Retina 2019
I²—Inspire Innovation

Program Directors
Mark S Humayan MD PhD and Judy E Kim MD

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

ASRS American Society of Retina Specialists

The Macula Society established in 1977

The Retina Society

Moscone Convention Center
San Francisco, California
Friday–Saturday, Oct. 11–12, 2019

Presented by:
The American Academy of Ophthalmology

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Mark W Johnson MD
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2019 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 San Francisco and **Retina 2019: I²—Inspire Innovation**.

Mark S Humayun MD PhD
Program Director

1Co., Inc.: C,O,P
Alcon Laboratories, Inc.: C,L
Allergan: C,L | Clearside: C
Duke Eye Center: P
Eyemedix: C,O,P,S
Iridex: P | John Hopkins University: P
Lutronic Vision: C,O | MTTR: C,O
Regenerative Patch Technologies (RPT): C,O,P
Replenish: C,O,P | Santen, Inc.: C,L
Second Sight Medical Products, Inc.: O,P
University of Southern California: E,P

Judy E Kim MD
Program Director

Allergan: C
Cellcure: C
Clearside: C
Eyepoint: C
Genentech: C
Kodiak: C
Notal Vision, Inc.: S
Novartis: L
Optos, Inc.: S

Mark W Johnson MD

Apellis: S
Pfizer, Inc.: C
Syneos Health: C

Srinivas R Sadda MD

4DMT: C
Allergan: C,S
Amgen: C | Bayer: C
Carl Zeiss Meditec: C,S
Centervue: C
Genentech: C
Heidelberg Engineering: C
Nidek: L
NightstarRx: C
Novartis Pharma AG: C
Optos, Inc.: C
ThromboGenics, Inc.: C
Topcon Medical Systems Inc.: L

2019 Subspecialty Day Advisory Committee

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Alphaeon: O
Avedro: C,L,O
Concierge Key Health: O,C
Eyegate Pharma: C
Hoopes Durrie Rivera Research Center: C
iOR Holdings: O
iOR Partners: O
Johnson & Johnson Vision: C,L
Strathspey Crown LLC: O

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None

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Celgene: O
KalVista: C
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National Eye Institute: S
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Mynosys: C
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Novartis Institute for Biomedical Research: C
Ocular Therapeutix, Inc.: C
Santen, Inc.: C | Shire: C
Thieme Medical Publishers: C
U.S. Food and Drug Administration: C,S

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Retina 2019 Contents

CME Credit

The 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.

2019 Retina Subspecialty Day Meeting Learning Objectives

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

- Present established and innovative approaches to the medical and surgical management of vitreoretinal diseases and disorders
- Identify imaging tests that are most helpful in the diagnosis and management of retinal conditions and discuss emerging developments in retinal imaging
- Describe new vitreoretinal surgical techniques and instrumentation
- Identify new developments in the understanding of hereditary retinal degenerations, retinal vascular disease, AMD, and other macular diseases, pediatric retinal diseases, uveitis and ocular oncology
- Summarize current and new clinical trial data for retinal diseases such as AMD, diabetic retinopathy, hereditary retinal conditions, and retinal vein occlusion

2019 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.

Teaching at a Live Activity

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

Scientific Integrity and Disclosure of Conflicts of 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.

Control of Content

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

2019 Retina Subspecialty Day CME Credit

The American Academy of Ophthalmology is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The Academy 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.

Attendance Verification for CME Reporting

Before processing your requests for CME credit, the American Academy of Ophthalmology must verify your attendance at AAO 2019 and/or Subspecialty Day. Badges are no longer mailed before the meeting. Picking up your badge onsite will verify your attendance.

Badge Scanning and CME

Getting your badge scanned does not automatically grant CME credit. You still need to record your own educational activities. NOTE: You should claim only the credit commensurate with the extent of your participation in the activity.

CME Credit Reporting

Onsite, report credits earned during Subspecialty Day and/or AAO 2019 at CME Credit Reporting kiosks located in South Lobby, West Lobby, and the Academy Resource Center, West, Booth 7337.

Registrants whose attendance is verified at AAO 2019 will receive an email on **Monday, Oct. 14**, with a link and instructions for claiming credit online. Attendees can use this link to report credits until **Wednesday, Oct. 30**.

Starting **Thursday, Nov. 14**, attendees can claim credits online through the Academy's CME web page, aao.org/cme-central.

Academy Members

The CME credit reporting receipt is not a CME transcript. CME transcripts that include AAO 2019 credits entered at the Academy's annual meeting will be available to Academy members through the Academy's CME web page beginning **Thursday, Nov. 14**.

The Academy transcript cannot list individual course attendance. It will list only the overall credits claimed for educational activities at Subspecialty Day and/or AAO 2019.

Nonmembers

The American Academy of Ophthalmology provides nonmembers with verification of credits earned and reported for a single Academy-sponsored CME activity. To obtain a printed record of your CME credits, claim them onsite at the CME Credit Reporting kiosks. Nonmembers choosing to claim credits online through the Academy's CME web page after **Thursday, Nov. 14**, will have one opportunity to print a certificate.

Proof of Attendance

The following types of attendance verification are available during AAO 2019 and Subspecialty Day for those who need it for reimbursement or hospital privileges, or for nonmembers who need it to report CME credit:

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

You must have obtained your proof of attendance at the CME Credit Reporting kiosks onsite, located in South Lobby, West Lobby, and in the Academy Resource Center, West, Booth 7337.

The 2019 Retina Hall of Fame Award

The *Retina Hall of Fame* was established in 2016. The founders, each with a history of leadership in the field of retina disease, desire to honor the significant contributions of their colleagues. Each retina specialist in the Hall of Fame is recognized for his or her innovation and dedication to both patients and research.

We honor Dr. Alice R McPherson for her extraordinary contributions to the field of retinal diseases and celebrate the contributions of Dr. McPherson on the 50th anniversary of the creation of The Retina Research Foundation.

Friday, Oct. 11, 2019
9:15 AM – 9:25 AM

Alice R McPherson MD

Alice McPherson is one of the world's leading vitreoretinal specialists. She earned her bachelor of science (1948) and medical degrees (1951) from the University of Wisconsin (UW), and she completed a fellowship in retinal diseases and retinal surgery at the Massachusetts Ear and Eye Infirmary (1959).

After serving as a clinical instructor in ophthalmology at UW, Dr. McPherson moved to Houston, Texas. There she established herself as one of the pioneers in the field. Along with her private practice, she founded the retina service at Baylor College of Medicine, where she has taught ever since. Dr. McPherson promoted several procedures that are now accepted as basic elements in retinal detachment surgery, and she contributed greatly to the understanding and treatment of diabetic retinopathy and retinopathy of prematurity.

In 1969, Dr. McPherson founded the Retina Research Foundation (RRF) in Houston, Texas, dedicated to the eradication of retinal disease. Under her leadership as president and scientific adviser, the RRF has funded more than 1,000 grants and helped to launch the careers of many major vision researchers in the United States and abroad. The RRF has also established major awards in collaboration with the leading ophthalmologic societies, chairs and professorships at universities and research institutions, travel grants for young scientists, and international fellowships of advanced subspecialty training. With an endowment valued at over $55 million dollars, the foundation has awarded over $34 million for retina research to date.

In 2002, her vision, inspiration, and support were critical in the establishment of the McPherson Eye Research Institute (MERI) at UW-Madison. She served for 12 years on the UW Foundation Board of Directors; she was the founding president of the UW Ophthalmology Alumni Association; and she has been responsible for establishing endowed chairs and lectureships at the university.

Dr. McPherson has written over 70 book chapters and articles in peer-reviewed journals and has given scores of lectures and presentations all over the world. She has served on the editorial boards of *Ophthalmology*, *Survey of Ophthalmology*, and *American Journal of Ophthalmology*, among others. Co-authored with Dr. Daniel M. Albert, a history of the first 50 years of the Retina Research Foundation was recently published.

Dr. McPherson's numerous honors include an honorary doctor of science degree in 1997 from UW-Madison, where she served as commencement speaker in 1995. She has held countless offices, committee memberships, and honorary appointments, including multiple offices at UW, the office of vice-president and president of the Retina Society, and multiple offices in the American Academy of Ophthalmology and the Pan-American Association of Ophthalmology. Dr. McPherson is a member of the Club Jules Gonin and a charter member of the Retina Society and the Vitreous Society. Her many honors include Fellow of the Royal Society of Medicine; the Charles L. Schepens Honor Award, the Senior Honor Award, Distinguished Alumni Professional Achievement Award of Harvard Medical School, and the Guest of Honor award from the American Academy of Ophthalmology; the Gonin Medal and lectureship, and appearances in Best Doctors in America and multiple *Who's Who* lists.

The Charles L Schepens MD Lecture

Retinal Gene Therapy: From Theory to Practice

Jean Bennett MD PhD & Albert M Maguire MD

Friday, Oct. 11, 2019
9:30 AM – 9:50 AM

Jean Bennett MD PhD

- Director, Center for Advanced Retinal and Ocular Therapeutics (CAROT), University of Pennsylvania Perelman School of Medicine
- Professor of Ophthalmology; Cell & Developmental Biology, University of Pennsylvania Perelman School of Medicine
- Vice chairman for Research, Scheie Eye Institute, University of Pennsylvania Perelman School of Medicine
- Scientist, Department of Pediatric Ophthalmology, the Children's Hospital of Philadelphia

Dr. Bennett is a physician-scientist with experience/expertise in molecular biology, vector development, and gene therapy translational studies. She has developed gene transfer approaches to test treatment strategies for retinal degenerative and ocular neovascular diseases, to elucidate retinal differentiation pathways and to identify pathogenetic mechanisms that lead to blindness. Dr. Bennett has established a true "from bench to bedside" program, and thus she is familiar with the steps that are needed to go from proof of concept all the way to testing of safety and efficacy in humans with blinding disease. Dr. Bennett was the scientific leader of a team that translated reversal of blindness in animal models to demonstration of efficacy and safety in children and adults. Her team was the first to enroll pediatric subjects with a nonlethal disease as gene therapy participants. The team completed the first randomized, controlled, multicenter Phase 3 gene therapy trial targeting a genetic disease. This work led to the first and only approved gene therapy for inherited disease in the United States and in Europe and the first approved gene therapy product targeting a retinal disease worldwide.

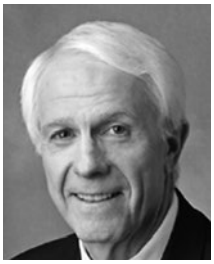
Albert M Maguire MD

- Professor of Ophthalmology, senior attending in Vitreoretinal Surgery, Scheie Eye Institute
- Retina attending in the Division of Pediatric Ophthalmology at the Children's Hospital of Philadelphia
- Co-director, Center for Advanced Retinal and Ocular Therapeutics (CAROT), Penn Medicine

Albert M Maguire is a professor in the Department of Ophthalmology at the University of Pennsylvania Perelman School of Medicine, where he is a retina specialist and vitreoretinal surgeon. He is also the attending physician for retina at the Children's Hospital of Philadelphia. Dr. Maguire is most well known for developing and carrying out the surgical procedures that are now used in a large number of gene therapy clinical trials testing interventions for blindness. He is also known for directing the first Phase 1-3 gene therapy clinical trials for congenital blindness, which demonstrated efficacy and safety in children and adults. Dr. Maguire was instrumental in all of the proof-of-concept studies that first showed that gene-based intervention of blindness was possible. Results from the clinical trials that he directed led to the first approved gene therapy drug for genetic disease worldwide and the first USFDA-approved recombinant virus-based gene therapy product for a genetic disease. Prof. Maguire's preclinical studies led to several gene therapy clinical trials other than the ones he directed. In the process, he developed a gene therapy surgical training program that has certified retinal surgeons around the world for retinal gene therapy delivery. Professor Maguire received a bachelor's degree in psychology from Princeton University and a medical degree from Harvard Medical School, completed an internship in surgery at Yale University School of Medicine, a residency in ophthalmology at the Wilmer Eye Institute, Johns Hopkins School of Medicine, and a combined medical/surgical fellowship in retina at William Beaumont Hospital, Royal Oak, Michigan. While serving as chief resident at the Wilmer Eye Institute, he was recruited to University of Pennsylvania and the Children's Hospital of Philadelphia.

Professor Maguire has received numerous awards, including the American Academy of Ophthalmology Achievement Award, the Paul Kayser International Award in Retina Research, the Association for Retinopathy of Prematurity and Related Diseases Award, the Retina Research Foundation Pyron Award, the Clinical Innovator Award from the National Medical Association, and the António Champalimaud Vision Award. Dr. Maguire has established a Center for Excellence in gene therapy at both the Children's Hospital of Philadelphia and the University of Pennsylvania School of Medicine, where patients with bi-allelic congenital blindness due to *RPE65* deficiency are now treated. He continues to run several other gene therapy clinical trials for blinding diseases. He is also co-director of the Center for Advanced Retinal and Ocular Therapeutics (CAROT), a center that aims to develop treatments for a wide range of blinding diseases and to train the next generation of physician/scientists.

Faculty



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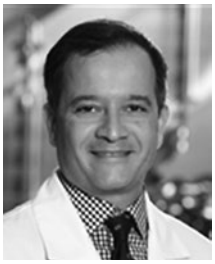
Detroit, MI



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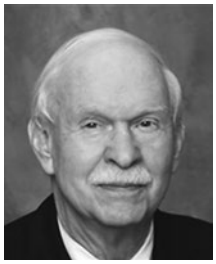

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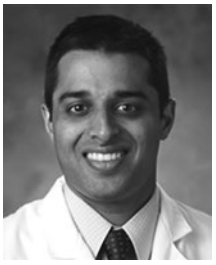

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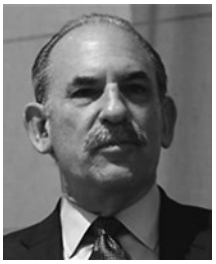

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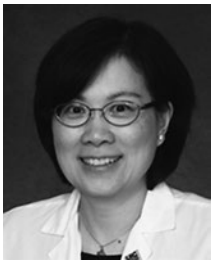

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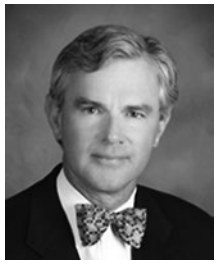

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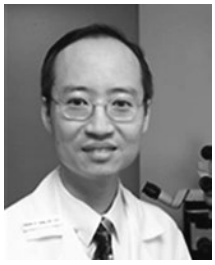

Stephen H Tsang MD PhD
New York, NY

No photo available

Robin A Vora MD
Piedmont, CA

George A Williams MD
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Lejla Vajzovic MD
Durham, NC

Nadia Khalida Waheed MD
West Roxbury, MA

David J Wilson MD
Portland, OR

Demetrios Vavvas MD
Boston, MA

John A Wells III MD
West Columbia, SC

Sebastian Wolf MD PhD
Bern, Switzerland

Tien Yin Wong MBBS
Singapore, Singapore

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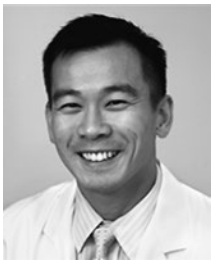
David N Zacks MD PhD
Ann Arbor, MI

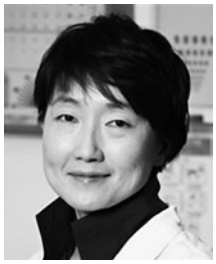
Charles C Wykoff MD PhD
Houston, TX

Young Hee Yoon MD
Seoul, Korea

Marco A Zarbin MD PhD FACS
Chatham, NJ



Steven Yeh MD
Atlanta, GA



Seung Young Yu MD PhD
Seoul, Korea

Retina 2019: I²—Inspire Innovation

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

FRIDAY, OCTOBER 11

7:00 AM	CONTINENTAL BREAKFAST		
8:00 AM	Opening Remarks	Mark S Humayun MD PhD* Judy E Kim MD*	

Section I: Vitreoretinal Surgery, Part I

Moderators: Gary W Abrams MD*

8:05 AM	Precision Subretinal Delivery for Cell and Gene Therapy	Allen C Ho MD*	1
8:12 AM	The Benefit of the Bag-in-the-Lens IOL for Vitreoretinal Surgery	Claus Eckardt MD*	5
8:19 AM	Giant Retinal Tears: Tips, Tricks, and a Novel Tamponade	Steven T Charles MD*	6
8:26 AM	Hypersonic Vitrectomy: Continued Technical and Clinical Developments	Carl C Awh MD*	9
8:33 AM	Approaches to Difficult Macular Holes	Michael Koss MD	10
8:40 AM	Should We Operate on Lamellar Macular Holes?	Stanley Chang MD*	13
8:47 AM	Management of Retinal Detachment Without Vitrectomy Adjuncts	Mark W Johnson MD*	14
8:54 AM	Proliferative Diabetic Retinopathy Surgery: How to Improve the Success Rate	Maria H Berrocal MD*	16
9:01 AM	New Instrumentation for Vitreoretinal Surgery	David R Chow MD*	17
9:08 AM	Surgery for Infectious Retinitis: When Medical Therapy Is Not Sufficient	J Fernando Arevalo MD FACS*	18

Retina Hall of Fame 2019 Award

9:15 AM	Introduction	Jerald Bovino MD Mark S Humayun MD PhD*	
9:20 AM	Retina Hall of Fame 2019 Award	Alice R McPherson MD*	

The Charles L Schepens MD Lecture

9:25 AM	Introduction of the 2019 Charles L Schepens MD Lecturer	David W Parke II MD*	
9:30 AM	Retinal Gene Therapy: From Theory to Practice	Jean Bennett MD PhD* Albert M Maguire MD*	20
9:50 AM	REFRESHMENT BREAK		

Section II: The Business of Retina

Moderators: Reginald J Sanders MD* and David F Williams MD*

10:30 AM	Are You AT the Table or ON the Menu?	Purnima S Patel MD	21
10:35 AM	AAO Update on Retina	George A Williams MD	23
10:39 AM	Update From Washington	David W Parke II MD*	24
10:43 AM	Retinal Relativity and Reimbursement Roulette	John T Thompson MD*	25

* Indicates that the presenter has financial interest. No asterisk indicates that the presenter has no financial interest.

10:50 AM	Business of Retina Panel Discussion Panel Moderator: Reginald J Sanders MD* Panelists: William L Rich III MD FACS, Andrew P Schachat MD*, Gaurav K Shah MD*, John T Thompson MD*, and David F Williams MD*		

Section III: My Best Medical Retina Cases

Moderator: William F Mieler MD

Virtual Moderator: Ivana K Kim MD*

11:05 AM	Case Presentation	H Richard McDonald MD*	28
11:08 AM	Discussion		
11:11 AM	Case Presentation	Lee M Jampol MD*	28
11:14 AM	Discussion		
11:17 AM	Case Presentation	Carol L Shields MD*	28
11:20 AM	Discussion		
11:23 AM	Case Presentation	Anita Agarwal MD	28
11:26 AM	Discussion		
11:29 AM	Case Presentation	William F Mieler MD	28
11:32 AM	Discussion		

Section IV: Medical Retina

Moderators: Caroline R Baumal MD* and Lawrence J Singerman MD*

11:35 AM	Predictors of Post-injection Endophthalmitis: A Multivariable Analysis Based on Injection Protocol and Povidone Iodine Strength	Tarek S Hassan MD*	29
11:42 AM	Pentosan Polysulfate Maculopathy	Nieraj Jain MD	32
11:49 AM	Retinal Ophthalmic Technology Assessments That Will Change Your Practice	Stephen J Kim MD	34
11:56 AM	Systemic Management of Acute Retinal Artery Occlusions	Timothy W Olsen MD*	36
12:03 PM	Update on Hereditary Retinal Diseases	Stephen H Tsang MD PhD*	38
12:10 PM	Injection Index in Neovascular AMD Pigment Epithelial Detachment Predicts Long-term Visual Outcomes	Steven D Schwartz MD*	39
12:17 PM	LUNCH		

Section V: Uveitis

Moderators: Janet Louise Davis MD* and Narsing A Rao MD

1:37 PM	Emerging Infectious Diseases	Steven Yeh MD*	40
1:44 PM	Treating Uveitic Edema	Albert T Vitale MD*	44
1:51 PM	Update on Uveitis Comparative Effectiveness Trials: MUST, POINT, MERIT, and ADVISE	Douglas A Jabs MD MBA	45
1:58 PM	Effect of Fluocinolone Acetonide Insert on the Presence of Uveitic Macular Edema: Outcomes at 36 Months	Quan Dong Nguyen MD*	46

* Indicates that the presenter has financial interest. No asterisk indicates that the presenter has no financial interest.

2:05 PM	Uveitis Panel Discussion: Mistakes Made in Caring for the Uveitis Patient and How to Avoid Them Panel Moderator: Sunil K Srivastava MD* Panelists: Thomas A Albini MD*, Janet Louise Davis MD*, Lisa J Faia MD*, Phoebe Lin MD PhD, Narsing A Rao MD*, and Albert T Vitale MD		

Section VI: Pro–Con Debates

Moderators: Alexander J Brucker MD and Suber S Huang MD MBA*

2:20 PM	We Should Peel Epiretinal Membranes in Eyes With Good Visual Acuity: Pro	Colin A McCannel MD*	47
2:23 PM	We Should Peel Epiretinal Membranes in Eyes With Good Visual Acuity: Con	Harry W Flynn Jr MD	47
2:26 PM	Audience Vote		
2:27 PM	Anti-VEGF Therapy Is the Best Treatment for Proliferative Diabetic Retinopathy: Pro	Jeffrey G Gross MD*	49
2:30 PM	Anti-VEGF Therapy Is the Best Treatment for Proliferative Diabetic Retinopathy: Con	Dean Eliott MD*	49
2:33 PM	Audience Vote		
2:34 PM	Nonproliferative Diabetic Retinopathy Should Be Treated Routinely With Anti-VEGF Therapy: Pro	Diana V Do MD*	50
2:37 PM	Nonproliferative Diabetic Retinopathy Should Be Treated Routinely With Anti-VEGF Therapy: Con	Yannek I Leiderman MD PhD*	50
2:40 PM	Audience Vote		
2:41 PM	OCT Angiography Is Essential for Clinical Practice: Pro	Nadia Khalida Waheed MD*	51
2:44 PM	OCT Angiography Is Essential for Clinical Practice: Con	Richard S Kaiser MD*	51
2:47 PM	Audience Vote		
2:48 PM	When Treating Neovascular AMD, Macular Fluid Should Not Be Tolerated: Pro	David M Brown MD	52
2:51 PM	When Treating Neovascular AMD, Macular Fluid Should Not Be Tolerated: Con	Joan W Miller MD	52
2:54 PM	Audience Vote		

Section VII: Pediatric Retina

Moderators: Philip J Ferrone MD* and Michael T Trese MD*

2:55 PM	Anti-VEGF Safety in ROP	Robert L Avery MD*	53
3:02 PM	ROP in Adolescents and Adults	Antonio Capone Jr MD*	54
3:09 PM	OCT Angiography in Children	Lejla Vajzovic MD*	55
3:16 PM	Prophylactic Scleral Buckling in Children	Yoshihiro Yonekawa MD	56
3:23 PM	Pediatric Retina Panel Discussion Panel Moderator: Darius M Moshfeghi MD* Panelists: Audina M Berrocal MD*, Cagri G Besirli MD*, R V Paul Chan MD*, Kimberly A Drenser MD PhD*, and Cynthia A Toth MD*		
3:38 PM	REFRESHMENT BREAK		

* Indicates that the presenter has financial interest. No asterisk indicates that the presenter has no financial interest.

Section VIII: Late Breaking Developments, Part I

Moderator: Mark S Humayun MD PhD*

Panelists: Sophie J Bakri MD*, Wiley Andrew Chambers MD, Tara A McCannel MD, and Paul Sternberg Jr MD*

4:18 PM	Results of Cohorts 1-5 for the RGX-314 Phase I/IIa Study of Gene Therapy for Neovascular Wet AMD	Jeffrey S Heier MD*	57
4:23 PM	Discussion		
4:26 PM	24-Week Results of Phase 1 Study of Intravitreal Gene Therapy With ADVM-022 for Neovascular AMD (OPTIC Trial)	Szilard Kiss MD	57
4:31 PM	Discussion		
4:34 PM	Abicipar for Neovascular AMD: Two-Year Results From CEDAR and SEQUOIA Phase 3 Clinical Trials	Rahul Khurana MD*	57
4:39 PM	Discussion		
4:42 PM	Primary Results From Phase 2 Study of Risuteganib in Intermediate Dry AMD	David S Boyer MD*	57
4:47 PM	Discussion		
4:50 PM	A Multicenter Phase 3 Double-Masked Randomized Controlled Noninferiority Trial Comparing the Clinical and Cost Effectiveness of Ranibizumab (Lucentis) vs. Aflibercept (Eylea) vs. Bevacizumab (Avastin) in Macula Edema Due to Central Retinal Vein Occlusion (LEAVO)	Philip G Hykin MBBS*	57
4:55 PM	Discussion		

Section IX: First-time Results of Clinical Trials

Moderators: Judy E Kim MD* and Elliott H Sohn MD*

4:58 PM	Extended Durability in Exudative Retinal Diseases Using the Novel Intravitreal Anti-VEGF Antibody Biopolymer Conjugate KSI-301: Results From the Phase 1b Study in Patients with wAMD, DME, and RVO	Charles C Wykoff MD PhD	58
5:05 PM	VICI Study of Eplerenone for Central Serous Retinopathy	Andrew J Lotery MBChB*	60
5:12 PM	Vitreous Substitutes Following Vitrectomy Surgery	Andrew A Chang MBBS*	64
5:19 PM	An Update on New Retinal Drugs	Peter K Kaiser MD*	65
5:27 PM	Closing Remarks	Mark S Humayun MD PhD* Judy E Kim MD*	

SATURDAY, OCTOBER 12

7:00 AM	CONTINENTAL BREAKFAST		
8:00 AM	Opening Remarks	Mark S Humayun MD PhD* Judy E Kim MD*	

Section X: Imaging

Moderators: Gemmy Chui Ming Cheung MB BChir FRCOphth* and Ursula M Schmidt-Erfurth MD*

8:05 AM	Ultrawide-Field Swept Source OCT for Dynamic Observations of Vitreous	Kyoko Ohno-Matsui MD*	67
8:12 AM	Microcirculation in Systemic Diseases: What Can We Learn From OCT Angiography?	Nicole Eter MD*	69
8:19 AM	All Macular Cystoid Cavities Are Not Cystoid Macular Edema	Alain Gaudric MD *	71

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8:26 AM	Retinal Metabolic Assessment Using Mitochondrial Oxidative Stress Imaging: A New Clinical Tool for Detecting and Monitoring Substructural Disease	Richard B Rosen MD*	73
8:33 AM	Taking the Guesswork Out of Pachychoroid	Philip J Rosenfeld MD PhD*	75
8:40 AM	En Face OCT: Patho-anatomical Insights Into the Macula and Its Related Disorders	David Sarraf MD*	77
8:47 AM	Machine Learning to Automate Biomarker Detection From OCT Scans	Sebastian Wolf MD PhD*	78
8:54 AM	Imaging Panel Discussion: Pathognomonic Retinal Imaging Findings That You Don't Want to Miss Panel Moderator: Jay S Duker MD* Panelists: Michael S Ip MD*, Brandon J Lujan MD*, Philip J Rosenfeld MD PhD, and Seung Young Yu MD PhD*		

Section XI: Late Breaking Developments, Part II

Moderators: Susanne Binder MD and Srinivas R Sadda MD*

Panelists: Rajendra S Apte MD PhD*, Michael A Singer MD*, and Demetrios Vavvas MD

9:09 AM	Prevalence of Maculopathy Associated With Pentosan Polysulfate Therapy in Kaiser Permanente Northern California	Robin A Vora MD	79
9:14 AM	Discussion		
9:17 AM	Results of a Phase 1/2 Trial of an Optimized Gene Therapy in Adults and Children With Retinal Dystrophy Associated With Bi-allelic Variants in RPE65	Michel Michaelides MD*	79
9:22 AM	Discussion		
9:25 AM	Subretinal Human Retinal Progenitor Cells in Retinitis Pigmentosa: A Phase I/IIa Study	Pravin U Dugel MD*	79
9:30 AM	Discussion		
9:33 AM	Port Delivery System With Ranibizumab for Neovascular AMD: Ladder Phase 2 Trial End of Study Results	Carl D Regillo MD FACS*	79
9:38 AM	Discussion		
9:41 AM	Comparison of the Efficacy and Safety of Brolucizumab vs. Aflibercept in Eyes With Polypoidal Choroidal Vasculopathy: 96-Week Results From the HAWK Study	Glenn J Jaffe MD*	79
9:46 AM	Discussion		
9:49 AM	Data Supporting the Sustained Efficacy of Faricimab, a Bispecific Antibody Neutralizing Both Angiopoietin-2 and VEGF-A	Karl G Csaky MD*	79
9:54 AM	Discussion		
9:57 AM	REFRESHMENT BREAK and AAO 2019 EXHIBITS		

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Section XII: Neovascular AMD

Moderators: Mark S Blumenkranz MD* and William E Smiddy MD

Virtual Moderator: Jason HSU MD*

10:28 AM	The Functional Impact of Fluctuating Retinal Thickness in the IVAN and CATT Trials: A Meta-analysis	Usha Chakravarthy MBBS PhD*	80
10:35 AM	OCT Angiography in Neovascular AMD: Can We Predict Treatment Response?	Amani Fawzi MD	81
10:42 AM	Does Type 1 Neovascularization Slow Macular Atrophy in Eyes With AMD?	K Bailey Freund MD*	82
10:49 AM	New Meta-analysis of Anti-VEGF Dosing in AMD	Richard F Spaide MD*	83
10:56 AM	Anatomic Predictors of Visual Outcomes After Long-term Anti-VEGF Therapy	Srinivas R Sadda MD*	84

Section XIII: Oncology

Moderators: Timothy G Murray MD MBA* and Jerry A Shields MD

11:03 AM	Forty Years' Experience With Proton Therapy to Treat Patients With Uveal Melanoma	Evangelos S Gragoudas MD*	86
11:08 AM	Retinal Toxicity of Cancer Drugs	Jasmine H Francis MD	88
11:13 AM	Current Management of Uveal Melanomas	Prithvi Mruthyunjaya MD*	90
11:18 AM	Molecular Insights Into Uveal Melanoma	J William Harbour MD*	92
11:23 AM	Indications and Surgical Techniques for Choroidal Tumor Biopsy	Zelia M Correa MD	93
11:28 AM	Strategies to Treat and Prevent Radiation Retinopathy	Amy C Schefler MD*	95
11:33 AM	LUNCH and AAO 2019 EXHIBITS		

Section XIV: Diabetes

Moderators: David J Browning MD PhD* and Daniel F Martin MD

12:53 PM	Artificial Intelligence for Diabetic Retinopathy Screening	Tien Yin Wong MBBS*	97
1:00 PM	Protocol T Extension Results	John A Wells III MD*	100
1:07 PM	Predicting 2-Year Outcomes Based on Visual Acuity or OCT Changes Following 3 Anti-VEGF Injections for Diabetic Macular Edema	Neil M Bressler MD*	101
1:14 PM	Findings From Wide-Field Color Photography for Diabetic Retinopathy Prognosis	Lloyd P Aiello MD PhD	103
1:21 PM	Management of High-risk Nonproliferative Diabetic Retinopathy Without Diabetic Macular Edema: Results From PANORAMA	Rishi P Singh MD*	104
1:28 PM	Anti-VEGF Treatment Can Diminish Signs of Diabetic Retinopathy Without Reducing Nonperfusion	Ramin Tadayoni MD PhD*	105
1:35 PM	Treatment of Centrally Involved Diabetic Macular Edema With Better Vision: Protocol V	Jennifer K Sun MD*	106
1:42 PM	Role of Steroids in Diabetic Macular Edema	Anat Loewenstein MD*	107
1:49 PM	Diabetes Panel Discussion Panel Moderator: Julia A Haller MD Panelists: Susan B Bressler MD*, Donald J D'Amico MD*, James C Folk MD*, Mary Elizabeth Hartnett MD FACS*, and Nancy M Holekamp MD*		

* Indicates that the presenter has financial interest. No asterisk indicates that the presenter has no financial interest.

Section XV: Innovative Retinal Interventions

Moderators: Tamer H Mahmoud MD* and Kirk H Packo MD*

2:04 PM	Results of a Phase I Study of Near Infrared Photobiomodulation of Diabetic Macular Edema	Mark C Gillies MD PhD*	108
2:11 PM	Home OCT Monitoring: The Future of AMD Management	Judy E Kim MD*	109
2:18 PM	Toward Robotic Vitreoretinal Surgery	Jean-Pierre Hubschman MD*	111
2:25 PM	Amniotic Membrane for AMD	Stanislao Rizzo MD	112
2:32 PM	Innovative Retinal Interventions Panel Discussion Panel Moderator: Marco A Zarbin MD PhD FACS* Panelists: Raymond Iezzi MD, Judy E Kim MD*, Stanislao Rizzo MD, and David N Zacks MD PhD*		

Section XVI: Non-neovascular AMD

Moderators: Mark W Johnson MD* and John S Pollack MD*

2:47 PM	Spectral Domain OCT Signs Suggestive of OCT Angiography–Defining Abnormal Choroidal Neovascular Complexes in Eyes With Large Drusen	Robyn H Guymer MBBS PhD*	113
2:54 PM	Risk Factors for Geographic Atrophy Progression Secondary to AMD	Frank G Holz MD*	114
3:01 PM	The Role of Neuroprotection in Retinal Diseases	Baruch D Kuppermann MD PhD*	119
3:08 PM	New Classification for Macular Atrophy	Giovanni Staurenghi MD*	123

Section XVII: Vitreoretinal Surgery, Part II

Moderators: Ehab N El Rayes MD PhD and Jonathan L Prenner MD*

3:15 PM	Outcomes of Combined Phaco/Pars Plana Vitrectomy vs. Sequential Surgery	Jennifer Irene Lim MD*	125
3:22 PM	Update on Intraoperative OCT	Justis P Ehlers MD*	129
3:29 PM	Vitreoretinal Surgery Panel Discussion Panel Moderator: Jonathan L Prenner MD* Panelists: Robert G Devenyi MD FACS FRCSC MBA*, Ehab N El Rayes MD PhD, Sunir J Garg MD FACS*, Andrew A Moshfeghi MD MBA*, and Dante Pieramici MD		
3:44 PM	REFRESHMENT BREAK and AAO 2019 EXHIBITS		

Section XVIII: Medical Retina and Vein Occlusion

Moderators: Linda A Lam MD MBA* and Young Hee Yoon MD

4:31 PM	LEAVO vs. SCORE2: A Comparison of 2 CRVO Comparative-Effectiveness Trials for the Treatment of Macular Edema With Anti-VEGF Agents	Barbara Ann Blodi MD	130
4:38 PM	Improved Cone Function in Retinitis Pigmentosa by Oral *N*-Acetylcysteine	Peter A Campochiaro MD*	133
4:45 PM	Long-term Effects of the Phase 2 Ciliary Neurotrophic Factor Treatment of Macular Telangiectasia Type	Emily Y Chew MD	134
4:52 PM	Complications and Costs of Gene- and Cell-Based Therapy	David J Wilson MD*	136

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Section XIX: Video Surgical Complications—What Would You Do?

Moderators: Hugo Quiroz-Mercado MD* and Kourous Rezaei MD*

4:59 PM	ILM Peeling	Kazuaki Kadonosono MD	137
5:02 PM	Discussion		
5:05 PM	Intraocular Scissors	Khalid K Sabti, MD*	137
5:08 PM	Discussion		
5:11 PM	Dexamethasone Intravitreal Implant Injection	Andre Maia MD	137
5:14 PM	Discussion		
5:17 PM	Scleral Buckling	Geoffrey G Emerson MD PhD*	138
5:20 PM	Discussion		
5:23 PM	Trauma and Contact Lens	Carl C Claes MD*	138
5:26 PM	Discussion		
5:29 PM	Closing Remarks	Mark S Humayun MD PhD*	
5:30 PM	ADJOURN	Judy E Kim MD*	

* Indicates that the presenter has financial interest. No asterisk indicates that the presenter has no financial interest.

Precision Subretinal Delivery for Gene and Cell Therapy

Allen C Ho MD

I. Introduction

Subretinal delivery affords direct surgical access to target retinal pigment epithelial cells (RPE) and retinal cells/photoreceptors. Direct access to these cell targets in the subretinal space may be important for gene and cell therapies for retinal diseases. 2017 FDA approval of subretinal delivery of voretigene for RPE65 Leber congenital amaurosis and RPE65 retinitis pigmentosa, as well as evidence from other clinical trials for other retinal degenerations and neovascular AMD, have established the feasibility and safety of transvitreal subretinal delivery after pars plana vitrectomy. Improving gene and cell therapies requires not only refining viral vectors, transgenes, and cell lines but also improving surgical delivery techniques and designing new instrumentation to achieve these goals.

Evolution of subretinal surgical techniques includes preoperative surgical planning with multimodal imaging to identify the target zone of delivery, improved dose precision with real-time surgeon-controlled foot pedal delivery and handheld microdose injection instrumentation, real-time intraoperative OCT imaging for microcatheter placement in the correct tissue plane (eg, subretinal space vs. suprachoroidal space), volumetric OCT imaging to calculate dose volume in the subretinal space after subretinal delivery, and new strategies to limit egress into the vitreous by retinotomy tamponade or via delivery to the subretinal space without a retinotomy (ab externo suprachoroidal to subretinal delivery).

Transvitreal subretinal delivery without vitrectomy and suprachoroidal injection delivery for gene therapies are also under investigation.

II. Transvitreal Subretinal Delivery After Pars Plana Vitrectomy

Used for most retinal gene and cell therapy studies—good safety profile, familiar procedure, and direct visualization, improved precision with MicroDose Injection kit, which is performed with surgeon foot pedal control via viscous fluid injection (VFI) system

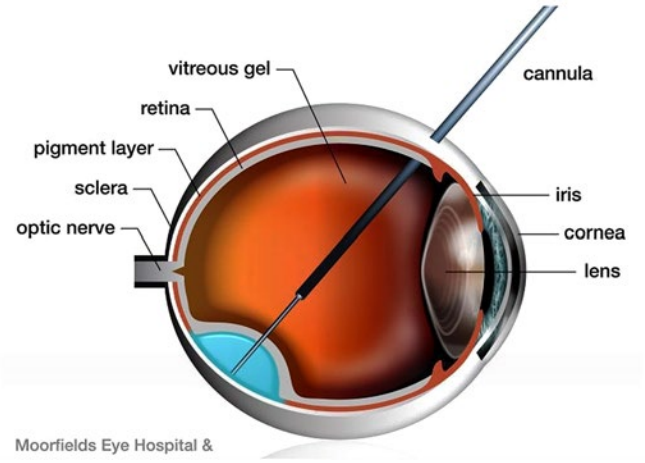


Figure 1. Credit: Moorfields Eye Hospital.

A. Procedure

1. Preoperative site planning and load MicroDose injection syringe connected to Viscous Fluid Injection system and 41-gauge flexible cannula to prepare for delivery with no air bubbles
2. Test system to create drip from 41-gauge cannula (typically 10-20 mmHg)
3. Pars plana vitrectomy with posterior vitreous detachment induction
4. 41-gauge cannula to subretinal space with simultaneous foot pedal injection (optional intraoperative OCT)
5. MicroDose syringe allows measured subretinal volume, typically 100-250 µl
6. ± air–fluid exchange

B. New instrumentation: improved control and precision with MicroDose Injection Kit

1. 1-cc syringe: aspirate or back fill and remove air bubbles
2. Adaptor to VFI system of vitrectomy machine for foot pedal control
3. Low pressure setting to create drip rate from 41-gauge cannula

Figure 2.

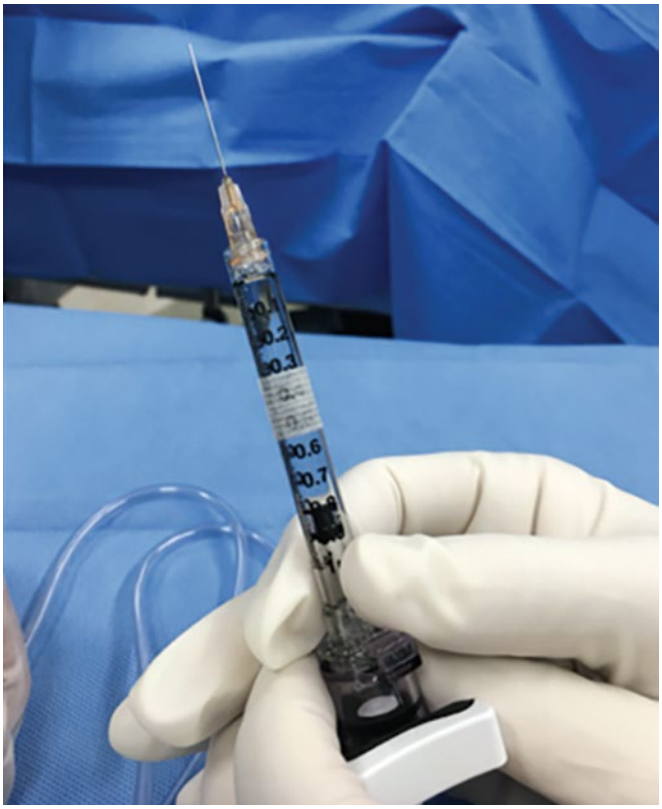


Figure 3.

C. Dosing variability with retinotomy?

1. Retinotomy dosing imprecision is due to egress of intervention into the vitreous cavity; this may diminish efficacy but may also cause safety issues (for example, inflammation and membrane formation).
2. Cell therapy egress creates preretinal membrane formation.
3. Some advocate for a subretinal air bubble for tamponade or air–fluid exchange to minimize egress through the retinotomy into the vitreous cavity, although the efficacy of this remains unproven.

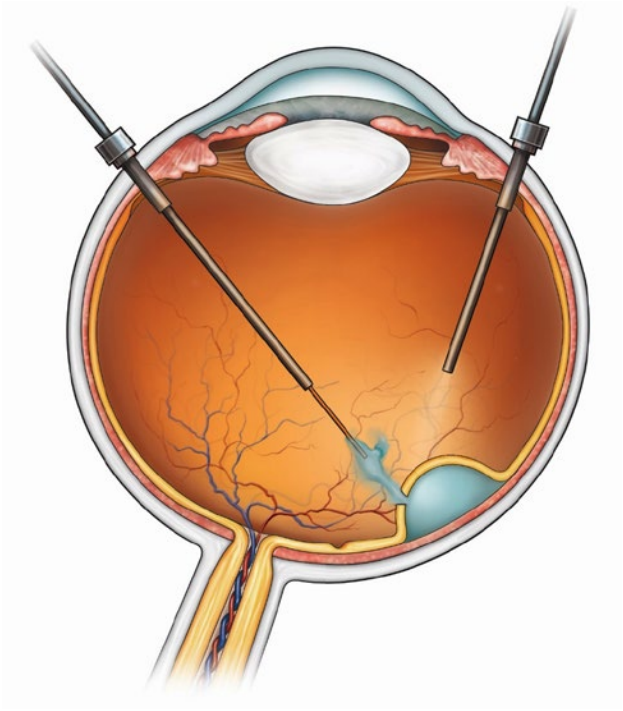


Figure 4.

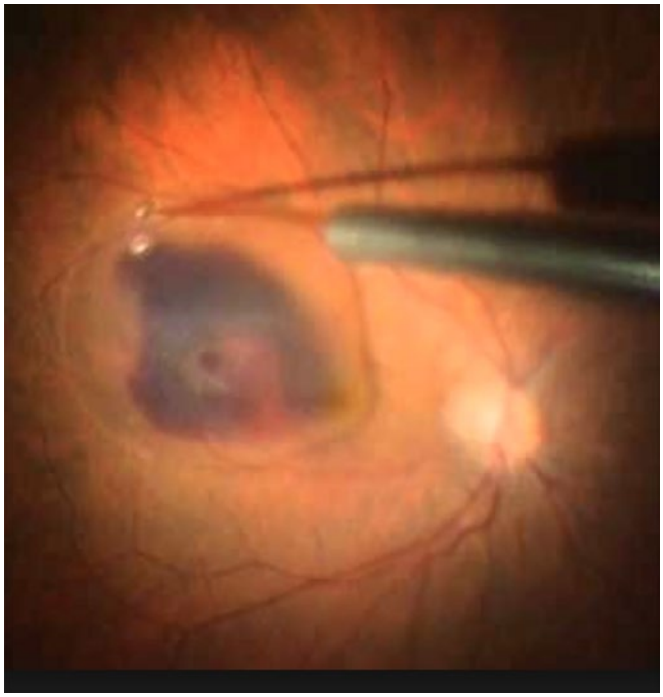


Figure 5.

III. Transvitreal Subretinal Delivery Without Pars Plana Vitrectomy

A subretinal delivery method that may reduce complications of pars plana vitrectomy (for example, cataract progression) is transvitreal injection to the subretinal space without vitrectomy. This technique is being considered in a gene therapy clinical trial. Instrumentation is in development.

IV. Ab Externo Subretinal Delivery

The retina and RPE are accessible target tissues, with vitreous surgery techniques for delivery of therapies to the subretinal space; however, transvitreal approaches necessitate a retinotomy. Ab externo approaches to the subretinal space may be less invasive, may avoid vitrectomy and vitrectomy complications like progressive cataract, and may deliver more precise subretinal dosing.

A. New FDA-approved instrumentation: flexible, dual bore catheter with microadjustable advancing microcatheter and positioning system

1. Flexible suprachoroidal catheter inserted through sclerotomy
2. 38-gauge microadjustable advancing microcatheter can delivery saline or switch to intervention.
3. Third arm with multiple degrees of freedom allows hands-free positioning of catheter.

B. Ab externo suprachoroidal to subretinal procedure

1. Flexible suprachoroidal catheter inserted through sclerotomy into suprachoroidal space
2. Advance catheter under direct microscopic, chandelier-illuminated, wide-field viewing
3. Microneedle advancement when reach target zone and visualize advancing microneedle
4. Saline subretinal bleb first to open subretinal space
5. Switch to intervention, see leading air bubble, and then intervention will deliver to the subretinal space
6. Retract microneedle and withdraw catheter

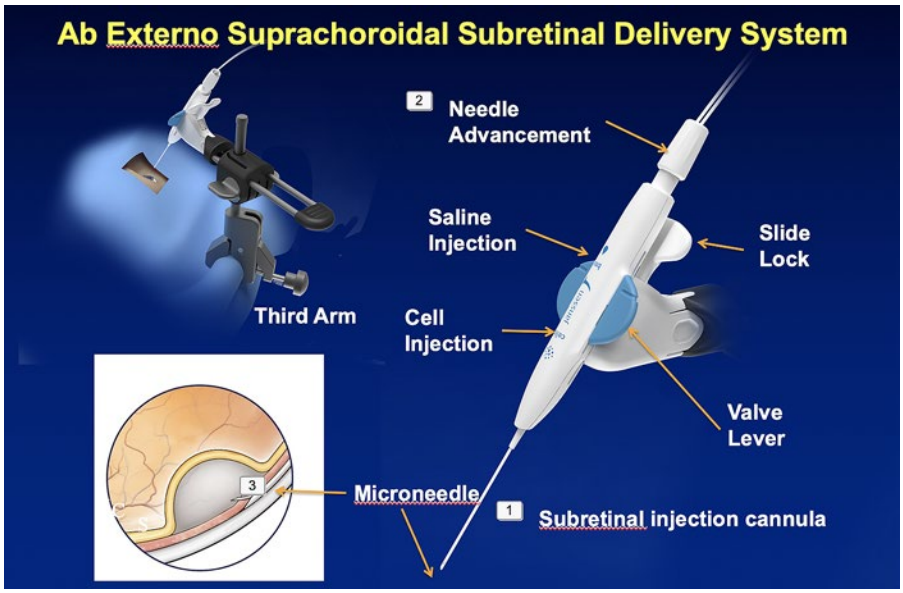


Figure 6.

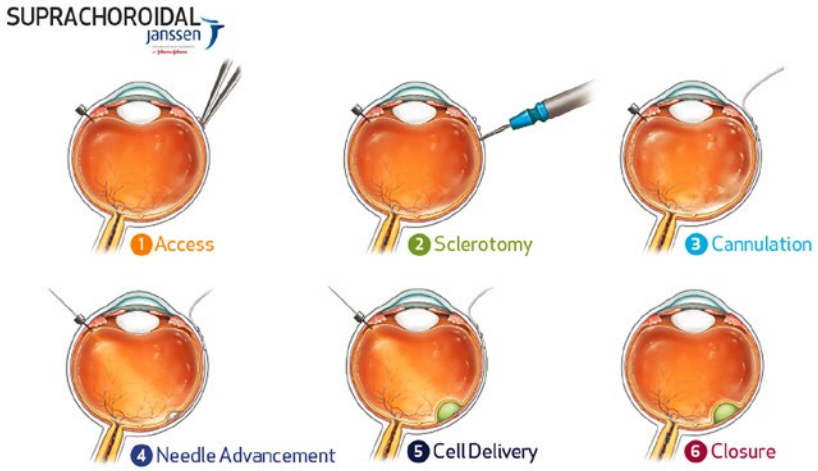


Figure 7.

IV. Preoperative and Intraoperative Imaging Technology May Improve Subretinal Delivery

Preoperative multimodal imaging may help localize a specific target zone for subretinal delivery—for example, at the border of geographic atrophy or away from a preferred retinal fixation locus. Intraoperative real-time OCT may help identify the correct surgical plane for transvitreal or ab externo surgical approaches to achieve more precise subretinal dosing.

A. Intraoperative OCT may improve subretinal delivery accuracy.

B. Intraoperative OCT may improve subretinal dosing accuracy.

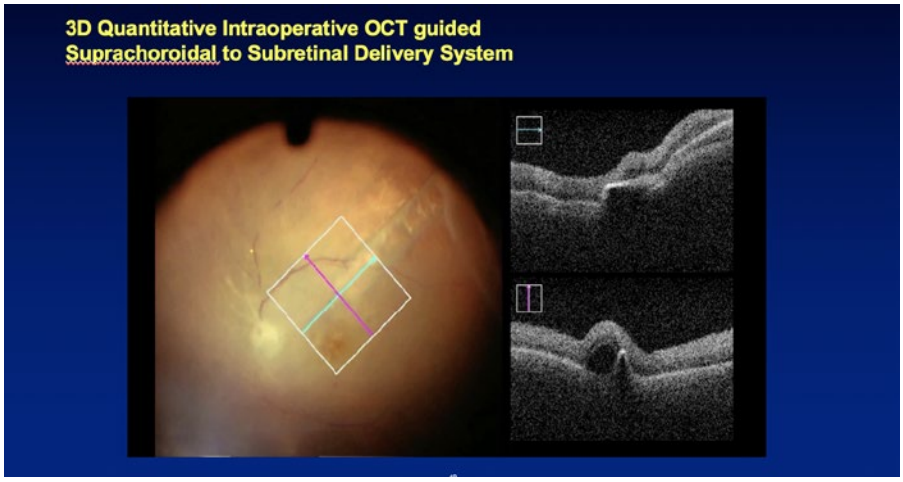


Figure 8.

V. Suprachoroidal Injection Is Being Explored to Simplify Delivery of Gene And cell and Other Retinal Therapies

A. Does not deliver to the subretinal space, but preclinical work suggests transfection of retinal cells

B. Can be an office-based procedure; may avoid OR surgery

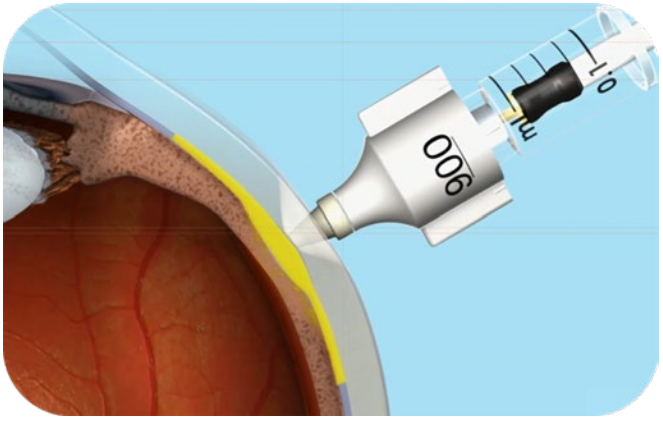


Figure 9.

VI. Summary

Progress with new surgical instrumentation, surgical techniques, and intraoperative imaging have improved the precision of subretinal delivery of gene and cell therapy. Improving gene and cell therapies requires not only refining viral vectors, transgenes, and cell lines but also improving surgical delivery techniques and designing new instrumentation to achieve these goals. Subretinal delivery can be quantified with imaging techniques to determine dosing consistency; a retinotomy necessarily creates variable dosing.

References

1. Maguire AM, Simonelli F, Pierce EA, et al. Safety and efficacy of gene transfer for Leber's congenital amaurosis. *N Engl J Med*. 2008; 358: 2240-2248.
2. Bennett J, Wellman J, Marshall KA, et al. Safety and durability of effect of contralateral-eye administration of AAV2 gene therapy in patients with childhood-onset blindness caused by RPE65 mutations: a follow-on phase 1 trial. *Lancet* 2016; 388:661-672.
3. Ho AC, Chang TS, Samuel M, Williamson P, Willenbucher RF, Malone T. Experience with a subretinal cell-based therapy in patients with geographic atrophy secondary to age-related macular degeneration. *Am J Ophthalmol*. 2017; 179:67-80.
4. Schwartz SD, Regillo CD, Lam BL, et al. Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label Phase 1/2 studies. *Lancet* 2015; 385(9967):509-516.
5. Xue K, Groppe M, Salvetti AP, MacLaren RE. Technique of retinal gene therapy: delivery of viral vector into the subretinal space. *Eye* 2017; 31:12308-1316.
6. Rakoczy EP, Lai CM, Magno AL, et al. Gene therapy with recombinant adeno-associated vectors for neovascular age-related macular degeneration: 1 year follow-up of a Phase 1 randomised clinical trial. *Lancet* 2015; 386:2395-2403.
7. Fischer MD, Hickey DG, Singh MS, MacLaren RE. Evaluation of an optimized injection system for retinal gene therapy in human patients. *Hum Gene Ther Methods*. 2016; 27:150-158.
9. Ding K, Shen J, Zibran H, et al. Widespread ocular transgene expression after AAV8 vectored suprachoroidal gene transfer. ARVO 2019 Poster #2923.
10. Yiu G, Chung S, Mollhoff I, et al. Suprachoroidal injection of AAV8 for ocular gene delivery in the nonhuman primate. ARVO 2019 Poster#A0091.

The Benefit of the Bag-in-the-Lens IOL for Vitreoretinal Surgery

Claus Eckardt MD

The implantation technique of Tassignon's so-called bag-in-the-lens (BIL) IOL comprises several steps: A clear corneal incision using a 2.8-mm keratome is performed, and a 5-mm well-centered anterior capsulorrhexis is carried out with the help of a ring caliper placed onto the anterior lens capsule. After cataract removal and cleaning the capsular bag, an incision of the posterior capsule is performed and viscoelastic is injected into the retrolenticular space in order to displace the anterior hyaloid and to separate it from the posterior capsule, respectively. This is followed by a posterior capsulorrhexis of the same size as the anterior capsulorrhexis. Finally, the foldable hydrophilic acrylic BIL is injected into the anterior chamber with an injector. Implantation is completed by placing the capsulorrhexis edges into the groove, which runs 360° along the rim of the optic of the lens.

For vitreoretinal surgery, the BIL IOL offers the following benefits: In combined phaco-vitrectomy it guarantees an excellent and stable centration of the lens, even during scleral indentation. Postoperatively, there will be no IOL decentration, no matter what kind of an intraocular tamponade is used—air, gas, or silicone oil. No posterior capsular opacification or contraction of the remaining anterior capsule can occur. Another important benefit is that even in eyes with acute or chronic inflammation, no posterior synechiae can develop since the capsulorrhexis edges are hidden in the lens groove and no proliferating lens epithelial cells can get in contact with the iris. Even diabetic eyes with an already existing iris neovascularization do not develop posterior synechiae after phaco-vitrectomy. Finally, an additional advantage of the lens is that even after many years it can be easily removed and exchanged if needed because of an altered binocular refractive situation.

Selected Readings

1. Tassignon MJ, De Groot V, Vrensen GF. Bag-in-the-lens implantation of intraocular lenses. *J Cataract Refract Surg*. 2002; 28:1182-1188.
2. Tassignon M-J, Dhubhghaill SN, van Os L, eds. *Innovative Implantation Technique: Bag In-the-Lens Cataract Surgery*. Basel: Springer Nature Switzerland; 2019.

Giant Retinal Tears: Tips, Tricks, and a Novel Tamponade

Medium-term Perfluoro-n-Octane for Inferior Retinal Detachments, Giant Retinal Tears, and Macular Patch Graft

Steven T Charles MD

I. Medium-term Perfluoro-n-Octane (PFO) Without Scleral Buckle for Inferior Retinal Detachment

A. Medium-term PFO is off label.

B. No supine or face-down positioning; patient can sit, stand, fly, drive, and work.

C. Slow, safe posterior vitreous detachment (PVD) over 14 days; no need for aggressive PVD induction associated iatrogenic retinal break risk in young myopes without PVD

D. No induced refractive error, unlike buckles; ideal after cataract and refractive surgery

E. Unlike scleral buckles, no strabismus, pain, no ocular surface disorder (poor conjunctival closure) or corneal or conjunctival damage (future glaucoma surgery)

F. Effective in phakic, IOL, or aphakic eyes

G. Remove PFO in 14 days

H. See Sigler EJ, Randolph JC, Charles S. Foreign body response within postoperative perfluoro-n-octane for retinal detachment repair. *Retina* 2014; 34(2):237-246; Sigler EJ, Randolph JC, Calzada JI, Charles S. 25-gauge pars plana vitrectomy with medium-term postoperative perfluoro-n-octane tamponade for inferior retinal detachment. *Ophthalmic Surg Lasers Imaging*. 2013; 44(1):34-40.

