the best vision for the patient.

III. A retinal detachment consists of two components:
   A. Retinal tear(s)
   B. Subretinal fluid

IV. If a retinal detachment can be reduced to a retinal tear (permanently remove subretinal fluid), should the tear(s) be treated any differently had the tears presented before subretinal fluid developed?
   If not, why do anything more than laser or cryopexy, and perhaps a temporary plombage or gas bubble to keep the break closed while the laser/cryo bond forms?

V. Retina reattachment has been proven possible without a permanent scleral buckle or vitrectomy.
   A. Pneumatic retinopexy
   B. Temporary buckles
      1. Lincoff balloon
      2. Wedge with wings
   C. Single-operation success may be lower with temporary buckles, but if single-operation failure does not adversely affect the outcome, these procedures may be worth trying first.
   D. Failure is usually due to the development of new (or missed) retinal breaks.
   E. New breaks may occur as the natural course of an evolving vitreous separation, not the procedure.

VI. Vitrectomy for Primary Retinal Detachment Repair: Mechanism of Action
   A. Releases (internal) vitreous traction on the break(s)
   B. Removes subretinal fluid
   C. Allows for immediate laser retinopexy (focal vs. 360 laser), which creates an immediate adhesion between the sensory retina and retinal pigment epithelium
   D. If complete, removes 360 anterior/posterior vitreous traction at the vitreous base
   E. Removes floaters
   F. If concurrent internal limiting membrane peeling, minimizes chances for macular pucker

VII. What does the addition of a partial or 360-degree buckle add?
   A. If 360 shaving of the vitreous base is not possible (young patient, phakic eye, limited view/access of the retinal periphery), the permanent plombage may prevent new tears from developing, or if they do develop, the buckle may prevent the accumulation of subretinal fluid even if the break is not treated.
   B. If there is anterior proliferative vitreoretinopathy (PVR) with anterior loop traction, which cannot be released internally, the buckle and laser may isolate the anterior pathology.
   C. The buckle may reduce the need for 360 laser.

VIII. The Literature
   A. Buckling
   B. Schwartz, Flynn (2008) literature review showing no benefit adding scleral buckle
   C. Other reports (see references below)
IX. Conclusion

In cases of primary retinal detachment, in an eye that allows for a complete vitrectomy with shaving of the vitreous base, without anterior PVR, scleral buckling is not necessary. The success rates are similar and better vision is attained for the anatomy of the eye is not changed by a permanent buckle.

References


Combination Macular Surgery and Cataract Extraction (Phacoemulsification/IOL Implantation) Is Better for the Patient: Pro

Timothy G Murray MD MBA

I. Introduction

Macular surgery is aimed at improving best visual function via restoration of macular anatomy. Diagnostic evaluation, surgical techniques, and vitreoretinal instrumentation have significantly improved over the last 5 years, enabling outstanding surgical results, improved patient outcomes, and decreased iatrogenic complications. These improvements have been associated with evolving surgical indications that have demanded better visual outcomes for our patients.

Epiretinal membrane and/or vitreomacular traction
A. Surgical indications: traditionally 20/60 or worse BCVA with metamorphopsia
B. Currently reports on outcomes for visual acuity (VA) 20/30 or worse with focus on severity of metamorphopsia
C. Expected outcomes: Historically 2-line improvement of VA
D. Currently VA outcomes of 20/40 or better expected

II. Macular Surgery and Cataract

Pre-existing age-related cataract (even if not visually significant) will significantly progress within the first 12 months after macular surgery. The visual impact of progressive cataract will significantly limit post-macular surgery, typically occurring within 6 months after surgery. Visual limitation from cataract progression is most pronounced in patients with best VA outcomes.

III. Patient Expectations

Patient expectations focus on VA and functional visual improvement. Earlier visual recovery (MIVS) is critical, but sustained visual recovery is expected by the patient undergoing macular surgery. Visual compromise from progressive cataract (particularly early) is commonly associated by the patient as a “complication” of surgery, as is “early” secondary cataract surgery.

IV. Complications

Secondary cataract surgery after macular surgery is associated with higher complication rates, including zonular compromise, capsular compromise, dislocated nuclear/cortical fragments, and higher rates of cystoid macular edema. Secondary cataract surgery may be associated with recurrent macular hole rates as high as 10%.

V. Advantages of Combined Surgery

Combined macular surgery (particular microincisional vitrectomy surgery, MIVS) and small-incision torsional phacoemulsification enable rapid and sustained VA outcomes with minimal incremental surgical risk. Initial concerns regarding large-incision surgical cataract management (ECCE) combined with larger-gauge vitrectomy surgery have been virtually eliminated with advanced anterior segment instrumentation coupled with advanced posterior segment surgical technologies. Recent platforms have integrated state-of-the-art anterior and posterior segment systems into a single console idealy positioned for combined macular surgery and cataract extraction/IOL implantation.

VI. Surgical Approach

A. Presurgical evaluation, including spectral domain OCT, IOL calculation, and comprehensive clinical assessment imperative
B. Surgical setup, including combined anterior/posterior vitrectomy platform, preselected IOL, and MIVS approach
C. Transconjunctival cannula placement using valved cannulas is preferred. Small-incision torsional phacoemulsification with placement of IOL of choice (acrylic preferred over silicone). Toric IOL placement not compromised, but currently not recommending multifocal IOLs in patients with significant macular pathology (decreased contrast sensitivity); IOL placement and 10-nylon closure of clear corneal biplanar incision effective but not necessary for fluidic stability. Standard pars plana vitrectomy management of macular pathology. Intravitreal triamcinolone acetonide placement at conclusion of case enhances rapidity of resolution of pre-existing macular edema. Standard evaluation of sclerotomies and wound stability do not require routine closure.

VII. Surgical Outcomes

A. Enhanced recovery of best and sustained VA and function associated with single surgical procedure. Combined vitrectomy with phacoemulsification/IOL implantation eliminates visual loss from pre-existing cataract and its associated postsurgical progression. No significant increases in endophthalmitis, hypotony, choroidal detachment. Single surgical recovery eliminates any risk associated with planned secondary cataract extraction.

B. Currently the routine surgical approach for most centers providing macular surgery in patients with pre-existing cataract when managed outside of North America.

C. Not commonly accepted for most referral programs within North America.
D. Evolving demographics and sustained health-care cost pressures may shift surgeons within North America to more closely emulate the combined surgical approach to managing macular pathology and cataract of our international colleagues.

Selected Readings


Combination Macular Surgery and Cataract Extraction Is Better for the Patient: Con

Nancy M Holekamp MD
My Coolest Surgical Videos

Persistent Optic Pit Maculopathy: Surgical Management with Autologous Fibrin
*Sengul C Ozdek MD*

Bilateral Gunshot Injury
*Grazia Pertile MD*

Novel, OVDs Prior to PFO Injection Prevents Migration of PFO
*Taiji Sakamoto MD PhD*

Not New Technique: Coat’s Disease
*Shunji Kusaka MD*
Heads Up: No-Microscope Vitreoretinal Surgery

Claus Eckardt MD

I. Introduction

A. Definition: In “heads-up” surgery, the surgeon no longer looks through the microscope oculars as in conventional microsurgical procedures. Instead, the surgeon wears lightweight 3-D glasses and sees the surgical field on a large flat screen that displays a high-definition, 3-dimensional image from a camera mounted onto the microscope (see Figure 1).

Figure 1. Heads-up surgery without looking into the oculars.

B. Purpose: To report the clinical experience of the routine use of heads-up surgery for vitreoretinal procedures and phaco/vitrectomy cases.

II. Methods

A. Visualization system: TrueVision System (Santa Barbara, Calif.) consisting of a 3-D high dynamic range (HDR) surgical camera, specialized image capture and display software, and a 46” 1080p 3-D passive LCD display monitor. The camera is mounted onto a Leica M822 Microscope (Heerbrugg, Switzerland).

B. Cases: During a period of more than 4 months, heads-up surgery was performed routinely on all cases in the daily schedule, including cataract surgery and all kinds of vitreoretinal procedures (more than 300 vitrectomies in total).

III. Conclusion

The 3-D visualization system has the potential to have a significant positive impact on vitreoretinal surgery. Further benefits (eg, use of computed graphical overlays for surgical guidance) can be expected as the technology is developed.

Selected Reading

Ophthalmology’s goal in protecting quality patient eye care remains a key priority for the American Academy of Ophthalmology (the Academy). All Eye M.D.s should consider their contributions to the following three funds as (a) part of their costs of doing business and (b) their individual responsibility in advocating for patients:

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

Your Eye M.D. colleagues serving on the Academy’s Secretariat for State Affairs commit many hours on your behalf while strategizing and collaborating with state ophthalmology society leaders to ensure the success of Surgery by Surgeons. Their ultimate goal—protecting quality patient eye care in the states—requires a robust Surgical Scope Fund, and we need every single Eye M.D. to step up to the plate and deliver with their checkbooks.

The Academy’s federal advocacy arm works to protect ophthalmology practices from payment cuts, burdensome regulations, and scope of practice threats, as well as to advance the profession by promoting funding for vision research and expanded inclusion of ophthalmology in public and private programs. It is critical for our OPHTHPAC Fund to also be strong.

**Surgical Scope Fund**

The Surgical Scope Fund (SSF) provides grants to state ophthalmology societies to support their legislative, regulatory and public education efforts. Since its inception, the Surgery by Surgeons campaign, in partnership with state ophthalmology societies and with support from the SSF, has helped 31 state/territorial ophthalmology societies reject optometric surgery proposals.

2014 has proved to be a challenging year, with several battleground states facing major optometric surgery initiatives. A number of state ophthalmic societies benefited from SSF disbursements and were able to successfully implement patient safety advocacy campaigns to defeat attempts by optometry to expand its scope of practice to include surgery. The Nebraska Academy of Eye Physicians and Surgeons was successful in its patient advocacy and public education efforts to derail legislation that would have granted optometrists the authority to perform eyelid surgery and injections. Additionally, the Arizona Ophthalmological Society succeeded in protecting patients by stopping legislation that would have allowed optometrists to gain authority to perform injections. The SSF is also at work assisting ophthalmic societies with their efforts to protect patients in California, Delaware and Massachusetts.

Proactively, the Georgia Society of Ophthalmology introduced a bill that would establish a formal definition of “surgery” into state law. While the legislative session expired before the bill could advance, Georgia ophthalmologists will be back in 2015 in an effort to pass this important safeguard for their patients.

2014 was certainly not without its challenges. Despite a vigorous battle for patient safety on the part of the Tennessee Academy of Ophthalmology, the Tennessee Medical Association and the Academy, the legislature passed a bill allowing optometrists to inject anesthesia into the eyelids. Previously, optometrists were authorized to perform only therapeutic injections and any surgical procedure that required no more than a topical anesthetic.

And in Louisiana, the Academy, the Louisiana Ophthalmology Association, and the Louisiana State Medical Society vigorously opposed legislation that would authorize optometrists to perform certain scalpel and laser surgeries and injections. On June 1, 2014, Louisiana Governor Bobby Jindal signed into law a laser surgery bill that will allow optometrists to perform scanning laser trabeculoplasty and argon laser trabeculoplasty glaucoma surgery procedures, as well as YAG capsulotomy surgery procedures, with the completion of as little as 32 hours coursework. The Academy’s Secretariat for State Affairs knows from past experience that with this success in Louisiana, organized optometry will push hard in 2015 to see if they can gain additional surgery states. This is why everyone must “advocate for patients,” engage in the state political process, and aggressively support the SSF.

California, Delaware, and Massachusetts remain “in play” and are still faced with active O.D. surgery legislation. When it comes to state legislation of any kind, California and Massachusetts are often considered bellwether states for the rest of the nation. Now more than ever, your contribution to the SSF is needed as a critical tool of the Surgery by Surgeons campaign to protect quality surgical care for our patients. The Academy relies not only on the financial contributions to the SSF from individual Eye M.D.s and their business practices, but also on the contributions made by ophthalmic state, subspecialty and specialized interest societies. The American Society of Retina Specialists (ASRS), the Macula Society and the Retina Society contributed to the Surgical Scope Fund in 2013, and the Academy counts on their contributions in 2014.

**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 as well as protecting ophthalmology from federal scope-of-practice threats. Established in 1985, today OPHTHPAC is one of the largest and most successful political action committees in the physician community. In the past, Politico highlighted OPHTHPAC as one of the most successful health PACs in strategic giving. By making strategic election campaign contributions and independent expenditures, OPHTHPAC helps us elect friends of ophthalmology to federal leadership positions, ultimately resulting in beneficial outcomes for all Eye M.D.s. For example, in the 2012 election cycle, OPHTHPAC was able to help retain 20 physicians in Congress. Among the significant impacts of OPHTHPAC are the following:

- Prevented onerous national patient prescription requirements for compounded drugs and preserved access to most ophthalmic compounded drugs for office use
- Averted significant cuts to Medicare payments due to the Sustainable Growth Rate (SGR) formula

Alan A Kimura MD MPH
### Surgical Scope Fund
- To derail optometric surgical scope-of-practice initiatives that threaten patient eye safety and quality of surgical care
- Political grassroots activities, lobbyists and media; no funds may be used for candidates or PACs
- Contributions: Unlimited.
- Contributions are 100% confidential.

### OPHTHPAC® Fund
- Ophthalmology’s interests at the federal level – Support for candidates for U.S. Congress
- Campaign contributions, legislative education
- Contributions: Limited to $5,000
- Contributions above $200 are on the public record.

### State EyePAC
- Support for candidates for State House and Senate
- Campaign contributions, legislative education
- Contribution limits vary based on state regulations.
- Contributions are on the public record depending upon state statutes.

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- Protected practice expense increases for ophthalmology when other specialties sought legislative carve-outs
- Protected ophthalmologists’ ability to provide in-office diagnostic testing without triggering self-referral violation
- Prompted congressional action that helped reduce ophthalmology’s multiple procedure payment reduction
- Secured appointment of full-time ophthalmology national program director in the U.S. Department of Veterans Affairs
- Provided further exemptions from both the Electronic Prescribing and Meaningful Use EHR penalties

Leaders of the three retina societies are part of the Academy’s Ophthalmic Advocacy Leadership Group (OALG), which has met for the past seven years in 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 2014 OALG meeting included a focus on the collaboration needed among the Academy and its OALG partners on the issue of compounding. As a 2014 Congressional Advocacy Day (CAD) partner, the three retina societies ensured a strong presence of retina specialists to support ophthalmology’s priorities as nearly 400 Eye M.D.s had scheduled CAD visits to members of Congress in conjunction with the Academy’s 2014 Mid-Year Forum in Washington, D.C. The three retina societies remain crucial partners with the Academy in its ongoing federal and state advocacy initiatives.

### State Eye PAC
We all must also support our respective State Eye PACs, because state ophthalmology societies cannot count on the Academy’s SSF alone. 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 also critical. The Secretariat for State Affairs strategizes with state ophthalmology societies on target goals for state eye PAC levels.

### ACTION REQUESTED: Advocate for your patients!!

Academy Surgical Scope Fund 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 should be considered the costs of doing business. Surgical Scope Fund 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 who are volunteering their time on your behalf to serve on the OPHTHPAC* and Surgical Scope Fund** Committees, as well as your state ophthalmology society leaders, when they call on you and your subspecialty society to contribute. Advocate for your patients now!

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Management of Posterior Uveal Melanoma: Past, Present, and Future

Jerry A Shields MD

The Past
Prior to the 1970s enucleation was performed for almost any fundus lesion suspected to be melanoma. However, many enucleated eyes proved to have benign lesions, rather than melanoma.

The Present
In the mid-1970s indirect ophthalmoscopy, fluorescein angiography, ultrasonography, and needle biopsy improved diagnostic accuracy. Alternatives to enucleation, including irradiation and surgical resection, were increasingly employed. However, despite earlier diagnosis and improved methods of treatment, many patients still succumb to metastasis.

The Future
The use of reported risk factors and multimodal imaging and the cytogenetic identification of high-risk patients may allow for diagnosis and treatment of very small uveal melanomas, which carry a better prognosis. Research to clarify molecular pathways that lead to melanoma may permit development of agents that will interrupt these pathways and prevent or cure more patients. Although there is much to be done, there is hope on the horizon for better and earlier management of uveal melanoma.
“Big Data”: What It Is and How It Will Change the Profession

William L Rich III MD

Big data? Let’s start with a definition: Big data is a blanket term for any collection of data sets so large and complex that it becomes difficult to process using on-hand database management tools or traditional data processing applications. Today the term is often used to describe the huge data sets collected by Google and the NSA to observe correlations that direct inquiry. It is characterized by high volume (petabytes or greater), high velocity (real time), random users, and unstructured data from multiple sources.

Big data has revolutionized retail sales, the financial world and national security. Amazon uses its huge database to make suggestions on new book or merchandise purchases based on your previous buying experience, browsing habits, how long you linger over a site and what colors may make a difference in the presentation. Target moves its in-store displays from week to week based on historic sales related to weather, time of year and national buying trends. Equity sales occur in real time and are executed in nanoseconds. “Simply put, because of big data, managers can measure, and hence know, radically more about their businesses, and directly translate that knowledge into improved decision making and performance. More accurate analyses may lead to more confident decision making. And better decisions can mean greater operational efficiencies, cost reductions and reduced risk” (Harvard Business Review, Oct. 2012).

Immediately following 9/11 the FBI, CIA and Defense Intelligence Service were unable to identify the hijackers. They turned to a data mining company that was able to identify the miscreants and their accomplices within three days by looking at pizza deliveries and rental records.

Medical “big data” does not require the volume and velocity used in these applications. But are there examples of the use of medical big data in use now? The FDA has developed the Sentinel Initiative, which monitors in real time 138 million patients in electronic databases with the intent to pick up early signals of adverse device and drug performance to enhance patient safety. Unstructured medical data can be collected from EHRs and evaluated in a registry like Intelligent Research in Sight (IRIS). This is a perfect vehicle by which to collect and analyze large amounts of unstructured clinical data to better understand the natural history of chronic ophthalmic diseases, observe unsuspected factors that correlate with better outcomes, develop new evidence to drive real-time feedback to physicians to improve patient care and move to personalized medicine.

IRIS was launched in April of 2014 with a goal of contracting with 2200 practices by Jan. 1, 2017. By June 2014 IRIS had contracted with 3100 ophthalmologists, with another 4000 waiting in the wings, and 1600 ophthalmologists had been mapped to their EHRs, with 7.03 million visits from 2.37 million patients. This included 49,663 patients with wet AMD. It is now estimated that IRIS will cover 38 million patients in 2017. That is a lot of data! Outcomes researchers and industry stakeholders are already petitioning IRIS to begin looking longitudinally at the natural course of geographic AMD, factors impacting the natural course of diabetic retinopathy beyond blood pressure, lipid, and HgA1C levels, and evaluating the reasons why some African Americans have a milder course of glaucoma after adjusting for socioeconomic status.

Using IRIS and large clinical data sets extracted from EHRs will enable us to analyze variations in care, provide an analytical infrastructure to interpret the data and improve care delivery in ways we have never dreamed possible.
The Affordable Care Act: The Sky Is Falling – Pro

George A Williams MD

The Patient Protection and Affordable Care Act (ACA) of 2010 created a fundamental restructuring of health-care delivery. The ACA requires that all health insurance plans provide coverage for a defined set of essential health benefits, proscribes health-based underwriting, eliminates policy rescissions, eliminates lifetime benefit caps, and limits insurance company underwriting profits. A primary goal of the ACA is to decrease the number of uninsured through the creation of health insurance exchanges and expansion of Medicaid. Starting in 2014, people may purchase individual or family plans (termed “nongroup plans”) through the exchanges and may be eligible for premium and cost-sharing subsidies on an income-based sliding scale. In many but not all states, people with incomes up to 133% of the federal poverty level are now eligible for Medicaid. Also, the ACA instituted alternative payment models. By June of 2014, 8 million people signed up for health insurance through the exchanges and 3 million people were added to Medicaid. So far, so good. What could possibly go wrong?

The first thing to go wrong was the impact of the “essential health benefits” requirement on existing individual policies that were no longer compliant, resulting in mass plan cancellations. The Kaiser Family Foundation estimated in June that approximately 43% of the 8 million people enrolled through the exchanges were previously insured. For many of these people, the president’s promise about being able to keep their insurance rang hollow. The disruption in the individual market was so severe that the Centers for Medicare and Medicaid Services delayed the implementation date for small employers until 2016. How these employer-based policies will be affected is uncertain, but the history with individual policies is likely to be repeated.

A critical problem with the ACA is the effect of the insurance mandates on premiums, deductibles, and copayments. The ACA did not repeal the rules of actuarial science, which price insurance based on the risk of the covered population. That risk is a function of the cost of the required benefits and the health of the covered population. The less-than-expected enrollment of healthier, younger people compounds the risk. The Kaiser Family Foundation reports that enrollees in the exchange nongroup plans are more likely to be in fair or poor health. As a result, there are predictions of significant growth in premiums for 2015 and beyond.

Since the inception of the ACA, there has been a steady increase in the growth of high-deductible insurance plans. When the small employer mandates go into effect in 2016, this trend will probably accelerate. The impact of high-deductible plans has already created problems for both patients and doctors. The net effect will be increasing premiums, deductibles, and copayments that will increase the demand to cut health-care costs despite growing access to health-care services. Something has to give.

So, is the sky falling? I can’t tell. It’s too cloudy.

Reference
The Affordable Care Act: The Sky Is Falling – Con

Paul Sternberg Jr MD

The Affordable Care Act initiated a number of reforms to healthcare coverage dedicated to reducing the unsustainable rise in the cost of health care while also addressing the problem of the large segment of our citizenry that lacks coverage. Many of the initiatives directed at cost reduction were directed at the following value proposition: making sure patients receive “everything they need and nothing more.” As ophthalmologists and retina specialists, we have great opportunities, whether it be in optimizing frequency of visits or number of ancillary tests or standardizing diagnosis and management. While these changes may reduce revenue when it is reimbursed on a fee-for-service basis, they will better position us to provide care in a population-management or risk-sharing setting. Further, the increased number of covered patients, be it through the insurance exchanges or Medicaid expansion, will allow us to be reimbursed for much of the care that we are currently providing without compensation. In addition, it should lead to patients receiving care at an earlier stage of their disease.
The Future of Retina: A SWOT Analysis

David W Parke II MD

Retina cannot be considered in isolation from ophthalmology. While the subspecialty of retina pertains to a particular subset of ophthalmologic diseases, treatments, and procedures, we are all ophthalmologists. We use many of the same codes as other ophthalmologists, we are considered ophthalmologists by health plans and by patients in terms of access to patients and delivery of care, and we depend on other ophthalmologists for the bulk of our referrals. Finally, many retina specialists also deal with non-retina topics—anterior uveitis, cataracts, neovascular glaucoma, tumors, and so on.

I’m also going to limit my remarks to the policy, economics, and politics of retina. Much can be said about the future of the science of retina—leading to new discoveries, drug and device therapies, and procedures. Yet this is one of our field’s undeniable strengths.

Strengths

Perceived value of our services
Many of the core diseases we manage (AMD, retinal detachment, diabetic retinopathy, ROP, etc.) have blindness as a frequent natural outcome. This resonates with the public and with policymakers. We can therefore place a high social and economic priority on our services.

Unique nature of our services
It is rare for non-retina-trained ophthalmologists to do scleral buckles or pars plana vitrectomies. This gives retina unusual market power for contracting and for relationships with integrated health-care systems.

Scientific basis for our services
Many of the pivotal multicenter prospective randomized trials have been in retina, dealing with AMD and diabetic retinopathy. They form the basis for Preferred Practice Patterns and for process and outcomes measures. This provides the Academy with a firm foundation for appealing payer noncoverage decisions and for designing measures that economically advantage retina through programs such as the Physician Quality Reporting System.

Move to the ambulatory surgery environment
This is a huge potential strength. It provides control—and sometimes ancillary income—to retina specialists. More importantly, it allows retina practices more control over the package pricing of episodes of care and even bundling of longitudinal disease management.

Unattractiveness to integrated systems
Retina specialists, even those who operate in hospitals, bring little ancillary revenue to integrated health-care systems. We don’t (generally) put people in ICUs, we don’t use lots of laboratory tests, and we don’t (generally) use expensive diagnostic imaging. (Those who do a high volume of ROP screening are a notable exception.) Therefore, retina subspecialists are much less likely to be pressured into tight employment relationships with systems. This allows operational independence.

Weaknesses

Concentration of services
For the average retina subspecialist, most income pertains to a very limited set of ICD-9 codes and CPT codes, which creates some vulnerability to changes in treatments and valuation of codes. What would happen if the family of vitrectomy codes was devalued by 25%? What would happen if AMD or diabetic retinopathy treatments were markedly simplified?

Total societal cost of retina services
The total cost within Medicare for treatment of both AMD and diabetic retinopathy ranks within the Top Twenty for all diseases. This puts retina very much on the radar screen for those health-care economists and policymakers searching for ways to cut costs.

Part B drugs pricing
While the small margin due to (nominally) ASP+4 (average sales price + 4%) reimbursement is nice for practice economics, retina’s heavy dependence on the current Medicare Part B pricing model hurts it. It distorts individual practice finances and physician compensation models, it is a public relations nightmare, it confuses the compounding issue, and it interferes with physician-patient relationships.

Vulnerability to RUC procedural valuation process
The Relative Update Committee (RUC) process has become increasingly focused on intraoperative time and, to a lesser extent, number of postoperative visits as the determinants of economic value. As those two factors decrease, so does the valuation of retina procedures.

Opportunities

New outcomes data
Scientific innovation and the IRIS (Intelligent Research in Sight) clinical data registry both offer retina the opportunity to develop hard numbers as to aggregate and individual practice value. This has enormous value, not only for individual patients but for the positioning of practices specifically and retina generically.

Capture more of the pyramid base
Retina subspecialists, as subspecialists, are considered either tertiary or quaternary providers. They are therefore somewhat isolated and threatened with marginalization as health care becomes increasingly focused on wellness, disease prevention, and avoidance of the need for tertiary and quaternary services. While a threat, it is also an opportunity for retina to reposition itself. Retina practices should not shun “low impact” referrals and services but should develop mechanisms to welcome and accommodate them.
Take local and regional health-care systems leadership
As new health-care delivery systems and employer and patient coalitions develop, retina should be at the table. Every system must develop or adopt clinical standards of care, referral guidelines, and service expectations. Retina, as a largely independent group, must participate in these discussions. Otherwise, retina subspecialists will be contractually bound to standards developed by non-retina physicians—or by nonphysicians.

Threats

New science
While an opportunity, this can also present a threat. How would your practice respond if AMD treatment required only 1 injection a year? How would it respond if macular surgery became largely a thing of the past? The threat here is not the science, it’s the inability to anticipate the need for change, to change, and to remain flexible.

Loss of market niche
It is the nature of most business and product cycles that unique niches erode. They erode for two basic reasons: (1) other businesses develop (or project themselves to have developed) the niche capability, and (2) the niche evaporates with innovation elsewhere. Apple’s niche with the iPad eroded as others entered the space. The landline telephone’s niche exploded with innovations in mobile technology. Who wants to project themselves into retina’s space? What innovation may evaporate aspects of retina’s niche? One solution is always to look for new niches.

Trivialization and commoditization
Retina would do well to heed the experience of the refractive surgeons and of many cataract surgeons. If we trivialize the real complexity, required training and skill set, time required, and impact of what we do, it will result in trivialization by policymakers and in an inappropriate set of expectations by patients and by payers. What we do is important, challenging, and complex. Project it accurately.
Wide-Field Imaging in Pediatric Retinal Diseases

Antonio Capone Jr MD

I. Introduction
Includes color fundus photographs, fluorescein angiography (FA), indocyanine green angiography

II. Definition
A. Standard view: 30 degrees
B. Wide-field view: up to 60 degrees
C. Early Treatment Diabetic Retinopathy Study 7-standard fields: up to 100 degrees
D. Ultrawide-field: up to 200 degrees

III. Evolution of Wide-Field Imaging
A. Drawings, film photographs, digital imaging, wide-field imaging
B. Montage, contact-lens based system, noncontact nonmydriatic system
C. Commercially available systems: Heidelberg with Staurenghi Lens, Retcam, Optos

IV. The Value Added to Wide-Field Imaging
A. Facilitates diagnosis and management
B. Unmasks pathology (extent of disease and novel findings), which were heretofore unappreciated (familial exudative vitreoretinopathy [FEVR], persistent fetal vasculature syndrome [PFVS], Coats)
C. Rapid turnaround screening tool for affected family members in some conditions (FEVR)

V. Clinical Utility in Pediatric Retinal Disease
A. ROP
1. Has assumed a place in the standard of care for ROP evaluation/management
2. Fluorescein angiography useful to distinguish the features of posterior ROP
3. Wide-field angiography particularly useful in assessing status of eyes treated with anti-VEGF for residual activity
B. FEVR
1. Most effective method to assess extent of disease and monitor longitudinally
2. Guides peripheral retinal ablation
3. Quickly screens blood relatives
C. Coats disease and facioscapulohumeral muscular dystrophy
1. Full extent of disease typically extends well beyond clinically apparent findings.
2. Guides peripheral retinal ablation, which typically requires multiple sessions
3. Unmasks occult findings in the companion eye
D. PFVS: Helps distinguish from overlapping FEVR phenotype in patient
E. Other conditions: Norrie disease, incontinentia pigmenti, mass lesions, retinal degenerations

VI. Limitations
A. Our understanding of peripheral retinal anatomic features and vascular findings has been limited by the relative novelty of wide-field angiography.
B. As these technologies become more widespread, we will have a better appreciation for what constitutes normal and abnormal peripheral retinal vascular findings.
C. Currently available wide-field fundus imaging technologies cannot supplant indirect ophthalmoscopy with scleral depression due to the inability to fully image the entire retina.
D. Poor images of the superior and inferior retina limits Optos’ application in cases of inflammatory disease, given the inferior predominance of a number of common conditions such as intermediate uveitis.

VII. Future Directions
A. The full range of “normal” peripheral findings are yet to be characterized.
B. A number of ocular diseases with peripheral retinal findings are yet to be fully characterized as well.
C. Wide-field imaging provides a tool for acquiring further information on these conditions.
D. A number of other companies are working on wide-field digital imaging solutions, including portable handheld smartphone-based retinal cameras capable of capturing high-quality, wide-field fundus images.
E. As the price-point of the technology declines, we can anticipate broader application in provision of ROP evaluation/management services.

VIII. Conclusion
A. As with adult retinal conditions, viewing only the posterior pole is no longer enough.
B. Wide-field imaging has assumed a place in the standard of care for ROP evaluation and management.
C. Wide-field imaging is critical for adequate diagnosis and management of pediatric retinal conditions, most notably FEVR and Coats disease.
D. The full potential of wide-field imaging has not been realized.
Selected Readings


Universal Screening for Pediatric Eye Disease

Darius M Moshfeghi MD, Douglas Frederick MD, Natalia F Callaway MD, Mark S Blumenkranz MD

Introduction

Presently, there is no mandated screening of children for ophthalmic problems other than at age 5 prior to entry into kindergarten or for eligible preterm infants for screening of ROP. Depending on the patient population, amblyopia (potentially reversible decreased vision) has prevalence in the United States of 2.5% (ranging from 1% to 5.3%).1,2 Screening programs that have assessed the utility of identifying and treating those children at risk for blindness have focused efforts usually between the ages of 3 and 5 years, occasionally as early as 12 months of age.3 Little benefit in the way of restoration or creation of normal visual function has been demonstrated from these screening programs. This stems largely from the chronicity of the problem—a scar from previous ocular hemorrhage in the center of vision is not amenable to therapy 5 years after the fact. Much of amblyopia is due to strabismus, and the data clearly demonstrate that the economic value added from early diagnosis and treatment ranges from $5.9 to $38.2 billion a year in the United States.1,4 In the pediatric retina community, it is recognized that removing visual axis impediments—blood, cataract, retinal detachment, corneal opacity—results in improvement of visual function if performed within the critical 8-12 week time period. The child has to be monitored closely to determine if surgical and/or amblyopia-patching intervention will be needed. The problem is that, except in cases of suspected trauma, no one is ever looking at these infants to determine if they have a media opacity that needs monitoring and intervention. In children older than 3 years, approximately 80% of amblyopia is due to strabismus. However, what is not clear is how much of that strabismus is de novo and how much is secondary to other problems (cataract, hemorrhage, retinal detachment). The untreated sequelae of cataract, congenital glaucoma, retinal detachment, vitreous hemorrhage, or macular hemorrhage include development of strabismus and amblyopia.

In the United States, all newborn infants are mandated to have hearing evaluations, even though the incidence of hearing loss in high-risk populations is around 5% and substantially lower in a general population. However, no such mandate currently exists for ophthalmic screening of infants. In the United States and the developed world, ROP is the leading cause of childhood blindness and occurs only in premature infants. Standardized screening protocols exist to identify patients for treatment-warranted ROP. There are 80,000 infants eligible for screening for ROP out of 4.1 million live births each year. Each of those 80,000 infants is evaluated during the 8-12 weeks of acute-phase screening for ROP, and yet we often identify other problems such as endophthalmitis, hemorrhage, cataract, retinoblastoma, coloboma, persistent fetal vasculature, glaucoma, and viral retinitis. None of these other entities occur more frequently in a premature patient population than in the general population of newborns, and yet none of the remaining 4.02 million live births in the United States are being screened. In general, the socioeconomic benefit of disease screening tilts in favor of screening if the disease prevalence exceeds 2% and causes lasting detriment.

At Stanford, we have a novel, nationally recognized program to screen for ROP in low birth weight infants. The Stanford University Network for Diagnosis of Retinopathy of Prematurity (SUNDROP) telemedicine screening network facilitates the standardization of ROP screening as well as extending the capabilities of an expert, quaternary ROP screener to more than just the hospital neonatal intensive care unit (NICU). The SUNDROP telemedicine network is the largest ROP screening network in North America and is a hub-and-spoke, store-and-forward telemedicine program. The hub is the Byers Eye Institute, where the images are read, and the spokes are 6 outlying NICUs. At-risk infants are identified, and the images are obtained, stored electronically, and forwarded in a compliant fashion to the secure SUNDROP servers maintained at Stanford University. These images are interpreted; a report is generated with specific recommendations for future screening and/or treatment.

We are in Year 9 of SUNDROP, and the data to date have been good: sensitivity of 100%, specificity of 99.8%, negative predictive value of 100%, and positive predictive value of 95.5%. All babies at risk for retinal detachment and blindness have been identified and treated. The SUNDROP telemedicine screening program has served as the paradigm for ROP telemedicine screening programs in the United States and around the world. It has been featured at the American Academy of Ophthalmology and evaluated by the Ophthalmic Mutual Insurance Company (OMIC), and it was one of the programs relied upon for the new recommendations for ROP screening promulgated by the American Academy of Ophthalmology, American Academy of Pediatrics, and the American Association of Pediatrion Ophthalmology and Strabismus.

The infrastructure that we have built into the SUNDROP screening program allows for vertical and horizontal integration. We can also expand into other areas, such as universal screening of newborn infants. Our experience with SUNDROP has demonstrated that what we propose to do with universal newborn screening is not only feasible but also practical, with the ability to identify all at-risk infants.

Newborn Eye Screen Testing (NEST)

Objectives
1. To identify all perinatal causes of preventable blindness through universal screening of infants with the development of a telemedicine network center at the Byers Eye Institute
2. To create a template and training module for similar newborn eye screening telemedicine programs around the world
3. To use data derived from the NEST program to serve as mandated national screening for all newborns to have eye examinations within 48 hours of birth
4. To develop a partnership with low-vision foundations to help them get involved at an earlier period for all newborns who are at risk for blindness
Design

**Phase I**

We performed screening of live-birth newborns at Lucile Packard Children’s Hospital within 48 hours of birth. This was accomplished using a digital fiber optic camera system (RetCam III, Clarity Medical Systems; Pleasanton, Calif.) operated by trained nurses. These nurses obtained a standard panel of 1 external facial and 6 ocular photographs in each eye (1 external photograph of the anterior segment, eyelids, and orbit; 5 fundus photographs of the retina—centered, superior, inferior, nasal, temporal). These photographs were uploaded into the camera and then automatically synchronized with the RCRS software (Clarity Medical Systems) running on the secure, redundantly backed-up SUNDROP servers operated by Stanford Information Technology. Images were read each day, with a report prepared indicating future interventions, if any. Additionally, as the year progressed and equipment became available, all screened patients underwent OCT with the Envisu SD-OCT (Biopigen; Morrisville, NC). It was anticipated that most infants would require only the 1 NEST exam. However, if any pathology was noted, the report indicated the timing and location of appropriate follow-up with either pediatric ophthalmology or the pediatric retina service.

**Phase II**

Phase II will be 2-fold: (1) expansion of NEST to Lucile Packard Children's Hospital-affiliated and SUNDROP-affiliated hospitals and (2) creation of NEST training facility at the Byers Eye Institute.

**Scientific Validation**

Global Universal Eye Screen Testing (GUEST) Validation Study

The GUEST protocol involves approximately 10,000 infants from China and Brazil who have been screened for eye examinations by other physicians not affiliated with NEST using the wide-angle RetCam fundus camera. These patients differed from the NEST patients in 2 significant ways: (1) qualitative description of ocular photographs in each country, but not part of a study, and (2) lack of longitudinal follow-up (ie, a true “snapshot” in time). However, the photographs themselves can be used to scientifically validate the technique of universal screening of infants in the following manner: (1) identify population differences in rates of ocular pathology and (2) identify concordance (rates of agreement) among and between different cohorts of readers.

The primary goal of universal newborn screening is to identify ocular pathology in a timely fashion for potential intervention to prevent blindness. However, it is equally important to generate confidence in the parents that a negative (ie, “normal”) exam is truly within normal limits. Most infants will obviously have normal eye exams. In the remainder of infants with abnormal examinations, we want to validate 2 things: (1) that if an abnormal finding is present on the photographs, different groups of observers will be able to agree on the presence of abnormality with a kappa (agreement level) of 0.98 (2% disagreement rate or less; a kappa of greater than 0.8 is considered almost perfect agreement), and (2) that the photographs capture almost all abnormalities. To demonstrate this, all images from all patients have been de-identified, assigned new numbers and fictitious dates of birth and examination. Then, we will have cohorts of 4 individuals, each of similar levels of training, evaluate 2000 consecutive images and grade them for kappa. We will start with the highest levels of training and move to progressively lower levels until we reach the least-trained (therefore the least expensive) cohort that can achieve a kappa of 0.98.

The present status of the GUEST protocol is that all patients have been de-identified, randomized, reassigned fictitious data, and entered into the database. We have obtained institutional review board approval from Stanford University and set up an independent REDCap database. We have a smart data entry form that is being completed by Stanford IT services and should be available by September 1, 2014.

**Preliminary Findings**

Data through 1 year indicate the following pathology on > 200 consecutively screened infants:

- Retinal hemorrhages in greater than 15%
- Optic nerve hemorrhages in greater than 10%
- Retinal pigmentary changes (grouped pigmentation, polar bear spots)
- Subconjunctival hemorrhages
- Choroidal nevi
- Ptosis

Macular development courses and trends have also been identified and will be discussed in further detail.

**Summary**

Universal screening is an emerging tool and technology for pediatric eye disease and pathology that will likely see greater expansion throughout the developed world in the near future, based upon the prevalence of ocular findings that can be treated. Longitudinal follow-up of infants in the NEST study will continue through 5 years with pediatric ophthalmology to identify rates of amblyopia and strabismus in patients with ocular pathology. Concomitant application of photographic and OCT testing will likely deepen our understanding of normal and abnormal macular development in infants. The GUEST study will provide scientific validation of inter- and intra-grader variability of reading wide-angle fundus photographs in infants.

**References**

The Workup of the Retinal Vein Occlusion Patient: When Is It Necessary and What to Order?

J Michael Jumper MD

I. Pathophysiology of RVO

A. Virchow’s Triad

The earliest known description of venous thrombosis dates back to ~1400 AD. Rudolf Ludwig Karl Virchow (1821-1902) is attributed with the theory describing the pathogenesis of venous thrombosis to include (1) alterations in blood flow, (2) vascular endothelial injury, and (3) alteration in the constitution of the blood. This triad remains clinically relevant more than 150 years later.

B. Degenerative changes in the vessel wall

The concept that injury to the vascular intima predisposes to thrombosis predates the work of Virchow. Histologic examination of eyes with retinal vein occlusion have revealed changes in the tunica intima and tunica media at the point of arteriovenous crossing. It has been proposed that sclerosis of the retinal arteriole can lead to these venous changes, perhaps from compression and turbulence that predispose to thrombosis. Indeed, risk factors such as atherosclerosis, hypertension, diabetes, hyperlipidemia, and smoking have been implicated in the development of RVO.

II. Systemic Risk Factors Associated With RVO

A. Age: RVO affects all ages.

1. ~50% of patients with RVO are > 65 years old at presentation of initial RVO.
2. There is increasing rate of RVO with advancing age.
   a. < 64: 0.93/1000
   b. ≥ 65: 5.36/1000

B. Hypertension: Population attributable risk (PAR%) = 50%

C. Diabetes mellitus: PAR% = 5%

D. Hyperlipidemia: PAR% = 20%

E. Atherosclerotic vascular disease
   1. Coronary artery disease
   2. Peripheral vascular disease

F. Hypercoagulable states: The role of thrombophilic factors in the development of RVO is controversial, with no consensus about whether the various known coagulation disorders are relevant risk factors.
   1. Hyperhomocysteinemia
   2. Anticardiolipin antibodies: A meta-analysis by Janssen and coworkers suggests that risk factors for arterial vascular disease as well as venous thrombosis (hyperhomocysteinemia and anticardiolipin antibodies) are significantly associated with RVO, whereas other risk factors are not.
   3. Activated protein C resistance (Factor V Leiden mutation)
   4. Prothrombin gene mutation: The factor V Leiden and prothrombin mutations are confined to ethnic groups with white European ancestry and is undetectable in true Asian and black African populations.
   5. Protein C deficiency
   6. Protein S deficiency
   7. Antithrombin deficiency: To date, the limited studies of anticoagulant protein deficiencies (proteins S and C and antithrombin III) have not shown a significant role in the majority of RVO patients.
   8. Increased fibrinogen levels

G. Hyperviscosity states
   1. Leukemia
   2. Lymphoma
   3. Polycythemia vera
   4. Multiple myeloma

H. Vasculitis
   1. Sarcoidosis
   2. Syphilis
   3. Systemic lupus erythematosus
   4. Behçet disease

I. Drugs/exogenous agents
   1. Oral contraceptives
   2. Diuretics
   3. Cigarette exposure

J. Abnormal platelet function

III. Ocular Risk Factors Associated With RVO

A. Glaucoma
B. Ischemic optic neuropathy
C. Pseudotumor cerebri
D. Optic nerve head drusen
E. Compressive lesions (tumor, thyroid ophthalmopathy)
F. Trauma
   1. Direct or indirect
   2. Retrobulbar injection

IV. Baseline Investigations for the RVO Patient\textsuperscript{4,11}
A. Blood pressure measurement; if elevated, check:
   1. Creatinine clearance
   2. Urinalysis
   3. Consider renal ultrasonography
B. Complete blood count with differential
C. Urea and electrolytes
D. Fasting serum glucose and lipids
E. Hemoglobin A1C
F. Homocysteine level; if elevated, check:
   1. Serum folate level
   2. Serum B12 levels

V. Additional Investigations in Select RVO Patients
A. Should be considered in a young patient (< 50) with:
   1. No obvious risk factors after baseline investigation
   2. Bilateral, simultaneous RVO
   3. Personal history of thrombosis
   4. Family history of thrombosis
B. Testing to consider
   1. Antiphospholipid antibodies
      a. Lupus anticoagulant
      b. Anticardiolipin antibodies
   2. Antithrombin III levels and activated protein C resistance (Factor V Leiden mutation) in patients with white European ancestry
   3. Functional protein C and protein S levels
   4. Factor XII (Hageman factor)
   5. Prothrombin gene mutation (G20210A)

VI. Conclusions
Retinal vein occlusion is a multifactorial disease. While it represents thrombosis in a retinal venule, the risk factors are more aligned with those associated with atherosclerosis, including hypertension, hyperlipidemia, and diabetes mellitus. Every patient who has an RVO should be thoroughly evaluated, and a detailed ophthalmic examination should include evaluation of an afferent pupillary defect, examination of the undilated pupil, and assessment of the visual field. One should consider the possibility of glaucoma as a risk factor for CRVO. The blood pressure should be measured and a directed lab evaluation should be conducted. For the majority of patients, labs should be drawn to rule out common hematologic abnormalities and diabetes. Based on the history or examination findings, one should consider directed labs to rule out inflammatory causes of RVO or thrombophilia. Testing for thrombophilia should be considered for young (< 50 years) patients with no obvious risk factors after baseline evaluation, atypical presentation (eg, bilateral RVO), or a family history of thrombosis.

References
Vein Occlusions: An Evidence-Based Approach to Initiation of Therapy—Clinical Trials and Subgroup Analysis

Julia A Haller MD

NOTES
What’s New on the Horizon for Retinal Vein Occlusion?

Joan W Miller MD

I. Therapy: Past and Present
   A. Macular edema
      1. Anti-VEGF
      2. Steroids
   B. Ischemia and neovascularization: Retinal ablation
   C. Hypercoagulability: Tissue plasminogen activator (tPA)
   D. Local compression

II. Macular Edema; Altered Blood-Retinal Barrier
   A. Non-VEGF pathways
      1. Angiopoietin 1
      2. TGF-β
      3. PDGF B
      4. Energy sensors (AMPK)
      5. Tight junction proteins: claudins, occludin, junctional adhesion molecules, zonula occludens (ZO) proteins
      6. Wnt/β-catenin via claudins
      7. Protein kinase C (PKC)
      8. Glucocorticoids
   B. Inflammation
      C. Astrocytes, Müller cells, and pericyte contributions to blood-retinal barrier

III. Improving Ischemia
   Reperfusion of capillary occlusion

IV. Systemic and Local Factors
   A. Recanalization of occluded vessels
   B. Vascular remodeling of the retinal vessels
   C. Altering coagulability

V. Neuroprotection
   Preventing photoreceptor and ganglion cell death

VI. Regeneration
   A. Trophic support
   B. Integration of stem cells and repopulation of retinal tissue

VII. Future Diagnostics
   Identifying patients at risk
   A. Vessel wall changes
   B. Flow changes

Selected Readings

BRIGHTER and CRYSTAL Studies

Jordi M Monés MD

Introduction

The efficacy and safety of ranibizumab 0.5 mg in retinal vein occlusion (RVO) has been established in two 12-month, Phase 3 trials (CRUISE and BRAVO) and in extension trials, up to 4 years.1,6 BRIGHTER (NCT01599650) and CRYSTAL (NCT01535261) are 2 ongoing 24-month trials designed to provide long-term data on the efficacy and safety of flexible, stabilization criteria-driven p.r.n. dosing of ranibizumab 0.5 mg, in a broad population of patients with branch RVO (BRVO) and central RVO (CRVO).

Methods

Both studies recruited adults with visual impairment due to macular edema secondary to BRVO (BRIGHTER) or CRVO (CRYSTAL), who had a BCVA score at baseline of between 73 and 19 ETDRS letters. Inclusion/exclusion criteria were expanded to include patients with longer disease duration, broad BCVA scores and ischemia (retinal ischemia defined as capillary loss in any location of center, inner, or outer subfields, detected by central reading center-assessed fluorescein angiography at screening). In BRIGHTER, patients with longer disease duration, broad BCVA scores and ischemia (retinal ischemia defined as capillary loss in any location of center, inner, or outer subfields, detected by central reading center-assessed fluorescein angiography at screening). In BRIGHTER, patients with longer disease duration, broad BCVA scores and ischemia (retinal ischemia defined as capillary loss in any location of center, inner, or outer subfields, detected by central reading center-assessed fluorescein angiography at screening). In CRYSTAL, all patients with CRVO (N=356) received ranibizumab 0.5 mg. In both studies patients received monthly intravitreal injections of ranibizumab 0.5 mg until visual acuity (VA) was stable for 3 consecutive visits; patients were then monitored monthly and treated on a p.r.n. basis until Month 12, when monitoring frequency could be reduced. The primary endpoint in both studies was mean change in BCVA from baseline at Month 6 (with a superiority assessment vs. laser: BRIGHTER) and Month 12 (CRYSTAL).

Results

In the BRIGHTER study, baseline ocular characteristics were generally balanced across treatment groups, with slight differences in baseline BCVA (59.5, 56.6, and 56.5 letters for ranibizumab, ranibizumab with laser, and laser groups, respectively); almost 20% of patients had a disease duration of >12 months, and approximately a quarter had ischemia. By Month 6 the primary endpoint was met, and superiority was shown for ranibizumab with or without laser vs. laser alone, with BCVA gains of 14.4 and 14.8 vs. 6.0 (P<.0001). The mean number of injections was 4.8 and 4.5 for the ranibizumab and ranibizumab with laser groups, respectively. Ranibizumab treatment provided similar VA gains in both ischemic and nonischemic patients, and patients with lower baseline BCVA showed higher BCVA gains across all treatment groups. No imbalances in adverse events (AEs) and serious AEs were reported between the treatment groups over the 6-month study period.

In the CRYSTAL study, mean age at baseline was 65.5 years; approximately 25% of patients had a disease duration of ≥9 months, with a mean disease duration of 8.9 months (maximum: 261 months), which may better represent the CRVO patient population. In addition, ischemic disease was identified in 15% of patients at baseline. Despite lowering the BCVA inclusion criteria to 19-73 letters, mean baseline BCVA was 53.0. By Month 12 the mean change in BCVA from baseline was 12.3 letters, and the mean number of injections administered in that time was 8.1. High baseline BCVA and long disease duration impacted VA gains; however, patients with disease duration ≥9 months still had gains of >10 letters. Ocular and non-ocular serious AEs were reported by 2.5% and 8.1% of patients, respectively.

Conclusions

In BRIGHTER, ranibizumab with or without laser was superior to laser alone over 6 months; BCVA gains were similar to those in BRAVO, despite a lower mean number of injections.2 In addition, ranibizumab provided similar BCVA gains for ischemic and nonischemic patients. CRYSTAL was designed to include an expanded CRVO patient population as compared to CRUISE, and allowed patients with both longer disease duration and ischemia to be included.4 Disease duration was long, and VA gains were affected by disease duration and baseline VA. The primary analysis results from these ongoing RVO studies further support the proven efficacy of ranibizumab in BRVO and CRVO and additionally provide new evidence to support a flexible stabilization criteria-driven p.r.n. regimen. No new safety findings were observed compared with previous studies.1,3 Further long-term results from both studies are expected in 2015.

References


VIBRANT Trial

Intravitreal Aflibercept Injection for Macular Edema Secondary to Branch Retinal Vein Occlusion: Efficacy and Safety From the VIBRANT Study

Robert E Leonard II MD

I. Introduction

A. Retinal vein occlusion (RVO) is the second most common retinal vascular disorder after diabetic retinopathy and is a significant cause of visual impairment.1

B. Of the two main types of RVO, central retinal vein occlusion and branch retinal vein occlusion (BRVO), the latter is more common.1

C. The VIBRANT trial was the first study to compare the efficacy and safety of an anti-VEGF treatment with that of laser.

II. Methods

A. The VIBRANT study was a Phase 3, multicenter, randomized, double-masked, active-controlled, 52-week trial.

Treatment-naïve patients with unilateral macular edema secondary to BRVO were included in the study if they were diagnosed within 12 months and had a BCVA between 73 and 24 letters (20/40 to 20/320 Snellen equivalent).

C. Patients received either intravitreal aflibercept injection (IAI) 2 mg every 4 weeks (n = 91) or laser (n = 92) from baseline to Week 20. From Week 24 onward, eyes in the IAI group received IAI 2 mg every 8 weeks and if they required rescue could receive laser at Week 36; eyes in the laser group that required rescue could receive IAI 2 mg every 8 weeks after 3 initial monthly doses.

D. The primary efficacy endpoint was the proportion of eyes that gained ≥ 15 letters in BCVA from baseline at Week 24.

III. Results

A. The proportion of eyes that gained ≥ 15 letters from baseline to Week 24 was 53% and 27% (P < .001) in the IAI and laser groups, respectively.

B. The corresponding mean improvement in BCVA from baseline to Week 24 was 17.0 and 6.9 letters (P < .0001), respectively.

C. The mean reduction in central retinal thickness from baseline to Week 24 was 280.5 and 128.8 μm (P < .0001) in the IAI and laser groups, respectively.

D. The most common ocular adverse events in IAI eyes were conjunctival hemorrhage (19.8%) and eye pain (4.4%).

E. Traumatic cataract in an eye treated with IAI was the only ocular serious adverse event (SAE) that occurred over the first 24 weeks of study.

F. The incidence of non-ocular SAEs was 8.8% and 9.8% in the IAI and laser groups, respectively.

G. One death due to pneumonia and one Anti-Platelet Trialists’ Collaboration-defined event of nonfatal stroke occurred during the first 24 weeks of study, both in patients in the laser group.

IV. Conclusions

Monthly intravitreal aflibercept injections provided significantly greater visual benefit and reduction in CRT at 24 weeks than did grid laser photocoagulation in eyes with macular edema secondary to BRVO.

Reference

LUMINOUS Study

Paul Mitchell MD PhD

Introduction
Randomized clinical trials are critical for demonstrating the safety and efficacy profile of a drug and for gaining regulatory approval. However, stringent inclusion and exclusion criteria, short follow-up periods, and limited geographic diversity of recruited patients often mean there is clear complimentary value in postapproval observational “real-world” studies to further inform clinical practice and healthcare policies.

Methods
LUMINOUS (clinicaltrials.gov; NCT01318941) is a prospective, 5-year, global, observational, multicenter study aiming to evaluate long-term safety, effectiveness, and treatment patterns of intravitreal ranibizumab 0.5 mg in routine clinical practice across all approved indications: neovascular age-related macular degeneration (nAMD), visual impairment (VI) due to diabetic macular edema (DME), VI due to macular edema secondary to branch or central retinal vein occlusion (BRVO, CRVO), and VI due to choroidal neovascularization (CNV) secondary to pathologic myopia (myopic CNV). Initiated in March 2011, LUMINOUS aims to recruit a total of 30,000 patients by March 2015, with a minimum follow-up period of 12 months. As of 1 September 2014, a total of 26,664 patients have been enrolled in the study (nAMD, 81.5%; DME, 12.0%; BRVO, 3.2%; CRVO, 2.6%; mCNV, 0.7%) ranibizumab treatment naïve, or who have previously received ranibizumab or other ocular treatments. Patients have been recruited from 40 countries worldwide. The UK (n = 10,001), Canada (n = 2865), and Japan (n = 2100) are the highest recruiters to date. Results from the second interim analyses are now available, including baseline characteristics of patients enrolled up to March 2014, Year 1 analysis of patients enrolled up to March 2013, and Year 2 analysis of patients enrolled up to March 2012.

Results
Baseline data from 20,085 patients from over 30 countries were available for analyses (nAMD, n = 17,545; DME, n = 1758; BRVO, n = 393; CRVO, n = 350). The age range was wider than that of pivotal trials (mean age, years: nAMD, 77.4; DME, 64.2; BRVO, 69.0; CRVO, 68.2; mCNV, 63.2). For nAMD, 23.5% of patients were 85 years or older. Ethnic diversity of patients was also greater than previous studies (79.5% white, 16.7% Asian). Common comorbidities included hypertension (58%), hypercholesterolemia/lipidemia (32%), and diabetes (22%). A wide range in baseline visual acuities (VA) was observed for all indications, and baseline VA was higher in patients who received prior ranibizumab treatment vs. treatment-naïve patients for all indications. Approximately 40% of nAMD patients had pigment epithelial detachment at baseline and 5%-8% had polypoidal choroidal vasculopathy. One-year follow-up data are available for 9790 patients recruited prior to March 2013. Treatment-naïve patients gained vision from baseline (mean letter change: nAMD, +4.4; DME, +4.5; BRVO, +7.0; CRVO, +13.2), while those receiving prior ranibizumab either gained or maintained vision (mean letter change: nAMD, −1.5; DME, +3.2; BRVO, +8.0; CRVO, +1.4), with relatively low numbers of injections and monitoring visits. Vision was maintained in nAMD patients who had previously received ranibizumab, even in those patients in their 6+ year of treatment. The most frequent non-ocular serious adverse events (SAEs) (total, n = 638) were myocardial infarction (n = 43; 0.4%), pneumonia (n = 43; 0.4%), and cerebrovascular accident (n = 39; 0.4%). The most frequent ocular SAEs (total, n = 53) were endophthalmitis (n = 13, 0.1%) and retinal detachment (n = 10, 0.1%). In the 24-month follow-up of 2001 nAMD patients recruited prior to March 2012, mainly recruited from Australia (44%) and the UK (41%), change in VA from baseline was 3.4 and −1.4 letters at 12 months and 2.0 and −3.0 letters at 24 months for the treatment-naïve and prior ranibizumab treatment groups, respectively. In total, 13.3% non-ocular SAEs and 0.7% ocular SAEs were reported.

Conclusions
This interim analysis of patients in a real-world setting from the LUMINOUS study reinforces the well-established efficacy and safety profile of ranibizumab.
iDEAL Phase 2 Study of Intravitreal iCo-007 for Diabetic Macular Edema

Quan Dong Nguyen MD

I. Introduction
   A. Antisense technology
   B. iCo-007 as second-generation antisense

II. Preclinical Studies of iCo-007

III. Phase 1 Clinical Trial of iCo-007 in Eyes With DME

IV. Phase 2 Clinical Trial of iCo-007 in Eyes With DME

V. A Randomized, Multicenter, Phase 2 Study of the Safety, Tolerability, and Bioactivity of Repeated Intravitreal Injections of iCo-007 as Monotherapy or in Combination With Ranibizumab or Laser Photocoagulation in the Treatment of Diabetic Macular Edema with Involvement of the Foveal Center (the iDEAL Study)
   A. Study design
   B. Randomization

VI. Primary Outcomes of the iDEAL Study: Visual Acuity

VII. Safety Outcomes at Primary Endpoint

VIII. Key Secondary Outcomes: Preliminary OCT analyses

IX. Discussion and Future Directions
Development of Atrophy in Neovascular AMD Treated with Anti-VEGF Therapy: Results of the HARBOR Study

SriniVas Sadda MD, Lisa Tuomi PharmD, Beiying Ding PhD, J Jill Hopkins MD

Background

Advanced AMD is a progressive, vision-threatening disease that manifests in 2 forms, geographic atrophy (GA) and neovascular AMD (wet AMD). GA generally progresses over several years and may not immediately threaten central vision, while choroidal neovascularization (CNV) in wet AMD can significantly reduce vision within a year. GA and wet AMD may occur concurrently in the same eye.

The pivotal, Phase 3 clinical trials in wet AMD—MARINA and ANCHOR—demonstrated that treatment with ranibizumab, a humanized, monoclonal antigen binding fragment that inhibits all active forms of VEGF-A, can generally improve and maintain vision in patients with wet AMD. Following 2 years of monthly-administered intravitreal ranibizumab 0.3 mg or 0.5 mg, patients achieved mean BCVA gains of +5.4-10.7 Early Treatment Diabetic Retinopathy Study (ETDRS) letters from baseline, compared with losses of −14.9 letters with sham treatment (MARINA) or −9.8 letters with verteporfin photodynamic therapy (prior standard of care; ANCHOR). Vision improved or stabilized in the majority of patients treated with ranibizumab (90%-92% of patients lost < 15 letters at 2 years), and increased areas of GA were not associated with visual acuity loss. After the introduction of anti-VEGF therapeutics for the treatment of AMD, vision loss or blindness attributable to wet AMD was reduced by ~50% in multiple countries.

Three potential contributing pathophysiologic mechanisms are considered in the development of atrophy in anti-VEGF-treated eyes. First, the new GA in CATT and IVAN may be the natural progression of underlying dry AMD over time (ie, true classically defined GA). Alternatively, the pathophysiology of the atrophy observed in wet AMD may differ from true GA and may be better described as macular atrophy. The macular atrophy may be associated with the CNV lesion, caused either by retinal/subretinal fluid and hemorrhage or CNV extension and contraction resulting from ischemia or anti-VEGF-induced regression of abnormal blood vessels. Finally, macular atrophy may be influenced by a class effect of anti-VEGF agents, potentially resulting from the inhibition of constitutive VEGF production in the retina. Macular atrophy in wet AMD patients treated with anti-VEGF agents may be unique compared with classically defined GA.

Methods

This study reports a retrospective analysis of macular atrophy in the Phase 3 HARBOR trial, which evaluated the efficacy and safety of intravitreal ranibizumab 0.5 mg or 2.0 mg administered monthly or p.r.n. for the treatment of wet AMD. Methods for assessing macular atrophy in the HARBOR data set were developed to address variability in definitions of atrophy, differing grading protocols for atrophy assessment, and the use of different modalities for visualizing atrophy (see Figure 1).

1. Method 1, Nonadjacent: FA and CFP images were manually graded for GA following the protocol developed in CATT, described above.
2. Method 2, All-Inclusive: Grading of FA and CFP images was repeated using more inclusive criteria (ie, to include atrophy immediately adjacent and nonadjacent to CNV lesions).
3. Multimodal grading methods, combining results from FA, CFP, and spectral-domain OCT are also being examined.
Results

Detailed results of the retrospective analysis of macular atrophy in HARBOR will be discussed.

Key findings of the analysis included:

- Mean BCVA improved over time in patients with macular atrophy present at baseline with monthly or p.r.n. treatment (see Figure 2).
- Presence of macular atrophy at baseline was not associated with an increased proportion of patients losing ≥15 letters of vision.
- Patients with any concurrent (ie, new or baseline) macular atrophy at Month 12 and Month 24 had comparable mean BCVA to patients without macular atrophy at Month 12 and Month 24.

Discussion

- Atrophy developing in the setting of treated wet AMD may differ from classically defined GA, therefore the term “macular atrophy” is used in the HARBOR analysis to describe this entity.
- There is currently a lack of “gold-standard” criteria for defining macular atrophy in patients treated with anti-VEGF agents.
- Based on existing data, the risk of developing GA or macular atrophy does not appear to outweigh the benefits of ranibizumab therapy for wet AMD.
  - Vision gains are substantial even in the presence of macular atrophy through 24 months.
  - The risk of undertreatment with ranibizumab therapy remains a potentially greater threat to vision.
- Going forward, there is a need to work toward understanding the pathophysiology of macular atrophy in wet...
AMD and anti-VEGF-treated wet AMD. This will aid in the development of the best treatment algorithms for patients with wet AMD.

References


Switching: Does It Improve Outcomes?

Rishi P Singh MD

The idea of switching between therapies in medicine is not novel. Diseases such as rheumatoid arthritis, multiple sclerosis, and others have well-documented studies on switching therapies in patients, especially those with insufficient response or intolerable adverse events. In the treatment of exudative AMD, we have employed various methods of addressing inadequate response, including reducing treatment intervals, combining therapies with different modes of action, or switching to a different drug. Retina specialists are fortunate to have multiple treatment options for exudative macular degeneration to choose from, including ranibizumab (Lucentis, Genentech; S. San Francisco, Calif.), bevacizumab (Avastin, Genentech; S. San Francisco, Calif./Roche; Basel, Switzerland), and aflibercept (Eylea, Regeneron; Tarrytown, NY/Bayer; Leverkusen, Germany). Unfortunately, the trials that registered these drugs with the FDA excluded patients with previous treatment. Thus we currently lack outcome data from large prospective clinical studies to validate switching therapies.

There are lots of complexities when designing a study evaluating switching of therapies. The first is assigning the exact definition of treatment failure. Many retrospective and fewer prospective switching trials enrolled patients unresponsive to treatment (no improvement or deterioration in visual acuity and morphology, ie, stable or increasing sub- or intraretinal fluid as assessed by OCT). However, in randomized prospective clinical studies, 55% to 71% have persistent fluid (retinal edema, subretinal fluid, or retinal pigment epithelial detachment) despite monthly injections of ranibizumab, aflibercept, or bevacizumab for extended periods. Therefore, the inclusion of persistent fluid may not be an adequate definition for enrollment in a “switcher” study. Other definitions such as those patients requiring frequent injection, those with disciform scars, or RPE atrophy or rip following treatment may also be relevant for inclusion. Thus, a universally accepted definition of treatment failure is still being sought.

One of the first approaches to address treatment failure is to increase the frequency of the anti-VEGF injection regimen. In clinical practice, few retina specialists adhere to the strict schedule of regular monthly intravitreal anti-VEGF injections for 2 years, as established by the 2 major trials of ranibizumab. Variable regimens have become the de facto practice because of the financial costs of the drug and procedure, patient preferences, and practice workload. The 2012 Preferences and Trends Survey administered by the American Society of Retina Specialists revealed that 66.5% of retina specialists use bevacizumab monotherapy to treat typical wet AMD with subfoveal CNV of up to 1 disc diameter in size. Of the survey respondents, 44% indicated that they would recommend a switch to aflibercept after previous nonresponse to bevacizumab monotherapy.

Decreasing the time between intervals seems like one approach to treatment failure patients. Clinically, this amounts to injecting bevacizumab every month alternative with monthly ranibizumab or aflibercept for a net biweekly anti-VEGF injection. The improvement in drug binding has been theoretically summarized and anecdotal evidence exists, but clinical prospective data are lacking. Moreover, the treatment burden is high, with patients returning every 2 weeks for an intravitreal injection.

Another tactic is to increase the dosage, but higher dose studies have led to variable improvements. In the HARBOR trial, 1097 treatment-naïve wet AMD patients were randomized to treatment frequency and dosage, and endpoints were evaluated at 1 year. In these treatment-naïve eyes, 2.0-mg ranibizumab showed no benefit over the currently approved 0.5-mg dose in terms of visual acuity. No safety issues were observed with the 4-fold increase in dosage.

In the SAVE trial, 2-mg high-dose ranibizumab was given monthly or every 6 weeks in treatment-non-naïve eyes. Seventy-nine patients with previously injected recalcitrant disease were followed over 1 year. A gain of 4.1 letters in BCVA was observed and maintained over 1 year in both dosing regimens. Similar to the HARBOR study, no significant safety concerns arose, but switching poorly responsive eyes from 0.5-mg ranibizumab to 2.0-mg ranibizumab further improved macular thickness by -33 µm to -40 µm and visual acuity by +3.3 to +4.1 letters at 3 to 6 months.

Lastly, switching to a different anti-VEGF drug might result in a superior anatomical and visual outcomes. In the prospective clinical trial that our group published recently, we have observed a number of eyes that seem to have had long-term visual and anatomical benefits following a switch to an alternative anti-VEGF agent. However, current published studies are for the most part retrospective and performed in a nonstandardized manner, with different indications for switching, follow-up periods, and retreatment criteria owing to significant problems with interpretation. In a meta-analysis of these switcher studies, switching did not appear to have a significant functional effect on visual acuity although it appeared to give some anatomical improvement.

In conclusion, the results of switcher studies are challenging to interpret for a multitude of reasons. We tend to switch subjects who are not doing well. Some are truly not doing well, but others are only apparently not doing well, either because of temporary random variation or because they in fact will do well with longer follow-up. It remains unclear to what degree these short-term results are due to tachyphylaxis to the prior therapy and whether eyes switched to an alternative anti-VEGF may ultimately develop tachyphylaxis to this agent and benefit from a switch to an alternative agent following the initial switch. Ultimately, experience and good clinical judgment will help the physician choose the best cases in which to try switching agents. Future prospective studies with predetermined entry criteria and follow-up are recommended to fully explore the impact of switching anti-VEGF therapy.

References


Beyond Anti-VEGF: Is It Really a Choroidal Neovascular Membrane?

Pravin U Dugel MD
Sustained Drug Delivery: Where Do We Stand?

Glenn J Jaffe MD

I. Why local drug delivery?
   A. Topical, systemic, injection therapy disadvantages
      1. Depend on patient compliance
      2. Drug levels not constant
      3. Limited effect duration, limited achievable drug levels
      4. Side effects (systemic and ocular)
   B. Local sustained drug delivery advantages
      1. Can tailor delivery system for specific disease
      2. Patient compliance not an issue
      3. Can eliminate systemic side effects
      4. Provide constant, sustained delivery
      5. Can deliver directly to posterior segment

II. Sustained Delivery Platforms for Neovascular AMD
   ■ Encapsulated cell technology (Neurotech)
   ■ Nanostructured Tethadur (Psivida)
   ■ Refillable reservoir (Foresight)
   ■ Refillable programmable pump (Replenish)
   A. Encapsulated cell technology (ECT)
      1. Genetically engineered cells
      2. Cells designed to overproduce protein of interest
      3. Multiyear implant cell viability
      4. Encapsulated in nonbiodegradable delivery system
      5. Can incorporate different drugs for different targets
      6. Retinal degenerations (eg, hereditary, geographic atrophy associated with AMD), optic neuropathies
         a. CNTF
         b. NGF
         c. BDNF
      7. Proliferative diseases (eg, neovascular AMD, proliferative diabetic retinopathy)
         a. Soluble vascular endothelial growth factor (VEGF) receptor
         b. Bevacizumab
         c. Ranibizumab
         d. Anti-platelet derived growth factor (PDGF)
         e. Bispecific (anti-VEGF/anti-PDGF)
         f. pigment epithelium derived factor (PEDF)
         g. DARPin
         h. Tie2
   8. ECT Clinical Trials
      a. ECT containing VEGF receptor decoy
      b. Double implant approximately 2 lines better than single implant at 10 months
      c. Almost 2-line gain with double implant at 10 months
      d. Approximately 150-μ decrease in central subfield thickness in double implant, 60-μ decrease with single implant at 10 months
      e. Acceptable safety profile
      f. Top of dose response not yet demonstrated with single or double implants.
      g. Phase 2 study initiated to evaluate generation 3 implant with 2-3 fold higher release rate.
      h. Future implants could combine more than 1 therapy (eg, anti-VEGF/anti PDGF).
   B. Nanostructured Tethadur
      1. Injectable microparticulate peptide / protein delivery technology that relies on adsorption of a target molecule into customized molecular pores (like eggs in an eggbox)
      2. Nanostructured and porous material manufactured from elemental silicone
      3. Tunable (micromachinable; These are not nanoparticles.)
      4. Adsorbed molecules are stabilized in the porous matrix.
      5. Release from the matrix can be controlled over days to months.
      6. A commercial peptide / protein solution can be withdrawn from vial, mixed with Tethadur particles, and administered to patient to provide sustained delivery.
      7. Biodegradable
      8. Biocompatible
      9. Provides shortcut from Biosimilar to patent-protected BioBetter
C. Refillable reservoir / port delivery system (PDS)
   1. Refillable, long-term drug delivery implant
   2. Placement with standard surgical techniques
      a. Placed pars plana (subconjunctival) 3.2-mm incision
      b. No scleral sutures
      c. 10 min. procedure
      d. Minimally invasive office-based refill procedure
      e. Sustained drug release between refills
   3. Clinical Data Phase 1 data
      a. 20 subjects
      b. Single arm study
      c. PDS filled with ranibizumab
      d. Most adverse events (AEs) mild, transient
      e. 3 SAEs (2 nonclearing vitreous hemorrhage, 1 endophthalmitis)
      f. No SAEs with device removal
      g. Ex vivo drug release similar to unimplanted implants
      h. Average increased visual acuity about 2 lines at 1 year
      i. 50% 3-line gain at 1 year
      j. 10% 3 line loss at 1 year
      k. About 100-120 μ decreased central subfield thickness at 1 year

D. Implantable, refillable, programmable pump delivery system (Replenish)
   1. Comprises 5 subcomponents
      a. Electronics/battery
      b. Drug reservoir chamber (60 μl capacity)
      c. Refill port-accessible with transconjunctival 31-gauge needle
      d. Electrolysis chamber and check valve
      e. Intraocular cannula-release microdose into vitreous cavity
   2. Phase 1 clinical data
      a. 11 implanted eyes with diabetic macular edema
      b. 90-day follow-up
      c. No SAEs
      d. Surgically feasible; no surgical complications
      e. 7/11 delivered proper dose
      f. Decreased macular edema in eyes dosed properly
      g. Four delivery systems may have been damaged during surgical implantation.
Other Anti-VEGF Agents in Clinical Trials

David G Callanan MD
Update on Gene Therapy for AMD

Jeffrey S Heier MD

I. Gene Therapy Background
   A. What is gene therapy?
      Therapy in which genetic material is introduced into cells to effect protein transduction by the cells
      1. Compensate for structurally abnormal or missing genes
      2. May also be used to induce targeted host cells to constitutively secrete a naturally occurring or engineered therapeutic protein as an alternative to repeated (intravitreal) injections
   B. Focus of gene therapy
      1. Initially established to treat hereditary diseases with single gene defects
         a. Muscular dystrophy
         b. Hemophilia
      2. Current focus includes polygenic or noninherited diseases with high prevalence
         a. Cancer
         b. Macular degeneration
   C. Desirable features of best viral vectors
      1. Able to introduce and transfect target cells with cDNA resulting in protein production
      2. No activation of the immune response
      3. Vector incapable of causing disease
      4. Much or all of the vector’s genetic material can be replaced by the therapeutic gene.
      5. Adeno-associated virus
         a. Advantages
            i. non-disease causing passenger virus that affects humans (and other primates)
            ii. very low immunogenicity
            iii. nonintegrating (does not insert message into host DNA): no risk of insertional mutagenesis
            iv. approximately 100 trials worldwide
         b. Disadvantage: small size
   II. Gene Therapy for Retinal Disease
      The human retina is ideally suited for developing gene-based therapies.
      A. Eye is small and relatively protected / isolated.
         1. Allows local delivery of gene therapy product to desired site
         2. Allows high concentration with injection of a small amount of vector
         3. Reduced likelihood / severity of immune response / adverse event
      B. Injection sites are readily accessible.
         1. Intravitreal
         2. Subretinal
      C. Noninvasive assessment of retinal function and structure
         1. Function
            a. BCVA
            b. Visual field
            c. Contrast sensitivity
            d. Microperimetry
         2. Structure
            a. OCT
            b. Fundus photography
            c. Autofluorescence
            d. Angiography (fluorescein angiography, indocyanine green angiography)
            e. Adaptive optics imaging
      D. Many natural animal models of retinal disease have shown benefit.