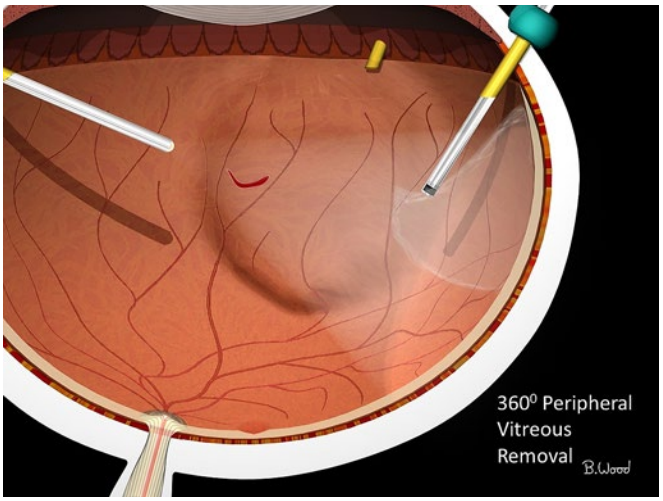


Figure 1.

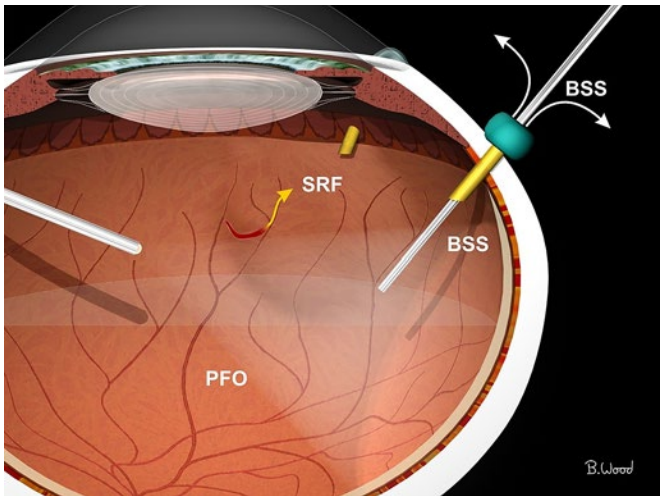


Figure 2.

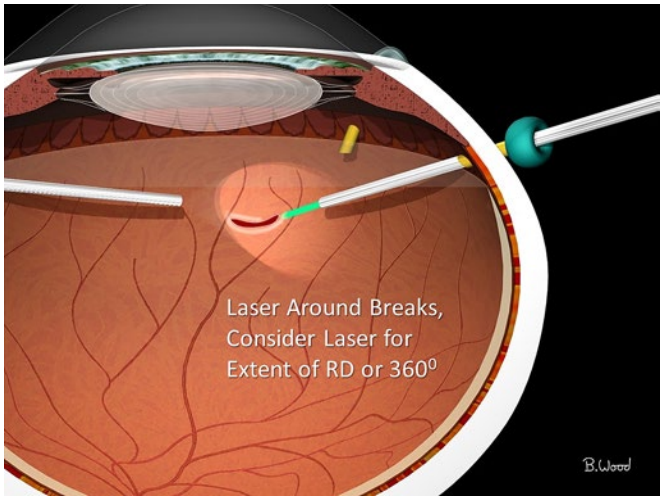


Figure 3.

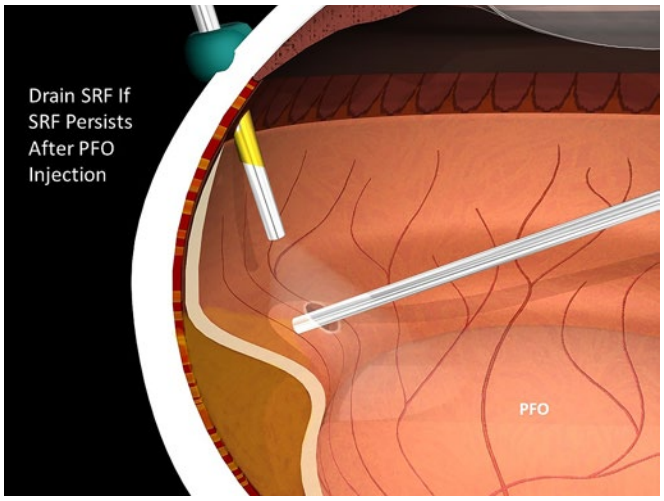
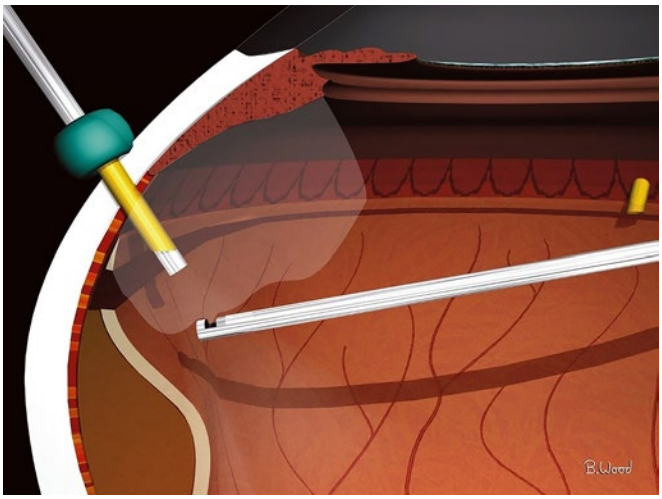


Figure 4.



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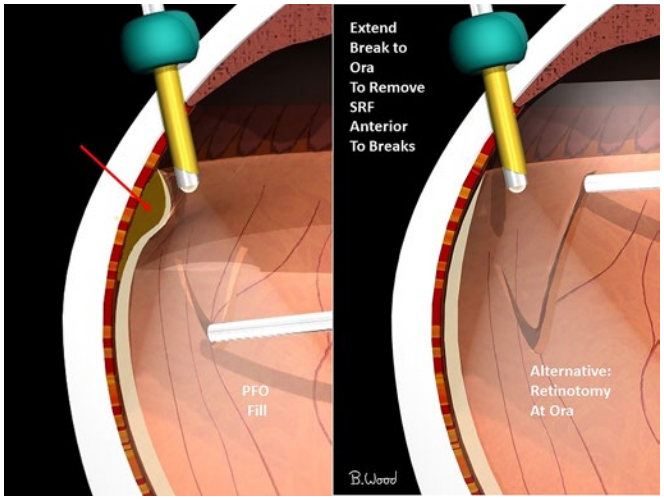

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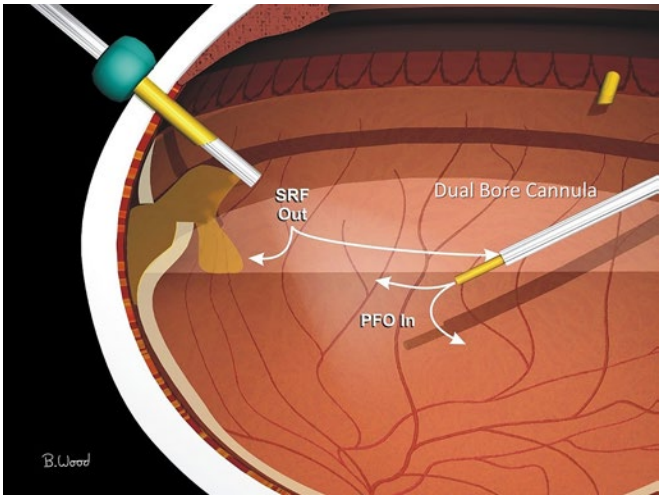


Figure 7.

II. Medium-term PFO for Inferior, Nasal, or Temporal Giant Retinal Tears (GRTs)

A. Use medium-term PFO for inferior, nasal, or temporal GRTs to prevent slippage.

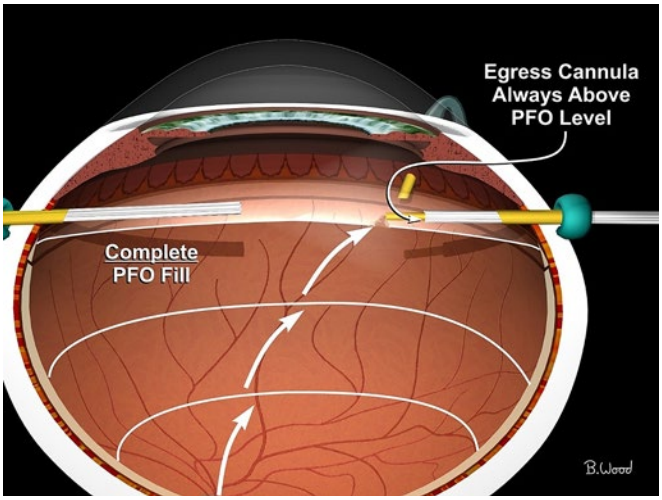
B. Inject PFO over the optic nerve using a dual bore cannula and viscous fluid control (VFC) at 8 psi; retract tip during injection, keeping tip at PFO–BSS interface to ensure a single PFO bubble.

C. Apply confluent endolaser to break, extend to ora at both ends of giant tear.

D. No scleral buckle

E. Topical difluprednate b.i.d. unless steroid responder

F. Remove PFO in 14 days.



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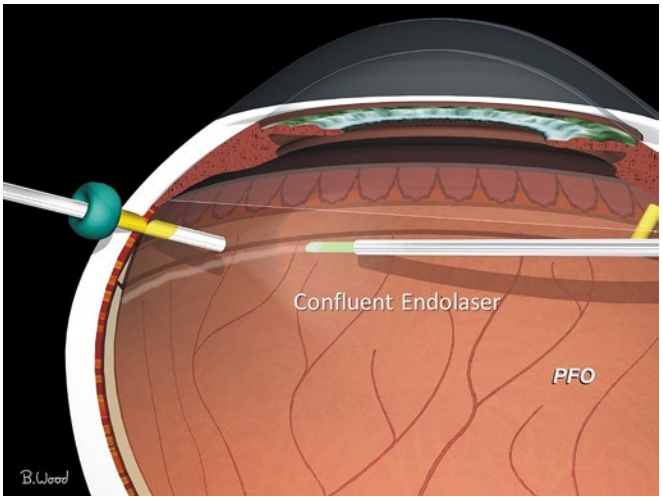


Figure 9.

III. Superior GRT

A. PFO–gas exchange *or* PFO–silicone oil exchange for superior GRT. Oil if proliferative vitreoretinopathy.

B. Chandelier illumination; VFC with silicone injection cannula in one hand, extrusion cannula without soft-tip in the other hand

C. Use VFC at 80 psi to inject oil through a sclerotomy cannula, *not* an infusion cannula, with short, thin-walled, low-resistance cannula

D. Keep extrusion cannula tip at oil or gas interface, with PFO in *periphery* to avoid slippage during exchange by removing BSS, subretinal fluid, and liquid vitreous *before* PFO.

E. Move focus down to follow cannula tip as exchange proceeds to optimize view of interface.

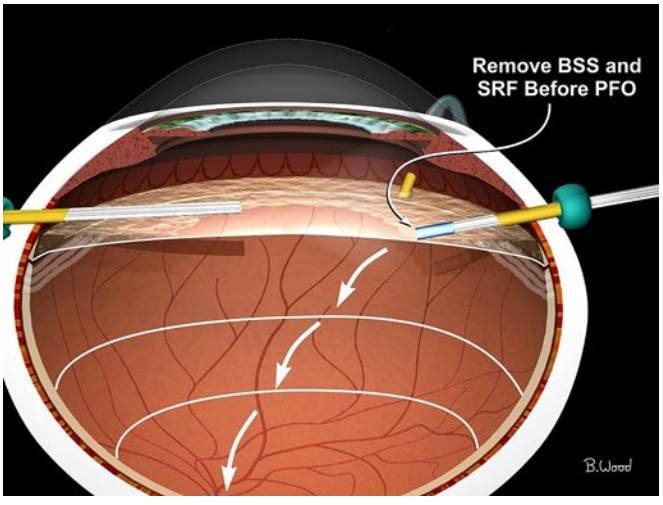


Figure 10.

IV. Autologous Macular Patch Graft

A. Developed by Tamer Mahmoud

B. Move graft from donor location to macular hole "under" PFO with DSP internal limiting membrane forceps to prevent scrolling and inversion; do not lift leading edge of graft.

C. PFO provides much better graft oxygenation than silicone oil (Steve Charles) because of higher oxygen solubility and extraction ratio; vitrectomy decreases viscosity 800X, thereby increasing partial pressure of oxygen by 12 mmHg; PFO enables graft oxygenation from anterior surface, not just choriocapillaris.

D. Remove PFO in 7 days. Grewal DS, Charles S, Parolini B, Kadonosono K, Mahmoud TH. Autologous retinal transplant for refractory macular holes: Multicenter International Collaborative Study Group. *Ophthalmology*, 2019.

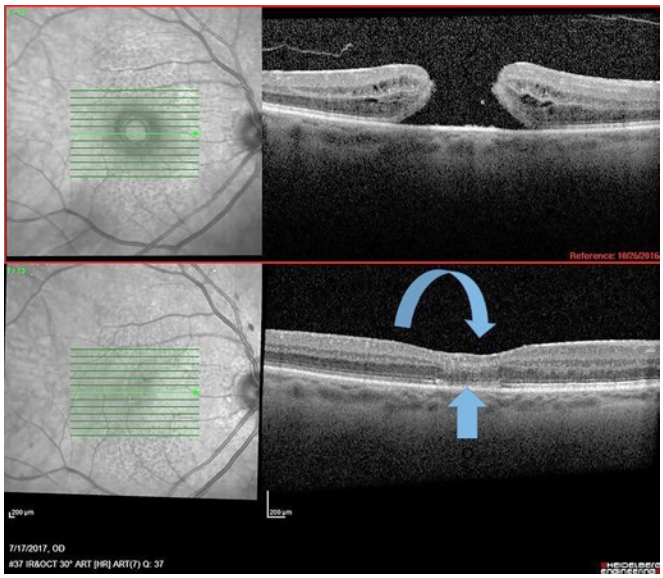


Fig 11. Increased oxygen diffusion post-PPV because of 800X viscosity decrease.

V. PFO vs. Oil Oxygen Transport

A. "PFCs can hold as much as 3 times the oxygen as human blood."

B. Lower total oxygen carrying capacity observed for perfluorinated fluid emulsions is balanced by their much higher oxygen extraction efficiencies. Adapted from Krafft MP, Riess JG. Perfluorocarbons: life sciences and biomedical uses. *J Polym Sci A Polym Chem*. 2007; 45:1185-1198.

C. "Silicone oil hinders oxygen mass transfer compared to air-water system. Decreases of kLa up to 25% have been noted."

Hypersonic Vitrectomy: Continued Technical and Clinical Developments

Carl C Awh MD

To date, over 200 surgical cases by 17 surgeons have been performed using a 23-gauge hypersonic vitrectomy device. Preoperative diagnoses include the following:

- Macular epiretinal membrane
- Macular hole
- Retained lens material
- Rhegmatogenous retinal detachment
- Proliferative diabetic retinopathy
- Tractional retinal detachment
- Vitreous hemorrhage
- Vitreous opacities
- Endophthalmitis
- Retained silicone oil

Intraoperative efficacy, outcomes, and complications will be reported.

Continuing clinical experience has revealed aspects of performance unique to the hypersonic vitrectomy device and has stimulated further technical refinement. Significant improvements in hypersonic vitrectomy performance have been achieved, with additional modifications to port design and ultrasound parameters. Although "stroke" (longitudinal oscillation distance) had previously been identified as a key variable, further research has revealed that modifications in ultrasound frequency have significant impact on performance. Examples will be presented.

Approaches to Difficult Macular Holes

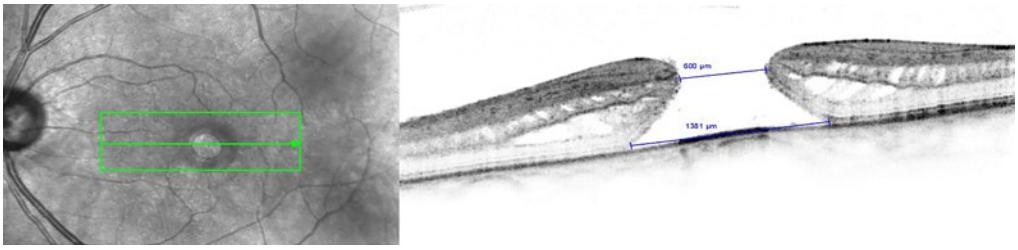
Michael J Koss MD, Slawek Cisiecki MD PhD, and Carsten Meyer MD PhD

What is considered a "difficult macular hole" today—in the time of high surgical closure rates and low complication rates? In 1991 the treatment of full-thickness macular holes (FTMH) by pars plana vitrectomy (PPV) and consecutive gas tamponade was first described by Kelly and Wendel, and this technique has been modified since then to improve the functional and anatomical outcome.[1] Anterior-posterior (anomalous posterior vitreous detachment) and tangential forces (epiretinal membrane [ERM]/internal limiting membrane [ILM] complex) seem to cause the pathology,[2] and the current standard treatment is by removing vitreous adhesions including the ERMs and the adherent ILM with vitrectomy and in most cases a gas endotamponade. Using this approach, most authors report an anatomical closure rate greater than 90% in primary FTMH cases.[3]

Nawrocki et al firstly described the inverted ILM flap technique,[4] which also works nicely in very large macular holes or in refractory macular holes (see Figure 1 and Table 1) that had previously failed surgeries.

Refractory (Large) Macular Holes—and Different Approaches

Risk factors for primary failed surgeries, and thus so called refractory macular holes (MH), are high myopia associated with or without staphyloma, trauma, or duration of the macular hole. The ILM preparation technique can also be achieved successfully in these rare cases, where there is no parafoveal ILM left, in a so called free flap technique, when extramacular ILM is used.[5]



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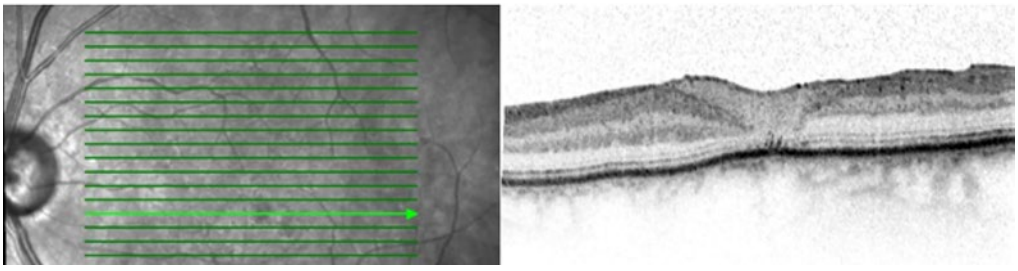

B

Figure 1. (A) Patient 5 months pre- and (B) 36 months post-inverted flap technique. Authors' data, unpublished.

Table 1. Large Macular Holes (Minimum Diameter > 500 µm) Operated With Inverted ILM Flap Technique

Patient	DOB	Sex	Diagn	Min	Max	VA Pre (dez)	VA Post (dez)	Outcome
				µ	µ			
1	06.09.49	w	Cat, MH	625	968	0.05	0.3	closed
2	18.12.44	w	Cat, MH	624	1176	1//25	1//35	flat open
3	14.07.38	w	Cat, MH	652	1445	0.05	0.1	closed
4	30.12.49	w	Cat, MH	561	733	0.05	0.2	closed
5	17.01.47	w	Cat, MH	561	1376	0.05	0.1	closed
6	23.05.52	w	Cat, MH	709	853	0.1	0.2	closed
7	11.01.52	w	MH	533	1074	0.1	0.2	closed

Authors' data, unpublished.

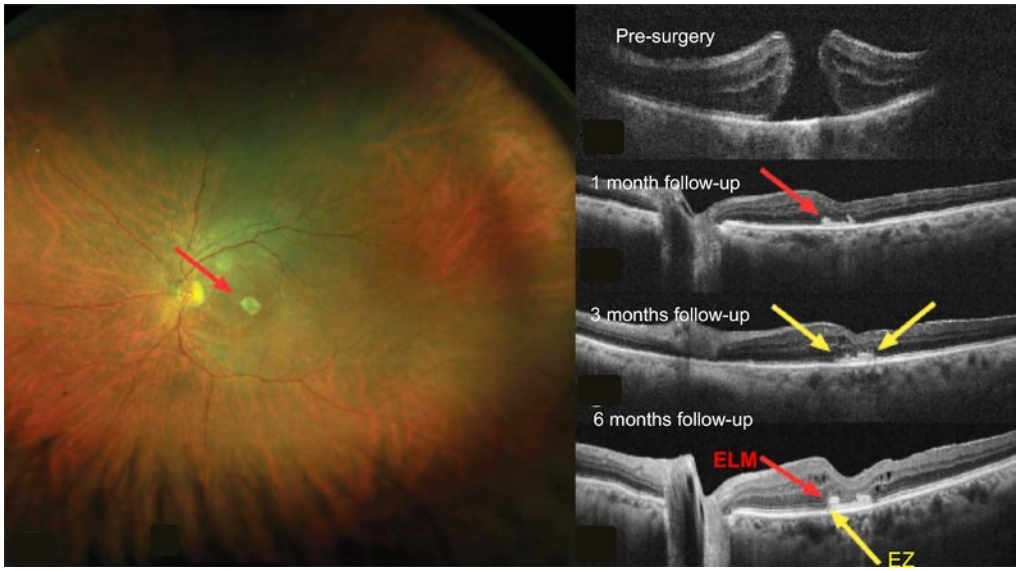

Figure 2. Postsurgical course of an amniotic macular patch by Rizzo et al. Reprinted by permission from Rizzo S, Caporossi T, Tartaro R, et al. A human amniotic membrane plug to promote retinal breaks repair and recurrent macular hole closure. *Retina*. Epub ahead of print 2018 Oct 3. doi: 10.1097/IAE.0000000000002320.

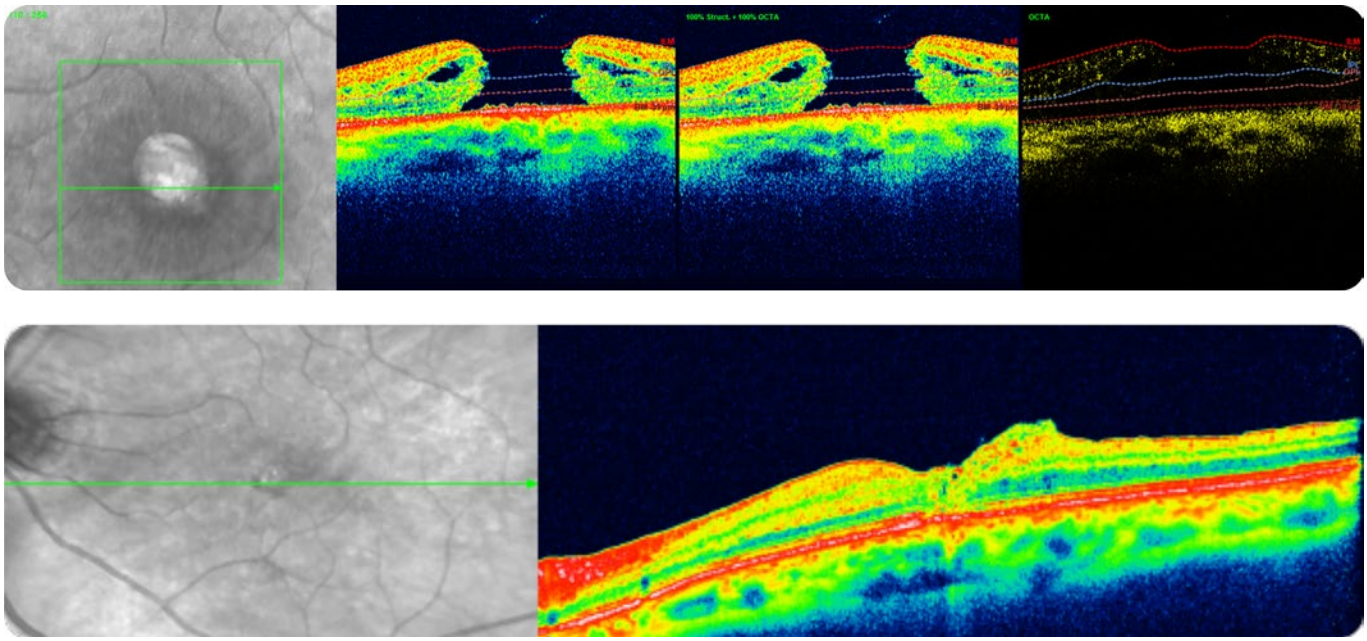

Figure 3. Refractory macular hole closure 9 months after PPV and lens capsular patch and oil tamponade. Reprinted by permission from Cisiecki S, Karolina Bonińska, Maciej Bednarski, Schaller I, Koss MJ, submitted to *Acta Scand Ophthalmologica*.

Recently another free flap technique has been firstly described and evaluated in a multicenter international study. The authors found an anatomic closure rate of 87% with an autologous retinal transplant technique, and they described the technique as safe in this initial study for closure of refractory MHs.[6]

Rizzo et al[7] investigated closure rates in treatment of difficult large holes with the use of amnion patches, used as a plug in cases of failed ILM preparation techniques (Figure 2). Both anatomical and functional outcomes are promising when the patch size, which is today prepared with a trephine, fits the MH space.

The strategy to seal a refractory macular hole with autologous tissue has been additionally extended to the anterior segment (Figure 3). Peng et al recently reported about 9 out of 10 eyes (7 phakic and 3 aphakic) that closed with the posterior lens capsule and autologous blood.[8]

Retinal Relaxation Surgery

In preoperated failed (refractory) macular hole cases, we find a secondary alteration between the photoreceptors and the retinal pigment epithelium (RPE), which may induce a firm adhesion between the neuroretina and adjacent RPE-choriocapillaris complex, thus preventing a natural relocation of the retracted (and normally) elastic neuroretina. *As opposed to all techniques mentioned above, a relaxation of the retracted retina might be sufficient to close a MH*. By inducing a posterior retinal detachment with a 41-gauge subretinal catheter and BSS application during a PPV with gas or oil endotamponade, such a retinal relaxation and thus a reproximation and closure of the MH can be achieved. (See educational video by Carsten Meyer at https://www.aao.org/clinical-video/how-to-close-macular-hole-using-subretinal-fluid.)

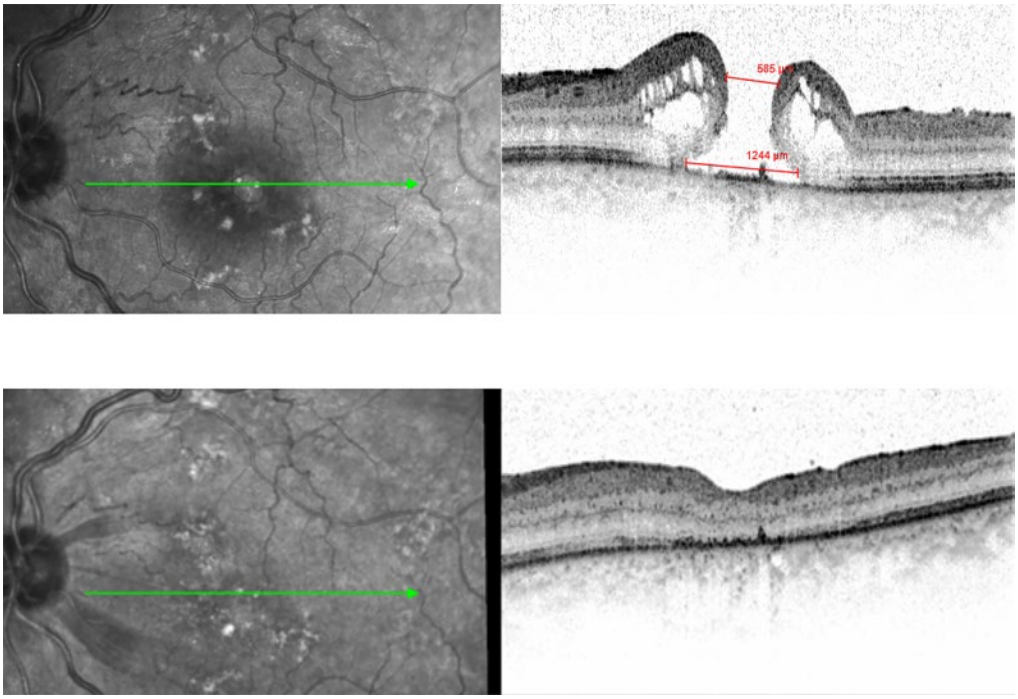

Figure 4. Macular hole closure (bottom: 3 months post-surgery) after subretinal retinal relaxation technique in a patient with long-standing refractory macular hole. Authors' data, unpublished.

Gonvers, Bove, and Wolfensberger firstly presented a case series of SR fluid application in FTMH during the Jules Gonin Meeting 2010 in Montreux. Independently Oliver and Wojcik published their technique in 2011 in a case report.[9] Wong et al described his technique in greater detail and published his case series.[10] He reported a closure rate of over 80% and recommended this technique for experienced vitreoretinal surgeons as a secondary novel subretinal option to close FTMH.

We are currently examining the surgery outcomes of 46 eyes from 17 international retinal surgeons who used the retinal relaxation surgery technique in large, refractory macular holes (International Retinal Relaxation Study Group), because for every retinal surgeon a difficult macular hole is primarily the one that did not close in the first attempt.

Selected Readings

1. Kelly NE, Wendel RT. Vitreous surgery for idiopathic macular holes: results of a pilot study. *Arch Ophthalmol*. 1991; 109:654-659.
2. Sebag J, Niemeyer M, Koss MJ. Anomalous posterior vitreous detachment and vitreoschisis. In: Sebag J, ed. *Vitreous*. New York: Springer; 2014.
3. Tognetto D, Grandin R, Sanguinetti G, et al. Internal limiting membrane removal during macular hole surgery: results of a multicenter retrospective study. *Ophthalmology* 2006; 113:1401-1410.
4. Michalewska Z, Michalewski J, Adelman RA, Nawrocki J. Inverted internal limiting membrane flap technique for large macular holes. *Ophthalmology* 2010; 117(10):2018-2025.
5. Giansanti F, Tartaro R, Caporossi T, et al. An internal limiting membrane plug and gas endotamponade for recurrent or persistent macular hole. *J Ophthalmol*. 2019; 2019:6051724.
6. Grewal DS, Charles S, Parolini B, Kadonosono K, Mahmoud TH. Autologous retinal transplant for refractory macular holes: Multicenter International Collaborative Study Group. *Ophthalmology*. Epub ahead of print 2019 Jan 31. pii: S0161-6420(18)32595-7.
7. Rizzo S, Caporossi T, Tartaro R, et al. A human amniotic membrane plug to promote retinal breaks repair and recurrent macular hole closure. *Retina*. Epub ahead of print 2018 Oct 3. doi: 10.1097/IAE.0000000000002320.
8. Peng J, Chen C, Jin H, Zhang H, Zhao P. Autologous lens capsular flap transplantation combined with autologous blood application in the management of refractory macular hole. *Retina* 2018; 38(11):2177-2183.
9. Oliver A, Wojcik EJ. Macular detachment for treatment of persistent macular hole. *Ophthalmic Surg Lasers Imaging*. 2011; 42(6):516-518.
10. Wong R, Howard C, Orobona GD. Retina expansion technique for macular hole apposition: efficacy, closure rate, and risks of a macular detachment technique to close large full-thickness macular holes. *Retina* 2018; 38(4):660-663.

Should We Operate on Lamellar Macular Holes?

Stanley Chang MD and Won Seok Choi MD

Introduction

In 1975, Gass first described lamellar macular hole (MH) as a partial-thickness, round, inner foveal defect seen on slit-lamp biomicroscopy using a narrow vertical beam in patients who had pseudophakic cystoid macular edema.[1] For almost two decades after, there was controversy about the outcomes of vitrectomy and epiretinal membrane peeling on this condition since decisions for surgical intervention were made on the clinical appearance and the reduction of visual acuity. As OCT imaging improved the visualization of vitreoretinal interface, abnormalities such as pseudoholes, premacular membranes with foveoschisis, and lamellar hole–associated proliferation have been described.[2] Each type of proliferation may affect the foveal structure differently and may result in different outcomes after vitrectomy. Understanding these changes by studying the pre- and postoperative spectral domain OCT findings would provide a tailored surgical approach and yield better outcomes.

In the past year, the International Lamellar Macular Hole Study Group was formed to standardize the definition of and to determine the diagnostic criteria (based on OCT) for lamellar MHs. They determined that the major criteria were as follows: (1) an irregular foveal contour, (2) foveal cavitation, and (3) apparent loss of foveal tissue. Minor characteristics included (1) preretinal macular proliferation (thicker, homogeneous of medium reflectivity), (2) foveal bump, and (3) loss of ellipsoid layer.[3] These features may be seen after reviewing multiple OCT scans. Some have classified this type of lamellar MH as "degenerative" lamellar MH.[4]

Natural Course

Lamellar MHs with preretinal macular proliferation tend to have greater progression of visual loss, mainly through thinning of the outer foveal layer and disruption of the outer ellipsoid layer. One study found that in 5% of eyes the visual acuity had a functional decline of 0.3 logMAR units over a mean follow-up time of 26 months.[5] The medium reflective preretinal material often is observed to have luteal pigment and thought to consist of Müller cells. It has been noted that myopic eyes are more likely to have MHs. Infrequently, lamellar MHs can progress to full-thickness MHs. Surprisingly, full-thickness MHs with a lamellar type of epiretinal proliferation can also close spontaneously.

Surgical Outcomes

We studied retrospective results of vitrectomy for patients[6] with lamellar MHs and patients with full-thickness MHs and lamellar type proliferation, comparing these results to those for eyes undergoing vitrectomy for premacular membranes with foveoschisis changes. The indications for vitrectomy were a progressive symptomatic loss of visual acuity or disabling metamorphopsia. This group of eyes represented only 10% of all eyes undergoing macular surgery over a 3-year period. The eyes with lamellar proliferation had a greater prevalence of outer retinal thinning and disruption of the ellipsoid zone. Following vitrectomy, eyes with lamellar MHs had a much smaller degree of visual improvement than eyes with highly reflective premacular membranes or full-thickness MHs with lamellar proliferation. However, it seems that eyes with lamellar MH did have stabilization of visual acuity despite a modest improvement of visual acuity. Our findings were also similar to a previous report.[7]

Thus my recommendation for vitrectomy in lamellar MHs would be for patients who note a progressive loss of vision and want to stop the progression of visual loss, and for those patients who progress to full-thickness MHs with lamellar type proliferation.

References

1. Gass JD. Lamellar macular hole: a complication of cystoid macular edema after cataract extraction: a clinicopathologic case report. *Trans Am Ophthalmol Soc.* 1975; 73:231-250.
2. Duker JS, Kaiser PK, Binder S, et al. The International Vitreomacular Traction Study Group classification of vitreomacular adhesion, traction, and macular hole. *Ophthalmology* 2013; 120(12):2611-2619.
3. Hubschmann JP, Govetta A, et al. The International Lamellar Macular Hole Study Group Report 1: definitions of lamellar macular hole, premacular membrane foveoschisis, macular pseudohole. Under review.
4. Govetto A, Dacquay Y, Farajzadeh M, et al. Lamellar macular hole: two distinct clinical entities? *Am J Ophthalmol.* 2016; 164:99-109.
5. Pang CE, Spaide RF, Freund KB. Comparing functional and morphologic characteristics of lamellar macular holes with and without lamellar hole-associated epiretinal proliferation. *Retina* 2015; 35(4):720-726.
6. Choi WS, Merlau DJ, Chang S. Vitrectomy for macular disorders associated with lamellar macular hole epiretinal proliferation. *Retina* 2018; 38:664-669.
7. Witkin AJ, Ko TH, Fujimoto JG, et al. Redefining lamellar holes and the vitreomacular interface: an ultrahigh-resolution optical coherence tomography study. *Ophthalmology* 2006; 113(3):388-397.

Management of Retinal Detachment Without Vitrectomy Adjuncts

Mark W Johnson MD and Eric W Schneider MD

I. Surgical Repair of Primary Uncomplicated Retinal Detachment (RD)

A. Scleral buckling is preferred for young phakic eyes without posterior vitreous detachment.

B. Pars plana vitrectomy (PPV) has a dominant role for other cases.

C. Uncertain benefit to adjuvant procedures during vitrectomy, such as:

1. Scleral buckling
2. 360° endolaser photocoagulation
3. Routine use of heavy liquids

II. Hypothesis Regarding Vitrectomy for Primary RD Repair

A. Based on pathogenesis of rhegmatogenous RD (RRD), high single-operation success rate should result from:

1. Elimination of dynamic vitreous traction
2. Identification and treatment of *all* retinal breaks

B. Given equivalent outcomes, the simplest procedure is best, since it avoids cost and morbidity of unnecessary measures.

III. Vitrectomy Without Adjuvant Procedures for Repair of Primary RD (Schneider, Geraets, and Johnson)

A. Purpose

To analyze anatomical and functional outcomes of consecutive series of primary uncomplicated RRDs treated with vitrectomy PPV alone without adjuvant procedures

B. Methods

1. Retrospective, noncomparative study
   a. Single surgeon, 10-year period
   b. Standard approach to noncomplex RD
      i. *either* scleral buckle (young eyes without PVD)
      ii. *or* vitrectomy
      iii. not both
2. Consecutive patients undergoing PPV for RRD (n = 177)
3. Analysis limited to primary uncomplicated RD (n = 93)
4. Excluded (n = 84)
   a. Previous vitreoretinal surgery
   b. Complex RD
   c. Less than 6 months' follow-up
5. Surgical technique
   a. Wide-angle viewing
   b. Thorough (not aggressive) trimming of vitreous skirt
      i. special attention to breaks and sclerotomies
      ii. extensive scleral depression used in only 38.7%
   c. Meticulous search for all retinal breaks
   d. Treatment of all breaks/suspicious lesions
      i. cryotherapy (prior to fluid-gas exchange) for most small anterior breaks
      ii. endolaser for others
      iii. no prophylactic treatment of normal retina
   e. Endodrainage and C^3F^8 gas (titrated), with careful postoperative positioning
   f. Perfluorocarbon liquid only for excessive retinal mobility (n = 2)
   g. No scleral buckling

C. Results

1. Baseline characteristics
   a. Age (mean yrs ± SD): 60.1 ± 12.1
   b. Macular status (% macula off): 52.7%
   c. Lens status (% phakic): 43.0%
   d. Inferior breaks: 35%
2. Anatomic outcomes (n = 93)
   a. Follow-up (mean): 31 months (range: 6-103)
   b. Single-operation success rate: 95.7% (89/93)
   c. Final anatomic success rate: 98.9% (92/93)
   d. Results did not differ by lens or macular status.
3. Primary anatomic failures
   a. Causes of recurrent RD after initial surgery (n = 4)
      i. proliferative vitreoretinopathy (PVR) = 3 eyes
      ii. incomplete closure of pathogenic break = 1 eye
      iii. new retinal breaks (without PVR) = 0 eyes

b. Single reoperation was successful in 3/3 eyes. Scleral buckling was employed in 2 cases.

c. Final patient (with baseline anterior ischemic optic neuropathy) declined further surgery.

4. Functional outcomes

a. Final BCVA ≥ 20/40: 77.4%

b. No difference in visual outcome by lens status

5. Complications (n = 93)

a. Cystoid macular edema: 3.2%

b. PVR (with recurrent RD): 3.2%

c. Epiretinal membrane (visually significant): 2.2%

IV. Vitrectomy With Adjuvant Procedures: Recent Comparative Series

A. Tabandeh H, et al (Retina Society, 2019)

1. Retrospective consecutive single-surgeon case series (n = 300)

2. Single-surgery reattachment rate

a. PPV+SB = 95.2%

b. PPV alone = 94.7% (P = 1.0)

B. Wang J, et al (Retina Society 2019)

1. Multicenter retrospective study of eyes undergoing PPV or PPV+SB for RD (n = 2248)

2. Use of 360° laser retinopexy:

a. No improvement in single-surgery success rate

b. Associated with lower final anatomical success and worse final VA (P < 0.001)

V. Why Do Surgeons Use Adjuncts to Vitrectomy? Debunking the Common "Indications"

A. Treatment of missed retinal breaks

1. With emphasis on meticulous intraoperative search, we found no cases of recurrent RD from missed breaks.

2. We believe careful search is preferable to morbidity of routine scleral buckling or 360° laser.

B. Prevention of new retinal breaks from postoperative "vitreous base contraction"

1. We found no new breaks (or other evidence of vitreous base contraction) in absence of frank PVR.

2. This challenges need to "support vitreous base" with buckling or to perform prophylactic 360° laser.

C. Treatment of inferior retinal breaks

1. Our study and others show excellent results without adjuvant procedures.

VI. Number Needed to Treat

Even if we assume that an adjunct procedure (eg, scleral buckle) could be proven to raise the primary success rate from 95.7% to 99%:

A. We would need to expose 33 patients to morbidity/cost of adjuvant in order to prevent 1 recurrent RD.

B. Adjuvant procedures do not seem justified on this basis.

VII. Conclusions

A. When vitrectomy is chosen for repair of primary uncomplicated RD, thorough PPV alone provides

1. High anatomic and functional success rates

2. Low complication rates

B. Adjuvant procedures (scleral buckling, 360° laser retinopexy, routine use of perfluorocarbon liquid) are unnecessary in eyes without PVR or significant risk factors for PVR.

C. Such adjuncts may unnecessarily increase the cost and morbidity of the procedure.

D. In the absence of frank postoperative PVR, contraction of vitreous base is not a clinically relevant phenomenon.

Selected Readings

1. Schneider EW, Geraets RL, Johnson MW. Pars plana vitrectomy without adjuvant procedures for repair of primary rhegmatogenous retinal detachment. *Retina* 2012; 32:213-219.

2. Schneider EW, Johnson MW. Repair of primary noncomplex rhegmatogenous retinal detachment. *US Ophthalmic Review* 2013; 6:135-143.

3. Johansson K, Malmsjo M, Ghosh F. Tailored vitrectomy and laser photocoagulation without scleral buckling for all primary rhegmatogenous retinal detachments. *Br J Ophthalmol*. 2006; 90:1286-1291.

4. Algvere PV, Hallnas K, Dafgard E, et al. Panretinal photocoagulation aggravates experimental proliferative vitreoretinopathy. *Graefes Arch Clin Exp Ophthalmol*. 1990; 228:461-466.

5. Sharma A, Grigoropoulos V, Williamson TH. Management of primary rhegmatogenous retinal detachment with inferior breaks. *Br J Ophthalmol*. 2004; 88:1372-1375.

6. Martinez-Castillo V, Verdugo A, Boixadera A, et al. Management of inferior breaks in pseudophakic rhegmatogenous retinal detachment with pars plana vitrectomy and air. *Arch Ophthalmol*. 2005; 123:1078-1081.

7. Weichel ED, Martidis A, Fineman MS, et al. Pars plana vitrectomy versus combined pars plana vitrectomy-scleral buckle for primary repair of pseudophakic retinal detachment. *Ophthalmology* 2006; 113:2033-2040.

8. Johansson K, Malmsjo M, Ghosh F. Tailored vitrectomy and laser photocoagulation without scleral buckling for all primary rhegmatogenous retinal detachments. *Br J Ophthalmol*. 2006; 90:1286-1291.

9. Chong DY, Fuller DG. The declining use of scleral buckling with vitrectomy for primary retinal detachments. *Arch Ophthalmol*. 2010; 128:1206-1207.

Proliferative Diabetic Retinopathy Surgery: How to Improve the Success Rate

Maria H Berrocal MD

I. Indications for PDR Surgery
   A. Vitreous hemorrhage
   B. Tractional retinal detachment
   C. Tractional and rhegmatogenous retinal detachment
II. Key to Success: Avoid and Treat Complications
III. Intraoperative Complications
   A. Visibility problems
      1. 3-D viewing systems: periphery, view under air
      2. Optimize cornea
      3. Macular contact lens
      4. Mark breaks with diathermy
   B. Bleeding
      1. Control patient's blood pressure during surgery
      2. Preoperative anti-VEGF 2-5 days before
      3. Valved cannulas
      4. IOP control
      5. Diathermy, laser; pressure on vessel
   C. Iatrogenic breaks
      1. 27-gauge lift and shave
      2. Highest cutting speed possible
      3. Bimanual techniques when needed
      4. Viscodissection
      5. If created, remove all traction
IV. Peri- and Postoperative Complications
   A. Bleeding
      1. Lower intraoperative pressure to check for bleeding
      2. Avoid hypotony, 27g
      3. Wound construction and closure techniques
      4. Smallest gauge
      5. Angled entry
      6. Closure at low IOP
      7. Anti-VEGF at end of vitrectomy
      8. Needle in opposite direction 27 or 30 gauge
      9. Partial air–fluid exchange
   B. Rebleeding
      1. Air–fluid exchange in the office
      2. Wide-field fluorescein angiography
   C. Redetachment
      1. Reoperation to find cause of failure: residual traction, open breaks
      2. Consider oil in 1-eyed patients

Selected Readings

1. Berrocal MH. All-probe vitrectomy dissection techniques for diabetic tractional retinal detachments: lift and shave. *Retina* 2018; 38 (Suppl 1): S2-S4. Reply: *Retina* 2019; 39(5):e18-e19.
2. Khan MA, Kuley A, Riemann CD, Berrocal MH, et al. Long-term visual outcomes and safety profile of 27-gauge pars plana vitrectomy for posterior segment disease. *Ophthalmology* 2018; 125(3):423-431.
3. Cruz-Iñigo YJ, Berrocal MH. Twenty-seven-gauge vitrectomy for combined tractional and rhegmatogenous retinal detachment involving the macula associated with proliferative diabetic retinopathy. *Int J Retina Vitreous*. 2017; 3:38.
4. Berrocal MH, Acaba AM. Surgical treatment of diabetic retinopathy. In: CR Baumal and J Duker, eds. *Current Management of Diabetic Retinopathy*. Elsevier; 2017, ch. 9.

New Instrumentation for Vitreoretinal Surgery

David R Chow MD

NOTES

Surgery for Infectious Retinitis: When Medical Therapy Is Not Sufficient

J Fernando Arevalo MD FACS

I. Cytomegalovirus Retinitis (CMVR)

A. Introduction

1. Most frequent ocular opportunistic infection in acquired immunodeficiency syndrome (AIDS) patients (CD4+ < 50 cells/μL)
2. It occurred in 30% of AIDS patients in the pre–combination antiretroviral therapy (cART) era.
3. It occurred in < 1% of patients in the cART era. (cART: protease inhibitors and/or nucleoside reverse transcriptase inhibitors and/or anti-nucleoside analogue inhibitors regimes)

B. Retinal detachment (RD)

1. RD develops in 20% of patients with CMVR.
2. The current rate of detachment may be reduced by improved therapies for CMVR.
3. The number of new patients acquiring CMVR has fallen, resulting in a lower incidence of these detachments.
4. Extent of retinitis and activity are risk factors.
5. For longer patient survival we need to select surgical strategies that will provide the best long-term visual outcome.
6. Vitrectomy with planned removal of silicone oil, scleral buckle, vitrectomy with gas tamponade, and laser demarcation are strategies that may provide excellent visual and anatomic results for RDs with various characteristics.
7. The final selection of the surgical approach depends on the mechanical factors of the detachment and patient factors such as immune status, expected survival, control of retinitis, and visual needs.
8. Cataract

C. Immune recovery uveitis

D. Vitrectomy + laser + silicone oil

E. Polymerase chain reaction (PCR) and inflammation

1. Sample preparation for PCR
2. The choice of biopsy site must be guided by disease suspicion; individual patient factors such as media opacity, anterior chamber depth, or coexistence of vitreous pathologic conditions; and the comfort level of the ophthalmologist with anterior chamber paracentesis or vitreous biopsy.
3. Very little tissue is needed for PCR; samples as small as 1 μL can be processed for testing.
4. Typically, 50- to 100-μL samples are ideal, as they allow for possible retesting if necessary.

II. Acute Retina Necrosis (ARN) and AIDS

A. Retinal detachment

1. Fifty percent to 75% of untreated eyes, usually within 1 to 2 months following the onset of ARN symptoms
2. Vitreous inflammation can lead to vitreous organization and proliferative vitreoretinopathy with subsequent tractional retinal detachment.
3. Vitrectomy
4. Prophylactic vitreous surgery could be a possible choice for patients who have poorly or nonresponsive, progressive retinal lesions, especially when they become close to the posterior pole.
5. Vitreous surgery has been recognized as a procedure that is indicated for cases with RD, one of the main late-stage complications.
6. We have experienced several cases that were resistant to medical therapy but showed dramatic improvement of retinal necrotic lesions immediately after the vitreous surgery.
7. Vitrectomy
8. Reports on the vitreous fluid obtained from the patients with ARN indicate the presence of inflammatory cytokines (interleukin [IL]-6 and IL-10 and interferon gamma), suggesting that the removal of these inflammatory cytokines induces a remission of retinal lesions.
9. Silicone oil tamponade is ideal for RD and as a tamponade for short-term usage only.
10. Endolaser photocoagulation is applied at the time of vitrectomy on normal retina to surround the posterior edge of necrotic lesions by 2 to 3 adjacent rows.

B. Summary

1. Options
   a. Silicone oil surgery
   b. Silicone oil removal (+phacoemulsification)
   c. Vitrectomy with gas tamponade
   d. Scleral buckle
   e. Laser demarcation

2. As in the repair of any RDs, surgical success requires permanent closure of retinal holes and relaxation of vitreous traction that might cause new tears.
3. Pars plana vitrectomy with silicone oil injection obviously accomplishes these objectives; even failed cases with open inferior breaks will generally have the RD well enough demarcated that the macula remains attached.
4. If good adhesion is achieved, oil removal can be considered at a later date combined with phacoemulsification.

References

1. Heiden D, Tun N, Smithuis FN, et al. Active cytomegalovirus retinitis after the start of antiretroviral therapy. *Br J Ophthalmol*. 2019; 103(2):157-160.
2. Port AD, Alabi RO, Koenig L, Gupta MP. Cytomegalovirus retinitis in the post-cART era. *Curr Ophthalmol Rep*. 2018; 6(2):133-144.
3. Jabs DA, Van Natta ML, Holland GN, Danis R; Studies of the Ocular Complications of AIDS Research Group. Cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome after initiating antiretroviral therapy. *Am J Ophthalmol*. 2017; 174:23-32.
4. Yen M, Chen J, Ausayakhun S, et al. Retinal detachment associated with AIDS-related cytomegalovirus retinitis: risk factors in a resource-limited setting. *Am J Ophthalmol*. 2015; 159(1):185-192.
5. Kempen JH, Jabs DA, Dunn JP, West SK, Tonascia J. Retinal detachment risk in cytomegalovirus retinitis related to the acquired immunodeficiency syndrome. *Arch Ophthalmol*. 2001; 119(1):33-40.
6. Schoenberger SD, Kim SJ, Thorne JE, et al. Diagnosis and treatment of acute retinal necrosis: a report by the American Academy of Ophthalmology. *Ophthalmology* 2017; 124(3):382-392.
7. Hillenkamp J, Nölle B, Bruns C, Rautenberg P, Fickenscher H, Roider J. Acute retinal necrosis: clinical features, early vitrectomy, and outcomes. *Ophthalmology* 2009; 116(10):1971-5.e2.

Retinal Gene Therapy: From Theory to Practice

Jean Bennett MD PhD and Albert M Maguire MD

NOTES

Are You AT the Table or ON the Menu?

Purnima S Patel MD

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

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

Please join the dedicated community of ophthalmologists who are contributing to protect quality patient eye care for everybody.

The OPHTHPAC Committee is identifying Congressional Advocates in each state to maintain close relationships with federal legislators to advance ophthalmology and patient causes. At Mid-Year Forum 2019, we honored three of those legislators with the Academy's Visionary Award. This served to recognize them for addressing issues important to us and to our patients. The Academy's Secretariat for State Affairs is collaborating closely with state ophthalmology society leaders to protect Surgery by Surgeons at the state level.

Our mission of "protecting sight and empowering lives" requires robust funding of both the Surgical Scope Fund and OPHTHPAC. Each of us has a responsibility to ensure that these funds are strong so that ophthalmology can be represented "at the table."

OPHTHPAC®

OPHTHPAC represents the profession of ophthalmology to the U.S. Congress and operates to protect you and your fellow ophthalmologists from payment cuts, burdensome regulations, scope-of-practice threats, and much more. OPHTHPAC also works to advance our profession by promoting funding for vision research and expanded inclusion of vision in public and private programs—all of which provide better health-care options for your patients. OPHTHPAC is your federal voice in Washington, D.C., and we are very successful in representing your professional needs to the U.S. Congress.

Among OPHTHPAC's most recent victories are the following:

- Securing greater flexibility in the new Medicare Payment System
- Ensuring proper reimbursement of Medicare Part B drugs
- Blocking onerous administrative burdens on contact lens prescribers
- Preserving access to compounded drugs
- Preventing additional cuts to Medicare

However, ophthalmology's federal issues are a continuous battle, and OPHTHPAC is always under pressure to ensure we have strong political connections in place to help protect ophthalmology, its members, and their patients.

The support OPHTHPAC receives from invested U.S. Academy members helps build the federal relationships that advance ophthalmology's agenda on Capitol Hill. These relationships allow us to have a seat at the table with legislators willing to work on issues important to us and our patients. We also use these congressional relationships to help shape the rules and regulations being developed by federal agencies. Help strengthen these bonds and ophthalmology's legislative support.

Right now, major transformations are taking place in health care. To ensure that our federal fight and our PAC remain strong, we need the support of every ophthalmologist to better our profession and ensure quality eye care for our patients. Invest with confidence in the strongest PAC working to ensure your success as an ophthalmologist.

Contributions to OPHTHPAC can be made here at AAO 2019, online at www.aao.org/ophthpac, or by texting MDEYE to 41444.

At Mid-Year Forum 2019, the Academy and the three retina societies ensured a strong presence of retina specialists to support ophthalmology's priorities. Ophthalmologists visited members of Congress and their key health staff to discuss ophthalmology priorities as part of Congressional Advocacy Day. The American Society of Retina Specialists (ASRS), Macula Society, and Retina Society remain crucial partners with the Academy in its ongoing federal and state advocacy initiatives.

Surgical Scope Fund

The Surgical Scope Fund (SSF) provides grants to state ophthalmology societies to support their efforts to protect patient safety from dangerous optometric surgery proposals. Since its inception, the Surgery by Surgeons campaign and the SSF, in partnership with state ophthalmology societies, have helped 40 state/territorial ophthalmology societies reject optometric scope-of-practice expansions into surgery.

Thanks to the 2019 SSF contributions from ophthalmologists just like you, SSF has had a successful year, preserving patient safety and surgical standards in state legislatures across the country, including six critical wins in Alabama, Texas, Vermont, Wyoming, Maryland, and Iowa. The 2019 battle is far from over, though. For example, Pennsylvania and Massachusetts are under attack, and California and Illinois are facing threats.

If you have not yet made a 2019 SSF contribution, contributions can be made at our booth at AAO 2019 or online at www.aao.org/ssf. If you already have made that 2019 contribution, please go to www.safesurgerycoalition.org to see the impact of your gift.

Dollars from the SSF are critical to building complete cutting-edge political campaigns, including media (TV, radio, and social media), educating and building relationships with legislators, and educating the voting public to contact their legislators. This work helps to secure success in protecting patient safety by defeating optometry's surgical initiatives.

Each of these endeavors is very expensive, and no one state has the critical resources to fight big optometry on their own. Ophthalmologists must join together and donate to the SSF at www.aao.org/ssf to fight for patient safety.

Surgical Scope Fund	OPHTHPAC® Fund	State EyePAC
To protect patient safety by defeating optometric scope-of-practice initiatives that threaten patient safety and quality surgical care	Ophthalmology's interests at the federal level Support for candidates for U.S. Congress	Support for candidates for state House, Senate, and governor
Political grassroots activities, government relations, PR and media campaigns *No* funds may be used for campaign contributions or PACs.	Campaign contributions, legislative education	Campaign contributions, legislative education
Contributions: Unlimited Individual, practice, and organization	Contributions: Limited to $5,000	Contribution limits vary based on state regulations.
Contributions are *100% confidential.*	Contributions above $200 are on the public record.	Contributions are on the public record depending upon state statutes.

The Secretariat for State Affairs thanks the Retina Society, which joined state ophthalmology societies in already contributing to the SSF in 2019, and it looks forward to 2019 support from the other two retina organizations. These ophthalmic organizations complete the necessary SSF support structure for the protection of our patients' sight.

State Eye PAC

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

ACTION REQUESTED: Help Ophthalmology Ensure a "Seat at the Table"

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

Please respond to your Academy colleagues and be part of the community that contributes to OPHTHPAC, the SSF, and your State Eye PAC. Please be part of the community that ensures ophthalmology has a strong voice in advocating for patients.

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AAO Update on Retina

George A Williams MD

The American Academy of Ophthalmology remains active in Washington, DC, on a variety of issues that directly impact retinal practice. This presentation will provide an update on the following issues:

- Preauthorization
- Step therapy
- Drug pricing
- Office of the Inspector General investigation into services provided on the same day as injections of ranibizumab and aflibercept

Update From Washington

David W Parke II MD

I. Retina-Intensive Issues
   A. Compounding and drug availability
   B. Part B drugs
   C. Step therapy
II. Ophthalmology-Intensive Issues
   A. Generic drug availability
   B. Modifier-25
   C. Remote imaging and AI
III. Physician-Intensive Issues
   A. MACRA: MIPS and APMs (aka Medicare Access and CHIP Reauthorization Act: Merit-Based Incentive Payment System and Advanced Alternative Payment Models)
   B. Registries
   C. RUC (RVS [Relative Value Scale] Update Committee) integrity and future
   D. EHR interoperability and functionality
   E. Prior authorization relief
   F. Payment: Site neutrality
   G. Scope of practice
   H. Congressional access
   I. Value-based payment system
IV. Health Care–Intensive Issues
   A. Single payer/Medicare for all
   B. Drug costs
   C. Data and public health

Selected Readings

1. Blendon RJ, Benson JM, McMurtry SM. The upcoming U.S. health care cost debate—the public's views. *N Engl J Med*. Epub ahead of print 2019 May 29. doi: 10.1056/NEJMp1905710.
2. Califf RM, Slavitt A. Lowering cost and increasing access to drugs without jeopardizing innovation. *JAMA* 2019; 321:1571-1573.
3. Basch E, Schrag D. The evolving uses of "real-world" data. *JAMA* 2019; 321:1359-1360.
4. Berenson RA, Ginsburg PB. Improving the Medicare physician fee schedule: make it part of value-based payment. *Health Affairs* 2019; 38:246-252.
5. Neuman P, Jacobson GA. Medicare Advantage checkup. *N Engl J Med*. 2018; 379:2163-2172.
6. Berwick DM. Politics and health care. *JAMA* 2018; 320:1437-1438.