Figure 1. Rationale for sustained delivery.
III. AAV2-sFlt01 Delivery to the Eye
   A. Two approaches/routes of delivery studying AAV2-sFlt01
   B. Intravitreal fusion protein containing sFlt binding domain
   C. Subretinal approach with naturally occurring sFlt

IV. Clinical Program: Intravitreal
   Two stages:
   A. Stage 1
      1. Advanced neovascular AMD
      2. Dose escalation
         a. 4 doses
         b. Safety assessments
   B. Stage 2
      1. Chronic AMD with or without subfoveal scarring
      2. Single cohort
      3. Maximally tolerated or tested dose
   C. 19 patients total
   D. Preclinical testing suggests a safe and efficacious treatment.
   E. Phase I clinical trial is ongoing at recognized centers of excellence.

V. Clinical Program: Subretinal
   A. Two cohorts
      1. Low dose
         a. 3 active patients
         b. 1 control
      2. High dose
         a. 3 active patients
         b. 1 control
   B. Safety: No adverse safety signals
   C. Efficacy: Biologic activity demonstrated
      1. Anatomic
      2. Visual acuity
   D. Very low retreatment rate
   E. Phase 2 trial ongoing
The development of anti-VEGF therapies for wet AMD has provided significant improvements in visual outcomes. However, inferior visual outcomes result when patients are treated less frequently than recommended by clinical studies. In a 2006-2010 analysis of ~500,000 Medicare beneficiaries, nearly 60% of patients received 4 or fewer injections in the first year after initiating treatment, and 57% discontinued therapy within the first year. However, a recent 7-year follow-up study showed disease was still active in a majority of patients, most of whom were receiving long-term treatment.

Repeated injections are a burden to patients, caregivers, retina specialists/staff, and the health-care system and likely contribute to the magnitude of anti-VEGF undertreatment.

**Encapsulated Cell Technology (ECT)**

To address the need for continuous, long-term therapy for retinal diseases, Neurotech developed the Encapsulated Cell Technology (ECT) platform, which utilizes a proprietary, immortalized, nontumorigenic retinal pigmented epithelial cell line that is genetically engineered to constitutively produce therapeutic proteins, a matrix that supports cell survival/function, and a semipermeable membrane that enables the outward passage of therapeutics, while permitting access of the cells to oxygen and nutrients. These components are contained within a device that is surgically implanted into the vitreous cavity through a ≤ 3-mm scleral incision during a brief procedure, similar to that used for Vitrasert and Retisert, and sutured to the scleral wall using its titanium clip.

The ECT platform has many potential advantages over other therapies. It can support the continuous delivery of a wide array of therapeutic proteins into the vitreous, singly or in combination, and consistently deliver proteins for at least 2 years to treat a broad range of retinal diseases. In addition, avoiding frequent, bolus injections with an ECT implant may minimize local and systemic adverse events. Perhaps, most importantly, ECT implants are easily retrievable, if necessary, and do not modify the host genome, unlike gene therapy.

**NT-503 for the Treatment of Wet AMD**

Neurotech’s lead ECT product candidate, NT-503, has been engineered to continuously produce a soluble VEGF receptor (sVEGFR) fusion protein for the treatment of wet AMD.

**Design Evolution of the NT-503 Device**

Neurotech has designed several NT-503 device configurations to support dose escalation across a wide range of release rates. By varying device size, cell counts, and membrane permeability, and by increasing the number of chambers in each device, the release rates have been augmented thus far by ~30-fold. The highest producing configuration for the NT-503 program is a 5-chamber device, being evaluated in GLP toxicology studies (see Figure 1). This configuration also allows for individual chambers to be loaded with more than one protein-expressing cell line for combination therapy.

**Nonclinical Evaluation of NT-503**

**Pharmacology**

In vitro, NT-503-produced sVEGFR protein binds with picomolar affinity to human VEGF-A (see Figure 2), similar to the reported values for aflibercept and with approximately 10 times greater efficiency than ranibizumab (see Table 1).

**Table 1. In Vitro Binding Affinities of Several Anti-VEGF Therapies**

<table>
<thead>
<tr>
<th>Molecule</th>
<th>KD (pM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab*</td>
<td>2900</td>
</tr>
<tr>
<td>Ranibizumab*</td>
<td>140</td>
</tr>
<tr>
<td>Aflibercept*</td>
<td>0.5</td>
</tr>
<tr>
<td>NT-503 Protein</td>
<td>0.7</td>
</tr>
</tbody>
</table>

* Based upon published data; KD (pM) = equilibrium dissociation constant between the antibody and its antigen in picomolars.

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Figure 1. Single-chamber (ECT 1/2) and multichamber (ECT 3) configurations.
Pharmacodynamics
The ability of sVEGFR produced by the NT-503 cell line to neutralize VEGF and prevent neovascular development was evaluated in a rodent model of CNV. A 95% reduction in CNV lesion size was demonstrated after a single intravitreal injection (see Figure 3).

Pharmacokinetics
In vitro studies show the release rates of sVEGFR of 3 NT-503 configurations, ranging from ~300 ng/d to 10,000 ng/d (see Figure 4a). In vivo studies in rabbits with NT-503 demonstrated continuous and steady delivery of NT-503 at the 0.4-0.5 µg/day (ECT 1) and 2.0-2.5 µg/day (ECT 2) doses over 18 months (see Figure 4b). The ECT 3, a 5-chamber device, is anticipated to increase vitreous dose levels ~4-5 fold over that achieved with the ECT 2 configuration.

Toxicology
Through 6 months of an ongoing GLP toxicology study in rabbits, the ECT 3 implant is well tolerated with no significant clinical, electroretinographic, laboratory, or histopathologic findings.
Section VIII: Neovascular AMD

Clinical Dose-Ranging Efficacy and Safety Studies With NT-503

Two doses are being evaluated in an ongoing, dose-escalating study: 2.0-2.5 µg/d (1 device) and 4.0-5.0 µg/d (2 devices). Rescue therapy with ranibizumab is administered based on standardized OCT or vision criteria. A dose response has been observed for both the improvement of visual acuity and the reduction in central retinal thickening for 12 months of follow-up (see Figure 5). To date, 11 of 26 patients (42.3%) implanted with a single device required rescue therapy, and 3 of 16 patients (18.8%) who received 2 implants were rescued. Single-implant patients received an average (range) of 0.80 (0-5) rescue injections, while patients receiving 2 implants received an average (range) of 0.25 (0-2) rescue injections.

To date, the latest NT-503 configuration, with 2 implanted devices, has been well tolerated. There have been no severe or serious adverse events, and there have been no discontinuations or explants.

Conclusion

NT-503 is well tolerated and achieves clinical meaningful improvements in visual acuity and reductions in macular thickening over 12 months following surgical implantation in patients with wet AMD. The ECT 3 configuration, which achieves a ~2-fold increase in release rates over that tested in the ongoing trial, is expected to have efficacy at least comparable to existing anti-VEGF therapies and will be evaluated in an upcoming randomized, controlled trial.

References

Squalamine Eye Drops for Retinal Disease

*Thomas A Ciulla MD*

I. Squalamine Chemical Structure
A. Small molecule aminosterol
B. Originally isolated from dogfish shark liver
C. Chemically synthesized

II. Squalamine Background
A. Novel intracellular, anti-angiogenic mechanism of action
B. Inhibitor of VEGF, platelet derived growth factor (PDGF), and basic fibroblast growth factor signaling through chaperoning of the modulatory protein calmodulin
C. Being developed by Ohr Pharmaceutical as an eye drop
D. Awarded Fast Track designation for wet AMD by the U.S. FDA in May 2012

III. Blocks VEGF-Stimulated Phosphorylation of Focal Adhesion Kinase (FAK) and Actin Reorganization in Endothelial Cells

IV. Squalamine Does Not Inhibit Endothelial Nitric Oxide Synthase (eNOS)

V. Previous Clinical Experience, IV
A. Previously studied using intravenous infusions
   1. 250+ patients with wet AMD
   2. Safely tested in wet AMD at doses of up to 160 mg per infusion
   3. Trial design: Weekly IV x 4 weeks, monthly IV thereafter
B. Clinical data in wet AMD trials
   1. Demonstrated biological effect
   2. Gains in visual acuity
   3. Strong maintenance of vision
   4. Positive effect in advanced, low vision wet AMD

VI. Intravenous Administration Challenges
Suboptimal dosing due to rapid plasma clearance and short plasma half-life. Rapid plasma clearance eliminates ability to maintain posterior ocular therapeutic concentrations.

VII. OCT Case 1: IV Clinical

VIII. Right Drug, Wrong Delivery?
A. IV results demonstrated clear activity even though dosed suboptimally. IV dosing to achieve optimal posterior concentrations is not practical (> 1 per week, long infusions).
B. Could we formulate an eye drop with the ability to deliver drug optimally and achieve sustained inhibitory concentrations?

IX. Topical Drug Delivery Routes to the Posterior Segment
A. Periocular
B. Uveal

X. Squalamine has ideal properties of a topical agent to treat CNV.
A. High potency at a nanomolar level
B. Ability to inhibit multiple angiogenic growth factors, including VEGF and PDGF.
C. Diffusion from the front of the eye into the posterior sclera and then into the choroid, where the CNV process actually occurs.
D. Long retention time in the choroid

XI. Squalamine Eye Drops
A. Formulated Squalamine Eye Drops
B. In vivo studies in rabbits to evaluate:
   1. Biodistribution
   2. Squalamine concentrations in posterior sclera/choroid
   3. Rate of uptake relative to dose frequency
   4. Trough concentrations over a 14-day administration
   5. Levels after single administration
C. Ocular safety
   1. Clinical observations (swelling, redness, etc.)
   2. Toxicity to ocular tissues
D. Comparison of eye drop with previous IV clinical data

XII. Single-Dose Biodistribution
A. Rapid uptake
B. Significant residence time
XIII. Posterior Tissue Trough Levels
   A. Trough levels well in excess of squalamine’s threshold level to inhibit tissue angiogenesis
   B. Rapid uptake, more pronounced with higher frequency dosing

XIV. Summary of Eye Drop Data
   A. Sustained posterior sclera / choroid concentrations consistently maintained above threshold therapeutic level. Ability to overcome challenge of IV suboptimal dosing through continuously replenishing therapeutic concentrations in a noninvasive manner
   B. Rapid uptake in a dose-responsive manner
   C. Safe to ocular tissues on long-term administration
   D. Eye drop overcomes limitations of previous IV dosing

XV. Phase 2 Clinical Trial: Wet AMD
   A. Enrollment under way at 24 U.S. clinical sites
   B. Newly diagnosed wet AMD patients
   C. Duration: 9-month treatment period with interim analysis (50% completed)
   D. Randomized, double masked, placebo controlled study

XVI. Phase 2 Trial
   A. Rescue treatment of Lucentis when specific OCT and visual acuity parameters are met as per protocol
   B. Efficacy endpoints
      1. 1°: Mean number of Lucentis injections
      2. 2°: Mean time to Lucentis retreatment
      3. 2°: Visual acuity gains, maintenance, and safety
   C. Primary endpoint is powered (90%) to detect a 1.5-injection difference between the arms.
   D. 60 patients per arm (120 total)

XVII. Potential Clinical Outcomes
   A. Adjunct to anti-VEGF injections
   B. Single agent: If significant group of patients do not need rescue anti-VEGF treatment in the Phase 2 trial

XVIII. Current Investigator-Sponsored Trials With Squalamine Eye Drops
   A. Proliferative Diabetic Retinopathy: Dr. Michael Elman; Baltimore, MD (5 patients)
   B. Retinal Vein Occlusions, BRVO/CRVO: Dr. John Wroblewski; Hagerstown, MD (20 patients, 10 BRVO, 10 CRVO)
Update on Integrin Antagonists

Hugo Quiroz-Mercado MD

Introduction

The molecular events involved in the development of wet AMD and proliferative diabetic retinopathy (PDR)/diabetic macular edema (DME) have not been fully elucidated; however, vascular endothelial growth factor (VEGF) has been shown to play a major role in the process. Integrins α5β1, αvβ3, and αvβ5 are implicated in the angiogenic process as well and are known to be expressed in neovascular ocular tissue from patients with wet AMD, DME, and PDR. As an integrin antagonist with a unique mechanism of action, ALG-1001 inhibits and regresses neovascularization while reducing vascular leakage by targeting these 3 integrin receptor sites implicated in angiogenesis.

Anti-VEGF therapy is currently the only class of pharmaceutical treatment options approved to treat the very large pool of patients with retinal vascular diseases.

Allegro Ophthalmics, in collaboration with CalTech, has developed an anti-integrin oligopeptide as a first in class therapeutic for vitreoretinal eye diseases, including wet AMD, DME, and focal symptomatic vitreomacular traction (VMA). Specifically, Allegro has discovered a peptide sequence that effectively binds to the integrin receptor sites associated with wet AMD, DME, and PDR: α5β1, αvβ3, and αvβ5.

Intravitreal injections of the anti-integrin compound ALG-1001 demonstrate anti-angiogenesis and vitreolysis affects in human subjects that is found to both be safe upon repeated injections and to reduce subretinal and intraretinal fluid by a mechanism that is distinctly different than that of anti-VEGF therapy. These results were also seen in multiple animal models.

Based upon human and animal studies completed to date, as well as data still being generated, ALG-1001 has the potential to be a new class of treatment for wet AMD and DME/PDR. The two key potential patient benefits from ALG-1001 based upon clinical data generated to date and elucidated below are (1) requiring fewer injections, since the benefits from ALG-1001 appear to last at least 3 months off-treatment in monotherapy and (2) providing an alternative treatment option for patients who have either plateaued or are not responding to anti-VEGF therapy since clinical benefit has been demonstrated for this category of patients in multiple ALG-1001 human clinical studies to date.

Supporting Animal Efficacy Studies

ALG-1001 demonstrated a statistically significant reduction in neovascularization in a well-published laser CNV mouse model that mimics wet AMD conducted by Dr. Peter Campochiaro at the Wilmer Eye Institute.
Further studies also demonstrated the equivalent potency in the reduction of CNV when ALG-1001 was compared to Eylea (see Figure 5).

Supporting Animal Safety Studies

Alongside these pre-clinical efficacy studies, Allegro’s in vivo pre-clinical safety studies of ALG-1001 in rabbits with both a single injection and repeated multiple injections have shown excellent safety and efficacy profiles across multiple studies. Furthermore, a maximum tolerated dose of approximately 15 mg per human intravitreal injection has been extrapolated from this data.

Wet AMD Human Study

The objective of this Phase 1b/2a study was to evaluate the safety, initial efficacy, and dose escalation of ALG-1001 solution for intravitreal injection as monotherapy in human subjects with wet AMD. The primary endpoint was the observation of dose limiting toxicity, with secondary endpoints being observation of a clinical benefit in BCVA and OCT central macular thickness of 2.0 mg and 3.2 mg of ALG-1001 solution for intravitreal injection.

Fifteen human subjects with wet AMD completed this open label study at 4 study sites, and were divided into 2 study groups. Eight subjects received 2.0 mg of ALG-1001, and 7 subjects received 3.2 mg of ALG-1001. An additional group with 5.0-mg ALG-1001 dosing was added later in the study, with the data from this group to be forthcoming.
Subjects received 3 monthly injections of ALG-1001 in stand-alone therapy following a 45-day washout period from anti-VEGF or laser therapy. Subjects were followed for a total of 180 days, including 4 months off-treatment after the last injection. Safety measurements were followed by BCVA, slitlamp evaluation, dilated fundus exam, IOP measurements, OCT, fluorescein angiography, and fundus photography.

Following the endpoints of BCVA and OCT central macular thickness, there appeared to be a clear indication of a biologic effect of the drug in this patient population, particularly in the 3.2-mg study arm. Further, the observed changes of BCVA letters in the groups following last treatment with ALG-1001 demonstrated a strong dose-response curve.

At study Day 90, one month after completion of the loading dose, the 2.0-mg group lost an average of -6.6 letters while the 3.2-mg group gained +4.0 letters on average (See Figures 6 and 7). The difference between the 2.0-mg and 3.2-mg groups continued to diverge over time, with a peak gain of +5.2 letters in the 3.2-mg group at study day 120 and -13.2 letters lost in the 2.0-mg group at study day 120. These responses indicate a likely dose response curve with the effects of ALG-1001 solution for intravitreal injection demonstrating clinically significant improvements in both retinal lesion regression and improvements in ETDRS BCVA at the 3.2-mg dose.

Three monthly intravitreal injections of ALG-1001 at 2.0 or 3.2 were well tolerated in all study eyes. There were no reported serious adverse events (SAEs) in among the 22 subjects, and there were no significant AEs. AEs were primarily limited to injection-related events such as transient IOP elevation and transient anterior chamber inflammation that was usually self-limited.

Supporting Human DME Studies
In late 2011, prior to the Phase 1b/2a Wet AMD Study, a 15-subject open label study in end-stage DME patients was completed. Three monthly intravitreal injections of 2.0 mg of ALG-1001 were given following a 90-day washout period, following subjects for an additional 3 months off treatment. There were no SAEs. Eight of 15 subjects reported a 3- to 5-line increase in BCVA after receiving 3 injections, with up to a corresponding 79% reduction in central macular thickness on OCT.

Supporting Animal Safety and Efficacy Studies
The human results presented here closely mirror the preclinical information that demonstrates the safety and repeated efficacy of 2.0-mg ALG-1001 in several animal models of CNV, preretinal NV, and vascular permeability.

Summary
The most common treatment for wet AMD is currently Avastin (off-label), Lucentis, or Eylea, all of which are anti-VEGF treatments that are very large antibodies or aptamers that bind up existing VEGF supplies or their receptors. These molecules must be administered at 4-to-8 week intervals potentially indefinitely and at substantial inconvenience, cost, and cumulative risk of infection.

ALG-1001, with its unique mechanism of action and distinctive mode of intervention in the angiogenic cascade from current treatment standards, has the potential to be the next generation of treatment options for vitreoretinal indications. The use of ALG-1001 has the potential to be both effective as a stand-alone solution and complementary to existing anti-VEGF treatments due to its unique mechanism of action and extended duration of effect.
References


4. A second mechanism of action of, ALG-1001 is vitreolysis, as the oligopeptide binds to α3β1 integrin that has been shown to be involved with the vitreoretinal interface and posterior vitreous detachment formation associated with VMA.
Update on Anti-PDGF Drugs for AMD

_Elias Reichel MD_

I. Background
A. Four PDGF isoforms (A, B, C, D)-dimerize
B. Isoforms bind to receptors (α, β) and dimerize receptors (αα, αβ, ββ)

II. PDGF Function
Acts on mesenchymal cells: Vasculogenesis (PDGF B-pericytes). Roles in wound healing, cancer, fibrosis

III. Role in Pathologic Neovascularization: Pericytes
A. Produce VEGF and protect endothelial cells
B. Result in anti-VEGF resistance

IV. PDGF Inhibition in Pathologic Neovascularization and Fibrosis
A. Blocking PDGF-B leads to pericyte stripping, therefore increasing sensitivity of naked endothelial cells to anti-VEGF
B. Tumor and ocular angiogenesis: Neovascular regression
C. Anti-fibrosis

V. Clinical Trials of PDGF inhibition for CNV
A. Fovista (Ophthotech)
   1. Pegylated aptamer (inhibits PDGF-B)
   2. Combined with anti-VEGF
   3. Phase 2b (449 patients, 6 months): significant visual benefit compared to ranibizumab alone; anatomic benefits as well (resolution of CNV and reduced fibrosis)
   4. Phase 3 (1900 patients): in progress combined with bevacizumab, ranibizumab, or aflibercept
B. REGN2176-3 (Regeneron)
   1. Antibody to PDGFR-β
   2. Coformulated with aflibercept
   3. Phase 1 in progress (12-24 patients)
C. DE-120 (Santen)
   1. Anti-VEGF/PDGF
   2. Phase 1 in progress (9 patients)
Intraoperative OCT

*Justis P Ehlers MD*

I. Background

A. Potential utility
   1. Providing rapid feedback to surgeons
   2. Enhancing surgical education
   3. Visualize acute impact of surgical maneuvers
   4. Improve understanding of pathophysiology of surgical vitreoretinal diseases
   5. Open door to new surgical interventions and disease management opportunities

B. Hurdles to utilization
   1. Integrative solutions
      a. System portability and maneuverability
      b. Microscope integration
      c. Lack of surgical instrument compatibility
      d. Real-time tracking
   2. Cost
      a. System costs
      b. Potential delay in OR time
   3. Intraoperative-specific software solutions: Analysis of rapid changes in tissue architecture
   4. Understanding the clinical applications and impact

II. Device Solutions

A. Modified table-top system
   1. Allows for excellent image quality
   2. Logistically difficult
   3. Special setup
   4. Limited portability

B. Handheld spectral domain OCT probe
   1. Portable
   2. Versatile imaging in multiple situations
   3. Limited scan repeatability
   4. Lack of tracking
   5. Significant learning curve

C. Microscope-mounted portable system
   1. Foot pedal control of X-Y-Z translation
   2. Improved stability from microscope mounting

D. Microscope-integrated intraoperative OCT systems
   1. Allows for immediate feedback without pausing surgery
   2. Provides visualization of instrument-tissue interaction
   3. Parfocal with surgeon view
   4. Allows for rapid localization to area of interest

III. Clinical Applications

A. Macular hole
   1. Architectural alterations
   2. Anatomic normalization

B. Vitreomacular traction: Confirmation of retinal integrity

C. Epiretinal membrane: Completion of peel

D. Retinal detachment: Visual prognosis

IV. Novel Approaches to Integrative Technology

A. Heads-up display: Various options for feedback

B. Instrument refining
   1. Optimized optical properties
   2. Enhanced visualization of underlying tissues and instrument profile

C. Automated tracking: Methods for focusing on area of interest

D. Intraoperative OCT software solutions
   1. Pathology-specific segmentation
   2. Surgeon feedback system

E. Possible swept source technology

V. Integrated System Clinical Examples

A. Vitreoschisis
B. Viscodissection
C. Instrument-tissue interaction
   1. Forceps
   2. Diamond-dusted membrane scraper

D. Subretinal biopsy
E. Occult macular hole
F. Identification of subretinal fluid
Swept Source OCT

Richard F Spaide MD

There has been a remarkable development of imaging based on OCT over the last 2 decades. Scanning speeds, image quality, and associated software analysis have created an astounding imaging modality. With improvements in technology has come an increased range of structures that can be imaged in the eye.

In time domain OCT each point in the tissue is sampled one at a time. The probing beam illuminates the tissue, but information is obtained from a small portion of the tissue at any given instant. This means time domain OCT is less efficient at extracting information from tissue at any given total light exposure. The total amount of light that can be delivered to tissue is limited by safety standards.

Spectral domain OCT (SD-OCT) takes the light from the interferometer and passes it through a grating to separate out the component wavelengths. Using a Fourier transform it is possible to determine where, and how strongly, different reflections in the sample arm originated from simultaneously. In effect, all layers produce signal during each A-scan. Because of this feature SD-OCT devices are much more efficient at extracting information from tissue at any given light exposure. This increase in efficiency is often translated to increased scanning speeds, and SD-OCT instruments typically scan the eye with speeds up to 100 times faster than time-domain OCT instruments.

There are some problems inherent in SD technology. The deeper tissues produce higher frequency signals, but the way the grating and detector sample this frequency is not linear. The higher frequencies are bunched together to a greater extent than lower frequencies. In addition, the sensitivity of the detector decreases with increasing frequency. This causes SD-OCT to have decreasing sensitivity and resolution with increasing depth.

Swept-source OCT (SS-OCT) uses a frequency-swept light source and detectors, which measure the interference output as a function of time. The sensitivity of SS-OCT varies with depth as well, but the roll-off in sensitivity is not as great as seen with SD-OCT. In addition, SS-OCT uses a longer center wavelength, which has improved ability to penetrate through tissue. Therefore both the vitreous and choroid can be imaged simultaneously; there is no need to pick one or the other.

There are trade-offs with swept-source OCT that have to be considered. Although longer wavelengths of light may penetrate tissue to a greater degree, the problem is that water absorbs longer wavelengths of light. This restricts the range, or bandwidth, of wavelengths that can be used in the eye, since the vitreous is mostly water. Increasing the center wavelength has the effect of decreasing the resolution for any given bandwidth. Water absorption of longer wavelengths is an important impediment to expanded bandwidth of current 1-micron swept light sources, which limits the ability to overcome the decrease in resolution by increasing the bandwidth.

Newer light sources operating at shorter wavelengths are being developed, and these light sources may avoid the problem of water absorption. For example, a SS-OCT using a large bandwidth light source with a center wavelength of 850 nm could provide very high-speed, high-resolution imaging with potentially less fall-off in sensitivity with depth as compared with SD-OCT implementations.

Imaging the Retina

Each implementation of OCT can provide images of the retina that are fairly similar. The resolution of an OCT in the axial dimension is a function of the center wavelength and the bandwidth of the light source. For any given bandwidth, longer center wavelengths result in lower resolution. So far the light sources used in swept-source OCT is longer than that used in spectral domain OCT. To compensate it is possible to increase the bandwidth of the light sources in swept-source OCTs to a certain extent, but for longer wavelengths water absorption becomes important. In practical terms the resolution of the retina is not significantly degraded by using SS-OCT as compared with SD-OCT.

Imaging the Vitreous

Imaging the vitreous is challenging because it is nearly transparent, it moves, and the depth of the structure is long compared with other features in the eye such as the retina or choroid. SS-OCT is a good choice to image the vitreous because of relatively low fall-off in sensitivity with depth. To improve the imaging even further, it is possible to dynamically focus the instrument through the depth of the vitreous cavity.

Imaging the Choroid

The increased penetration secondary to the longer wavelength coupled with the decreased fall-off in sensitivity with depth means SS-OCT is adapted to imaging the choroid. It is possible to image the sclera and even the subarachnoid space in some individuals.

References

Ultrahigh Resolution OCT

Jay S Duker MD

Introduction to OCT

Since its clinical description over 20 years ago, optical coherence tomography (OCT) has evolved into the most important imaging technology in ophthalmic practice. Akin to ultrasound but employing light instead of sound waves, OCT is based on the principle of optical reflectometry. The echo time delay of light is used to detect differences in the reflectivity of tissues. Since the speed of light that is reflected back from the tissues cannot be measured directly, OCT employs low coherence interferometry, CCD/CMOS cameras, or photodetectors to indirectly measure the distance between the various reflectivities of the tissue layers to generate high-resolution cross-sectional images of the retinal microstructure.1

With the advancement of OCT technology from time-domain to spectral domain OCT (SD-OCT) over the past few years, an improved visualization of the retinal microstructure close to an in-vivo optical biopsy has been achieved through better axial resolution, higher imaging speed, and improved signal-to-noise ratio.2,3 At present, SD-OCT has become standard in clinical practice and is used extensively for clinical decision making and monitoring of various posterior segment diseases through analysis of retinal thickness, optic nerve head, and the nerve fiber layer. More recently, with the introduction of techniques such as image averaging and enhanced depth imaging,4 an assessment of the details of the choroid has become possible in retinal diseases using SD-OCT.

Ultrahigh-Resolution OCT (UHR-OCT)

Besides commercially available SD-OCT, research prototype OCT systems have contributed to an ever-growing field of research involving ocular imaging. The goal of developing research prototype systems and the clinical research being carried out with these systems is to better understand disease processes. One way to achieve an improved understanding of disease processes is to increase the axial resolution of the OCT images so that a microstructural detail as close as possible to histology can be achieved. The axial resolution of OCT is dependent on the bandwidth of the light source used within the system. Standard commercial SD-OCT uses superluminescent diodes as a light source and achieves an axial resolution of ~5-6 microns in tissue. By increasing the bandwidth of the light source, the axial resolution of OCT can potentially be improved.5 This concept underlies the development of ultrahigh-resolution OCT (UHR-OCT), which is able to achieve axial image resolutions of ~3 microns in human tissue and ~1 micron in animal tissue.6,7 Such fine axial resolution using OCT allows a better delineation of retinal layers than standard clinical SD-OCT.

UHR-OCT at New England Eye Center

We and our collaborators at the Massachusetts Institute of Technology (MIT) developed a research prototype UHR-OCT system and have deployed it at the New England Eye Center, Tufts Medical Center, Boston, for clinical research use. This system uses a Superlum T870-HP semiconductor laser diode as the light source for imaging that generates a 180-nm full-width half-maximum bandwidth centered at a wavelength of 870 nm. The broader bandwidth of the light source allows this system to achieve an axial resolution of ~3 microns in tissue. The fiber-optic interferometer and other optical components in the system are optimized to support the broader bandwidth of the laser light source. A high-speed (~91,000 A scans per second), high-sensitivity electronic detection system is built to achieve improved dynamic range and high-sensitivity UHR-OCT imaging.7 Using this system, an improved assessment of retinal layers is possible, especially at the level of retinal pigment epithelium/Bruch membrane, photoreceptors, external limiting membrane, and the vitreoretinal interface.7,8

Figure 1. Image of a normal eye obtained using high-speed UHR-OCT system with approximately 2-micron axial resolution. Note the degree of detail in the outer retina, with 6 distinct bands visible.
References

Adaptive Optics

Mina Chung MD

I. Adaptive Optics (AO) Imaging Technology
   A. High-resolution, noninvasive in vivo retinal images
   B. Compensates for higher-order aberrations in the eye
   C. Wavefront sensor to measure higher-order aberrations
   D. Deformable mirror to correct the aberrated wavefront

II. Imaging Capabilities
   A. Scanning laser ophthalmoscope (AOSLO) enables through-focus images.
      1. Transverse resolution of 2 microns
      2. Reflectance imaging of foveal cones, rods
   B. Fluorescence (FAOSLO) using a dual imaging technique to register fluorescence images with reflectance
      1. Retinal pigment epithelium (RPE) cells
      2. Fluorescein angiography
   C. Two-photon imaging
      1. Excite short wavelength fluorophores
      2. Functional cone measurements

III. Clinical Applications
   A. Quantitative measures
      1. Cell density, spacing, regularity
      2. Normative data
   B. Retinal degenerations and dystrophies
      1. Early detection of disease changes
      2. Elucidation of pathophysiology
   C. Macular diseases
      1. AMD
      2. Macular telangiectasia
   D. Clinical trials
      1. Longitudinal evaluation
      2. Demonstration of therapeutic efficacy

References

Wide-Field Imaging  
Ultrawide-Field Imaging of the Retina  
Szilárd Kiss MD

The peripheral retina is the site of pathology in many vision-threatening eye diseases. Evaluation of the retinal periphery may be important for screening, diagnosis, monitoring, and treatment of a variety of disease manifestations. Traditional fundus cameras have offered a 30- to 50-degree field of view. Technology has advanced to provide up to a 200-degree field of view—“ultrawide field” in a single nonsteered image. For many disorders, especially retinal vascular disorders such as diabetes and retinal vein occlusion, ultrawide-field (UWF) imaging is becoming the standard of care for the diagnosis, evaluation, and follow-up of patients.

The two most widely used commercially available UWF systems are the Optos Optomap and the Heidelberg Spectralis. The Optos is an ellipsoid mirror-based system that provides views of the fundus out to 200 degrees in a single image. The noncontact wide-field lens from Heidelberg allows for up to 110-degree views of the fundus. A direct comparison between the two systems shows that the area of retina imaged is significantly greater with the Optos than with the Spectralis. Nonetheless, both systems provide a view of the retina that is considerably greater than that seen on traditional imaging, including the conventional montaged 7 standard fields obtained by eye steering.

It is important to realize that all UWF systems produce images of the fundus that are distorted, or more accurately, nonlinear. The reasons behind this are two-fold. First, the projection of a sphere onto a flat surface leads to over-representation of objects away from the equator (eg, the size of Greenland on a Mercator-projected map appears to be 3 times that of the United States, when in reality it is only 1/3 as large). Second, the distortions introduced by the lens or mirror, be it a pincushion or barrel distortion (eg, the edges on a panoramic photograph appear nonlinear due to the distortion from the lens itself). This peripheral nonlinearity is specific to each system and is found on all UWF imaging platforms. Optos has developed software to correct for the nonlinearity introduced by its machines. This allows for not only more accurate visual representations of the fundus, but also precise measurements and quantification of peripheral pathologies (eg, peripheral tumors or nonperfusion).

UWF imaging has transformed the diagnosis, monitoring, treatment, and follow-up of numerous retinal disorders, including diabetic retinopathy, retinal vein occlusion, AMD, retinal detachment, ROP, retinal degenerations, uveitis, choroiditis, and imaging through small pupil including permanent keratoprosthesis, among others. Undoubtedly, as UWF imaging is more broadly adopted, we will gain more and more insight into other diseases, and even perhaps begin to unlock underlying pathophysiological mechanisms of ocular disorders that were not evident on traditional fundus imaging.

Selected Readings
What’s Next in Fluorescein Angiography

Richard B Rosen MD

I. Retinal Vascular Contrast Imaging Evolution
   A. 1961: Film, filters, and fluorescein dye
   B. 1991: Digital sensors, filters, fluorescein, indocyanine green (ICG) dye
   C. 1996: Confocal scanning laser ophthalmoscopy (cSLO), fluorescein/ICG
   D. 2000: Adaptive optics (AO) cellular imaging
   E. 2012: AO SLO motion contrast and offset pinhole angiography
   F. 2013: AO with motion contrast imaging
   G. 2013: Micro AO-SLO fluorescein angiography
   H. 2014: OCT angiography (motion contrast)

II. Micro AO-SLO Fluorescein Angiography
   A. AO enables cellular level resolution imaging.
   B. Reveals multiple capillary layers and components (eg, pericytes, microaneurysms)
   C. Single segment capillary – microvascular perfusion vs. nonperfusion
   D. Quantitative capabilities – vascular density, tortuosity index
   E. Serial imaging – changes of microvascular circulation over time

III. Motion Contrast Vascular Imaging
   A. Nonpharmacological contrast imaging
   B. Interprets minute differences between frames
   C. Stroboscopic flood flash illumination or scanning light ophthalmoscope
   D. No detection of leakage, only perfusion voids
   E. Enhanced ability to visualize slow-perfusing deeper capillary beds
   F. Offset-pinhole, diffused illumination enhancements
   G. Multisegmented detectors (split detector approach)
   (Need to explain what it generates in the image the clinician sees)
Figure 3. Motion contrast capillaries.

Figure 4. Offset pinhole capillaries.

Figure 5. OCT angiogram, normal.

Figure 6. OCT angiogram, Coats.

IV. OCT Angiography
   A. Enface aspect OCT
   B. Motion contrast techniques – phase variance, SAADA (angio-OCT)
   C. No leakage revealed but demonstrates nonperfusion, tortuosity, collaterals
   D. Intermediate screen for pharmaceutical fluorescein angiography
   E. Fast, incorporated into normal OCT exam
   F. Limited field of view, may be expended by stitching
   G. Quantitation of change-flow index measurements
V. Overall Trends
A. Continued transition from analog to digital acquisition of signals (information)
B. Conventional pharmaceutical contrast agents supplanted by increasingly sophisticated digital contrast algorithms
C. Optical filters supplanted by lasers and LED sources in multispectral arrays
D. Multiple detector imaging enhances 3-D perspective.
E. Minimally invasive imaging revolution championed by OCT continues.

Selected Readings

Adaptive optics vascular imaging / Micro FA

Motion contrast vascular imaging

OCT angiography
Fundus Autofluorescence: What Are We Looking At?

Christine A Curcio PhD

Introduction

Fundus autofluorescence (FAF) is a powerful tool for monitoring the health of the retinal pigment epithelium (RPE). This monolayer supporting photoreceptors and choroid is involved in many chorioretinal disorders, especially AMD. FAF using a fundus spectrophotometer and confocal scanning laser ophthalmoscope (cSLO) was introduced independently in 1995 by Delori and von Ruckman, respectively.1,2 New instrumentation enables the quantification of FAF levels across patient populations by introducing a fluorescent standard into the light path.3 To utilize this new information for patient benefit, it is essential that we understand the sources of FAF signal.

Fluorescence and Its Detection

Fluorescence is emission of light by a fluorophore that has absorbed light or other electromagnetic radiation. Fluorescence occurs when orbital electrons relax to a ground state by emitting a photon of light after being excited to a higher quantum state by energy. FAF is detected by cSLO systems and modified fundus cameras over slightly different excitation and emission ranges (see Table 14). In general, longer wavelengths circumvent absorption of exciting light by the aging lens.

RPE Lipofuscin

A strong FAF signal derives from RPE lipofuscin. Lipofuscin is a long-lasting intracellular deposit of lipids and proteins localized to the lysosomal compartment, associated with aging in postmitotic cells that do not dilute this material. Each cell’s lipofuscin is unique in composition, ultrastructure, and life history. For reference, brain lipofuscin is 2/3 bioactive lipid derivatives that fluoresce at short wavelengths, its major protein source is mitochondria incompletely degraded by self-renewing autophagy, and it is inconsistently associated with frank pathology.

In contrast, RPE lipofuscin fluoresces at wavelengths consistent with vitamin A derivatives (590-600 nm, yellow-orange).5 The first identified and best-studied bisretinoid is A2E, the precursors of which are formed in photoreceptors from retinaldehydes and phosphatidylethanolamine, as investigated intensively by Sparrow and colleagues.6,7 Compositional analysis of isolated RPE lipofuscin washed to ultrastructural purity indicates that only 2% of total mass is protein, and the largest component is lipid.8 RPE lipofuscin uniquely originates from outside the cell, starting as photoreceptor outer segments disks shed daily. RPE lipofuscin granules are 0.7 µm in diameter, with irregular shape and a surface structure consistent with many smaller aggregates.9,10 It is distinguishable from rod-shaped melanosomes of similar length in apical RPE. Lipofuscin granules form a cushion in the RPE midsection and accumulate in healthy eyes throughout life, especially in the early decades. RPE of older adults contain many melanolipofuscin granules, accompanied by a decrease of melanosomes.11 Granules in the aggregate fluoresce at longer wavelengths in older persons than in younger persons.12 Lysosomal enzyme activity is always present, suggesting dynamism. The topography of histological autofluorescence follows that of photoreceptors, with high values in the elliptical ring of high rod density 2-4 mm from the fovea, and a dip in the fovea.13,14 The topography of lipofuscin-attributable autofluorescence has been recently dissociated from the topography of A2E, which dominates in peripheral RPE but not macula.15,16 Additional fluorophores responsible for macular FAF await further identification.

FAF Is Multifactorial

Several physical and biological factors combine to create the total FAF available for clinical viewing. These include (1) fluorescence efficiency of any particular fluorophore for absorbing the exciting wavelengths, (2) fluorophore emission spectrum, which is in turn dependent on the overall fluorophore mix, relative to sensitivity of detector, (3) number and concentration of lipofuscin granules, which varies with age and retinal location, (4) blocking of light by RPE melanosomes anterior to the lipofuscin cushion, (5) path length of exciting light through the lipofuscin cushion, as dictated by variations in RPE cell size, shape, stacking, and motility, (6) blocking of light by entities anterior to RPE, including subretinal drusenoid deposit,17 photoreceptor pigment, macular pigment, edema, blood, and vitreous opacities, and (7) adaptation state of photoreceptors, as bleached photoreceptors absorb less incoming light and allow more light to excite RPE fluorophores.18

The cellular correlates of FAF have been investigated for geographic atrophy (GA) associated with AMD. GA features one or more areas of sharply decreased FAF surrounded by variable

<table>
<thead>
<tr>
<th>Technology</th>
<th>Vendor</th>
<th>Excitation λ, nm</th>
<th>Emission λ, nm</th>
</tr>
</thead>
<tbody>
<tr>
<td>cSLO</td>
<td>Heidelberg</td>
<td>488</td>
<td>500-700</td>
</tr>
<tr>
<td>cSLO</td>
<td>Optos</td>
<td>500</td>
<td>600-800</td>
</tr>
<tr>
<td>Fundus camera, modified</td>
<td>Topcon</td>
<td>530-580</td>
<td>615-715</td>
</tr>
<tr>
<td>Fundus camera, modified</td>
<td>Zeiss Meditec</td>
<td>510-585</td>
<td>600-750</td>
</tr>
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</table>
FAF, with areas of hyper-FAF postulated as predictors of rapid progression. The overall area does progress to atrophy because the disease is active. However, when all FAF pixels (both hypo- and hyper-FAF) are accounted for, hyper-FAF on a granular level does not predict atrophy any better than chance. RPE morphology in AMD is predictably variable as captured by a grading system, including anteriorly migrated cells and basolaterally shed fragments. Histological study of 10 donor eyes with GA found that AF variations in the transition zone were linked closely to rounded or stacked cells (see Figure 1; gray arrow indicates light path). Concentration of AF in individual cells did not vary significantly when cell area was accounted for. Thus hyper-FAF should not necessarily be attributed to higher intracellular concentration of RPE lipofuscin, without independent verification of RPE cross-sectional morphology with SD-OCT.

Figure 1.

References


Difficult Retinal Diagnosis With Multimodal Imaging

Giovanni Staurenghi MD

The modern approach to retinal diagnosis includes the analysis of multimodal imaging: color picture (CP), infrared imaging (IR), autofluorescence imaging (AF), optical coherence tomography (OCT), fluorescein angiography (FA), and indocyanine green angiography (ICGA).

The definition of classic choroidal neovascularization, divided into predominantly classic and minimally classic, and occult choroidal neovascularization, could be better classified in different type of neovascularization such as type 1 and 2 choroidal neovascularization, retinal angiomatous proliferation (RAP) or type 3 and polypoidal lesion. Moreover, lesions such as pseudovitelliform lesions can sometimes be misdiagnosed as occult or classic neovascularization if only FA is used. To better identify these lesions a multimodal imaging approach is needed.

Each lesion has different characteristics.

I. RAP
   A. CP: Small flame hemorrhage in perimacular area
   B. IR: Presence of reticular pseudodrusen
   C. AF: Possible visualization of cystic lesions with blue autofluorescence
   D. OCT
      1. In OCT, presence (not always) of cystoid edema
      2. In OCT, presence (not always) of interrupted retinal pigment epithelial (RPE) layer of a RPE detachment with more reflective, usually oval area
   E. FA and ICGA
      1. Feeding retinal vessel bigger than surroundings perifoveal vessels (blood shunting)
      2. Leakage in late ICGA
      3. In stereo ICGA floating net (Floating means between retinal vessel layer and choroidal vessels.)
      4. In case of RPE detachment: In FA the “hot spot” is always in the center of detachment.
   F. Indirect sign
      1. If you have a RPE detachment that disappears immediately after anti-vascular endothelial growth factor (anti-VEGF) treatment, there is a good chance that it was a RAP.
      2. Other eye if advanced neovascular membrane, usually a retinal choroidal anastomosis

II. Polypoidal Lesions
   A. In late ICGA, wash-out
   B. In case of RPE detachment, in FA the “hot spot” is always at the edge of the detachment.
   A. CP
      1. Clinically visible orange-red subretinal nodules better visible in retroillumination
      2. RPE detachment with blood level is very suspicious of polypoidal choroidal vasculopathy.
   B. IR
      1. Usually shows the presence of homogenous appearance with hyper-reflective and hyporeflective areas
      2. Usually not visible reticular pseudodrusen (2.2%)²
   C. AF: Patchy increase of AF around the lesion due generally to lack of photoreceptor outer segments
   D. OCT: In OCT visible oval shape with a sharp border beneath or more frequently over RPE
   E. FA and ICGA
      1. In FA leakage patterns that resemble either classic or occult³⁴
      2. Possible fine net with dilation in the periphery of it, visible in early ICGA
      3. Possible large vessels usually departing from optic nerve head
      4. In late ICGA, wash-out
      5. In case of RPE detachment in FA the “hot spot” is always at the edge of the detachment.
      6. During filling time possible pulsation of the vessel (usually the draining vein) and the bulge
   F. Indirect sign: A lack of response to anti-VEGF therapy

III. Vitelliform Lesions
   A. CP: Round elevated yellowish material. If heterogeneous, the yellowish part is normally more concentrated in the lower part.
   B. IR
      1. Round elevated area with sometimes hyper-reflective lines due to mottling pigment
      2. The yellowish material is usually more reflective and lighter than the surrounding area.
C. AF

1. Hyperfluorescent material that could be masked by macular pigment if using blue-autofluorescence. (Green autofluorescence sometimes reveals small hyperfluorescences not visible in blue autofluorescence, just because they are masked by the macular pigment.)

2. Sometimes characterized by the presence of irregular hyperfluorescent dots

3. If area of patchy atrophy of the RPE, these appear as round-shaped dark areas.

D. OCT

1. The compact yellowish material appears as dense hyporeflective material that partially masks the choroid visualization.

2. Elongated outer segment also known as “shaggy” photoreceptors. These do not mask the visualization of the choroid.

3. Sometimes presence of ??

E. FA and ICGA

1. In FA early hypofluorescence (corresponding to yellowish material)

2. In FA late hyperfluorescence usually limited in the area of the yellowish material

3. Sometimes in FA possible round-shaped hyperfluorescence areas since the early phase, corresponding to RPE atrophy

4. In ICGA masking hypofluorescence throughout the exam where the yellowish material is present. Choroidal vessels are not visible.

5. In the area of “shaggy” photoreceptor, ICGA images appear a little bit darker than surrounding retina. Choroidal vessels are still visible.

F. Indirect sign

1. Usually bilateral

2. If present in the fellow eye atrophy of the RPE usually round-shaped involving the center of the fovea

References


The Real Meaning of Biomarker Assessment in Clinical Trials: Useful or Useless?

Jason S Slakter MD

I. Definition
A. Biomarker = Biological marker
1. Measureable indicator of some biological state or condition
2. Characteristic that is objectively measured and evaluated
3. Used as indicator of various features
   a. Normal biological processes
   b. Pathogenic processes
   c. Pharmacological response to therapeutic intervention
B. For ocular/retinal diseases, takes several forms
   1. Imaging
      a. Color fundus photography
         i. Early Treatment Diabetic Retinopathy Study, diabetic severity scoring
            a. Treatment response in predominantly classic subgroup
            b. Treatment limitations / risks in larger occult lesions
         ii. VIVID/VISTA for aflibercept
      b. Retinal vascular caliber assessment
         a. Marker of incidence and progression of type I and II diabetes
         b. Marker of response to pharmacologic intervention
      c. Age-Related Eye Disease Study
         a. Risk categorization for clinical practice / observation
         b. Enhancement of patient pool for “risk reduction” studies
   2. Genetic testing
   3. Proteomic testing
   4. Local/systemic serum markers

II. Imaging
A. Color fundus photography
   1. Early Treatment Diabetic Retinopathy Study, diabetic severity scoring
      a. Determination/categorization of disease state
      b. Monitoring of response to treatment in diabetic macular edema studies
         i. RIDE/RISE for ranibizumab
         ii. VIVID/VISTA for aflibercept
      c. Monitoring of progression / regression in disease prevention studies
   2. Retinal vascular caliber assessment
      a. Marker of incidence and progression of type I and II diabetes
      b. Marker of response to pharmacologic intervention
   3. Age-Related Eye Disease Study
      a. Risk categorization for clinical practice / observation
      b. Enhancement of patient pool for “risk reduction” studies

B. Fluorescein angiography: Disease classification for treatment selection
   1. Photodynamic therapy with verteporfin
      a. Treatment response in predominantly classic subgroup
      b. Treatment limitations / risks in larger occult lesions
      2. Fovista: Phase 2 treatment benefits studied in smaller classic, containing lesions only
C. Fundus autofluorescence
   1. Topographic mapping of lipofuscin distribution in retinal pigment epithelium (RPE)
   2. Provides “functional” imaging of RPE
   3. Used for identifying and quantifying geographic atrophy (GA) for outcome testing
   4. Hyper-autofluorescence patterns used to stratify / enhance patient pool for studies
D. Spectral domain OCT
   1. Indicator of disease activity and response to treatment for exudative conditions
      a. Exudative AMD
      b. Diabetic macular edema
      c. Retinal vascular occlusive disease
   2. Determination of subretinal hyper-reflective material
      a. May represent neovascular complex / exudative debris / fibrosis
      b. Observed to change with treatment with Fovista – may be biomarker for anti-platelet derived growth factor activity
   3. Indicator of state of photoreceptor / RPE / choroidal complex
      a. Measurement of GA for monitoring of progression and response to treatment
      b. Drusen area / volume assessment for risk determination and treatment response
      c. Choroidal thickness measurement for risk determination for GA
      d. Status of inner segment/outer segment junction, ellipsoid layer for visual outcomes in macular surgery
   4. Vitreoretinal interface changes as indicator of disease progression and response to vitreolytics
E. Adaptive optics
   1. Visualization of microscopic morphological features not easily visualized with current clinical OCT/SLO systems
2. Microscopic volumetric features at the edge of GA may be targeted for study of disease progression and efficacy of therapies.

F. Experimental imaging systems

1. OCT angiography
   a. Visualization of retinal vasculature in noninvasive manner
   b. Selective assessment of individual vascular layers within retina
   c. May provide means to measure response of retinal microvasculature to pharmacologic interventions for multiple retinal diseases

2. In vivo molecular imaging
   a. Utilizes hairpin nucleic acid functionalized gold nanoparticles
   b. In vivo optical imaging of experimental hypoxia and inflammation induced disease

III. Genetics

A. Complement Factor H/PLEKHA1/ARMS2/HtrA1
   1. Risk factors for development of advanced AMD
   2. Some shown to be potential markers for response to anti-VEGF therapy
   3. CFH marker for response to experimental pazopanib tyrosine kinase inhibitor program for exudative AMD

B. Complement factor I
   1. Risk factor for natural history of GA progression
   2. Marker for response to anti-Factor D agent in treatment of GA

IV. Proteomics

A. Carboxyethylpyrrole (CEP)
   1. Docosahexaenoate (DHA) abundant in the outer retina
   2. Generation of a reactive DHA species that covalently binds to proteins causing oxidative damage
   3. Modified proteins or CEP adducts are more abundant in the Bruch membrane, RPE, and choroid from AMD patients as compared to age-matched controls.
   4. CEP-adducts and autoantibodies to CEP adducts are present in the plasma of AMD patients, and an increase in their levels is associated with disease progression.

B. Oxidative and stress proteins – experimental potential
   1. Prohibitin
      a. Originally known as “antiproliferative protein”

b. Involved in alternative complement pathway of complement C activation

c. Prohibitin expression in RPE altered under oxidative stress

2. Crystallins
   Upregulated and phosphorylated under stress

3. Erythropoietin
   Linked to timing of oxidative stress

IV. Conclusions

A. Imaging biomarkers are key to current treatment decision making and risk assessment.

B. Recent clinical trials incorporate imaging biomarkers for monitoring of outcomes and assessing biologic activity of pharmacologic agents, as well as for enrichment of patient population for therapeutic and risk reduction studies.

C. Genetic markers are actively utilized in current clinical trials for patient selection and potential determinants of treatment outcomes.

D. Future studies are likely to incorporate combinations of existing and experimental biomarkers to shorten study timelines by enriching patient populations, identifying optimal treatment responders, and determining more precise biological responses to therapeutic interventions.

E. Final answer: Biomarkers are useful!

References


Late Breaking Developments, Part III

NOTES
Anti-VEGF Therapy Is a Sustainable Treatment Model for Diabetic Macular Edema: Pro

Lloyd P Aiello MD PhD
Anti-VEGF Therapy Is a Sustainable Treatment Model for Diabetic Macular Edema: Con

Harry W Flynn Jr MD

Although anti-VEGF therapy for diabetic macular edema (DME) has been shown to reduce macular thickness and improve visual acuity, the financial and societal burdens of frequent anti-VEGF injections are unsustainable. In addition to the health-care system costs associated with expensive medications and frequently repeated procedures, an ever increasing number of patient visits are required due to the short duration of anti-VEGF treatment. More time is also required by the physician and staff on post-procedure issues and insurance verification. It is hard to measure the cost burden from lost productivity for the patient and the persons accompanying them for these multiple examinations and intravitreal injections. Since the average age of wet AMD patients is 79, compared to 53 in DME patients, it is anticipated that longer duration of anti-VEGF treatments and follow-up will be needed in diabetic patients.

Numerous clinical trials, most notably Protocol I of the Diabetic Retinopathy Clinical Research Network and the RISE and RIDE studies, have shown long-term benefit of anti-VEGF for DME. The peaks and valleys of anti-VEGF therapeutic effect may not be ideal, however, and better options should be considered. Perhaps a trained nurse practitioner could administer the injections, which is already happening in some centers in the United Kingdom. However, this approach raises a host of medicolegal and philosophical concerns.

What are the currently available treatment options? The first and most basic step is to achieve better metabolic control, including improvements in blood sugar, blood pressure, and serum lipids. In years past, modified Early Treatment Diabetic Retinopathy Study style grid or focal laser treatment was the strategy of choice for DME. Intravitreal injectable steroids (especially in pseudophakic patients), dexamethasone or fluocinolone implants, or micropulse laser are available alternatives. Pars plana vitrectomy was shown to have minimal visual benefit when used for the indication of DME except in the setting of epiretinal membranes or traction on the macula. Sustained-release drug delivery devices and/or combination therapies may prove to be better treatment strategies. These options include the possibility of episcleral or trans-scleral delivery systems, topical or systemic treatments, nanotechnology approaches, and many others. Already, a refillable reservoir with ranibizumab is being used in a clinical study. Twelve-month data from this study showed significant visual gains. In order to maximize visual outcomes and reduce the many burdens of treatment, newer long-acting strategies are greatly needed for patients with DME.

References

There Are Systemic Safety Concerns With Anti-VEGF Therapy: Pro

Robert L Avery MD

I. Reduced VEGF levels have been observed after intravitreal anti-VEGF agents.
   A. Plasma VEGF
   B. Serum VEGF: IVAN
   C. Fc-containing agents have a greater effect (bevacizumab and aflibercept).

II. Fellow Eye Effects
   A. Proliferative diabetic retinopathy (PDR): Low-dose bevacizumab can alter PDR
   B. Uveitic CME
   C. AMD
   D. ROP
   E. DME
      1. Bevacizumab, not ranibizumab
      2. Aflibercept

III. Systemic Adverse Events

IV. Stroke Risk
   A. Meta-analysis of early ranibizumab trials
   B. Aflibercept European Public Assessment Report
   C. RISE – RIDE
   D. VISTA - VIVID

Selected Readings

There Are Systemic Concerns With Anti-VEGF Agents: Con

Usha Chakravarthy MBBS PhD

Why are there concerns that inhibiting VEGF might be inimical to health?

Vascular endothelial growth factor (VEGF) is a key mediator of angiogenesis that has been studied extensively and is recognized for its trophic roles in health and the normal functioning of many mammalian tissues and cells. It maintains a nonthrombogenic vascular endothelium and promotes regeneration of endothelial buds in newly formed vessels, ensuring the patency of fenestrations in microvascular beds. It is also trophic to the neural cells of the developing brain, axons of the spinal cord, lung epithelium, retinal neurons, and the retinal pigment epithelium. Thus concerns have been expressed following its use as a therapeutic agent in the amelioration of the exudative manifestations of neovascular AMD (nAMD).

What anti-VEGF agents are available, and at what dose are they used?

Ranibizumab, the first of the monoclonal antibodies to be commercially developed for nAMD, underwent considerable testing, and systemic absorption was not found to occur as there was almost no detectable drug in peripheral blood. Documents that were submitted to the European Medicines Agency (EMA) (www.ema.europa.eu/docs/en_GB/document) state that following monthly intravitreal administration of ranibizumab (Lucentis) to patients with neovascular AMD, serum concentrations of ranibizumab were generally low, with maximum levels (Cmax) lower than that necessary to inhibit the biological activity of VEGF by 50% (11-27 ng/ml, as assessed in an in vitro cellular proliferation assay). Cmax was dose proportional over the dose range of 0.05 to 1.0 mg/eye. The licensed therapeutic dose of ranibizumab is 0.5 mg, and its marketing authorizations have been extended to include retinal vein occlusions (RVO) with macular edema, myopic neovascularization, and diabetic macular edema (DME).

Another commonly used anti-VEGF is bevacizumab, which is used at a concentration of 1.25 mg. This biological is not licensed for any exudative maculopathy, but when tested in nAMD against ranibizumab it appears to be equally effective in maintaining acuity and in reducing the exudative manifestations. A more recent addition to the therapeutic armamentarium is the anti-VEGF aflibercept, which has a marketing authorization for use in nAMD and more recently in DME and RVO. The licensed dose for aflibercept is 2 mg.

What data are there to suggest systemic effects?

Meta analyses of the original pivotal clinical trials reported that the rates of systemic adverse events in the groups that received anti-VEGF treatment were similar to those in natural history groups and to photodynamic therapy-treated groups. However, subsequent analyses combining the data from MARINA,ANCHOR, and a further smaller Phase 2 trial of ranibizumab (FOCUS) found that cerebrovascular events were more common in patients exposed to ranibizumab (2.2%) than they were in nonexposed patients (0.7%). An open-label extension study, SAILOR, which compared 2 doses of 0.3 mg with 2 doses of 0.5 mg, showed a 1.2% occurrence rate of stroke in the 0.5-mg arm vs. 0.3% in the lower-dose arm, but with continuing follow-up this difference was no longer statistically significant. Interestingly the SAILOR data suggested that the stroke risk was greatest among patients with a prior history of stroke. These contrasting findings suggest that the increased risk of stroke might be due to the presence of confounders such as age or that if a true elevation of risk is present that this is extremely small.

The widespread off-label use of bevacizumab also for nAMD and the subsequent comparative effectiveness trials are also useful sources of information. Pooled data from 2 large trials (CATT and IVAN) showed no differences between drugs in risk of death or arteriothrombotic events (ATEs). With longer follow-up the serious adverse events (SAEs) accruing in the second year in the IVAN trial shifted the 2-year odds ratio (OR) almost to unity, suggesting that there may be no true increase in risk. Particularly intriguing is the finding of an increased frequency of SAEs when treatment is not administered monthly. The pooling of the SAEs observed in the CATT p.r.n. with the IVAN discontinuous treatment arms showed a significant difference in systemic SAE, which was mainly due to the increased frequency of death. Specifically, 18 of 895 participants who received monthly dosing and 36 of 900 who received less frequent dosing died. The OR of 0.49 (0.27, 0.86) was only just statistically significant. There is no biologically plausible explanation and these findings are counter-intuitive in the conventional dose response framework.

Clinical trials are limited in their size and the eligibility criteria that they impose, and thus their findings cannot be entirely applicable either to rare SAEs that may manifest over time or in populations that may be more susceptible, such as patients with comorbid conditions that rule them out from trial participation but who might nevertheless be treated in routine practice. Therefore a number of databases such as those maintained by organizations such as Medicare have been scrutinized to identify potential adverse events. Initial analyses of such registries suggested a higher risk of ATEs with bevacizumab; however, with adjustment for potential confounders such as socioeconomic class, these differences were negated. A Canadian study where the exposure of interest was the use of an anti-VEGF administered as an intraocular treatment in the 180 days preceding an ATE (defined as MI, stroke, and any venous thromboembolism) found no increase in risk between exposed and unexposed cases. Neither did a difference in risk emerge by drug type, namely bevacizumab vs. ranibizumab. However, findings of the analyses from other routinely accrued datasets are at variance from one another. The analyses of another population-based registry found a higher incidence of ATEs in patients with nAMD with the 12-month rate of myocardial infarctions nearly 2-fold greater with an OR of 2.3 (1.2, 4.5) in persons exposed to any anti-VEGF compared to historical controls treated with photodynamic therapy. There was no difference between ranibizumab and bevacizumab, nor was there any difference in rates of stroke or gastrointestinal bleeds.
Concerns have also been raised about the safety of aflibercept, an anti-VEGF drug with a slightly different mechanism of action. Anti-VEGF agents are now the standard of care for exudative pathology of the retina such as DME and RVO. Serum concentrations of VEGF inhibitors measured in a limited number of DME patients indicate that a slightly higher systemic exposure cannot be excluded compared to those observed in neovascular AMD patients. Serum ranibizumab concentrations in RVO patients were similar or slightly higher than in those observed in neovascular AMD patients. However, none of the trials undertaken in these conditions have revealed differences in the frequency of occurrence of adverse events between drug and control arms.

Conclusions
Anti-VEGF agents given intraocularly do egress into the systemic circulation and have the potential to influence vascular health and small increases in the absolute risk of ATEs; notably, stroke and MI cannot be ruled out. However, the body of evidence to date suggests no difference in risk of serious systemic adverse events due to anti-VEGF agents or between anti-VEGF agents.

References
What Is the Long-term Effect of Anti-VEGF Treatment for Diabetic Retinopathy?

Michael S Ip MD

Introduction

RIDE and RISE were randomized, Phase 3, double-masked, sham injection-controlled clinical trials of ranibizumab in patients with diabetic macular edema (DME). A total of 759 patients were randomized 1:1:1 to monthly 0.3-mg or 0.5-mg ranibizumab, or to sham injections. Beginning at Month 3, macular laser was available to all patients per protocol-specified criteria. Primary results at Month 24 showed that monthly intravitreal injection with 0.3- or 0.5-mg ranibizumab was superior to sham injection across all major functional and anatomical outcomes assessed. A higher proportion of participants treated with ranibizumab experienced improvement in diabetic retinopathy (DR) on the Early Treatment of Diabetic Retinopathy Study (ETDRS) DR severity scale, and a lower proportion of patients had retinopathy worsening as measured on the ETDRS DR severity scale. Using a composite endpoint of DR progression, fewer eyes experienced new proliferative DR (PDR)-related events in the ranibizumab vs. sham arms. Visual acuity (VA) gains and improvements in macular anatomy as measured by OCT achieved at Month 24 were maintained through Month 36 with continued therapy. Participants in the sham arm were eligible to cross over to receive monthly injections of 0.5-mg ranibizumab starting at Month 25. At Month 36, on average these patients had a +4.5 ETDRS VA letter score gain, which was less than the 11.2-12.4 letter score gain achieved by patients who were originally randomized to ranibizumab and received early treatment.

All patients who had not discontinued treatment and completed Month 36 of the core studies were eligible to enroll in the open-label extension study (OLE) to evaluate the long-term safety, tolerability, and efficacy of intravitreal injections of 0.5-mg ranibizumab administered using a criteria-based treatment regimen. The retreatment criteria in the OLE were designed to maintain the VA (ETDRS chart) and macular anatomy (OCT) stability achieved with monthly injections while adding flexibility to patient visiting and dosing schedules.

Methods

During the OLE, participants were eligible to receive 0.5-mg ranibizumab according to predefined treatment criteria of evidence of DME on OCT (intraretinal fluid or cysts, subretinal fluid, or subretinal pigment epithelium fluid) or worsening of vision by ≥ 5 ETDRS letter score compared with Month 36 (due to DME and not another cause). Participants were evaluated after 30 days if they received an injection at their previous visit and had their interval extended to 60 or 90 days (at investigator discretion) if they were not treated at the previous visit. All participants were required to have a Month 48 visit. The predetermined conclusion of the study was scheduled to occur at Month 60, or 30 days after the approval of ranibizumab for DME in the United States; therefore not all patients had follow-up through Month 60 (study end). Since patient characteristics and outcomes were similar between studies, data from RIDE and RISE were pooled for the analyses presented here. To account for the variable follow-up time and patient attrition during the OLE, descriptive statistics are provided based on observed data for efficacy and safety analyses with no imputation of missing data. Month 36, the final scheduled visit in the core study, was used as a baseline for calculation of change during the OLE. Analyses are presented by prior treatment group in the core studies (sham with crossover to ranibizumab 0.5 mg, monthly 0.3-mg ranibizumab, and monthly 0.5-mg ranibizumab). Progression of DR was comprehensively evaluated in a time-to-event analysis of new PDR events using a composite outcome endpoint that included both changes in DR severity on fundus photographs plus the occurrence of clinically significant adverse events or procedures. A new PDR event was defined by the first occurrence of (1) progression from nonproliferative DR (DR severity score < 60) at baseline to PDR (DR severity score ≥ 60) at a later time point, (2) use of PRP laser, (3) vitreous hemorrhage (AE or slitlamp grade 0 at baseline to > 0 at a later time point), (4) cases identified by ophthalmoscopy, (5) use of vitrectomy for reasons related to DR or its complications, (6) iris neovascularization AE, or (7) retinal neovascularization AE.

Results

- A total of 500 patients enrolled in the extension study, with n = 289 and n = 7 completing Months 48 and 60, respectively.
- The mean follow-up during the OLE was 14.1 months.
- Approximately 25% of patients who entered the OLE met the VA and macular anatomy (OCT) stability criteria and did not require any treatment with 0.5-mg ranibizumab during the OLE.
- The mean annualized rate of injections given during the OLE was 3.8 (see Figure 1).
- VA gains achieved after 12-36 months of monthly therapy with ranibizumab were maintained with less-than-monthly ranibizumab 0.5 mg; the mean change in BCVA was stable between Months 36 and 54 (see Figure 2).
- Consistent with what was seen after initial crossover, patients randomized to sham injection never achieved vision gains on par with those of patients who were initially treated with ranibizumab (Figure 2).
- Subjects in the ranibizumab groups had a lower risk of developing a new PDR event compared with subjects originally randomized to sham over time through Month 54 (see Figure 3).
- Under the dosing regimen used in the RIDE and RISE Extension study, patients continued to demonstrate ≥ 2- and ≥ 3-step improvement in ETDRS DR severity level.
- The occurrence of ocular and systemic serious adverse events was consistent with what was observed in the core study.
Figure 1. Distribution of ranibizumab exposure in the RIDE and RISE open-label extension phase.

Figure 2. Pooled mean BCVA change from baseline (observed data).

*Data become unstable after Month 54 due to the low number of patients at that point. †Treatment during core study.

Pooled data from RISE and RIDE (Observed data). BCVA=best-corrected visual acuity; ETDRS=Early Treatment Diabetic Retinopathy Study; RBZ=ranibizumab
Conclusions

The OLE of the RIDE and RISE studies in DME demonstrated that the VA and OCT outcomes achieved with monthly ranibizumab therapy can be maintained with less-than-monthly treatment, with a mean of 3.8 annualized injections of 0.5-mg ranibizumab given during a mean follow-up of 14.1 months in the OLE. Patients continued to experience DR benefits during OLE as compared to baseline. Safety observations in the OLE were consistent with what was seen in the core studies.

In summary, monthly ranibizumab therapy rapidly achieves improvement in vision and improves DR severity in patients with baseline DME, and these improvements can be maintained long term with a less frequent injection schedule.
Update on the DRCR Studies

Lee M Jampol MD
Update on Anti-VEGF Trials for Diabetic Macular Edema

Dante J Pieramici MD

I. Pegaptanib (Macugen)
   A. Phase 2 trial suggests benefit over sham / laser, though benefit was modest.
   B. Phase 2/3 study included 260 subjects: 0.3 mg vs. sham, treated every 6 weeks for 102 weeks. At Week 102, pegaptanib group gained 6 letters vs. 1 letter in am/laser.
   C. First anti-VEGF agent approved for intraocular use in neovascular AMD (2004)
   D. Currently not approved for diabetic macular edema (DME). Phase 3 trials necessary.