Retinal Relativity and Reimbursement Roulette

John T Thompson MD

I. In 1992, Medicare changed the way they pay physicians to a resource-based relative value scale (RBRVS). The values of medical procedures were based on a study by Hsiao and coauthors that attempted to develop an equitable way to value one procedure relative to another.

   A. The public is allowed to comment on Medicare policies, so the AMA created the Relative Value Scale Update Committee (RUC) in 1991 to advise Medicare about the relative value of various procedures based on the new RBRVS system.

      1. The RUC committee has 31 members; 21 are members of specialty societies representing most major areas of medicine, and there are 4 additional rotating seats, 2 in internal medicine, 1 in primary care, and 1 another specialty. The other 6 seats are the RUC chair and a representative from the AMA, the CPT Panel, the Health Care Professional Advisory Committee, and the Practice Expense Review Committee.

      2. One of those specialty society seats is reserved for the American Academy of Ophthalmology (the Academy); Dr. Jeffrey Edelstein, an oculoplastic surgeon, is the ophthalmology voting member.

      3. Dr. David Glasser (anterior segment) presents the recommendations of the Academy to the RUC. For retina-related codes, I serve as an advisor representing the American Society of Retina Specialists (ASRS), and Ankoor Shah represents the Academy. Other advisors assist from other ophthalmic subspecialties when the reviewed code relates to their subspecialty.

      4. The RUC members vote on the value of every code after a detailed review by several non-ophthalmology RUC voting members, discussion, and a 2/3 majority to approve the new value.

   B. Medicare is not obligated to accept the RUC recommendations.

      1. A decade ago, they accepted the RUC recommendations over 90% of the time.

      2. More recently the percentage has dropped into the 80s.

II. RUC Valuation of a Code Based on RBRVS

   A. The RUC has created a very detailed process to value almost all CPT codes, including surgical procedures, in-office procedures, diagnostic testing, and office visits.

      1. The value is expressed as a relative value unit (RVU), which has a particular value for Medicare based on the conversion factor ($36.0391 per RVU in 2019).

      2. The RVU recommendations from the Academy are based on surveys of time to perform the procedure and complexity relative to other procedures within and outside the specialty.

      3. The RVU is composed of 3 portions: physician work, practice expense, and liability expense.

         a. Work takes into account the time and intensity required by the physician to perform a procedure, but increasingly time has become much more important than intensity.

         b. Work includes preservice time (such as greeting a patient in the OR and identifying the correct eye, positioning, and scrubbing), intraservice time (the time it takes to actually perform the procedure), and postservice time (dictating an operative report, talking to family, checking on patient in recovery room, and giving postoperative instructions).

         c. Practice expense (PE) is very important, as it includes all of the costs attributed to the physician for performing the procedure. This includes surgical coordinator time; ophthalmic technician time for postoperative appointments; and the cost of equipment such as exam rooms, slit lamps, and disposable supplies. PE is not determined by survey but instead by an expert panel from the Academy/ASRS. Very detailed spreadsheets are created for practice expense, including the cost of eyedrops to anesthetize and dilate the eye, cotton tip applicators, etc. Dr. John McAllister, an anterior segment surgeon, is the lead presenter for PE at the RUC.

         d. For many surgical procedures in ophthalmology, practice expenses comprise close to 50% of the total value of a procedure, with physician work also close to 50%. Liability expense is relatively small for ophthalmology and has minimal effect on the total RVU.

III. Impact on Retinal Reimbursement and Relativity

   A. Figures 1 through 4 show the effect of Medicare revaluations for our major procedures and imaging. Most retinal procedures have seen large reductions over the past decade.

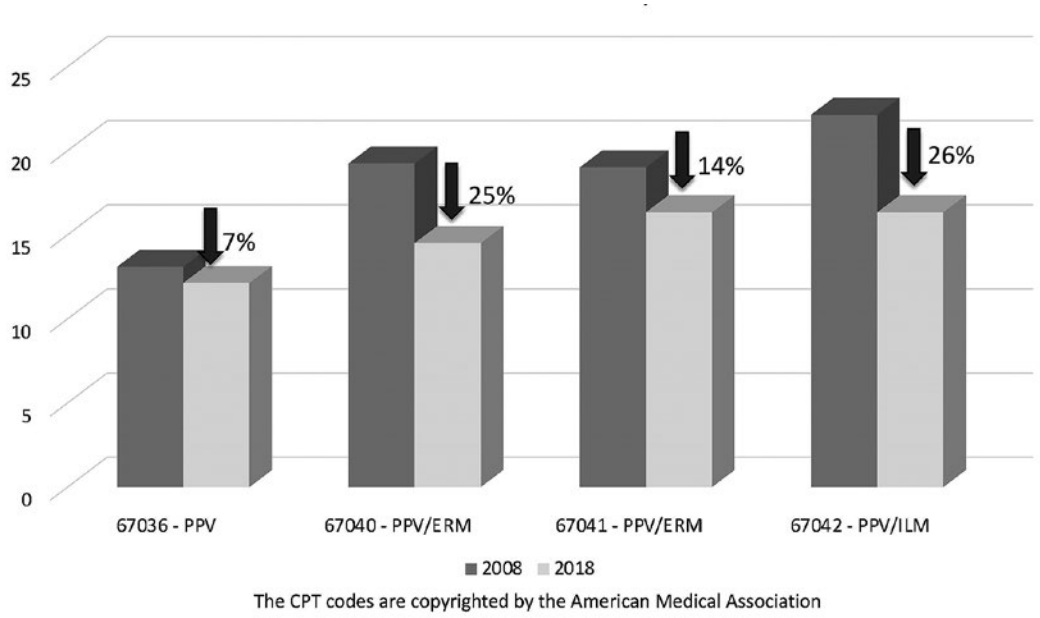

Figure 1. Work value for vitrectomy codes.

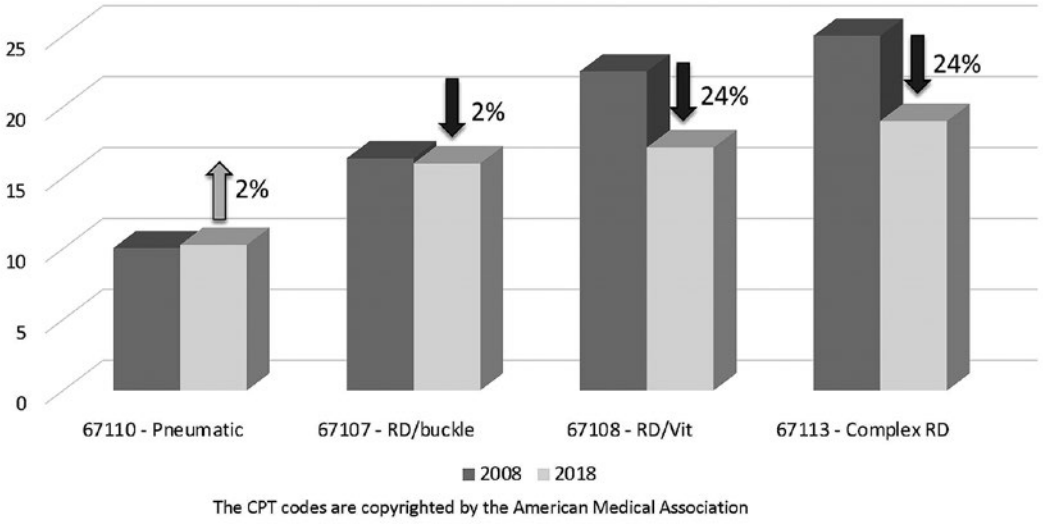

Figure 2. Work RVU for retinal detachment codes.

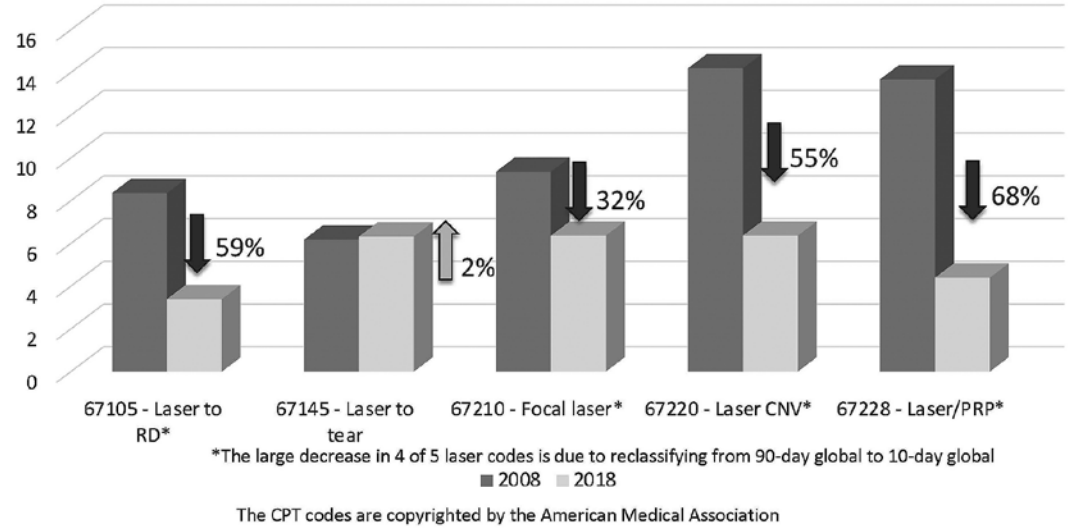

Figure 3. Work RVU for office laser codes.

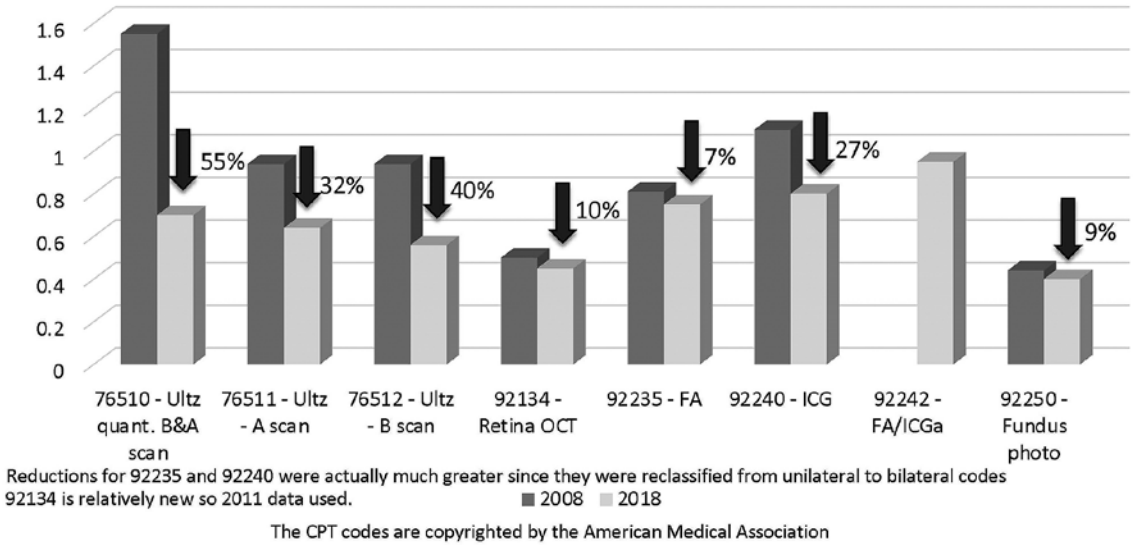

Figure 4. Work RVU for retinal imaging.

B. Reduced reimbursement is a result of decreased time to perform the procedures reported by retina specialists in the RUC surveys.

C. The reductions are also influenced by a perception that ophthalmology procedures are overvalued compared to the cognitive specialties/primary care; this was highlighted by Hsiao.

D. RUC surveys for retinal procedures are emailed to a random sample of ASRS and AAO members. *This is the most important survey you will ever receive, so please take the time to carefully complete it.*

Reference

1. RVS Update Committee (RUC): understand the role the AMA/Specialty Society RUC plays in providing physicians a voice in shaping Medicare relative values. AMA website. https://www.ama-assn.org/about/rvs-update-committee-ruc/rvs-update-committee-ruc.

My Best Medical Retina Cases

Anita Agarwal MD, Lee M Jampol MD, H Richard McDonald MD, William F Mieler, MD, Carol L Shields MD

NOTES

Predictors of Postinjection Endophthalmitis: A Multivariable Analysis Based on Injection Protocol and Povidone Iodine Strength

Tarek S Hassan MD

I. Introduction

A. Multiple series have shown that in the management of wet AMD and diabetic macular edema (DME), more anti–vascular endothelial growth factor (VEGF) injections correlate with better visual outcomes.

B. Each intravitreal injection carries risks, including endophthalmitis.

II. Endophthalmitis After Anti-VEGF Injections

A. Uncommon but threatening to long-term visual acuity (VA)

1. Published endophthalmitis rates are low: 1:1200 to 1:6450.[1,2]

2. Meta-analysis of 43 studies with $n > 350{,}000$ injections: Endophthalmitis rate of 1:1800[3]

B. Approximately 50% of endophthalmitis eyes do not return to preinfection levels of VA despite standard of care management with intravitreal antibiotics.[1,3]

C. Increasing numbers of patients, increasing numbers of injections, and thus increasing severe sight-threatening risks: These emphasize the need for endophthalmitis prevention.

III. Measures to Prevent Endophthalmitis

A. The only prophylaxis shown to reduce endophthalmitis incidence: topical pre-procedural povidone-iodine (PVI) to ocular surface[4,5]

1. No published optimal or standard of care concentration exists in our field.

a. Most use between 1.25% and 10% PVI

b. Some evidence of paradoxical effect—lower concentrations of PVI may have increased bactericidal activity because of greater availability of free iodine in lower concentrations.[6,7]

B. Other parts of the injection protocol have not been found to influence endophthalmitis rates (use of topical antibiotics, the injection site, or use of lid speculum[2,8])

IV. Identify Predictive Factors for Endophthalmitis After Intravitreal Injection to Potentially Reduce Incidence

A. Study: Multivariable analysis of injection protocol and providence iodine strength

1. Site: Associated Retinal Consultants, Royal Oak, Michigan

a. Retrospective review of injections of bevacizumab, ranibizumab (0.3 mg and 0.5 mg), and aflibercept over 39 months for wet AMD, DME, and retinal vein occlusion, given by 15 providers

b. Identified cases of postinjection endophthalmitis

c. Evaluated provider's intravitreal injection protocol: technique and use of preparatory meds and materials

i. Lid speculum

ii. Gloves

iii. Strict no-talking policy

iv. PVI (5%, 10%)

v. 0.5% tetracaine (TetraVisc)

vi. 2% lidocaine gel

vii. Subconjunctival 2% lidocaine

viii. Conjunctival displacement

ix. Topical antibiotics during the visit

x. Choice of anti-VEGF medication

xi. Injection site (superior vs. inferior)

d. Injection practices common to all

i. PVI use

ii. Preinjection anesthesia: subconjunctival lidocaine (9 providers), topical lidocaine (6 providers)

iii. All placed another drop of PVI as the final step before injection.

2. Study results

a. Incidence: Between 1/1/14 and 3/31/17: 154,198 anti-VEGF injections were evaluated; 58 cases of resultant endophthalmitis = incidence of 0.038% (1:2659)

i. 41% culture-positive results

ii. Exclusion: Same-day bilateral injections and those by physicians with inconsistent injection protocols

iii. 98,960 unilateral injections available for multivariable analysis

iv. 40 eyes with endophthalmitis = incidence of 1:2474, 42.5% culture positive

b. Multivariate analysis

i. Independent predictors of endophthalmitis

(a) Preinjection use of 2% lidocaine jelly: 11 times greater odds of endophthalmitis (OR, 11.28; $P < .001$)

(b) Preinjection use of 0.5% tetracaine: 4 times greater odds of endophthalmitis (OR, 3.95; $P = .03$)

ii. Not found to be independent predictors of endophthalmitis: strength of PVI solution (5% vs. 10%), use of lid speculum, gloves, strict no-talking policy, subconjunctival lidocaine, conjunctival displacement, topical antibiotics, choice of anti-VEGF agent, or injection site (superior vs. inferior)

B. Key study findings

1. Use of both 2% lidocaine jelly and 0.5% tetracaine as independent risk factors for endophthalmitis—not previously reported

a. Higher strength topical PVI did not alter this increased risk.

i. Studies support the use of both higher and lower concentrations of PVI.[6,9,10]

ii. Recommendations regarding best concentration are not possible.

b. Other clinical series did not show a significant correlation between the timing of PVI and gel or tetracaine application, relative to one another, and endophthalmitis risk, but overall risk in these series is higher than ours (1:1100).[11]

c. In vitro studies have shown increased microbial survival when lidocaine gel is used prior to the application of PVI[12,13]—a possible explanation for our results.

2. No other variable evaluated with multivariate analysis correlated with increased endophthalmitis; agrees with multiple other series.[2,8,14,15]

C. Study strengths and weaknesses

1. Strengths: large number of injections, multivariable logistic regression, single practice

2. Weaknesses: retrospective series and injection protocol among treaters was not entirely standardized (eg, interval between application of PVI and injection)

V. Conclusions

A. Incidence of endophthalmitis after anti-VEGF injection = 1:2659 over a 39-month period

1. Lower than 1:1800 incidence reported in a large meta-analysis of more than 350,000 injections

2. Associated with use of preinjection topical lidocaine gel and tetracaine as independent risk factors

3. Not improved or worsened with the use of 5% PVI vs. 10% PVI

B. Further investigation is warranted, particularly with prospective analyses

VI. Citation for This Study

Stem MS, Rao P, Lee AJ, et al. Predictors of endophthalmitis after intravitreal injection. *Ophthalmol Retina*. 2019; 3:3-7.

References

1. Xu K, Chin EK, Bennett SR, et al. Endophthalmitis after intravitreal injection of vascular endothelial growth factor inhibitors: management and visual outcomes. *Ophthalmology* 2018; 125:1279e1286.
2. Shah CP, Garg SJ, Vander JF, et al. Outcomes and risk factors associated with endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents. *Ophthalmology* 2011; 118:2028e2034.
3. Fileta JB, Scott IU, Flynn Jr HW. Meta-analysis of infectious endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents. *Ophthalmic Surg Lasers Imaging Retina*. 2014; 45:143e149.
4. Modjtahedi BS, van Zyl T, Pandya HK, et al. Endophthalmitis after intravitreal injections in patients with self-reported iodine allergy. *Am J Ophthalmol*. 2016; 170:68e74.
5. Grzybowski A, Kanclerz P, Myers WG. The use of povidone-iodine in ophthalmology. *Curr Opin Ophthalmol*. 2018; 29:19e32.
6. Berkelman RL, Holland BW, Anderson RL. Increased bactericidal activity of dilute preparations of povidone-iodine solutions. *J Clin Microbiol*. 1982; 15:635e639.
7. Zamora JL. Chemical and microbiologic characteristics and toxicity of povidone-iodine solutions. *Am J Surg*. 1986; 151: 400e406.
8. Park Y, Kim KS, Park YH. Acute endophthalmitis after intravitreal injection and preventive effect of preoperative topical antibiotics. *J Ocul Pharmacol Ther*. 2013; 29:900e905.
9. Hosseini H, Ashraf MJ, Saleh M, et al. Effect of povidone-iodine concentration and exposure time on bacteria isolated from endophthalmitis cases. *J Cataract Refract Surg*. 2012; 38: 92e96.
10. van Rooij J, Boks AL, Sprenger A, et al. The concentration of povidone-iodine for preoperative disinfection: relation to endophthalmitis incidence. *Am J Ophthalmol*. 2011; 152:321; author reply 321e322.
11. Lad EM, Maltenfort MG, Leng T. Effect of lidocaine gel anesthesia on endophthalmitis rates following intravitreal injection. *Ophthalmic Surg Lasers Imaging*. 2012; 43:115e120.

12. Doshi RR, Leng T, Fung AE. Povidone-iodine before lidocaine gel anesthesia achieves surface antisepsis. *Ophthalmic Surg Lasers Imaging*. 2011; 42:346e349.

13. Boden JH, Myers ML, Lee T, et al. Effect of lidocaine gel on povidone-iodine antisepsis and microbial survival. *J Cataract Refract Surg*. 2008; 34:1773e1775.

14. Cheung CS, Wong AW, Lui A, et al. Incidence of endophthalmitis and use of antibiotic prophylaxis after intravitreal injections. *Ophthalmology* 2012; 119:1609e1614.

15. Storey P, Dollin M, Pitcher J, et al. The role of topical anti- biotic prophylaxis to prevent endophthalmitis after intravitreal injection. *Ophthalmology* 2014; 121:283e289.

Pentosan Polysulfate Maculopathy

A Clinician's Primer on Pentosan Polysulfate Maculopathy

Nieraj Jain MD

We recently described a unique pigmentary maculopathy in patients with chronic exposure to pentosan polysulfate sodium (PPS; trade name: Elmiron; Janssen Pharmaceuticals; Titusville, NJ).[1] This drug has been on the market for decades, potentially leaving thousands of patients at risk for macular disease. Because this condition resembles other maculopathies such as AMD and pattern dystrophy, many affected patients may currently be misdiagnosed. This summary serves as a clinician's primer on PPS maculopathy.

Background

Pentosan polysulfate sodium is a glycosaminoglycan-like macromolecule that is widely used to treat interstitial cystitis (IC). First used in the mid-20th century, it received FDA approval for management of IC in 1996, and remains the only FDA-approved oral treatment for this condition. Interstitial cystitis is a chronic pain syndrome involving the bladder and pelvic region that affects more than 1 million U.S. adults.[2] PPS is thought to provide symptomatic relief to individuals with IC by coating and protecting the bladder epithelium.[3]

Association Between PPS Exposure and Macular Disease

In our initial report, we described characteristic macular pigmentary changes in 6 PPS-exposed patients seen by a single clinician over a 2-year period. Although these findings implicated the drug, they did not exclude the possibility that IC itself or one of its many off-label therapies was responsible.

We thus performed a retrospective cross-sectional study evaluating all patients with IC seen at our institution over a 4-year period. We identified 219 patients with IC, 80 of whom had prior PPS exposure. Masked reviewers graded available imaging for all IC patients, and identified 14 cases of the characteristic maculopathy. All 14 cases occurred in the PPS-exposed group. Not a single case of this maculopathy was observed among the 139 patients who had not taken PPS. Among all drug exposures and other potential risk factors, PPS exposure emerged as the only factor that was significantly associated with this unique maculopathy.[4]

On a larger scale, we also performed a retrospective matched-cohort study of claims data from a large U.S. insurer. We identified practice patterns suggesting that hundreds of thousands of individuals have likely been exposed to the drug within the U.S. alone. Within this database, PPS-exposed patients were found to have significantly increased odds of being diagnosed with a new macular disease at 7 years.[5]

Incidence

Although we don't have a robust estimate of the incidence of PPS maculopathy, it appears that chronic exposure is an important factor. Our primary concern at present is that this medication has been on the market for many years. Hundreds of thousands of patients have been exposed to it, and there are likely many patients with PPS maculopathy who have yet to be identified.

Anecdotally, at our tertiary care institution, approximately half of our retina faculty have seen at least 1 case of PPS maculopathy over the past 4 years. Affected patients typically presented with a referral diagnosis of AMD or pattern dystrophy.

Key Clinical Features

PPS maculopathy appears to exhibit a fairly well-defined clinical spectrum, as observed in a retrospective study of 70 eyes of 35 patients across 4 institutions.[6] All patients reported chronic PPS exposure (median: 14.5 years; range: 3-21.9 years). Of note, most of these patients experienced years of visual symptoms prior to the diagnosis, suggesting that the exposure threshold for disease onset may be lower than expected.

Affected patients often presented with blurred vision (49%) and prolonged dark adaptation (43%) in spite of relatively preserved visual acuity (median Snellen VA = 20/25; range: 20/15-20/400). We have found that these patients express great frustration with their functional deficits.

Key imaging findings include the following:

- Color fundus photography revealed relatively nondescript fundus changes, typically with paracentral pigment clumps amidst a background of yellow-orange subretinal deposits.
- Fundus autofluorescence imaging revealed striking abnormality, typically with a densely packed pattern of hyper- and hypo-autofluorescent spots that were centered on and involved the fovea. Fundus alterations were typically confined to the posterior pole, although they occasionally extended to the retinal periphery.
- OCT demonstrated nodular lesions at the level of the retinal pigment epithelium that corresponded to the hyperpigmented macular spots.

Some eyes developed RPE atrophy, which involved the central fovea in advanced cases. Nine eyes of 6 patients manifested cystoid macular edema, which responded well to a range of topical and intravitreal therapies. One eye had what was thought to be choroidal neovascularization.

Longitudinal evaluation in a limited number of cases demonstrated this to be a fairly dynamic disease process. The disease can extend peripherally with time, and pigmented macular spots appeared to give way to retinal pigment epithelial atrophy.

Recommendations

Although additional data are needed to guide screening programs, we have adopted the following approach at our institution:

- For patients anticipating a long-term course of PPS therapy, we recommend that they discuss dosing strategies with their prescriber, with the goal of using the lowest necessary dose and duration of therapy
- We perform a baseline examination with comprehensive fundus imaging (color fundus photography, OCT, and fundus autofluorescence imaging).
- We perform repeat screening 5 years after PPS initiation and annually thereafter.
- Patients with potentially elevated risk, including those with an atypical dosing regimen, those with a history of smoking or macular disease, as well as those with comorbidities involving renal, hepatic, or splenic function, may benefit from more frequent screening examinations, or drug avoidance altogether.

For patients diagnosed with PPS maculopathy, we recommend drug cessation and coordination with the prescribing physician to explore alternative regimens for IC management.[7] Although we do not fully understand the natural history of this condition, we caution affected patients that visual symptoms may persist, and possibly worsen, even after drug cessation.

Conclusions

Given the emerging evidence for a PPS-induced macular toxicity, retina specialists have a new role, identifying affected patients and preventing others from developing this vision-threatening condition. These patients may be easily misdiagnosed.[8] However, as in the case with hydroxychloroquine and other drug-associated maculopathies, a detailed medication history and modern fundus imaging techniques will aid in the identification of affected patients. We look forward to ongoing studies to improve our understanding of the pathobiology, incidence, and prognosis of this unique condition.

References

1. Pearce W, Chen R, Jain N. Pigmentary maculopathy associated with chronic exposure to pentosan polysulfate sodium. *Ophthalmology*. 2018; 125(11):1793-1802.
2. Nickel JC, Moldwin R. FDA BRUDAC 2018 criteria for interstitial cystitis/bladder pain syndrome clinical trials: future direction for research. *J Urol*. 2018; 200(1):39-42.
3. Hanno P. Analysis of long-term Elmiron therapy for interstitial cystitis. *Urology* 1997; 49(5):93-99.
4. Hanif AM, Shah R, Yan J, et al. Strength of association between pentosan polysulfate and a novel maculopathy. *Ophthalmology*. Epub ahead of print 2019 Apr 18. doi: 10.1016/j.ophtha.2019.04.024.
5. Li AL, Jain N, Yu Y, VanderBeek BL. Association of macular disease with long-term use of pentosan polysulfate sodium: findings from a large U.S. national insurance database. Poster presented at: Association for Research in Vision and Ophthalmology; April 28–May 2, 2019; Vancouver, BC, Canada.
6. Hanif AM. Expanded clinical spectrum of pentosan polysulfate sodium-associated pigmentary maculopathy. Paper presented at: Association for Research in Vision and Ophthalmology; April 28–May 2, 2019; Vancouver, BC, Canada.
7. Giusto L, Zahner P, Shoskes D. An evaluation of the pharmacotherapy for interstitial cystitis. *Expert Opin Pharmacother*. 2018; 19(10):1097-1108.
8. Hanif AM, Yan J, Jain N. Pattern dystrophy: an imprecise diagnosis in the age of precision medicine. *Int Ophthalmol Clin*. 2019; 59(1):173–194.

Retinal Ophthalmic Technology Assessments That Will Change Your Practice

Stephen Jae Kim MD

Introduction

The goal of an Ophthalmic Technology Assessment (OTA) is to systemically review the best available evidence for clinical efficacy and safety of a technology and/or intervention. Assessments of individual committees (Retina, Cornea, Pediatrics, etc.) undergo a rigorous and intensive review process by national and international organizations and experts in the field. Published assessments are approved by the Trustees of the American Academy of Ophthalmology (the Academy) and consequently have the full backing of the Academy. Over the last several years, the Retina Ophthalmic Technology Assessment Committee has tackled several important and wide-ranging topics, including toxoplasmosis, central retinal vein occlusion, diabetic macular edema, nonsteroidal anti-inflammatory drugs (NSAIDs) and cataract surgery, branch retinal vein occlusion, acute retinal necrosis, and age-related macular degeneration (AMD). This talk will summarize the Retina Ophthalmic Technology Assessment Committee's most recent findings and comment on what may constitute best practice.

I. Background of Ophthalmic Technology Assessments

II. Interventions for Toxoplasma Retinochoroiditis

No level 1 evidence to support routine use of antibiotics or corticosteroids

III. Topical Nonsteroidal Anti-inflammatory Drugs and Cataract Surgery

A. No evidence that NSAIDs improve vision

B. No evidence of pharmacologic drug synergy with corticosteroids

C. No uniform method of reporting cystoid macular edema

IV. Diagnosis and Treatment of Acute Retinal Necrosis

A. Polymerase chain reaction testing is useful.

B. Initial oral or intravenous antiviral therapy is effective.

C. Adjunctive use of intravitreal foscarnet may be more effect than systemic therapy alone.

D. Role of prophylactic laser retinopexy or early vitrectomy is unclear.

V. Therapies for Macular Edema Associated With Branch Retinal Vein Occlusion

A. Intravitreal pharmacotherapy with anti-VEGF agents is safe and effective.

B. Intravitreal corticosteroids are effective but have greater safety concerns.

C. Delay in treatment is associated with less visual improvement.

D. Laser photocoagulation is safe and effective, but results lag behind anti-VEGF therapy.

VI. Anti-VEGF Pharmacology for AMD

A. Intravitreal pharmacotherapy with anti-VEGF agents is safe and effective for neovascular AMD over 2 years.

B. Longer-term safety data and comparative efficacy of these agents are needed.

VII. Therapies for Macular Edema Associated With Central Retinal Vein Occlusion

A. Intravitreal anti-VEGF pharmacotherapy is safe and effective over 2 years for macular edema associated with central retinal vein occlusion.

B. Delay in treatment is associated with worse visual outcomes.

C. Intravitreal corticosteroids demonstrate short-term efficacy but high frequency of adverse events.

Selected Readings

1. Kim SJ, Scott IU, Brown CC, et al. Interventions for toxoplasma retinochoroiditis: a report by the American Academy of Ophthalmology. *Ophthalmology* 2013; 120:371-378.
2. Kim SJ, Schoenberger SD, Thorne JE, Ehlers JP, Yeh S, Bakri SJ. Topical nonsteroidal anti-inflammatory drugs and cataract surgery: a report by the American Academy of Ophthalmology. *Ophthalmology* 2015; 122:2159-2168.
3. Schoenberger SD, Kim SJ, Thorne JE, et al. Diagnosis and treatment of acute retinal necrosis: a report by the American Academy of Ophthalmology. *Ophthalmology* 2017; 124(3):382-392.
4. Ehlers JP, Kim SJ, Yeh S, et al. Therapies for macular edema associated with branch retinal vein occlusion: a report by the American Academy of Ophthalmology. *Ophthalmology* 2017; 124(9):1412-1423.
5. Bakri SJ, Thorne JE, Ho AC, et al. Safety and efficacy of anti-vascular endothelial growth factor therapies for neovascular age-related macular degeneration: a report by the American Academy of Ophthalmology. *Ophthalmology* 2019; 126(1):55-63.
6. Yeh S, Kim SJ, Ho AC, et al. Therapies for macular edema associated with central retinal vein occlusion: a report by the American Academy of Ophthalmology. *Ophthalmology* 2015; 122:769-778.

Systemic Management of Acute Retinal Artery Occlusions

"What Do I Do Now?"

Timothy W Olsen MD

Occlusion of the retinal arteries is considered an ischemic stroke in the central nervous system, according to an updated (2013) definition of a stroke, the American Stroke Association, and the American Heart Association: "A central nervous system infarction is defined as brain, spinal cord, or retinal cell death attributable to ischemia, based on neuropathological, neuroimaging, and/or clinical evidence of permanent injury episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction."[1]

Based upon this definition, stroke guidelines apply to the management of retinal artery occlusions, including symptomatic branch-, ophthalmic-, and central retinal artery occlusions. In 2017, a panel from the American Academy of Ophthalmology created a new Preferred Practice Pattern (PPP), based upon evolving trends in management of retinal artery occlusions.[2] The highlighted recommendations for patient care include the following:

- An ophthalmic artery occlusion (OAO) or retinal artery occlusion (RAO), central retinal artery occlusion (CRAO), or, less commonly, a branch retinal artery occlusion (BRAO) in patients over 50 years of age should raise immediate clinical suspicion for giant cell arteritis (GCA) or other life-threatening conditions (eg, carotid occlusive or cardiac valve disease). The clinician should evaluate appropriately and consider the role of urgent systemic corticosteroid therapy in an attempt to preserve or recover vision in the affected eye.[3,4]
- An OAO or RAO patient of any age should have a systemic evaluation for vascular occlusive disease; generally, a vasculitis or hypercoagulable workup in younger patients[5] and an embolic workup in older patients.
- Acute, symptomatic OAO or CRAO from embolic etiologies should prompt an immediate referral to the nearest stroke referral center for prompt assessment for consideration of an acute intervention. However, the current evidence is limited for a similar referral for patients with an asymptomatic BRAO.
- In general, there are no proven therapies or treatments for the ocular manifestations of CRAO, BRAO, or OAO. Nevertheless, posterior segment arterial occlusions require prompt evaluation and management. These occlusions may be an important clinical indicator of a more severe systemic disorder or of an embolic, inflammatory, infectious, or other process. As such, they may require the clinician or the patient's medical doctor to initiate a systemic medical evaluation that is urgent and targeted to the patient.
- In vascular occlusive disorders of the eye, there is an increased risk for posterior and/or anterior segment neovascularization. The schedule for follow-up visits should consider the extent of retinal or ocular ischemia. Specifically, patients with greater ischemia require more frequent follow-up.

The key to current practice patterns is to establish a relationship with your local stroke center in anticipation of future patients who may present with a retinal artery occlusion. Then, "follow the guidelines" to treat acute, symptomatic OAO, CRAO, and BRAO promptly and according to current guidelines.[2,6] Many authors have identified the high risk of concurrent or imminent stroke or myocardial infarction risk following such an event.[7-13] A population-based study in Olmstead County also suggests an increased risk, yet lower than that in prior studies (Chodnicki, Pulido, Bhatti, Klaas, Hodge, and Chen, AAO 2019).

As an example, we currently work with our colleagues in Neurology at the Mayo Clinic, and our protocol is as follows:

1. Acute OAO, CRAO, BRAO (< 24 hours from onset of symptoms)
   a. Immediate referral to the Emergency Department (ED)
      i. Carotid imaging prior to discharge
      ii. Brain MRI
      iii. Echocardiogram (preferably transesophageal)
      iv. Referral to the Transient Ischemic Attack (TIA) Clinic (Neurology)
      v. Holter monitor (48 hours in duration) scheduled within 1-2 weeks
2. Subacute OAO, CRAO, BRAO (24 hours to 2 weeks from onset of symptoms):
   a. Referral to TIA Clinic in Neurology
   b. If unable to accommodate within 48 hours, send to ED.
   c. Studies
      i. Brain MRI
      ii. MRA head and neck
      iii. Echocardiogram (preferably transesophageal)
      iv. Holter monitor (48 hour in duration) scheduled within 1-2 weeks
3. Chronic OAO, CRAO, BRAO (> 2 weeks)
   a. Refer to TIA Clinic
   b. Begin full-dose aspirin

c. Studies
   i. MRI brain
   ii. MRA head and neck
   iii. Echocardiogram (preferably transesophageal)
   iv. Holter monitor (48 hours in duration)

Note: If contraindication to MRI (metal, pacemaker, other implant), then order CT head and CT angiogram, head neck, or carotid ultrasound.

Selected Readings

1. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013; 44:2064-2089.
2. Olsen TW, Pulido JS, Folk JC, Hyman L, Flaxel CJ, Adelman RA. Retinal and Ophthalmic Artery Occlusions Preferred Practice Pattern®. *Ophthalmology* 2017; 124:P120-P143.
3. Mazlumzadeh M, Hunder GG, Easley KA, et al. Treatment of giant cell arteritis using induction therapy with high-dose glucocorticoids: a double-blind, placebo-controlled, randomized prospective clinical trial. *Arthritis Rheum*. 2006; 54:3310-3318.
4. Weyand CM, Goronzy JJ. Giant-cell arteritis and polymyalgia rheumatica. *Ann Intern Med*. 2003; 139:505-515.
5. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014; 45:2160-2236.
6. Biousse V, Nahab F, Newman NJ. Management of acute retinal ischemia: follow the guidelines! *Ophthalmology* 2018; 125:1597-1607.
7. Lee J, Kim SW, Lee SC, Kwon OW, Kim YD, Byeon SH. Co-occurrence of acute retinal artery occlusion and acute ischemic stroke: diffusion-weighted magnetic resonance imaging study. *Am J Ophthalmol*. 2014; 157:1231-1238.
8. Lauda F, Neugebauer H, Reiber L, Juttler E. Acute silent brain infarction in monocular visual loss of ischemic origin. *Cerebrovasc Dis*. 2015; 40:151-156.
9. Park SJ, Choi NK, Yang BR, et al. Risk and risk periods for stroke and acute myocardial infarction in patients with central retinal artery occlusion. *Ophthalmology* 2015; 122:2336-2343 e2332.
10. Dattilo M, Biousse V, Newman NJ. Update on the management of central retinal artery occlusion. *Neurol Clin*. 2017; 35:83-100.
11. Hong JH, Sohn SI, Kwak J, et al. Retinal artery occlusion and associated recurrent vascular risk with underlying etiologies. *PLoS One* 2017; 12:e0177663.
12. Lavin P, Patrylo M, Hollar M, Espaillat KB, Kirshner H, Schrag M. Stroke risk and risk factors in patients with central retinal artery occlusion. *Am J Ophthalmol*. 2018; 196:96-100.
13. Mir TA, Arham AZ, Fang W, et al. Acute vascular ischemic events in patients with central retinal artery occlusion in the United States: a nationwide study 2003-2014. *Am J Ophthalmol*. 2019; 200:179-186.

Update on Hereditary Retinal Diseases

Stephen H Tsang MD PhD

Precision medicine seeks to treat disease with molecular specificity. Advances in genome sequence analysis, gene delivery, and genome surgery have allowed clinician-scientists to treat hereditary disorders at the level of their pathology. As a result, progress in treating retinal disease using genetic tools has advanced tremendously over the past several decades. Breakthroughs in gene delivery vectors, both viral and nonviral, have allowed the delivery of genetic payloads in preclinical models of retinal disorders and have paved the way for numerous successful clinical trials. Moreover, the adaptation of CRISPR-Cas systems for genome surgery has enabled the correction of both recessive and dominant pathogenic alleles, expanding the disease-modifying power of gene therapies.

Here, we highlight the translational progress of gene supplementation therapy and genome surgery of several retinal disorders, including RPE65-, CEP290-, and GUY2D-associated Leber congenital amaurosis, as well as choroideremia, achromatopsia, Mer tyrosine kinase (MERTK) and RPGR X-linked retinitis pigmentosa, Usher syndrome, X-linked retinoschisis, Stargardt disease, Leber hereditary optic neuropathy, and neovascular AMD.

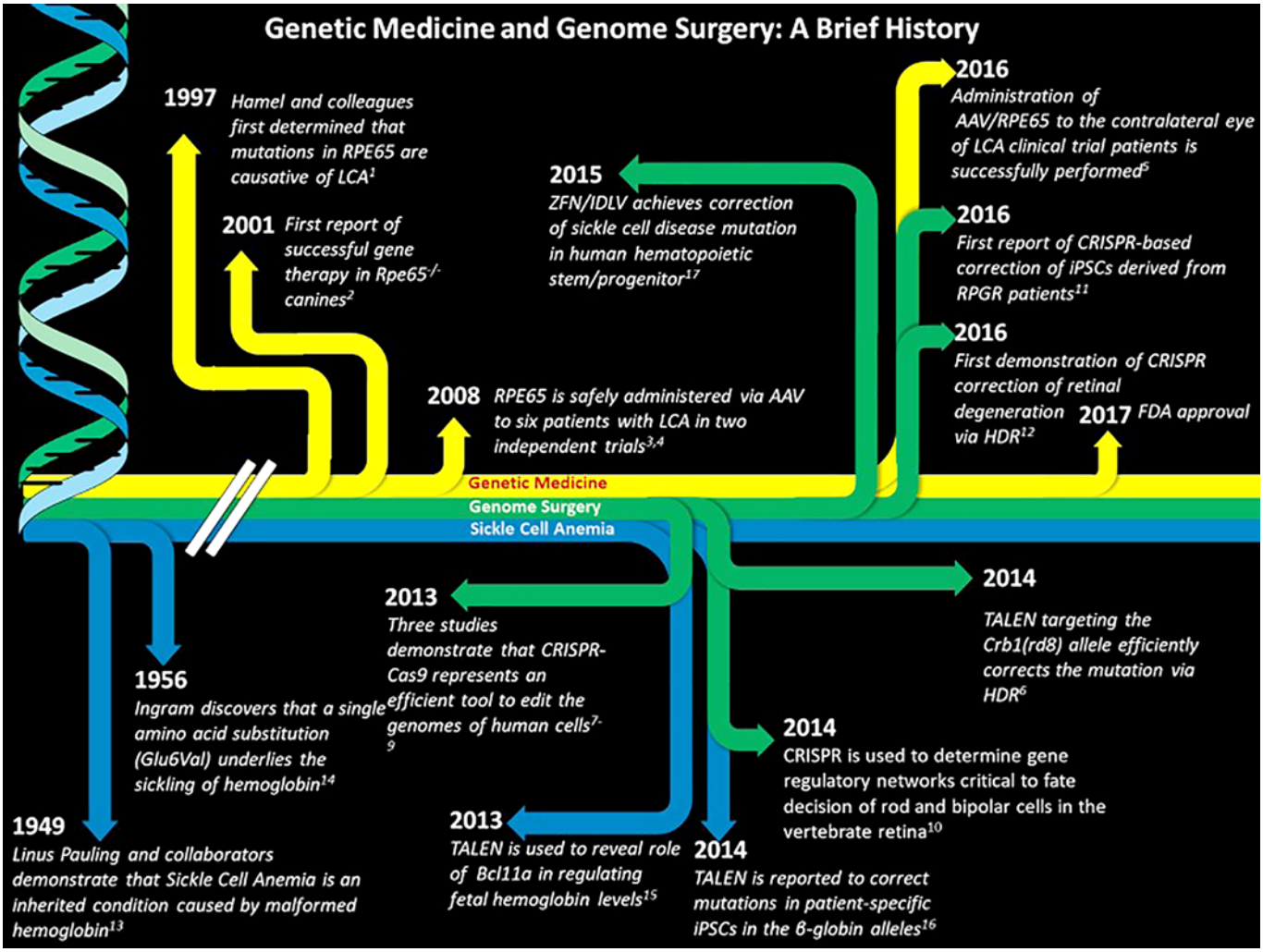

Figure 1.

Injection Index in Neovascular AMD Pigment Epithelial Detachment Predicts Long-term Visual Outcomes

Steven D Schwartz MD

NOTES

Emerging Infectious Diseases

Steven Yeh MD and Jessica G Shantha MD

I. Emerging Infectious Disease (EID)
   A. Definition: Diseases whose incidence in humans have increased during the last two decades or which threaten to increase in the near future (World Health Organization [WHO])
   B. With an increasingly interconnected world and globalization, the risk of rapid and uncontrolled spread of disease across national and international borders, as well as continents, is increasing at a fast rate.
   C. Public health systems measures and health care systems that are broken as a result of conflict or economic collapse are risk factors for EIDs.

II. Impact of EIDs
   A. Epidemics of EIDs are a growing threat to life, health, and prosperity.
   B. EIDs disproportionately affect low-income countries where needs are often the greatest.
   C. Recent outbreaks including Ebola, severe acute respiratory syndrome (SARS), and Zika have claimed thousands of lives and cost billions of dollars, with health and economic impact for years to come (eg, Ebola $2.2 billion dollars; SARS $54 billion dollars).

III. Overview of EIDs: Recent Global Examples
   A. 54% of EIDs are due to bacteria, and many are due to drug-resistant microbes.
   B. Ebola virus disease in the Democratic Republic of Congo (DRC): Ongoing in eastern DRC, 3 Ebola outbreaks over last 3 years in DRC
   C. Middle East respiratory syndrome coronavirus (MERS-CoV) in Oman, Saudi Arabia, and the United Kingdom
   D. Plague in Madagascar
   E. Cholera in Kenya, Nigeria, and Zambia

IV. WHO Blueprint List of Priorities (2018)
   A. Filovirus diseases (Ebola and Marburg)
   B. Crimea Congo hemorrhagic fever
   C. Emerging coronaviruses: MERS-CoV and SARS
   D. Lassa fever virus
   E. Nipah and henipaviral diseases
   F. Rift Valley fever
   G. Zika
   H. Disease X

V. Viral Hemorrhagic Fevers: Filoviruses and Manifestations
   A. Ebola virus disease (EVD)
      1. Clinical features
         a. West African EVD outbreak was the largest in history, with 28,600 affected and over 11,300 deaths, including >800 health care workers.
         b. Three EVD outbreaks within the DRC from 2017 to 2019
         c. Caused by 1 of 5 strains of Ebola virus, Zaire Ebola virus is the most fatal strain.
         d. Clinical features: severe diarrhea, vomiting, electrolyte abnormalities, hypotension, encephalopathy in late stages
      2. Ophthalmic features during acute EVD
         a. Subconjunctival hemorrhage
         b. Conjunctivitis
         c. Anterior uveitis
         d. Vision loss of unclear etiology
      3. Ophthalmic features during EVD convalescence
         a. Spectrum of eye disease ranging from anterior uveitis to aggressive, sight-threatening panuveitis
         b. Associated with Ebola virus persistence (Ocular immune privilege plays a role.)
         c. Uveitis identified in 13%-34% of West African EVD survivors
         d. Severe vision impairment or blindness observed in nearly 40% of EVD survivors
         e. Other features: iris heterochromia, anterior uveitis, intermediate uveitis, chorioretinal scarring, posterior synechiae, dense white uveitic cataract
         f. Ebola Virus Persistence in Ocular Tissues and Fluids (EVICT) Study showed no evidence of Ebola virus RNA persistence in aqueous humor by RT-PCR at >19 months after acute Ebola virus infection.
         g. Risk of Ebola virus in vitreous/retina remains unknown and under investigation.
      4. Ebola vaccine development
         a. Promising results from Merck rVSV-EBOV vaccine trial (Ebola Ca Suffit) during West African EVD outbreak

b. Recombination, replication competent vesicular stomatitis virus-based candidate vaccine expressing Zaire Ebolavirus surface glycoprotein

c. Substantial protection against EVD, with no cases identified 10 days after vaccination in randomized and nonrandomized clusters of patients in vaccine trial

B. Marburg virus disease

1. Clinical features

a. Incubation period from 2 to 21 days

b. High fever, severe headache, and severe malaise with muscle aches and pains; severe watery diarrhea, abdominal pain and cramping

c. Severe hemorrhagic manifestations between 5 and 7 days, with hematemesis, bleeding from gums, mucous membranes, shock, and severe blood loss, with death between 8 and 9 days

2. Ophthalmic features

a. Acute hypertensive anterior uveitis following clearance of Marburg virus from bloodstream (described from Johannesburg outbreak in 1975)

b. Keratic precipitates

c. Elevated IOP

d. Marburg virus culture of aqueous humor positive during acute anterior uveitis with inclusion bodies in cytoplasm of Vero cells

e. Negative virus culture 2 weeks after initial Marburg virus-positive culture

C. Lassa virus/Lassa hemorrhagic fever

1. Clinical features

a. Rodent-borne arenavirus responsible for Lassa viral hemorrhagic fever endemic to West Africa

b. Mild disease or unrecognized in 80% of patients

c. 20% of patients show severe disease, including facial swelling, hepatic and renal abnormalities, pulmonary edema, and hemorrhage

d. Case fatality rate is ~1%; and among hospitalized patients, >15%.

2. Treatment

a. Supportive care

b. Intravenous ribavarin considered investigational

3. Ophthalmic features

a. Conjunctivitis observed in acute phase of illness

b. Lassa virus identified in anterior uvea of infected guinea pigs

VI. Arboviruses and Manifestations

A. Flaviviruses (Zika, dengue, West Nile virus, yellow fever)

B. Zika virus (Flavivirus)

1. Acquired Zika infection (AZI)

a. Disease features

i. Maculopapular rash, arthritis, nonpurulent conjunctivitis

ii. Symptoms present in only 20% of patients

iii. Confirmation of Zika virus infection by ZIKV RNA with RT-PCR, serology (IgM), or plaque-reduction assay

b. Ocular findings in AZI

i. Conjunctivitis

ii. Acute hypertensive anterior uveitis

iii. Unilateral acute idiopathic maculopathy

iv. Bilateral posterior uveitis

2. Congenital Zika syndrome (CZS)

a. Disease features

i. Severe microcephaly with partially collapsed skull

ii. Brain abnormalities: thin cerebral cortices and subcortical calcifications

iii. Congenital contractures: clubfoot, arthrogryposis

iv. Early hypertonia, symptoms of extrapyramidal involvement

v. Hearing loss

b. Ocular findings in CZS

i. Most common posterior segment disease findings: pigment mottling and chorioretinal atrophy, commonly seen in macular region (first described in Pernambuco in NE Brazil, then other states in Brazil, and subsequently Colombia and Venezuela)

ii. OCT findings: discontinuity of ellipsoid zone and hyper-reflectivity under RPE, retinal and choroidal thinning, colobomatous-like appearance

iii. Posterior segment disease findings: optic nerve and retinal vascular disease

iv. Other findings: iris coloboma, lens subluxation, cataract, glaucoma, and microphthalmia

v. Ventura et al described 32 infants with CZS where all children showed cortical or cerebral visual impairment (CVI) due to brain damage, often affecting visual processing centers or visual pathways of the brain

c. Treatment

i. Multidisciplinary care with trained physicians and therapists given that children with CZS present with severe and multiple disabilities

ii. Ophthalmologists play a key role, in assessment of visual function, visual milestones, and functional vision assessment

iii. Children may need magnifying glasses, patching, visual stimulation therapy, and in select cases, strabismus surgery

C. West Nile virus

1. Disease features

a. First isolated in 1937 in West Nile district of Uganda

b. Single-stranded RNA flavivirus, zoonotic disease transmitted by *Culex* mosquito

c. Subclinical infection in 80%/febrile illness in 20%

d. Severe neurologic disease (meningoencephalitis) in less than 1% of patients, most frequently associated with medical comorbidities (elderly patients, diabetics)

2. Ophthalmic features

a. Multifocal chorioretinitis = most common manifestation (80%)

b. Active lesions: circular, deep, creamy lesions

c. Inactive lesions: "target-like" lesions with central pigmentation and hypopigmented halo

d. Other manifestations: anterior uveitis, retinal vasculitis, optic neuritis, neuroretinitis

D. Dengue

1. Clinical features

a. 25% of dengue virus infections are symptomatic; 5% present with severe, life-threatening disease called *severe* dengue

b. Transmission via *Aedes* species of mosquito

c. Acute onset of fever, headache, body aches, and truncal rash spreading centrifugally

d. Severe dengue is dengue with any of the following symptoms: severe plasma leakage leading to shock, fluid accumulation with respiratory distress, severe bleeding, or severe organ impairment including elevated transaminases >1000 IU/L, impaired consciousness or cardiac involvement.

2. Ophthalmic features

a. Onset of ocular symptoms within 2-5 days of fever, typically 1 day after the peak of thrombocytopenia

b. Ocular symptoms include eye pain, blurred vision, photophobia, and floaters

c. Dengue maculopathy: well-recognized and thought to be serotype and geography-related (DENV-1 epidemic caused 10% incidence of maculopathy and no cases during DENV-2 epidemic.)

d. Dengue retinopathy including retinal vasculopathy and macular edema may threaten vision.

E. Yellow fever

1. Clinical features

a. Described as the original viral hemorrhagic fever

b. Severe yellow fever: pan-systemic viral sepsis with viremia, fever, prostration, hepatic, renal and myocardial injury, shock, and case fatality rate ranging from 20% to 50%

c. Symptoms include fevers, chills, headache, lower back pain, Faget sign (increased temperature with decreased heart rate), epigastric pain, and dehydration

d. Hepatic-induced coagulopathy produces severe hemorrhage, petechiae, ecchymosis, and hematemesis

2. Ophthalmic findings

a. Retinal nerve fiber layer infarcts in >50% of patients

b. Superficial hemorrhages and deep grayish lesions at level of outer retina and choroid

c. Elevated aspartate aminotransferase (AST) levels, total bilirubin levels, serum creatinine, severe thrombocytopenia and *severe Yellow fever* classification associated with retinopathy

VII. Measles, Mumps, and Rubella

A. Measles (Rubeola)

1. From January 1 to June 27, 2019, nearly 1,100 cases of measles were confirmed in 28 states.

2. **This is the greatest number of cases in the U.S. since 1992 and since measles were eliminated in 2000.

3. Measles outbreaks (defined as 3 or more cases) are ongoing in 2019 in the following jurisdictions (per www.cdc.gov): New York State, Rockland County, New York City, California, Butte County, Washington)

4. CDC recommends that children get 1 dose at the following ages: first dose: 12-15 months; second dose: 4-6 years

5. Scientific studies and reviews identify no link between vaccines, vaccine ingredients, and autism.

6. Clinical and ophthalmic findings
    a. High fever (Temperature may be more than 104 degrees), cough, runny nose and watery eyes
    b. Tiny white spots (Koplik spots) 2-3 days after symptoms
    c. Measles rash with small raised bumps on top of flat red spots 3-5 days after symptoms (begins on face at hairline and spreads downward to neck, trunk, arms, legs, and feet)
    d. Measles posterior uveitis presents with painless visual loss associated with optic disc swelling, arteriolar attenuation, diffuse retinal edema, and stellate macular lesions
    e. Optic disc pallor, vascular sheathing, and pigmentary retinopathy with disease resolution
    f. Findings of measles posterior uveitis/retinopathy associated with subacute sclerosing panencephalitis (SSPE) or measles encephalitis

B. Rubella (German measles)
    1. Eliminated from the U.S. in 2004 but remains a problem in other parts of the world; <10 cases per year in the U.S., primarily from acquired infection
    2. Last major Rubella epidemic in the U.S. in 1964-65, with an estimated 12.5 million people with rubella, 20,000 with congenital rubella syndrome (CRS)
    3. Signs/symptoms: low-grade fever, headache, conjunctivitis, lymphadenopathy, cough, rhinorrhea, facial and truncal rash
    4. *Congenital rubella syndrome*: salt-and-pepper retinopathy, cataract in association with sensorineural hearing loss and cardiovascular defects
    5. Rubella persistence may lead to Fuchs heterochromic iridocyclitis, diagnosed via metagenomic deep sequencing, RT-PCR, and intraocular antibody testing

VIII. Disease X
A. Represents the knowledge that a serious international epidemic could be caused by a pathogen currently unknown to cause human disease
B. Definition: The serious threat that *unknown* viruses may pose to human health
C. WHO deems it a priority.
D. Finding, naming, and characterizing a disease before it affects human health

IX. Role of the Ophthalmologist
A. Recognition of novel clinical phenotypes, either from direct lytic viral infection or physiologic changes (retinal hemorrhages, cotton-wool-spots)
B. Potential for viral persistence given unique ocular immune privilege
C. Unknown risk of transmission of disease from ocular reservoirs (ie, Ebola virus persistence in ocular fluid) and risk to ophthalmologist, eye care nurses

References

1. Røttingen JA, Gouglas D, Feinberg M, et al. New vaccines against epidemic infectious diseases. *N Engl J Med*. 2017; 376(7):610-613.
2. Klohe K, Amuasi J, Kaducu JM, et al. The 2017 Oslo conference report on neglected tropical diseases and emerging/re- emerging infectious diseases: focus on populations underserved. *Infect Dis Poverty*. 2019; 8(1):40.
3. Yeh S, Shantha JG, Hayek B, Crozier I, Smith JR. Clinical manifestations and pathogenesis of uveitis in Ebola virus disease survivors. *Ocul Immunol Inflamm*. 2018; 26(7):1128-1134.
4. Varkey JB, Shantha JG, Crozier I, et al. Persistence of Ebola virus in ocular fluid during convalescence. *N Engl J Med*. 2015; 372(25):2423-2427.
5. Henao-Restrepo AM, Camacho A, Longini IM, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!). *Lancet* 2017; 389(10068):505-518.
6. Kuming BS, Kokoris N. Uveal involvement in Marburg virus disease. *Br J Ophthalmol*. 1977; 61(4):265-266.
7. Kofman A, Choi MJ, Rollin PE. Lassa fever in travelers from West Africa, 1969-2016. *Emerg Infect Dis*. 2019; 25(2):245-248.
8. Gary JM, Welch SR, Ritter JM, et al. Lassa virus targeting of anterior uvea and endothelium of cornea and conjunctiva in eye of guinea pig model. *Emerg Infect Dis*. 2019; 25(5):865-874.
9. Ventura CV, Ventura LO. Ophthalmologic manifestations associated with Zika virus infection. *Pediatrics* 2018; 141(suppl 2):S161-S166.
10. Brandão-de-Resende C, Cunha LHM, Oliveira SL, et al. Characterization of retinopathy among patients with yellow fever during 2 outbreaks in Southeastern Brazil. *JAMA Ophthalmol*. Epub ahead of print 2019 Jun 20. doi:10.1001/jamaophthalmol.2019.1956.
11. Singh S, Kumar A. Ocular manifestations of emerging flaviviruses and the blood-retinal barrier. *Viruses* 2018; 10(10).
12. Centers for Disease Control. Measles (Rubeola). www.cdc.gov/measles/. Last reviewed June 18, 2019.
13. Centers for Disease Control. Rubella (German Measles, Three-Day Measles). www.cdc.gov/rubella/. Last reviewed September 15, 2017.
14. Gonzales JA, Hinterwirth A, Shantha J, et al. Association of ocular inflammation and rubella virus persistence. *JAMA Ophthalmol*. 2019; 137(4):435-438.