II. Bevacizumab (Avastin)
   A. Widely used off-label for the treatment of numerous retinal diseases
   B. Early case reports are encouraging; demonstrate rapid reduction in retinal and subretinal fluid in some cases. Also reduces neovascularization
   C. Phase 2: DRCR.net
      1. 121 eyes, 12-week study
      2. Groups treated with 1.25 or 2.50 mg at baseline and 6 weeks did better than laser group at Week 12 (more visual improvement and reduced CST)
   D. Phase 3: BOLT Trial (N = 80)
      Single center randomized 1.25 mg intravitreal ranibizumab (IVB) vs. laser (2 groups), 3 injections then p.r.n. treatment
      1. 1- and 2-year results similar
      2. At 2 years, mean BCVA was 20/50 IVB and 20/80 laser (P = 0.005)
      3. Mean gain of 8.6 letters IVB vs. 0.5 laser group
      4. 3 line gainers 32% of eyes with IVB vs. 4% laser (P = .004)
      5. Central subfield improved in both groups at Year 2
      6. Mean number of treatments IVB in year 1 = 9 and in year 2 = 4.
      7. Despite vision gains, many patients still have central edema at Year 2 (40%).
      8. Appeared safe systemically and intraocularly
   E. Future trials: DRCR Protocol T
      1. Comparison trial of anti-VEGFs in the treatment of center involved DME (aflibercept, ranibizumab, and bevacizumab)

   2. Similar to Comparison of AMD Treatment Trial (CATT) trial but for DME
   3. Will provide more Phase 3 data for bevacizumab

III. Ranibizumab (Lucentis)
   A. Early experience
   B. Phase 2 trials
      1. Read-2 (N = 126)
         a. Randomized to 0.5-mg intravitreal ranibizumab (IVR) at baseline, month 1, 3, 5 then p.r.n. vs. laser vs. combination.
         b. IVR was beneficial for patients at 2 years. Combination with laser might reduce treatment burden.
      2. Read-3 (N = 153)
         a. Treatment of DME with 0.5 mg vs. 2.0 mg monthly
         b. 12 months study
         c. BCVA at 1 year +7.4 in 2.0 mg vs. +10.88 in 0.5 mg (P = .03)
         d. No difference in change CST
      3. Resolve (N = 151)
         a. 12-month study: multicenter, randomized clinical trial
         b. IVR 0.3 mg or 0.5 mg vs. sham with rescue laser for all groups
         c. Three loading doses and then p.r.n. Could use double dose after Month 1.
         d. At 12 months BCVA improved on average 10 letters vs. declined by 1.4 in sham (P < .00001).
         e. Nearly 4 times the average reduction in central macular edema with IVR
   C. Phase 3 Results
      1. Ranibizumab Plus Laser in Diabetic Macular Edema (RESTORE; N = 345)
         a. Phase 3 Trial in Europe
         b. Ranibizumab 0.5 mg vs. IVR and laser vs. laser
         c. 3 monthly injections then p.r.n.
         d. 3 years reported to date (12-month core study and 2 year extension, all groups could receive IVR 0.5 mg p.r.n. years 2 and 3
e. IVR with and without laser superior to laser alone.
   Average BCVA change IVR +6, IVR and laser +6, laser +0.8 ($P < .0001$) at 12 months
f. Extension trial (2 years following core trial)
   i. Visions maintained, laser group demonstrates gains when switched to IVR
   ii. IVR alone +8 letters, IVR and laser +7, Laser switched 0.5 IVR +6 letters average improvement BCVA
   iii. Average number of treatments in Year 3 was 2.4 to 2.9.

g. No safety issues

2. RISE/RIDE ($N = 377; N = 382$)
   a. Two parallel multicenter, randomized trials. Compared ranibizumab 0.3 or 0.5 mg every 4 weeks vs. laser and sham injections. Laser available to ranibizumab group at 3 months.
   b. Met primary endpoint at 1 and 2 years
   c. Improvement in vision as early as 7 days maintained at 2 and 3 years
   d. Percentage with 3-line gains at 2 years: ranibizumab 0.3 mg = 33.6% to 44.8%, 0.5 mg = 39% to 46%, Sham/laser = 12% to 18%

   e. In Year 3 patients continued on therapy assigned at baseline; however, laser/sham offered treatment with 0.5-mg ranibizumab. They did not catch up to visual gains of the patients treated from baseline with ranibizumab.
   f. Extension trial: At the end of Year 3 all patients permitted to continue on p.r.n. treatment with 0.5-mg ranibizumab. Overall visual improvements at 12 or 36 months maintained on p.r.n. therapy. (Average 4.5 injections over 14 months.) One-quarter needed no further injections.
   g. Overall excellent systemic and ocular safety of both doses of ranibizumab.

3. DRCR Protocol I ($N = 850$)
   a. 0.5-mg ranibizumab with prompt or deferred laser vs. IVK with prompt laser vs. sham injections and prompt laser
   b. 4 loading doses followed by a p.r.n. protocol
   c. At 1 year BCVA was 9 letters in the ranibizumab vs. 4 letters in IVK and 3 letters in laser.
   d. At 2 years the visions were maintained with fewer injections. 8 to 9 injections in the first year and 2 to 3 in the second year.

4. RETAIN ($N = 370$)
   a. Test treat and extend (T&E) ranibizumab 0.5 mg vs. T&E IVR and laser vs. p.r.n. IVR.
   b. At 12 months all groups gained 5 to 6 letters. T&E noninferior to p.r.n. At 24 months all groups gained another letter or 2 on average BCVA.
   c. Average number of injections slightly higher in T&E (12-13) than p.r.n. (11) at 24 months.
   d. T&E had 40% fewer visits than p.r.n., with 70% being monitored at 2 months or greater.

D. First FDA approved anti-VEGF agent for DME

IV. Aflibercept (Eylea)

A. Phase 1 trial. Encouraged proceeding to Phase 2/3 (Do et al, 2009)

B. Phase 2: DA VINCI ($N = 221$)
   1. Multicenter, randomized into 5 groups/ sham controls
   2. Included 0.5-mg and 2.0-mg groups every 4 weeks and 2.0 mg every 8 weeks or p.r.n. after 3 monthly loading doses
   3. Visual improvement ranged from 9.7 to 13.1 letters in IVA vs. loss of 1.3 letters in laser at 1 year. No difference between IVA groups at 4 or 8 weeks.

C. Phase 3: VIVID ($N = 404$)/VISTA ($N = 461$)
   1. Double-masked parallel Phase 3 multicenter studies designed for FDA approval for center involved DME
   2. Half of patients in VISTA (46%) not treatment naive to anti-VEGF, MOST patients in VIVID (90%-94%) were treatment naive.
      Similar anatomic and visual results between subgroups with and without previous anti-VEGF
   3. Aflibercept administered 2 mg every 4 or 8 weeks following 5 monthly loading vs. laser/sham in patients with center DME
   4. Patients treated with aflibercept did superior to laser. Mean letter improvement was +10.5 to +12.5 in IVA vs. +1.0 in the laser group at 1 year.
   5. All other vision parameters: percentage gaining 3 or more lines or losing 3 or more lines favored aflibercept heavily.
   6. Greater mean reduction in CST in IVA vs. laser ($P < .0001$)
   7. Some fluctuations in every-8-week group in CST, but did not affect vision.
8. Two-year results demonstrate sustained benefits from Year 1.
   a. At 100 weeks BCVA +11.5 in the every-4-week (loss of letter from 52 weeks), +11.1 in every-8-week (gain 0.5 from Week 52), and in laser, 0.9 letter (gain of 0.7 from Week 52).
   b. Afiblercept safety at 52 and 100 weeks similar to laser. ATCs at 100 weeks 8% in every-4-week group, 7% in every-8-week, and 6% in laser group.

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Subthreshold Laser for Diabetic Macular Edema

NH Victor Chong MD

Introduction

Anti-VEGF therapies have changed the dynamic in the management of patients with diabetic macular edema (DME); increasingly, they are the treatment of choice when there is extensive edema in fovea-involving DME.

The role of laser in the anti-VEGF era has to be re-examined. Despite the efficacy of laser, the mechanism of laser treatment remains unclear. In this presentation, I would discuss how laser may reduce macular edema and how can we do it better.

When laser was first introduced for DME, we were taught to “shoot at the red dots.” The red dots are microaneurysms, and shooting at them directly suggested that laser works by direct coagulation. But over the years, physicians began to notice that edema would improve even if they missed the microaneurysms.

Then we gained a better understanding of the absorption of laser energy, with the commonly used argon laser, with a blue-green wavelength at the time, where the majority of the energy is absorbed by the retinal pigment epithelium (RPE). The blood (oxy-hemoglobin) inside the microaneurysms (red dots) is not well absorbed by the laser, and hence the concept of direct coagulation has been bought into doubt.

Furthermore, clinical studies of the treatment of DME comparing argon green and krypton red (which are not absorbed by blood) (Olk, 1990) showed no differences in efficacy. Therefore, it is unlikely that direct coagulation is needed in reducing edema.

- So direct coagulation is not needed!

Subthreshold Conventional Laser Such as Endpoint Management

Bandello and colleagues (2005) suggested that “light” laser is as effective as “classic” laser treatment. Since we now know that laser scar is not needed, as anti-VEGF does not create any laser scar but yet is effective for reducing edema in DME, the concept of moving to lighter treatment is not new.

Recently, “endpoint management” (Lavinsky, et al., 2014) was proposed, suggesting that it can reduce collateral damage and can still be effective. The concept is to reduce the energy to just not visible in color photos but with mild changes in OCT. So far, there is no prospective randomized controlled trial to suggest that it is effective; however, there is a similar study to suggest that it might not be more effective than modified ETDRS laser.

The DRCR.net (Fong, et al., 2007) compared mild macular grid laser (MMG) with modified ETDRS laser treatment, citing the latter as the most commonly used method in performing laser for DME at the time of the study among the network investigators. MMG burns were located over the entire posterior pole, from 500 to 3000 microns from the center of macula, without burns within 500 microns of the optic disc. The burn intensity of the grid laser was barely visible (light grey); 200 to 300 burns in total were distributed evenly over the treatment area (approximately 2 to 3 burn widths apart). The MMG burns were lighter and more diffused in nature and were distributed over the whole macula in both areas of thickened and unthickened retina.

Microaneurysms were not directly photocoagulated. In contrast, the modified ETDRS laser treated only areas of thickened retina (and areas of retinal nonperfusion) and leaking microaneurysms. MMG did not show any superiority over modified ETDRS laser treatment. However, MMG did work in reducing edema.

- Treating normal retina is not necessary.
- More energy might be better.
- Targeting microaneurysms might be useful.

Subthreshold Micropulse Laser

The concept of micropulse laser is to deliver more energy to the RPE cells without the collateral damage to the neurosensory retina. Laser energy is delivered in pulses. For example, using a 5% duty cycle at 200 ms duration, there is a very short active (on) energy (0.1 ms) followed by a period of no (off) energy (1.9 ms). With each “burn” of 200 ms duration, there would be 100 of these short pulses. The “off” period allows the tissue to cool off, and hence more energy can be delivered to the targeted tissue (RPE) without heating the surrounding neurosensory retina.

We have published one of the first prospective randomized controlled trials to suggest that micropulse laser is as good as modified ETDRS treatment but with less scarring (Figueira, et al., 2009).

Vujosevic and colleagues (Vujosevic, et al., 2010) confirmed our findings but also showed that retinal sensitivity is significantly better in patients treated with micropulse laser. Furthermore, not only were the laser scars not visible in clinical examination, but fundus autofluorescence never changed in the micropulse diode laser group, even after retreatment.

Once we understand that micropulse laser works through activation of the RPE cells and it does not cause any visible collateral damage, it seems to make sense to remove the spacing between laser “burns.” This was confirmed in a prospective randomized controlled trial that high-density treatment is more effective (Lavinsky, et al., 2011) than low-density and modified ETDRS treatment.

High-density treatment means a lot more laser spots; often 5 to 10 times more spots are required if the small spot size is used. So larger spot size is often used, and using multispot laser can reduce treatment time.

One of the most common causes of treatment failure with micropulse laser is undertreatment; laser surgeons are used to treating with gaps, and as the laser treatment is invisible during treatment, it is more difficult to be sure where the laser spots have been placed. A tracking laser might be able to improve this problem and make treatment easier.

Summary

Modified ETDRS laser treatment is the most commonly performed laser treatment for DME; however, there is significant collateral damage, with retinal scarring, paracentral scotoma, and reduced retinal sensitivity. Other laser modalities have been proposed, but so far only subthreshold micropulse laser has...
shown potential superiority over modified ETDRS laser treatment. Multispot and/or tracking laser might make micropulse laser treatment easier.

My current power settings for a micropulse laser:

- Wavelength: 577 yellow laser
- Spot size: 140 to 160 microns
- Laser lens: Area Centralis (laser correction x 0.94) or equivalent
- Duty cycle: 5% (0.1 ms on, 1.9 ms off)
- Duration: 200 ms
- Power: 50% of “just threshold” power
- Treatment: High density with no gaps guided by OCT

References


Sustained-Release Steroids for Diabetic Macular Edema: Ozurdex

Albert J Augustin MD

I. The pathogenesis of diabetic retinopathy (DR) is multifactorial and involves both inflammation and oxidative stress.1

- Advanced glycation end products (AGEs), which are produced secondary to hyperglycemia in diabetes, are thought to have a significant role in the activation of inflammatory pathways and the production of reactive oxygen species that cause microvascular complications in DR.2

AGE activation of AGE receptors (RAGE) has been associated with up-regulation of interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF), and AGE-related changes in mitochondrial respiration cause increased formation of reactive oxygen species.

- Diabetic macular edema (DME), the most common cause of vision loss in patients with diabetes, results from leakage of blood components from dilated hyperpermeable capillaries and microaneurysms, leading to fluid accumulation in and beneath the retina.

- Although the pathogenesis of DME is multifactorial and not completely understood, steroids are a rational choice for the treatment of DME because they inhibit multiple inflammatory processes involved in the breakdown of the blood-retinal barrier that leads to DME.

  1. Steroids inhibit the production and release of VEGF and other cytokines, reduce leukocyte migration, and stabilize vascular endothelial junctions.3

  2. The multifactorial nature of DME may explain why some patients are refractive to anti-VEGF treatment but respond to steroids.

II. Preliminary Data on Steroids in the Treatment of DME

- Intravitreal triamcinolone acetonide (TA) is commonly used off-label for treatment of DME

A large, randomized DRCR.net study4 showed similar efficacy through 1 year between intravitreal TA injections and laser (with retreatment at 4-month intervals as needed) in patients with DME; development of cataracts in phakic eyes reduced the benefit of intravitreal TA treatment after 1 year.

III. Need for Sustained-Release Implant

- Dexamethasone is a corticosteroid with more potent anti-inflammatory activity than TA, but dexamethasone is cleared rapidly from the vitreous after intravitreal injection.

- Because of the short half-life of dexamethasone and the chronic nature of DME, a sustained-release implant of dexamethasone is needed to provide therapeutic levels of steroid at the macula without need for frequent injections.

IV. Sustained-Release Dexamethasone Intravitreal Implant (DEX Implant)

- DEX implant is a biodegradable implant that provides slow release of dexamethasone over several months.5

- DEX implant is approved for treatment of macular edema secondary to retinal vein occlusion and for treatment of noninfectious posterior segment uveitis, and it is under investigation for regulatory approval for the treatment of DME.

V. Phase 3 Study of DEX Implant in DME6

A. Study design and patients

  1. A 3-year, randomized, multicenter, masked, sham-controlled phase 3 study (MEAD) evaluated the safety and efficacy of DEX implant 0.7 mg and 0.35 mg for treatment of DME.6

  2. Patient eligibility criteria included diagnosis of DME, BCVA between 34 and 68 ETDRS letters, and central subfield retinal thickness (CRT) ≥ 300 µm by OCT in the study eye.

  3. Patients were seen at up to 40 scheduled visits during the study, and patients who met retreatment eligibility criteria could be retreated no more often than every 6 months.
4. No adjunctive treatments for DME were allowed during the study; any patient who required escape treatment (any treatment other than DEX implant for DME) was exited from the study prior to receiving the escape treatment.

5. The primary endpoint for the U.S. FDA was achievement of ≥ 15-letter improvement in BCVA from baseline at study end in the intent-to-treat population with last-observation-carried-forward for missing values.

6. An area-under-the-curve (AUC) approach was taken for analysis of mean average change from baseline BCVA using observed values over the course of the study for European regulatory agencies.

7. Safety measures included adverse events and IOP.

B. Results

1. A total of 1048 patients with a mean duration of DME of 24.9 months were enrolled; DME had been previously treated with laser, intravitreal steroid, and/or intravitreal anti-VEGF in 72.2% of patients.

2. The mean number of DEX implant treatments received over 3 years was 4.1 for DEX implant 0.7 mg, 4.4 for DEX implant 0.35 mg, and 3.3 for sham.

3. DEX implant met the primary endpoint of the study: the percentage of patients with ≥ 15-letter improvement in BCVA from baseline at study end was greater with DEX implant 0.7 mg (22.2%) and DEX implant 0.35 mg (18.4%) than sham (12.0%) (P ≤ .018).

   In the analysis for European regulatory agencies, mean average change from baseline BCVA was also greater with DEX implant 0.7 mg (3.5 ETDRS letters) and DEX implant 0.35 mg (3.6 letters) than sham (2.0 letters) (P ≤ .023) (AUC approach).

4. Anatomic improvements (mean average change in CRT from baseline) were also greater with DEX implant 0.7 mg (−111.6 µm) and DEX implant 0.35 mg (−107.9 µm) than sham (−41.9 µm) (P < .001).

5. Visual improvement was consistent each year of the study in eyes that were pseudophakic at study entry.

   a. The percentage of baseline pseudophakic eyes that had ≥ 15-letter improvement in BCVA from baseline at study end was 23.3% in the DEX implant 0.7-mg group, 15.9% in the DEX implant 0.35-mg group, and 10.9% in the sham group (P = .024 for DEX implant 0.7 mg vs. sham).

   b. Mean average BCVA improvement over the course of the study in baseline pseudophakic eyes was 6.5 ETDRS letters in the DEX implant 0.7-mg group, 5.9 letters in the DEX implant 0.35-mg group, and 1.7 letters in the sham group (P ≤ .001 for DEX implant 0.7 mg and 0.35 mg vs. sham) (AUC approach, see also Figure 2).

6. In eyes that were phakic at study entry, improvement in BCVA in the DEX implant treatment groups was reduced after year 1, because visual outcomes were confounded by steroid-induced cataract.

   Among patients who were phakic at baseline, 67.9%, 64.1%, and 20.4% had 1 or more cataract-related adverse events and 59.2%, 52.3%, and 7.2% underwent cataract surgery in the DEX implant 0.7-mg, DEX implant 0.35-mg, and sham groups, respectively.

7. After cataract surgery and recovery, visual improvement in phakic eyes treated with DEX implant reached the same level as in baseline pseudophakic eyes.

8. The most common adverse event, after cataract, was increased IOP.

   a. IOP ≥ 25 mmHg occurred in 32.0%, 27.4%, and 4.3% of patients in the DEX implant 0.7-mg, DEX implant 0.35-mg, and sham groups, respectively.

   b. IOP-lowering medication was used during the study by 41.5%, 37.6%, and 9.1% of patients, respectively.

   c. Only 1 patient (0.3%) in each DEX implant treatment group required glaucoma incisional surgery to manage steroid-induced increased IOP.
C. Conclusions

1. An average of 4-5 injections of DEX implant over 3 years provided clinically significant gains in BCVA and CRT.

2. Improvements were more robust in pseudophakic eyes because of the development of steroid-induced cataract in phakic eyes.

3. Treatment benefit of DEX implant was restored in phakic eyes after cataract extraction.

4. The safety profile of DEX implant was favorable compared with other intraocular steroids.

VI. Published studies of the off-label use of DEX implant in DME are confirmatory.

A. In a prospective, 6-month study, 55 difficult-to-treat patients with DME and prior pars plana vitrectomy showed improvement in BCVA and CRT after a single DEX implant, and there were no cases of elevated IOP requiring a laser or surgical procedure.7

B. In another prospective study, 16 eyes with chronic DME nonresponsive to bevacizumab treatment (demonstrated by no clinically significant improvement in CRT after at least 3 monthly bevacizumab injections) were administered DEX implant and showed significant improvement in BCVA and CRT up to 3 months after the implant.8

C. In a retrospective case series of 58 patients with long-standing DME that was refractory to treatment with laser, intravitreal anti-VEGF and/or intravitreal steroid treatment with a single DEX implant provided significant improvement in BCVA and foveal thickness up to 6 months after the implant.9

D. Favorable results were also reported in other smaller case series of eyes with persistent DME that were treated with DEX implant.10,11

References


Sustained-Release Steroids for Diabetic Macular Edema: Iluvien

Baruch D Kuppermann MD PhD

Background

Diabetic macular edema (DME) is a progressive disease that results in severe impairment of vision if left untreated. Longer duration of diabetes is an established risk factor for progression of retinopathy, which is associated with an increased incidence of DME. It has also been established that as retinopathy progresses, the levels of multiple cytokines increase relative to vascular endothelial growth factor (VEGF), which may explain the lack of sufficient response to ranibizumab seen in some patients with longer-duration DME. Consequently, therapies that address only 1 aspect of disease pathology may become less effective over the course of the disease. Currently available first-line therapies for DME are limited to the anti-VEGF inhibitors ranibizumab and aflibercept, as well as the dexamethasone implant Ozurdex in pseudophakic patients and phakic patients scheduled for cataract surgery. The multicenter, randomized, sham-controlled Phase 3 clinical trials—Fluocinolone Acetonide in Diabetic Macular Edema (FAME)—were unique in that they required prior macular laser treatment to qualify for randomization. This enriched the population with patients with longer-duration DME and thereby allowed for the demonstration of significant efficacy in patients with chronic DME when treated continuously with daily submicrogram fluocinolone acetonide (FAc). A validation of the finding in the FAME trial of a transition in DME so that it no longer primarily mediated by VEGF was seen in the Phase 3 clinical trials for ranibizumab for the treatment of DME (RIDE and RISE). These trials showed that patients who received ranibizumab later in the course of disease did not experience the same benefit as those treated early, suggesting that these patients may have transitioned into a chronic-phase DME in which disease pathology is driven by multiple factors and may no longer respond to targeted VEGF therapy. The FAc intravitreal implant 0.2 μg/d (Iluvien) has received marketing authorization in several European countries for the treatment of vision impairment associated with chronic DME considered insufficiently responsive to available therapies; it is currently undergoing review by the U.S. Food and Drug Administration.

Methods

The FAME trials included a preplanned efficacy analyses to stratify patients based on the median duration of DME at baseline. The median duration of DME at baseline was determined to be 3 years using the algorithm that was prespecified (year of randomization) − (year of diagnosis) + 1; the addition of 1 year was included to prevent any patient from having a reported duration of DME of 0 years. Analysis of the FAME data using this algorithm showed that the benefit of receiving sustained, low-dose FAc was greater in patients with DME for ≥ 3 years vs. patients with DME for < 3 years.

To more precisely determine the median duration of DME at baseline, a second algorithm was tested. This second algorithm included both the month and day of diagnosis. For the 10% of patients with no available information about the day of diagnosis, the 15th was imputed. For the 15% of patients for whom only the year of diagnosis was available, July 1 was imputed. The 2 algorithms were then compared to determine concordance, and the effect on visual acuity in patients with chronic and non-chronic DME was evaluated using the new algorithm.

Results

The more precise algorithm resulted in a median duration of DME at baseline for all patients of 1.73 years; 475 patients had a duration of DME of < 1.73 years (nonchronic DME), and 477 patients had a duration of DME of > 1.73 years (chronic DME). The original algorithm resulted in categorization of 416 patients to the nonchronic group and 536 to the chronic group. Thus, the more precise algorithm corrected an imbalance in the chronic and nonchronic populations, yet 92% of patients retained the same categorization with either algorithm. Concordance with the original algorithm was significant (kappa = 0.8508, P < .0001). The proportion of patients gaining ≥ 15 ETDRS (Early Treatment Diabetic Retinopathy Study) letters from baseline was similar regardless of the algorithm used (see Figure 1). In patients with a duration of DME < 1.73 years, the proportion of patients with ≥ 15-letter improvement after 36 months was 28.4% for sham treatment compared with 25.0% for 0.2 μg/d FAc (P = .447). Among patients with a duration of DME > 1.73 years, the proportion of patients with ≥ 15-letter improvement was 11.7% for sham treatment compared with 32.8% for 0.2 μg/d FAc (P < .001). Safety outcomes were also similar regardless of the algorithm used.

Conclusions

The significant concordance between the patients assigned to chronic or nonchronic strata by either algorithm, as well as the similarity between safety and efficacy data, indicates that the more precise algorithm results in a more accurate estimate of the duration of DME at baseline in the FAME trials (1.73 years). Currently, the only way to identify a chronic pathology in patients with DME is by their differential response to therapy. Evidence from other large Phase 3 clinical trials in DME have...
suggested that patients who receive ranibizumab 2 years after randomization are not able to achieve gains in vision similar to those of patients who were initially randomized to ranibizumab. Similarly, the duration of DME in patients with chronic DME in the FAME trials close to 2 years and may provide evidence for the timing of a transition in the pathology of DME. Iluvien is currently approved in 17 countries in Europe and is the only therapy approved specifically for chronic DME.

References


What’s Next in the Treatment of Diabetic Macular Edema?

Peter A Campochiaro MD

I. Current Therapies for Diabetic Macular Edema (DME)

A. First-line treatment
   Intraocular injections of vascular endothelial growth factor (VEGF) binding proteins
   1. Currently available VEGF-binding proteins
      a. Ranibizumab
      b. Bevacizumab
   2. Under consideration by FDA as of June 2014: Aflibercept
   3. Possibly on the horizon: VEGF-binding designed ankyrin repeat protein (DARPin)

B. Second-line treatment
   Focal/grid laser. Are there new laser technologies that may improve efficacy?

C. Third-line treatment
   Intraocular steroids
   1. Currently available off-label: triamcinolone acetonide
   2. Available in Europe: triamcinolone acetonide implant (Iluvien)
   3. May be available soon in United States as of June 2014: dexamethasone implant (Ozurdex) and triamcinolone implant

II. Investigational Agents

A. AKB-9778
   A small molecule inhibitor of vascular endothelial-protein tyrosine phosphatase (VE-PTP) that activates Tie2.
   Tie2 is receptor tyrosine kinase present in vascular endothelial cells. Its endogenous agonist is angiopoietin 1 and its endogenous antagonist is angiopoietin 2. When angiopoietin 1 binds to Tie2 it stimulates phosphorylation, which initiates signaling of the Tie2 pathway and activation of downstream molecules that have the net effect of stabilizing the endothelial cells and making them less responsive to VEGF. Therefore activation of Tie2 suppresses VEGF-induced leakage and neovascularization. Angiopoietin 2 blocks activation of Tie2 and therefore makes endothelial cells more responsive to VEGF. Angiopoietin 2 is increased in the vitreous of patients with DME.
   VE-PTP is a phosphatase that deactivates Tie2 and therefore it acts like angiopoietin 2. It is increased by ischemia or hypoxia just like angiopoietin 2. By inhibiting VE-PTP, AKB-9778 keeps Tie2 in an activated state. In animal models, AKB-9778 strongly suppresses ocular neovascularization and vascular leakage. In a Phase 1b study, subcutaneous injections of doses of 15 mg b.i.d. or above for 1 month caused substantial reductions in intraretinal fluid and improved vision in several patients. A Phase 2 study is under way in which patients with DME are being randomized to 15 mg b.i.d. of AKB-9778, 0.3 mg ranibizumab, or both for 3 months.

B. Darapladib
   A selective oral inhibitor of lipoprotein-associated phospholipase A2.
   Darapladib is being investigated as an anti-atherosclerosis agent. In a randomized, double-masked, placebo-controlled Phase 2a study, 36 patients were randomized to Darapladib and 18 to placebo. At the 3-month primary endpoint, the Darapladib group had a 4-letter mean improvement from baseline BCVA and a reduction in center subfield thickness of 57 µm, compared to 1.7-letter improvement and 37-µm reduction in the placebo group.

C. ALG-1001
   Peptide with RGD sequence.
   Reduces ocular neovascularization and excessive vascular leakage in mouse models. Ex-U.S. clinical trials in patients with DME show good safety profile and suggest antipermeability activity.

D. Sustained delivery approaches
   1. Pars plana implant that slowly releases ranibizumab into the vitreous cavity
   2. Nanoparticles
Conbercept Clinical Trials
A New Anti-Vascular Endothelial Growth Factor Therapy

Peter K Kaiser MD

Introduction
Conbercept (KH902, Chengdu Kanghong Biotechnology Co., Ltd.) is a novel, 100% humanized, recombinant, fusion protein consisting of extracellular domain 2 of VEGFR-1 (FLT1), extracellular domain 3 and 4 of VEGFR-2 (KDR), and the human IgG Fc fragment. This decoy receptor is a dimeric glycoprotein with a molecular weight of 143 kDa. Since conbercept contains the extracellular domain 4 of VEGFR-2, which plays an important role in dimerization of receptor molecules and further increases the binding of VEGF to VEGFR-2, it may be more effective in capturing VEGF and preventing VEGF-mediated activation of the angiogenesis pathway than other anti-VEGF drugs. The drug blocks all isoforms of VEGF-A, VEGF-B, and placental growth factor. The affinity of conbercept to VEGF is 0.1-0.3 pM, about 200 times higher than ranibizumab (Lucentis, Genentech/Roche).

Clinical Studies
After establishing the preclinical safety profile of conbercept, clinical trials were performed in China.

1. A single-dose, Phase 1a dose-escalation study (N = 28, completed)
The results from the single-dose, dose-escalating clinical trial of conbercept for wet AMD showed that a single intravitreal injection of conbercept (from 0.05 mg to 3.0 mg) is safe, well tolerated, and effective. At the end of study at 42 days, the mean change in visual acuity was +19.6 letters, with no patients losing any visual acuity. The visual acuity improved ≥15 letters (3 lines) from the baseline in 57% patients. There was a mean change in the central retinal thickness (CRT) of −77.2 µm and a mean decrease in lesion size of −0.6 mm³ and a mean decrease in CNV size of 12.6%.

2. A 52-week safety, dose-ranging Phase 1b study (Hope study, N = 36, completed)
The HOPE study enrolled patients with wet AMD and treated them with a monthly loading dose of either 0.5 mg or 2 mg conbercept for 3 months followed by monthly assessments and as needed (p.r.n.) dosing for 1 year. The HOPE study demonstrated that using this as needed, p.r.n., regimen after 3 consecutive monthly injections significantly improved patients’ vision and anatomic features. After 52 weeks, both groups exhibited a significant improvement in vision compared to baseline in the 0.5-mg group of +14.3, +9.3, +12.4, and +15.4 in the 0.5mgPRN, 0.5mgq1m, 2.0mgPRN, and 2.0mgq1m group, respectively. Mean CRT improved in all 4 groups with a reduction of −119.8 µm, −129.7 µm, −152.1 µm, and −170.8 µm in the 0.5mgPRN, 0.5mgq1m, 2.0mgPRN, and 2.0mgq1m group, respectively.

3. A 52-week Phase 2 dose-ranging study (Aurora study, N = 111, completed)
The Aurora study treated patients with wet AMD with either 0.5 mg or 2 mg/eye monthly for 3 months. Patients were then randomized into 4 groups: continue to receive monthly injections of 0.5 mg or 2.0 mg (q1m), or follow an as-needed (p.r.n.) regimen. At 52 weeks, the mean change in vision from baseline significantly improved in all groups: as +14.3, +9.3, +12.4, and +15.4 in the 0.5mgPRN, 0.5mgq1m, 2.0mgPRN, and 2.0mgq1m group, respectively. Mean CRT improved in all 4 groups with a reduction of −119.8 µm, −129.7 µm, −152.1 µm, and −170.8 µm in the 0.5mgPRN, 0.5mgq1m, 2.0mgPRN, and 2.0mgq1m group, respectively.

4. A 52-week Phase 3 study (Phoenix study; N = 124, completed)
The Phoenix study enrolled treatment-naïve wet AMD patients and treated them with either 0.5-mg/eye monthly for 3 months followed by 0.5-mg/eye fixed dosing every 3 months (normal treatment) or delayed treatment, in which patients received sham injections for 3 months followed by 0.5-mg/eye monthly for 3 months followed by 0.5-mg/eye every 3 months. After the 3-month loading period, the normal treatment group had a significant improvement in vision of +9.2 letters and a −79.2 µm mean decrease in CRT, while BCVA and CRT in the delayed treatment group remained unchanged from baseline in the same time period. After 52 weeks, the normal treatment group had a +9.9 letter mean improvement in vision while the delayed treatment group also had an +8.8 letter improvement, with statistical significance demonstrated in both groups compared with baseline. At Month 12, the mean change in CRT in the normal and delayed treatment groups were −90.9 µm and −135.4 µm, respectively.

5. Clinical trials in other indications such as diabetic macular edema, CNV secondary to pathologic myopia, and macular edema due to retinal vein occlusion are ongoing in China.

Safety
Overall, the product has shown a good safety profile, with adverse events (AEs) analogous to other anti-VEGF drugs. There was no increase in drug-related abnormalities in laboratory analyses, electrocardiogram, drug-related serious AEs, or specific cardiovascular events (Antiplatelet Trialists’ Collaboration events) related to VEGF inhibition, compared to those that have been reported for other anti-VEGF agents, and no specific drug-related immunogenicity developed in any subject.
COMRADE-B Retinal Vein Occlusion Trial

Simon Rj Taylor PhD FHEA FRCOphth

Introduction

Until the last decade, macular laser treatment was the standard of care for persistent macular edema secondary to branch retinal vein occlusion (BRVO). Now, two approved intravitreal pharmaceutical treatments are also available: the anti-VEGF agent ranibizumab (RAN) and the sustained-release dexamethasone implant (DEX). The anti-VEGF decoy receptor aflibercept (AFL) is also currently under review by the U.S. FDA.

Vascular endothelial growth factor (VEGF) is the major cytokine released by hypoxic retinal tissue in RVO and thus forms a significant therapeutic target. RAN (Lucentis) was approved in June 2010 by the FDA for the treatment of visual impairment due to macular edema following BRVO and central retinal vein occlusion (CRVO) based on the results of two Phase 3 randomized controlled studies, BRAVO and CRUISE.1,4-12 The alternative treatment approach centers on corticosteroids, based on their anti-inflammatory effects as well as their ability to reduce vascular permeability. DEX (Ozurdex), a sustained-release biodegradable dexamethasone implant, was approved by the FDA in 2011, based on the results of the Phase 3 randomized sham-controlled GENEVA trial.5,6

Because of the differences in patient cohorts and trials designs, however, comparative analysis between the RAN and DEX trials is problematic. Thus, a 6-month study was designed to compare directly the efficacy and safety of RAN with that of DEX in patients with BRVO—the COMRADE B (Efficacy and Safety of RAN Intravitreal Injections Versus Dexamethasone Intravitreal Implant in Patients With BRVO) study.

Methods

COMRADE-B was a Phase 3b, multicenter, randomized, 2-treatment arm (RAN vs. DEX), double-masked study funded by Novartis AG. It was designed to show that RAN had superior efficacy and safety compared to DEX over a 6-month period. In the treatment phase, eligible patients received consecutive monthly intravitreal injections with 0.5-mg RAN until visual acuity (VA) stability was achieved (defined as a patient’s VA being stable for 3 consecutive monthly assessments performed while on RAN treatment), followed by a p.r.n. retreatment if there was a decline from stable VA levels, or a single intravitreal DEX (700 µg) and sham injections thereafter. The COMRADE-B study was registered with clinicaltrials.gov as NCT01396057.

Results

A total of 337 patients were recruited into this study between July 2011 and December 2012; 93 patients failed the screening procedure and 244 patients were randomized and received at least 1 dose of study drug 0.5-mg RAN (n = 126) or DEX (n = 118) at 64 sites in Germany, the United Kingdom, Poland, Hungary, and Czechoslovakia. The mean time from diagnosis of BRVO to baseline visit was 57 ± 71 days. Mean baseline BCVA letter scores were 57 ± 12 and 58 ± 12 and mean baseline CRTs were 540 ± 169 µm and 546 ± 173 µm for the RAN and DEX groups, respectively.

Efficacy

After treatment initiation, mean BCVA improved steadily from baseline to 72.0 ± 12.5 and 71.4 ± 12.0 letters in the RAN and the DEX groups at Month 2, respectively. This level of BCVA was maintained approximately constant under p.r.n. regimen with RAN until Month 6 (74.4 ± 12.9). However, in the DEX group the mean BCVA decreased to 67.3 ± 13.3 letters at Month 3 and remained nearly constant until study end (67.3 ± 13.7). Over all post-baseline values, patients in the RAN group gained a mean BCVA of 14.2 letters (95% CI; 12.5, 15.7) compared to 9.7 (7.9, 11.4) in the DEX group (P < .0001).

Along with the improvements in BCVA, there was a rapid decrease of central retinal thickness (CRT) in both treatment groups. Mean CRT decreased by 245 ± 173 µm in the RAN and by 269 ± 173 µm in the DEX group after 2 months. There was then a rebound increase, but this was more pronounced in the DEX group.

Safety

A total of 135 patients (55%) experienced an ocular adverse event in the study eye, and 156 patients (64%) experienced a systemic adverse event, but most were not considered to be related to the study drug. In the RAN group, 8% of patients had a study drug-related ocular adverse, and 4% had a study drug-related systemic adverse event; the figures for the DEX group were 25% and 15%, respectively. Significantly more patients (P < .0001) in the DEX group had an ≥ 10% increase in IOP from baseline over time than patients under RAN treatment.

Conclusions

This is the first study to assess RAN and DEX in a head-to-head randomized controlled trial. Changes in BCVA and CRT were initially similar in both groups, but these were maintained in the RAN group, whereas the DEX group declined from peak from Month 3 onward. Ocular and systemic adverse events were common, although few were considered to be related to the study drugs. As expected, IOPs were more likely to increase with DEX than with RAN, but only 1 patient reached the criteria for a severe ocular adverse event. This study suggests that treating to visual stability with RAN followed by a p.r.n. reinjection regime achieves better results over a 6-month period than a single injection of DEX.

References


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MEAD: Diabetic Macular Edema Trial Subanalysis

Anat Loewenstein MD

I. Treatment of Diabetic Macular Edema (DME)

Steroids are a treatment option for DME because they inhibit multiple inflammatory processes involved in the pathogenesis of DME.1,2

A. Release of cytokines including vascular endothelial growth factor (VEGF), leukocyte migration, leukostasis, and disruption of vascular endothelial cell tight junctions are inflammatory processes involved in the breakdown of the blood-retinal barrier and vascular leakage leading to DME.

B. Steroids inhibit all of these processes.

II. Sustained-Release Dexamethasone Implant

A. Dexamethasone is a potent corticosteroid that differs from other intraocular steroids (triamcinolone acetonide and fluocinolone acetonide) in lipid solubility, pharmacologic activity, and delivery requirements.3

B. Because dexamethasone is rapidly cleared from the vitreous humor after intravitreal injection, a sustained-release implant is needed to provide therapeutic levels of drug to the posterior segment for treatment of chronic conditions.

C. Dexamethasone intravitreal implant (DEX implant) (Ozurdex; Allergan, Inc.) is a biodegradable sustained-release implant that releases dexamethasone over a period of up to 6 months.4

D. DEX implant is currently approved for treatment of macular edema secondary to retinal vein occlusion and treatment of noninfectious posterior segment uveitis.

E. In off-label use, DEX implant has demonstrated efficacy in the treatment of DME that is persistent and resistant to anti-VEGF and laser treatment.5,6

III. MEAD Study for Regulatory Approval of DEX Implant for Treatment of DME

A. Study design

This was a 3-year, randomized, multicenter, masked, sham-controlled Phase 3 study.

1. Two clinical trials with identical protocols were conducted and the results were pooled for analysis.

2. A report of the primary analyses of the study results is in press.7

B. Patient selection

1. Key inclusion criteria for study eyes included diagnosis of DME, BCVA between 34 and 68 Early Treatment Diabetic Retinopathy Study (ETDRS) letters, and central subfield retinal thickness (CRT) ≥ 300 µm by OCT.

2. Key exclusion criteria included treatment with intravitreal anti-VEGF within 3 months of study entry, treatment with intravitreal triamcinolone within 6 months of study entry, history of intraocular laser or incisional surgery in the study eye within 90 days of study entry, diagnosis of glaucoma, history of marked steroid-induced IOP increase, ocular hypertension in the study eye without adequate control with antiglaucoma medication.

C. Intervention and assessments

1. Patients were randomized to treatment with DEX implant 0.7 mg, DEX implant 0.35 mg, or a sham injection procedure and received the first study treatment after baseline evaluations on Day 0.

2. Patients were seen at up to 40 scheduled visits during the 3-year study.

a. Visits were scheduled every 1.5 months during the first year and every 3 months during the second and third years.

b. Patients were also seen at safety visits at 1, 7, and 21 days after each DEX implant or sham treatment.

3. Patients who met retreatment eligibility criteria could be retreated no more often than every 6 months.

4. Patients who required treatment other than DEX implant for DME were exited from the study prior to receiving the escape treatment.

This aspect of the study design differentiates MEAD from the Phase 3 trials of anti-VEGF8 (RISE, RIDE), which allowed rescue laser treatment and led to a relatively lower rates of study completion.

5. The primary endpoint was achievement of ≥ 15-letter improvement in BCVA from baseline at study end (analyzed in the intent-to-treat population with last-observation-carried-forward for missing values).

6. Secondary efficacy endpoints included average change in BCVA from baseline during the study (area-under-the-curve approach), mean change in BCVA from baseline at each study visit, percentage of patients with BCVA of 20/40 or better at each study visit, and average change in CRT from baseline during the study by OCT (area-under-the-curve approach).
7. Safety measures included adverse events and IOP.
8. Preplanned subgroup analyses evaluated selected outcome measures in patient subgroups defined by demographics, duration of diabetes, duration of DME, baseline HbA1c, prior laser treatment, treatment-naïve status, lens status at baseline, and diabetic retinopathy (DR) severity at baseline.

D. Results in total study population
1. 1048 patients were enrolled in the study.
2. The mean number of study treatments received over 3 years was 4.1 in the DEX implant 0.7-mg group, 4.4 in the DEX implant 0.35-mg group, and 3.3 in the sham group.
3. DEX implant met the primary efficacy endpoint: the percentage of patients with ≥ 15-letter improvement in BCVA from baseline at study end was greater with DEX implant 0.7 mg (22.2%) and DEX implant 0.35 mg (18.4%) than sham (12.0%) (P ≤ .018).
4. DEX implant 0.7 mg and 0.35 mg also demonstrated better efficacy than sham in secondary efficacy endpoints.

E. Subgroup analysis results
1. Effects of DEX implant on BCVA relative to sham were similar to those in the total population for the following patient subgroups:
   a. Male vs. female
   b. Age 45-65 years vs. > 65 years
   c. White vs. non-white
   d. HbA1c ≤ 8% vs. > 8%
   e. Diabetes duration ≤ 15 years vs. > 15 years
   f. DME duration ≤ 3 years vs. > 3 years
   g. Previous laser treatment vs. no previous laser treatment
2. Patient subgroups based on baseline lens status (phakic vs. pseudophakic)
   a. Improvement in BCVA in DEX implant-treated phakic eyes was reduced during the second year of the study because of cataract development.
   After cataract surgery and time for recovery, BCVA improvement returned to the levels seen in baseline pseudophakic eyes.
   b. Improvement in BCVA was consistent each year of the study in DEX implant-treated pseudophakic eyes.
   c. The percentage of patients with ≥ 15-letter improvement in BCVA from baseline at study end was similar in the baseline phakic and pseudophakic subgroups of DEX implant-treated patients.
3. Patient subgroups based on baseline DR severity (moderately severe or better vs. severe or worse): Patients with severe or worse DR had better outcomes relative to sham.

F. Conclusions
1. Subgroup analysis showed benefit of DEX implant treatment in subgroups defined by demographics, diabetes status, duration of diabetes and DME, and prior treatment.
2. BCVA improvement after Year 1 was consistent in DEX implant-treated pseudophakic eyes but not phakic eyes, because of the development of steroid-induced cataract.
3. After cataract extraction, treatment benefit of DEX implant in patients with baseline phakic lens status was restored.
4. Treatment benefit was seen in patients with severe DR at baseline.

References
Lucentis Compared to Avastin Study: Two-Year Results
A Treat-and-Extend Protocol

Karina Berg MD for the LUCAS Investigators

Introduction

Today, several randomized multicenter trials (CATT, IVAN, MANTA, GEFAL, ANCHOR) have confirmed similar efficacy between ranibizumab and bevacizumab when treating patients with neovascular AMD monthly or as-needed (pro re nata, p.r.n.). The Lucentis Compared to Avastin Study (LUCAS) is the first randomized multicenter trial comparing bevacizumab and ranibizumab following a treat-and-extend protocol.

Background

The landmark studies MARINA and ANCHOR showed a remarkable improvement in visual acuity compared to sham treatment and photodynamic therapy, respectively, when monitored and given ranibizumab every month. This regimen is, however, difficult for older patients to maintain and also creates a heavy burden on health-care systems. Clinical trials have since then explored different treatment modalities, such as the p.r.n. treatment, where patients are seen monthly and treated if signs of exudation appear. Monthly monitoring is, however, required in order to reveal early recurrences before visual decline appears. Today, many practitioners use an individualized approach to anti-VEGF treatment. With a treat-and-extend protocol, the patients are treated at each visit regardless of activity. If there is no sign of activity, the control and treatment intervals are extended gradually, while if there are signs of recurrence the intervals are shortened.

Aims

The purpose of the randomized multicenter study LUCAS is to demonstrate if the two agents bevacizumab and ranibizumab are equivalent regarding both efficacy and safety through 2 years. A total of 441 patients with objective evidence of wet AMD were randomized to a double-blind treatment with ranibizumab or bevacizumab. The primary outcome was the mean change in visual acuity, with a noninferiority limit of 5 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart. The treatment interval was determined by a treat-and-extend protocol. The shortest interval was 4 weeks; and the longest, 12 weeks. The aim of this protocol was to investigate whether such an individually developed treatment regimen is efficacious and can minimize the number of recurrences with a fewer number of injections.

Patients and Methods

Men and women of 50 years of age or more with previously untreated active neovascular AMD in 1 eye and BCVA between 20/25 and 20/320 were included in the study. The diagnosis was confirmed by CNV leakage on fluorescein angiography (FA) and intraretinal and/or subretinal fluid as determined by OCT. Pigment epithelial detachments (PED) with no associated intraretinal or subretinal edema, as well as lesions comprising more than 50% blood and/or fibrosis were excluded. If it became necessary to treat the nonstudy eye during the course of the trial, then the same drug being used in the study eye was used in the nonstudy eye.

The treat-and-extend protocol connotes the following: Initial follow-up and injection with a 4-week interval until the macula is dry. When dry, then follow-up and injection will be increased by 2 weeks at a time. If the patient has a recurrence of wet AMD, then the interval is reduced by 2 weeks at a time until the macula is once again dry. The shortest interval is 4 weeks. When once again extending, the treatment interval shall not be as long as the interval of the original recurrence, as this could confer risk for new activity. Therefore further follow-up and injection occurs at the “ideal” interval, which is hereby defined as being 2 weeks less than that of the original recurrence. With this method, the patient receives an injection at each follow-up, presuming that no complications occur. The maximum interval is limited to 12 weeks.

Safety parameters will be evaluated, including incidence and severity of ocular and non-ophthalmological adverse events.

Conclusion

The 2-year results from LUCAS will be presented during the Subspecialty Day at AAO 2014.

References

VIVID/VISTA for Diabetic Macular Edema: Two-Year Results

Diana V Do MD on behalf of the VISTA-DME and VIVID-DME Study Investigators

I. Introduction
   A. Clinically significant diabetic macular edema (DME) is a leading cause of vision loss in patients with diabetes.
   B. Two Phase 3 trials were conducted to compare the efficacy and safety of 2 regimens of intravitreal aflibercept injection (IAI) with laser photocoagulation for treatment of DME.

II. Methods
   A. VISTA-DME and VIVID-DME are 2 similarly designed, double-masked, Phase 3 trials that randomized and treated 461 and 402 DME patients, respectively, to receive either IAI 2 mg every 4 weeks (2q4), IAI 2 mg every 8 weeks (2q8, following 5 initial monthly doses), or laser.
   B. The primary efficacy endpoint was the mean change from baseline in BCVA at Week 52.

III. Results
   A. The mean BCVA gain from baseline to Week 52 in the 2q4 and 2q8 groups vs. the laser group was 12.5 and 10.7 vs. 0.2 letters ($P < .0001$) in VISTA-DME, and 10.5 and 10.7 vs. 1.2 letters ($P < .0001$) in VIVID-DME, respectively.
   B. The corresponding proportion of patients who gained ≥ 15 letters from baseline at Week 52 was 41.6% and 31.1% vs. 7.8% ($P < .0001$) in VISTA-DME, and 32.4% and 33.3% vs. 9.1% ($P < .0001$) in VIVID-DME, respectively.
   C. The proportion of 2q4 and 2q8 patients vs. laser patients who had a ≥ 2-step improvement in the Diabetic Retinopathy Severity Scale score was 33.8% and 29.1% vs. 14.3% ($P < .01$) in VISTA, and 33.3% and 27.7% vs. 7.5% ($P < .001$) in VIVID.
   D. The mean reduction in central retinal thickness from baseline to Week 52 in the 2q4 and 2q8 groups vs. the laser group was 185.9 and 183.1 vs. 73.3 μm ($P < .0001$) in VISTA, and 195.0 and 192.4 vs. 66.2 μm ($P < .0001$) in VIVID.
   E. The most frequent ocular adverse events (AEs) were conjunctival hemorrhage, eye pain, and vitreous floaters.
   F. The most frequent non-ocular AEs included hypertension and nasopharyngitis, which occurred with similar frequency across treatment groups.
   G. The overall incidence of ocular and non-ocular AEs and serious AEs, including the Anti-Platelet Trialists’ Collaboration (APTC)-defined arterial thromboembolic events, was similar across treatment groups.

IV. Conclusions
   A. In both VISTA-DME and VIVID-DME, IAI demonstrated significant superiority in visual and anatomic endpoints over laser at Week 52, with similar efficacy in the 2q4 and 2q8 groups.
   B. IAI was generally well tolerated with no overall difference between treatment groups in serious systemic AEs, including APTC events.
Study Assessing Double-Masked Uveitis Treatment (SAKURA) Phase 3 Trial
Sunil K Srivastava MD

I. Introduction
A. Uveitis disease overview
   1. Epidemiology\textsuperscript{1-4}
      a. Uveitis incidence is between 17 and 52 per 100,000 person-years.
      b. The disease prevalence is 38 to 714 cases per 100,000 people, increases with age, and is more prevalent in females and people of European (white) descent.
   2. Burden of disease
      a. Uveitis is accountable for 3\%-20\% of legal blindness in the United States and Western world; 10\%-15\% in the United States.
      b. Uveitis may lead to vision-threatening complications such as cataracts, glaucoma, cystoid macular edema, retinal scarring, band keratopathy, and hypotony, among others.
      c. As uveitis is more predominant in younger patients and carries the risk of severe vision loss, there is potentially a greater socioeconomic impact than diseases affecting mostly older people.
   3. Current treatment options
      a. Guidelines for treatment include systemic corticosteroids for acute noninfectious uveitis as they are potent and rapidly effective.\textsuperscript{5-7}
      b. However, given the side effects of chronic corticosteroid use, steroid-sparing immunosuppressive agents are recommended for chronic therapy to minimize toxicities and reduce recurrence risk.\textsuperscript{6,7}
      c. Immunosuppressive agents such as antimetabolites (methotrexate, mycophenolate mofetil, azathioprine), T cell inhibitors (cyclosporine, tacrolimus, sirolimus), and alkylating agents (cyclophosphamide, chlorambucil) are used off label and are nonspecific to disease. All of these agents can have some severe systemic complications.\textsuperscript{6,7}
      d. Long-term local steroid therapy is available (fluocinolone acetonide implant). Complications of long-term local steroids include high rates of cataracts, glaucoma, and glaucoma surgery. The NEI MUST Study\textsuperscript{8,9} comparing systemic corticosteroid and immunosuppressive therapy with fluocinolone acetonide implant found the following:
         i. Visual acuity not significantly different between implant and systemic treatment arms ($P = .16$)
         ii. Implant associated with cataract surgery (80\%), elevated IOP (61\%), and glaucoma (17\%)
         iii. Systemic therapy: greater number of infections requiring treatment (0.60 vs. 0.36/person-year, $P = .034$)
         iv. Local therapy arm had fewer active patients at 1 year.
B. Rationale
   1. The current treatment options can cause adverse events, both systemic and ophthalmic, particularly with chronic use.
   2. Alternative treatments with improved efficacy, safety, and method of delivery are needed for patients that require therapy after acute steroid administration.

II. Overview of Sirolimus (DE-109)
A. Sirolimus is an immunosuppressive agent that works as an inhibitor of mammalian target of rapamycin (mTOR). It is currently being investigated for intravitreal use in posterior segment noninfectious uveitis (PSNIU).
B. Studies showed that when injected into the vitreous, DE-109 forms a solid depot and diffuses from the vitreous into the retina / choroid. A near steady-state concentration is maintained for ~2 months in the vitreous after injection of 220 µg in NZW rabbits.\textsuperscript{9}

III. SAKURA Clinical Program
A. Study design and methodology
   1. Phase 3, multinational, multicenter, randomized, double-masked study: The Safety and Efficacy of Intravitreal Injections of DE-109 (Three Doses) for the Treatment of Active, Non-Infectious Uveitis of the Posterior Segment of the Eye
   2. SAKURA 1 enrolled 347 patients. SAKURA 2 aims to enroll 250 patients and is currently enrolling.
B. Objective
   1. To evaluate the safety and efficacy of intravitreal injections of 44-µg, 440-µg, and 880-µg sirolimus
   2. To evaluate the long-term safety of multiple injections of 880-µg intravitreal sirolimus.
c. To evaluate the durability of effect of 880-µg intravitreal sirolimus
d. SAKURA 1 will focus on 44- and 440-µg doses, with primary endpoint at Month 5.
4. The principal eligibility criteria are as follows:
   Age ≥ 18 years, diagnosis of active noninfectious uveitis (NIU) of the posterior segment (investigator determined), vitreous haze (VH) score >1+ in study eye (modified SUN scale), BCVA ≥ 19 letters or 20/400 (study eye), vision ≥ 20/200 (fellow eye)
5. The exclusion criteria are uncontrolled glaucoma (evidenced by IOP > 21 mmHg while on medical therapy), active infectious uveitis, ocular or periocular infection, vision-compromising ocular diseases, lens opacities, previous vitrectomy, recent intraocular surgery
6. Subjects randomized to receive either 44-µg, 440-µg, or 880-µg intravitreal injection dose every 2 months.
7. The primary endpoint is percentage of study eyes with vitreous haze score of 0 at Month 5.
8. Secondary endpoints include percentage of patients with:
   a. VH score of 0 or 2-step reduction in vitreous haze score at Month 5
   b. VH score of 0 or 0.5+ at Month 5
   c. Tapered to prednisone dose ≤ 5 mg at Month 5
B. Results
1. The study was conducted in 15 countries across 103 sites in 348 study eyes of 347 subjects. Patient demographics will be shown, but baseline characteristics across treatment arms are comparable. The subject disposition will be shown.
2. Result of key efficacy endpoints
   a. Primary endpoints
      i. 22.8% of eyes in the 440-µg arm achieved vitreous haze score of 0, in comparison to 10.3% in the 44-µg arm and 16.6% in the 880-µg arm (P-value = .025).
      ii. Improvements from baseline in VH scores were seen as early as 2 weeks.
   b. Secondary endpoints
      i. At Month 5 the proportions of subjects in the 440-µg arm achieving a VH score of 0 or with 2-step improvement score was 28.1%, vs. 16.2% in the 44 µg arm (P-value = .039).
      ii. At Month 5, 52.6% of subjects in the 440-µg arm achieved a VH score of 0 or 0.5+, in comparison to 43.1% in the 880-µg arm and 35% in the 44-µg arm (P-value = .008).
   iii. 69 subjects entered the SAKURA study on oral corticosteroids. The tapering success rate in the 440-µg group was higher than that in the 44-µg group (76.9% vs. 63.6%) but this was not statistically significant.
3. Safety results
   a. Endophthalmitis: There were 0 cases of culture-positive endophthalmitis among the 3 study arms and 1 case of culture-negative endophthalmitis in the 880-µg arm.
   b. Noninfectious endophthalmitis: 0% in the 44-µg arm, 0.9% in 440-µg arm, and 3.4% in the 880-µg arm
   c. Glaucoma: 0.9% in the 44-µg arm, 0.9% in 440-µg arm, and 0% in the 880-µg arm
   d. Progression of cataract: 0.9% in the 44-µg arm, 1.8% in 440-µg arm, and 2.6% in the 880-µg arm
C. Summary and Conclusion
1. Intravitreal sirolimus is a novel, noncorticosteroid, local immunoregulatory therapy shown to be safe and effective for noninfectious uveitis of the posterior segment.
2. The SAKURA Study 1 has achieved its primary endpoints. Twenty-three percent of subjects treated with 440-µg intravitreal sirolimus achieved a VH score of 0 at Month 5. Fifty-three percent of subjects treated with 440-µg intravitreal sirolimus achieved a VH score of 0 or 0.5+ at Month 5.
References


How to Treat Uveitis

NOTES


Natural History of Geographic Atrophy: What Do I Tell My Patient?

Philip J Rosenfeld MD PhD

I prefer to stay positive when I talk to my AMD patients with geographic atrophy (GA). First, I start with the good news. I tell them their condition progresses slowly, and they don’t have to get injections into their eyes, at least not yet. Many respond by asking, “Isn’t it better to have the wet AMD rather than the dry AMD; after all, the wet AMD can be treated with injections and the injections improve vision, right?” I explain that it’s not that simple, that dry and wet AMD aren’t two separate diseases, but rather different stages of the same disease. I explain that everyone with AMD starts with dry AMD and the disease progresses slowly over decades, with only a minority of patients progressing from dry AMD to wet AMD. I tell them that, most likely, they’ll never need eye injections for wet AMD, and that, by the way, not everyone sees better after getting the injections. I explain that the injections stop the rapid vision loss from wet AMD, but even if the injections are successful, the best-case scenario is that the injections convert the wet AMD back to dry AMD. So, I reassure them that it’s always better to have dry than wet AMD, but that’s a little misleading.

While that’s good news for most AMD patients with early stage GA, there’s still plenty of bad news ahead, which I slowly weave into the conversation. I explain that GA is the loss of tissue (photoreceptors) in the back of the eye, and once these cells are lost, they can’t regenerate. I explain that the loss of this tissue is similar to losing the digital sensor or film in a camera. I explain that the eye is like a camera, and even though the camera’s lenses may be perfectly intact and the most powerful lenses available, the image can’t be recorded correctly if the digital sensor or film is damaged. So it is with the eye; I can prescribe the best possible pair of glasses, but the vision won’t improve.

Pathophysiology of Geographic Atrophy

The characteristic appearance of GA results from the loss of the photoreceptor layer, retinal pigment epithelium (RPE), and choriocapillaris. In most cases, GA first appears in the parafoveal location and progresses around the fovea and then through the fovea, with concomitant loss of central visual acuity. Early in the disease process, patients often complain of difficulty with glare, reading, and adjusting to dim light situations, even though the GA has not yet progressed through the foveal center. These complaints have been attributed to the presence of parafoveal scotomas from the GA and to dysfunctional rod and cone photoreceptors outside the area directly involved with GA. While the appearance of GA has been associated with the disappearance of drusen, GA can also appear in areas without pre-existing drusen.

The exact cause for the appearance and progression of GA remains elusive. Current theories to explain the appearance of GA include nutritional deprivation due to the thickened Bruch membrane and/or the presence of drusen, oxidative damage to the RPE, the toxic accumulation of lipofuscin within the RPE, inflammatory damage to the retina and/or RPE that may be mediated by the dysregulation of the complement system, and vascular insufficiency of the underlying choroid. Whether GA results from an initial insult to photoreceptors, RPE, or the choriocapillaris remains unknown.

The appearance and progression of GA has been extensively studied using reflectance fundus imaging, autofluorescence (AF) imaging, and spectral domain OCT (SD-OCT) imaging. These imaging strategies have provided some clues regarding the appearance and progression of GA. Autofluorescence imaging has identified different hyperautofluorescence patterns of the RPE, and these patterns have been associated with different growth characteristics of GA. SD-OCT has identified subretinal drusenoid deposits and abnormalities of the RPE and photoreceptors at the margins of GA that may be associated with the expansion of GA. However, none of these imaging strategies has reliably predicted an area in the macula where GA is likely to appear or predicted the growth of GA over 1 year once it appears.

To help predict where GA is likely to appear and grow, investigators have relied on functional testing of the retina. The loss of photoreceptors away from the edge of GA has been identified histopathologically, and dysfunctional photoreceptors have been detected away from the edge of GA using electrophysiology and microperimetry threshold testing. These histopathologic, electrophysiologic, and microperimetric findings in eyes with GA, along with the early visual function deficits and symptoms observed in patients even before GA develops, suggest that photoreceptor dysfunction precedes the appearance and progression of GA in some eyes. These findings would also suggest that an anatomic correlate should exist away from the margin of GA that could be visualized using SD-OCT imaging. Such an anatomic correlate could involve the photoreceptor layer. To test this possibility, we focused on the inner segment/outer segment (IS/OS) boundary of photoreceptors that can be easily visualized using SD-OCT imaging.

The Patient’s Perspective

Wherever GA appears in the macula, photoreceptors are lost and the patient will see a black spot in the vision. Once again, there’s the opportunity to apply a good news, bad news approach. The good news is that GA grows slowly and usually first appears away from the foveal center, and central vision is retained as long as the GA stays away from the central macula. The bad news is that GA will progress relentlessly through the central macula and cause significant impairment of vision and quality of life. Further, even before the central macula is lost, most patients experience debilitating symptoms. They report significant deficits in low luminance vision, reading, and the ability to adapt between bright and dim light situations. Fine detail discrimination and facial recognition are often impaired or lost and patients become constantly debilitated by glare. For those patients with GA involving the central macula, there’s mostly bad news. As their central vision becomes significantly impaired, they lose the ability to drive, and with it, their independence. The only good
news is that they will retain their peripheral vision and never go completely blind.

Unfortunately, there is even more bad news for patients with GA who still have good vision. We don’t have any effective treatment to stop the progression of GA. Currently, the only published and recommended treatments to slow the progression of dry AMD involve the use of oral supplements based on the AREDS2,24 a healthy lifestyle including cessation of smoking, and a diet rich in green leafy vegetables. But following these recommendations only slows the normal disease progression from dry to wet AMD and doesn’t slow the relentless enlargement of GA. As the disease progresses toward the central macula, the black spot or scotoma enlarges and becomes more obvious to the patient. We suggest that patients use bright light when trying to read, as well as low vision aids to help magnify the images. However, the GA will continue to enlarge.

Clinical Trials for Geographic Atrophy

Patients with good visual acuity and non-central GA have two options. They can remain uninvolved and hope their disease progresses slowly, or they can get involved in clinical trials designed to test novel therapies in the hope of slowing down their disease. Often times, one eye is more advanced than the other, and this gives the patients an idea of what to expect if nothing is done. While clinical trials offer no guarantees and some patients can’t tolerate the uncertainty of receiving an experimental therapy or the idea of getting a placebo, trials do offer patients the opportunity to do something rather than just waiting for their vision to deteriorate. In the past, clinical trials for wet AMD offered the opportunity for patients to receive novel, effective therapies years before they became commercially available.

While it’s possible that current clinical trials might successfully test drugs that can slow or stop the enlargement of GA, it is unlikely that any treatment will restore vision in eyes with central GA. There are still good reasons for patients with vision loss and central GA to participate in clinical trials: Since AMD is a bilateral disease, these patients are motivated to participate in the hope of identifying effective therapies that could slow disease progression in their fellow eyes. In addition, patients with central GA may participate with the hope of helping family members afflicted with the disease or at risk of developing AMD. Finally, many patients participate for purely altruistic reasons to help society as a whole. Whatever their motivation, the participation of patients in clinical trials should be encouraged, as it’s the only way to achieve a breakthrough therapy and prevent blindness from GA.

Currently, several promising therapies are being investigated in ongoing clinical trials or in trials that will begin in the near future. These therapies include drugs that suppress inflammation, in particular drugs that inhibit complement activation, drugs that provide neuroprotection, drugs that modulate the visual cycle, and cell therapies designed to slow disease progression. The following trials and tables are meant to highlight the ongoing trials that are relevant to our patients with GA.

Drugs That Suppress Inflammation (see Table 1)

The complement cascade is likely to play a role in the pathogenesis of dry AMD. Studies demonstrating an association between AMD and certain at-risk alleles of genes encoding complement proteins have led to strategies that inhibit complement activation by targeting complement components.25 The complement inhibitor eculizumab (Soliris) is a humanized monoclonal antibody derived from a murine anti-human C5-specific antibody, and this drug prevents complement activation and formation of the membrane attack complex (MAC) by binding C5 and preventing the cleavage of C5 into C5a and C5b. Intravenous eculizumab was studied for the treatment of GA, but it failed to slow the progression of GA enlargement.26,27

More recently, intravitreal FCFD45145 (lampalizumab), an antigen-binding fragment (Fab) of a humanized, monoclonal antibody directed against complement factor D, was studied in trials to slow the enlargement of GA. Lampalizumab inhibits Factor D, which is a rate-limiting enzyme involved in the activation of the alternative complement pathway. A Phase 1 study demonstrated that the intravitreal injection of the drug in a single dose was safe and well tolerated up to a dose of 10 mg with no related ocular or systemic adverse events.28

The positive results of a Phase 2 clinical trial (NCT01602120), designed to assess the long-term safety and tolerability of repeated intravitreal injections of lampalizumab for the treatment of GA, were released in 2013 at several meetings. Subjects received intravitreal injections of lampalizumab (10 mg) either monthly or every other month for 18 months. This randomized, multicenter, single-masked, controlled study showed a positive outcome in slowing the progression of GA in eyes injected every month with lampalizumab. The drug resulted in a 20.4% reduction rate in the growth of GA as assessed with fundus autofluorescence at 18 months (P < .1170, statistically significant prespecified protocol criteria). No effect was observed in the group treated every other month. In a subset of patients carrying the at-risk allele for complement factor I (CFI), which was present in 57% of the subjects, the treatment effect increased to a 44% reduction in growth rate (P < .005), compared with a 20.4% reduction found in all the monthly treated subjects at 18 months. In addition, when subjects with this CFI at-risk allele and baseline BCVA of 20/50-20/100 were compared with sham-injected subjects, the reduction in the growth rate of GA increased to 54% (P < .005). This drug is about to enter a large Phase 2/3 trial, and enrollment should be under way in the second half of 2014.

Another complement inhibitor is LFG316, which is a fully human antibody that also targets the complement factor C5. A Phase 1 dose escalation trial has been completed (NCT01255462), and a Phase 2 trial (NCT01527500) to evaluate the ability of LFG316 to reduce the growth of GA with monthly intravitreal injections during a 12-month period is ongoing, with results expected in the second half of 2014.

Iluvien (fluocinolone acetonide) is being studied as a possible treatment for patients with bilateral GA due to AMD in a Phase 2 clinical trial (NCT00695318). The randomized, double-masked, interventional study is evaluating the safety and efficacy of the fluocinolone acetonide intravitreal implant (0.2 and 0.5 µg/day) compared with sham injection for reducing the growth rate of GA. This study is not enrolling patients.

Oracea is a tetracycline derivative approved for treatment of inflammatory lesions of rosacea in adults and contains 30 mg immediate and 10 mg delayed-release beads of doxycycline. Additional drug activities thought to be beneficial in AMD include reducing reactive oxygen species, inhibiting metalloproteinases that are involved in the breakdown of the barrier between the RPE and the Bruch membrane, inhibition of caspase activation and prevention of cell death, prevention of complement activation, and inhibition of cytokine production through its effect on microglia and T-cell activation. It is well tolerated, has an excellent long-term safety profile demonstrated by mul-
multiple studies, has efficacy toward inhibition of chronic systemic inflammation, and has demonstrated activity against molecular pathways that are suspected to be important in the evolution of dry AMD.

Neuroprotective Drugs (see Table 2)

Neuroprotective drugs appear to act by preventing the apoptosis of viable RPE cells and photoreceptors and preserving the macular function. Brimonidine tartrate is an alpha-2 adrenergic receptor agonist and is the same substance that is available as an eye drop at different concentrations for the treatment of open-angle glaucoma. Brimonidine has been shown to protect photoreceptors from retinal degeneration in animal models by stimulating the production of neurotrophic factors, but the precise mechanism is still unknown. Brimonidine tartrate was formulated as an intravitreal implant, and this biodegradable delivery device was used in a clinical trial in an attempt to slow the progression of GA in eyes with AMD. Since the results of the Phase 2 trial (NCT00658619) showed encouraging results, a second study is under way (NCT02087085).

GSK933776 is a humanized monoclonal antibody that is directed against the N-terminal sequence of amyloid-β. A Phase 2 multicenter, randomized, double-masked, placebo-controlled study is under way in patients with GA (NCT01342926). The primary endpoint of the study is the change in the area of GA compared with baseline. Patients are treated monthly with GSK933776 (3–6 mg/kg intravenously) or placebo and then followed for 18 months.

Drugs That Increase Choroidal Blood Flow (see Table 3)

Recent studies have investigated whether a decrease in choroidal circulation may be involved in the development and progression of AMD. This theory presumes that the administration of vasodilators may restore the choroidal blood flow, avoiding the release of vascular endothelial growth factor (VEGF) and the consequent neovascularization. MC-1101 is a topically administered eye drop developed to increase choroidal blood flow. It was originally developed as an antihypertensive drug, and its mechanism of action is associated with the generation of nitric oxide (NO) to produce vasodilation. A Phase 1 trial (NCT01013376) has shown that MC-1101 is safe and well tolerated in humans. A Phase 2/3 trial (NCT01601483) is currently ongoing to evaluate the efficacy and safety of topical 1% MC-1101 administered 3 times a day.

Visual Cycle Modulator (see Table 4)

The goal of visual cycle modulation is to reduce the accumulation of toxic fluorophores in the RPE and prevent the loss of the RPE and photoreceptors. ACU-4429 (emixustat hydrochloride) is a nonretinoid molecule developed to be a selective visual cycle modulator that targets rod cells. The oral administration of ACU-4429 is intended to reduce the accumulation of toxic products by binding and inhibiting the activity of the isomerase known as the RPE-specific 65-kDa protein (RPE65), thereby preventing the conversion of all-trans-retinol to 11-cis-retinol. However, the side effects of reducing the levels of 11-cis retinol include difficulties with dim light vision, dark adaptation, and dyschromatopsia. A Phase 1 trial (NCT00942240) with healthy volunteers compared oral emixustat with placebo and demon-
strated that all the doses of emixustat (5, 10, 20, 30, and 40 mg) were well tolerated, and no serious adverse effects were identified. The visual symptoms presented during the study were transient. A subsequent Phase 2 study (NCT01002950) enrolled 72 subjects with GA and has been completed, but no results have been published as yet. A large Phase 2/3 trial (NCT01802866) is designed to compare the efficacy and safety of ACU-4429 with placebo and to determine whether the drug reduces the rate of progression of GA in subjects with dry AMD. This study is fully enrolled.

**Cell Therapies (see Table 5)**

Cell therapy is also emerging as a treatment approach for dry AMD. Stem cell therapy is being investigated as a way to replace damaged RPE cells, prevent progression of the disease and the deterioration of the photoreceptors, and sustain visual function. MA09-hRPE, RPE cells derived from embryonic stem cells, have been transplanted to treat patients with dry AMD and Stargardt disease. Two clinical trials (NCT01344993 and NTC01674829) are currently under way to evaluate the safety and tolerability of subretinal transplantation of human embryonic stem cell MA09-hRPE in eyes with GA secondary to AMD and Stargardt disease. Another trial using the same cells is under way in Korea (NCT01674829). A Phase 1/2 study of subretinal transplantation of human central nervous system (HuCNS-SC) stem cells (NCT01632527) in eyes with GA, designed to evaluate the safety and efficacy of this treatment, is currently under way.