Treating Uveitic Edema

Albert Vitale MD

NOTES

Update on Uveitis Comparative Effectiveness Trials: MUST, POINT, MERIT, and ADVISE

Douglas A Jabs MD MBA

The MUST Trial

The MUST Trial compared systemic therapy with oral corticosteroids and immunosuppression to regional (ocular) therapy with the 0.59-mg fluocinolone acetonide intraocular implant (Retisert) for noninfectious intermediate, posterior, or pan-uveitides. At 7 years of follow-up, the risk of blindness was nearly doubled in the regional therapy group due to retinal damage from uveitis relapse. Other than an increased use of antibiotics with systemic therapy, there were no significant differences in systemic side effects between systemic therapy and regional therapy. Conversely, there were significantly increased rates of ocular side effects in the regional therapy group, including cataract, elevated IOP, and glaucoma. These results suggest that systemic therapy may be a better initial choice.

Selected Readings

1. The Multicenter Uveitis Steroid Treatment Trial Research Group. Randomized comparison of systemic anti-inflammatory therapy versus fluocinolone acetonide implant for intermediate, posterior and panuveitis. *Ophthalmology* 2011; 118:1916-1926.
2. The Multicenter Uveitis Steroid Treatment Trial Follow-up Study Research Group. Quality of life and risks associated with systemic anti-inflammatory therapy versus fluocinolone acetonide intraocular implant for intermediate uveitis, posterior uveitis, or panuveitis: 54-month results of The Multicenter Uveitis Steroid Treatment Trial and Follow-up Study. *Ophthalmology* 2015; 1222:1976-1986.
3. Multicenter Uveitis Steroid Treatment (MUST) Trial Follow-up Study Research Group. Benefits of systemic anti-inflammatory therapy versus fluocinolone acetonide intraocular implant for intermediate, posterior and panuveitis: 54 month results of the Multicenter Uveitis Steroid Treatment (MUST) Trial Follow-up Study. *Ophthalmology* 2015; 122:1967-1975.
4. The Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up Study Research Group. Association between long-lasting intravitreous fluocinolone acetonide implant vs systemic anti-inflammatory therapy and visual acuity at 7 years among patients with intermediate, posterior, or panuveitis. *JAMA* 2017; 317:1993-2005.

The POINT Trial

Among patients with uveitic macular edema treated with systemic therapy, adjunctive short-acting regional corticosteroid injections frequently are needed for the macular edema, but typically only 1 or 2 are needed. The POINT Trial compared periocular triamcinolone, intraocular triamcinolone, and the intraocular dexamethasone implant (Ozurdex) for the treatment of uveitic macular edema. Intravitreal triamcinolone and intravitreal dexamethasone implant were superior to periocular triamcinolone for improving and resolving uveitic macular edema. The dexamethasone implant was noninferior to intravitreal triamcinolone. There were no significant differences among the 3 groups in the rate of IOP elevation to > 30 mmHg. These results suggest that intravitreal approaches might be preferred for treating uveitic macular edema.

Selected Reading

1. The Multicenter Uveitis Steroid Treatment Trial Research Group. Periocular triamcinolone versus intravitreal triamcinolone versus intravitreal dexamethasone implant for the treatment of uveitic macular edema: the PeriOcular versus INTravitreal corticosteroids for uveitic macular edema (POINT) Trial. *Ophthalmology* 2019; 126:283-295.

The MERIT Trial

Approximately 40% of eyes with uveitic macular edema will have persistent or relapsed edema at 2 years of treatment despite control of evident inflammation and use of adjunctive regional corticosteroid injections. Second corticosteroid injections provide benefit in approximately one-half of these eyes. Pilot data suggest that alternative approaches may be of benefit, namely, anti-VEGF injections and intravitreal methotrexate injections. The MERIT Trial is a randomized comparative effectiveness trial of the intravitreal dexamethasone implant vs. intravitreal ranibizumab vs. intravitreal methotrexate injections for the treatment of persistent or relapsed uveitic macular edema. The trial currently is ongoing.

The ADVISE Trial

Adalimumab is a fully human monoclonal antibody to TNF-α, which is USFDA-approved for the treatment of noninfectious intermediate-, posterior-, or panuveitis. The trials that led to its approval used a placebo comparator and rapid prednisone taper, thereby demonstrating its effectiveness. However, its effectiveness relative to conventional immunosuppression (antimetabolites and/or calcineurin inhibitors) is unknown. The ADVISE Trial is a randomized comparative effectiveness trial of adalimumab vs. conventional immunosuppression with either antimetabolites of calcineurin inhibitors for patients with noninfectious intermediate-, posterior-, or panuveitis. The primary outcome is successful corticosteroid-sparing, defined as inactive uveitis and a prednisone dose ≤ 7.5 mg/day for 2 consecutive visits, at least 28 days apart. An innovative design feature is the use of disease-specific testing and disease-specific guidelines for determining inactive uveitis. The trial currently is ongoing.

Effect of Fluocinolone Acetonide Insert on the Presence of Uveitic Macular Edema: Outcomes at 36 Months

Quan Dong Nguyen MD

Introduction

Uveitis is a significant cause of vision impairment in developed countries. Uveitic macular edema (ME), the main condition associated with vision loss in uveitis, results from a variety of inflammatory processes that lead to accumulation of fluid in the central retina.[1] Glucocorticoids along with systemic immunosuppressive and immunomodulatory therapy are the standards for treating noninfectious uveitis affecting the posterior segment of the eye.[2] A product that is relatively simple to administer in-office and that delivers corticosteroid directly to the intended site of action for an extended period may offer significant treatment benefits.

Clinical Trial

A double masked, randomized, prospective, sham-controlled trial was designed to evaluate the hypothesis that a single injection of a fluocinolone acetonide intravitreal insert (FAi) capable of delivering daily microdoses of drug for 3 years can reduce the proportion of patients that have a recurrence of noninfectious posterior uveitis.

129 subjects with at least a 1-year history of recurrent noninfectious uveitis affecting the posterior segment of the eye were randomly assigned to FAi insert (n = 87) or sham injection (n = 42) at 33 multinational sites.

Efficacy Outcomes

Uveitis recurrence

Thirty-six-month uveitis recurrence rates were significantly reduced in the FAi injected eyes. Recurrence rates were 56.3% for FAi and 92.9% for sham. The median time to the first recurrence was 1051 days in the FAi-treated eyes and 95 days in the eyes randomized to sham injection.

Macular edema

Resolution of macular edema was reported in 85% (34/40) of FAi-treated eyes vs. 70% (16/23) of sham eyes with edema at baseline. Central foveal thickness was reduced in both groups. More rapid reduction was observed in FAi-treated eyes.

BCVA

A visual acuity improvement of 3 or more ETDRS lines was recorded for 33% of the FAi-treated eyes and 14.7% of eyes in the sham group.

Safety Outcomes

IOP

Mean IOP was similar in the 2 treatment groups. Medication to lower IOP was used by 42% of subjects in the FAi group and 33% of the sham-treated eyes.

Cataract

Cataract extractions were more frequent in FAi-treated eyes (74% vs 24%).

Conclusion

These results indicate that long-term continuous treatment of noninfectious posterior uveitis with an office-based intravitreal insert injection can be an effective approach to resolving macular edema. Side effects are consistent with those expected from a corticosteroid treatment and are manageable with standard therapies.

References

1. Fardeau C, Champion E, Massamba N, LeHoang P. Uveitic macular edema. *Eye (Lond.)* 2016; 30(10):1277-1292.
2. Barry RJ, Nguyen QD, Lee RW, Murray PI, Denniston AK. Pharmacotherapy for uveitis: current management and emerging therapy. *Clin Ophthalmol.* 2014; 8:1891-1911.

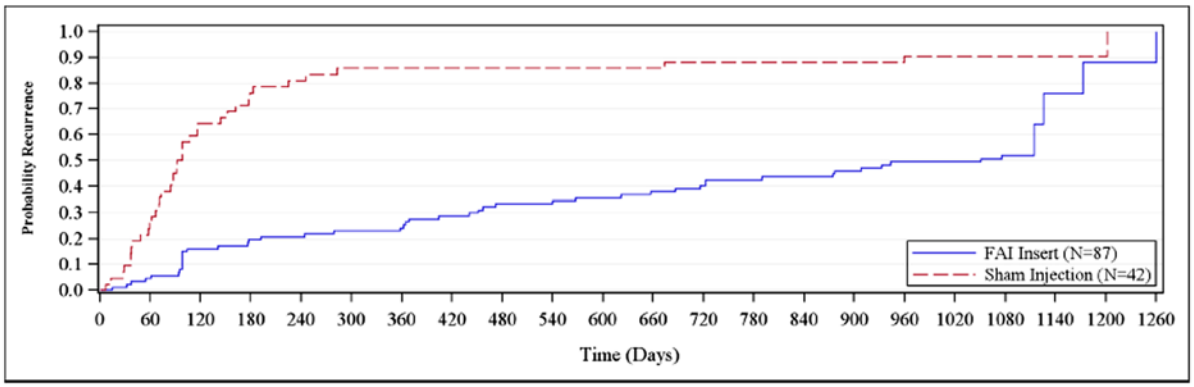

Figure 1. Kaplan-Meier plot of time to first recurrences of uveitis in the study eye at 36 months.

We Should Peel Epiretinal Membranes in Eyes With Good Visual Acuity: Pro

Colin A McCannel MD

Macular epiretinal membrane is a common diagnosis, with a reported prevalence ranging from 1.4% to 29% among a group of epidemiologic studies. Epiretinal membranes can affect vision quality by reducing visual acuity, causing metamorphopsia and loss of binocular functioning, or any combination of these symptoms.

Management of epiretinal membranes has become one of the most common surgical indications for retina specialists. It is highly effective in stopping progression of symptoms, resulting in improved visual acuity in approximately 2/3 of patients and usually resulting in improvement of metamorphopsia. It may also restore binocularity in cases where binocularity is affected. Furthermore, surgical intervention with pars plana vitrectomy and membrane peeling is a reasonably safe intervention. Indications for surgery vary, but this debater will argue that early intervention in eyes that still have good visual acuity is appropriate in many, if not most, cases.

We Should Peel Epiretinal Membranes in Eyes With Good Visual Acuity: Con

Harry W Flynn Jr MD and Nicolas A Yannuzzi MD

The Preferred Practice Patterns[1] guidelines from the American Academy of Ophthalmology stress a patient-centered approach to management of epiretinal membrane (ERM). "Patients should be informed that the majority of ERMs will remain relatively stable and do not require therapy. The decision to intervene surgically in patients with ERM depends on the severity of patient's symptoms, especially the impact on their activities of daily living." The fact that a patient has "symptoms" is not enough to justify surgery in its own right. Patients must have sufficient visual symptoms to make an impact on daily activities, and within this more severe subgroup, surgical intervention can be considered.

There are a number of retrospective observational case series addressing the issue of managing patients with ERM and good baseline visual acuity (VA). Heier et al[2] reported a large series of 201 eyes with newly diagnosed idiopathic ERM with VA of 20/40 or better. In this series, surgery was offered when vision worsened to 20/50 or beyond or patients reported a significant symptom burden. This report showed that only 13% of eyes progressed to require surgery at 7 years. Loss of foveal contour was a marker for those patients who were more likely to receive surgery. However, only 17% of patients with incomplete loss of contour and 16% of patients with complete loss of foveal contour progressed to surgery during the follow-up period. In another study by Damasceno and colleagues of 174 eyes,[3] patients of average age 74 with a diagnosis of ERM and good VA were divided the cohort into 2 groups: one with 20/30 or better and one with 20/40-20/50 acuity. In the first group, initial and final VA averaged 20/25 and there was not a statistically significant change. In the second group, the average acuity was 20/44 at baseline and 20/45 at follow-up, demonstrating that both cohorts had stable visual outcomes with observational management. A separate 5-year analysis of ERMs in older adults not stratified by VA reported that 71% of all ERMs either remained stable or regressed during the follow-up period.[4]

There are surgical series regarding pars plana vitrectomy/membrane peeling (PPV/MP) for ERM in patients with good VA. In a study by Thompson,[5] patients with ERM and VA of 20/50 or better were managed by PPV/MP. The mean VA improved from an average of 20/50 to 20/40 by last follow-up. However, 21 of the 40 eyes in the cohort were phakic preoperatively, and 14 of these eyes had had cataract surgery by last follow-up. Furthermore, in the 7 eyes that were still phakic by the last clinical examination, the VA had decreased 2 letters. This data suggest that much of the benefit after ERM peel in eyes

Table 1. ERM in Eyes With Good Baseline Visual Acuity

Favoring Observation	Favoring or Not Favoring Surgery for ERM
Low rate of progression but also low rate of spontaneous release[a]	Modest VA improvements and partial improvement in distortion
Low rate of complications with observation	All risks of PPV: cataract,[b] RD, macular hole, endophthalmitis, light toxicity, CRAO, etc.
Special considerations	Special considerations
Patient's only useful seeing eye	Anticoagulation status
Patient's needs for daily living	Multiple follow-up visits by patient and family / accompanying persons
Phakic status	

Abbreviations: ERM, epiretinal membrane; VA, visual acuity; PPV, pars plana vitrectomy; RD, retinal detachment; CRAO, central retinal artery occlusion.

[a]Walter SD, Flynn HW Jr., 2016.[8]

[b]Do DV, Gichuhi S, Vedula SS, Hawkins BS, 2013.[9]

with good VA may be achieved via cataract surgery alone. In a study by Lehpamer et al,[6] an improvement in mean VA from 20/40 to 20/28 was reported with PPV/MP. Although there is a potential for improvement, visual gains are often modest.

Complications following ERM surgery may not be trivial. Parke et al[7] conducted an IRIS Registry analysis of returns to the operating room after vitrectomy surgery to treat macular hole or ERM. This cohort included over 70,000 eyes with ERM. In the ERM group, 5.5% of patients had a second surgery that was not a cataract surgery within 1 year. This included 1.4% for vitrectomy with ERM removal, 1.4% for complex retinal detachment repair, 1.3% for macular hole, 1.1% for retinal detachment repair, and 0.9% for vitrectomy with laser. The rate of these retinal complications is not insignificant.

In conclusion, eyes with ERM and good VA can be safely observed as their visual outcomes are largely stable over an extended follow-up. A small percentage of these patients may eventually progress and be considered for surgery. In patients with phakic ERM, a conservative approach is the best initial management, as many of these patients may report satisfactory vision with cataract surgery alone and this may obviate some of the more significant risks associated with vitrectomy surgery. Key considerations are patient's symptoms and the impact on activities of daily life, which should guide considerations for surgery, not the appearance of the OCT.

References

1. AAO Preferred Practice Guidelines, 2019. Idiopathic ERM and VMT Management.
2. Chen X, Klein KA, Shah CP, Heier JS. Progression to surgery for patients with idiopathic epiretinal membranes and good vision. *Ophthalmic Surg Lasers Imaging Retina*. 2018; 49(10):S18-S22.
3. Damasceno EF, Damasceno NA, Crane AM, Yannuzzi NA, Relhan N, Smiddy WE, Flynn Jr HW. The clinical course of patients with idiopathic epiretinal membranes and good visual acuity managed without surgery. Manuscript in review.
4. Fraser-Bell S, Guzowski M, Rochtchina E, Wang JJ, Mitchell P. Five-year cumulative incidence and progression of epiretinal membranes: the Blue Mountains Eye Study. *Ophthalmology* 2003; 110(1):34-40.
5. Thompson JT. Epiretinal membrane removal in eyes with good visual acuities. *Retina* 2005; 25(7):875-882.
6. Lehpamer BP, Carvounis PE. Pars plana vitrectomy for symptomatic epiretinal membranes in eyes with 20/50 or better preoperative visual acuity. *Retina* 2015; 35(9):1822-1827.
7. Parke DW 3rd, Lum F. Return to the operating room after macular surgery: IRIS Registry Analysis. *Ophthalmology* 2018; 125(8):1273-1278.
8. Walter SD, Flynn HW Jr. Spectral domain optical coherence tomography documentation of macular pseudohole evolution and spontaneous resolution. *Retin Cases Brief Rep*. 2016; 10(4):377-381.
9. Do DV, Gichuhi S, Vedula SS, Hawkins BS. Surgery for post-vitrectomy cataract. Cochrane Database of Systematic Reviews 2013, Issue 12. Art. No.: CD006366.

Anti-VEGF Therapy Is the Best Treatment for Proliferative Diabetic Retinopathy: Pro

Jeffrey G Gross MD

The DRCR Protocol S and the CLARITY studies demonstrated that anti-VEGF injections were either noninferior (Protocol S) or superior (CLARITY) to panretinal photocoagulation (PRP) for the treatment of proliferative diabetic retinopathy. Anti-VEGF treatment rapidly regresses neovascularization and treats diabetic macular edema with a single form of treatment. In many patients the effects of anti-VEGF therapy can be durable. Anti-VEGF therapy is associated with fewer complications and less need for surgery than PRP. PRP remains an effective and proven treatment for PDR; however, it suffers from significant side effects such as reduced visual fields, increased macular edema, and decreased night vision. Thus, the beneficial effects of anti-VEGF therapy combined with few complications make it the best treatment for PDR.

References

1. Gross JG, Glassman AR, Liu D, et al; Diabetic Retinopathy Clinical Research Network. Five-year outcomes of panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA Ophthalmol.* 2018; 136(10):1138-1148.
2. Sivaprasad S, Hykin P, Prevost AT, et al. Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial. *Lancet* 2017; 389(10085):2193-2203.
3. Gross JG, Glassman AR, Jampol LM, et al; Writing Committee for the Diabetic Retinopathy Clinical Research Network. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA.* 2015; 314(20):2137-2146.

Anti-VEGF Therapy Is the Best Treatment for Proliferative Diabetic Retinopathy: Con

Dean Eliott MD

NOTES

Nonproliferative Diabetic Retinopathy Should Be Treated Routinely With Anti-VEGF Therapy: Pro

Diana V Do MD

Background

Eyes with severe nonproliferative diabetic retinopathy (NPDR) are at high risk of progression to proliferative diabetic retinopathy. Pharmacologic inhibition of VEGF has been demonstrated to be effective and safe in reducing the diabetic retinopathy severity score in eyes with NPDR.

Purpose

To review the medical literature and demonstrate the evidence that shows the benefit of intravitreal VEGF inhibitors in reducing diabetic retinopathy severity and preventing vision-threatening complications.

Methods

Analysis of data from published clinical trials that have evaluated the use of intravitreal VEGF inhibitors for the treatment of severe NPDR. Outcomes and safety will be discussed.

Conclusions

Multiple randomized clinical trials have provided Level I evidence to demonstrate the efficacy and safety of intravitreal VEGF inhibitors in reducing the diabetic retinopathy severity score in eyes with high-risk NPDR. In these high-risk NPDR eyes, intravitreal anti-VEGF therapy should be routinely used.

References

1. Wykoff CC, Eichenbaum DA, Roth DB, Hill L, Fung AE, Haskova Z. Ranibizumab induces regression of diabetic retinopathy in most patients at high risk of progression to proliferative diabetic retinopathy. *Ophthalmol Retina*. 2018; 2(10):997-1009.
2. Wykoff CC. PANORAMA Trial: 1-year results. Presented at Angiogenesis, Exudation, and Degeneration Symposium; 2019; Miami, FL.
3. Ip MS, Zhang J, Ehrlich JS. The clinical importance of changes in Diabetic Retinopathy Severity Score. *Ophthalmology* 2017; 124(5):596-603.
4. Mitchell P, McAllister I, Larsen M, et al. Evaluating the impact of intravitreal aflibercept on diabetic retinopathy progression in the VIVID-DME and VISTA-DME studies. *Ophthalmol Retina*. 2018; 2(10):988-996.

Nonproliferative Diabetic Retinopathy Should Be Treated Routinely With Anti-VEGF Therapy: Con

Yannek I Leiderman MD PhD

NOTES

OCT Angiography Is Essential for Clinical Practice: Pro

Nadia Khalida Waheed MD

OCT angiography (OCT-A) is a new tool in the armamentarium of clinicians. In the 4 years since its introduction, OCT-A has crafted an important place in the clinic for the diagnosis of choroidal neovascularization and for the follow-up of patients with diabetic retinopathy and other retinal vascular disease. I would posit that OCT-A provides critical information for the clinician that is otherwise not readily available without invasive testing such as fluorescein angiography, and that it does so faster, more safely, and more reliably than the alternatives. All that holds us back from complete adoption of OCT-A is the financials in the United States, something that is readily demonstrated by the PAT surgery, which shows much wider adoption of OCT-A outside the USA than in the USA.

In summary, OCT-A has become an essential tool in the armamentarium of the retinal specialist.

OCT Angiography Is Essential for Clinical Practice: Con

Richard S Kaiser MD

OCT angiography (OCT-A), while a revolutionary advancement in technology and an interesting research tool, is not necessary for clinical practice. OCT-A is difficult to perform and frequently has many artifact and uninterpretable segments included in the images. At each retina location, in a volume scan, multiple B-scans are obtained and compared. Regional variation in images is inferred to represent motion, and thus any movement by the patient can be misinterpreted by the algorithm as vascular flow or an acquisition artifact. In addition, a media opacity such as a floater or significant lens change can cause an artifact.

Clinically relevant uses for OCT-A are limited. OCT-A is unable to demonstrate vascular permeability and leakage. Thus, for common diseases such as AMD and diabetes, the clinical relevance is limited. It is useful for detecting subtle choroidal neovascular membranes in cases of chronic central serous retinopathy, but these specific cases are rare.

In summary, OCT-A may indeed represent the future with regard to retina imaging, and it could replace fluorescein angiography in clinical practice; however, at this point, in 2019, it is not necessary to the practice of retina.

When Treating Neovascular AMD, Macular Fluid Should Not Be Tolerated: Pro

David M Brown MD

NOTES

When Treating Neovascular AMD, Macular Fluid Should Not Be Tolerated: Con

Joan W Miller MD

Exudative (neovascular) AMD is characterized by the presence of choroidal neovascularization (CNV) and typically results in severe vision loss. While fluorescein angiography (FA) has long been the gold standard for detecting and diagnosing new-onset CNV, the introduction of newer, less invasive imaging modalities such as optical coherence tomography (OCT) and OCT angiography (OCT-A) allow clinicians to more frequently and accurately monitor progression of disease and response to treatment.[1-4] Multimodal imaging has the ability to guide treatment decisions and has prompted investigations into subclasses of CNV in AMD, further stratifying exudative AMD patients to allow for personalized therapies and improved predictability of response to treatments.

A "quiescent" type of CNV was described by Querques and colleagues as subretinal pigment epithelium (RPE) CNV due to AMD occurring without intraretinal or subretinal exudation.[5] This has been well characterized with multimodal imaging, with FA showing a late-phase, ill-defined hyperfluorescent lesion without late-phase leakage or pooling, and OCT demonstrating an irregular elevation of the RPE without intraretinal or subretinal fluid.[5,6] In the absence of subretinal or intraretinal fluid, these eyes would otherwise be classified as nonexudative AMD.

Recently, our group has identified a subset of patients with exudative AMD and subthreshold CNV characterized by good vision and persistent or intermittent subretinal fluid. These patients typically maintain good visual acuity, and although the subretinal fluid waxes and wanes, it appears to be unaffected by treatment with intravitreal anti-VEGF agents. These findings suggest a subthreshold CNV category and support the hypothesis that some macular fluid can and should be tolerated.

References

1. Danis RP, Domalpally A, Chew EY, et al. Methods and reproducibility of grading optimized digital color fundus photographs in the Age-Related Eye Disease Study 2 (AREDS2 Report Number 2). *Invest Ophthalmol Vis Sci*. 2013; 54(7):4548-4554.
2. Holz FG, Sadda SR, Staurenghi G, et al. Imaging protocols in clinical studies in advanced age-related macular degeneration: recommendations from classification of atrophy consensus meetings. *Ophthalmology* 2017; 124(4):464-478.
3. Hee MR, Baumal CR, Puliafito CA, et al. Optical coherence tomography of age-related macular degeneration and choroidal neovascularization. *Ophthalmology* 1996; 103(8):1260-1270.
4. Malihi M, Jia Y, Gao SS, et al. Optical coherence tomographic angiography of choroidal neovascularization ill-defined with fluorescein angiography. *Br J Ophthalmol*. 2017; 101(1):45-50.
5. Querques G, Srour M, Massamba N, et al. Functional characterization and multimodal imaging of treatment-naive "quiescent" choroidal neovascularization. *Invest Ophthalmol Vis Sci*. 2013; 54(10):6886-6892.
6. Carnevali A, Cicinelli MV, Capuano V, et al. Optical coherence tomography angiography: a useful tool for diagnosis of treatment-naive quiescent choroidal neovascularization. *Am J Ophthalmol*. 2016; 169:189-198.

Anti-VEGF Safety in ROP

Robert L Avery MD

I. Anti-VEGF Therapy's Increased Role in ROP

BEAT ROP

A. Demonstrated efficacy

B. Underestimated systemic exposure

II. Systemic Exposure of Anti-VEGF Agents

A. In adult diseases

B. In ROP

III. Is There Evidence That Systemic Exposure Matters?

A. Serum concentrations reach levels that can have effects.

1. Free aflibercept detectable in serum

2. Free bevacizuamb at levels in ROP that can affect retinal neovascularization

B. Fellow eye effects

C. Systemic safety studies in adults

IV. Systemic Safety in ROP

A. Inherent difficulties

B. Power calculations

V. Dosing Concerns

A. Animal studies

B. ROP dosing studies

VI. Concluding Recommendations

Selected Readings

1. Mintz-Hittner HA, Kennedy KA, Chuang AZ; BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3 retinopathy of prematurity. *N Engl J Med*. 2011; 364:603-615.
2. Avery RL, Castellarin AA, Steinle NC, et al. Systemic pharmacokinetics following intravitreal injections of ranibizumab, bevacizumab or aflibercept in patients with neovascular AMD. *Br J Ophthalmol*. 2014; 98(12):1636-1641.
3. Kong L, Bhatt AR, Demny AB, et al. Pharmacokinetics of bevacizumab and its effects on serum VEGF and IGF-1 in infants with retinopathy of prematurity. *Invest Ophthalmol Vis Sci*. 2015; 56(2):956-961.
4. Karaca C, Oner AO, Mirza E, Polat OA, Sahiner M. Bilateral effect of unilateral bevacizumab injection in retinopathy of prematurity. *JAMA Ophthalmol*. 2013; 131(8):1099-1101.
5. Lien R, Yu M-H, Hsu K-H, et al. Neurodevelopmental outcomes in infants with retinopathy of prematurity and bevacizumab treatment. *PLoS One* 2016; 11(1):e0148019.
6. Morin J, Luu TM, Superstein R, et al. Neurodevelopmental outcomes following bevacizumab injections for retinopathy of prematurity. *Pediatrics* 2016; 137(4):e20153218.
7. Fan YY, Huang YS, Huang CY, et al. Neurodevelopmental outcomes after intravitreal bevacizumab therapy for retinopathy of prematurity: a prospective case-control study. *Ophthalmology*. Epub ahead of print 2019 Apr 5. doi: 10.1016/j.ophtha.2019.03.048.
8. Rodriguez SH, Peyton C, Lewis K, et al. Neurodevelopmental outcomes comparing bevacizumab to laser for type 1 ROP. *Ophthalmic Surg Lasers Imaging Retina*. 2019; 50(6):337-343.
9. Avery RL. Bevacizumab (Avastin) for retinopathy of prematurity: wrong dose, wrong drug, or both? *J AAPOS*. 2012; 16(1):2-4.
10. Lutty GA, McLeod DS, Bhutto I, Wiegand SJ. Effect of VEGF trap on normal retinal vascular development and oxygen-induced retinopathy in the dog. *Invest Ophthalmol Vis Sci*. 2011; 52:4039-4047.
11. Wallace DK, Kraker RT, Freedman SF, et al. Assessment of lower doses of intravitreous bevacizumab for retinopathy of prematurity: a Phase 1 dosing study. *JAMA Ophthalmol*. 2017; 135(6):654-656.
12. Wallace DK, Dean TW, Hartnett ME, et al. A dosing study of bevacizumab for retinopathy of prematurity: late recurrences and additional treatments. *Ophthalmology* 2018; 125(12):1961-1966.

ROP in Adolescents and Adults

Late Complications of ROP

Antonio Capone Jr MD

I. Evolution of ROP and Its Management
   A. Pre-1940s
   B. Through the mid-1980s
   C. Late 1980s
   D. 1990s–early 2000s
   E. 2000 and beyond

II. "Generations" of ROP
   A. Spontaneous involution
   B. Ablation generation
   C. Pharmacotherapy

III. Retinal Findings
   A. Minimal peripheral findings
   B. Vascular straightening and pigment stippling
   C. Cicatricial changes
   D. Posterior pole changes
   E. Macular ectopia
   F. Retinal tear and detachment in formerly premature adults

IV. Retinal Tear and Detachment in Formerly Premature Adults
   A. Failure, primary repair
   B. ROP after infancy: Cryo-ROP, 15-year follow-up
   C. New appearance of serious structural sequelae between the 10-year and 15-year examinations

V. Themes
   A. Progression of ROP over time in some eyes: lifetime disease
   B. Even with minimal cicatricial changes
   C. Importance of hyaloid
   D. Importance of avascular periphery

VI. Focal Hyaloidal Contraction
   A. Children
   B. Adults

VII. Diffuse Hyaloidal Contraction
   A. Infants
   B. Adults

VIII. Persistent Avascular Peripheral Retina
   A. Pre-treatment era: Incomplete regression of subthreshold disease
   B. Treated with an anti-VEGF agent: persistent avascular retina

IX. ROP-RRD in Adolescence With Lattice-like Changes

X. Conclusions
   A. Significant incidence of late retinal complications
   B. Variable presentation depending on ROP "generation"
   C. Importance of hyaloid
   D. Importance of avascular periphery

OCT Angiography in Children

Lejla Vajzovic MD

NOTES

Prophylactic Scleral Buckling in Children

Management of Traumatic Retinal Detachment in Young Patients With Self-Injurious Behavior

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Self-injurious behavior (SIB), a well-described feature in patients with cognitive impairment, often leads to sensory impairment including loss of vision from retinal detachment (RD). Visual prognosis is unfortunately poor due to ongoing ocular trauma from SIB leading to redetachment. The management of these patients, both intraoperative and in particular postoperative, is profoundly challenging and can be isolating for families and physicians who are comanaging these patients.

In this presentation, we present the largest study to date of patients with retinal detachment due to SIB. This is a multicenter, interventional, retrospective case series of 95 eyes with RD due to SIB in 68 patients with a median age of 12 and a median follow-up time of 1024 days. The most common diagnosis was autism spectrum disorder, most patients were male (73.5%), and the most common behaviors were hitting the face or head with their hands (54%) or intense eye rubbing (19.5%). Bilateral RD was present in 42.6% of patients. As the primary surgery, eyes with RD underwent vitrectomy (28.4%), scleral buckle (18.9%), combined vitrectomy/scleral buckle (31.6%), or no treatment (16.8%), and 5 eyes without RD underwent prophylactic scleral buckle.

The mean number of surgeries in each eye was 1.6, the redetachment rate was 49.5%, and the final attachment rate was 72%. Factors predicting worse final outcome included the presence of a funnel RD ($P = 9.6\text{x}10^{-5}$) and the presence of proliferative vitreoretinopathy ($P = 5.7\text{x}10^{-9}$). Factors predicting final attachment were the use of a scleral buckle in the primary surgery ($P = .04$) and the use of silicone oil in the primary surgery ($P = .003$). Unfortunately, patients showed minimal change in vision despite anatomical success (35.3% better than CF preop, 33.8% better than CF at final follow-up), and there was no significant correlation between improvement and any of the treatment groups ($P = .88$).

Overall, patients with SIB who present with RD have a high risk of redetachment and ultimate non-reattachment, likely due to ongoing trauma, but surgery in these patients can lead to anatomic success. Physicians should be aware of the risk of bilateral RD when taking patients to the OR for exam and treatment. Based on these data, surgery may have more success if it includes scleral buckle and/or the use of silicone oil tamponade with these difficult cases. If possible, primary scleral buckling may be the prudent treatment choice because it is not dependent on positioning, there is less risk of infection if postoperative drops cannot be instilled, and it is easier to monitor postoperatively. Prophylactic scleral buckling is an option also for eyes with retinal tears without RD. Earlier diagnosis and treatment are essential, so primary care physicians should have low thresholds to refer patients with SIB to ophthalmology teams.

Section VIII: Late Breaking Developments, Part I

Results of Cohorts 1-5 for the RGX-314 Phase I/IIa Study of Gene Therapy for Neovascular Wet AMD

Jeffrey S Heier MD

24-Week Results of Phase 1 Study of Intravitreal Gene Therapy With ADVM-022 for Neovascular AMD (OPTIC Trial)

Szilard Kiss MD

Abicipar for Neovascular AMD: Two-Year Results From CEDAR and SEQUOIA Phase 3 Clinical Trials

Rahul Khurana MD

Primary Results From Phase 2 Study of Risuteganib in Intermediate Dry AMD

David S Boyer MD

A Multicenter Phase 3 Double-Masked Randomized Controlled Noninferiority Trial Comparing the Clinical and Cost Effectiveness of Ranibizumab (Lucentis) vs. Aflibercept (Eylea) vs. Bevacizumab (Avastin) in Macula Edema Due to Central Retinal Vein Occlusion (LEAVO)

Philip G Hykin MBBS

Extended Durability in Exudative Retinal Diseases Using the Novel Intravitreal Anti-VEGF Antibody Biopolymer Conjugate KSI-301: Results From the Phase 1b Study in Patients With wAMD, DME, and RVO

Charles C Wykoff MD PhD

Background

Real-world visual outcomes at a population level for patients with neovascular AMD managed with anti-VEGF therapy appear to fall short of the visual outcomes achieved in published prospective clinical trials.[1,2] The limited intraocular durability of existing anti-VEGF pharmaceuticals is an important potential contributor, leading to exudative disease recurrence between patient visits. Medicines with meaningfully improved treatment durability could address these issues and have a significant, positive public health impact.

KSI-301, an Antibody Biopolymer Conjugate

The Antibody Biopolymer Conjugate (ABC) Platform is a class of molecules engineered to maintain effective drug levels in the eye over longer periods of time than are achieved with current-generation anti-VEGF therapeutics. ABCs consist of an antibody or protein stably attached to an optically clear, ultrahigh molecular weight, phosphorylcholine-based biopolymer (Figure 1). In preclinical experiments, ABC Platform bioconjugates substantially lengthen intraocular durability following intravitreal injection, and they demonstrate enhanced target-tissue penetration and bioavailability, improved stability, and improved potency relative to unconjugated antibodies and commercially available anti-VEGF agents.

KSI-301 is an anti-VEGF ABC formulated to a high concentration, 50 mg/mL (by weight of antibody). KSI-301 is administered via intravitreal injection as a clear aqueous solution. With a possible dosing interval as infrequent as once every 12-20 weeks after 3 loading doses for patients with neovascular AMD and diabetic macular edema (DME), KSI-301 could substantially improve anti-VEGF durability, thereby meaningfully improving consistent VEGF suppression in the setting of underdosing endemic to real-world clinical practice.

Clinical Studies of KSI-301

A Phase 1a single ascending dose study of KSI-301 in patients with DME has been reported.[3,4] A total of 9 patients (3 per cohort) were treated with a single intravitreal dose of 1.25, 2.5, or 5 mg of KSI-301 and followed for 12 weeks. KSI-301 was well tolerated at all 3 dose levels; no drug related adverse events, inflammation, or dose-limiting toxicities were observed. After a single dose, rapid visual and anatomic improvements were observed as early as 1 week after treatment. The treatment effect increased through 4 weeks, resulting in a median BCVA improvement of +12.5 letters and median CRT improvement of –120 microns from baseline, pooled across all 3 dose levels. At 12 weeks after the single dose, sustained median improvements in BCVA (median: +9 letters) and CRT (median: –121 microns) were observed, pooled across all 3 dose levels (Figure 2).

KSI-301 is now being evaluated in 2 multiple-dose studies. In a Phase 1b open-label study enrolling up to 90 treatment-naïve neovascular AMD, DME, and retinal vein occlusion (RVO) patients, 2 dose levels of KSI-301 are being evaluated, 2.5 and 5 mg. Each patient receives 3 initial monthly injections of KSI-301 and then is evaluated every 4 weeks; additional injections of KSI-301 are given when protocol-specified retreatment criteria are met. Follow-up is through week 36. Interim safety and efficacy results from the loading and follow-up periods of the ongoing Phase 1b study will be presented (NCT03790852, Figure 3, left panel).

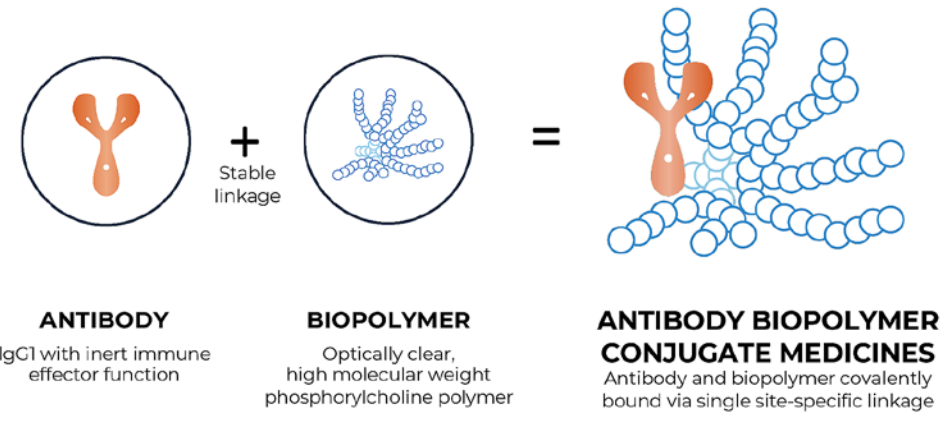
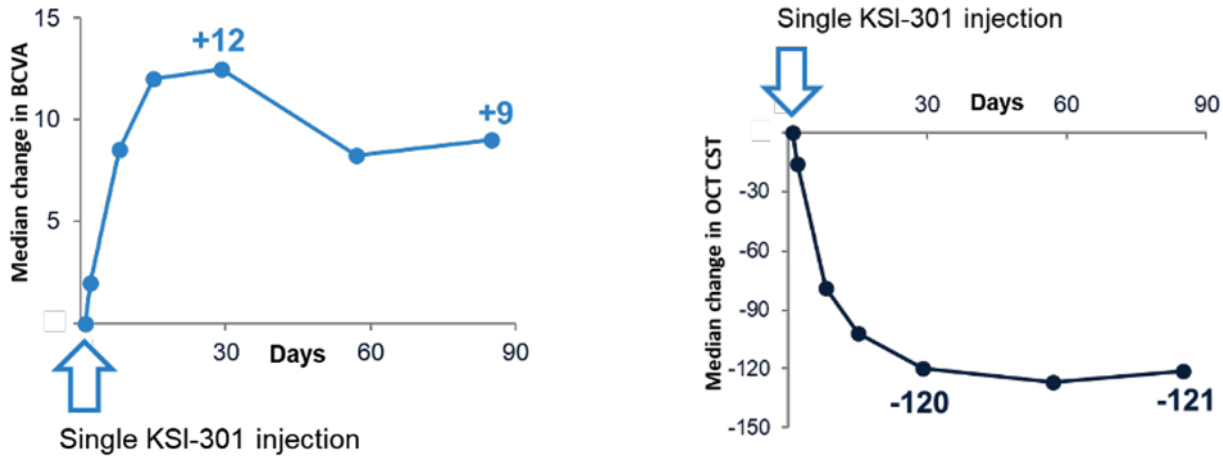


Figure 1. Design of ABC Platform medicines such as KSI-301, an anti-VEGF with improved durability.



A B

Figure 2. Median changes from baseline to week 12, pooled across 3 dose groups (N = 9 patients total) in Phase 1a study.

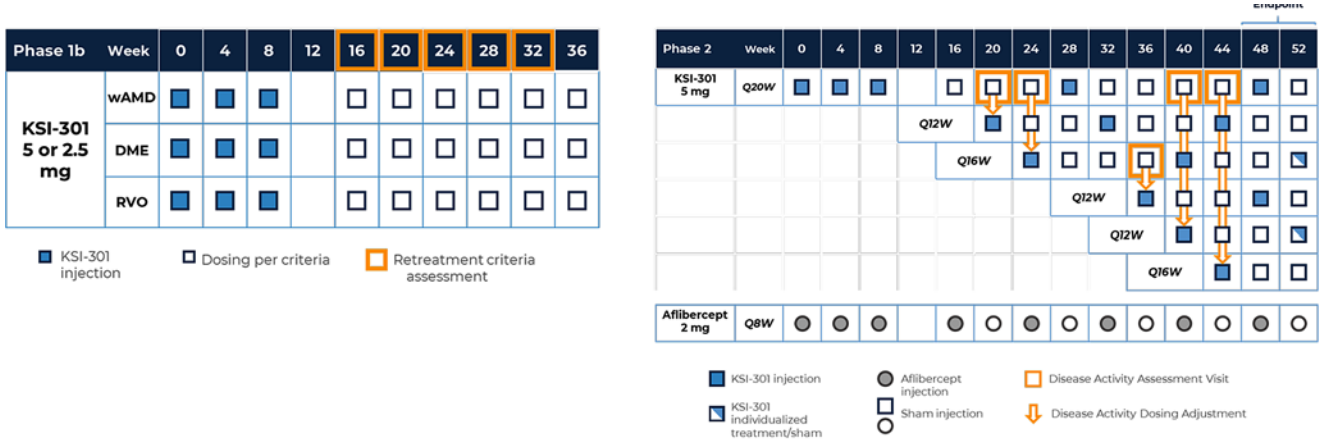


Figure 3. Designs of ongoing Phase 1b (left) and Phase 2 clinical trials of KSI-301 in treatment-naïve patients.

A Phase 2 study involving approximately 400 treatment-naïve wet AMD (wAMD) patients is also being initiated. Patients will be randomized 1:1 to receive 5 mg KSI-301 every 12 to 20 weeks or aflibercept 2 mg every 8 weeks, after 3 monthly doses. All KSI-301 patients will be on 12-week or longer dosing, and the dosing regimen for patients randomized to KSI-301 is based on protocol-specified disease activity criteria (Figure 3, right panel).

Additional ABC Platform medicines are in earlier stages of development for the treatment of high-prevalence ophthalmic diseases. For example, KSI-501 is a dual inhibitor of VEGF and IL-6 built on the ABC Platform.

References

1. Ciulla TA, Huang F, Westby K, et al. Real-world outcomes of anti-vascular endothelial growth factor therapy in neovascular age-related macular degeneration in the United States. *Ophthalmol Retina*. 2018; 2(7):645-653.
2. Rao P, Wood K, Salman C, et al. Real-world vision in age-related macular degeneration patients treated with single anti-VEGF drug type for 1 year in the IRIS Registry. *Ophthalmology* 2018; 125(4):522-528.
3. Do D. KSI-301: update on Phase 1 studies with a first in class antibody-biopolymer conjugate for treatment of wet AMD, DME, and other retinal vascular diseases. Presentation at Angiogenesis, Exudation, and Degeneration; February 9, 2019; Miami, FL.
4. Patel, S, et al. Phase 1 first-in-human study of KSI-301: a novel anti-VEGF antibody biopolymer conjugate with extended durability. ARVO, 2019.

VICI Study of Eplerenone for Central Serous Retinopathy

Clinical Efficacy and Mechanistic Evaluation of Eplerenone for Central Serous Chorioretinopathy: The VICI Randomized Trial

Andrew John Lotery MD on behalf of the VICI trial investigators

Central serous chorioretinopathy (CSCR) is the fourth most common vision-threatening retinopathy. Fluid spontaneously gathers under the retina (subretinal fluid [SRF]), causing widespread retinal abnormalities including localized retinal detachments and a thickened choroid with dilated vessels. The condition can spontaneously resolve, and it typically does so within 3 months (acute CSCR); however, the SRF can persist (chronic CSCR) and can lead to permanent vision loss in up to one-third of cases.[1] Following resolution, the condition can recur or affect the second eye. There are 10 new cases per 100 000 men and 2 new cases per 100 000 women each year.[2]

Standard care for chronic CSCR often consists of observation only. Studies using photodynamic laser therapy (PDT) with half-dose verteporfin have shown some positive results.[3,4] However, PDT is expensive, not always effective, and not available at many National Health Service (NHS) eye hospitals in the United Kingdom. Studies investigating anti-vascular endothelial growth factor therapies have not shown them to be efficacious for treating CSCR.[5]

Animal model studies found that choroidal vasodilation, one of the features of CSCR, was induced by aldosterone acting via an endothelial vasodilatory potassium channel KCA2.3. Aldosterone is a mineralocorticoid receptor (MR) activator; blockade of this pathway prevented aldosterone-induced choroidal thickening.[6] The two MR antagonists that have been most studied in humans for treating CSCR are spironolactone and eplerenone. Eplerenone is preferred, as spironolactone has undesirable side effects, including gynecomastia. Several small studies have investigated the efficacy of eplerenone in CSCR, with encouraging results; however, none have been adequately designed or powered to inform clinical practice.[7-9]

Aim and Outcomes

The aim of the VICI trial was to compare the efficacy and safety of eplerenone with usual care vs. placebo with usual care for chronic CSCR for 12 months in a Phase 3 randomized placebo-controlled clinical trial.[10]

The primary outcome was BCVA at 12 months, adjusted for baseline BCVA, measured using validated ETDRS vision charts with measurements made in accordance with a standardized protocol for trials in medical retina. Secondary outcomes included central subfield retinal thickness, choroidal response to treatment, fundus fluorescein angiography (FFA) phenotype, and changes in retinal pigment epithelium at 12 months; time to resolution of SRF; recurrence of SRF following resolution; incidence of CSCR in the second eye; patient-reported visual function; and the safety profile of eplerenone (see Table 1 for full details). Baseline DNA, serum, and plasma samples were collected and stored in a biobank for future genetic and mechanistic research.

Participants and Treatment Schedule

Eligible participants were aged ≥ 18 and ≤ 60 years with CSCR ≥ 4 months duration who had not received previous or current treatment with eplerenone, PDT, anti-VEGF therapy, intraocular steroid use, or thermal laser therapy for CSCR, did not have choroidal neovascularization or presence of any other disease that could cause retinal fluid or SRF to accumulate or affect visual acuity or myopia > 6 D, and had no evidence of hyperkalemia (blood serum potassium > 5.0 mmol/L).

114 eligible participants gave consent and were randomized by secure online computer system to receive either eplerenone (25 mg/day for 1 week, increased to 50 mg/day) or placebo for up to 12 months or until complete resolution of SRF. Participants were followed up at 1 week, 4 weeks, and 3, 6, 9, and 12 months post-randomization. As hyperkalemia is a common side effect of eplerenone, blood serum potassium was monitored at all follow-up visits; if it exceeded 5.0 mmol/L, participants ceased the trial drug permanently but were invited to continue with follow-up to 12 months. If SRF recurred following resolution, participants were restarted on the trial drug following the same dosing regimen. See Figure 1 for the study schema.

Participants, clinicians, outcome assessors, pharmacists, and the trial management team were masked to the allocation for the duration of the trial. Bottles of trial drug were labelled with a unique identifying number, with code break lists held only by the manufacturing pharmacy and the trial database programmer.

Table 1. VICI Trial Secondary Outcomes

1	Low luminance BCVA, measured immediately after measuring BCVA by adding a 2 log neutral density filter and recording the number of letters read
2	CSRT as measured by OCT recorded at 12 months, including CSRT measured at interim visits and adjusted for baseline CSRT
3	Change in SRF thickness as measured by OCT
4	Systemic and ocular adverse events at any time during the 12-month follow-up period
5	Proportion of patients with macular atrophy of the RPE defined as hypoautofluorescence at 12 months
6	Area change in macular RPE hypoautofluorescence at 12 months
7	Choroidal thickness as measured by enhanced depth imaging OCT at 12 months, adjusted for baseline choroidal thickness (measurements were made subfoveally)
8	Proportion of patients with reduced choroidal permeability on ICG at 12 months
9	Time to resolution of SRF
10	Classification of all study eyes as complete, partial, or no resolution of SRF at each time point of the study. Partial resolution of SRF was defined as a decrease of > 25% of central macular thickness from baseline. A nonresponder was defined as having an increase in SRF or decrease in SRF ≤ 25% from baseline.
11	Patient-reported visual function using Visual Function Questionnaire VFQ 25 was assessed at baseline and 12 months.
12	Classification of all study eyes by each FFA phenotype, such as smoke-stack, ink-blot, and chronic epitheliopathy, at baseline and 12 months
13	Classification of all study eyes as early, late, or non-responder. An early responder was defined as complete or partial resolution of subfoveal SRF by 3 months. A late responder was defined as complete or partial resolution of subfoveal SRF after 6 months.
14	Incidence of central serous chorioretinopathy in the fellow eye as measured by OCT, FFA, ICG angiography, or autofluorescence
15	Time to recurrence of SRF. Recurrence was defined as the appearance of new SRF in a study eye after complete resolution of SRF at any point.

Note: OCT, ICGA, FFA, and AF retinal images were graded by an independent ophthalmic reading center to address outcomes 2, 3, 5-10, and 12-15. Abbreviations: CSRT, central subfield retinal thickness; SRF, subretinal fluid; RPE, retinal pigment epithelium; ICG, indocyanine green; FFA, fundus fluorescein angiography.

Results and Conclusions

The last VICI trial follow-up visit occurred on February 28, 2019. The mean age of participants was 48.4 years (SD = 7.6), 85/114 participants (74.6%) were male, 99/114 (86.8%) were white, 13/114 (11.4%) were Asian, 1/114 (0.9%) were mixed ethnicity, and 1/114 (0.9%) were "other" ethnicity. At baseline, the median central macular thickness was 349 µm (IQR: 280-401), and 5 (4%), 72 (64%), and 37 (32%) participants had smoke-stack, ink-blot, or chronic epitheliopathy phenotypes on FFA, respectively. Twenty-seven participants (24%) were using steroids at baseline; topical creams were the most common method of administration (n = 13), followed by inhalation (n = 10). 109 participants donated samples to the biobank, providing a valuable resource for future studies. 105 participants attended the 12-month exit visit. The full dataset is currently being analyzed, and the results will be disclosed at the subspecialty meeting.

This is the first adequately designed and powered randomized controlled trial investigating the efficacy of eplerenone for treating CSCR. It will provide important data on the rate of and time to resolution of SRF and subsequent recurrence. Time to resolution is critical because if eplerenone is shown to be effective, it will help inform clinicians about how long to prescribe it and when to expect to see a response, if a patient is going to respond. This information is currently unknown, resulting in variations in practice.

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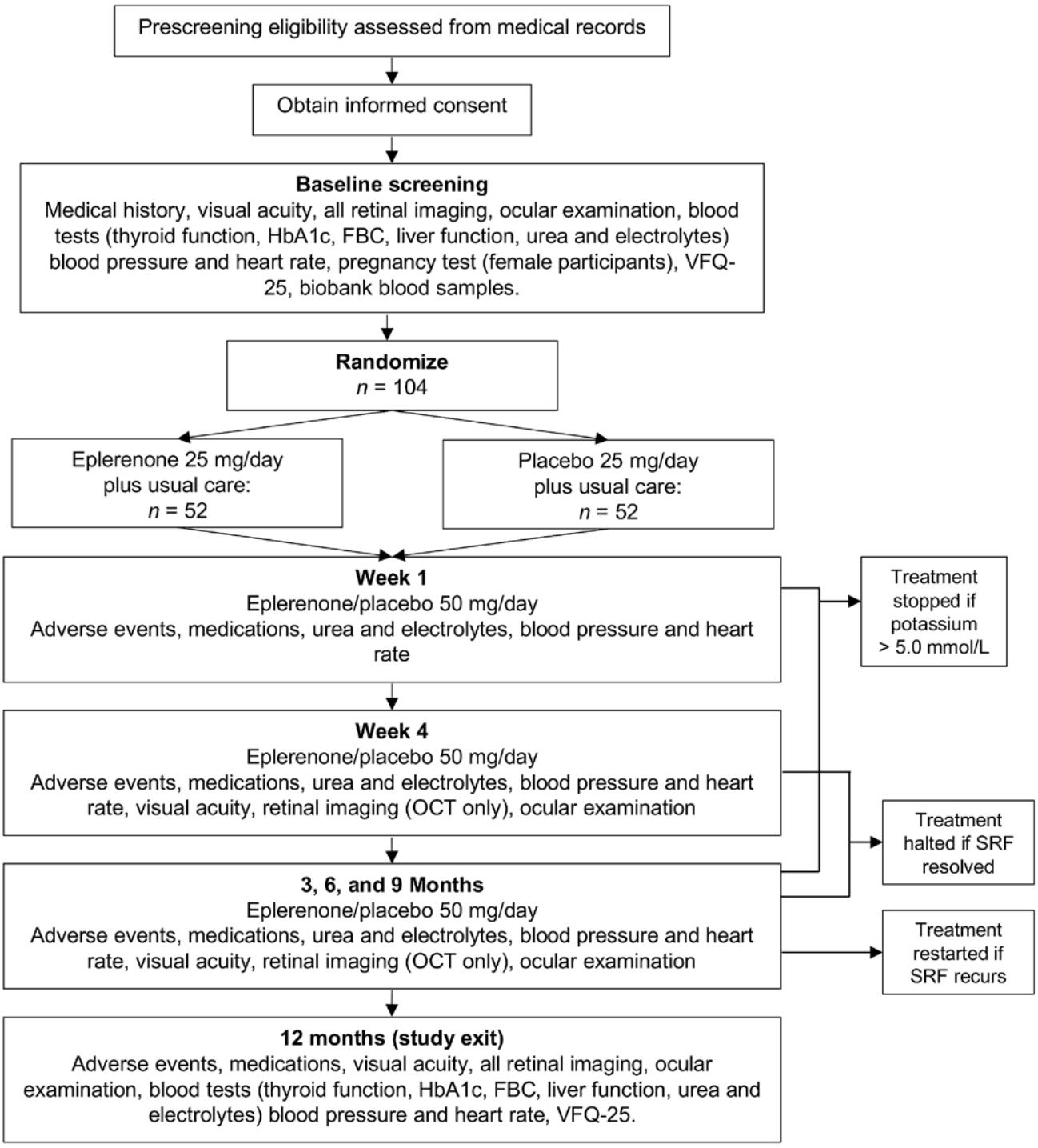


Figure 1. VICI trial schema. CONSORT diagram first reported in *Eye (Lond)*, 2019.[10]

References

1. Loo RH, Scott IU, Flynn HW Jr, et al. Factors associated with reduced visual acuity during long-term follow-up of patients with idiopathic central serous chorioretinopathy. *Retina* 2002; 22(1):19-24.
2. Gemenetzi M, De Salvo G, Lotery AJ. Central serous chorioretinopathy: an update on pathogenesis and treatment. *Eye (Lond)*. 2010; 24(12):1743-1756.
3. Chan WM, Lai TY, Lai RY, Liu DT, Lam DS. Half-dose verteporfin photodynamic therapy for acute central serous chorioretinopathy: one-year results of a randomized controlled trial. *Ophthalmology* 2008; 115(10):1756-1765.
4. van Dijk EHC, Fauser S, Breukink MB, et al. Half-dose photodynamic therapy versus high-density subthreshold micropulse laser treatment in patients with chronic central serous chorioretinopathy: the PLACE trial. *Ophthalmology* 2018; 125(10):1547-1555.
5. Chung YR, Seo EJ, Lew HM, Lee KH. Lack of positive effect of intravitreal bevacizumab in central serous chorioretinopathy: meta-analysis and review. *Eye (Lond)*. 2013; 27(12):1339-1346.
6. Zhao M, Celerier I, Bousquet E, et al. Mineralocorticoid receptor is involved in rat and human ocular chorioretinopathy. *J Clin Invest*. 2012; 122(7):2672-2679.
7. Ghadiali Q, Jung JJ, Yu S, Patel SN, Yannuzzi LA. Central serous chorioretinopathy treated with mineralocorticoid antagonists: a one-year pilot study. *Retina* 2016; 36(3):611-618.
8. Schwartz R, Habot-Wilner Z, Martinez MR, et al. Eplerenone for chronic central serous chorioretinopathy: a randomized controlled prospective study. *Acta Ophthalmol*. 2017; 95(7):e610-e618.
9. Rajesh B, Agrawal H, Peguda HK, Chhablani J. Predictors of outcome during eplerenone therapy in chronic central serous chorioretinopathy:a prospective, open-label pilot clinical study. *Ophthalmic Surg Lasers Imaging Retina*. 2018; 49(7):479-486.
10. Willcox A, Culliford L, Ellis L, et al. Clinical efficacy of eplerenone versus placebo for central serous chorioretinopathy: study protocol for the VICI randomised controlled trial. *Eye (Lond)*. 2019; 33(2):295-303.

Vitreous Substitutes Following Vitrectomy Surgery

Andrew Chang MBBS

Introduction

The ideal vitreous substitute is one that is biocompatible and degradable, allowing for retinal oxygenation while maintaining structural integrity. Such vitreous substitutes will enable both improved surgical outcomes and more rapid visual rehabilitation in the repair of retinal detachment, haemorrhage, and trauma. The potential for drug delivery would be an advantage.

Currently available vitreous substitutes include air and expansile gases such as sulfur hexafluoride and perfluoropropane, as well as perfluorocarbon liquids and silicone. These vitreous substitutes have limitations, including the need for postoperative posturing, further surgery to remove it, and toxicity to ocular tissues.

Vitargus is an injectable, transparent, oxihyaluronic acid-adipic acid dihydrazide hydrogel, transmitting all wavelengths of visible light. It has a refractive index of 1.34, close to that of human vitreous (1.33), and its injection into the vitreous cavity in liquid form should avoid the shear stress seen in preformed gels, while exerting sufficient compressive strength when it becomes a gel to perform its intended physiological function in holding the retina in place during healing.