**Summary**

Patients with GA need to be given hope and encouraged to participate in clinical trials. Currently there are no therapies that can slow the growth of GA. Several drugs and cell therapies are under investigation for the treatment of GA in dry AMD. These drug and cell therapies hold great promise to someday slow the disease progression. However, to prove the effectiveness of these therapies, it is crucial that patients participate in these clinical trials.

**References**


Notal Preferential Hyperacuity Perimeter

Susan B Bressler MD

Introduction

Visual acuity (VA) at the time that intravitreal anti-vascular endothelial growth factor (VEGF) is initiated for neovascular AMD is an important predictor of VA 1 and 2 years following initial treatment. Eyes that begin therapy with VA of 20/40 or better have a greater probability of retaining VA at this level following therapy compared to the probability that eyes that begin therapy with lower levels of VA will do so. Current monitoring of patients with AMD at high risk of developing CNV in the ophthalmic community results in fewer than 50% of patients maintaining VA of ≥20/40 at CNV diagnosis. Identifying new strategies for early detection of CNV, before vision decreases, to optimize VA outcomes following anti-VEGF therapy is critical to reducing vision impairment associated with this disorder.

Notal Vision, Ltd. (Tel Aviv, Israel) developed a home monitoring device that evaluates the macular visual field using preferential hyperacuity (or Vernier acuity). The device potentially detects the earliest functional abnormalities associated with CNV before the patient realizes they have symptoms. Utilizing a telemonitoring methodology, regular test results are reviewed at a monitoring center that alerts physicians to test findings that may represent progression from non-neovascular to neovascular AMD. Patients are then encouraged to promptly schedule an eye exam to facilitate CNV diagnosis.

The HOME Study

This multicenter, randomized, controlled clinical trial was jointly sponsored by the National Eye Institute and Notal Vision to determine whether home monitoring with the ForeseeHome device (FH) in conjunction with standard monitoring techniques resulted in earlier detection of CNV, reflected as better VA at CNV detection, when compared to standard care alone (SC). Standard care monitoring techniques, utilized in both arms of the trial, reflected the standard care of retinal specialists at 44 participating clinical centers in the United States in regard to frequency of prescheduled visits and instructions in self-administered monocular vision checks (which may have included Amsler grid). Participants randomly assigned to FH were asked to test daily.

Participants

1970 participants 53 to 90 years of age at high risk of CNV developing were screened. Of these, 1520 (77%) participants with a mean age of 72.5 years and mean VA of 20/25 (20/15-20/100) were enrolled. Bilateral large drusen were present in 83%, whereas the remainder had advanced AMD in a nonstudy eye and large drusen in their fellow study eye.

Results

The trial was stopped early following a recommendation of the Data and Safety Monitoring Committee based on 51 and 31 CNV events in the 763 FH and 757 SC participants, respectively, and a significant reduction in VA loss among the FH participants when compared to SC. During a mean follow-up of 1.4 years, participants in the device arm lost fewer letters from baseline to CNV detection (median: −4 letters; interquartile range [IQR], −11 to −1) compared with participants assigned to standard care (median, −9 letters; IQR, −14 to −4 letters; P = .021). Among the 35 of the 51 CNV events that developed among FH participants that had successfully established a baseline with the device and were using the FH a minimum of twice weekly, the median VA loss was −3 letters (IQR, −9 to −1 letters).

Secondary VA outcomes were consistent with the primary result, including a greater proportion of FH participants compared with SC participants at CNV detection that retained VA of 20/40 or better (87% vs. 62%, P = .014). All CNV lesion events identified by the following retinal specialists were to have stereo color photographs, fluorescein angiography (FA), and OCT following standardized protocols evaluated by an independent reading center masked to treatment assignment. Sixty-seven (82%) of these events were confirmed by the reading center: 34 on OCT and FA, 25 on OCT only, and 8 on FA only. Lesion size tended to be smaller among the FH CNV events among eyes confirmed on FA (median 0.69 disc areas FH vs. 0.99 disc areas SC), while among the OCT-confirmed cases both retinal thickness and the retinal pigment epithelial complex were thinner among FH CNV events than among SC CNV events. VA loss at CNV events confirmed by the reading center on either OCT or FA always favored the FH participants over SC participants (−4 vs. −12 letters, P = .006 among FA confirmed cases, −3 vs. −9 letters, P = .005 among OCT-confirmed cases).

The FH and SC participants had an average of about 2 visits prescheduled per year as part of the standard practice of their following ophthalmologists. Among these visits, CNV was seldom detected, occurring in <1% of these visits, with median VA loss of about 8 letters from baseline. In contrast, device or symptom realization triggered 318 additional office visits among FH participants, during which CNV was detected in 11.6% of these visits (95% CI, 8.1%, 15.2%), with median VA loss of 3 letters from baseline. In the SC group, 65 additional visits were prompted by symptom realization, resulting in CNV detection rate of 26% of these visits (95% CI, 15.5%, 36.8%) with median VA loss of 11.5 letters from baseline.

False positive device triggered alerts occurred in 161 (21%) FH participants, 54 of whom (7% of all FH participants) had more than 1 false positive alert visit. Extrapolation of the per-patient false positive rate estimates about an average of 1 false positive device triggered office visits for every 4.2 monitoring years.

Conclusions

Individuals with large drusen who are at high risk for neovascular AMD are likely to benefit from the ForeseeHome monitoring strategy. Among individuals who qualified to use the device and had VA of 20/60 or better, CNV was detected in the presence of better VA preservation when the FH strategy was pursued as compared to SC. The CNV lesions at time of diagnosis were small when present on FA and associated with more subtle OCT findings than those ordinarily detected by SC. The detection rate of CNV was 16 times greater at visits prompted by the FH strat-
egy than prescheduled visits, in addition to identifying the CNV in the setting of minimal vision compromise. It is anticipated that these findings will increase the likelihood of better long-term visual acuity outcomes following anti-VEGF therapy in eyes with early CNV detection facilitated by the FH strategy.

**Selected Readings**


Smartphone-Based Home Monitoring

Anne Fung MD

I. Prevalence of Mobile Smart Phones (iPhone/Android)
   A. 1.4 billion smartphones active around the world (as of January 2014)
      1. 58% of American adults are smartphone users.¹
      2. 49% of U.S. adults aged 50-64 years and 19% of U.S. adults 65 years and older have a smartphone.¹
      3. Smartphone usage is relatively consistent across various races/ethnicities and socioeconomic groups in the United States.¹
      4. Mobile media accounts for around 12% of Americans’ media consumption time.²

II. Why consider the use of mobile vision apps?
   A. Smartphones are ubiquitous in modern business and daily life.
   B. Smartphone vision applications have the potential to allow patients to efficiently monitor their vision on a regular basis.³⁻⁵ Large scalability due to smartphone prevalence across many different age groups and socioeconomic classes.
   C. Mobile care can empower patients to check their vision regularly and have better visual outcomes.³ This technology opens pathways of communication between patients and physicians.
   D. As the technology-prone generations age (around 18 to 44 years of age) and eye disease becomes more prevalent among that demographic, mobile health care will be increasingly important and relevant. Importance of developing and implementing apps that can meet this rising need.
   E. Smartphone-based technology may also ease burden for caregivers who assist in patient monitoring

III. The DigiSight (SightBook) Approach
   A. The SightBook application (DigiSight Technologies, Inc.; Portola Valley, Calif.) is a smartphone-based electronic VA (SEVA) testing algorithm (see Figure 1).
   B. This tool can be used to collect real-time, high-frequency patient visual data used for therapy management.
   C. All data are uploaded in real time to a cloud database that helps to establish a direct physician-patient relationship outside of regularly scheduled office visits.
      1. Physician’s view
         a. Patient data shared in real time with physician
         b. App generates alerts for vision loss and non-compliance.
      2. Patient’s view
         a. Access to personalized tests as prescribed by doctor
         b. Ability to monitor VA at home
         c. Receives reminders as set by physician
         d. Patient has another tool to detect disease progression and connect to physician.
   D. 10 standard vision tests, not just VA
      1. SightBook uses a simple algorithm to check for patient VA in a variety of situations.
      2. App dynamically recognizes when patients score worse or better than their last tests and can ask patients to repeat tests to confirm data.
   E. Several clinical trials have been conducted to validate SightBook’s methodology.⁶⁻⁸ Of note:
      1. Coady et al in 2011⁶
         a. This study evaluated the relationship between standard Snellen VA and various tests of near VA with a printed card and a back-illuminated liquid crystal display (LCD).
      b. This prospective study included 60 patients with VA better than 20/400. Patients were...
divided into 3 groups: calibration group \((n = 10 \text{ with macular disease})\), test group \((n = 30 \text{ with macular disease})\), and the control group \((n = 20 \text{ patients with no macular disease})\).

c. To calibrate the LCD screen, near vision was measured in the calibration group via Rosenbaum near card and via iPod-based back-illuminated LCD with various levels of contrast and fonts of various sizes. Font sizes on the LCD were adjusted to match readability of the Rosenbaum card. The calibrated LCD was used to evaluate the test and control groups.

d. This study found that measuring near VA and related visual function using a calibrated LCD screen was a viable platform on which to evaluate VA.

2. Yu et al, 2014

a. The study by Yu et al evaluated the use of the SEVA testing algorithm for remote monitoring and clinical research and its test-retest reliability compared with standard Early Treatment for Diabetic Retinopathy Study (ETDRS) testing.

b. This study included 210 eyes \((n = 210 \text{ patients})\), 80 with no eye disease, 35 with cataracts, 55 with diabetic retinopathy (DR), and 40 with AMD.

c. Test-retest reliability was high (intraclass correlation coefficients = 0.977 of all patients, 0.980 of subjects with no eye disease, 0.957 of AMD, 0.966 of cataract, 0.970 of DR; 95% limits of agreement ± 0.20 log MAR).

d. SEVA was strongly correlated with:
   i. Near VA with Good-lite LEA numbers chart
   ii. Distance VA by ETDRS

e. In addition, contrast sensitivity measured using SightBook was compared with conventional charts: Functional Acuity Contrast Test (FACT) and Contrast Sensitivity Testing System CSV-1000 (VectorVision) in 15 normal and 15 AMD patients.

f. In all categories of patients, the SightBook measurements were highly reproducible (SD/mean = 0.02-0.04), and closely correlated with the standard chart measurements (All \(R^2>0.86, P < .001\)).

g. SightBook application was found to have high test-retest reliability and good agreement with ETDRS distance VA and standard near vision testing.

F. High frequency approach allows for a robust clinical data stream. Stresses patient engagement and makes earlier detection of disease progression a possibility.

IV. The Vital Art and Science Approach (myVisionTrack, Vital Art and Science, Inc.; Richardson, Tex.)

How myVisionTrack Works

Figure 2. myVisionTrack’s algorithm for testing visual acuity (Vital Art and Science, Inc., 2014). Reprinted with permission.

A. myVisionTrack is based on a shape discrimination algorithm.

1. Drusen or macular edema reduces patient’s pattern discrimination sensitivity.

Maculopathy makes it difficult for patients to perform tasks that require global visual integration

2. Such as reading text.

3. Four circles – touch the one with distortion (see Figure 2)

   a. Uses fully/partially modulated or unmodulated circular Gaussian patterns as stimulus.

   b. The circles are laid out at random and users must differentiate between them with the device at arm’s length.

   c. Ability to function well requires healthy eyes (ie, no drusen or maculopathy).

4. 10-minute test done 2 times weekly or at physician’s discretion.

B. A study by Wang et al found results from myVisionTrack correlated well with VA.

1. Study included 100 subjects (27 with normal vision, 37 with AMD, and 36 with DR) with VA 20/100 or better.

2. The handheld shape discrimination hyperacuity (hSDH) test on a mobile device was found to be comparable to PC-based testing methods: \((r = 0.88, P < .0001; \text{slope of linear regression} = 0.91; 95\% \text{ CI}, 0.81-1.01)\).  

3. For subjects with VA of 20/100, the hSDH was also found to be significantly correlated with ETDRS VA \((r = 0.78, P < .0001; \text{slope of linear regression} = 1.05; 95\% \text{ CI}, 0.88-1.22)\) and Pelli-Robson letter CS \((r = 0.77; P < .0001; \text{slope of linear regression} = 1.01; 95\% \text{ CI}, 0.84-1.18)\).
4. Additionally, mVT scores were shown to reflect the severity of a patient’s eye disease (F>24, \( P < .0001 \)).

5. mVT data highlights more vision deficits than VA for patients whose vision is better than 20/32.

C. Results from each test are stored on a cloud database for patient and physician access. Patients can track progress from test to test and show their results to their physicians.

D. Kaiser et al\(^3\) in 2013 showed that 84% of patients using mVT consistently tested their vision once or more times a week. This study showed benefits of using a mobile Health Management Tool (HMT).

E. As of Feb 2013: by prescription only. Recently FDA cleared (http://myvisiontrack.com/myvisiontrack/myvisiontrack-overview/).

F. Value is in engaging patients to do their own disease tracking. About increasing compliance to create more timely treatments and improve clinical outcomes.

V. Alternative Approaches and Future Directions

There are many other vision apps currently available on the App store.

A. These include CVTlite, Visiontest, Eyehandbook, Amsler Chart, Eyechart

B. However, none of these applications offer the same robust cloud support for patient data.

References


Genetics and Risk of AMD

Emily Y Chew MD

Introduction
Age-related macular degeneration (AMD) is a complex disease with both heritable and environmental risks. Epidemiological studies demonstrated an increase in the risk of AMD with increasing age and smoking, and a protective effect of diet replete with fatty fish and green leafy vegetables. Since 2005, when complement factor H was demonstrated to be a major gene associated with AMD, genetic studies of AMD have increased exponentially as a direct result of tremendous gains from the Human Genome Project, genome-wide association studies, and the rapid development of other technology. Researchers have now identified 19 susceptibility loci that may explain more than 50% of the risk of AMD developing. These studies have pointed to biological pathways that may contribute to AMD pathogenesis, including the alternative complement activation, high-density lipoprotein cholesterol transport and metabolism, extracellular matrix integrity, and cell adhesion and angiogenesis.

Given this marked increase in genetic data, what is the role of genetic information in clinical practice? How do we incorporate these new data into everyday clinical practice? Can we predict who will develop the disease and who will progress? How will this genetic information help us manage our patients? More importantly, when should we be considering genetic testing for AMD?

Clinical Questions

Will genetic testing aid in diagnosis?
Currently, the diagnosis of AMD is a clinical one that includes a number of imaging modalities to help stage the severity of the disease. Specifically, the onset of neovascular AMD is particularly important to diagnose because of the importance of timely administration of intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents.

The complex disease of AMD is heralded by the hallmark of large drusen and the natural course of the growth and regression of drusen, which lead to late AMD, geographic atrophy, or neovascular AMD. However, in certain ethnic groups, drusen may not be a prominent feature of the disease. Would genetic testing be important for those without the hallmark drusen? Although complement factor H (CFH) may be 1 of the 2 important genes involved in the pathogenesis of AMD, the distribution of CFH varies in different racial groups. This is an important factor when considering genetic testing on a global scale. Many other factors need to be considered. For example, without a good preventive therapy, how would such genetic testing be helpful? How would one interpret the genetic testing, and would we need genetic counselors in our practices?

Will genetic testing assist in prediction of progression to late AMD?
Numerous researchers have evaluated a number of AMD-associated genes in addition to known risk factors to develop algorithms to help predict the future onset late AMD. Using the data from the Age-Related Eye Disease Study, the common polymorphisms in the gene CFH and LOC387715 (Chromosome 10) were evaluated for their role in the progression to late AMD, while adjusting for known AMD risk factors, such as smoking, body mass index, and AREDS supplements. The CFH and LOC387715 polymorphisms were each independently associated with progression from early or intermediate AMD to late AMD, neovascular or geographic atrophy. The odds ratios (ORs) were 2.6 (95% CI, 1.7-3.9) for CFH and 4.1 (95% CI, 2.7-6.3) for LOC 387716 for the homozygous risk genotype. The effect of LOC387715 was stronger for progression to neovascular disease (OR, 6.1; 95% CI, 3.3-11.2) compared with geographic atrophy (OR, 3.0; 95% CI, 1.4-6.5). Again using data from the AREDS study, investigators evaluated the role of genetics in progression to geographic atrophy. No association was found between growth rate and genotype for variants in CFH, C2, C3, APOE, and TLR3 genets. For LOC387715, there was a nominally significant association of geographic atrophy after Bonferroni adjustment (to account for multiple comparisons), but secondary analyses of the growth of geographic atrophy did not substantiate this finding.

In another attempt to use the genetic markers for predicting progression, the investigators designed a risk assessment model for the development of late AMD by including the phenotypic, demographic, environmental, and genetic risk factors (CFH Y402H and ARMS2 A69s), again using the AREDS study population. The model using Cox proportional hazards analyses worked well with good discrimination (C statistics = 0.87) and good overall performance (Brier score at 5 years = 0.08). The assessment model worked well with or without the genetic component.

The general conclusion is that genetic testing may be important, but that currently this does not add to the power derived from the phenotypic, demographic, and environmental factors in predicting the progression to late AMD.

Will genetic testing be important in the treatment of AMD?
This question has been evaluated in persons treated with anti-VEGF therapy. Numerous studies have evaluated the association of genetic testing and treatment with anti-VEGF drugs for neovascular AMD with retrospective analyses. There have been several studies with varying outcome variables and duration, resulting in no clear consensus about this association. Genetic information has not added to clinical factors such as visual acuity at baseline, lesion size, age, and interval between symptoms and treatment that appear to be important in determining the visual outcomes following treatment. Thus it is not necessary to add the genetics currently to the treatment of neovascular AMD with anti-VEGF therapies.

Klein et al evaluated possible genetic predictors of response to treatment with the AREDS supplement. Included in the analyses were all 867 AREDS participants with intermediate AMD (large drusen or extensive medium drusen in one or both eyes) or late AMD in one eye, and for whom DNA was available. The baseline AMD severity levels in these 867 individuals matched
guidelines for therapy with AREDS supplements. Single nucleotide polymorphisms (SNPs) in the $CFH$ (p.Y402H, rs1061170) and $ARMS2$ (p.A69S, rs10490924) genes were genotyped. Evidence for a possible interaction between the $CFH$ genotype and the benefit of treatment with antioxidants plus zinc was detected. Individuals with the homozygous nonrisk genotype for $CFH$ (TT) had a greater reduction in progression to late AMD than those with the homozygous risk genotype (CC), 68% vs. 11% ($P = .03$). There was no significant interaction between $ARMS2$ p.A69S genotype and treatment with any AREDS supplement regimen. Results of their study led Klein et al. to conclude that AREDS supplements were associated with a reduction in progression to late AMD in all genotypic groups, and that neither antioxidant alone nor zinc alone was superior to the combination of antioxidants and zinc in reducing progression to AMD in any genetic group. Although evidence for differences in treatment response to AREDS supplements for individuals with different genotypes was observed, the results for all groups were in the direction of a treatment benefit. These findings, together with the need for replication data and corroborative functional studies and the lack of available alternative interventions, led the authors to conclude that routine genetic testing was not indicated prior to prescribing AREDS supplements.

A more recent study by Awh et al. suggested that the administration of AREDS supplements should be modified in certain subgroups of patients based upon their $CFH$ and $ARMS2$ genotypes. This study examined a subset of the AREDS participants ($n = 995$) for whom DNA has been collected. We undertook a study to replicate these findings.

Of the 1237 genotyped AREDS participants of white/European ethnicity, 385 (31.1%) developed late AMD during the mean follow-up period of 6.6 years. As previously demonstrated, both $CFH$ genotype ($P = .005$), $ARMS2$ ($P < 0.0001$) and supplement were each individually associated with progression to late AMD. An interaction analysis found no evidence that the relative benefits of AREDS supplementation varied by genotype. Analysis of (1) $CFH$ rs1061170 and rs1410996 combined with $ARMS2$ rs10490924, with the 4 randomly assigned arms of AREDS supplement and (2) analysis of the combination of $CFH$ rs412852 and rs3766405 with $ARMS2$ c.372_815del443ins54 with the AREDS components resulted in no interaction ($P = .06$ and $P = .45$, respectively, before multiplicity adjustment).

The AREDS supplements reduced the rate of AMD progression across all genotype groups. Furthermore, the genotypes at the $CFH$ and $ARMS2$ loci did not statistically significantly alter the benefits of AREDS supplements. We found no statistically significant interaction between $CFH$/$ARMS2$ genotype and treatment with AREDS supplement, as determined by progression to late AMD in these retrospective analyses of the randomized controlled clinical trial. The findings from our study did not support the conclusions of Awh et al. that recommended altering the composition of AREDS supplements based upon an individual’s $CFH$ and $ARMS2$ genotypes, but they were similar to the recommendations of Klein et al. against routine genotyping prior to prescribing AREDS supplements. These data will be presented at the meeting.

Conclusion

The genetic information associated with AMD is important for research, and its clinical use is evolving. The Academy’s Task Force on Genetic Testing has made numerous suggestions regarding the genetic of ocular diseases, specifically those with monogenic disease. However, for the complex disease of AMD, the following suggestion was made in their recommendations:

Avoid routine genetic testing for genetically complex disorders like age-related macular degeneration and late-onset primary open-angle glaucoma until specific treatment or surveillance strategies have been shown in 1 or more published clinical trials to be of benefit to individuals with specific disease associated genotypes. In the meantime, confine the genotyping of such patients to research studies.

Genetic AMD testing for research purposes is definitely encouraged. The need for genetic testing for AMD for either prediction of future development or progression or the genetic influence on AMD therapies will require further research, including clinical trials that will test the use of genetic information in therapeutic trials.

References

Complement Inhibition
As a Potential Treatment for Geographic Atrophy

Carl D Regillo MD FACS

Introduction
Geographic atrophy (GA) is an advanced form of AMD characterized by loss of the retinal pigment epithelium in the macula that can lead to profound and irreversible visual acuity decreases if it progresses to involve the center of the fovea. Patients with earlier stages of GA typically experience visual function deficits, even before visual acuity is affected. The underlying pathophysiology of GA is not completely understood; however, complement hyperactivity leading to overactivation of the immune system and chronic inflammation in the macula is thought to be a contributing factor. Complement factors such as CFH and CFI are negative regulators of the alternative complement pathway that work together to deactivate C3b and halt the cascades that trigger proinflammatory responses and cell death.

The Complement System
The complement system is the key driver of the innate immune system. Activation of the complement system may be initiated by 1 of 3 biochemical pathways, including the classical, lectin, and alternative pathways. The classical pathway is driven primarily by the formation of antibody-antigen complexes, while the lectin pathway is activated by polysaccharides on microbial surfaces. Unlike the classical and lectin pathways, the alternative pathway is triggered by surface pathogens and does not rely on the formation of an immune complex. Each pathway converges on the cleavage of complement component C3 to C3b, which is a central step in complement activation and formation of the membrane attack complex (MAC).

Complement activation through the alternative pathway is initiated through the continuous hydrolysis of C3 to C3b. Complement factor B (CFB) binds to C3b to form the C3bB complex. Complement factor D (CFD), a rate-limiting enzyme in the alternative complement pathway, in turn cleaves the C3bB complex to form active C3 and C5 convertases. Complement factor H (CFH) and complement factor I (CFI) are negative regulators of the alternative complement pathway that work together to deactivate C3b and halt the cascades that trigger proinflammatory responses and cell death.

The Role of the Complement System in AMD
Dysregulation of the complement system is thought to play an important role in the development and progression of AMD. A number of complement activation products have been identified in drusen, including C3a, C5a, C5b-9 (ie, the MAC), and CFH. In addition, a strong genetic correlation exists between the risk of AMD and variations in genes encoding complement pathway proteins. CFH was the first complement gene shown to be associated with AMD risk. Additional genetic analyses, including a recent AMD gene consortium meta-analysis comprising more than 17,100 patients with advanced AMD and over 60,000 controls, identified genetic polymorphisms in complement pathway loci associated with advanced AMD risk, including complement component 2 (C2), C3, CFB, CFH, and CFI. Rare variants in CFI have recently been shown to contribute to the pathogenesis of AMD through dysregulation of alternative complement activation.

Investigational Agents Targeting the Complement Pathway
Currently, several complement inhibitors targeting various points along the complement pathway are being investigated for the treatment of GA, but none are yet approved. C5 inhibitors include eculizumab (a humanized monoclonal antibody; Alexion), LFG-316 (a fully human, full-length monoclonal antibody; Novartis/Morphosys), and ARC-1905 (an aptamer; Ophthotech). Eculizumab was evaluated in the Phase 2 COMPLETE Study (NCT00935883); however, intravenous administration of this C5 inhibitor did not significantly slow GA growth rate in patients with AMD at the 6-month endpoint or after an additional 6 months of follow-up after treatment cessation. LFG-316 is currently being investigated in a Phase 2 study in patients with GA. Plans for initiating a Phase 2/3 trial of ARC-1905 are reported to be under way. Further investigations into the C3 inhibitor, POT-4 (a cyclic peptide; Alcon) are being considered.

An additional complement inhibitor in advanced stages of clinical development is lampalizumab, a humanized, monoclonal, antigen-binding fragment that specifically inhibits the alternative complement pathway by targeting CFD (Genentech, a member of the Roche Group). The safety, tolerability, and evidence of activity of lampalizumab in patients with GA was assessed in the MAHALO Phase 2 trial (NCT01229215). Lampalizumab MAHALO Phase 2 Study Results
MAHALO was a prospective, multicenter, randomized, single-masked, sham-injection-controlled study in which 129 patients aged 60-89 years with GA secondary to AMD were randomized 2:1:2:1 to lampalizumab 10 mg monthly, sham monthly, lampalizumab 10 mg every other month, or sham every other month. The sham arms were pooled for the analyses. The primary endpoint was change in GA area from baseline to Month 18, as assessed by fundus autofluorescence imaging. The relationship between specific genetic polymorphisms associated with GA characteristics and lampalizumab treatment response was also explored.

In total, 123 patients received ≥ 1 sham or lampalizumab treatment and had at least 1 post-baseline primary efficacy measurement (sham pooled, n = 40; lampalizumab monthly, n = 42; lampalizumab every other month, n = 41), which satisfied prespecified criteria for evaluation. A 20.4% reduction in GA area progression was reported in the all-comer lampalizumab monthly arm relative to the pooled sham arm. This positive treatment effect was observed at Month 6 through Month 18. Furthermore, a 44% reduction in GA area progression relative to the sham control was observed in a CFI genetic biomarker-defined subpopulation treated monthly with lampalizumab; 57% of the patients who had DNA available for testing in the MAHALO study were CFI biomarker positive. Lampalizumab
demonstrated an acceptable safety profile in the Phase 2 study; there were no ocular or systemic serious adverse events suspected to be study drug-related.

**Conclusion**

Geographic atrophy represents a significant unmet medical need with no approved or effective treatments. Results from large-scale genetics studies support the role of aberrant activation of the alternative complement pathway in AMD pathophysiology. The lampalizumab Phase 2 clinical trial is the first study to show a positive treatment effect in reducing GA progression through complement inhibition. The positive effect observed following monthly lampalizumab treatment in the all-comer population was further magnified in the CFI biomarker-defined subpopulation. Phase 3 trials of lampalizumab are expected to begin in 2014.

**References**


Retinal Pigment Epithelial Transplantation

Jan C Van Meurs MD

Purpose
To report long-term BCVA outcomes following a free autologous retinal pigment epithelium (RPE)-choroid graft translocation in patients with exudative AMD. To reflect on the possible position of RPE grafts in treatment options in 2014.

Study Population
One hundred and thirty consecutive patients (133 eyes) with AMD who underwent RPE-choroid graft translocation between October 2001 and February 2006. The patients had a subfoveal choroidal neovascular membrane with or without blood and/or an RPE-tear and were not eligible for, or nonresponsive to, standard treatment at that time: photodynamic therapy.

Observation Procedures
Data collection included pre- and postoperative visual acuity measurements, fundus photography, fluorescein and indocyanine green angiography, and microperimetry.

Main Outcome Measure
Postoperative BCVA

Results
The mean preoperative BCVA was 20/250. Four years after surgery, 15% of the eyes had a BCVA of > 20/200, and 5% had a BCVA of ≥ 20/40. One patient maintained a BCVA of 20/32 up to 7 years after surgery.

Complications consisted of proliferative vitreoretinopathy (PVR) (n = 13), recurrent neovascularization (n = 13), and hypotony (n = 2).

Two patients with a follow-up of over 11 years have a BCVA of 20/40.

Conclusions
In patients with a free RPE-choroid graft, macular function can be maintained for up to 11 years after surgery, with PVR as the most severe complication. Our results in terms of BCVA suggest that the RPE-choroid graft rather than just removal of submacular hemorrhage and choroidal neovascular membrane was responsible for the preservation of some macular function.

We hypothesize that best results are to be expected in patients with a still preserved neuroretina and that therefore patient selection is of prime importance. In the years to come laboratory improved or laboratory-grown tissue may improve the outcome of RPE replacement therapy.
Stem Cell Trials
Cell Based Therapies for AMD

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 an accessible target tissue for delivery of cell-based therapies with vitreous surgery techniques.
   2. Ocular immune privilege may reduce rejection of cell-based therapies delivered to the retina or subretinal space.
   3. Diagnostic imaging techniques such as OCT, autofluorescent imaging, fluorescein angiography, adaptive optics, and multifocal electroretinography 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 in neovascular AMD and diabetic macular edema
   3. No effective treatment for other retinal diseases, for example, macular (perifoveal) telangiectasia

II. Cell-Based Therapy Sources: Stem Cells and Somatic Cells

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. Stem cell-based therapy: Sources
   1. Embryonic stem cells: cell cultures derived from blastocyst or earlier stage embryo

II. Cell-Based Therapy Sources: Stem Cells and Somatic Cells

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B. Stem cell-based therapy: Sources
   1. Embryonic stem cells: cell cultures derived from blastocyst or earlier stage embryo

2. Adult (somatic) stem cells: Pluripotent adult stem cells are rare; although they can be found in umbilical cord blood,3 most adult stem cells are lineage restricted multipotent or unipotent.4,5

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.5,7

C. Cell-based therapy (non stem cell): Lack the ability to divide without differentiation and are typically differentiated cells
   1. Autologous RPE sheet transplantation
   2. Human adult umbilical cord cells - CNTO 2476 (Janssen)

III. Cell-based products have the potential to meet some of these needs with two potential mechanisms of action: Trophic and Regenerative

A. Secretion of supportive trophic factors in the pathological microenvironment (tissue support). See Figure 1.

1. Trophic cell therapy studies (see Table 1)
   a. Adult umbilical cells CNTO 2476 (Centocor Janssen J&J) preserve retinal structure in the Royal College of Surgeons (RCS) rat retinal degeneration model.8 See Figure 2.

<table>
<thead>
<tr>
<th>Table 1. Trophic</th>
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<tr>
<td><strong>Product</strong></td>
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<td>CNTO 2476</td>
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<td>NT-501</td>
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b. Adult umbilical cells CNTO 2476 (Centocor Janssen [&]) and their culture media alone induce RPE phagocytosis in cell culture (G. Inana). See Figure 3.

B. Replacement of diseased cells and tissue (tissue regeneration). See Figure 4.

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

D. The diseased tissue complex (photoreceptor–Bruch membrane–RPE—choroidal vasculature) is a layered structure that may be amenable to tissue sheet implantation (California Blindness Project and London Project) or 3-dimensional biological tissue synthesis (3-D printing).

IV. 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 Age-related Macular Degeneration10 (Janssen / Johnson & Johnson) at Wills Eye Hospital and Retina Institute of California

A. Primary objective

To evaluate the safety and tolerability of CNTO 2476, administered subretinally using the iTrack Model 275 microcatheter in subjects with visual acuity impairment associated with the geographic atrophy (GA) secondary to AMD
B. Secondary objectives
   1. Select 2 optimal doses for Phase 2a
   2. Evaluate the effect of CNTO 2476 on clinical response
   3. Evaluate the safety and performance of the surgical instruments and delivery system

C. Key ocular inclusion criteria
   1. Subfoveal geographic atrophy O.U.
   2. BCVA ≤ 20/200 O.U. (Phase 1)

D. Key ocular exclusion criteria
   1. Neovascular AMD
   2. Evidence of other significant eye disease

E. Investigational cell product
   1. CNTO 2476 is human umbilical tissue-derived cells, an allogeneic cell-based product.
   2. Putative mechanism of action: Trophic factor influences
   3. Dose escalation 60K, 120K, 300K, 560K cells delivered

F. Phase 1 targeted surgical delivery of CNTO 2476 cells using the iTRACK 275 illuminated microcatheter to the subretinal space of the temporal macula (see Figure 5)
   Surgical technique includes sclerotomy, creation of choroidal fistula and subretinal bleb, microcatheter delivery of cells.
   1. Surgical technique refinement in animal eyes
   2. Endoptiks illuminated intraocular endoscope for improved surgical visualization

G. CNTO 2476 Trial Update: 29 subjects have been enrolled and 27 treated in an extended Phase 1 portion
   1. Safety results: CNTO 2476 was well tolerated but surgical delivery complications
   2. Clinical response: Potential visual acuity efficacy signal but preliminary and uncontrolled
   3. Potential alternative surgical approaches for Phase 2a (see Figure 6)
H. Summary

1. Cell-based therapies (stem cell and non-stem cell) are in clinical trials for atrophic AMD.
2. There are 2 mechanisms of action for cell therapies: trophic and regenerative (replacement).
3. To date, cell therapies have been well tolerated in subjects with atrophic AMD.
4. Improved delivery of cell therapies is required for optimal safety and potential efficacy of these potential treatments.

References

Visual Cycle Modulation

Jennifer I Lim MD

I. Visual Cycle

A. Actions
   1. Primary function = Regenerate 11-cis-retinaldehyde
   2. Secondary function = Generation of toxic by-products of chromophores (lipofuscin and A2E)

B. Pathway (simplified)
   1. Light induces isomerization of 11-cis-retinaldehyde to all-trans-retinaldehyde, which leads to rhodopsin transformation to metarhodopsin II.
   2. Metarhodopsin II then induces visual transduction cascade:
      3. cGMP-cation channels close, resulting in photoreceptor hyperpolarization.
      4. Metarhodopsin is inactivated to apo-opsin and all-trans retinaldehyde.
      5. All-trans retinaldehyde is transported to outer segments and cleared from the photoreceptor discs by binding to ATP-binding cassette transporter (ABCA4).
      6. All-trans retinaldehyde is reduced to all-trans retinol (vitamin A) via retinol dehydrogenases.
      7. All-trans retinol is released into interphotoreceptor matrix and binds to IRBP (interphotoreceptor binding protein).
      8. CRBP-1 has higher affinity for all-trans retinol and captures it into RPE cell.
      9. In RPE cell: CRBP-1 all-trans retinol esterified to all-trans retinyl ester by LRAT (lecithin:retinol acyl transferase).
      10. All-trans retinyl ester, which is then isomerized to 11-cis-retinol (via RPE isomerase).

II. Impact of Abnormal Visual Cycle Modulation on Retina

A. ABCA4 gene defects (Stargardt) result in increased free all-trans-retinaldehyde and N-ret-PE levels in the retina. Secondary nonenzymatic condensation results in A2PE-H2 within distal outer photoreceptors. RPE phagocytoses the outer segments. RPE cannot fully degrade all-trans-retinaldehyde, N-ret-PE, and A2PE-H2. A2E and lipofuscin accumulate in the RPE.

B. AMD and toxic byproduct
   1. AMD RPE processing of phagocyted retinoids is defective.
   2. Lipofuscin, A2E, and other toxic by-products accumulate.
   3. Vicious cycle ensues, as by-products are toxic to RPE, resulting in further RPE dysfunction.
   4. Geographic atrophy occurs: harbinger = areas of increased autofluorescence.
   5. AMD and ABCA4 mutations: Is vitamin A toxic?
      a. Mice: Higher levels of retinyl esters in the liver and RPE. Lipofuscin pigments were significantly increased (biochemical and morphologic analysis) in wild-type and abca4(-/-) mice fed the vitamin A-supplemented diet.
      b. Photoreceptor degeneration was observed in 11-month-old albino, but not pigmented, abca4(-/-) mice on both diets.