The optical properties allow visualization of the retina in the postoperative period as well as immediate visual rehabilitation for the patient. The gel is nonexpansile, and flying to altitude is possible. The gel does not require removal as it biodegrades.

Potential applications of Vitargus as a vitreous substitute include retinal detachment repair, management of diabetic retinal hemorrhage with traction retinal detachment, and following repair of penetrating eye trauma, including intraocular foreign body removal.

This Phase 1 clinical trial evaluaed the safety and tolerance of intravitreal Vitargus.

Methods

Eleven participants with retinal detachment or vitreous hemorrhage requiring vitrectomy and with a BCVA of 20/40 to 20/2000 were enrolled in the study. At the conclusion of vitrectomy surgery, Vitargus was injected in its liquid form, with subsequent gelation. All participants were followed up on days 1, 7, and 14 post-procedure, and then monthly up to day 120. Assessments included laboratory analysis of hematology, blood chemistry, and urinalysis at all visits, with an analysis of circulating serum hyaluronic acid. Ocular assessments included BCVA in EDTRS letters, IOP, slit-lamp examination, wide-field fundus photography, and spectral domain OCT.

Results

Three participants with retinal detachment and 7 with vitreous hemorrhage were recruited. One participant presented with both vitreous hemorrhage and retinal detachment. The mean age of the participants was 60 ± 5.9 years.

The study found the mean BCVA improved after surgery by 31.9 ± 32.8, 21.4 ± 44.0, 31.9 ± 32.8 letters (mean ± SD) at day 1, day 7, and month 1 respectively ($P < .05$), compared to 16.5 ± 21.2 letters at baseline. Vitargus was confirmed to fill the vitreous cavity. One participant experienced elevated IOP at day 2, diagnosed as closed-angle glaucoma requiring laser and trabeculectomy. Another participant underwent implantation of a drainage tube following elevated IOP at day 1. One participant experienced elevated IOP and the appearance of a sterile hypopyon at day 6 without a fibrinous reaction. The IOP elevations were attributed to physical characteristics of the eyes predisposing to glaucoma, including diabetic rubeosis iridis and the angle configuration.

Conclusion

The study found that Vitargus was a well-tolerated vitreous substitute. There was no apparent toxicity to ocular tissues or systemic adverse events that could be attributed to the material. Its optical properties allowed the patients to see well, and the fundus was viewed immediately following surgery. Vitargus sets as a stable semisolid gel adhering to the retina and maintains its position without the need of face-down positioning. The unique properties of Vitargus hold promise for its use following vitrectomy surgery.

Update on New Retinal Drugs

Peter K Kaiser MD

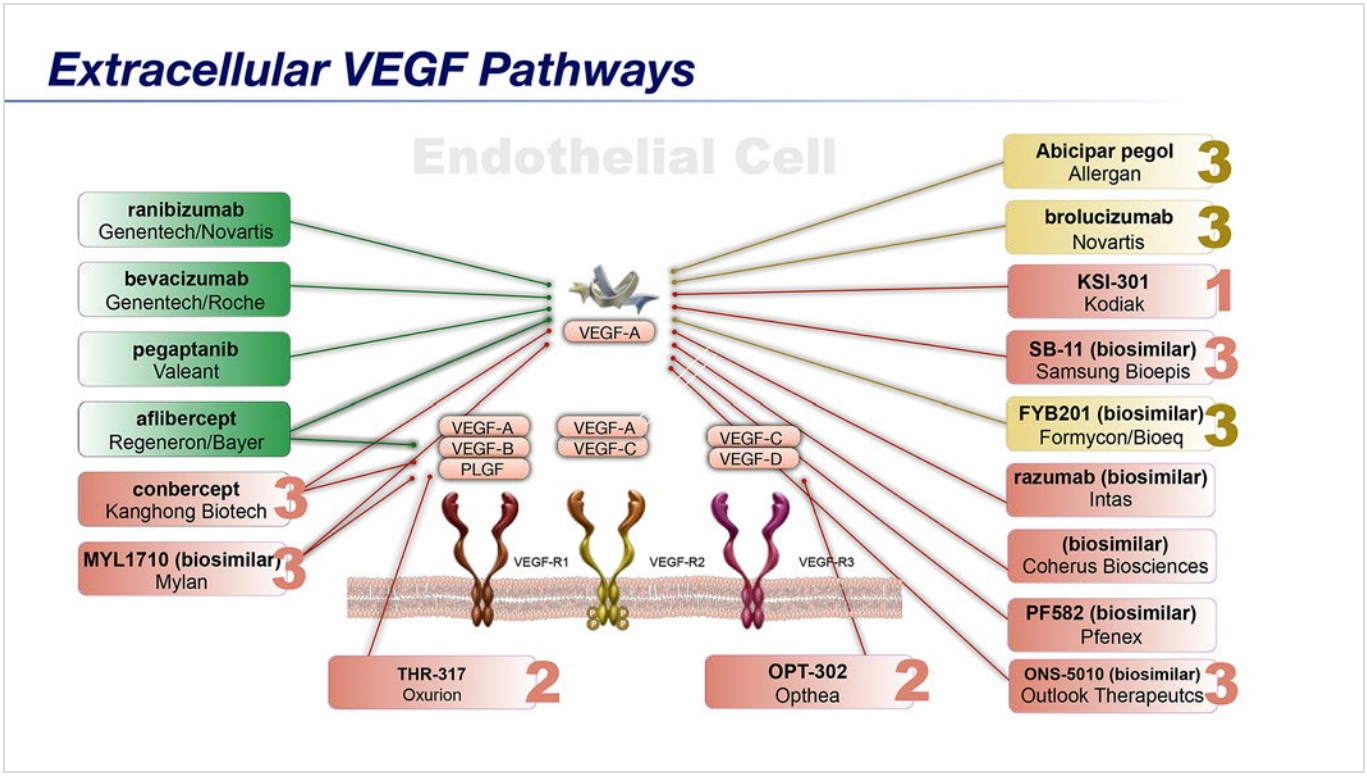


Figure 1.

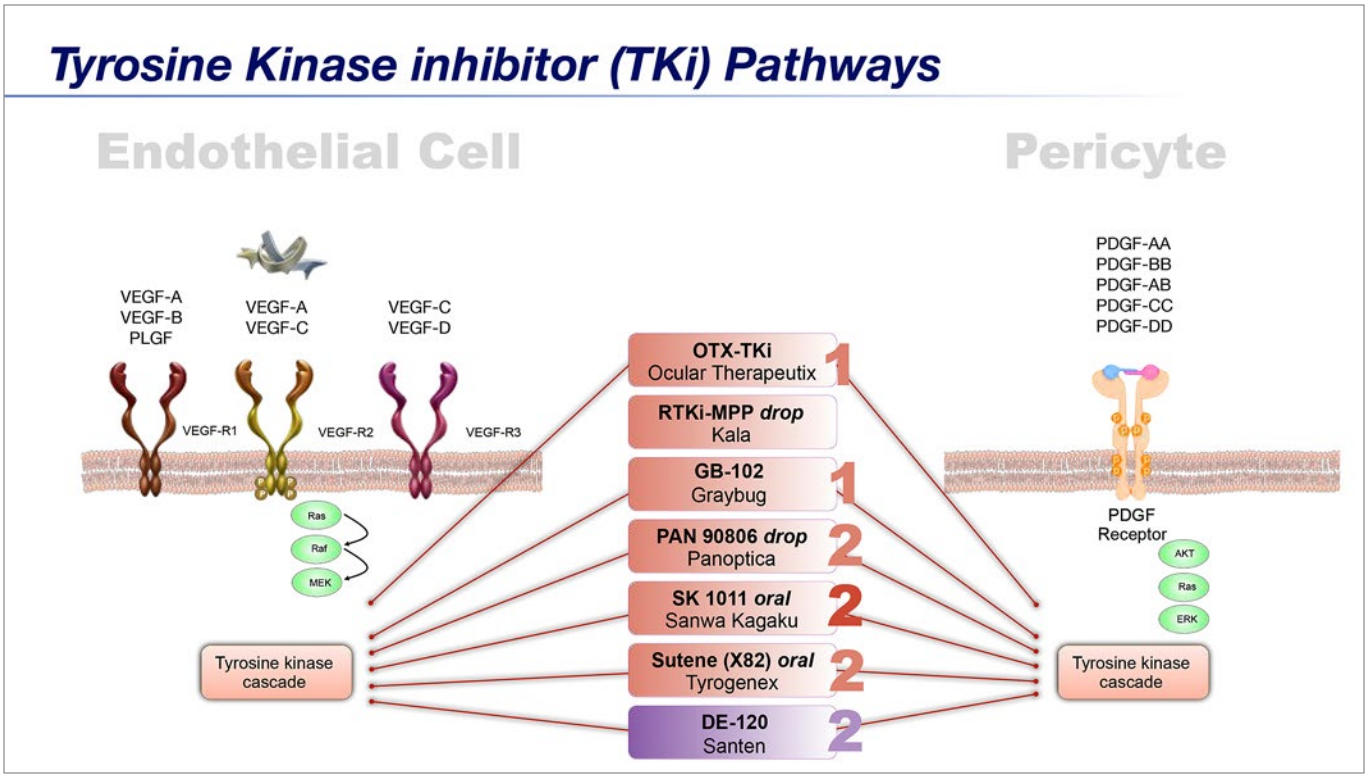


Figure 2.

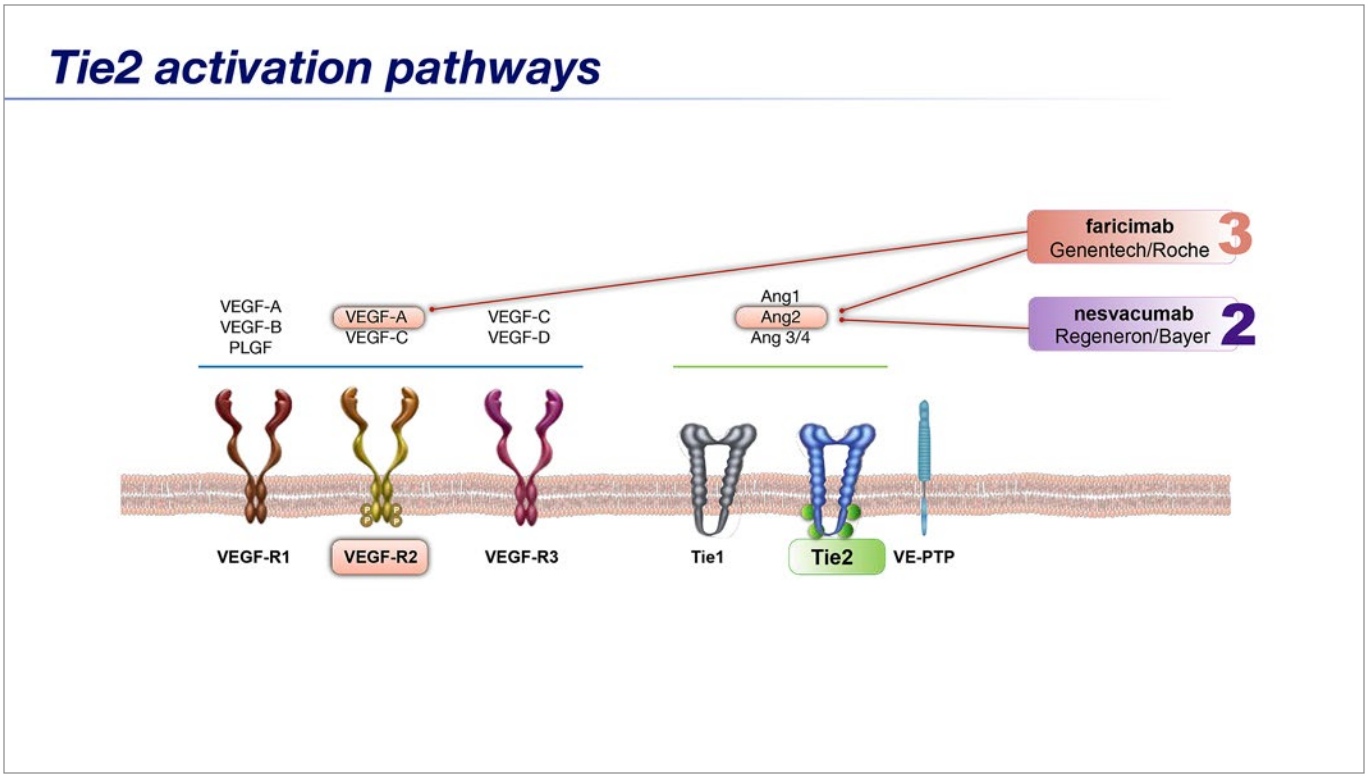


Figure 3.

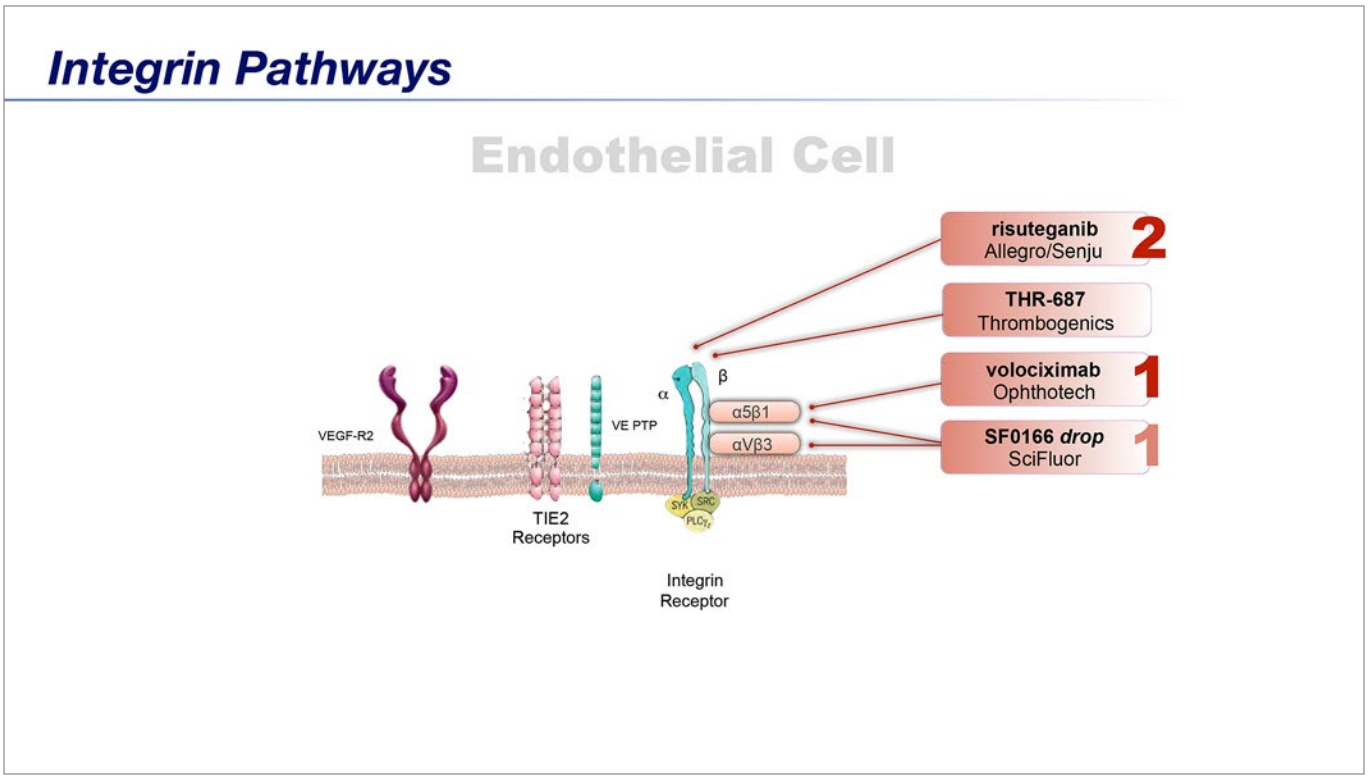


Figure 4.

Ultrawide-Field Swept Source OCT for Dynamic Observations of Vitreous

Kyoko Ohno-Matsui MD

Introduction

The vitreous is a gel-like structure that occupies four-fifths of the volume of the eye.[1,2] It consists of 98% water and 2% protein, and the proteins include collagen, hyaluronan, chondroitin sulfate, and other noncollagenous proteins. The vitreous is an important ocular structure that maintains the homeostasis of the different intraocular structures. It also acts as a shock absorber. The vitreous undergoes distinctive changes during normal aging and also under various pathological conditions. The pathologies include vitreomacular traction, proliferative vitreoretinopathy, and myopic macular retinoschisis. The pathological changes are important because they can play important roles in the development of pathology in other intraocular tissues.

Because the vitreous is difficult to observe, it has been analyzed mainly by histological examinations of autopsied eyes.[3-5] These histological studies revealed important aspects of the human vitreous, such as the presence of premacular bursa, internal cavities, and small cisterns within the vitreous. However, a noninvasive imaging method would reduce the artifactual damage to the vitreous structure that occurs during the dissection and preparation of the vitreous to make histological sections. In addition, the vitreous is a moving gel structure, and the movements are important when considering how the vitreous can act as a tractional force on the retina. However, the effects of movements can be analyzed only by in vivo examinations of the eyes. Imaging the vitreous in vivo is very difficult because it is a transparent structure and is generally not visible. Thus, it has been studied only by dark-field slit microscopy, clinical slit-lamp biomicroscopy, scanning laser ophthalmoscopy, and ultrasonography.

Swept Source OCT for Imaging Vitreous

Swept source OCT (SS-OCT) instruments have much higher resolution than conventional OCT instruments. SS-OCT uses a long wavelength laser in the 1 micron range, and because of its lower roll-off sensitivity with tissue depth, it is suitable for imaging thicker tissues from the vitreous to the choroid and sclera. SS-OCT has contributed significantly to the information about the vitreous body, as was shown in the observation of the entire structure of the posterior precortical vitreous pocket (PPVP) in vivo.[6]

To improve the viewing of the vitreous by SS-OCT, Spaide developed a technique that uses dynamic focusing and windowed averaging.[7] These techniques allowed him to view the vitreous in greater detail. However, the area of the fundus where the vitreous was visible was limited in the currently available SS-OCT devices. This is a shortcoming because the vitreous is a large tissue occupying 80% of the eye volume, and a change and movement over a wider range of the vitreous may act as tractional force in synchronicity.

Ultrawide-Field SS-OCT Images of Posterior Vitreous Over Large Areas

To overcome this difficulty, a prototype ultrawide-field SS-OCT (UWF-OCT) device has been developed that can analyze a region of interest of up to 23x20 mm and a depth of 5 mm (Figure 1). The usefulness of this UWF-OCT instrument has been reported mainly for eyes with pathologic myopia[8-10] and especially in viewing of the entire extent of large staphylomas. It can also be used to analyze the spatial relationship between myopic macular retinoschisis (MRS) and staphylomas.

Pathologically altered vitreous in highly myopic eyes may play an important role in the development of MRS. Vitreous surgeons frequently encounter a membranous structure on the retina in eyes with myopic traction maculopathy despite the presence of an apparent posterior vitreous detachment (PVD) with Weiss ring. UWF-OCT can obtain high-resolution tomographic images of the posterior vitreous cortex, and the images

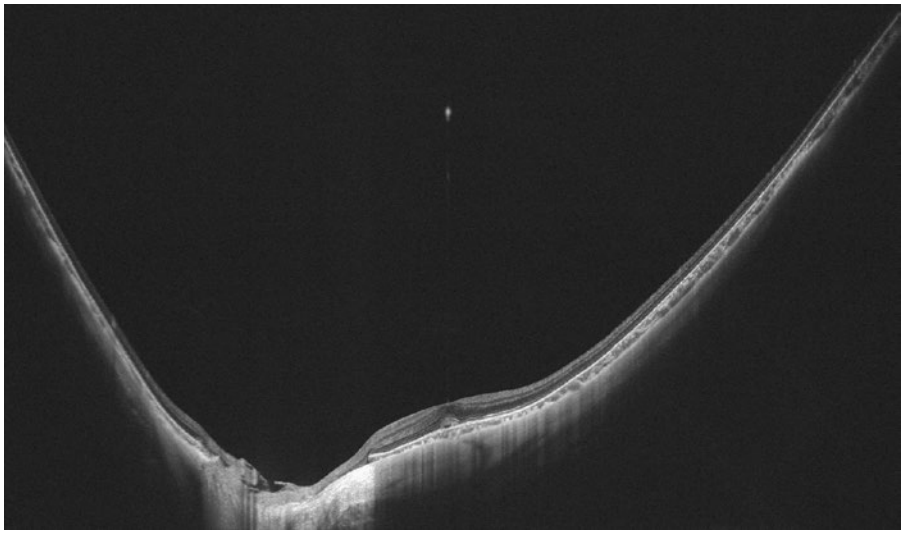


Figure 1. Ultrawide-field swept source OCT (UWF-OCT) image of an area spanning 23x20 mm and a depth of 5 mm of an eye with pathologic myopia shows a wide area of myopic macular retinoschisis up to the periphery.

reveal unusual vitreal changes over a wide area (Figure 2). The images also show one possibility for how such pathological vitreal changes can cause traction on the retinal vessels which could then result in the development of MRS.

Real-Time Dynamic Observation of Vitreous by UWF-OCT

The vitreous is a moving tissue, and its movement during eye movements needs to be analyzed when we try to determine how vitreous traction is exerted on the retina.

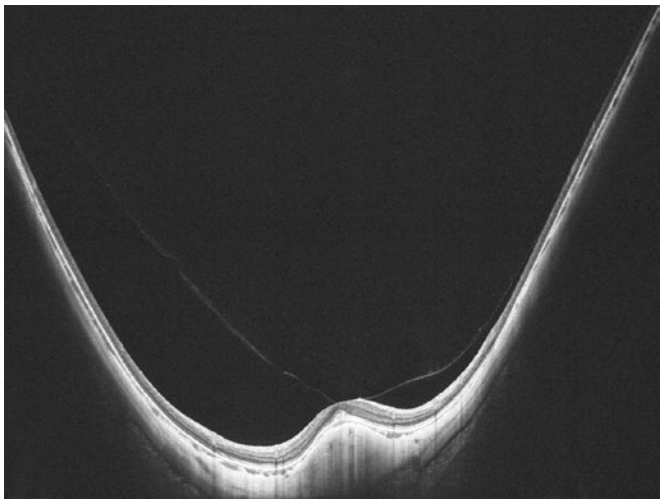
I would like to show the results of our preliminary study showing real-time dynamic images of vitreal movements recorded by UWF-OCT in various vitreoretinal diseases. These dynamic observations provide information that cannot be obtained in a single OCT scan, and we believe that UWF-OCT will become a powerful method to clarify the pathogenesis of some vitreoretinal disorders and the role of the vitreous in the development of these disorders.

Conclusions

The vitreous may be one of the most difficult ocular tissues to image in vivo because it is transparent and moving. Real-time dynamic observations with UWF-OCT may meet this challenge, and we predict that this technique will provide new and effective information on the pathogenesis of various vitreoretinal disorders. It should then offer new surgical strategies for treating many vitreoretinal diseases.

References

1. Hogan MJ, Alvarado JA, Weddell JE. The vitreous. In: Hogan MJ, Alvarado JA, Weddell JE, eds. *Histology of the Human Eye*. Philadelphia: W.B.Saunders; 1971:607-637.
2. Sebag J. *The Vitreous. Structure, Function, and Pathobiology*. New York: Springer-Verlag; 1989.
3. Eisner G. Postmortem slitlamp study of the vitreous body. 3. Relation to histology, biomicroscopy and clinical applications. *Graefes Arch Clin Exp Ophthalmol*. 1971; 182(1):23-40.
4. Worst JG, Los LI. Comparative anatomy of the vitreous body in rhesus monkeys and man. *Doc Ophthalmol*. 1992; 82(1-2):169-178.
5. Kishi S, Shimizu K. Posterior precortical vitreous pocket. *Arch Ophthalmol*. 1990; 108(7):979-982.
6. Kishi S. Impact of swept source optical coherence tomography on ophthalmology. *Taiwan J Ophthalmol*. 2016; 6(2):58-68.
7. Spaide RF. Visualization of the posterior vitreous with dynamic focusing and windowed averaging swept source optical coherence tomography. *Am J Ophthalmol*. 2014; 158(6):1267-1274.
8. Shinohara K, Tanaka N, Jonas JB, et al. Ultra-widefield optical coherence tomography to investigate relationships between myopic macular retinoschisis and posterior staphyloma. *Ophthalmology* 2018; 125(10):1575-1586.
9. Shinohara K, Shimada N, Moriyama M, et al. Posterior staphylomas in pathologic myopia imaged by widefield optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2017; 58(9):3750-3758.
10. Takahashi H, Tanaka N, Shinohara K, et al. Ultra-widefield optical coherence tomographic imaging of posterior vitreous in eyes with high myopia. *Am J Ophthalmol*. Epub ahead of print 2019 Mar 19. doi: 10.1016/j.ajo.2019.03.011.



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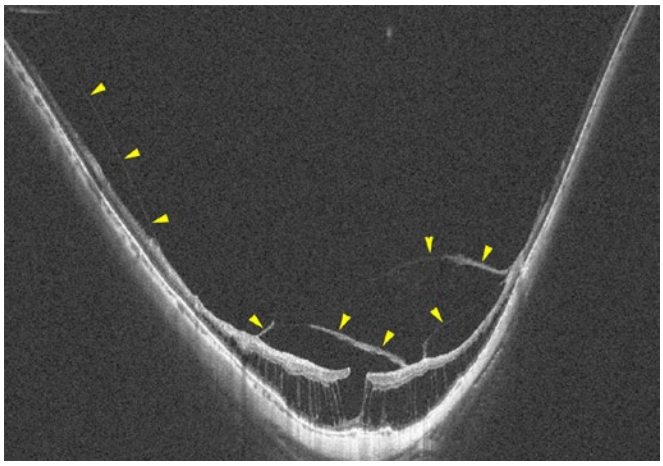

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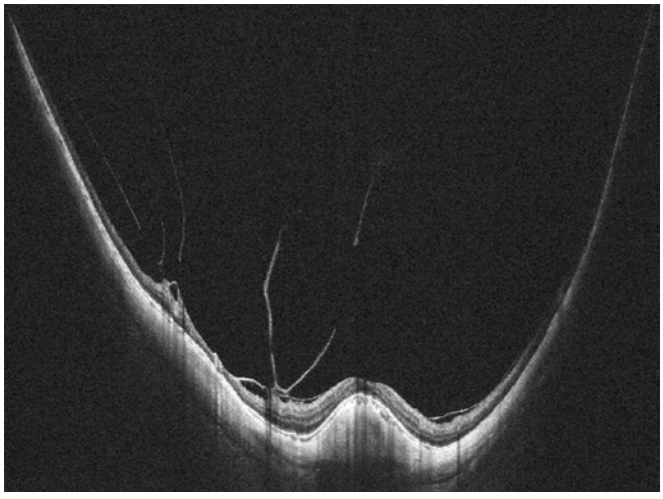

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Figure 2. Ultrawide-field swept source OCT images of vitreal changes in eyes with pathologic myopia. A. A perifoveal posterior vitreous detachment (PVD) is observed in a wide area in this eye with a dome-shaped macula. B. Multiple and multilayered posterior vitreous detachments (PVDs, arrowheads) in an eye with myopic macular retinoschisis.[10] C. Long vitreous strands that extend perpendicularly from the retina can be seen.[10]

Microcirculation in Systemic Diseases: What Can We Learn From OCT Angiography?

Nicole Eter MD and Maged Alnawaiseh MD

I. Conventional Methods for Blood Flow Imaging
   A. Laser Doppler flowmetry
   B. Laser speckle velocimetry
   C. Doppler ultrasound
   D. Particle imaging velocimetry
   E. Polarized light spectroscopy
   F. Capillaroscopy
   G. MRI angiography
   H. Photoacoustic microscopy
   I. Sidestream dark-field (SDF) videomicroscopy
   J. Incident dark-field illumination (IDF) videomicroscopy
   K. Fluorescein angiography
   L. Indocyanine green angiography

II. Factors Influencing OCT Angiographic (OCT-A) Measurement
   A. Age
   B. Gender
   C. Blood pressure
   D. Heart rate
   E. IOP
   F. Others

III. OCT-A and Cardiovascular Diseases
   A. Carotid artery stenosis
   B. Coronary heart disease
   C. Atrial fibrillation
   D. Hemorrhagic shock

IV. OCT-A and Neurologic Diseases
   A. Alzheimer disease
   B. Multiple sclerosis
   C. Parkinson disease
   D. CADASIL

V. OCT-A and Other Systemic Diseases
   A. Diabetes mellitus
   B. Systemic lupus erythematosus
   C. Systemic sclerosis
   D. Fabry disease
   E. Behçet disease
   F. Klinefelter syndrome

Selected Readings

1. Hessler M, Lehmann F, Arnemann PH, Eter N, Ertmer C, Alnawaiseh M. [Optical coherence tomography angiography in intensive care medicine: a new field of application?] *Ophthalmologe*. Epub ahead of print 2019 May 28. doi: 10.1007/s00347-019-0893-3.
2. Alten F, Nelis P, Schmitz B, Brand SM, Eter N. [Optical coherence tomography angiography as a future diagnostic tool in sports medicine?] *Ophthalmologe*. Epub ahead of print 2019 Apr 26. doi: 10.1007/s00347-019-0897-z.
3. Müller VC, Storp JJ, Kerschke L, Nelis P, Eter N, Alnawaiseh M. Diurnal variations in flow density measured using optical coherence tomography angiography and the impact of heart rate, mean arterial pressure and intraocular pressure on flow density in primary open-angle glaucoma patients. *Acta Ophthalmol*. Epub ahead of print 2019 Mar 22. doi: 10.1111/aos.14089.
4. Alnawaiseh M, Schubert F, Heiduschka P, Eter N. Optical coherence tomography angiography in patients with retinitis pigmentosa. *Retina* 2019; 39(1):210-217.
5. Lahme L, Esser EL, Mihailovic N, et al. Evaluation of ocular perfusion in Alzheimer's disease using optical coherence tomography angiography. *J Alzheimers Dis*. 2018; 66(4):1745-1752.
6. Lahme L, Marchiori E, Panuccio G, et al. Changes in retinal flow density measured by optical coherence tomography angiography in patients with carotid artery stenosis after carotid endarterectomy. *Sci Rep*. 2018; 21;8(1):17161.
7. Alnawaiseh M, Lahme L, Eter N, Mardin C. [Optical coherence tomography angiography: value for glaucoma diagnostics]. *Ophthalmologe*. Epub ahead of print 2018 Nov 9. doi: 10.1007/s00347-018-0815-9.
8. Mihailovic N, Brand C, Lahme L, et al. Repeatability, reproducibility and agreement of foveal avascular zone measurements using three different optical coherence tomography angiography devices. *PLoS One*. 2018; 18;13(10).
9. Alnawaiseh M, Ertmer C, Seidel L, et al. Feasibility of optical coherence tomography angiography to assess changes in retinal microcirculation in ovine haemorrhagic shock. *Crit Care*. 2018; 29;22(1):138.
10. Alnawaiseh M, Brand C, Bormann E, Sauerland C, Eter N. Quantification of macular perfusion using optical coherence tomography angiography: repeatability and impact of an eye-tracking system. *BMC Ophthalmol*. 2018; 18(1):123.
11. Schmitz B, Nelis P, Rolfes F, et al. Effects of high-intensity interval training on optic nerve head and macular perfusion using optical coherence tomography angiography in healthy adults. *Atherosclerosis* 2018; 274:8-15.

12. Alnawaiseh M, Müller V, Lahme L, Merté RL, Eter N. Changes in flow density measured using optical coherence tomography angiography after iStent insertion in combination with phacoemulsification in patients with open-angle glaucoma. *J Ophthalmol*. 2018; 2018:2890357.

13. Lauermann JL, Eter N, Alten F. Optical coherence tomography angiography offers new insights into choriocapillaris perfusion. *Ophthalmologica* 2018; 239(2-3):74-84.

14. Alnawaiseh M, Lahme L, Müller V, Rosentreter A, Eter N. Correlation of flow density, as measured using optical coherence tomography angiography, with structural and functional parameters in glaucoma patients. *Graefes Arch Clin Exp Ophthalmol*. 2018; 256(3):589-597.

15. Alnawaiseh M, Brand C, Bormann E, Wistuba J, Eter N, Heiduschka P. Quantitative analysis of retinal perfusion in mice using optical coherence tomography angiography. *Exp Eye Res*. 2017; 164:151-156.

16. Alnawaiseh M, Brand C, Lauermann JL, Eter N. [Flow density measurements using optical coherence tomography angiography: impact of age and gender]. *Ophthalmologe* 2018; 115(8):659-662.

17. Lauermann JL, Heiduschka P, Nelis P, et al. Comparison of choriocapillaris flow measurements between two optical coherence tomography angiography devices. *Ophthalmologica* 2017; 237(4):238-246.

18. Alnawaiseh M, Lahme L, Treder M, Rosentreter A, Eter N. Short-term effects of exercise on optic nerve and macular perfusion measured by optical coherence tomography angiography. *Retina* 2017; 37(9):1642-1646.

All Macular Cystoid Cavities Are Not Cystoid Macular Edema

Alain Gaudric MD

Introduction

Macular cystoid cavities are most often diagnosed on OCT B-scan, while the central macular thickness is assessed and monitored on OCT macular map. Intravitreal treatments are currently used to control cystoid macular edema (CME) with fairly good results, although these are often transient and the success rate depends on the cause of the CME. However, all macular cystoid cavities are not due to blood–retinal barrier (BRB) breakdown and do not require intravitreal treatment. Fluorescein angiography (FA), by showing the presence or the absence of dye leakage and pooling in cystoid cavities, helps to differentiate macular edema (ME) due to BRB breakdown from the many other conditions where cystoid cavities are due to other causes. We propose to use the term "CME" to name "vasogenic" ME[1] and to use the term "cystoid maculopathy" for the conditions not involving the BRB.

Cystoid Macular Edema

CME is an accumulation of fluid coming from the retinal circulation via a breakdown of the vascular endothelial barrier or from the choroidal circulation via a breakdown of the retinal pigment epithelium (RPE) barrier, resulting in the accumulation of fluid in cystoid cavities in the retina where no interstitial fluid is normally detected. Fluorescein serves as a tracer, showing the accumulation of fluid coming from the plasma, while OCT shows the volume of fluid retention in the macula without indicating its vascular origin.

Many retinal diseases of various origins may be complicated by CME. They share the particularity of having a hyperpermeability at the retinal vascular endothelium or the RPE, which can be corrected with steroids or anti-VEGF antibodies. The mechanism of BRB breakdown in the macula is not fully understood for diseases such as retinitis pigmentosa (RP), vitreoretinal interface diseases, choroidal melanoma, or peripheral exudative hemorrhage chorioretinopathy.

Table 1. Cystoid Macular Edema

Retinal vasculopathy	Diabetic retinopathy
	Retinal vein occlusion
	Macular telangiectasia type 1
	Radiation retinopathy
Inflammation	Pseudophakic macular edema
	Birdshot retinochoroidopathy
	Retinal vasculitis
	Intermediate uveitis
Inherited diseases	Retinitis pigmentosa
Drug toxicity	Fingolimod
	Acitretin (retinoid)
	Topical latanoprost, topical epinephrine
	Vemurafenib
Vitreoretinal interface diseases	Epiretinal membrane
	Vitreomacular traction
Tumors	Choroidal melanoma
	Choroidal hemangioma
	Vasoproliferative tumor (reactive astrocytic tumor)
AMD	Macular new vessels
	Peripheral CNV (peripheral exudative hemorrhagic chorioretinopathy)

OCT angiography has shown various degrees of capillary perfusion impairment in the etiologies in which it has been studied. The retinal capillary density is usually reduced in vasculopathies such as diabetic retinopathy or retinal vein occlusion, but may be normal in acute pseudophakic ME, or electively altered in the deep capillary plexus such as in RP.

Cystoid Maculopathy

Cystoid maculopathy may occur without BRB impairment because the fluid coming from the vitreous cavity may accumulate in the retina under different circumstances—tractional, degenerative, toxic, or other, involving Müller cell or RPE dysfunction, both playing a major role in the hydric transport and regulation in the retina. These cells are also involved in vasogenic edemas to eliminate excess fluid. Cystoid cavities do not fill with dye during FA.

Table 2. Cystoid Maculopathies

Inherited diseases	Retinitis pigmentosa
	X-linked retinoschisis
	Bestrophinopathy
	Enhanced S-cone dystrophy
	Gyrate atrophy
	Bietti crystalline dystrophy
	Dominant cystoid macular dystrophy
Acquired RPE dysfunction	Chronic central serous chorioretinopathy
	Cancer-associated retinopathy
Retinal vasculopathy	Macular telangiectasia type 2 (MacTel2)
Drug toxicity	Taxanes
	Tamoxifen
	Chloroquine retinopathy
	Nicotinic acid/niacin
Vitreoretinal interface diseases	Epiretinal membrane, vitreomacular traction, myopic foveoschisis
Optic nerve diseases	Optic nerve atrophy, optic nerve pit, glaucoma

Several inherited diseases may show macular cystoid cavities during their progression. In RP, cystoid cavities may stain, or not, with fluorescein, and OCT shows a higher proportion of cystic changes than FA. X-linked retinoschisis is known to be due to a loss of neuronal and glial cell–cell adherence induced by the absence of retinoschisin synthesis. In bestrophinopathy, the dysfunction of the RPE–photoreceptor coupling is thought to cause insufficient dehydration of the retina. In enhanced S-cone dystrophy and in other retinal dystrophies, the mechanism of cystic formation is unknown.

Among diseases with acquired RPE dysfunction, chronic central serous chorioretinopathy is frequently associated with cystoid changes in the macula or near the optic disc, without any dye staining of these cavities on FA. Increased choroidal hydrostatic pressure or RPE dysfunction could impair intraretinal fluid resorption.

MacTel2 is a special case in which there is some leakage from telangiectasia while cystoid cavities are not filled with dye during FA and do not respond to anti-VEGF therapy. They are thought to be more degenerative than exudative.

Tamoxifen and taxanes are among the drugs that may induce macular cystoid spaces and cavitations after prolonged use. Cystoid changes have also been described in chloroquine retinopathy due to drug overdose. In all cases, the lesion may reverse after treatment discontinuation. Epiretinal membranes (ERMs) may present with cystoid cavities that do not stain on FA and usually disappear after surgery. The difference with ERM complicated by angiographic CME is not well understood, but the presence of inflammation has sometimes been suggested in the latter.

Lastly, various causes of optic nerve atrophy may be complicated by microcystic changes located mainly in the inner nuclear layer of the macula, and optic disc pit may cause a microcystic thickening of the interpapillary-macular region associated, or not, with submacular fluid.

Conclusion

CME characterized by BRB breakdown may respond to topical, systemic, or intravitreal steroids; intravitreal anti-VEGF; or oral acetazolamide. Cystoid maculopathies sometimes respond to oral acetazolamide or to treatment discontinuation in case of drug toxicity, or to vitreoretinal surgery in case of epiretinal traction. Distinguishing these two forms of cystoid cavities, which may have the same aspect on OCT, is therefore useful in clinical practice.

References

1. Spaide RF. Retinal vascular cystoid macular edema. *Retina* 2016; 36(10):1823-1842.
2. Johnson AA, Guziewicz KE, et al. Bestrophin 1 and retinal disease. *Prog Retin Eye Res*. 2017; 58:45-69.
3. Salvatore S, Fishman GA, Genead MA. Treatment of cystic macular lesions in hereditary retinal dystrophies. *Surv Ophthalmol*. 2013; 58(6):560-584.
4. Makri OE, Georgalas I, Georgakopoulos CD. Drug-induced macular edema. *Drugs* 2013; 73(8):789-802.
5. Tawse KL, Hedges TR, Gobuty M, Mendoza-Santiesteban C. Optical coherence tomography shows retinal abnormalities associated with optic nerve disease. *Br J Ophthalmol*. 2014;98 Suppl 2.

Retinal Metabolic Assessment Using Mitochondrial Oxidative Stress Imaging: A New Clinical Tool for Detecting and Monitoring Substructural Disease

Richard B Rosen MD

High-resolution imaging has enhanced our ability to visualize the structural aspects of disease processes clinically to the cellular level. However, substructural change reflective of metabolic processes is still difficult to appreciate in early stages of various disorders. Many chronic ocular diseases are the result of damage induced by free radicals and reactive oxygen species generated by hyperglycemia, hypoxia, or photoperoxidation. Mitochondria, the major energy producing organelle of the cells, are adversely affected through a variety of pathways that lead to dysfunction, cell death, and ultimately organ failure. The ability to monitor oxidative stress at the stage of mitochondrial distress prior to tissue destruction has been elusive, until recently.

The electron transport cascade of the mitochondria contains a number of flavoproteins that fluoresce when subjected to increased oxidative stress. Flavoprotein fluorescence is a signature of this stress. The ability to quantitatively monitor this fluorescence provides an opportunity for noninvasive, label-free measurement of mitochondrial dysfunction.

Based upon studies that originated at the University of Michigan, a rapid, quantitative device for clinical imaging, Retinal Metabolic Analyzer (Ocumet Beacon), has been developed by Ocusciences, Inc. (Ann Arbor, MI). Mitochondrial flavoprotein fluorescence constitutes a shoulder of a broad-emission spectrum of other fluorophores, especially lipofuscin. The device projects a 467-nm filtered light beam onto the macula or optic nerve and records the fluorescent response with a narrow notch filter that allows detection of emissions at 535 nm. It is designed to minimize the noise of overlapping emissions from lipofuscin.

A number of clinical studies have validated flavoprotein as a biomarker of age and disease activity. Retinal pigment epithelial cell culture studies have demonstrated its response to oxidative stress from peroxides which mirror mitochondrial membrane permeability and the risk of apoptosis. Clinical studies have shown that flavoprotein fluorescence increases with age in normal eyes. Flavoprotein autofluorescence characteristics indicating dysfunction include high average intensity (AI) levels, indicating impaired metabolic activity, broad average curve width (ACW), consistent with disease affecting individual cells to different degrees, and AI and ACW asymmetry between eyes of the same individual. Patients with diabetes or diabetic retinopathy have shown significantly higher levels than controls at each advancing age.

Flavoprotein fluorescence has been shown to be elevated above control levels in the affected eye of patients with monocular central serous retinopathy. The uninvolved eye was also slightly higher than controls, but to a much lower extent. A similar phenomenon has been demonstrated in patients with pseudotumor cerebri (PTC). Flavoprotein fluorescence is able to detect the more affected of two eyes in patients with PTC with greater sensitivity than automated perimetry.

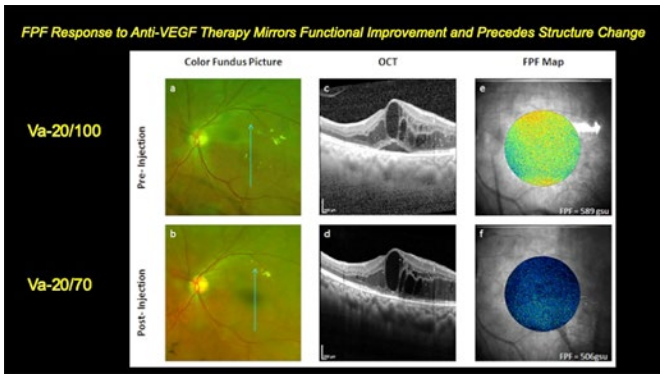

Figure 1.

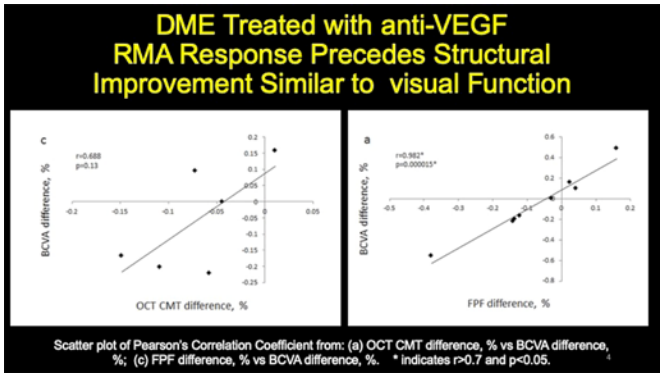

Figure 2.

Patients with AMD show progressive elevation of flavoprotein fluorescence with more advanced AREDS stages of disease. There is some degree of noise in the progression due to tissue loss in cases of atrophy. Heterogeneity of fluorescence is an additional marker that indicates disease and may be useful in following progression in cases of nonexudative AMD.

Application of flavoprotein fluorescence to optic nerve disease appears helpful for revealing impending damage from oxidative stress in the absence of other clinical signs. Patients with ocular hypertension exhibited significant elevations in fluorescence over normal. Interestingly, patients with advanced glaucoma did not show increasingly higher levels. This has been attributed to proportional ganglion cell and nerve fiber layer loss in these patients. Similarly, patients with acute optic nerve compression due to orbital pathology showed elevations that returned to near normal levels following therapeutic decompressions.

Therapeutic interventions for the treatment of diabetic macular edema using steroids or anti-VEGF drugs produce significant reductions in flavoprotein fluorescence. In a small study looking at patients receiving anti-VEGF therapy, flavoprotein fluorescence levels decreased following injection more rapidly than the edema resolved but in step with the visual acuity improvement reported. In a group of glaucoma patients given antioxidant, neuroprotective supplements, flavoprotein fluorescence of the optic nerve was significantly reduced following 1 month of treatment.

Retinal metabolic analysis of flavoprotein fluorescence offers a functional signal that is complementary to the structural information proved by OCT and OCT angiography. It appears to be more sensitive to early change than even the structural changes detected by OCT, and it may be found useful for detecting early response to therapies in clinical trials of new drugs.

Selected Readings

1. Andrade Romo JS, Lynch G, Liu K, et al. Flavoprotein fluorescence correlation with visual acuity response in patients receiving anti-VEGF injection for diabetic macular edema. *Oxid Med Cell Longev*. 2018; 2018:3567306.
2. Geyman LS, Suwan Y, Garg R, et al. Non-invasive detection of mitochondrial dysfunction in ocular hypertension and primary open-angle glaucoma. *J Glaucoma*. 2018; 27(7):592-599.
3. Field MG, Elner VM, Puro DG, et al. Rapid, noninvasive detection of diabetes-induced retinal metabolic stress. *Arch Ophthalmol*. 2008; 126(7):934-938.
4. Elner SG, Elner VM, Field MG, et al. Retinal flavoprotein autofluorescence as a measure of retinal health. *Trans Am Ophthalmol Soc*. 2008; 106:215-224.
5. Elner VM, Park S, Cornblath W, Hackel R, Petty HR. Flavoprotein autofluorescence detection of early ocular dysfunction. *Arch Ophthalmol*. 2008; 126(2):259-260.
6. Field MG, Yang D, Bian ZM, Petty HR, Elner VM. Retinal flavoprotein fluorescence correlates with mitochondrial stress, apoptosis, and chemokine expression. *Exp Eye Res*. 2011; 93(4):548-555.

Taking the Guesswork Out of Pachychoroid

Philip J Rosenfeld MD PhD, Hao Zhou PhD, Yingying Shi MD, Giovanni Gregori PhD, William J Feuer MS, and Ruikang Wang PhD

Introduction

The prefix "pachy-" is derived from ancient Greek and directly translates into "thick" or "thickness." Vision care specialists are familiar with the term when referring to pachymetry or pachymeters, which deal with the measurement of corneal thickness. More recently, the prefix "pachy-" has been combined with "choroid," and the term "pachychoroid" refers to an abnormally thick choroid. While the term "pachychoroid" is now defined as more than just an abnormally thick choroid, including features such as fundus appearance and choroidal vascularity, and is used to refer to the pachychoroid disease spectrum, the underlying premise is that the term has some diagnostic and pathophysiological significance.[1,2]

The choroid, a highly vascular layer located between the sclera and the retinal pigment epithelium (RPE), is composed of stroma and blood vessels. The blood vessels include arterioles and venules connected through the choriocapillaris. Interestingly, the choroidal thickness in normal eyes is primarily determined by the larger blood vessels.[3,4] However, the relationship between choroidal thickness and its blood vessels may be altered in different pathological states. For example, thicker choroids have been associated with ocular conditions such as central serous chorioretinopathy, polypoidal choroidal vasculopathy, macular neovascularization, macular telangiectasia type 2, and a wide range of inflammatory conditions.[2,5]

So why is it important to identify a condition in the pachychoroid disease spectrum? The answer depends on whether measurements of choroidal thickness and associated vascular changes are useful in the diagnosis of disease, in providing clues about the underlying pathophysiology, in determining the appropriate therapy, and in providing a quantitative parameter that can be followed to determine treatment efficacy and possible recurrence. However, if used without a strict definition, the term "pachychoroid" may give rise to confusion in the diagnosis and management of a given condition. A review of the literature shows varying definitions of a pachychoroid, especially with respect to the central diagnostic role of choroidal thickness measurements. While the limits of an abnormally thick choroid have not been rigorously defined, this hasn't prevented the widespread use of the term "pachychoroid."

What's a Pachychoroid?

Routine imaging of the choroid and measurements of choroidal thickness became possible with the use of optical coherence tomography (OCT). Enhanced depth imaging using spectral domain OCT was the first strategy that allowed for routine clinical measurements of the central macular choroid, usually from a small number of central macular B-scans.[5] With the development of faster scanning rates, denser raster scans, and the clinical introduction of swept source OCT, larger regions of the posterior pole could be imaged and measurements of choroidal thickness and vascularity became feasible.[3,6] Despite all these advances in imaging and the numerous descriptive reports on the wide spectrum of pachychoroidal diseases, we've yet to formally define the true extent of an abnormally thick choroid. As a result, there's confusion within the literature with respect to the choroidal thickness measurements that truly constitute a pachychoroid.

What's a Normal Choroid?

Before an abnormally thick choroid can be defined, we first need to define a normal choroid. Numerous reports have shown that in normal eyes, choroidal thickness depends on age and axial length, so both of these parameters must be considered whenever considering choroidal thickness.[7,8] Therefore, to define a normal choroid, we need to collect a normative database of eyes over a wide range of ages to calculate the 95% normal limits for choroidal thickness. While it's certainly possible to define a "normal" range for a given age and axial length based on 1 standard deviation (SD) from the mean (67% for Gaussianly distributed measurements) rather than 2 SDs, the common definition for a "normal" range uses a range that incorporates the 95% limit of normal eyes. By lowering the range, we could certainly develop a definition with high sensitivity for detecting all abnormal choroidal thickness measurements, but the specificity for such detection of what is truly abnormal would suffer as a result.

Does Choroidal Vascularity Influence the Definition of a Pachychoroid?

Recently, the definition of pachychoroidal diseases has evolved to consider the size of the choroidal vessels in close proximity to the area of pathology.[5] While the size and configuration of choroidal vessels may be atypical throughout the choroid, it's also possible that there are focal or regional differences in the choroidal vasculature relative to the absolute choroidal thickness that define a disease. Fortunately, with current OCT technology, it's now possible to get reliable measurements of the choroidal vasculature relative to the surrounding stroma, now known as the "choroidal vascularity index" based on measurements from OCT B-scans.[2] An increased ratio of the vascular area relative to choroidal thickness has been associated with central serous chorioretinopathy and polypoidal choroidal vasculopathy, while a decreased ratio has been associated with AMD, diabetes mellitus, retinal degenerations, and inflammatory conditions.[2]

Evaluating Normal Limits for Posterior Pole Choroidal Thickness and Vascularity

Swept source OCT imaging has the advantages of faster imaging speed, less sensitivity fall-off, and longer ranging distance, which enable dense raster scans of a region that can be 12x12 mm or larger at the macula with superior imaging of the choroid compared with spectral domain OCT imaging. Combined with automated algorithms capable of reliably detecting the choroidal–scleral interface,[9] it's now possible to routinely measure the choroidal thickness extending from the Bruch

membrane to the choroidal–scleral boundary. In addition, the choroidal vasculature can be segmented and the choroidal vessel volume and choroidal vessel volume density, which is similar to the choroidal vascularity index, can be measured throughout the scan area. Coupled with a normative database that we previously collected for the evaluation of age-dependent changes in choriocapillaris flow deficits,[10] we were able to generate the 95% normal limits for choroidal thickness, choroidal vessel volume, and choroidal vessel volume density measurements from the entire scan area, as well as different regions within the central and peripheral macula. The wide range of choroidal thickness measurements in normal eyes results in 95% normal limits for choroidal thickness that include most current definitions of a pachychoroid. However, due to the narrow range of the choroidal vessel volume density measurements, this parameter may be a better biomarker for identifying an abnormal choroid.

Summary

The results from our current research into the 95% normal limits of choroidal thickness and vascularity will be presented. To date, our results for choroidal thickness for any given age and axial length will challenge the currently perceived expectation that "pachychoroid" may be easily defined. We have found that normal choroidal thickness measurements cover a wide range that the literature has considered abnormal. However, the parameter known as "choroidal vascularity index" or "choroidal vessel volume density" may be far more useful in diagnosing pathological conditions, either alone or in conjunction with choroidal thickness measurements.

Perhaps the best strategy for eliminating the guesswork associated with "pachychoroid" is to just eliminate it as a diagnostic term except in extreme cases that clearly fall outside the normal limits. After all, our anterior segment colleagues never use the prefix "pachy-" to define an abnormally thick cornea, even though they routinely use pachymetry.

References

1. Cheung CMG, Lee WK, Koizumi H, et al. Pachychoroid disease. *Eye (Lond)*. 2019; 33(1):14-33.
2. Singh SR, Vupparaboina KK, Goud A, et al. Choroidal imaging biomarkers. *Surv Ophthalmol*. 2019; 64(3):312-333.
3. Zheng F, Gregori G, Schaal KB, et al. Choroidal thickness and choroidal vessel density in nonexudative age-related macular degeneration using swept-source optical coherence tomography imaging. *Invest Ophthalmol Vis Sci*. 2016; 57(14):6256-6264.
4. Singh SR, Invernizzi A, Rasheed MA, et al. Wide-field choroidal vascularity in healthy eyes. *Am J Ophthalmol*. 2018; 193:100-105.
5. Cheung CMG, Lee WK, Koizumi H, et al. Pachychoroid disease. *Eye (Lond)*. 2018.
6. Agrawal R, Seen S, Vaishnavi S, et al. Choroidal vascularity index using swept-source and spectral-domain optical coherence tomography: a comparative study. *Ophthalmic Surg Lasers Imaging Retina*. 2019; 50(2):e26-e32.
7. Barteselli G, Chhablani J, El-Emam S, et al. Choroidal volume variations with age, axial length, and sex in healthy subjects: a three-dimensional analysis. *Ophthalmology* 2012; 119(12):2572-2578.
8. Abbey AM, Kuriyan AE, Modi YS, et al. Optical coherence tomography measurements of choroidal thickness in healthy eyes: correlation with age and axial length. *Ophthalmic Surg Lasers Imaging Retina*. 2015; 46(1):18-24.
9. Zhou H, Chu Z, Zhang Q, et al. Attenuation correction assisted automatic segmentation for assessing choroidal thickness and vasculature with swept-source OCT. *Biomed Opt Express*. 2018; 9(12):6067-6080.
10. Zheng F, Zhang Q, Shi Y, et al. Age-dependent changes in the macular choriocapillaris of normal eyes imaged with swept-source optical coherence tomography angiography. *Am J Ophthalmol*. 2019; 200:110-122.

En Face OCT: Pathoanatomical Insights Into the Macula and Its Related Disorders

David Sarraf MD

I. Principle of En Face OCT
   A. Dense volume of cross-sectional B-scan data
   B. Projection onto a coronal or en face plane
   C. Binary reflectivity reproduced over a flat fundus or coronal view
   D. Projection of segmented planes

II. Advantages of En Face OCT
   A. Inter-relationship of hyper- and hyporeflective OCT lesions
   B. Pattern of OCT lesions
   C. Depth-resolved segmentation

III. En Face Hyper-reflective Dots
   A. New anatomical finding with en face OCT
   B. Hyper-reflective dots in the central fovea
   C. 0.2-0.6 μm in size
   D. Increase with age, especially after fifth decade
   E. Muller cell foot plates
   F. Basal lamina of the internal limiting membrane
   G. Vitreous hyalocytes (less likely)

IV. Inner-retinal Dimples or Dissociated Nerve Fiber Layer
   A. Due to avulsion of Muller cell end plates
   B. First identified with en face OCT at 1 month
   C. Number of dimples increases and then plateaus at 3 to 6 months.
   D. Postop nerve fiber layer edema masks dimples early in the postoperative period.

V. En face OCT of Paracentral Acute Middle Maculopathy (PAMM)
   A. Globular: central retinal artery occlusion (CRAO)
   B. Sectoral: branch retinal vein occlusion (BRAO)
   C. Perivenular: central retinal vein occlusion (CRVO)
   D. Perivenular PAMM and the ischemic cascade
   E. Outer hemorrhagic Henle maculopathy (OHMM)
   F. Retinal capillary plexus arrangement
   G. Major venous outflow at deep capillary plexus

V. OHHM Syndrome
   A. Features
      1. Radial hemorrhage
      2. Feathered border
      3. Petaloid
      4. Pericentral
      5. Deep round heme peripheral
   B. Mechanisms
      1. High retinal venous pressure
      2. Deep capillary plexus bleeding
      3. Henle layer tracking
   C. Systemic causes
   D. Local causes: Subretinal bleeding (polypoidal choroidal vasculopathy, myopia)

VI. Multiple Evanescent White Dot Syndrome (MEWDS)
   A. Spots: hyporeflective ellipsoid zone (EZ) loss
   B. Dots: hyper-reflective extensions from EZ loss
   C. Dots colocalize with spots with en face OCT.
   D. Spots recover before dots.

VII. Pitchfork Sign (or Wreath or Spike Sign)
   A. Pattern of pitchfork more like a spiked crown with en face OCT
   B. Associated with type 2 choroidal neovascularization (CNV)
   C. Identified in children (and adults)
   D. ?? Inflammatory component of CNV
   E. Adhesive and tractional factors may explain these characteristic findings.

VIII. Atrophy at Edge of Neovascular Complex
   A. Type 1 CNV may recapitulate the choriocapillaris.
   B. Type 1 CNV may reduce the risk of retinal pigment epithelial and outer retinal atrophy.
   C. Using en face OCT overlay over en face OCT angiography, atrophy is noted to grow away from the CNV complex.
   D. En face OCT can be an effective tool to quantitate progression of atrophy.