III. Clinical Trials on VCM in AMD Eyes

A. Isotretinoin
   Mechanism of action = Inhibits retinol dehydrogenases and RPE 65 isomerases, thereby reducing formation of 11-cis-retinaldehyde.
   Animal models:
   1. Aging-related lipofuscin and A2E accumulation are blocked.
   2. Blocked toxic fluorophores in ABCR/knockout mice
      Human NV AMD pilot study limited efficacy and side effects (dry mouth, labile mood, muscle aches).

B. N-(4-hydroxyphenyl) retinamide (Fenretinide, ReVision Therapeutics; San Diego)
   1. Oral synthetic retinoid that is anti-angiogenic, induces apoptosis, and enhances production of reactive oxygen
   2. Mechanism = Binds to RBP and prevents RBP binding to transthyretin. Nonbound RBP excreted, resulting in lower RBP levels. RBP-bound retinol that is available for uptake to RPE is thus reduced.
   3. Animal models: ABCR knockout mice showed arrested accumulation of A2E and lipofuscin; dark adaption mildly delayed.
4. Human cancer patients: rare acquired night blindness and dry eye

5. Phase 2 Clinical Trial on GA
   a. Purpose: Antagonism of serum retinol-binding protein (RBP) was used in a 2-year trial to determine whether retinol reduction would be effective in the management of geographic atrophy. Slowed lesion growth.
   b. 246 patients given 100 mg or 300 mg per day in a placebo-controlled double-masked trial that enrolled 246 patients at 30 clinical sites in the United States.
   c. Patients in the 300-mg group who achieved serum retinol levels of ≤ 1 μM (≤ 2 mg/dL RBP) showed a mean reduction of 0.33 mm in the yearly lesion growth rate compared with subjects in the placebo group (1.70 mm/year vs. 2.03 mm/year, respectively, \( P = .1848 \)).
   d. Retinol-binding protein reductions < 2 mg/dL correlated with further reductions in lesion growth rates (\( r = 0.478 \)).
   e. Fenretinide treatment also reduced the incidence of choroidal neovascularization (approximately 45% reduction in incidence rate in the combined fenretinide groups vs. placebo, \( P = .0606 \)). This therapeutic effect was not dose dependent and is consistent with anti-angiogenic properties of fenretinide, which have been observed in other disease states.

C. ACU 4429 (Acucela) Emixustat

1. Oral, nonretinoid that inhibits RPE 65 isomerase and prevents conversion of all-trans-retinyl ester to 11-cis-retinol.

2. Phase 1b Study: Randomized, double-masked, placebo-controlled study
   a. Evaluated the pharmacokinetics, tolerability, and safety of a 14-day course of oral emixustat (5, 10, 20, 30, or 40 mg) or placebo (3:1 ratio) once daily in healthy volunteers.
   b. 40 subjects (mean age 38 years, 75% men)
   c. Emixustat (\( N = 30 \)) was rapidly absorbed (median T(max), 3.0-5 hours) and eliminated (mean t(1/2), 4.6-7.9 hours), and mean C(max) and AUC (0-24) generally increased in proportion to dose. Mild ocular and systemic events occurred and resolved with cessation of drug.

3. Phase 2a safety and tolerability study in 72 patients with GA randomized to emixustat (2, 5, 7, or 10 mg AM or to 5 mg PM) vs. placebo for up to 90 days. Dose dependent biologic effect seen.

4. Phase 2b 3 SEATTLE (Safety and Efficacy Assessment Treatment Trials of Emixustat Hydrochloride Study) trial ongoing.
   a. Randomized, double-masked 100% enrolled March 2014 (508 patients)

Selected Readings


Dry AMD Trial Endpoints

Karl G Csaky MD

Background

It has been well established that visual acuity changes in patients with geographic atrophy (GA) associated with dry AMD occur slowly and do not correlate with the degree of enlargement of the GA.1 At the NEI/FDA Ophthalmic Clinical Trial Design and Endpoints Symposium in 2007, the FDA identified the expansion of geographic atrophy as an endpoint for trials in dry AMD.2 Loss of the retinal pigment epithelium (RPE) detected by reduced fundus autofluorescence (FAF) appears to be the most reliable method to detect areas of GA.3 However, the specifics of this endpoint were not delineated, including a predetermined rate of expansion that must be seen in the control group or the degree of slowing of the expansion that must be attained in the treatment group. No endpoint has been determined by the FDA for the treatment of dry AMD without GA.

More rapid rates of GA expansion, as determined by expanding fundus autofluorescence (FAF), appear to correlate with a prior rapid rate of enlargement, the presence of rim hyperautofluorescence,3 and multifocal areas of GA. An important question surrounding the use of FAF as an indicator of the boundary of the GA involves the state of the retina just beyond the edge of reduced FAF. Recently, several investigators have noted that the area immediately surrounding the reduced FAF demonstrates signs of retinal degeneration.4 Therefore, treatments to limit the expansion of GA must successfully treat already degenerated retina in addition to slowing the rate of RPE loss. These are some of the reasons that to date no drug has been approved for the treatment of GA.

Additional Considerations for an Anatomic Endpoint in Dry AMD Trials

To determine the effects on functional vision loss in the absence of visual acuity loss, reading speed, low luminance visual acuity, and mesopic microperimetry could be used. All of these measures are reduced in dry AMD and may provide important functional implications about the loss of retinal tissue.

Novel Functional Outcomes in Dry AMD Trials

Recently, additional functional assessments in patients with varying forms of dry AMD have begun to be explored. Of these, two are used in early stage multicenter trials:

Dark adaptometry

Based on the observation that thickening and changes in the composition of the Bruch membrane is an early and consistent finding in patients with dry AMD and thus alters the function of the retinal pigment epithelium, it has been found that dark adaptation is altered in patients with varying forms of dry AMD.5,6 Two units that are able to quantify dark adaptation include the Goldman-Weekers Dark Adaptometer and the AdapDx (Maculogix; Hummelstown, Penn.). The AdapDx has been most extensively studied in dry AMD patients. This machine measures the ability of the retina to respond to a low-luminance spot placed on the retina at various times following light exposure. The curve that is generated (see Figure 1A) indicates the time to light sensitivity of the rods at a time termed the “cone-rod break.” This time is progressively delayed in advancing forms of dry AMD (see Figure 1B).6 The exact correlates of quality of life for progressive loss of dark adaptation remains to be detailed, but this function now appears to be quantifiable.

Figure 1. Demonstration of results of dark adaptometry (A) showing the typical break in the slope of initial cone sensitivity to rod sensitivity that is markedly delayed in advancing forms of dry AMD (B).6
Scotopic microperimetry

It has been demonstrated that rod photoreceptors are preferentially affected before cone cells, leading to the finding of low-luminance deficits in patients with dry AMD. Therefore, selectively measuring rod sensitivities could be a useful measure of these low-luminance functional deficits. Using the fact that rod cells are more sensitive to blue light simulation, 2-color microperimetry has begun to be used to directly quantify rod function. The unit that is being most extensively studied is the Nidek Microperimeter -1S (Nidek; Padova, Italy). The unit has automated eye tracking and fixation analysis, allowing for reanalysis of exact points on the retina between study visits, as well as the ability to measure rod sensitivities over a 50-dB range. Patterns entailing 56 points centered over rod-intensive areas of the retina (see Figure 2) can be obtained over a period of 10-15 minutes following a period of dark adaptation. The unit is being incorporated in various trials, including those studying GA and Stargardt disease. As with dark adaptometry, though, correlates to low-luminance quality of life have not been determined.

Figure 2. Pattern of rod sensitivity points placed on the rod-rich areas in quantifying scotopic sensitivities.

References


Vitreoretinal Surgery, Part II

Removal of Migrated Ozurdex Implant
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The Lead Doesn’t Spare Anyone
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Subretinal Brilliant Blue in ILM Peeling
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Phacovitrectomy for Macular Hole—Zonular Deniscence, CTR, SCH . . . What Next?
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Surgical Correction of Posterior Retinal Folds
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Allergan: C
Clarity: L
ThromboGenics: C

**Maria H Berrocal MD**
Alcon Laboratories, Inc.: C,L
Hemera: O

**Mark S Blumenkranz MD**
Avalanche Biotechnology: O,P
Digisight: O
Oculogics: O
Optimedica: O,P
Presby Corp.: O
Vantage Surgical: C,O

**David S Boyer MD**
Alcon Laboratories, Inc.: C,L
Alimera Sciences, Inc.: C
Allergen: C,L,S
Bayer: C
Kemin Food L.C.: S
Neurotech: C
Notal Vision: S
Novartis Pharmaceuticals Corp.: C
Regeneron: C
Santen, Inc.: C

**Susan B Bressler MD**
Allergan: S
Bausch + Lomb: S
Bayer Healthcare Pharmaceuticals: S
Boehringer Ingelheim Pharma: S
Genentech: S
GlaxoSmithKline: C
Lumenis, Inc.: S
Notal Vision: S
Novartis Pharmaceuticals Corp.: S
Regeneron Pharmaceuticals, Inc.: S
Sanofi-Aventis Group: S
ThromboGenics: S

**Karina Berg MD**
Bayer Healthcare Pharmaceuticals: C
David M Brown MD
Acucl: S
Aerpio: S
Alcon Laboratories, Inc.: C,S
Alimera: C,S
Allegro Ophthalmics: S
Allergan, Inc.: C
Ampio: S
Bayer Pharmaceuticals: C
Carl Zeiss Meditec: C
Genentech: C,S
Genzyme: C,S
GlaxoSmithKline: S
Heidelberg Engineering: C,L
National Eye Institute: S
Novartis Pharmaceuticals Corp.: C,L
Paloma: C
Pfizer, Inc.: C,S
Regeneron: C,L,S
Santen, Inc.: S
Steba Biotech: C
ThromboGenics: C,S

Gary C Brown MD
Center for Value-Based Medicine: O

Alexander J Brucker MD
Escalon Medical Corp: O
GlaxoSmithKline: S
Merck & Co., Inc.: S
National Eye Institute: S
Neurovision: O

Brandon G Busbee MD
Akorn, Inc.: P
Genentech: C,S
Regeneron: C,S
Synergetics, Inc.: C

David G Callanan MD
Alcon Laboratories, Inc.: C
Allergan, Inc.: C,L,S
Bausch + Lomb Surgical: C,L
Forsight Vision4: O

Peter A Campochiaro MD
Advanced Cell Technology: C
Aerpio: C,S
Alimera Sciences, Inc.: C
Allergan: C
Applied Genetic Technologies: C
Gene Signal: C
Genentech: C,S
Genzyme: S
GlaxoSmithKline: S
Kala Pharmaceuticals: C
Norvoc: C
Oxford BioMedica: S
Regeneron: C

Antonio Capone Jr MD
Acucl: S
Alcon Laboratories, Inc.: C
Alimera Sciences: C
Allergan, Inc.: C,S
FocusROP, LLC: O,P
Genentech: C,S
GlaxoSmithKline: S
Novartis Pharmaceuticals Corp.: C
Retinal Solutions, LLC: O,P
Synergetics, Inc.: C
ThromboGenics: S

Usa Chakravarthy MBBS PhD
Alimera Sciences, Inc.: C
Bayer: C
Novartis Pharmaceuticals Corp.: C,L
Oraya Therapeutics: C,L
Roche: C

R V Paul Chan MD
None

Stanley Chang MD
Alcon Laboratories, Inc.: C

Steven T Charles MD
Alcon Laboratories, Inc.: C,P
Topcon Medical Systems: C,P

Felix Y Chau MD
None

Emily Y Chew MD
None

N H Victor Chong MD
Alcon Laboratories, Inc.: L
Allergan: C,S
Bayer Healthcare Pharmaceuticals: C,L
Heidelberg Engineering: L
Novartis Pharmaceuticals Corp.: C,S
Quantel Medical: C,L,S

David R Chow MD
Alcon Laboratories, Inc.: C
Allergan: L
Arctic Dx: O
Bausch + Lomb Surgical: L
Bayer Healthcare Pharmaceuticals: C
DORC International, bv/Dutch Ophthalmic, USA: L
Katalyst: C
Lumenis, Inc.: L
Novartis Pharmaceuticals Corporation: L
Synergetics, Inc.: C
ThromboGenics, Inc.: C

Mina Chung MD
Canon, Inc.: S
Lowy Medical Research Institute: S
National Eye Institute: S
Thome Foundation: S

Thomas A Ciulla MD
Alimera: S
Ampio: S
Lpath Inc.: S
Ohr: C,O,S
Ophthotec: S
Pfizer, Inc.: S
Stealth: C
ThromboGenics: C

Carl C Claes MD
Alcon Laboratories, Inc.: C,L

Borja F Corcostegui MD
Alcon Laboratories, Inc.: L
Bayer: L
Novartis Pharmaceuticals Corp.: L

Karl G Csaky MD
Acucl: C
Allergan: C
Genentech: C,L,S
Heidelberg Engineering: C
Isis Pharmaceuticals: C
Merck & Co., Inc.: C
Novartis Pharmaceuticals Corp.: C,L
Ophthotec: C,O
Roche Diagnostics: C
Santen, Inc.: C,S

Christine Curcio PhD
GENENTECH: S
National Eye Institute: S

Donald J D’Amico MD
Alcon Laboratories, Inc.: C
Genentech: C
Neurotech, Inc.: C,O
Ophthotec, Inc.: C,O
Optimedica, Inc.: C,O

Diana V Do MD
Allergan: C
Bausch + Lomb Surgical: C
Genentech: S
Heidelberg Engineering: S
Lpath, Inc.: C
Regeneron: S
Santen, Inc.: C

Kimberly A Drenser MD PhD
Allergan: C
FocusROP: O
Retinal Solutions: O
Synergetics, Inc.: C
ThromboGenics: L
Pravin U Dugel MD
Abbott Medical Optics: C
Acucela: C
Alcon Laboratories, Inc.: C
Alimera Sciences, Inc.: C, O
Allergan: C
ArticDx: C,O
Digisight: O
Genentech: C
LUX: C
Macusight: C,O
Neovista: C,O
Optphotech: C,O
Ora: C
Regeneron: C
ThromboGenics: C

Sharon Fekrat MD
Alcon Laboratories, Inc.: P
Prana: C
Regeneron Pharmaceuticals, Inc.: C

Frederick L Ferris MD
Bausch + Lomb: P

Philip J Ferrone MD
Alcon Laboratories, Inc., Inc.: C,S
Allergan: C, S
Arctic DX: C, O
Bausch + Lomb: C
Genentech: C, L, S
Regeneron: C, L, S

Donald Calvin Fletcher MD
None

Harry W Flynn Jr MD
None

James C Folk MD
IDx LLC: O

Cesare Forlini MD
None

K Bailey Freund MD
Bayer Healthcare Pharmaceuticals: C
Genentech: C
Heidelberg Engineering: C
Regeneron: C

Anne E Fung MD
Digisight: O
Genentech: E,S
Regeneron Pharmaceuticals, Inc.: S

Sunir J Garg MD FACS
Alcon Laboratories, Inc.: L,S
Allergan, Inc.: C
Xoma: S

Mark C Gillies MD PhD
Allergan: C,L,S
Bayer Healthcare Pharmaceuticals: C,L,S
Novartis Pharmaceuticals Corporation: C,L,S

Victor H Gonzalez MD
Allergan, Inc.: C
Genentech: C,L,S
Iconics: S
National Eye Institute: S
Panoptica: S
Pfizer, Inc.: L,S
Regeneron: L,S
ThromboGenics, Inc.: C,L,S
Valeant: C,L,S

Evangelos S Gragoudas MD
Aura Biosciences: C
QLT Phototherapeutics, Inc.: P

M Gilbert Grand MD
None

Craig M Greven MD
ThromboGenics, Inc.: C

Sunil Gupta MD
Alcon Laboratories, Inc.: C
Allergan: C
Genentech: C

Julia A Haller MD
Advanced Cell Technology: C
Allergan, Inc.: C
Lpath, Inc.: C
Merck & Co., Inc.: C
Regeneron: C
Second Sight Medical Products, Inc.: C
ThromboGenics: C

Lawrence S Halperin MD
Covalent: O
Regeneron Pharmaceuticals, Inc.: C

Dennis P Han MD
Allergan, Inc.: S
Genentech: S
Regeneron: S

Seenu Hariprasad MD
Alcon Laboratories, Inc.: C,L
Alimera Sciences, Inc.: C
Allergan, Inc.: C,L
Bausch + Lomb: C
Bayer: C
Clearside Biomedical: C,O
Genentech: C,L
Ocular Therapeutix: C,O
OD-OS: C,O
Optos, Inc.: C
Regeneron: C,L

Mary Elizabeth Hartnett MD FACS
American Diabetes Association: S
March of Dimes: S
National Eye Institute: S
WoltersKluwer Lippincott: P

Tarek S Hassan MD
Allergan: C
Artic DX: C,L,O
Bausch + Lomb Surgical: C,L
Genentech, Inc.: C,L
Insight Instruments: C,L
Optimedica: C,O
Regeneron: C,L
ThromboGenics: C

Jay S Duker MD
Alcon Laboratories, Inc.: C
Allergan: C
Carl Zeiss Meditec: C,S
EyeNETRA: C,O
Hemera Biosciences: O
Nicox: C
Optphotech: C,O
Optos, Inc.: C
ThromboGenics: C

Claus Eckardt MD
DORC International, bv/Dutch Ophthalmic, USA: P

Justis P Ehlers MD
Bioptrigen: P
National Eye Institute: S
Ohio Department of Development: S
Regeneron Pharmaceuticals, Inc.: L
ThromboGenics: C,L

Ehab N El Rayes MD PhD
Alcon Laboratories, Inc.: L
DORC International, bv/Dutch Ophthalmic, USA: P
Medone Surgical: P
Novartis Pharmaceuticals Corp.: C,L

Dean Elliott MD
Acucela: C
Advanced Cell Technology: S
Alimera: C
Arctic: C,O
Bausch & Lomb Surgical: C
Biogen Inc: C
GENENTECH: C
ReNeuron: C
ThromboGenics: C

Michel Eid Farah MD
None

Evangelos S Gragoudas MD
Aura Biosciences: C
QLT Phototherapeutics, Inc.: P

M Gilbert Grand MD
None

Craig M Greven MD
ThromboGenics, Inc.: C

Sunil Gupta MD
Alcon Laboratories, Inc.: C
Allergan: C
Genentech: C

Julia A Haller MD
Advanced Cell Technology: C
Allergan, Inc.: C
Lpath, Inc.: C
Merck & Co., Inc.: C
Regeneron: C
Second Sight Medical Products, Inc.: C
ThromboGenics: C

Lawrence S Halperin MD
Covalent: O
Regeneron Pharmaceuticals, Inc.: C

Dennis P Han MD
Allergan, Inc.: S
Genentech: S
Regeneron: S

Seenu Hariprasad MD
Alcon Laboratories, Inc.: C,L
Alimera Sciences, Inc.: C
Allergan, Inc.: C,L
Bausch + Lomb: C
Bayer: C
Clearside Biomedical: C,O
Genentech: C,L
Ocular Therapeutix: C,O
OD-OS: C,O
Optos, Inc.: C
Regeneron: C,L

Mary Elizabeth Hartnett MD FACS
American Diabetes Association: S
March of Dimes: S
National Eye Institute: S
WoltersKluwer Lippincott: P

Tarek S Hassan MD
Allergan: C
Artic DX: C,L,O
Bausch + Lomb Surgical: C,L
Genentech, Inc.: C,L
Insight Instruments: C,L
Optimedica: C,O
Regeneron: C,L
ThromboGenics: C
Sohan S Hayreh MD PhD DSc
None

Jeffrey S Heier MD
Acucela: C,S
Aerpio Therapeutics: C,S
Alcon Laboratories, Inc.: C,S
Allergan: C,S
Allegro: C
Allergan, Inc.: C,S
Bausch + Lomb: C
Bayer Healthcare: C,S
Endo Optiks, Inc.: C
Forsight Labs: C
Fovea Pharmaceuticals: S
Genentech: C,S
Genzyme: C,S
Heidelberg Engineering: C
Kala Pharmaceuticals: C
Kanghong: C
Kato Pharmaceuticals: S
Liquidia: C
Lpath, Inc.: S
Merz: C
Neurotech: C
Nicox: C
Notal Vision: C,S
Novartis Pharmaceuticals Corp.: S
Ohr Pharmaceutical: C,S
Ophthalmotech: S
Oraya: C
QLT Ophthalmics: C,S
Regeneron: C,S
Sanofi Fovea: C
Stealth Peptides: C
ThromboGenics: C
Xcovery: C

Allen C Ho MD
Acucela Laboratories, Inc.: C,L,S
Allergan: S
Endo Optiks, Inc.: C
Genentech: C,L,S
Janssen: C,L,S
NEI / NIH: S
Ophthalmotech: C,S
PanOptica: C,S
PRN: C,O,S
Regeneron: C,L,S
Second Sight: C,S
ThromboGenics: C,L,S

Nancy M Holekamp MD
Alimera Sciences, Inc.: C
Allergan: C,S
Genentech: C,L
Katalyst: C,O,P
Notal Vision: S
Quantel Medical: C
Regeneron Pharmaceuticals, Inc.: C,L
Sequenom CMM: C,L

Frank G Holz MD
Acucela: C
Bayer Healthcare: C,L
Carl Zeiss Meditec: C,S
Genentech: C,S
Heidelberg Engineering: C,L,S
Novartis Pharmaceuticals Corp.: C,L
Optos, Inc.: S
Pfizer, Inc.: C
Roche: C

Suber S Huang MD MBA
i2i Innovative Ideas, Inc.: O
Second Sight: C
Zeiss: L

Mark S Humayun MD PhD
Acucela Laboratories, Inc.: C,L,S
Bausch + Lomb Surgical: C,L,P,S
Clearside: C
Iridex: C,P
Liquidia: C
Reflow: C,L,O,P,S
Regenerative Patch Technologies (RFT): C,O,P
Replenish: C,L,O,P,S
Second Sight: C,L,O,P,S

Raymond Iezzi MD
Acucela Laboratories, Inc.: C
Alimera Sciences, Inc.: C,O

Michael S Ip MD
Allergan, Inc.: S
Genentech: C
Regeneron Pharmaceuticals, Inc.: C
Valiant: C

Glenn J Jaffe MD
Abbott Laboratories: C
Alcon Laboratories, Inc.: C
Heidelberg Engineering: C
Neurotech USA: C
pSivida: S

Lee M Jampol MD
Baxter BioScience: C
Jaeb Center/DRCR: S
Novartis Pharmaceuticals Corp.: L
Stem Cell Organization/Quintiles: C

Mark W Johnson MD
GlaxoSmithKline: C
Oraya: C

J Michael Jumper MD
Allergan: S
Covalent Medical: O
DORC International, bv/Dutch Ophthalamic, USA: L
Genentech: S
Ophthalmotech: S
Regeneron Pharmaceuticals, Inc.: S
ThromboGenics, Inc.: S

Kazuaki Kadonosono MD
None

Peter K Kaiser MD
Alcon Laboratories, Inc.: C
Allegra: C
Bayer: C
Chengdu Kanghong: C
Genentech: C
Novartis Pharmaceuticals Corp.: C
Ophthalmotech: C
Oraya: C
Regeneron Pharmaceuticals, Inc.: C
SKS Ocular LLC: C,O

Richard S Kaiser MD
Ophthalmotech: C,O
PanOptica: C
Regeneron Pharmaceuticals, Inc.: C

Rahul Khurana MD
Allergan, Inc.: C
GENENTECH: C,L
Regeneron: L,S
Topcon Medical Systems Inc.: C

Ivana K Kim MD
ArcticDx: C
Genentech: S

Judy E Kim MD
Allergan: C
Genentech: L

Alan E Kimura MD MPH
None

Szilárd Kiss MD
Alimera: C,L
Allergan, Inc.: C,L,S
Genentech: C,L,S
Optos, Inc.: C,L,S
Regeneron: C,L,S
ThromboGenics: C,L

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Faculty Financial Disclosures 155
<table>
<thead>
<tr>
<th>Name</th>
<th>Allergan</th>
<th>Bayer Healthcare Pharmaceuticals</th>
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<td>John W Kitchens MD</td>
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<td>Robert E Leonard II MD</td>
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<td>Jennifer Irene Lim MD</td>
<td>Genentech</td>
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<td>Paul Mitchell MD PhD</td>
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<td>Timothy G Murray MD MBA</td>
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<td>Albert M Maguire MD</td>
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<td>Travis A Meredith MD</td>
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<td>Pauline T Merrill MD</td>
<td>Abbvie</td>
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<td>National Eye Institute</td>
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<td>William F Mieler MD</td>
<td>Genentech</td>
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<td>Daniel Matthew Miller MD PhD</td>
<td>Alcon Laboratories, Inc.</td>
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<td>Joan W Miller MD</td>
<td>Alcon Laboratories, Inc.</td>
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<td>Joann W Miller MD</td>
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Quan Dong Nguyen MD
AbbVie Pharmaceuticals: S
Bausch & Lomb Surgical: C
Genentech: S
Heidelberg Engineering: S
Lux Biosciences, Inc.: S
Optos, Inc.: S
Regeneron Pharmaceuticals, Inc.: S
Sanofi Fovea: S
Santen, Inc.: C,S

Yuichiro Ogura MD PhD
Alcon Laboratories, Inc.: C
Bayer Healthcare Pharmaceuticals: C,L
Novartis Pharmaceuticals Corp.: C,L
Santen, Inc.: C
Wakamoto, Inc.: C

Masahito Ohji MD
Alcon Laboratories, Inc.: C,L
Allergan: C
Bayer Healthcare Pharmaceuticals: C,L
Novartis Pharmaceuticals Corp.: C,L
Otsuka Pharmaceutical: L
Pfizer, Inc.: C,L
Santen, Inc.: C,L
Sanwa Kagaku Kenkyusho: C
Senju Pharmaceutical: L
Shionogi: C

Timothy W Olsen MD
A Tissue Support Structure: P
Abraham J and Phyllis Katz Foundation: S
National Eye Institute: S
Research to Prevent Blindness: S
Scleral Depressor: P
The Fraser Parker Foundation: S
The R Howard Dobbs Jr Foundation: S

Yusuke Oshima MD
Alcon Laboratories, Inc.: L
Synergetics, Inc.: C

Sengul C Ozdek MD
Bayer Healthcare Pharmaceuticals: C

Andrew J Packer MD
None

Kirk H Packo MD
Abbott Medical Optics: S
Alcon Laboratories, Inc.: C,L,S
Allergan: S
Genentech: S
Regeneron Pharmaceuticals, Inc.: S
Vision Care Inc.: C,S

David W Parke II MD
OMIC-Ophthalmic Mutual Insurance Company: C

Sarju S Patel MD
None

Grazia Pertile MD
None

Dante Pieramici MD
Allergan: S
Bausch & Lomb: C
Genentech: C,S
QLT Photothertapeutics, Inc.: S
Regeneron: S
Santen, Inc.: C,S
ThromboGenics: C

Jonathan L Prenner MD
Alcon Laboratories, Inc.: C
Genentech: C
Ophthotech: C,O
Panoptica: C,O
Regeneron: C

Carmen A Puliafito MD MBA
Humphrey Zeiss: P

Graham E Quinn MD
National Eye Institute: S

Hugo Quiroz-Mercado MD
Allegro Ophthalmics LLC: O

P Kumar Rao MD
National Eye Institute: S
Regeneron Pharmaceuticals, Inc.: S

Carl D Regillo MD FACS
Abbott Medical Optics: C
Acucela: C,S
Advanced Cell Technology: S
Alcon Laboratories, Inc.: C,S
Alimera Sciences, Inc.: C,S
Allergan: C,S
Bausch & Lomb: C
Genentech: C,S
NotalVision, Ltd.: C,S
Novartis Pharmaceuticals Corp.: C
Pfizer, Inc.: C
Regeneron Pharmaceuticals, Inc.: C,S
Santen, Inc.: S
Second Sight Medical Products, Inc.: S
ThromboGenics, Inc.: C,S

Elias Reichel MD
Akorn Inc.: P
Alimera Sciences, Inc.: C
GENENTECH: C
GlaxoSmithKline: C
Hemera Biosciences: O
NewGen Biopharma: C,O
Ocular Instruments, Inc.: P
Ophthotech: C,O
Regeneron Pharmaceuticals, Inc.: C,L
Thrombogenics: C,L

Korous Rezaei MD
Alcon Laboratories, Inc.: C,L,S
Bayer Healthcare Pharmaceuticals: S
BMC: C,L
Genentech: L,S
Ophthotech: C,O
Regeneron: L,S
ThromboGenics: C,L,S

William L Rich MD
None

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None

Richard B Rosen MD
Allergan: S
Clarity: C
Genentech: S
OD-OS: L
Optovue: C

Philip J Rosenfeld MD PhD
Acucela: C,S
Advanced Cell Technology: S
Alcon Laboratories, Inc.: C
Boehringer Ingelheim: C
Carl Zeiss Meditec: S
Chengdu Kangbong Biotech: C
Digisight: O
GENENTECH: S
GlaxoSmithKline: S
Hoffman La Roche, Ltd.: C
Oraya: C
Xcovery Vision: C

Srinivas R Sadda MD
Alcon Laboratories, Inc.: C
Allergan, Inc.: C,S
Bausch & Lomb: C
Carl Zeiss Meditec: C,S
Genentech: C,S
Oftop, Inc.: C,S
Roche Diagnostics: C

Taiji Sakamoto MD PhD
Alcon Laboratories, Inc.: L
Bausch & Lomb: C
Bayer Healthcare Pharmaceuticals: L
Novartis Pharmaceuticals Corp.: C
Santen, Inc.: L
Senju: L
Wakamoto: C

Arturo Santos MD
Innovaciones Biomedicas Y Tecnologicas: O,P
Opko Health, Inc.: C,O
Replenish, Inc.: C,L,O
Andrew P Schachat MD  
Allergan: C  
Bausch + Lomb: C  

Steven D Schwartz MD  
Alcon Laboratories, Inc.: C  
Allergan, Inc.: C  
Bausch + Lomb Surgical: C,L  
Genentech, Inc.: C,L  
OptiMedica: C,L,O  
Optos, Inc.: C,L  

Ingrid U Scott MD MPH  
Alcon Laboratories, Inc.: C  
Genentech: C,L  
Sanofi Fovea: C  
Santen, Inc.: C  
ThromboGenics: C  

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None  

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Alcon Laboratories, Inc.: C  
ThromboGenics: C  

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Alcon Laboratories, Inc.: C,L  
Allergan, Inc.: C,S  
QLT Phototherapeutics, Inc.: C,L  
Regeneron Pharmaceuticals, Inc.: C,L  

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None  

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None  

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Alcon Laboratories, Inc.: S  
Allergan, Inc.: S  
ArcticDx, Inc.: C,O  
Genentech: S  
MacTel: S  
National Eye Institute: S  
Novartis Pharmaceuticals Corp.: S  
Ohr Pharmaceuticals: C,O,S  
Ophthotech: C,O,S  
ThromboGenics: S  

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Alcon Laboratories, Inc.: C  
Bausch + Lomb: C  
Bayer Regeneron: C,L,S  
Carl Zeiss Meditec: C,S  
Genentech: C,L,S  
ThromboGenics, Inc.: C,S  

Jason S Slakter MD  
Acucela: C,S  
Alimera: S  
Bayer HealthCare: S  
Centocor, Inc.: S  
Fovea/SanofiAventis: S  
Genentech: S  
GlaxoSmithKline: S  
Lpath, Inc.: C,S  
Ohr Pharma: C,S  
Oraeye Therapeutics: C,S  
Regeneron Pharmaceuticals: L,S  
Sanofi-Aventis: S  
Santen, Inc.: S  
SKS Ocular, LLC: O  
Xcovery Vision: C,S  

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None  

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None  

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Topcon Medical Systems: P  

Sunil K Srivastava MD  
Allergan: S  
Bausch + Lomb Surgical: C,S  
Biotig: P  
Novartis Pharmaceuticals Corp.: S  
Sanofi Fovea: C  
Santen, Inc.: C,L  
Synergics, Inc.: P  

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Alcon Laboratories, Inc.: C,L  
Bausch + Lomb: C,S  
DORC International, bv/Dutch Ophthalmic, USA: L  
ThromboGenics: L,S  

Giovanni Staurenghi MD  
Alcon Laboratories, Inc.: C,L  
Allergan, Inc.: C  
Bayer: C,L  
Boehringer: C  
GlaxoSmithKline: C  
Heidelberg Engineering: C,L  
Novartis Pharmaceuticals Corp.: C,L,S  
Ocular Instruments, Inc.: P  
OD-OS: C  
Optos, Inc.: C  
Optovue: S  
QLT Phototherapeutics, Inc.: C  
Roche: C  
Zeiss: C,S  

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None  

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None  

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Bayer Healthcare Pharmaceuticals: S  
GlaxoSmithKline: S  
Novartis Pharmaceuticals Corp.: C,L,S  
Santen, Inc.: C  

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None  

Paul E Tornambe MD  
Alcon Laboratories, Inc.: L  
Bausch + Lomb: C  
DORC International, bv/Dutch Ophthalmic, USA: C,L  
Genentech: C  
Humphreys Zeiss: C,L  
Insight Instruments: C,P  
Inspirx Pharmaceuticals, Inc.: C  
Nidek, Inc.: C  
Optos, Inc.: C,L  
Poway Retinal Technologies: O,P  
QLT Phototherapeutics, Inc.: C,L  
Stemedica: C  
ThromboGenics, Inc.: C,L  

Cynthia A Toth MD  
Alcon Laboratories, Inc.: P  
Biotigien, Inc.: S  
Genentech, Inc.: S  
National Eye Institute: S  

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Focus ROP: C,O  
Genentech: C  
Nu-Vue Technologies, Inc.: C,O  
Retinal Solutions LLC: C,O  
Synergetics, Inc.: P  
ThromboGenics, Inc.: C,O  

Adnan Tufail MD  
Alcon Laboratories, Inc.: C  
Allergan: C,L  
Bayer Healthcare Pharmaceuticals: C  
GENENTECH: C  
Heidelberg Engineering: C  
Notal Vision, Inc.: S  
Novartis Pharmaceuticals Corporation: C,L,S  

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DORC International bv, Dutch Ophthalmic, USA: P
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None

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Allergan: C
GENENTECH: C
Vestrum Health: O

George A Williams MD
Alcon Laboratories, Inc.: C,S
Allergan, Inc.: C,S
ForSight: C,O
Neurotech: C,S
OMIC-Ophthalmic Mutual Insurance
   Company: E
OptiMedica: C,O
ThromboGenics: C,O

Tien Yin Wong MBBS
Allergan Singapore Pte Ltd: C
Allergan, Inc.: C
Bayer Healthcare Company Limited: C
Bayer Healthcare Pharmaceuticals, Inc.: C
Novartis Pharma AG: C

Lihteh Wu MD
Alcon Laboratories, Inc.: L
Bayer Health: L

Lawrence A Yannuzzi MD
None

Steven Yeh MD
Clearside: C

Young Hee Yoon MD
Alcon Laboratories, Inc.: C,L
Allergan: C,L,S
Bayer: C,L,S

Leandro C Zacharias MD
None

Marco A Zarbin MD PhD FACS
Calhoun Vision, Inc.: C
Genentech: C
Helios, KK: C
Imagen Biotech, Inc.: C
Iridex: C
Novartis Pharmaceuticals Corp.: C
Pfizer, Inc.: C
Roche: C
Rutgers University: P

AAO Staff Disclosures

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None

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* Indicates that the presenter has financial interest.
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