IX. Conclusions
   A. The integration of en face OCT into clinical practice will enhance evaluation and understanding of OCT cross-sectional B-scan information.
   B. The patterns of OCT pathology will improve evaluation and management of macular disease.

Machine Learning to Automate Biomarker Detection From OCT Scans

Sebastian Wolf MD PhD, Martin Zinkernagel MD PhD, and Raphael Sznitman PhD

Optical coherence tomography (OCT) scans play an integral role in diagnosing and managing sight-threatening retinal diseases such as AMD and diabetic retinopathy. By providing micrometer resolution imaging of the retina, OCT has given ophthalmologists the ability to visualize retinal structures in three dimensions. Yet, examining OCT scans in clinical routine is time consuming, even for experts. With over 50 million OCT scans acquired each year worldwide and an increasing prevalence in chronic eye conditions, the human resources and expertise needed to assess OCT images, today and in years to come, are simply overwhelming.

Instead, machine learning provides a pathway to automating inspections of medical scans such as OCT images. By using datasets of annotated examples, trained machine learning algorithms are not only faster at assessing scans but more cost effective than human counterparts. These advantages have led to a surge of machine learning–based methods for retinal image analysis. These include impressive performances by methods that perform automated diagnosis, morphological shape estimation, treatment outcome estimation, and clinical referral support. Broadly, these developments have hinged on clinical insights, novel machine learning techniques, and large numbers of OCT scans.

At the same time, biological markers, or "biomarkers," of the retina have traditionally played a central role in both clinical routine and research. For instance, monitoring fluid biomarkers using OCT is an essential part of the standard of care for managing chronic retinal conditions, while other biomarkers have been linked to how well patients respond to treatments. However, given the dozens of established biomarkers, their identification is both time consuming and challenging due to their number, size, shape, and extent.

At the core of this work, we hypothesize that an automated method can identify biomarkers reliably and that these can then help answer routine clinical tasks as well. To show this, we present a machine learning method that automatically identifies a wide range of biomarkers in OCT scans. Our approach learns to identify biomarkers without needing to show the method by which they are located in training scans, and removes the need for burdensome segmentation annotations. By training our approach this way, not only is our method capable of identifying biomarkers more consistently than experienced experts, but it also allows a robust characterization of patient eyes that can be used to identify pathologies in OCT scans acquired with different OCT devices.

Section XI: Late Breaking Developments, Part II

Prevalence of Maculopathy Associated With Pentosan Polysulfate Therapy in Kaiser Permanente Northern California

Robin A Vora MD

Port Delivery System With Ranibizumab for Neovascular AMD: Ladder Phase 2 Trial End of Study Results

Carl D Regillo MD FACS

Results of a Phase 1/2 Trial of an Optimized Gene Therapy in Adults and Children With Retinal Dystrophy Associated With Bi-allelic Variants in RPE65

Michel Michaelides MD

Comparison of the Efficacy and Safety of Brolucizumab vs.Aflibercept in Eyes With Polypoidal Choroidal Vasculopathy: 96-Week Results From the HAWK Study

Glenn J Jaffe MD

Subretinal Human Retinal Progenitor Cells in Retinitis Pigmentosa: A Phase I/IIa Study

Pravin U Dugel MD

Data Supporting the Sustained Efficacy of Faricimab, a Bispecific Antibody Neutralizing Both Angiopoietin-2 and VEGF-A

Karl G Csaky MD

The Functional Impact of Fluctuating Retinal Thickness in the IVAN and CATT Trials: A Meta-analysis

Associations Between Fluctuation in Retinal Thickness and Visual Function

Usha Chakravarthy MBBS PhD, Barnaby C Reeves, and Rebecca Evans

Purpose

To investigate whether visual outcome in eyes with neovascular AMD (nAMD) is influenced by fluctuations in retinal thickness. We hypothesized that patients who experienced greater variation in retinal thickness over time when treated with anti-VEGF drugs for nAMD had worse visual outcome than patients who experienced less variation.

Methods

Foveal center point retinal thickness (CPT) was measured on OCT at quarterly intervals during the Alternative Treatments to Inhibit VEGF in Age-related Choroidal Neovascularisation (IVAN) clinical trial and monthly during the Comparison of AMD Treatment Trials (CATT), from baseline to 24 months. We extracted foveal CPT in all IVAN (N = 546) and CATT participants (N = 1165) after excluding those who did not have an exit visit with imaging or who had 3 or fewer CPT measurements. For each participant we standardized the CPT (S-CPT) to allow for the different OCT instruments. The standard deviation (SD) of each participant's S-CPT was calculated. Participants were grouped by quartile of S-CPT SD. BCVA at final visit and change from baseline to final visit were compared by quartiles of S-CPT SD for allocations to drug and treatment regimen. Linear regression was then used to examine the relationship between S-CPT SD quartile and BCVA at final visit, adjusting for baseline BCVA and original trial allocations.

Results

IVAN and CATT data were available on 1711 participants. Median S-CPT SD was 0.55 (interquartile range: 0.37-0.84) in the IVAN cohort and 0.41 (0.26-0.63) in the CATT cohort. Mean BCVA at the final visit was 73.2 letters (SD, 14.2) in participants in the lowest quartile of S-CPT SD (least variation in retinal thickness) and 59.4 (SD, 21.3) among those in the highest quartile of S-CPT SD (most variation). The adjusted regression model after adjustment for baseline BCVA and trial allocations confirmed a statistically significant trend across the quartiles of S-CPT SD (P < .001), spanning a difference of >5 letters between first and fourth quartiles (see Figure 1).

Conclusions

These analyses found that fluctuation in retinal thickness despite an optimal treatment frequency is adversely associated with visual outcome.

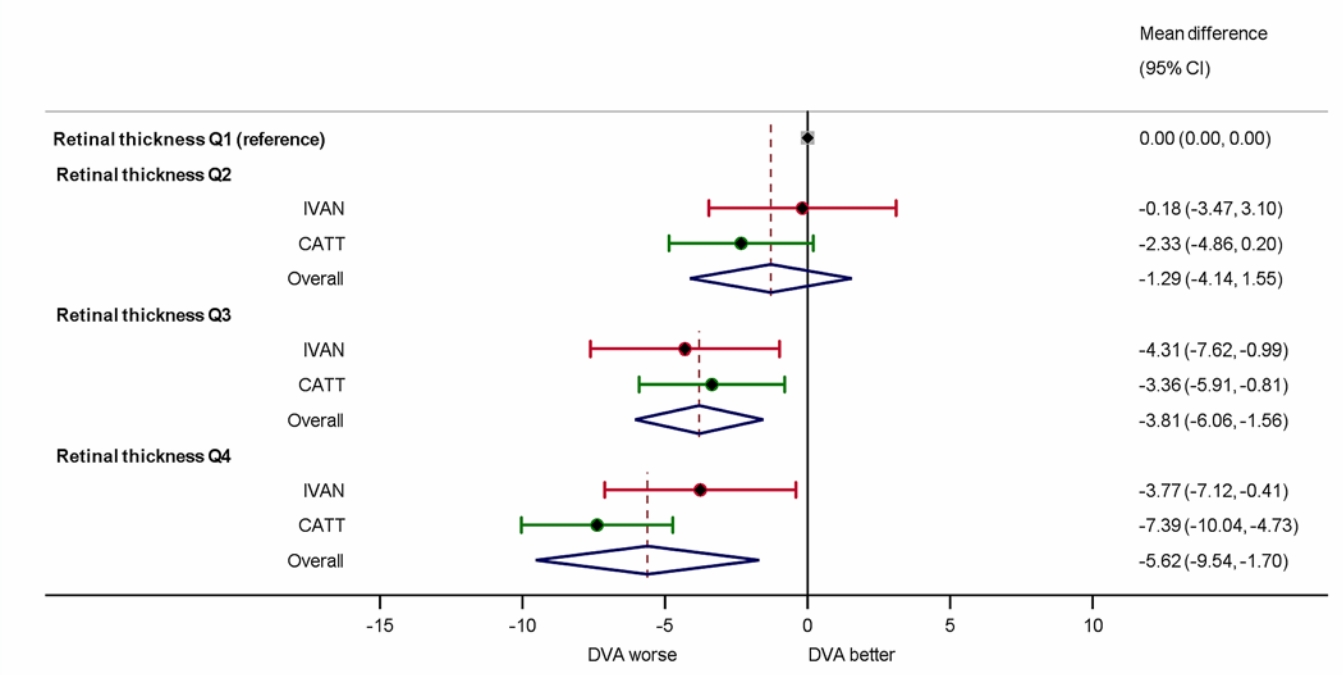

Figure 1. Meta-analysis of final DVA after adjustment for baseline DVA, treatment and treatment frequency.

OCT Angiography in Neovascular AMD: Can We Predict Treatment Response?

Amani Fawzi MD

Purpose

To explore whether quantitative 3-dimensional (3D) analyses of choroidal neovascularization (CNV) using projection-resolved OCT angiography (PR-OCTA) correlates with treatment response.

Methods

This retrospective study included 51 eyes of 49 patients undergoing individualized anti-VEGF therapy. Eyes were classified as "short term" or "long term" based on timing of OCTA imaging from initial treatment (less or more than 12 months, respectively). Based on anti-VEGF treatment interval, patients in each group were classified into 2 response groups: "low frequency" or "high frequency" responders, requiring injections at less or more frequently than 6-week intervals, respectively.

Cross-sectional PR-OCTA images were used to measure the distance between the Bruch membrane and the highest CNV flow signal. The number of flow layers within the CNV and the distance between these flow layers (CNV flow thickness) was also analyzed with PR-OCTA images. We used 3D volume-rendered PR-OCTA to confirm the number of CNV flow layers and further evaluate CNV complexity. OCTA parameters were compared between good and poor responders.

Results

In both short-term and long-term groups, high-frequency responders had significantly greater distance between the Bruch membrane and highest CNV flow signal on PR-OCTA (P = .045 and P = .027, respectively). In addition, high-frequency responders in the long-term group had greater CNV flow thickness (P = .011) and significantly more CNV flow layers (P = .005) compared to good responders. Volume-rendered PR-OCTA images provided confirmation of the number of CNV flow layers.

Conclusion

This study demonstrates that 3D volume-rendered PR-OCTA analysis of CNV is a novel, quantitative, and objective method for exploring the relation between CNV flow structure and treatment response in neovascular AMD. We found that the height of the vascular components of CNV lesions, as well as the 3D complexity (number of CNV flow layers) in the long-term group (treated for more than 1 year) correlated with the frequency of anti-VEGF during individualized therapy. These findings highlight the importance of exploring the 3-dimensional vascular structure of CNV in OCTA as a possible biomarker for the exudative properties of neovascular AMD and suggest that 3D OCTA parameters may be powerful for predicting CNV activity, especially as the lesions undergo vascular "normalization" and maturation.

Does Type 1 Neovascularization Slow Macular Atrophy in Eyes With AMD?

K Bailey Freund MD, Ling Chen MD PhD, Jeffrey D Messinger DC, Kenneth R Sloan PhD, Thomas A Swain MPH, Yoshimi Sugiura MD, and Christine A Curcio PhD

Background

Macular neovascularization (MNV) is a major sight-threatening complication of AMD. Type 1 MNV originates from the choroid and proliferates beneath the retinal pigment epithelium (RPE) and its basal lamina. Often, MNV is detected when associated with visual symptoms from fluid seen on OCT or leakage apparent with dye-based angiograph. Occasionally, type 1 MNV is detected as an incidental finding during routine retinal imaging of asymptomatic AMD patients. So called "quiescent" or "nonexudative" type 1 MNV may appear as occult staining on fluorescein angiography and a "plaque" of late hyperfluorescence on indocyanine green angiography corresponding to a shallow irregular RPE detachment on OCT that is also known as the "double-layer" sign.

The idea that type 1 MNV could be beneficial was raised by pathologists Grossniklaus and Green. They noted that the histology of excised MNV lesions and that in intact eyes suggested that type 1 MNV had the potential to recapitulate the morphology of the native choriocapillaris. They suggested that these vessels might support the overlying RPE and photoreceptors in ways normally served by the native choriocapillaris, such as oxygen exchange, metabolic supply, and hormonal influences.

This presentation correlates multimodal clinical imaging and high-resolution histology from an eye with nonexudative type 1 NV that exhibited not only a large, shallow, irregular RPE elevation on structural OCT and a occult staining on fluorescein angiography, but also a healthy outer retina and good vision, thus supporting the Grossniklaus-Green conjecture.

Purpose

To correlate multimodal retinal imaging with high-resolution epoxy resin histology aligned to in vivo tomograms in a patient with nonexudative type 1 MNV secondary to AMD.

Subject

A 79-year-old female of European descent who, following loss of central vision due to neovascular AMD in 1 eye, retained 20/30 visual acuity in her fellow eye, which had untreated nonexudative type 1 MNV documented with multimodal imaging over a > 9-year follow-up.

Methods

Retinal imaging, including fluorescein angiography, fundus autofluorescence, and eye-tracked spectral domain OCT, was correlated with ex vivo OCT and high-resolution histologic images of the donor eye. Outer retina status was determined by comparing OCT layer thicknesses at 10 years and 1 year prior to patient death.

Results

Histologic analysis showed extensive type 1 MNV, comprised of fibrovascular tissue with capillaries and small vessels, stroma, cells of RPE and non-RPE origin, and hemorrhage. The MNV was absent from surrounding regions not covered by the RPE elevation. The total area of histologically confirmed NV was 13.38 mm^2, similar to that measured from OCT at the last clinic visit (13.70 mm^2), despite the passage of 17 months. Transmission electron microscopy showed fenestrations and caveolae (transport vesicles) in neovessels beneath the RPE, as they were in native choriocapillaris. Over 9 years of tracked OCT, the thickness of the anatomical Henle fiber layer–outer nuclear layer in the foveal subfield, inner ring, and outer ring of the ETDRS grid overlying the type 1 MNV decreased by only 4 µm, 2 µm, and 6 µm, respectively.

Conclusion

This first clinicopathologic correlation of nonexudative type 1 MNV appearing as a shallow irregular RPE elevation on structural OCT shows the potential for this neovascular subtype to recapitulate the morphology of the native choriocapillaris and support the overlying RPE and photoreceptors in eyes with neovascular AMD.

Selected Readings

1. Grossniklaus HE, Green WR. Choroidal neovascularization. *Am J Ophthalmol*. 2004; 137(3):496-503.
2. Freund KB, Zweifel SA, Engelbert M. Do we need a new classification for choroidal neovascularization in age-related macular degeneration? *Retina* 2010; 30(9):1333-1349.
3. Dhrami-Gavazi E, Balaratnasingam C, Lee W, Freund KB. Type 1 neovascularization may confer resistance to geographic atrophy amongst eyes treated for neovascular age-related macular degeneration. *Int J Retina Vitreous*. 2015; 1(1):15.
4. Dansingani KK, Freund KB. Optical coherence tomography angiography reveals mature, tangled vascular networks in eyes with neovascular age-related macular degeneration showing resistance to geographic atrophy. *Ophthalmic Surg Lasers Imaging Retina*. 2015; 46(9):907-912.
5. Shi Y, Motulsky EH, Goldhardt R, et al. Predictive value of the OCT double-layer sign for identifying subclinical neovascularization in age-related macular degeneration. *Ophthalmol Retina*. 2019; 3(3):211-219.

New Meta-analysis of Anti-VEGF Dosing in AMD

Richard F Spaide MD

The introduction of anti-VEGF agents was a major advance in treating macular neovascularization in AMD. The magnitude of effect of the anti-VEGF medications ranibizumab and aflibercept was apparent from the initial monthly dosing studies. Later studies based on a pro re nata (p.r.n.) or a treat-and-extend (TE) dosing strategy produced visual acuity results that emulated, after a fashion, those obtained with monthly dosing. However, the results of these studies showed large variability, making the data challenging to incorporate into clinical decision making.

Evidence-based medicine is the conscientious, explicit, and judicious use of current best evidence integrated with clinical judgement in making decisions about the care of patients. Systematic reviews use a defined search strategy, along with grading of the quality of evidence and critical analysis of the data presented in the literature. Consequently, systematic reviews may be very helpful resources for making evidence-based medical decisions.

There have been dozens of systematic reviews of treatment of macular neovascularization in AMD with either ranibizumab or aflibercept, but most concentrate on a small number of core randomized controlled trials. The mean number of trials in 35 different systematic reviews involving ranibizumab or aflibercept in the treatment of macular neovascularization in AMD was 13, with 11 reviews evaluating 5 or fewer studies. The treatment frequency of macular neovascularization secondary to AMD in "real-life" studies does not approach that in fixed monthly dosing, or even in some as p.r.n. or TE studies. The outcomes that treating physicians can expect at any given treatment frequency are difficult to estimate from systematic reviews because of the sparse data from the limited number of trials used in those reviews.

There are dozens of observational studies that have not been incorporated into systematic reviews. Even though the likely bias and methodologic problems these studies may have are, on average, greater than those in randomized controlled studies, these studies may provide useful information, nonetheless. This review used relatively broad criteria for study selection and inclusion. The resultant data showed a dose-response characteristic that may be useful in providing a framework for patient expectations, establishing treatment goals, and planning for future studies.

In this literature review the dose frequency and visual acuity changes at year 1, medication used, and the treatment strategy employed were recorded. There was a linear response between the log number of injections and the visual acuity in the first year as expressed by the equation Letters Gained = −6.66 + 15.7*log(Injections in Year 1). A dosing frequency of 4 per year is expected to produce a gain of approximately 3 letters. With each injection per year there is an expected gain of 1 letter by month 12. Once the number of injections used per year was considered, neither the treatment strategy nor the medication used was a significant predictor, meaning injection frequency is the important variable associated with acuity improvement.

Intravitreal injection of anti-VEGF agents has been a revolutionary change in the treatment of exudative neovascular AMD, but much of the focus of our profession has been on how to give fewer injections. The disease is a burden. Treatments, rather than being a burden, are an opportunity to gain better vision.

Anatomical Predictors of Visual Outcomes After Long-term Anti-VEGF Therapy

Srinivas Sadda MD

I. Background

A. OCT features that predict worse visual outcome

1. Subretinal hyper-reflective material (SRHM; originally termed "subretinal tissue")

a. Keane et al, 2008

b. Confirmed in 5-year Comparison of AMD Treatment Trial (CATT) results

2. Foveal atrophy/ fibrosis, or "atrosis" (CATT, 7-UP)

3. Intraretinal fluid (CATT)

B. OCT features associated with better vision (CATT)

1. Subretinal fluid, sub–retinal pigment epithelial (RPE) fluid

2. Persistent epithelial defect (PED)/type 1 CNV, especially as CNV apex

C. What is "atrosis"?

1. In neovascular AMD, even areas that appear as atrophy on color photos/exam can demonstrate SRHM, which is also seen with fibrosis.

2. The principal difference between atrophy and fibrosis on OCT is the thickness of SHRM (thicker and brighter with fibrosis).

3. Given similar OCT appearance and similar functional impact due to overlying RPE/photoreceptor loss, "atrosis" may be the best descriptor.

D. There is some evidence to suggest that sub-RPE CNV may be protective, but optimal PED thickness has not yet been defined.

II. Methods

A. Multicenter, retrospective study

1. UCLA (Sarraf)

2. Emory (O'Keefe)

3. Houston Retina (Wykoff, Brown)

B. *N* = 204 eyes of 177 patients with neovascular AMD treated with anti-VEGF therapy and followed for at least 5 years

C. Cohort divided into 3 groups for analysis/comparison based on final vision

1. Poor vision (<20/200)

2. Intermediate vision (20/40-20/200)

3. Good vision (>20/40)

D. Number of injections was recorded.

III. Results

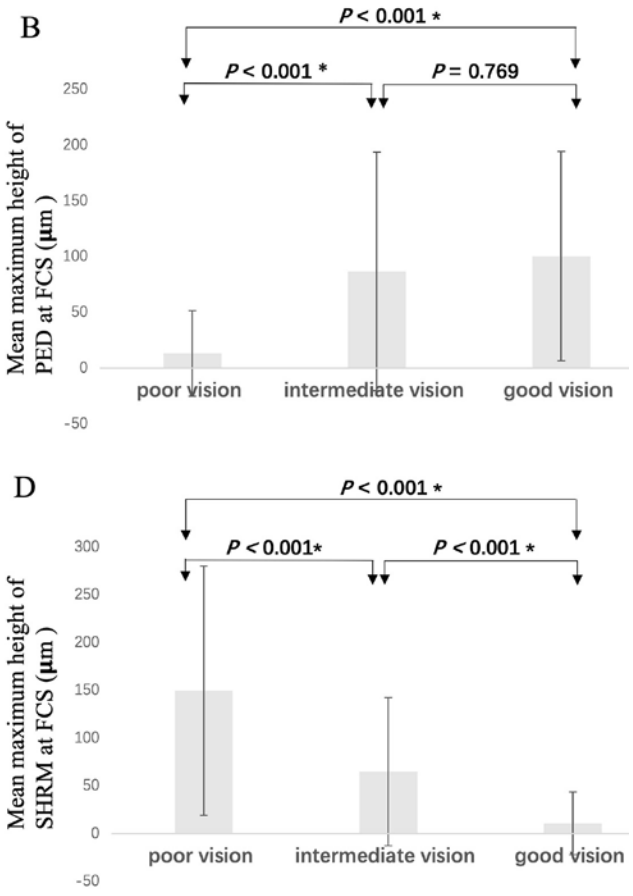

Figure 1.

A. Followed for mean 7.8 years; mean: 41 injections (5.2/yr)

B. Patients with best and worst vision received fewer injections on average. (The greatest number was given in the intermediate vision group.)

C. Thicker PED and thinner SHRM (especially under fovea) were associated with better vision.

D. Integrity of external limiting membrane, ellipsoid zone, and RPE band in fovea were strongly correlated with vision.

IV. Summary

A. The presence and thickness of the PED under the fovea was an important predictor of long-term vision in patients being treated for neovascular AMD.

B. The best morphology appears to be the absence of SRHM and a thicker PED with intact overlying retinal pigment epithelium.

C. As this is a retrospective analysis, the findings should be confirmed in prospective longitudinal trials, but if confirmed, the findings may have implications for defining the optimal endpoint for successful anti-VEGF therapy.

Forty Years' Experience With Proton Therapy to Treat Patients With Uveal Melanoma

Evangelos S Gragoudas MD

Introduction

Radiotherapy is currently the standard care for treating uveal melanoma. External beam radiation using protons is one of the most widely used modalities. The first proton treatment for a patient with ocular melanoma was completed in 1975 at the Massachusetts Eye and Ear Infirmary (MEEI), Massachusetts General Hospital (MGH), and Harvard Cyclotron. To date we have used protons to treat over 4000 patients with eye melanoma.

Proton Therapy

Proton therapy offers the advantage of highly localized and uniform dose distributions, which may optimize local control and minimize complications. Specifically, protons lose energy in tissue, with minimal scatter due to their mass, and deposit most energy at the end of their range (Bragg peak). This allows the design of a beam that covers the target volume with a uniform dose and reduces or eliminates the dose proximal and distal to the target. By modulating the beam of radiation, the Bragg peak can be broadened to conform to any tumor. A fixation angle can be selected during treatment planning to minimize radiation exposure to the lens, optic nerve, and macula. As a result, large tumors and tumors close to these sensitive structures can be treated with the possibility of fewer complications and retention of visual function.

Most patients receive a radiation dose of 70 Gy in 5 fractions. Based on findings of a dose reduction trial,[1] patients with small or medium-sized tumors located within 1 disc diameter (DD) of the optic nerve and/or fovea are now treated with 50 Gy.

Patient Outcomes After Proton Therapy

Patients diagnosed with uveal melanoma are at risk of vision loss, loss of the eye, and death from metastasis. Good functional outcomes are achieved using proton therapy. Visual prognosis is dependent upon tumor location and size. Local tumor control is realized in close to 100% of patients. However, patients still develop metastasis and die from this disease.

Visual acuity

The strongest predictor of poor visual outcome is proximity of the tumor to the optic nerve and fovea.[2] The 5-year rate of vision retention of 20/200 or better in patients with macular tumors (≤ 1 DD of macula and > 1 DD from optic nerve) is 35.5%, but visual prognosis is significantly better for patients with less elevated tumors and good baseline visual acuity.[3]

Eye retention

The 5-year rate of eye retention after proton therapy is 91%, and long-term prognosis remains good (the 15-year rate is 84%). Typically enucleation becomes necessary because either the tumor recurs or complications develop. Neovascular glaucoma is the most common complication leading to enucleation.[2] Patients with large tumors are at greater risk of eye loss, with 5-year and 10-year enucleation rates of approximately 23% and 30%, respectively.[4]

Complications

The most serious anterior segment complications are rubeosis iridis and neovascular glaucoma, which increase the risk of vision loss and loss of the eye. The most significant predictor of iris neovascularization is larger tumor volume, with a relative risk of 2.4 (95% CI, 2.1-2.8) per doubling volume.[5]

Radiation-induced vasculopathy is most likely to be vision threatening when the tumor is in close proximity to the optic nerve or fovea and radiation exposure of these structures is unavoidable. Five-year cumulative rates of maculopathy and papillopathy were 40% and 24%, respectively, for all patients treated with proton therapy at MEEI.[5]

Local control/tumor recurrence

Local recurrence after proton therapy occurs infrequently, with approximately 3% of tumors exhibiting growth,[2] most commonly at the tumor margin. The highest annual rate of recurrence (1%) is observed 1 year after treatment, although recurrences have occurred as late as 11 years after irradiation.

Metastatic uveal melanoma

Five-, 10-, and 15-year tumor-specific survival rates for patients treated with proton therapy at MEEI are 86%, 77%, and 73%, respectively. The highest annual death rates are observed between 3 and 6 years after treatment.[5] Despite high local control rates, melanoma-related deaths occur in over 50% of patients who present with high-risk characteristics by 10 years after treatment.[2] Early diagnosis of metastatic uveal melanoma does not appear to confer a survival benefit. No significant difference in median survival time (time from diagnosis of primary tumor to metastatic death) was found in a comparison of asymptomatic patients, diagnosed with metastasis incidentally or by routine surveillance, and symptomatic patients, diagnosed with metastasis after developing symptoms.[6]

This result is unlikely to change until improvements in available treatments for hepatic metastasis, the most common site in uveal melanoma, are achieved. To date, there have been no significant improvements in survival in patients who are treated for metastatic disease.[7]

Summary

Proton therapy is an effective method for treating patients with uveal melanoma. High rates of local control and eye conservation are achieved, and retention of useful vision is possible in many cases. The favorable dose distributions realized with proton irradiation allow treatment of large tumors and tumors near the optic nerve and fovea.

Nevertheless, significant ocular morbidity can develop after radiation treatment. Anti-inflammatory and anti-angiogenic agents may inhibit the deleterious effects of radiation. Preliminary findings from a Phase 1 study suggest that there may be visual benefits of prophylactic anti-VEGF therapy in patients with parapapillary or paramacular tumors treated by proton therapy,[8] but larger controlled trials are needed to confirm these findings.

Although local control of the tumor is achieved in almost all cases, rates of melanoma-related mortality are high, particularly for patients with certain tumor characteristics, suggesting that subclinical metastases may exist at the time of diagnosis and treatment. Although adjuvant interferon therapy after proton therapy was not effective for preventing metastasis,[9] adjuvant therapies may be the most promising approach for reducing melanoma-related mortality. Identifying patients at high metastatic risk based on molecular profiling of the primary tumor may be beneficial for developing targeted therapies and early intervention strategies to reduce or prevent uveal melanoma and its metastasis.

References

1. Gragoudas ES, Lane AM, Regan S, et al. A randomized controlled trial of varying radiation doses in the treatment of choroidal melanoma. *Arch Ophthalmol*. 2000; 118(6):773-787.
2. Gragoudas ES, Li W, Goitein M, Lane AM, Munzenrider JE, Egan KM. Evidence-based estimates of outcome in patients irradiated for intraocular melanoma. *Arch Ophthalmol*. 2002; 120(12):1665-1671.
3. Patel AV, Lane AM, Morrison MA, et al. Visual outcomes after proton beam irradiation for choroidal melanomas involving the fovea. *Ophthalmology* 2016; 123(2):369-377.
4. Papakostas TD, Lane AM, Morrison M, Gragoudas ES, Kim IK. Long-term outcomes after proton beam irradiation in patients with large choroidal melanomas. *JAMA Ophthalmol*. 2017; 135(11):1191-1196.
5. Gragoudas ES, Lane AM. Uveal melanoma: proton beam irradiation. *Ophthalmol Clin North Am*. 2005; 18(1):111-118, ix.
6. Kim IK, Lane AM, Gragoudas ES. Survival in patients with presymptomatic diagnosis of metastatic uveal melanoma. *Arch Ophthalmol*. 2010; 128:871-875.
7. Lane AM, Kim IK, Gragoudas ES. Survival rates in patients after treatment for metastasis from uveal melanoma. *JAMA Ophthalmol*. 2018; 136(9):981-986.
8. Kim IK, Lane AM, Jain P, Awh C, Gragoudas ES. Ranibizumab for the prevention of radiation complications in patients treated with proton beam irradiation for choroidal melanoma. *Trans Am Ophthalmol Soc*. 2016; 114:T2.
9. Lane AM, Egan KM, Harmon D, Holbrook A, Munzenrider JE, Gragoudas ES. Adjuvant interferon therapy for patients with uveal melanoma at high risk of metastasis. *Ophthalmology* 2009; 116(11):2206-2212.

Retinal Toxicity of Cancer Drugs

Jasmine H Francis MD

I. Introduction
   A. Recent expansion of cancer treatments beyond conventional chemotherapy to targeted agents and immunotherapy
   B. Brief review of retinal toxicity of conventional chemotherapy
II. Targeted Agents
   A. Mechanism of drugs
   B. Cancers treated with drugs
   C. Retinal toxicity
      1. Clinical findings
      2. Clinical course of toxicity
      3. Treatment
      4. Implications and prognosis of toxicity
III. Targeted Agents: Small Molecule Inhibitors
   A. Mechanism of drugs
   B. Cancers treated with drugs
   C. Retinal toxicity
      1. Clinical findings
      2. Clinical course of toxicity
      3. Treatment
      4. Implications and prognosis of toxicity
IV. Immunotherapy
   A. Mechanism of drugs
   B. Cancers treated with drugs
   C. Retinal toxicity
      1. Clinical findings
      2. Clinical course of toxicity
      3. Treatment
      4. Implications and prognosis of toxicity
V. Conclusion

Table 1.

Class	Biologic Drugs	Mechanism	Retinal Side Effects
Biologics			
	Interferon alpha 2b	• Recombinant protein connects adaptive and innate immune response • Apoptotic, anti-proliferative, anti-angiogenic, and immunoregulatory properties	Cotton wool spots, retinal hemorrhage, central retinal vein occlusion
	Denileukin diftitiox	• Fusion protein targets IL-2 receptors, delivers diphtheria toxin intracellularly. • Inhibits intracellular protein synthesis, leading to cell death	Macular pigment changes, decreased vision
	Trastuzumab	Binds human epidermal growth factor receptor 2 protein (HER-2)	Macular edema, hemorrhages, exudates
Small Molecule Inhibitors			
	Vemurafenib, dabrafenib, encorafenib	BRAF kinase inhibitor that inhibits specific mutated forms of BRAF in cancer cells	Uveitis, central macula edema
	Trametinib, cobimetinib, binimetinib, selumetinib, PD-325901	Inhibit MEK kinases, which are downstream factors in the MAPK pathway that regulate cell growth, proliferation, and differentiation	Foci of serous retinal detachments, retinal vein occlusion
	Crizotinib	Inhibits anaplastic lymphoma kinase (ALK)	Light/dark adjustment deficits
	Imatinib	Bcr-Abl tyrosine kinase inhibitor	Retinal hemorrhages, neovascularization, central macula edema, optic disc edema
Immunotherapy			
	Ipilimumab	Monoclonal antibody targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4)	Panuveitis, uveitis, vitritis, optic nerve edema, serous retinal detachment, choroidopathy, CNV, Vogt-Koyanagi-Harada-like syndrome
	Pembrolizumab, nivolumab	Programmed death protein 1 (PD-1) inhibitor	Panuveitis, uveitis, vitritis, optic nerve edema, vasculitis, cystoid macula edema, hypotony, uveal effusion syndrome, immune retinopathy, Vogt-Koyanagi-Harada-like syndrome
	Atezolizumab, avelumab, durvalumab	Programmed death ligand (PD-L1) inhibitor	Panuveitis, uveitis, vitritis, optic nerve edema, vasculitis, acute macula neuroretinopathy, uveal effusion syndrome

Current Management of Uveal Melanomas

Current Challenges and Future Promise

Prithvi Mruthyunjaya MD

I. Introduction

Times are changing for patients with uveal melanoma (UM), and this represents a stirring revolution in the field. Uveal melanoma remains the most common primary intraocular tumor in adults, and an unacceptably high percentage of patients develop metastatic disease, which is still, to date, uncurbable. However, the proliferation in knowledge about UM—including key topics such as tumor biology, tumor genetics, globe-sparing treatments, and bold forays into the treatment of metastatic disease with newer targeted agents—has moved the field of melanoma oncology forward. No longer an orphan disease with little attention beyond the ocular oncology community, UM has found allies in the fields of medical oncology, cancer biology, radiation oncology, and industry.

II. Primary UM Treatment Paradigms

A. Since being funded in 1985, the Collaborative Ocular Melanoma Study (COMS) has provided ophthalmologists and ocular oncologists with valuable data on the management of posterior uveal tract melanomas.

B. The 2 randomized trials in the COMS were conducted in 43 North American centers, with strict inclusion criteria with a primary endpoint of all-cause mortality.

C. The Medium Tumor trial randomized patients to iodine-125 plaque brachytherapy vs. enucleation, while the Large Tumor trial compared survival outcomes after enucleation with and without presurgical external beam radiotherapy.

1. The COMS has reported that no survival benefit was afforded to patients with medium-sized tumors (> 3.0 to 8 mm in height and ≤ 16 mm in diameter) treated with plaque brachytherapy over enucleation alone. These patients had equivalent (18% and 19%, respectively) 5-year cumulative mortality rates in both study arms.[1]

2. Radiation dose reduction strategies have been employed in limited settings.[2]

D. Data from proton beam radiation also show favorable results in appropriate patients, solidifying radiation therapy as the mainstay of primary tumor treatment.[3]

III. Accurate Diagnosis of UM

A. The accurate diagnosis of UM is less of an issue with larger tumors over 3 mm in thickness, as well-described clinical features are typically evident. The challenge can still remain with smaller lesions.[4]

B. One can separate melanocytic choroidal lesions into 3 broad categories: benign (low suspicion for malignancy), indeterminate (medium to high suspicion for malignancy), and high-risk malignant UM based on the following:

1. Patient history

2. Clinical examination

3. Ancillary imaging studies such as OCT and fundus autofluorescence, and standardized ultrasonography

4. Review of prior lesion documentation

5. Key features include pigmentation pattern, size and location of lesion, the presence and quality of subretinal fluid (eg, overlying or adjacent to the lesion), lipofuscin accumulation, drusen, or associated retinal pigment epithelial alterations.

6. Choroidal tumor biopsy may be used to aid in or confirm the diagnosis.[5]

IV. Assessment of Metastatic Risk in UM[6]

A. Clinical and histopathologic features of uveal melanoma (UM) tumors have been the root of traditional metastatic risk assessment.

Older patient age, high tumor thickness, high largest basal tumor diameter (LBD), ciliary body involvement, epithelioid tumor cell morphology, and extraocular tumor extension have all been identified as factors associated with increased risk of metastasis and disease-related mortality in UM.[7]

B. Chromosomal analysis has been used to identify individuals at risk for metastasis in UM.[8]

1. Monosomy of chromosome 3 and/or amplification of chromosome 8q (gain of chromosome 6p (in the absence of changes in chromosomes 3 and 8) and loss of chromosome 1p have been associated with more favorable outcomes).

2. Incorporating clinical, histologic, and genomic information allows for individualized prognostication in UM.[9]

C. RNA-based gene expression profiling (GEP)[10] groups UM tumors into highly prognostic molecular subgroups using a 15-gene array.

1. Class 1, which have low metastatic risk

2. Class 2, which have high metastatic risk and are associated with increasing age, high LBD, high tumor height, and ciliary body involvement[11,12]

V. Treatment of Metastatic UM[13]

Development of symptomatic or clinical detected metastatic disease requires treatment with poor systemic prognosis.

A. Liver directed therapy
   1. Local surgical resection
   2. Hepatic perfusion with chemotherapy

B. Systemic therapy
   1. Cytotoxic chemotherapy
   2. Immunotherapy

VI. Today's Presentation

The purpose of this presentation is to highlight key features of UM and review key concepts in early tumor diagnosis, clinical trials for primary UM treatment, and the treatment of metastatic or micrometastatic disease. These concepts are meant to guide the vitreoretinal specialist in the care of their patients with suspected or confirmed UM.

Topics to be addressed include the following:

A. Increased collaboration within ocular oncology and with medical oncology
   1. New National Cancer Care Network guidelines
   2. Collaborative Ocular Oncology Group
   3. Ocular Oncology Study Consortium
   4. American Joint Committee on Cancer (AJCC) Cancer Staging

B. Role of traditional clinical risk factors for detecting high-risk melanocytic lesions
   1. Imaging features
   2. Correlation with gene expression profiling as predictors for high-risk class 2 lesions

C. Clinical trials for novel, globe-sparing, nonradiation therapy for primary UV treatment: light-activated AU-011 (Aura Biosciences)

D. Clinical trial data for treatment of metastatic uveal melanoma
   1. Adjuvant therapy
      a. Sunitinib
      b. Crizotinib
   2. Liver directed therapy: Percutaneous hepatic perfusion therapy with melphalan (Delcath Systems, Inc.)
   3. Immunotherapy: GP-100 bispecific engineered T-cell receptor therapy (Immunocore)

References

1. Design and methods of a clinical trial for a rare condition: the Collaborative Ocular Melanoma Study. COMS Report No. 3. *Control Clin Trials*. 1993; 14:362-391.
2. Perez BA, Mettu P, Vajzovic L, et al. Uveal melanoma treated with iodine-125 episcleral plaque: an analysis of dose on disease control and visual outcomes. *Int J Radiat Oncol Biol Phys*. 2014; 89(1):127-136.
3. Papakostas TK, Lane AM, Morrison M, et al. Long term outcomes after proton beam irradiation in patients with large choroidal melanomas. *JAMA Ophthalmol*. 2017; 135(11):1191-1196.
4. Rishi P, Koundanya VV, Shields CL. Using risk factors for detection and prognostication of uveal melanoma. *Indian J Ophthalmol*. 2015; 63(2):110-116.
5. Finn AP, Materin MA, Mruthyunjaya P. Choroidal tumor biopsy: a review of the current state and a glance into future techniques. *Retina* 2018; 38 Suppl 1:s79-87.
6. Seider MI, Mruthyunjaya P. Molecular prognostics for uveal melanoma. *Retina* 2018; 38(2):211-219.
7. Force AOOT. International validation of the American Joint Committee on Cancer's 7th edition Classification of Uveal Melanoma. *JAMA Ophthalmol*. 2015; 133:376-383.
8. Berry DE, Schefler AC, Seider MI, Materin M, Stinnett S, Mruthyunjaya P; Ocular Oncology Study Consortium. Correlation of gene expression profile status and American Joint Commission on Cancer stage in uveal melanoma. *Retina*. Epub ahead of print 2018 Nov 8. doi: 1097/IAE.0000000000002385.
9. Eleuteri A, Damato B, Coupland S, Taktak A. Enhancing survival prognostication in patients with choroidal melanoma by integrating pathologic, clinical and genetic predictors of metastasis. *Int J Biomed Eng Tech*. 2012; 8:18.
10. Onken MD, Worley LA, Char DH, et al. Collaborative Ocular Oncology Group report number 1: prospective validation of a multi-gene prognostic assay in uveal melanoma. *Ophthalmology* 2012; 119:1596-1603.
11. Correa ZM, Augsburger JJ. Independent prognostic significance of gene expression profile class and largest basal diameter of posterior uveal melanomas. *Am J Ophthalmol*. 2016; 162:20-27 e21.
12. Walter SD, Chao DL, Feuer W, et al. Prognostic implications of tumor diameter in association with gene expression profile for uveal melanoma. *JAMA Ophthalmol*. 2016; 134:734-740.
13. Carvajal RD, Schwartz GK, Tezel T, Marr B, Francis JH, Nathan PD. Metastatic disease from uveal melanoma: treatment options and future prospects. *Br J Ophthalmol*. 2017; 101:38-44.

Molecular Insights Into Uveal Melanoma

J William Harbour MD

I. Early Initiating Mutations
   A. GNAQ
   B. GNA11
   C. CYSLTR2
   D. PLCB4

II. Later Prognostically Significant Mutations
   A. EIF1AX: Low metastatic risk (class 1A)
   B. SF3B1 and other splicing factors: Intermediate metastatic risk (class 1B)
   C. BAP1: High metastatic risk (class 2)

III. Chromosome Copy Number Aberrations (CNAs)
   A. Loss of 1p, 3, and 8p
   B. Gain of 6p and 8q

IV. Temporal Evolution of Genomic Aberrations and Their Clinical Significance

V. PRAME Expression
   A. Prognostic significance
   B. Association with CNAs

VI. Coevolution of Genomic Aberrations and Immune Microenvironment

VII. Conclusions

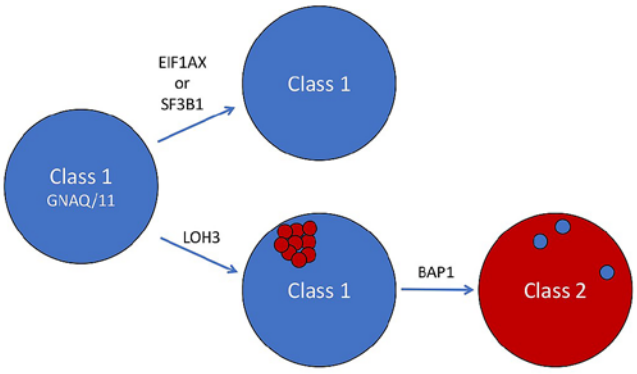

Figure 1. Hypothesis for tumor evolution in uveal melanoma. Initiating event occurs in GNAQ/11 or related genes, resulting in benign nevus. Further genomic aberrations drive tumor evolution along one of two major pathways, class 1 or class 2, depending on the later prognostic mutation that occurs.

Selected Readings

1. Cai L, Paez-Escamilla M, Walter SD, Tarlan B, Decatur CL, Perez BM, Harbour JW. Gene expression profiling and PRAME status versus tumor-node-metastasis staging for prognostication in uveal melanoma. *Am J Ophthalmol*. 2018; 195:154-160.
2. Decatur CL, Ong E, Garg N, et al. Driver mutations in uveal melanoma: associations with gene expression profile and patient outcomes. *JAMA Ophthalmol*. 2016; 134;728-733.
3. Field MG, Durante MA, Anbunathan H, et al. Punctuated evolution of canonical genomic aberrations in uveal melanoma. *Nat Commun*. 2018; 9:116.
4. Field MG, Decatur CL, Kurtenbach S, et al. PRAME as an independent biomarker for metastasis in uveal melanoma. *Clin Cancer Res*. 2016; 22:1234-1242.
5. Field MG, Durante MA, Decatur CL, et al. Epigenetic reprogramming and aberrant expression of PRAME are associated with increased metastatic risk in class 1 and class 2 uveal melanomas. *Oncotarget* 2016; 7:59209-59219.
6. Gezgin G, Luk SJ, Cao J, et al. PRAME as a potential target for immunotherapy in metastatic uveal melanoma. *JAMA Ophthalmol*. 2017; 135:541-549.
7. Harbour JW, Chao DL. A molecular revolution in uveal melanoma: implications for patient care and targeted therapy. *Ophthalmology* 2014; 121:1281-1288.
8. Harbour JW, Roberson ED, Anbunathan H, et al. Recurrent mutations at codon 625 of the splicing factor SF3B1 in uveal melanoma. *Nat Genetics*. 2013; 45:133-135.
9. Harbour JW, Onken MD, Roberson ED, et al. Frequent mutation of BAP1 in metastasizing uveal melanomas. *Science* 2010; 330:1410-1413.
10. Walter SD, Chao DL, Feuer W, Schiffman J, Char DH, Harbour JW. Prognostic implications of tumor diameter in association with gene expression profile for uveal melanoma. *JAMA Ophthalmol*. 2016; 134:734-740.

Indications and Surgical Techniques for Choroidal Tumor Biopsy

Zelia Maria Correa MD

Introduction

"Biopsy" may be defined as a surgical procedure intended to obtain a representative and sufficient specimen of cells or tissue for pathological or prognostic assessment. At least 4 different types of biopsy can be performed for a clinically identified tumor: excisional, incisional, aspiration, and exfoliative. The particular type of biopsy employed in a given patient depends on factors such as the anatomic site of the tumor, the diagnosis or differential diagnosis of the tumor, the planned analysis of the obtained specimen, and the anticipated benefits and risks of the procedure.

Aspiration biopsy with small caliber needle is widely used in ophthalmology, especially for choroidal tumors, due to its limited invasiveness. Fine needle aspiration biopsy (FNAB) is becoming widely used because of the development of prognostic testing for uveal melanoma.

Biopsy Indications

Diagnostic

A diagnostic biopsy is performed primarily to establish a pathologic diagnosis in cases with an uncertain clinical diagnosis; by definition, the clinical diagnosis for the lesion prompting biopsy must be a differential diagnosis that includes at least 1 malignant neoplasm or a microbial intraocular tumor at a reasonably strong level of probability. A biopsy of this type is usually performed as a separate surgical procedure and not generally in conjunction with therapeutic intervention for the tumor; some exceptions to this timing rule occur, including (a) when cytopathologic slides are prepared and reviewed in the operating room by a pathologist and a decision to provide treatment at that time is based on the pathologist's verbal report and (b) the differential diagnosis is between 2 malignant intraocular neoplasms (eg, amelanotic choroidal melanoma vs. non-ophthalmic primary cancer metastatic to choroid) for which treatment by plaque radiotherapy is planned regardless of which tumor type is identified by cytopathology.

Confirmatory

A confirmatory biopsy is performed primarily (a) to convince a skeptical patient about the accuracy of a clinical diagnosis and appropriateness of recommended treatment or (b) to justify patient management that may be complex, expensive, or potentially complicated (eg, intravenous chemotherapy, external beam radiation therapy) to professional colleagues who will have to provide that therapy. By definition, the prebiopsy clinical diagnosis for a confirmatory biopsy must be a single tumor type about which there is no clinically relevant doubt. In addition, a biopsy of this type is almost always clinical (ie, performed in the in vivo setting prior to any therapeutic intervention as a separate procedure).

Investigational

An investigational biopsy is performed to evaluate some aspect of performance of a particular method or set of instruments in a specific setting. A biopsy of this type may be clinical (in vivo) or performed following enucleation or resection (in vitro) and may be performed for tumors of any clinical diagnosis or differential diagnosis under IRB supervision.

Prognostic

A prognostic biopsy is performed to obtain a representative specimen of a tumor of a particular clinical type for prognostic classification using a validated method of specimen analysis performed in a CLIA-certified laboratory. A biopsy of this type may be clinical or performed after enucleation or resection.

Biopsy Techniques

Nowadays, FNABs are mostly performed using 27-gauge, sharp, disposable, hollow lumen needles without an obturator connected to a disposable 20-inch plastic tubing and a 10-mL plastic syringe to obtain biopsy specimens. The needle length depends on tumor location and route.

Clinical (in vivo) FNAB of posterior segment intraocular tumors whose anterior margin is located at or anterior to the ocular equator are performed trans-sclerally with a short (5/8 inch long) 27-gauge biopsy needle advancing into the choroidal tumor.

Clinical (in vivo) FNAB of posterior segment intraocular tumors whose anterior margin is located posterior to the ocular equator are performed using a transvitreal approach via a lamellar scleral incision parallel to the limbus in the pars plana region (usually about 3.5 mm from the limbus) in the meridian of the tumor with indirect ophthalmoscopy visualization of the passage of the tip of the biopsy needle through the vitreous and into the visible intraocular tumor. A 27-gauge long (1.5 inch) biopsy needle is used for such biopsies. Tumors < 2 mm thick usually benefit from pending the needle tip to an angle of 45 to 60 degrees relative to the needle shaft to avoid perforating the posterior sclera.

Clinical (in vivo) FNAB of posterior segment intraocular tumors whose anterior margin is located posterior to the ocular equator may also be performed using a vitrector cutter using a full pars plana vitrectomy approach.

Post-enucleation and post-transscleral resection (in vitro) biopsies of selected tumors can be performed for investigational or prognostic purposes immediately following surgical excision. Most of the post-enucleation FNABs are performed by direct puncture of full-thickness sclera over the tumor (as localized by post-enucleation transillumination) in the intact eye.

Take-Home Message

Performing FNAB of an intraocular tumor simply "because it is there" seems to be a futile exercise. In my experience, intraocular tumors should be biopsied only if there is a substantial likelihood that they are malignant. Clinical FNABs of nonmelanocytic intraocular tumors are rare unless patient management is likely to be influenced by this invasive testing.

Biopsy technique is directly influenced by indication and tumor location. Careful planning prior to FNAB increases the chances of sufficient yield and fewer complications.

Strategies to Treat and Prevent Radiation Retinopathy

Amy C Schefler MD

I. Background

Radiation retinopathy is a common and devastating visual side effect of brachytherapy or external beam radiotherapy for uveal melanoma and other ocular cancers. Treatment methods for visual stabilization or improvement in these patients are sorely needed. Although local tumor control rates in the Collaborative Ocular Melanoma Study (COMS) and other reports are excellent for small to medium-sized choroidal melanoma,[1] long-term visual acuity outcomes have been poor for many patients. In the COMS report examining visual outcomes at 3 years, 43% of patients had a visual acuity of 20/200 or worse and 49% had a loss of 6 or more lines from the pretreatment level at 3 years post-treatment.[2] Furthermore, in the COMS, as soon as poor visual outcome was observed, improvement in vision to a level that no longer met the definition of poor vision was rare. The most common reason for irreversible vision loss is radiation retinopathy. In Kaplan-Meier analysis, rates of nonproliferative and proliferative disease at 5 years after plaque therapy are 42% and 8%, respectively.[3]

Anti-VEGF injections have been used on label in millions of patients worldwide for diseases as diverse as diabetic macular edema, AMD, and myopic choroidal neovascular membranes. These medications have also been used off label at many centers for patients with radiation retinopathy. Several large retrospective reviews of these patients have been published, noting some success, mostly utilizing an approach in which initiation of treatment occurs immediately at the time of radiation.[4-6] However, there has been only 1 prospective randomized trial examining the use of an anti-VEGF agent for this condition.[7]

II. Treatments for Radiation Retinopathy

A. Laser

B. Subtenon steroids

C. Intravitreal steroids

D. Anti-VEGF therapy: Previous prospective publications with > 8 patients

1. Kim IK, Lane AM, Jain P, Awh C, Gragoudas ES. Ranibizumab for the prevention of radiation complications in patients treated with proton beam irradiation for choroidal melanoma. *Trans Am Ophthalmol Soc*. 2016; 114:T2.

a. 40 patients, Phase 1, single center, 2 years

b. Cohorts: Intravitreal ranibizumab 0.5 mg (30 patients) or 2.0 mg (10 patients) every 2 months from time of proton beam therapy

c. Brief results: At 24 months, BCVA ≥ 20/200 was 30/31 (97%) in the study group vs. 92/205 (45%) in historical controls ($P < .001$). Clinical evidence of radiation maculopathy at month 24 was seen in 8/24 patients (33%) with small/medium tumors vs. 42/62 (68%) of historical controls ($P = .004$).

2. Schefler AC, Fuller D, Fuller T, Anand R, Bretana ME, Kim RS. Ranibizumab for radiation retinopathy (RRR): a prospective, multicenter trial of monthly versus prn dosing for radiation retinopathy-related cystoid macular edema. In press.

a. 40 patients, Phase 2, multicenter, randomized

b. 3 cohorts: monthly 0.5-mg ranibizumab for 1 year; monthly ranibizumab with targeted panretinal photocoagulation (PRP to ischemic areas identified on wide-field fluorescein angiography) for 1 year; p.r.n. ranibizumab with targeted PRP for 1 year; for year 2, all 3 cohorts were treated with a standardized treat-and-extend protocol.

c. Brief results: All 3 groups treated with 0.5-mg intravitreal ranibizumab had significantly better visual outcomes than historical controls; patients treated with monthly ranibizumab had significant visual gains compared to patients treated with a p.r.n. approach; the addition of targeted PRP to monthly ranibizumab did not result in visual gain over monthly ranibizumab at the 12-month time point; in year 2, with a treat-and-extend approach, patients in the monthly cohort trended toward their baseline BCVA, although still with improvement over historical controls.

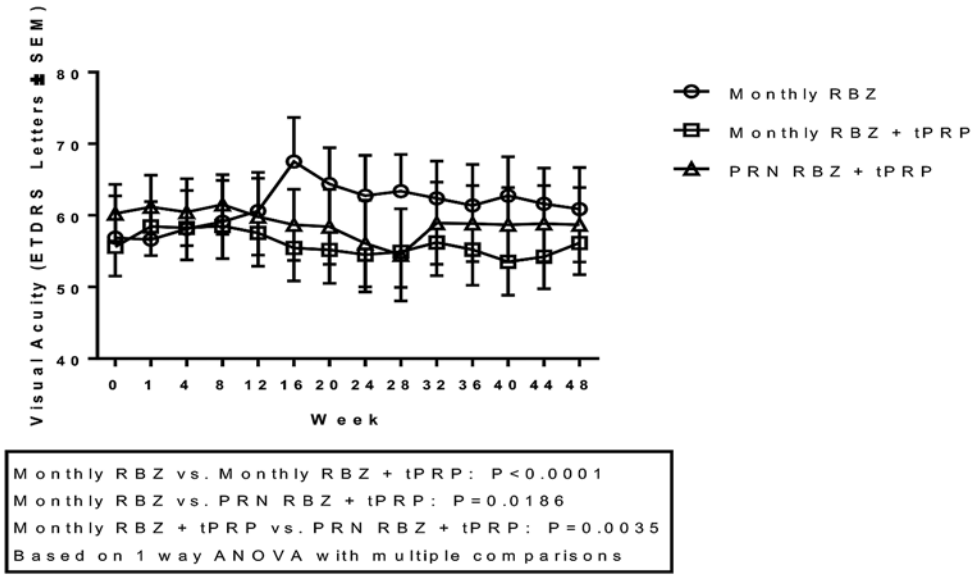

Figure 1. Mean number of letters (BCVA) in 3 cohorts over first year of Ranibizumab for Radiation Retinopathy study. The monthly ranibizumab group had the most improvement, 4 letters at 1 year. Source: Schefler AC, Fuller D, Fuller T, Anand R, Bretana ME, Kim RS. Ranibizumab for radiation retinopathy (RRR): a prospective, multicenter trial of monthly versus prn dosing for radiation retinopathy-related cystoid macular edema. In press.

E. Future directions
   1. Larger scale prospective trials
   2. Combination therapy
   3. Avoidance of radiation entirely (ie, AU-011)

References

1. Jampol LM, Moy CS, Murray TG, et al. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: IV. Local treatment failure and enucleation in the first 5 years after brachytherapy. COMS report no. 19. *Ophthalmology* 2002; 109:2197-2206.
2. Melisa BM, Abramson DH, Albert DM, et al. Collaborative Ocular Melanoma Study (COMS) randomized trial of I-125 brachytherapy for medium choroidal melanoma. I. Visual acuity after 3 years. COMS report no. 16. *Ophthalmology* 2001; 108:384-366.
3. Gunduz K, Shields JA, Cater J, Freire JE, Brady LW. Radiation retinopathy following plaque radiotherapy for posterior uveal melanoma. *Arch Ophthalmol*. 1999; 117:609-614.
4. Finger PT, Chin KJ, Semenova EA. Intravitreal anti-VEGF therapy for macular retinopathy: a 10-year study. *Eur J Ophthalmol*. 2016; 26(1):60-66.
5. Khan MA, Mashayekhi A, Shields JA, Shields CL. Intravitreal aflibercept as rescue therapy for post-radiation cystoid macular edema resistant to intravitreal bevacizumab: outcomes at 1 year. *Ocul Oncol Pathol*. 2017; 3(4):313-319.
6. Shah SU, Shields CL, Bianciotto CG, et al. Intravitreal bevacizumab at 4-month intervals for prevention of macular edema after plaque radiotherapy of uveal melanoma. *Ophthalmology* 2014; 121(1):269-275.
7. Kim IK, Lane AM, Jain P, Awh C, Gragoudas ES. Ranibizumab for the prevention of radiation complications in patients treated with proton beam irradiation for choroidal melanoma. *Trans Am Ophthalmol Soc*. 2016; 114:T2.

Artificial Intelligence for Diabetic Retinopathy Screening

Tien Yin Wong MBBS

Artificial intelligence (AI) using deep learning (DL) technology is a major disruptive innovation in medicine. AI and DL have been developed in several areas in ophthalmology. The two most prominent are, firstly, in the assessment of fundus photographs for detection of diabetic retinopathy (DR),[1-6] AMD,[7-9] glaucoma,[10,11] and ROP,[12,13] and, secondly, in the segmentation and assessment of OCT images for diagnosis of DR, AMD, diabetic macular edema (DME) and other retinal diseases.[14-16]

In particular, DL algorithms for DR screening have made significant progress with landmark studies in the application of AI in medicine, as well as the first approval and registration of a fundus camera for DR screening by the FDA.[17] The paper by Gulshan and colleagues from Google Health has shown that DL technology shows extremely high sensitivity and specificity in detecting referable DR from fundus photographs.[3] These developments have thus been cited in mainstream media and editorials.[18] Despite the promise and potential hype, there remain significant challenges in the actual translation and implementation of AI-DL technology for DR screening in a community setting.

Current Status and Challenges in Developing and Maintaining a DR Screening Program

While the rationale to screen for DR among patients with diabetes is clear, there are significant challenges in designing and sustaining a community-wide DR screening program. Systematic or national screening programs for DR using digital fundus photography are currently implemented at primary care levels in only a few countries, such as the UK and Singapore.

Diagnosis of DME also requires identification of macular fluid and thickening and thus the need to incorporate OCT in DR screening programs. This adds complexity to the program, as interpretation of both retinal photographs and OCT requires specialized knowledge and expertise in diabetic eye diseases and retinal imaging.

Most importantly, DR screening programs are capital- and labor-intensive, limiting our ability to rapidly scale and expand DR screening programs to meet growing global diabetes epidemic.

AI-DL Provides a Possible Strategy for DR Screening

A fully automated AI-DL system has significant potential for increasing efficiency, reproducibility, and coverage of DR screening programs, reducing cost and access barriers, and improving patient outcomes by providing accurate early detection of DR and thus referral for appropriate treatment.

Previously, machine learning (an older spectrum of AI research) was developed for DR detection based on feature extraction and/or pattern recognition. However, these traditional machine learning algorithms have not been able to reach a high level of sensitivity and specificity for clinical adoption, with a consequent plateau in performance.

DL was a major advance in AI, and it appears to have overcome the "ceiling performance" of prior AI technology. DL permits algorithms to be trained using millions of parameters and large amounts of data through a "convolutional neural network" (CNN). CNN can be simply described as reflecting the ability of human brains to learn complicated patterns in data by altering strengths of synaptic connections between neurons. AI-DL with CNNs have shown superior performance for automated classification for DR,[1-5] retinal diseases,[14-16] and glaucoma,[10,11] equal to or better than that of ophthalmologists. While traditional machine learning models require specific features (eg, microaneurysms) to be extracted manually, in DL, such features are automatically detected by CNN and fed into a classifier for classification. No specific lesion-based features are needed in DL, and thus steps of lesion segmentation can be skipped. DL approaches may also identify "new features" (eg, nontraditional signs of DR, such as retinal arteriolar tortuosity or venular width).

Current AI-DL Systems for DR Screening Using Fundus Photographs

FDA-approved fundus camera system (IDx-DR)

IDx-DR has been developed by Abramoff et al using a DL algorithm based initially on the Messidor-2 dataset.[2] The DL system has been further evaluated using data collected prospectively from 819 subjects recruited from 10 primary care sites in the United States, showing high sensitivity (87.2%) and specificity (90.7%). The DL system has also been evaluated in primary care settings in countries outside the U.S. In 2018, IDx-DR obtained FDA first approval for detecting greater than a mild level of DR in adults who have diabetes without assisted interpretation by a clinician.[17] The case of IDx-DR highlights one of the earliest successes of an DL-based screening tool completing the regulatory process.

Google Health and other cloud-based programs

A major development in DL for DR detection was the study by Gulshan et al from Google Health, which developed a DL system for detecting referable DR using 128,175 retinal photographs which were graded 3 to 7 times for DR, DME, and image gradeability by a panel of > 50 ophthalmologists and senior residents.[3] The DL algorithm achieved high sensitivity (≥ 87%), specificity (≥ 90%), and AUC (≥ 0.99) in the external validation using 2 public databases (EyePAC-1: n = 9963 and Messidor-2: n = 1748).[3] Other groups have reported similar results.[4-6]

Singapore Eye Lesion Analyzer (SELENA)

A third development addresses a gap in previous studies in which the AI-DL algorithms were not trained to detect other common sight-threatening conditions, such as glaucoma and AMD. Ting and colleagues developed an AI-DL system to screen not only for DR but also for glaucoma and AMD.[1] The

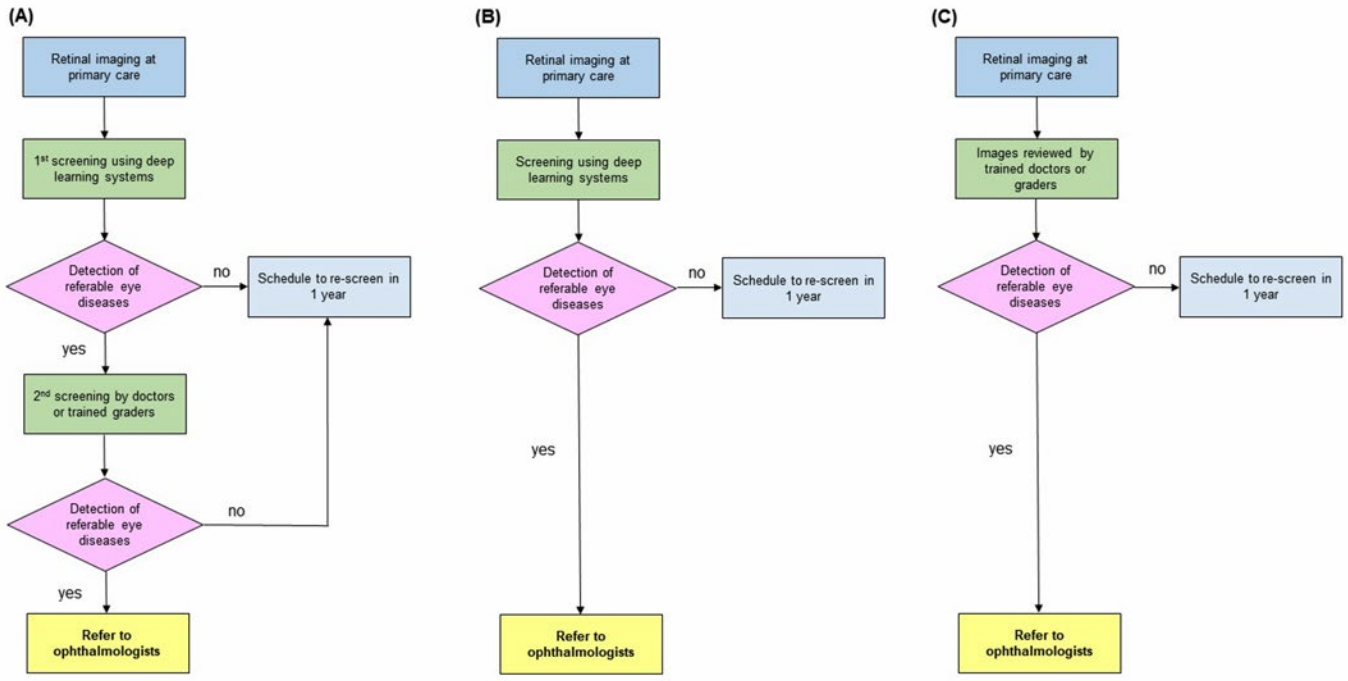

Figure 1. Two AI-based models for DR screening have been proposed: (A) a "triage" semi-automated model wherein retinal images will be firstly analyzed by the AI-DL systems. Images will then be read by human graders (second screening) and (B) a fully automated "replacement" model, in which retinal images will be fully analyzed by the AI-DLsystems. The existing DR screening model by human assessors is shown in (C).

AI-DL system was validated using retinal photographs collected from the Singapore DR screening program and 10 additional multiethnic datasets from different countries.[1] In the primary validation dataset of 71,896 images, the AUC of the DL system was 0.936 for referable DR, 0.958 for vision-threatening DR, 0.941 for glaucoma suspect, and 0.931 for referable AMD. The system had AUCs between 0.889 and 0.983 for referable DR on 10 additional datasets. The system could also achieve high sensitivity (> 90%), specificity (> 73.3%), and AUC (> 0.89) for identifying other referable eye conditions.

Current AI-DL Systems for Detecting DME From OCT

A major issue in DR screening is the detection of DME, not easily captured from 2-D fundus photographs. Thus, recent groups have focused on developing AI-DL algorithms using OCT images. Kermany et al firstly applied AI-DL using transfer learning techniques in detection of DME as well as choroidal neovascularization, drusen, and normal from OCT images.[14] They showed in their models a high level of performance (sensitivity, ≥ 96%; specificity, ≥ 94%; and AUC, ≥ 0.99).[14] Another study by Google's Deepmind group applied a combined 3-D segmentation and classification CNN for interpreting OCT.[15] The group developed an AI-DL algorithm using 877 segmented OCT scans for segmentation work, and 14,884 OCT scans with multiple clinical diagnoses and referral decisions (urgent, semi-urgent, routine, and observation).

How Does an AI-DL System Fit Into DR Screening Programs?

A critical question in the conceptualization of using AI-DL technology for DR screening is "Where does the AI-DL system fit"? AI-DL systems could potentially be deployed in 2 different settings.[1,18] Figure 1 illustrates the 2 proposed DL-based screening models for DR, compared with an existing DR screening model.

Triage model (A)

First, the AI-DL system could be used as a "triage" and incorporated into existing DR screening programs, such as in UK or Singapore, to assist human assessors.[1] In this model, retinal images are analyzed by the AI-DL system first, and human assessors only review "referable" or "ungradable" images (second screening). This model reduces the workload in DR screening programs and also avoids over-referral of false-positive cases to ophthalmologists.

Replacement model (B)

Second, the AI-DL system can be a fully automated model wherein all retinal images can be analyzed by the system. This will be useful in communities without any existing DR screening programs. When using this model, the sensitivity of the DL system may need to be set higher in order to minimalize false-negative cases.

Current Challenges of AI-DL for DR Screening

The performance of current AI-DL algorithms is extremely promising. However, there are still several challenges and complexities that limit the ability to move ahead quickly.

First, the "AI black box" remains unacceptable to physicians and likely patients. AI-DL algorithms use data from millions of image features that are most predictive for DR classification rather than explicitly detecting clinical signs of DR that physicians are familiar with (eg, microaneurysms, hard exudates). It is unclear exactly what the machine "sees or thinks."[18] One

method to visualize what the AI-DL algorithm learns is to use a "heat map" analysis.[4,14]

Second, AI-DL models require large amounts of high-quality data with "gold-standard labelling." Thus, training that uses a single clinical dataset is limited by potential biases, which may affect performance and generalizability. Using datasets from diverse settings and populations for training the AI-DL algorithm is important, but the availability of such diverse datasets is currently limited. Furthermore, data sharing across countries and centers is complex and requires regulatory approval.

Third, most current AI-DL algorithms are developed in "research settings." To be applicable, the performance of AI-DL algorithms in "real-world" settings is essential. A prospective study design in appropriate clinical settings is critical to evaluate the "real" performance of the AI-DL algorithms.

Fourth, before the AI-DL algorithms are deployed in the clinical workflow of DR screening, medicolegal and operational issues need to be addressed. Issues relating to physician and health-care system responsibility for missing false-negative cases need to be addressed before actual clinical deployment.

Conclusions

AI-DL technology is now entering the mainstream of clinical medicine and ophthalmology. AI has the potential to substantially impact DR screening by improving performance and enhancing the cost-effectiveness, efficiency, and accessibility of DR screening programs.

References

1. Ting DSW, Cheung CY, Lim G, et al. Development and validation of a deep learning system for diabetic retinopathy and related eye diseases using retinal images from multiethnic populations with diabetes. *JAMA* 2017; 318(22):2211-2223.
2. Abramoff MD, Lou Y, Erginay A, et al. Improved automated detection of diabetic retinopathy on a publicly available dataset through integration of deep learning. *Invest Ophthalmol Vis Sci*. 2016; 57(13):5200-5206.
3. Gulshan V, Peng L, Coram M, et al. Development and validation of a deep learning algorithm for detection of diabetic retinopathy in retinal fundus photographs. *JAMA* 2016; 316(22):2402-2410.
4. Gargeya R, Leng T. Automated identification of diabetic retinopathy using deep learning. *Ophthalmology* 2017; 124(7):962-969.
5. Li Z, Keel S, Liu C, et al. An automated grading system for detection of vision-threatening referable diabetic retinopathy on the basis of color fundus photographs. *Diabetes Care* 2018; 41(12):2509-2516.
6. Kanagasingam Y, Xiao D, Vignarajan J, Preetham A, Tay-Kearney ML, Mehrotra A. Evaluation of artificial intelligence-based grading of diabetic retinopathy in primary care. *JAMA Netw Open*. 2018; 1(5):e182665.
7. Burlina PM, Joshi N, Pacheco KD, Liu TYA, Bressler NM. Assessment of deep generative models for high-resolution synthetic retinal image generation of age-related macular degeneration. *JAMA Ophthalmol*. Epub ahead of print 2019 Jan 10. doi: 10.1001/jamaophthalmol.2018.6156.
8. Peng Y, Dharssi S, Chen Q, et al. DeepSeeNet: a deep learning model for automated classification of patient-based age-related macular degeneration severity from color fundus photographs. *Ophthalmology* 2018; 126(4):565-575.
9. Burlina PM, Joshi N, Pacheco KD, Freund DE, Kong J, Bressler NM. Use of deep learning for detailed severity characterization and estimation of 5-year risk among patients with age-related macular degeneration. *JAMA Ophthalmol* 2018; 136(12):1359-1366.
10. Li Z, He Y, Keel S, Meng W, Chang RT, He M. Efficacy of a deep learning system for detecting glaucomatous optic neuropathy based on color fundus photographs. *Ophthalmology* 2018; 125(8):1199-1206.
11. Medeiros FA, Jammal AA, Thompson AC. From machine to machine: an OCT-trained deep learning algorithm for objective quantification of glaucomatous damage in fundus photographs. *Ophthalmology* 2019; 126(4):513-521.
12. Redd TK, Campbell JP, Brown JM, et al. Evaluation of a deep learning image assessment system for detecting severe retinopathy of prematurity. *Br J Ophthalmol*. Epub ahead of print 2018 Nov 23. doi: 10.1136/bjophthalmol-2018-313156.
13. Brown JM, Campbell JP, Beers A, et al. Automated diagnosis of plus disease in retinopathy of prematurity using deep convolutional neural networks. *JAMA Ophthalmol*. 2018; 136(7):803-810.
14. Kermany DS, Goldbaum M, Cai W, et al. Identifying medical diagnoses and treatable diseases by image-based deep learning. *Cell* 2018; 172(5):1122-1131 e9.
15. De Fauw J, Ledsam JR, Romera-Paredes B, et al. Clinically applicable deep learning for diagnosis and referral in retinal disease. *Nat Med*. 2018; 24(9):1342-1350.
16. Schlegl T, Waldstein SM, Bogunovic H, et al. Fully automated detection and quantification of macular fluid in OCT using deep learning. *Ophthalmology* 2018; 125(4):549-558.
17. FDA permits marketing of artificial intelligence-based device to detect certain diabetes-related eye problems. USFDA website. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm604357.htm?fbclid=IwA R2h4qBpSAD6vx8EErts2nhhundX8654ZUL3xwvVahXyLxnSYSxCAOMEias. April 11, 2018.
18. Wong TY, Bressler NM. Artificial intelligence with deep learning technology looks into diabetic retinopathy screening. *JAMA* 2016; 316(22):2366-2367.

Protocol T Extension Results

John A Wells III MD

I. Introduction

A. DRCR Retina Network Protocol T, a randomized trial, evaluated treatment with aflibercept, bevacizumab, or ranibizumab for diabetic macular edema (DME) through 2 years following a DRCR treatment algorithm.[1,2]

1. The 2-year visit was completed by 88% of participants (578 of 660).

2. For eyes with better visual acuity (VA) at baseline, VA outcomes were similar across treatment groups. However, among eyes with worse VA at baseline, participants in the aflibercept group had superior 2-year VA outcomes compared with bevacizumab.

3. For the aflibercept, bevacizumab, and ranibizumab groups, respectively, at the 2-year visit, center-involved DME on OCT was present in 25%, 54%, and 34% of eyes with worse VA at baseline and in 33%, 63%, and 36% of eyes with better VA at baseline.

B. There are several published trials on the effects of anti-VEGF therapy on DME following a specific treatment regimen beyond 2 years.[3-5] However, more information is needed to assess information on treatment course, changes in visual acuity, and DME after protocol-specific treatments are stopped.

II. Methods

Participants randomized in Protocol T were asked to return to complete a follow-up visit approximately 5 years after they were randomized in the protocol. The extension visits included an assessment of DME and diabetic retinopathy treatments since the 2-year visit, ocular and medical history, best-corrected E-ETDRS visual acuity, dilated eye exam, OCT, HbA1c, color fundus photographs, and an assessment of APTC events since the 2-year visit.

III. Results

A. 317 participants (55%) who completed the 2-year visit returned for the 5-year follow-up visit.

B. Additional results for VA and DME at 5 years: Treatments used, injection frequencies, treatment for diabetic retinopathy, diabetic retinopathy, and APTC events occurring since the 2-year study visit will be presented.

References

1. Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med*. 2015; 372(13):1193-1203.

2. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. *Ophthalmology* 2016; 123(6):1351-1359.

3. Bressler SB, Glassman AR, Almukhtar T, et al. Five-year outcomes of ranibizumab with prompt or deferred laser versus laser or triamcinolone plus deferred ranibizumab for diabetic macular edema. *Am J Ophthalmol*. 2016; 164:57-68.

4. Brown DM, Nguyen QD, Marcus DM, et al. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two Phase III trials: RISE and RIDE. *Ophthalmology* 2013; 120(10):2013-2022.

5. Boyer DS, Nguyen QD, Brown DM, Basu K, Ehrlich JS. Outcomes with as-needed ranibizumab after initial monthly therapy: long-term outcomes of the Phase III RIDE and RISE Trials. *Ophthalmology* 2015; 122(12):2504-2513.e1.

Predicting 2-Year Outcomes Based on Visual Acuity or OCT Changes Following 3 Anti-VEGF Injections for Diabetic Macular Edema

Neil M Bressler MD

Adapted from Bressler NM, Beaulieu WT, Maguire MG, Glassman AR, Blinder KJ, Bressler SB, Gonzalez VH, Jampol LM, Melia M, Sun JK, Wells JA 3rd; for the Diabetic Retinopathy Clinical Research Network. Early response to anti-vascular endothelial growth factor and two-year outcomes among eyes with diabetic macular edema in Protocol T. Am J Ophthalmol. 2018; 195:93-100.

I. Background

A. Analysis of DRCR Network Protocol I data showed a strong relationship between 12-week change in VA and 1-year and 3-year change in VA among eyes treated with ranibizumab for DME.

1. ~25% of eyes with < 5-letter gain at 12 weeks gained ≥ 10 letters at 3 years.
2. ~75% of eyes with ≥ 10-letter gain at 12 weeks gained ≥ 10 letters at 3 years.

B. However, these estimates are not precise enough to determine course of vision gain or loss for an individual eye, nor do they imply that switching to alternative therapies would improve outcomes.

C. Questions

1. Do the data from Protocol T provide further clarification?
2. Would findings from Protocol I be supported when using the Protocol T treatment regimen with ranibizumab?
3. Do similar associations exist when using aflibercept or bevacizumab within the Protocol T treatment regimen for DME?
4. Is OCT central subfield thickness response at 12 weeks also associated with long-term vision outcomes?

II. Results

A. Visual acuity response at 12 weeks following 3 monthly injections was associated with 2-year outcomes, regardless of anti-VEGF agent used.

B. However, when continuing to follow the DRCR Network treatment regimen for DME beyond 12 weeks, a suboptimal response (< 5-letter gain) from baseline to 12 weeks often was followed by subsequent meaningful vision improvement (ie, ≥ 2-line gain) from baseline to 2 years.

1. A majority of the eyes with < 5-letter gain from baseline to 12 weeks gained 5-9 letters, or 10 or more letters from baseline to 2 years.
2. Eyes with < 5-letter gain from baseline to 12 weeks typically had good visual acuity (20/25–20/32) at 2 years.

III. Conclusions

A. Visual acuity response at 12 weeks following 3 monthly injections was associated with 2-year outcomes, regardless of whether aflibercept, bevacizumab, or ranibizumab was used.

B. However, a suboptimal response at 12 weeks did not preclude further meaningful vision improvement (ie, ≥ 2 lines) without switching therapy.

C. About two-thirds of the variation in 2-year outcomes remains unexplained.

1. Factors such as the level of visual acuity at presentation, the change in visual acuity from baseline to the 12-week visits (after 3 injections), but not CST, do influence response to treatment.
2. However, these factors account for no more than approximately one-third of the variability in change in visual acuity from baseline to 2 years.

D. There also is little evidence to suggest that switching from DRCR.net anti-VEGF treatment regimen for DME will result in better vision results. For example, Protocol U showed that mean VA improvement by 6 months was no better in the Combination Group (dexamethasone + ranibizumab) than in the Sham Combination Group (sham + ranibizumab group), even though, on average, there was a greater reduction in retinal thickness in the Combination Group.

E. Future studies are still needed to compare continuation of DRCR.net anti-VEGF treatment regimen for DME with alternatives among eyes with inadequate response.

References

1. Diabetic Retinopathy Clinical Research Network; Elman MJ, Qin H, Aiello LP, et al. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: three-year randomized trial results. *Ophthalmology* 2012; 119:2312-2318.
2. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. *Ophthalmology* 2016; 123:1351-1359.

3. Bressler NM, Beaulieu WT, Glassman AR, et al. Persistent macular thickening following intravitreous aflibercept, bevacizumab, or ranibizumab for central-involved diabetic macular edema with vision impairment: a secondary analysis of a randomized clinical trial. *JAMA Ophthalmol*. 2018; 136:257-269.

4. Gonzalez VH, Campbell J, Holekamp NM, et al. Early and long-term responses to anti-vascular endothelial growth factor therapy in diabetic macular edema: analysis of Protocol I data. *Am J Ophthalmol*. 2016; 172:72-79.

5. Maturi RK, Glassman AR, Liu D, et al. Effect of adding dexamethasone to continued ranibizumab treatment in patients with persistent diabetic macular edema: a DRCR Network Phase 2 randomized clinical trial. *JAMA Ophthalmol*. 2018; 136:29-38.

Findings From Wide-Field Color Photography for Diabetic Retinopathy Prognosis

Lloyd P Aiello MD PhD

NOTES

Management of High-risk Nonproliferative Diabetic Retinopathy Without Diabetic Macular Edema: Results From PANORAMA

Rishi P Singh MD on behalf of the PANORAMA study investigators

I. Introduction

A. PANORAMA (NCT02718326) is the first large prospective trial of eyes with moderately severe to severe (high-risk) nonproliferative diabetic retinopathy (NPDR) in patients without diabetic macular edema (DME) since the Early Treatment Diabetic Retinopathy Study.

B. Vascular endothelial growth factor inhibitors have been shown to slow disease progression in eyes with diabetic retinopathy in patients with DME.

C. In the Phase 3 VISTA and VIVID studies, more eyes treated with intravitreal aflibercept injection (IAI) had a ≥ 2-step improvement in Diabetic Retinopathy Severity Scale (DRSS) score vs. laser photocoagulation in patients with both diabetic retinopathy and DME.

D. PANORAMA compared the efficacy and safety of IAI vs. sham in moderately severe to severe NPDR in patients without concurrent DME.

II. Methods

A. Eligible patients were aged ≥ 18 years with type 1 or 2 diabetes mellitus and moderately severe to severe NPDR (DRSS score 47 or 53), absence of center-involved DME (CI-DME), and a baseline BCVA score of ≥ 69 letters (approximately ≥ 20/40) in the study eye.

B. In total, 402 eyes were randomized to IAI 2 mg every (q) 16 weeks after 3 monthly doses and 1 q8 interval (2q16, n = 135), IAI 2 mg q8 weeks after 5 monthly doses (2q8, n = 134), or sham (n = 133).

C. The primary endpoint was the proportion of eyes with a ≥ 2-step improvement in DRSS score at week 52.

III. Results

A. Overall, 44.0% of patients were women, with a mean (SD) age of 55.7 (10.5) years. The mean (SD) baseline BCVA score was 82.4 (6.0) letters.

B. At week 52, 65% and 80% of 2q16 and 2q8 eyes, respectively, vs. 15% of sham eyes had a ≥ 2-step improvement in DRSS score (P < .0001 for both).

C. A total of 9% and 15% of 2q16 and 2q8 eyes, respectively, vs. <1% of sham eyes had a ≥ 3-step improvement in DRSS score (nominal P < .001 for both).

D. In addition, 4% of 2q16 eyes and 3% of 2q8 eyes vs. 20% of sham eyes (P < .0001 for both) developed a vision-threatening complication (VTC; proliferative diabetic retinopathy or anterior segment neovascularization). Compared with sham, IAI significantly reduced the risk of developing a VTC by 85% and 88% in the 2q16 and 2q8 groups, respectively.

E. Through week 52, the incidence of CI-DME was lower in the 2q16 (7%) and 2q8 (8%) groups vs. the sham group (26%, P < .001 for both). Compared with sham, IAI significantly reduced the risk of developing CI-DME by 79% and 73% in the 2q16 and 2q8 groups, respectively.

F. No new safety signals were identified with IAI.

IV. Conclusion

IAI improved diabetic retinopathy and prevented disease progression in eyes with moderately severe to severe NPDR in patients without DME.

Anti-VEGF Treatment Can Diminish Signs of Diabetic Retinopathy Without Reducing Nonperfusion

Ramin Tadayoni MD PhD

I. Anti-VEGF Can Improve Diabetic Retinopathy Severity Scale (DRSS) on Color Photos

As expected from an effective anti-angiogenic agent, anti-VEGF drugs have been shown to be able to control new vessels in diabetic retinopathy eyes. It has also been shown that the DRSS on color fundus photos can improve after intravitreal injections of anti-VEGF.[1,2]

II. Color Fundus Photo Signs Are Validated Surrogates for Estimating Retinal Perfusion in Untreated Eyes but Their Value After Injections Has Never Been Established

Anti-VEGF intravitreal injections, as steroid injections, can clean the fundus from hemorrhages and signs of VEGF impregnation without eliminating risks of neovascularization shortly after discontinuation of the treatment.[3] This may indicate that the ischemia persists despite improvement of the fundus.

III. After 3 Anti-VEGF Injections, on Fluorescein Angiography We Didn't Find Reperfusion of Vessels Despite DRSS Improvement on Color Photos

A. Methods:

Ultrawide field (UWF) color photography (Optos California, Optos; Scotland, UK) and fluorescein angiography (FA) at baseline (M0) and 1 month after 3 monthly anti-VEGF injections (M3) for DME in consecutive naïve eyes were used to compare UWF-FA assessment of nonperfusion changes and color photos. All images were carefully aligned, cropped to keep the common parts, and divided into 16 "boxes" for masked analysis and comparison by 2 retina specialists.

B. Results:

When the DRSS score improved by at least 1 stage in 11/18 eyes (61%) ($P < .0001$), no reperfusion of arterioles or venules was observed in or around nonperfusion areas. Then, evaluating carefully retinal perfusion after 3 intravitreal injections of anti-VEGF with fluorescein angiography, we did not find reperfusion of vessels despite DRSS improvement on color photos.[4]

IV. OCT Angiography Confirmed FA Findings at Capillary Levels

With a similar method but this time using widefield OCT angiography (WF OCT-A) (PlexElite, Carl Zeiss Meditec; California, USA), we found that DRSS improved quickly (M3 or before) after anti-VEGF treatment by at least 1 stage in most of the eyes (8/10) and that new vessels, when present, regressed. However, OCT-A with a better precision proved that no reperfusion occurred, including at capillary level.[5]

Evaluation of nonperfusion after intravitreal injections: color photo DRSS seems insufficient, and OCT-A appears superior to FA in the area it can cover.

A. DRSS decorrelates from perfusion status after intravitreal injections:

Both our studies show that DRSS can improve with no reperfusion. This invalidates reliance only on DRSS for grading nonproliferative diabetic retinopathy after intravitreal injections. However, changes in new vessels in proliferative diabetic retinopathy cases were visible in all imaging modalities.

B. OCT-A is superior to FA for evaluating nonperfusion:

All nonperfusion areas detected on UWF-FA were also detected on WF OCT-A images, while in nearly 1/3 of boxes (29% at M0 and 39% at M3), WF-OCTA exhibited some extra areas of nonperfusion compared to UWF-FA. Apparent changes in FA brightness of the background in the areas of nonperfusion could mislead to the diagnosis of reperfusion when WF OCT-A found no reappearance of capillaries. WF OCT-A can cover an area larger than 7 standard field 30-degree color fundus photographs (ETDRS photos) but not the whole area covered by UWF-FA. Then this latter remains still useful for examining areas not reached by WF OCT-A.

References

1. Ip MS, Domalpally A, Sun JK, Ehrlich JS. Long-term effects of therapy with ranibizumab on diabetic retinopathy severity and baseline risk factors for worsening retinopathy. *Ophthalmology* 2015; 122(2):367-374.

2. Writing committee for the Diabetic Retinopathy Clinical Research Network: Gross JG, Glassman AR, Jampol LM, et al. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA*. 2015; 314(20):2137-2146.

3. Wubben TJ, Johnson MW; Anti-VEGF Treatment Interruption Study Group. Anti-VEGF therapy for diabetic retinopathy: consequences of inadvertent treatment interruptions. *Am J Ophthalmol*. Epub ahead of print 2019 Mar 13. doi: 10.1016/j.ajo.2019.03.005.

4. Bonnin S, Dupas B, Lavia C, et al. Anti-vascular endothelial growth factor therapy can improve diabetic retinopathy score without change in retinal perfusion. *Retina* 2019; 39(3):426-434.

5. Couturier A, Rey PA, Erginay A, et al. Swept-source wide-field OCT-angiography versus ultra-wide-field fluorescein angiography assessments of retinal non-perfusion in diabetic retinopathy and edema treated with anti-VEGF. *Ophthalmology*. In press.

Treatment of Centrally Involved Diabetic Macular Edema With Better Vision: Protocol V

Jennifer K Sun MD

NOTES

The Role of Steroids in Diabetic Macular Edema

Anat Loewenstein MD

I. Is There a Role for Steroids in Diabetic Macular Edema (DME)?
   A. Anti-VEGF is most frequent first-line treatment for DME.
   B. The pathogenesis of ME and steroids
   C. Persistent edema after anti-VEGF; duration and extent of edema and association with VA results

II. Possible Role for Steroids
   A. Steroids for noncompliant patients
   B. Steroids during pregnancy
   C. Steroids in case of stroke?
   D. Steroids and chronic edema
   E. Steroids and intraretinal lipids
   F. Steroids and pseudophakia

III. DRCR.net Protocol U Results: How Will They Affect DME Management?

Selected Readings

1. Bressler NM, Beauliu WT, Glassman AR, et al; for the Diabetic Retinopathy Clinical Research Network. Persistent macular thickening following intravitreous aflibercept, bevacizumab, or ranibizumab for central-involved diabetic macular edema with vision impairment: a secondary analysis of a randomized clinical trial. *JAMA Ophthalmol*. 2018; 136(3):257-269.
2. Mishra SK, Gupta A, Patyal S, et al. Intravitreal dexamethasone implant versus triamcinolone acetonide for macular oedema of central retinal vein occlusion. *Int J Retin Vitr*. 2018; 4(13).
3. Mehta H, Fraser-Bell S, Yeung A, et al. Efficacy of dexamethasone versus bevacizumab on regression of hard exudated in diabetic maculopathy: data from the BEVORDEX randomised clinical trial. *Br J Ophthalmol*. 2016; 100(7):1000-1004.
4. Gonzalez VH, Campbell J, Holekamp NM, et al. Early and long-term response to anti-vascular endothelial growth factor therapy in diabetic macular edema: analysis of Protocol I data. *Am J Ophthalmol*. 2016; 172:72-79.
5. Maturi RK, Glassman AR, Liu D, et al; for the Diabetic Retinopathy Clinical Research Network. Effect of adding dexamethasone to continued ranibizumab treatment in patients with persistent diabetic macular edema: a DRCR Network Phase 2 randomized clinical trial. *JAMA Ophthalmol*. 2018; 136(1):29-38.

Results of a Phase 1 Study of Near Infrared Photobiomodulation of Diabetic Macular Edema

Mark Cedric Gillies MD PhD

Introduction

VEGF inhibitors can be extremely effective for diabetic macular edema (DME), but they usually need to be injected many times over several years before the disease stabilizes and they may not be freely available in many parts of the world with high prevalences of poorly controlled diabetes. Photobiomodulation (PBM) therapy has recently emerged as a potential treatment for a variety of conditions of the central nervous system, including the retina. Tissue is exposed to a low-intensity light at wavelengths ranging from far red to near-infrared (NIR; 600 to 1000 nm).

Design

Open-label dose escalation clinical trial

Participants

Participants with center-involving DME and visual acuity between 20/30 and 20/200

Methods

Since light emitting diode (LED)-delivered PBM may be associated with random scattering of incoherent irradiation that is variably filtered and absorbed by ocular structures, NIR therapy was performed with a custom-built NIR laser (Ellex Integer) that had a central masked area of a 1.0-mm diameter within the 4.5-mm diameter treatment zone. Participants were allocated sequentially at 2 clinical sites in Australia, Sydney Eye Hospital and Royal Adelaide Hospital, to Group 1, receiving 25 mW/cm^2; Group 2, 100 mW/cm^2; or Group 3, 200 mW/cm^2 each for 90 seconds. Twelve treatments were administered over 5 weeks.

Main Outcome Measures

The primary endpoint was the central macular thickness (CMT) change from baseline to 2 and 6 months. Secondary outcomes included BCVA assessed on a logarithm of minimal angle of resolution (logMAR) chart and proportion of eyes that required rescue treatment with a VEGF inhibitor over 6 months.

Results

Seven eyes were allocated to each group. The mean baseline CMT of the 3 groups ranged from 395 to 455 µm, while VA ranged from 64.3 to 68.8 letters. There was a modest overall reduction in mean (SD) CMT at month 2, from baseline of –19.4 (31.7) µm ($P < .01$), which was more pronounced at month 6 (–69.8 [35.7] µm, $P < .01$) even though no treatments were given between month 2 and month 6. There was a significantly greater reduction in CMT in Groups 2 and 3 than in Group 1 at month 6. BCVA of all groups combined improved from baseline to month 2 by a mean (SD) of 4.0 (7.1) letters ($P = .02$) but, unlike the effect on CMT, this was not sustained at 6 months. Rescue standard of care treatment was administered in 5 eyes: 3 from Group 1 (43%), 2 from Group 2 (293.%), and none from Group 3.

Discussion

We found anatomical evidence of efficacy of PBM for DME in this dose escalation study. There was an overall dose-dependent reduction in CMT at 6 months following NIR laser therapy. The groups receiving higher-power NIR laser (100 mW/cm^2 and 200 mW/cm^2) had greater reduction of CMT, which was comparable to CMT reduction reported for eyes treated with conventional laser photocoagulation for DME. There were also no eyes within Group 3 (highest power application) that required rescue treatment with standard of care, suggesting that 200 mW/cm^2 NIR laser was the most efficacious of the 3 doses we tested.

Few other clinical trials have reported the effects of NIR on DME in the clinical setting, with much of the literature focused on in vitro and animal disease models. A similar 20% reduction in macular thickness to what we observed was reported in a small series of patients who underwent NIR treatment with non–center involving DME.

More research is warranted to evaluate the potential benefits of NIR laser for DME. One question is whether it can be used to reduce the requirement intravitreal injections of VEGF inhibitors, which is the current first-line treatment. Twelve administrations of NIR laser at 90 second exposure was applied over 5 weeks in this study, resulting in sustained anatomical resolution of DME up to 6 months in many eyes. No significant adverse events were noted in this study even when the NIR laser was applied at its highest power. Further research is also warranted to assess the long-term effects of PBM, as well as to determine the interval for additional treatments. A strength of this study is that NIR laser was administered in a standardized way in a formal clinic setting using a laser. LEDs, which is how PBM has often been administered in previous studies, may have a role in PBM in future, but the early clinical trials will produce better and more accurate outcomes data if the dosage is precisely controlled.

Home OCT Monitoring: The Future of AMD Management

Judy E Kim MD

I. AMD Represents an Enormous Global Disease Burden[1]

A. 200 million affected by 2020

B. 300 million by 2040

II. The Burden of Management Is Equally Enormous and Has Profound Socioeconomic Implications

A. Frequent visits with OCT imaging (direct health-care costs, time costs, lost wages costs for caregivers) combined with lost GDP due to unemployment was estimated to have a macroeconomic impact of $7.5B in 2012.[2]

B. Frequent anti-VEGF treatments (direct health-care costs, recovery time costs)

C. Anti-VEGF treatment protocols have significantly increased direct health-care costs with estimates.[3]

III. Home-Based OCT Monitoring Could Reduce Health-Care Costs Associated With AMD

A. Reduce treatment-not-needed patient surveillance visits (saving direct health-care, time, and lost wage costs); patient visits only when treatment is necessary

B. Potentially enhance treat-and-extend (T&E) management strategies (further reducing costs)

IV. Clinical Need for Home-Based OCT Monitoring

A. VA outcomes falling short of the VA outcomes in pivotal studies

B. Patients being undertreated, or non-optimally treated; need for personalized injection regimen

Initially, the "on-label" monthly or bimonthly treatment evolved to monthly or bimonthly p.r.n. The burden of frequent visits, ongoing decision making, and lack of predictability in the logistics and authorization of the drugs led to implementation of T&E. However, patients are still arriving to the clinic 4-5 times/year and are often treated with a dry macula, and T&E is limited by the longest extension of ~12 weeks due to patient's unpredictable variability.

C. Unknown dynamic knowledge about a given drug's treatment response on a day-to-day basis

D. The implementation of the upcoming longer-acting drugs must be able to handle the unpredictable variability in treatment response among individuals.

V. Home-Based OCT System Requirements

A. Self-installed and operated OCT in home environment by elderly patient

B. Low-cost device, affordable for a single user in a subscription model (use as long as you need, no major investment by the patient)

C. Reliable transmission of large files at low cost

D. Imaging quality sufficient for identification of small amounts of intra- and subretinal fluid (specific "fluid finder" design)[4]

E. Automated analysis that can process a large number of images transmitted daily and provide high-quality fluid classification and quantification over time

F. Seamless integration of the testing results and notifications into clinic systems and workflow, from prescription to alerts, report and interfaces

G. Infrastructure to handle large numbers of patients, including on-boarding, training, tech support, compliance management, and alerts management

H. A viable market access and business model

VI. Notal OCT V2.5 Is a Self-operated OCT for Use by Patients at Home

A. Spectral domain OCT

B. Meets ANSI laser safety standard; evaluated and validated for all required safety parameters

C. Findings from a study performed to compare detection rates by standard office-based OCT and the Notal OCT V2.5 for intraretinal and subretinal fluid in eyes with AMD will be presented.

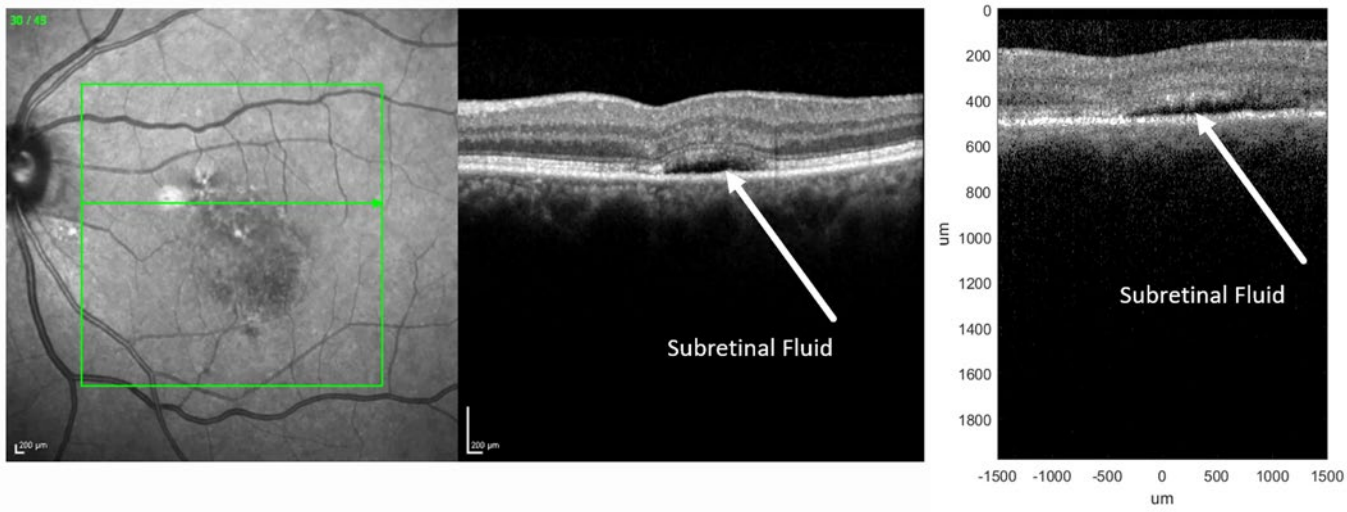

Figure 1. A small pocket of subretinal fluid is evident in images captured by Heidelberg Spectralis and NOTAL-OCT V2.5.

VII. Key Message

Notal OCT V2.5 meets the requirements of patient self-operation and image quality necessary to make home OCT monitoring a reality in the near future.

References

1. Wong WL, Su X, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health*. 2014; 2:e106-116.
2. Schumier J, Levine J. Economic impact of progression of age-related macular degeneration. *US Ophth Review*. 2013; 6(1):52-57.
3. Day S, Acquah K, Lee PP, Mruthyunjaya P, Sloan FA. Medicare costs for neovascular age-related macular degeneration, 1994-2007. *Am J Ophthalmol*. 2011; 152:1014-1020.
4. Chakravarthy U, Goldenberg D, Young G, et al. Automated identification of lesion activity in neovascular age-related macular degeneration. *Ophthalmology* 2016; 123(8):1731-1736.

Toward Robotic Vitreoretinal Surgery

Jean-Pierre Hubschman MD

Robotic systems have found widespread use across many surgical applications due to their increased precision, higher maneuverability, and improved visualization over traditional surgical techniques. In 2012, the da Vinci Surgical System (Intuitive Surgical, Inc.) accounted for approximately 450,000 surgical procedures performed, including surgeries in the fields of gynecology, urology, and general surgery. However, despite the advance of robotic systems into surgical practice, the adoption of robotic systems into vitreoretinal surgery has lagged behind. The delayed adoption can be attributed to the unique advantages of intraocular ophthalmic surgery: the direct 3-dimensional and high-magnification view of intraocular structures, the minimally invasive nature of intraocular instrumentation, and the unhindered maneuverability of surgical instruments.

Robotic surgical systems can help during vitreoretinal surgery primarily through improved feedback and increased precision. Tightly integrated visualization modalities such as digital microscopy and OCT can supersede the current practice of using optical stereo surgical microscopes due to their improved resolution and depth-sensing capabilities. Additional benefits of robotic surgery in ophthalmology include the possibility of more precise surgical manipulations and augmented visual and tactile feedback, as well as system/surgeon collaborative capabilities potentially including full-task automation.

In general, robotic systems specifically designed for intraocular surgical procedures can be categorized into handheld systems and teleoperated systems. In the area of handheld systems, one approach is for the surgical instrument to be simultaneously held by the surgeon and an actively controlled robot arm. By measuring forces applied on the surgical tool, deflections can be corrected by the robot arm and used to provide smooth, tremor-free, precise, and scaled motion of the tool. Another approach is to use a completely handheld device where hand tremor can be reduced by integrated actuators to provide a smooth, scaled motion during surgical procedures.

In the area of teleoperated systems (similar to the Da Vinci Surgical System), the surgeon controls the system through joysticks or other similar input devices. These systems can incorporate motion scaling, tremor compensation, and scaled force feedback to improve the surgeon's natural performance. Such systems are currently evaluated and have demonstrated very promising capabilities. The world's first in-human, robot-assisted retinal vein cannulation and membrane peel have been performed in Europe.

Finally, the ability for a robot to autonomously perform a surgical procedure without input from a human surgeon has also been explored. Semiautomated lens extraction on animal models has been demonstrated by a partially automated surgical robotic system integrated with OCT feedback.

In the future, we may see surgical robots with artificial intelligence and the resulting capacity to make surgical decisions without the input of a human surgeon. More likely, we may see fully automated surgical robots perform a very specific and routine task independently from the surgeon. Such feats will be accomplished with improved feedback from OCT or other image modalities, tightly integrated and registered into the surgical system.

Amniotic Membrane for AMD

Stanislao Rizzo MD

Introduction

AMD represents the leading cause of legal blindness in adults of 65 years or older. Geographic atrophy (GA) and choroidal neovascularization (CNV), the 2 late forms of AMD, lead to severe visual acuity reduction.

AMD is usually characterized by the degeneration of the Bruch membrane and the dysfunction and loss of retinal pigment epithelial (RPE) cells. Nowadays, no effective treatments are available for GA and subretinal fibrosis resulting from advanced CNV.

Replacement of the diseased RPE cells with the in vitro cultured RPE cells as a preformed monolayer on a substitute substrate has been shown to be one of the new potential approaches for late AMD. In this presentation, I would like to discuss the use of a subretinal implant of human amniotic membrane (hAM) in patients affected by late AMD.

Background Observations

I will describe the surgical outcomes of 11 patients affected by late AMD treated with a subretinal implant of human amniotic membrane (hAM). We performed a prospective, interventional pilot study. We included 11 patients affected by late AMD: 5 patients suffered from atrophic AMD and 6 from AMD CNV with a massive subretinal hemorrhage.

Mean preoperative BCVA was 20/2000 (2 logMAR). Mean final BCVA was 20/400 (1.31 logMAR), ranging from 20/2000 to 20/100 (2-0.7 logMAR).

Structural OCT was used at every follow-up to show the correct position of the hAM patch under the retina, the correct adhesion of the retina over the hAM, and the changes in the retinal layers. The hAM plug remained stable under the retina for the entire follow-up period in all 11 cases. Wide-field retinography was used during the entire follow-up to monitor the evolution of hAM plug positioning.

Adaptive optics was performed over the retinal area where the highest functionality was observed, using microperimetry. The images showed a photoreceptor presence over the membrane.

Our technique introduces the use of the hAM plug with good anatomical results and a relatively simple surgical technique, comparable to the more complex existing procedure. The hAM seems to act as a mechanical scaffold/basement membrane, promoting a migration/sliding of pre-existing photoreceptors from the area of the healthy retina through the treated retina overlying the hAM patch. The hAM can produce a wide variety of growth factors, and we could hypothesize that it may work as a potential reservoir of neurotrophic factors, with a potential trophic effect on the residual neuroepithelium.

Multimodal imaging is fundamental to understanding the interaction between the amniotic membrane and the retina. Further studies are necessary to determine the efficacy of this new technique.

Spectral Domain OCT Signs Suggestive of OCT Angiography–Defined Abnormal Choroidal Neovascular Complexes in Eyes With Large Drusen

Robyn H Guymer MBBS PhD

Introduction

Early treatment at the onset of symptomatic exudation from macular neovascularization (MNV) is important for preventing the permanent loss of central vision that results from a delay in treatment. The early detection of nonexudative MNV (NE-MNV) in asymptomatic eyes helps to identify those patients at highest risk of exudation.[1]

Background

Imaging with OCT angiography (OCT-A) has been used to identify NE-MNV, and these have been associated consistently with a low-lying retinal pigment epithelial (RPE) elevation, known as a double layer sign in the context of type 1 NE-MNV.[2-5] However, there is little information about the specific features typical of this sign, which we would also be able to identify on more ubiquitous structural OCTs. We aimed to identify the key structural characteristics of the RPE elevations seen on structural OCT that were suggestive for the presence of NE-MNV and to determine the ability of this sign to predict the presence of OCT-A–defined NE-MNV.

Findings

We defined the shallow, irregular RPE elevation (SIRE) above the Bruch membrane (BM) on spectral domain OCT imaging to predict the presence of NE-MNV. We describe an irregular RPE elevation BM with a greatest transverse linear dimension of at least 1000 µm, a height above BM of less than 100 µm, an irregularity of the RPE layer, and a nonhomogenous internal reflectivity as characteristic features of NE-MNV. These features were then used to perform masked grading of a cohort of 233 eyes with large drusen to determine its predictive values for NE-MNV. Ten percent of eyes were identified with a SIRE; 6 were found to have definite NE-MNVs on OCT-A, and all 6 were positive for the SIRE (sensitivity = 100%). The positive predictive value for a SIRE was 25%, and the negative predictive value was 100%.

Take-home Message

SIRE can be detected on structural OCT imaging and when present indicates a 1 in 4 chance of having detectable NE-MNV on OCT-A imaging. Once NE-MNV is diagnosed, then more frequent follow-up and diligent home monitoring are recommended for early detection of exudation.

References

1. de Oliveira Dias JR, Zhang Q, Garcia JMB, et al. Natural history of subclinical neovascularization in nonexudative age-related macular degeneration using swept-source OCT angiography. *Ophthalmology* 2018; 125(2):255-266.
2. Sato T, Kishi S, Watanabe G, Matsumoto H, Mukai R. Tomographic features of branching vascular networks in polypoidal choroidal vasculopathy. *Retina* 2007; 27(5):589-594.
3. Roisman L, Zhang Q, Wang RK, et al. Optical coherence tomography angiography of asymptomatic neovascularization in intermediate age-related macular degeneration. *Ophthalmology* 2016; 123(6):1309-1319.
4. Carnevali A, Cicinelli MV, Capuano V, et al. Optical coherence tomography angiography: a useful tool for diagnosis of treatment-naive quiescent choroidal neovascularization. *Am J Ophthalmol.* 2016; 169:189-198.
5. Shi Y, Motulsky EH, Goldhardt R, et al. Predictive value of the OCT double-layer sign for identifying subclinical neovascularization in age-related macular degeneration. *Ophthalmol Retina.* 2019; 3(3):211-219.

Risk Factors for Geographic Atrophy Progression Secondary to AMD

Frank G Holz MD

Background

Geographic atrophy (GA) due to AMD leads to progressive and irreversible loss of visual function. GA is estimated to affect approximately 5 million globally, and its prevalence increases exponentially with age.[1,4] GA is defined by the presence of sharply demarcated atrophic lesions of the outer retina, resulting from loss of photoreceptors, retinal pigment epithelium (RPE), and underlying choriocapillaris. The term "complete RPE and outer retinal atrophy (cRORA)" has recently been introduced by the CAM group and is distinguished from "incomplete RPE and outer retinal atrophy (iRORA)."[10] GA typically appears first in the perifoveal macula, initially sparing the foveal center but over time expanding and coalescing to include the fovea. Although the kinetics of GA progression are highly variable among individual patients, a growing body of evidence suggests that specific characteristics are important in predicting disease progression and outcomes.

Geographic Atrophy Progression

Overall, GA progression rates reported in the literature for total study populations range from 0.53 to 2.6 mm^2/year (median: ~1.78 mm^2/year).[1,4,6,9] Measurement of lesion size has been primarily based on fundus photography and fundus autofluorescence (FAF) imaging.[5] Potentially prognostic for an individual's progression rate are lesion features in the affected (Figure 1) as well as the fellow eye (Figure 2).[1] Genetic, environmental, and demographic factors may also contribute.

Because BCVA does not correspond directly to GA lesion enlargement due to foveal sparing, alternative assessments are being explored to capture the relationship between anatomic progression and visual function decline, including microperimetry, low-luminance visual acuity, reading speed assessments, and patient-reported outcomes. Understanding GA progression and its individual variability is critical in the design of clinical studies, in the interpretation and application of clinical trial results, and for counseling patients on how disease progression may affect their individual prognosis.

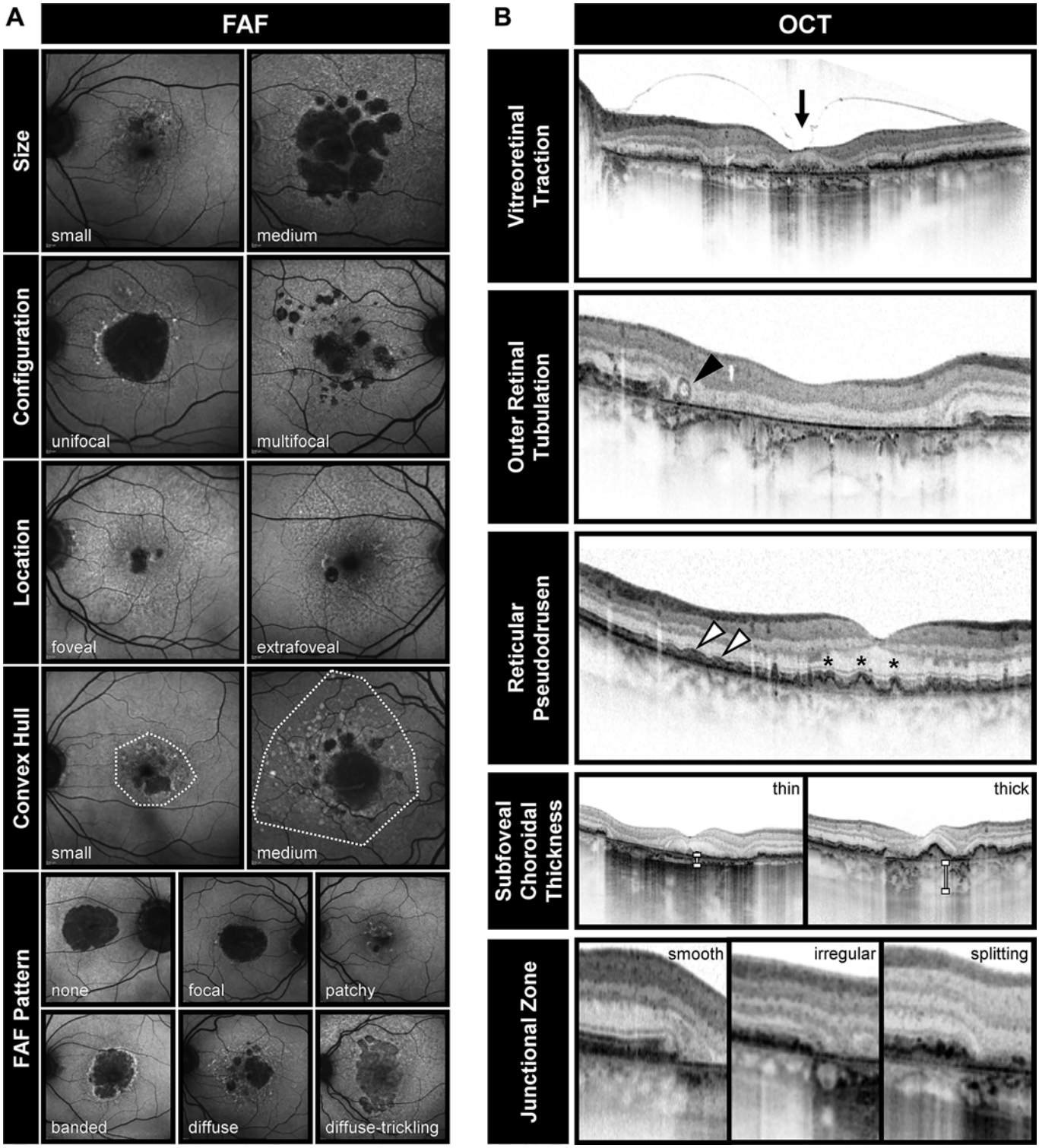

Figure 1. Lesion features associated with progression of geographic atrophy (GA). Lesion features on (A) fundus autofluorescence and (B) OCT. Dotted line: extent of convex hull; black arrow: vitreoretinal traction; black arrowhead: outer retinal tubulation; white arrowheads: reticular pseudodrusen; asterisks: soft drusen; vertical bar: choroidal thickness.[1]

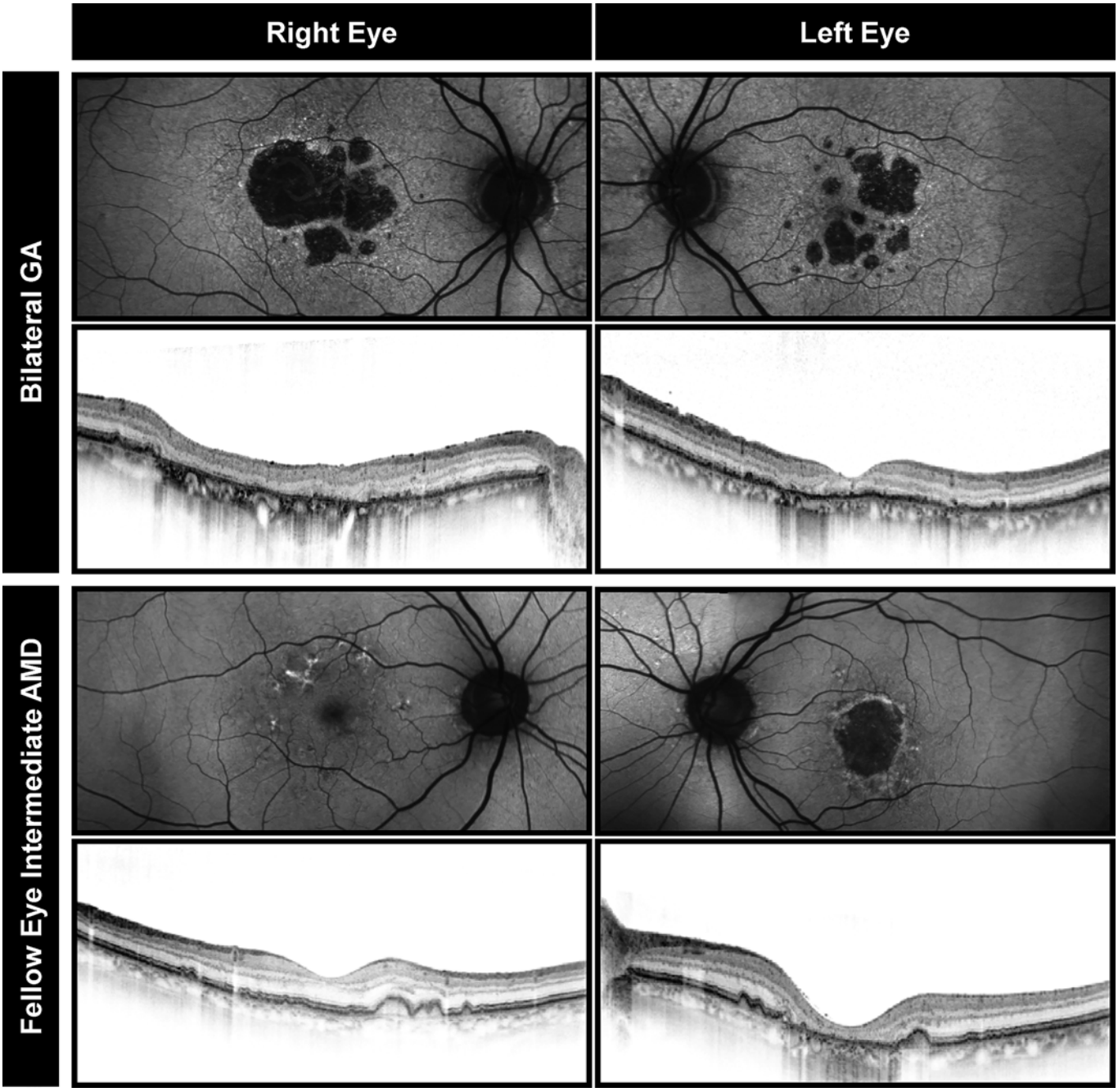

Figure 2. Fellow eye features associated with geographic atrophy (GA) progression rate in the affected eye. Fundus autofluorescence and OCT images from left and right eyes of the same patient. Top, bilateral GA; both eyes are at risk for a relatively higher rate of GA lesion progression. Bottom, geographic atrophy in the affected eye (left) and intermediate AMD in the fellow eye (right); the affected eye is at risk for a relatively lower rate of GA lesion progression.[1]

Lesion Features and Specific Characteristics of the Affected Eye

Lesion size

Baseline GA lesion size is consistently associated with progression; smaller baseline lesion size is associated with lower progression rates. For example, in the Fundus Autofluorescence in Age-related Macular Degeneration (FAM) study, the median progression rate of the lowest baseline size quartile (0.74 mm^2/year for lesions < 1 DA = 2.54 mm^2) was significantly lower than that of larger lesion quartiles (mm^2/year, 1–3 DAs: 1.56 mm^2/year; 3–5 DAs: 1.80 mm^2/year; 5–10 DAs: 1.88 mm^2/year).[3] Studies may report progression rates normalized for baseline lesion size, using the square-root transformation or other mathematical strategies. When applied to the AREDS data set, the association between baseline lesion size and progression rate was no longer significant.

Lesion location

Extrafoveal GA lesions progress faster than foveal lesions. In the Geographic Atrophy Progression (GAP) study, extrafoveal lesions progressed at significantly greater rates than foveal

lesions (2.05 vs. 1.28 mm^2/year, respectively; $P = 0.001$). An analysis of directional progression kinetics among FAM study patients with baseline foveal sparing also revealed that lesion progression toward the periphery was 2.8-fold faster than progression toward the fovea (square-root transformation: 0.319 vs. 0.116 mm/year, respectively).

Lesion shape-descriptive factors: lesion focality, perimeter, and circularity

Eyes with multifocal lesions have GA enlargement rates significantly higher than eyes with unifocal lesions. To quantify this, a circularity index was proposed based on GA lesion perimeter and deviation from circularity. Eyes with the lowest circularity index (ie, lesions deviating most from a circle) were generally multifocal and had higher progression rates than eyes with higher GA circularity index.[8]

Fundus autofluorescence patterns and extent of abnormal fundus autofluorescence

In most eyes, the hypoautofluorescent patches signifying GA lesions are surrounded by varying degrees of hyperautofluorescence, particularly at junctional regions of atrophy. The FAM study investigated the correlation between FAF hyperautofluorescence patterns and GA progression rates as its primary objective.[3] The FAF patterns were classified as none, focal, banded, patchy, or diffuse; diffuse patterns were further categorized as reticular, branching, fine-granular, fine-granular with peripheral punctate spots, or trickling. The GA progression rate was associated with FAF patterns, with the lowest observed in eyes with no or focal patterns and the highest with banded or diffuse patterns. Eyes with the diffuse-trickling pattern represented a subgroup with particularly rapid progression. This relationship between FAF patterns and GA progression rate has been replicated in other cohorts.

GA progression rates have been positively correlated with the extent of hyperautofluorescence surrounding the lesion, defined as rim-area focal hyperfluorescence or as the convex hull (the convex polygon outlining the increased FAF area surrounding the lesion).

Junctional zone features

Structural abnormalities at the junctional zone of atrophy on OCT, including irregular RPE elevations, splitting of the band corresponding to the RPE–Bruch membrane complex, and increased inner nuclear layer thickness, are associated with faster progression rates compared with lesions with smooth margins. Splitting of the RPE–Bruch membrane complex band is also seen in eyes with the rapid-progressing diffuse-trickling phenotype seen on FAF. These features correlate with hyperautofluorescent areas on FAF and may reflect the presence of excessive basal laminar deposits detectable once a critical vertical extension of extracellular material is reached.

Ellipsoid zone disruption

The area of ellipsoid zone disruption on OCT may predict the location of future GA progression, but not progression rate. In a study assessing the ellipsoid zone using en face OCT, 43% of eyes demonstrated a pattern of disruption outside the baseline GA lesion that predicted the 1-year location of GA progression.

Outer retinal tubulations

Outer retinal tubulations are branching tubular structures in the outer nuclear layer oriented parallel to en face OCT scans, appearing as circles on cross-sectional scans. Both the presence and absence of outer retinal tubulations were reported with greater GA enlargement rates; the reason for this conflict is unclear and requires further study.

Choroidal thickness

Reduced subfoveal choroidal thickness correlated with higher progression rates in some studies. In addition, the fast-progressing diffuse-trickling FAF pattern demonstrates a significantly thinner choroid than non–diffuse trickling phenotypes. Overall, eyes with GA have reduced subfoveal choroidal thickness compared with age-matched healthy eyes.

Vitreomacular traction

Vitreomacular traction on OCT is associated with GA progression. Mechanical stress of vitreoretinal traction may affect the natural history of GA; structural distortion of the RPE layer has been hypothesized.

Reticular pseudodrusen

Eyes with GA have a high prevalence of reticular pseudodrusen, which correlate with subretinal drusenoid deposits anterior to the RPE layer on OCT and histopathology. Their presence strongly associates with the progression of intermediate AMD to GA but might not correlate with GA lesion progression rates. Reticular pseudodrusen regression is associated with outer retinal atrophy development in some eyes and may predict future locations of GA development. Reticular pseudodrusen are also associated with the development of multifocal lesion configurations, which progress faster than unifocal configurations.

Choriocapillaris flow impairment

Flow voids on OCT angiography are thought to indicate choriocapillaris flow impairment. Recent observations suggest that GA lesion growth correlates with choriocapillaris flow impairment around the atrophic lesions.[7]

Coexistence of type 1 CNV

Recent observations indicate that the presence of quiescent and exudative type 1 CNV is associated with a reduced overall and localized RPE-atrophy progression. This may highlight the potential protective effect of CNV on the RPE and overlying neurosensory retina.

Fellow Eye Characteristics

The presence of GA in 1 eye is a strong predictor of future GA in the second eye. Overall, intereye progression rates are highly correlated among patients with bilateral GA, although there is some individual variability. Fellow-eye disease status also associates with progression; GA progresses at greater rates when the fellow eye has GA (bilateral GA), lower rates when the fellow eye has early/intermediate AMD, and intermediate rates when the fellow eye has choroidal neovascularization.

Genetic, Environmental, and Demographic Factors

Although many studies have identified genetic, environmental, and demographic characteristics associated with GA development, evidence for their effect on GA progression is sparse. No consistent demographic or environmental factors have been linked to GA progression rate, including age, gender, hypertension, or diabetes. Smoking status predicted faster GA progression in the Blue Mountains Eye Study and Multicenter Group on AMD cohorts, but not in FAM or AREDS.

There is strong evidence for a role for genetics in the development of advanced AMD. The largest genome-wide association study to date identified 52 variants in 34 loci involved in the complement cascade, lipid metabolism, extracellular matrix remodeling, and other pathways, nearly all of which confer a similar risk of neovascular AMD and GA.

In contrast, no single nucleotide polymorphism examined has been consistently linked to GA progression rate. Of note, *ARMS2*_rs10490924 was significantly associated with increased GA progression in the AREDS and AREDS+FAM combined cohorts, but not in the FAM cohort alone. Single nucleotide polymorphisms in *C3*, *CFH*, *CFI*, and *CFB* have also been linked to GA progression, but the results have not been replicated.

In a recent study by Grassmann et al, 935 patients with longitudinal GA progression data were analyzed to determine the contribution of common genetic variants to GA lesion growth.[2] Two gene loci with conservative genome-wide significance were identified. Each minor allele of the genome-wide associated variants increased the GA growth rate by a mean of about 15%, or 0.05 mm per year. Gene prioritization within each locus suggested the protein arginine methyltransferase 6 gene (PRMT6) and the lanosterol synthase gene (LSS) as the most likely progression-associated genes.

Additional large studies with appropriate controls for potential confounders are needed to confirm these findings. To this end, several ongoing interventional and observational studies are prospectively evaluating potential effects of genetic factors on GA progression.

References

1. Fleckenstein M, Mitchell P, Freund KB, et al. The progression of geographic atrophy secondary to age-related macular degeneration. *Ophthalmology* 2018; 125(3):369-390.
2. Grassmann F, Harsch S, Brandl C, et al. Assessment of novel genome-wide significant gene loci and lesion growth in geographic atrophy secondary to age-related macular degeneration. *JAMA Ophthalmol*. Epub ahead of print 2019 May 23. doi: 10.1001/jamaophthalmol.2019.1318.
3. Holz FG, Bindewald-Wittich A, Fleckenstein M, Dreyhaupt J, Scholl HP, Schmitz-Valckenberg S; FAM-Study Group. Progression of geographic atrophy and impact of fundus autofluorescence patterns in age-related macular degeneration. *Am J Ophthalmol*. 2007; 143(3):463-472.
4. Holz FG, Strauss EC, Schmitz-Valckenberg S, van Lookeren Campagne M. Geographic atrophy: clinical features and potential therapeutic approaches. *Ophthalmology* 2014; 121(5):1079-1091.
5. Holz FG, Sadda SR, Staurenghi G, et al; CAM Group. Imaging protocols in clinical studies in advanced age-related macular degeneration: recommendations from Classification of Atrophy Consensus Meetings. *Ophthalmology* 2017; 124(4):464-478.
6. Sunness JS, Margalit E, Srikumaran D, et al. The long-term natural history of geographic atrophy from age-related macular degeneration: enlargement of atrophy and implications for interventional clinical trials. *Ophthalmology* 2007; 114(2):271-277.
7. Nassisi M, Baghdasaryan E, Borrelli E, Ip M, Sadda SR. Choriocapillaris flow impairment surrounding geographic atrophy correlates with disease progression. *PLoS One*. 2019; 22;14(2).
8. Pfau M, Lindner M, Goerdt L, Thiele S, et al; Fundus Autofluorescence in Age-Related Macular Degeneration Study Group. Prognostic value of shape-descriptive factors for the progression of geographic atrophy secondary to age-related macular degeneration. *Retina*. Epub ahead of print 2018 May 16. doi: 10.1097/IAE.0000000000002206.
9. Schmitz-Valckenberg S, Sahel JA, Danis R, et al. Natural history of geographic atrophy progression secondary to age-related macular degeneration (Geographic Atrophy Progression Study). *Ophthalmology* 2016; 123(2):361-368.
10. Sadda SR, Guymer R, Holz FG, et al. Consensus definition for atrophy associated with age-related macular degeneration on OCT: classification of atrophy report 3. *Ophthalmology* 2018; 125(4):537-548.

The Role of Neuroprotection in Retinal Diseases

Baruch D Kuppermann MD PhD

I. Apoptosis: Cell Suicide

A. Normal process of genetically programmed cell death that destroys cells that are injured or unneeded

B. Apoptotic cell morphology

1. Shrinkage of cellular nucleus and cytoplasm
2. Chromatin condensation
3. Formation of apoptotic bodies
4. Internucleosomal DNA fragmentation

C. Debris from apoptotic cells is eliminated through phagocytosis; no inflammatory response.

D. Normally an important homeostatic function

1. Excessive or uncontrolled apoptosis is implicated in the pathogenesis or poor outcome of many ocular diseases, including glaucomatous optic neuropathy, diabetic macular ischemia, chronic macular edema, retinitis pigmentosa, retinal detachments, and geographic atrophy (GA).
2. Apoptosis also implicated in CNS diseases such as Alzheimer and Parkinson diseases.

II. Cell Death Signals

Cell death signals include the following:

A. Apoptosis: programmed cell death

B. Glutamate excitotoxicity/NMDA receptor activation

C. Intracellular Ca++

D. Caspases

E. Mitochondrial cytochrome c leakage

F. Expression of apoptosis-promoting genes (eg, *bax*)

G. Underexpression of apoptosis-inhibitory genes (eg, *bcl-2, bcl-xL*)

H. Inflammatory cytokines (eg, TNFα, interleukins)

I. Nitric oxide and reactive oxygen species (free radicals)

III. Cell Survival Signals

Cell survival signals include the following:

A. Neurotrophins, or growth factors (eg, CNTF, BDNF, bFGF)

B. Expression of apoptosis-suppressing genes (eg, *bcl-2, bcl-xL*)

C. Endogenous antioxidants (eg, glutathione, catalase, SOD)

D. Adrenergic alpha2-receptor–mediated pathways (eg, *bcl-2, bcl-xL*)

IV. Stopping Retinal Neuronal Cell Death Is a Balancing Act

A. In normal eyes, various factors promote either the survival or death of retinal neurons and photoreceptors.

B. Retinal cell viability depends on balance between cell survival and death signals.

C. The goal of neuroprotective therapy is to tip the balance in favor of cell survival.

1. Block cell death signals
2. Enhance cell survival signals

V. Neuroprotection for Retinal Disease

A. There is a significant unmet need for neuroprotection in posterior segment diseases, including diabetic macular ischemia, chronic macular edema, retinal detachment, GA, and retinitis pigmentosa.

B. Multiple potential pathways merit exploration as targets for neuroprotection.

1. Brimonidine, a selective α-2 receptor agonist
2. CNTF (ciliary neurotrophic factor)
3. Memantine (NMDA antagonist)
4. Corticosteroids
5. Complement inhibition
6. Integrin peptide inhibition
7. Stem cell neurotrophic products

VI. Geographic Atrophy: A Significant Unmet Medical Need

There are no approved treatments for geographic atrophy.

A. AMD is the primary cause of blindness and visual disability for adults > 60 years of age in the developed world.[1] GA accounts for one-third of late-stage AMD.[2]

B. Prevalence of GA in the United States is estimated at ~650,000 individuals over the age of 80, representing 6.9%.[3]

VII. Brimonidine: Evidence of Cyto/Neuroprotective Effects From Alpha 2 Receptor Antagonism

A. In vitro, cytoprotective effects have been demonstrated in retinal pigment epithelial and Müller cells.

B. In vivo, cyto/neuroprotective effects have been demonstrated across a variety of models of retinal disease.

C. In humans, topical use of brimonidine (as compared with a β-blocker) prevented visual field loss in glaucoma patients, with similar degree of IOP lowering in the Low-Pressure Glaucoma Treatment Study.

D. Brimonidine drug delivery system (Brimo DDS) investigational product; generation 1 used in Phase 2a Study 190342-032D.

1. Formulated as a biodegradable polymer that contains brimonidine
2. Doses of 132 µg (n = 49) and 264 µg (n = 41) brimonidine (200-µg and 400-µg brimonidine tartrate) vs. sham (n = 23)
3. Administered via intravitreal injection using a 22-gauge needle and proprietary applicator system
4. Drug slowly diffuses out of implant into vitreous humor.
5. Polymer biodegrades over several months; injected at baseline and at month 6, patients followed for 24 months with primary endpoint at 12 months
6. ClinicalTrials.gov identifier: NCT00658619
7. Key inclusion criteria for study eye: GA lesion area at baseline between 2.02 and 32.28 mm^2 and BCVA of 35-70 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (20/200 – 20/40 Snellen equivalent)
8. Primary endpoint: change in GA lesion area[2] from baseline
9. Brimo DDS results summary: Efficacy
   a. Overall, the study was not powered to show statistically significant differences between treatment groups.
   b. Mean GA area growth was observed to be significantly lower in both treated groups at month 3.
   c. Efficacy trends maintained at month 24.
   d. Reductions in GA progression rate of 18.8% and 27.5% observed at month 12 in the 132- and 264-µg Brimo DDS-treated groups, respectively.
   e. Post hoc analysis on the effective diameter for patients with lesions at mid to high risk of progression (baseline GA lesion area > 9 mm^2) indicated that Brimo DDS 132 and 264 µg reduced GA progression rate by 33.0% and 37.4% at month 12, respectively.
10. Results summary: Safety
    a. Repeat administration of Brimo DDS (Generation 1) had an acceptable safety profile over 24 months.
    b. The majority of treatment-related adverse events were attributed to the injection procedure.

VIII. The Complement System

A. Part of the innate immune system
1. Three main activation pathways (classical, alternative, lectin)
2. Activated by various molecular structures
3. A series of endogenous proteins act as inhibitors to prevent excessive activation and protect host cells.
4. Defend the body from infection
5. Modulate immune and inflammatory responses

B. Complement in dry AMD: inhibition of complement activation
1. Apellis (C3 inhibition)
2. Eculizumab (C5 inhibition)
3. ARC1905 (C5 inhibition)
4. Genentech lampalizumab (complement factor D inhibition)
5. FCFD4514S (TNX-234; factor D inhibition)
6. Replacement of complement factor H

IX. Apellis FILLY Trial Summary

APL-2 complement C3 inhibitor 15 mg given for 12 months either monthly (n = 86), every other month (n = 79), monthly sham (n = 41), or every other month sham (n = 40); patients were followed for 18 months. Efficacy and safety showed:

A. APL-2 inhibits C3 and the downstream effects of the complement cascade.

B. When given monthly or every other month, APL-2 demonstrated statistically significant differences in GA growth over 18 months as compared to sham: 20.4% and 16.3%, respectively (monthly/every other month), compared to sham.

C. Upon discontinuation of APL-2 at month 12, the treatment effect declined.

D. Safety profile was consistent with other IVT injection therapies.

1. APL-2 subjects were at a higher risk of developing neovascular AMD, especially those with ocular history of CNV in the fellow eye.
2. The risk/benefit profile at 18 months supports the decision to initiate a Phase 3 study, now under way (DERBY and OAKS Phase 3 pivotal trials).

X. Integrin Peptide Inhibition

A. Integrins are cell surface receptors.

1. Cell adhesion (structural)
2. Cell signaling (functional)

B. Integrins are upregulated with cellular oxidative stress.

C. Integrins downregulate the extracellular matrix and molecules that activate downstream stress pathways.

D. Integrins are derived from the RGD family, which are one of the most evolutionary conserved cellular patterns of interaction.

E. As of the date of this outline submission, only topline results are available.[4]

1. The primary endpoint of the Phase 2 study was the proportion of subjects with ≥ 8 letters of vision gain with 2 risuteganib injections vs. 1 sham treatment.
2. The trial was a prospective, randomized, double-masked, placebo-controlled, multi-center U.S. study that evaluated the safety and efficacy of risuteganib in patients with intermediate dry AMD.
3. At baseline, 40 patients were randomized to receive either intravitreal 1.0-mg risuteganib or sham injection.
4. At week 16, patients in the risuteganib arm received a second dose of 1.0-mg risuteganib, and patients in the sham arm crossed over and received a single dose of 1.0-mg risuteganib.
5. The primary endpoint was the percentage of the population with ≥ 8 letters ETDRS BCVA gain from baseline to week 28 in the 1.0-mg risuteganib arm vs. from baseline to week 12 in the sham arm.
6. The primary endpoint was prespecified as ≥ 8 letters to account for the variability in visual acuity measurements among patients with intermediate dry AMD.
7. The primary endpoint was met with 48% of patients in the risuteganib arm at week 28 and 7 percent of patients in the sham group at week 12 gaining ≥ 8 letters from baseline (P = .013).
8. Risuteganib was found to be safe, with no reported drug related serious adverse events.
9. Secondary outcomes, including microperimetry, color vision, and low luminance visual acuity, are currently being evaluated; results will be released subsequently.

XI. Stem Cell Neurotrophic Products: Human Retinal Progenitor Cells for Retinitis Pigmentosa

A. Description: Allogeneic progenitor cells (proprietary to jCyte)

B. Biology: *Not* pluripotent; predifferentiated; low immunogenicity; no tumor formation

C. Mechanism of action: Neurotrophic; treats disease, not underlying mutation (non-gene specific)

D. Intravitreal injection (the only cell therapy program using intravitreal injection of an ocular cell type, vs. subretinal)

E. Topical anesthesia

F. No immunosuppression

G. Potentially repeatable: Animal studies on repeat same eye injections showed no complications: fellow eye clinical study is currently ongoing.

H. Retreatment anticipated to be annually or every 18 months

I. No evidence of immune rejection

J. Encouraging safety and efficacy results from Phase 1/2a study

1. Dose escalation study 0.5 M, 1.0 M, 2.0 M, or 3.0 M cells injection in 50 mcL as a single injection, results at 1 year compared to fellow eye with dose response curve noted: 1.38 vs. 1.0 vs. 4.83 vs. 9.0 letters gained at 12 months, respectively
2. Only one serious adverse event reported: Grade 2 migratory pain; initially reported as possibly related to study drug. After considerable evaluation, determined to be unlikely related to study drug.
3. Most adverse events were minor and transient; the only Grade 3 events (1 subject) were visualization of cells in the anterior chamber, reported as "investigations, medical observations normal."

K. Other potential indications include retinal degenerations such as AMD and other retinal dystrophies; retinal vascular diseases such as diabetic retinopathy, ROP, and retinal vascular occlusions; and optic nerve diseases such as glaucoma and optic neuropathies.

XII. Neuroprotection for Retinal Disease: Summary

A. There is a significant unmet need for neuroprotection in posterior segment diseases including diabetic macular ischemia, chronic macular edema, retinal detachment, GA, and retinitis pigmentosa.

B. Multiple potential pathways merit exploration as targets for neuroprotection, including:

1. Brimonidine, a selective α-2 receptor agonist
2. CNTF ciliary neurotrophic factor
3. Memantine (NMDA antagonist)
4. Corticosteroids, particularly dexamethasone
5. Complement inhibition
6. Stem cell neurotrophic products

C. Studies are under way.

References and Selected Readings

1. Wubben TJ, Zacks DN, Besirli CG. Retinal neuroprotection: current strategies and future directions. *Curr Opin Ophthalmol*. 2019; 30(3):199-205.
2. Pietrucha-Dutczak M, Amadio M, Govoni S, Lewin-Kowalik J, Smedowski A. The role of endogenous neuroprotective mechanisms in the prevention of retinal ganglion cells degeneration. *Front Neurosci*. 2018; 12:834.
3. Jin ZB, Gao ML, Deng WL, et al. Stemming retinal regeneration with pluripotent stem cells. *Prog Retin Eye Res*. 2019; 69:38-56.
4. Allegro Ophthalmics announces positive topline vision results of Phase 2 study evaluating risuteganib in patients with intermediate dry age-related macular degeneration. Allegro website. www.allegroeye.com/allegro-ophthalmics-expands-its-anti-integrin-portfolio-with-new-front-of-the-eye-drug-candidate-alg-1007-for-the-treatment-of-dry-eye-disease-3-2-2/. June 4, 2019.
5. Levin LA. Neuroprotection in optic neuropathy. *Asia Pac J Ophthalmol (Phila)*. 2018; 7(4):246-250.
6. Pardue MT, Allen RS. Neuroprotective strategies for retinal disease. *Prog Retin Eye Res*. 2018; 65:50-76.

New Classification for Macular Atrophy

Giovanni Staurenghi MD

An international group of retinal specialists, experts in anatomy and histopathology, and bioengineers called the CAM (Classification of Atrophy Meeting) Group suggested a new approach for the classification of macular atrophy. It was clear that under the name of "macular atrophy" we probably include a series of different pathologies, and the difference in growth and the different preferred location seems not common in all the lesions.[1] The first step was to identify the best method for visualizing the changes.

Autofluorescence images are used to evaluate new pharmaceutical compounds. Lack of retinal pigment epithelium (RPE) is demonstrated by the black area in autofluorescence images. But to identify earlier changes, the group suggested images acquired with spectral domain OCT or swept source OCT.[2]

Based on OCT imaging progression and its correlation with histopathology, a different classification was suggested in an attempt to identify new and early stages of macular atrophy.

Table 1 outlines the definitions and the acronyms of four different stages.

Table 1. Stages of Macular Atrophy

Definitions	Acronyms
Complete RPE and outer retinal atrophy	cRORA
Incomplete RPE and outer retinal atrophy	iRORA
Complete outer retinal atrophy	cORA
Incomplete outer retinal atrophy	iORA

cRORA is defined when the following specific OCT criteria are present[3]:

1. A region of hypertransmission of at least 250 mm in diameter
2. A zone of attenuation or disruption of the RPE of at least 250 mm in diameter
3. Evidence of overlying photoreceptor degeneration
4. Absence of scrolled RPE or other signs of an RPE tear

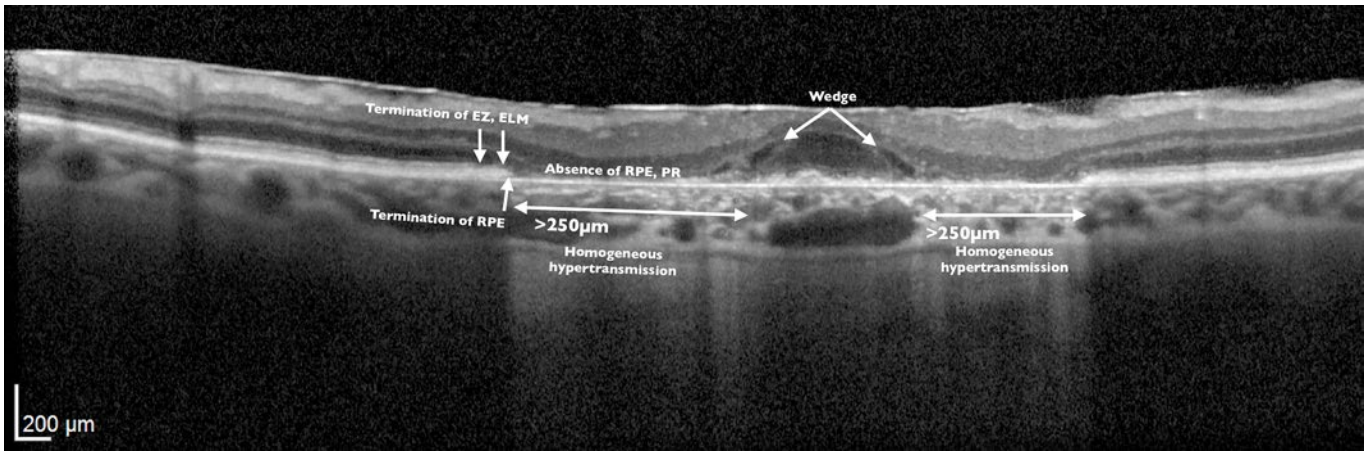

Figure 1.

iRORA is defined as having all of the following 3 OCT features[4]:

1. A region of signal hypertransmission into the choroid
2. A corresponding zone of attenuation or disruption of the RPE
3. Evidence of overlying photoreceptor degeneration, when the definition of cRORA is not met. The term "iRORA" should not be used when there is an RPE tear.

Longitudinal studies confirmed the progression from iRORA to cRORA.

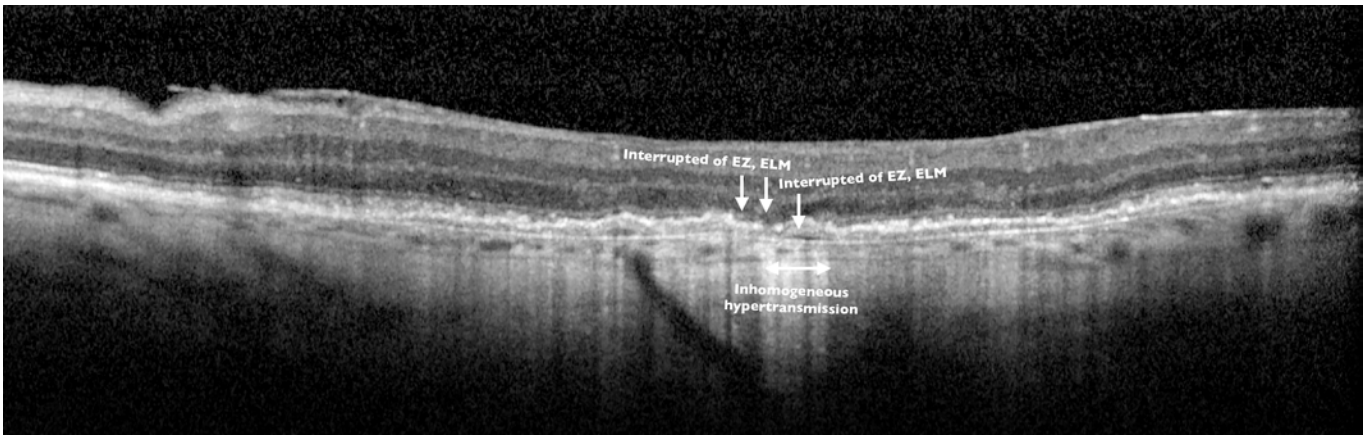

Figure 2.

References

1. Schmitz-Valckenberg S, Sadda S, Staurenghi G, Chew EY, Fleckenstein M, Holz FG; CAM (Classification of Atrophy Meeting) Group. Geographic Atrophy: Semantic Considerations and Literature Review. *Retina* 2016; 36(12):2250-2264.
2. Holz FG, Sadda SR, Staurenghi G, et al; CAM Group. Imaging protocols in clinical studies in advanced age-related macular degeneration: recommendations from Classification of Atrophy consensus meetings. *Ophthalmology* 2017; 124(4):464-478.
3. Sadda SR, Guymer R, Holz FG, et al. Consensus definition for atrophy associated with age-related macular degeneration on OCT: Classification of Atrophy report 3. *Ophthalmology* 2018; 125(4):537-548. Erratum in: *Ophthalmology* 2019; 126(1):177.
4. Guymer RH, Rosenfeld PJ, Curcio CA, et al. Incomplete retinal pigment epithelial and outer retinal atrophy (iRORA) in age-related macular degeneration: CAM report 4. *Ophthalmology*. Under review.

Outcomes of Combined Phaco/ Pars Plana Vitrectomy (Phacovitrectomy) vs. Sequential Surgery

Jennifer I Lim MD

I. Indications for Combined Surgery

A. Retinal/macular disease requiring pars plana vitrectomy (PPV) and concomitant clinically significant cataract. Treatment options = cataract and then PPV, PPV and then cataract surgery, or combined phacovitrectomy. Early on, described by Dr. D. Jackson Coleman in 30 patients.[1]

B. Retinal/macular disease requiring PPV when a lens opacity is present. Cataract is more likely to progress faster to a clinically significant cataract if there is a preop cataract present.

C. Retinal/macular disease requiring PPV with use of intraocular gas tamponade, with/without cataract present. Presence of gas will cause a cataract to develop.

II. Risks and Benefits of Combined Phacovitrectomy vs. Sequential Surgery

A. Benefits of phacovitrectomy

1. Intraoperative factors

a. Visualization of retina, posterior segment improved

b. More complete vitreous base shaving enabled

2. Postoperative factors

a. More rapid visual rehabilitation; reduced recovery time

b. No need for second procedure (cataract surgery); rate of cataract formation is up to 95% at 2 years.

c. Improved quality of life[2]

d. Possibly lower rate of secondary opacification of posterior capsule (PCO)[3]: PCO rate 1 year after cataract surgery was 12.5% (7/56) for phacovitrectomy, 24.2% (8/33) for sequential surgery, and 4.6% (6/130) for control group.

3. Economic factors: 1 procedure with 17%-20% savings to Medicare per procedure[4]

B. Risks of phacovitrectomy

1. Longer duration of surgery with intraoperative risks of 2 procedures

2. IOL calculation inaccuracies

C. Risks of sequential surgery

1. Higher rate of complications with cataract surgery in vitrectomized eyes (posterior capsular rupture[5])

2. Prior PPV factors: undilatable pupil, posterior synechiae, damaged lens capsule, zonular laxity

III. Special Considerations With Phacovitrectomy

A. Effective lens position shifts posteriorly with PPV; refractive index of vitreous is different from aqueous; myopic shift –0.13 to 0.50 D with PPV[6-11]

B. Decreased accuracy of IOL power calculations; IOL movement of 1 mm causes myopia of –1.5 D.[12]

C. Primary capsulotomy may result in anterior chamber gas.

D. Calcification of the Akreos hydrophilic acrylic lens with concomitant PPV[13]

IV. Safety and Anatomic Outcomes of Phacovitrectomy

A. Outcomes of phacoemulsification plus PPV for various retinal conditions

1. 25/27 gauge PPV, Pavlidis et al,[14] Höhn et al[15]

2. Macular hole

a. Muselier et al[16]: At 12 months, closure rates similar; postop BCVA significantly improved in both combined and consecutive surgery groups ($P < .0001$). At 6 months, VA was not significant in consecutive ($P = .06$) but was in combined surgery group ($P < .0001$).

b. Rogers et al[17]: At 1 year, good closure rates and no safety concerns in 57 eyes (no control)

3. ERM

a. Kauffmann et al[18]: Final BCVA associated with age ($P = .040$), duration of symptoms ($P = .025$), initial BCVA ($P = .002$), inner segment/outer segment junction disruption ($P = .010$).

Preoperative 10-point predictive score including these parameters reached 82% sensitivity and 66% specificity. With score > 5, ≥56% chance of recovering 20/20 vs. ≤27% when score was ≤ 5.

b. Yiu et al[20]: Retrospective, comparative case series study of 81 eyes

i. Mean logMAR improved in both groups at 6 months ($P < .001$) and 1 year ($P < .001$); no statistical difference in VA improvement at 6 months ($P = .108$) or 1 year ($P = .094$).

ii. Mean central macular thickness of both groups also significantly decreased after surgery ($P = .002$).

iii. Complication rates (IOP elevation, epiretinal membrane [ERM] recurrence, reoperation) were similar; nonstatistical trends toward greater ERM recurrence ($P = .084$) and need for reoperation ($P = .096$) for combined surgery.

c. Dugas et al[21]: 174 eyes with ERM plus internal limiting membrane removal, combined surgery ($n = 109$) and consecutive surgery ($n = 65$). Similar VA, but faster VA recovery at 12 months for combined.

d. Lim, University of Illinois at Chicago series: 19 phacovitrectomy vs. 8 sequential, with 35 months follow-up. No differences in final VA, OCT reductions in central subfield thickness, or complication rates. Sequential group required cataract extraction at 9.5 months post-PPV. Combo group VA best by month 1 postop.

4. Vitreomacular traction, macular hole, ERM, Savastano et al[19]: No difference in incidence of retinal detachment (RD) ($P = .19$) or cystoid macular edema (CME) ($P = 1.00$) between high-speed 25-gauge PPV phacovitrectomy vs. PPV in pseudophakes

5. Complex vitrectomy

a. Macula-sparing rhegmatogenous RD, Kim et al[22]: Higher PCO, ERM, CME

b. Rhegmatogenous RD, Moon et al[23]: 10% ERM rate

c. Complex vitreoretinal diseases, Sisk et al[24]: Good outcomes in 114 eyes

6. Diabetics

a. Proliferative diabetic retinopathy, Yang et al[25]: Safe and effective, although combined had a higher incidence of fibrinous exudation.

b. Diabetic eyes, Silva et al[26]: Equivalent VA improvement over 4 years after PPV or phacovitrectomy. Visual outcomes and retinopathy progression rates were not significantly different.

c. Proliferative diabetic retinopathy complications requiring PPV, Lahey JM et al[27]: 223 patients (153 vitreous hemorrhage, 58 traction RD, and 12 macular traction)

i. mean 4.3 Snellen lines gained at mean follow-up of 10 months

ii. postop RD, 5%; DME, 12%; CME, 3%; vitreous hemorrhage requiring reop, 11%

B. IOL implants

Single vs. 3-piece IOLs, Leiderman et al[28]: Postop complications similar ($P = .80$): synechiae, 2.7% vs. 5.3%, $P = .61$; pupillary capture, 0.7% and 2.6%, $P = .36$; lens subluxation, 1.4% and 0%, $P > .99$; use of intravitreal tamponade, $P = .67$. Diabetics (56% cohort) vs. nondiabetics ($P = .13$) similar.

V. Visual Acuity Outcomes of Phacovitrectomy Compared With Phacoemulsification

A. Prospective clinical trial, Hamoudi et al[7]

1. 62 phakic eyes with ERM allocated to (1) cataract surgery and subsequent PPV (CAT group), (2) PPV and subsequent cataract surgery (VIT group), or (3) phacovitrectomy (COMBI group)

2. Mean refractive error was a small myopic shift of −0.36 D in all groups 1 month after surgery, decreasing after 12 months to −0.17 D; absolute value of the refractive area range: 0.49-0.68 D after 12 months

3. Higher incidence of CME in the CAT group

4. No significant difference in final refractive error, BCVA, and CST between the groups

5. Four cases (17%) in the CAT group had resolved visual complaints and improved BCVA after cataract surgery, resulting in no need for PPV within the follow-up period.

B. Similar visual and anatomic outcomes to phacoemulsification results

1. Hamoudi et al[7]: Review of 15 series found no difference in visual acuity outcomes; myopic shift found with all 3 options.

2. Hotte et al[8]: Study of 39 macular hole (27.9%), 88 ERM (62.9%), and 13 vitreous floater (9.3%) eyes

a. Retrospective review of 140 eyes

b. −0.31 D for macular holes vs. −0.045 for ERMs plus floaters as a group; use of gas tamponade associated with more refractive error at 1 month. Stable at 3 months.

c. Holladay II results in greater myopic error than SRK/T formula.

d. Preop spherical equivalent and preop axial length were strong predictors of refractive error.

3. von Geest et al[9]: Study of ERM (55%) and macular hole (11%), vitreous floaters, vitreous hemorrhage, and vitreomacular traction
    a. Retrospective comparative case series: 133 phacovitrectomy vs. 132 phacoemulsification
    b. No myopic error found using IOL (PCI) Master and Haigis IOl calculation method
        i. mean errors: –0.06 ± 0.50 phacovitrectomy vs.–0.08 ± 0.47 phacoemulsification, $P = .74$; range NS
        ii. 94.6% vs. 94.9 % achieved final refraction within ± 1.00 D of target by 1 month postop
    c. No differences between groups for indications for PPV, outcomes, use of gas, macular pathology
4. Shi et al[10]: Study of ERM eyes, 50 phacovitrectomy vs. 50 phacoemulsification
    a. No differences for hyperopia, myopia, or astigmatism outcomes: 68%-70% and 68%-76% were within ± 0.50 D of target refraction at 5 months postop.
    b. No CME, endophthalmitis, or hypotony in follow-up period

C. Dissimilar outcome to phacoemulsification

Kim et al[11]: Case control study of ERM eyes, 39 eyes in each group

Combined phacovitrectomy for ERM resulted in significantly more myopic shift than cataract extraction alone, for both A-scan and IOLMaster.

References

1. Coleman DJ. Phakoemulsification with vitrectomy through the pars plana. *Ophthalmic Surg*. 1975;6:95-8.
2. Wang Y, Liang X, Gao M, et al. Vision-related quality of life after pars plana vitrectomy with or without combined cataract surgery for idiopathic macular hole patients. *Int Ophthalmol*. Epub ahead of print 2019 May 29. doi: 10/1007/s10792-019-01124-6.
3. Roh JH, Sohn HJ, Lee DY, et al. Comparison of posterior capsular opacification between a combined procedure and a sequential procedure of pars plana vitrectomy and cataract surgery. *Ophthalmologica* 2010; 224:42-46.
4. Deider MI, Lahey J, Fellenbaum PS. Cost of phacovitrectomy versus vitrectomy and sequential phacoemulsification. *Retina* 2014; 34:1112-1115.
5. Lee JY, Kim KH, Shin KH, et al. Comparison of intraoperative complications of phacoemulsification between sequential and combined procedures of pars plana vitrectomy and cataract surgery. *Retina* 2012; 32:2026-2033.
6. Hamoudi H, La Cour M. Refractive changes after vitrectomy and phacovitrectomy for macular hole and epiretinal membrane. *J Cataract Refract Surg*. 2013; 39:942-947.
7. Hamoudi H, Correll Christensen U, La Cour M. Epiretinal membrane surgery: an analysis of 2-step sequential- or combined phacovitrectomy surgery on refraction and macular anatomy in a prospective trial. *Acta Ophthalmol*. 2018; 96:243-250.
8. Hötte GJ, de Bruyn DP, de Hoog J. Post-operative refractive prediction error after phacovitrectomy: a retrospective study. *Ophthalmol Ther*. 2018; 7:83-94.
9. Van der Geest LJ, Siemerink MJ, Mura M, et al. Refractive outcomes after phacovitrectomy surgery. *J Cataract Refract Surg*. 2016; 42:840-845.
10. Shi L, Chang JS, Suh LH, Chang S. Differences in refractive outcomes between phacoemulsification for cataract alone and combined phacoemulsification and vitrectomy for epiretinal membrane. *Retina*. 2019; 39(7):1410-1415.
11. Kim M, Kim HE, Lee DH, et al. Intraocular lens power estimation in combined phacoemulsification and pars plana vitrectomy in eyes with epiretinal membranes: a case-control study. *Yonsei Med J*. 2015; 56:805-811.
12. Olsen T. Calculation of intraocular lens power: a review. *Acta Ophthalmol Scand*. 2007; 85:472-485.
13. Walker NJ, Saldanha MJ, Sharp JA, et al. Calcification of hydrophilic acrylic intraocular lenses in combined phacovitrectomy surgery. *J Cataract Refract Surg*. 2010; 36:1427-1431.
14. Pavlidis M, Körber N, Höhn F. Surgical and functional results of 27-gauge vitrectomy combined with coaxial 1.8 mm microincision cataract surgery: a consecutive case series. *Retina* 2016; 36:2093-2100.
15. Höhn F, Kretz F, Pavlidis M. Surgical and functional results of hybrid 25-27-gauge vitrectomy combined with coaxial 2.2 mm small incision cataract surgery. *J Ophthalmol*. 2016; 2016:9186351.
16. Muselier A, Dugas B, Burelle X, et al. Macular hole surgery and cataract extraction: combined vs consecutive surgery. *Am J Ophthalmol*. 2010; 150:387-391.
17. Rogers S, Madhusudhana KC, Kang HK, et al. Combined phacovitrectomy for macular hole: long-term results. *Ophthalmic Surg Lasers Imaging*. 2007; 38:452-456.
18. Kauffmann Y, Ramel JC, Lefebvre A, et al. Preoperative prognostic factors and predictive score in patients operated on for combined cataract and idiopathic epiretinal membrane. *Am J Ophthalmol*. 2015; 160:185-192.
19. Savastano A, Savastano MC, Barca F, et al. Combining cataract surgery with 25-gauge high-speed pars plana vitrectomy: results from a retrospective study. *Ophthalmology* 2014; 121:299-304.
20. Yiu G, Marra KV, Wagley S, et al. Surgical outcomes after epiretinal membrane peeling combined with cataract surgery. *Br J Ophthalmol*. 2013; 97:1197-1201.
21. Dugas B, Ouled-Moussa R, Lafontaine PO, et al. Idiopathic epiretinal macular membrane and cataract extraction: combined versus consecutive surgery. *Am J Ophthalmol*. 2010; 149:302-306.
22. Kim KN, Lee HJ, Heo DW, et al. Combined cataract extraction and vitrectomy for macula-sparing retinal detachment: visual outcomes and complications. *Korean J Ophthalmol*. 2015; 29:147-154.
23. Moon H, Sohn HJ, Lee DY, et al. Combined 23-gauge sutureless vitrectomy and clear corneal phacoemulsification for rhegmatogenous retinal detachment repair. *Int J Ophthalmol*. 2015; 8:122-127.

24. Sisk RA, Murray TG. Combined phacoemulsification and sutureless 23-gauge pars plana vitrectomy for complex vitreoretinal diseases. *Br J Ophthalmol*. 2010; 94:1028-1032.

25. Yang Y, Zhang J, Yan H. Comparison of combined and sequential surgery for proliferative diabetic retinopathy: a single surgeon study. *PLoS One* 2014; 9:e108933.

26. Silva PS, Diala PA, Hamam RN, et al. Visual outcomes from pars plana vitrectomy versus combined pars plana vitrectomy, phacoemulsification, and intraocular lens implantation in patients with diabetes. *Retina* 2014; 34:1960-1968.

27. Lahey JM, Francis RR, Kearney JJ. Combining phacoemulsification with pars plana vitrectomy in patients with proliferative diabetic retinopathy: a series of 223 cases. *Ophthalmology* 2003; 110:1335-1339.

28. Leiderman YI, Andreoli MT, Sun B, Dawood S. Pars plana vitrectomy combined with cataract extraction: a comparison of surgical outcomes using single-piece and multipiece foldable intraocular lenses. *Retina* 2015; 35:1059-1064.

Update on Intraoperative OCT

Justis P Ehlers MD

I. Background: Potential Advantages of OCT in the OR
   A. Provides rapid feedback to surgeons
   B. Enhances surgical education
   C. Visualizes acute impact of surgical maneuvers
   D. Improves understanding of pathophysiology of surgical vitreoretinal diseases
   E. Opens door to new surgical interventions and disease management opportunities

II. Device Solutions
   A. Handheld OCT systems
      1. Portable
      2. Versatile imaging in multiple situations
      3. Limited scan repeatability
      4. Lack of tracking
      5. Significant learning curve
   B. Microscope-mounted portable system
      1. Foot pedal control of X-Y-Z translation
      2. Improved stability from microscope mounting
   C. 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
      3. Modeling hole closure speed
   B. Epiretinal membrane: Completion of peel
   C. Therapeutic delivery: Confirmation of optimal therapeutic placement

IV. Novel Approaches to Integrative Technology
   A. Visualization options; various options for feedback
   B. Instrument refining
      1. Optimized optical properties
      2. Enhanced visualization of underlying tissues and instrument profile
   C. Intraoperative OCT software solutions
      1. Pathology-specific segmentation
      2. Surgeon feedback system
   D. New OCT technology

LEAVO vs. SCORE2: A Comparison of 2 CRVO Comparative-Effectiveness Trials for the Treatment of Macular Edema With Anti-VEGF Agents

Barbara Blodi MD

I. LEAVO[1] vs SCORE2[2] Background

A. Based on the variation in disease-specific results from the Comparison of AMD Treatment Trial (CATT) and DRCR Protocol T, it became clear several years ago that there was a need for a comparative effectiveness trial in retinal vein occlusion (RVO).

B. Two Phase 3 CRVO trials were funded nearly simultaneously by National Institute for Health Research (UK) and National Eye Institute (U.S.) to study treatment of macular edema from central RVO with anti-VEGF agents. Enrollment began for both trials in 2014.

C. Similarities and differences between SCORE2 and LEAVO trials are outlined below. (Please note that LEAVO results are based on an ARVO presentation, 2019.[3])

II. Trial Design, Inclusion Criteria, Baseline Data, and Topline Results

See Tables 1-4.

Table 1. LEAVO vs. SCORE2 Clinical Trial Design[4]

	SCORE2	LEAVO
Type of trial	Multicenter randomized noninferiority trial with 5-letter margin	Multicenter randomized noninferiority trial with 5-letter margin
Anti-VEGF agents	2 arms: aflibercept and bevacizumab	3 arms: ranibizumab, aflibercept, and bevacizumab
Primary outcome	Mean change in visual acuity from baseline to month 6	Mean change in visual acuity from baseline to week 100
Injection schedule	• Month 0 to month 5: 6 monthly mandated injections • Months 6 to 11 – Good responders: monthly vs. treat-and-extend – Poor responders: switched to an alternative treatment • Months 12 to 24: treatment per discretion of clinician (off protocol)	• Week 0 to week 12: 4 monthly mandated injections • Weeks 16 and 20: mandated visits with p.r.n. injection • Weeks 24 to 96 – 4 weekly follow-up visits and p.r.n. injection – 8 weekly follow-up visits if "stability" criteria are met (stability is 3 consecutive visits in which retreatment criteria are not met)
Retreatment guidelines	At month 6, retreatment is given for good responders randomized to treat-and-extend based on OCT ≥ 300 µm (≥320 µm if Heidelberg Spectralis) or presence of intraretinal or subretinal fluid	At month 4, no retreatment if VA is ≥ 83. If VA is less than 83, retreatment is given if visual acuity is improving or worsening by 5 letters from last visit or OCT ≥ 320 µm or increased by 50 µm.

Table 2. LEAVO vs. SCORE2 Inclusion Criteria

	SCORE2	LEAVO
RVO type	CRVO and HRVO	CRVO
Macular edema	OCT ≥ 320 µm on Heidelberg or ≥ 300 on Zeiss	OCT CSF ≥ 320 µm
Visual acuity	Between 20/40 and 20/400 (19 to 73 ETDRS letters)	Between 20/32 and 20/400 (19 to 78 ETDRS letters)
Previous anti-VEGF treatment	Allowed if more than 2 months prior to enrollment; approximately 33% of population	None

Table 3. LEAVO vs. SCORE2 Baseline Data

	SCORE2[5]	LEAVO
First patient in	September 2014	December 2014
Participant characteristics		
Total number	362	463
Mean age	69 years	69 years
Percent women	43%	43%
Racial status	76% white, 15% black, 10% Hispanic	93% white, 1% black, 5% Asian, 1% other
Ocular characteristics		
CRVO/HRVO	85% CRVO; 15% HRVO	100% CRVO
Mean visual acuity	20/100 (50 letters)	20/100 (54 letters)
Mean OCT central subfield	665 microns	694 microns

Table 4. LEAVO vs. SCORE2 Topline Results

	SCORE2	LEAVO
Mean change in VA score at primary outcome	Aflibercept: +18.9 Bevacizumab: +18.6	Ranibizumab: +12.5 Aflibercept: +15.1 Bevacizumab: +9.8
Proportion of patients with 15+ letter gain at primary outcome	Aflibercept: 65.1% Bevacizumab: 61.3%	Ranibizumab: 47% Aflibercept: 52% Bevacizumab: 45%
Mean reduction in CSF at primary outcome	Aflibercept: 288u Bevacizumab: 231u	Ranibizumab: 405u Aflibercept: 378u Bevacizumab: 334u

III. LEAVO vs. SCORE2 Summary

A. Differences in trial design

1. SCORE2 had fixed monthly injections until month 5 before primary outcome was measured at month 6; then randomized to monthly or treat-and-extend for good responders through month 11.
2. LEAVO had 4 mandated injections, then investigators followed an algorithm for retreatment. Participants could have injection withheld if no improvement or worsening.

B. Differences in trial results

1. SCORE2 trial showed bevacizumab to be noninferior to aflibercept at month 6.
2. LEAVO trial showed that aflibercept is noninferior to ranibizumab, but that bevacizumab is *not* noninferior to either ranibizumab or aflibercept after 2 years of treatment.

C. Similarities

1. Both trials show that anti-VEGF is effective in preventing vision loss in patients with CRVO; however, visual acuity gains can be difficult to maintain long term.
2. Both trials demonstrate the need for long-term follow-up and close monitoring of patients with CRVO.

References

1. LEAVO: A multicentre Phase III double-masked randomised controlled non-inferiority trial comparing the clinical and cost effectiveness of intravitreal therapy with ranibizumab (Lucentis) vs aflibercept (Eylea) vs bevacizumab (Avastin) for macular oedema due to central retinal vein occlusion. Sponsored by National Institute for Health Research (NIHR), UK and the NIHR Biomedical Research Centre, Moorfields Eye Hospital, UK.
2. SCORE2: Study of comparative treatments in retinal vein occlusion 2. Sponsored by National Eye Institute (NEI), National Institutes of Health, U.S. Department of Health and Human Services.
3. Scott IU, VanVeldhuisen PC, Ip MS, et al. SCORE2 report 2: study design and baseline characteristics. *Ophthalmology* 2017; 124(2):245-256.
4. Ophthalmology Innovation Summit. Protocol V, LEAVO among retina highlights at ARVO 2019. May 1, 2019. https://ois.net/protocol-v-leavo-among-retina-highlights-at-arvo-2019/.
5. Scott IU, VanVeldhuisen PC, Ip MS, et al; for the SCORE2 Investigator Group. Effect of bevacizumab vs aflibercept on visual acuity among patients with macular edema due to central retinal vein occlusion. The SCORE2 Randomized Clinical Trial. *JAMA*. 2017; 317(20):2072-2087.

Improved Cone Function in Retinitis Pigmentosa by Oral *N*-Acetylcysteine

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Background

In retinitis pigmentosa (RP), rod photoreceptors die from one of many mutations, after which cones are compromised by oxidative stress. *N*-acetylcysteine (NAC) reduces oxidative damage and increases cone function and survival in an RP model. We tested the safety, tolerability, and visual function effects of oral NAC in RP patients.

Methods

Patients (n = 10 per cohort) received 600-mg (Cohort 1), 1200-mg (Cohort 2), or 1800-mg (Cohort 3) NAC b.i.d. for 12 weeks and then t.i.d. for 12 weeks, followed by 12 weeks of observation. BCVA, microperimetry, ellipsoid zone (EZ) width, and aqueous NAC were measured every 4 weeks.

Results

There were 9 drug-related gastrointestinal adverse events, which resolved spontaneously or with reduction from t.i.d. to b.i.d. dosing (MTD 1800 mg b.i.d.). Mean aqueous NAC peaked at 250-300 ng/mL for both 1200 and 1800 mg b.i.d. During the 24-week treatment period, mean BCVA improved in each cohort (0.4, 0.5, and 0.2 letters per month; $P \leq .02$ by general linear mixed model), and microperimetry showed mean net increases in sensitivity of 3, 20, and 68 dB ($P = .012$ for Cohort 1 vs. Cohort 3). There was no significant change in mean EZ width in any cohort.

Conclusion

Patients with moderately advanced RP have suboptimally functioning macular cones that may show improved function with oxidative stress reduction. A large, placebo-controlled trial is needed to determine if oral NAC can provide long-term stabilization and/or improvement in visual function in patients with RP.

Long-term Effects of the Phase 2 Ciliary Neurotrophic Factor Treatment of Macular Telangiectasia Type 2

Emily Y Chew MD; the Mac Tel Project Research Group

Introduction

Macular telangiectasia type 2 (MacTel type 2) is a bilateral degenerative disease characterized by perifoveal telangiectatic vessels and neurosensory atrophy.[1,2] The affected eye may show the loss of retinal transparency, crystalline deposits, decrease or absence of macular pigment, and hyperplasia of the retinal pigment epithelium. Although the natural course of visual loss is gradual, at approximately 1 letter lost per year,[3] affected individuals experience profound reduced visual function, especially for reading.[4] While there are no current proven therapies for this condition, a Phase 2 clinical trial of an implant of ciliary neurotropic factor (CNTF) delivered by genetically modified retinal pigment epithelial cells demonstrated a beneficial effect.[5]

Objectives

To report the long-term effects of a sham-controlled randomized clinical trial (RCT) of CNTF delivered in a device (NT-501). The outcome is the change from baseline area of the ellipsoid zone (EZ) loss at 2, 3, and 4 years of follow-up, as measured by en face imaging by spectral domain OCT.

Method

This multicenter, single-masked, sham-controlled RCT in 11 clinical sites in the United States and Australia enrolled participants with MacTel type 2. If both eyes were eligible for the study, one eye was randomized to the intravitreal implant or sham procedure while the fellow received the other treatment. Unilateral eyes were randomized to treatment or sham. The primary outcome was the change in area of EZ loss at 24 months compared with baseline. Functional changes included microperimetry, reading speed, and the National Eye Institute Visual Function Questionnaire. An extension study provided an opportunity to evaluate the long-term effects of the CNTF on the outcomes of the progression of neurodegeneration beyond the clinical trial at annual visits through 4 years.

Results

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

Two deaths occurred during the course of the RCT. No participants were otherwise lost to follow-up, and all surviving participants were followed to the final 24-month study visit for the primary outcome of the RCT. The CNTF implant reduced the risk of progression of the area of the EZ break at 24 months ($P = .039$). This beneficial effect persisted at 36 months ($n = 92$ eyes). At 48 months, this beneficial effect was seen in a subset of eyes that were graded to be *free* of lesions known as OCT hyper-reflectivity. Such hyper-reflectivity on OCT was considered to be present by the Reading Center at Duke University when mounds of hyper-reflective material extended internally from the retinal pigment epithelium, associated linear vertical or oblique hyper-reflective retinal streaks were present, with or without hyper-reflectivity with shadowing corresponding to retinal pigment plaques seen on color fundus photograph or fundus autofluorescent image. When OCT hyper-reflectivity was present, the beneficial treatment of the CNTF implant was not seen.

Visual Function Outcomes

As expected, there was no change in visual acuity between the treatment groups at 24 months and subsequent follow-up. There was a stabilization of the reading speed in the treated eyes, while the sham eyes continued to experience reduced reading speed ($P = .016$) at month 24 compared with baseline. However, this beneficial effect did not persist throughout subsequent follow-up. Other secondary analyses on visual acuity and microperimetry will be presented.

Safety Concerns

Consistent with previous studies of NT501 CNTF implant in other ocular conditions such as retinitis pigmentosa and geographic atrophy associated with AMD, the device was well tolerated. No study participant had the implant removed. Short-term adverse effects related to surgery resolved without any sequelae. Miosis, a previously known effect of CNTF implant, was noted in 18% of the study eyes initially. This extended to a larger proportion of study participants. The miosis persisted throughout the extended follow-up.

Conclusion

CNTF treatment delivered by NT501 was safe and well tolerated. CNTF had a beneficial effect and reduced the progressive loss of photoreceptors, compared to untreated eyes, persisting up to 36 months and 48 months. The nature of the OCT hyper-reflectivity requires further clarification with future studies involving OCT angiography. Because of these promising results, two Phase 3 studies of CNTF are currently recruiting.

References

1. Charbel Issa P, Gillies MC, Chew EY, et al. Macular telangiectasia type 2. *Prog Retin Eye Res*. 2013; 34:49-77.
2. Powner MB, Gillies MC, Tretiach M, et al. Perifoveal Muller cell depletion in a case of macular telangiectasia type 2. *Ophthalmology* 2010; 117(12):2407-2416.
3. Clemons TE, Gillies MC, Chew EY, et al. The National Eye Institute Visual Function Questionnaire in the Macular Telangiectasia (MacTel) Project. *Invest Ophthalmol Vis Sci*. 2008; 49(10):4340-4346.
4. Finger RP, Charbel Issa P, Fimmers R, Holz FG, Rubin GS, Scholl HP. Reading performance is reduced by parafoveal scotomas in patients with macular telangiectasia type 2. *Invest Ophthalmol Vis Sci*. 2009; 50(3):1366-1370.
5. Chew EY, Clemons TE, Jaffe GJ, et al. Effect of ciliary neurotrophic factor on retinal neurodegeneration in patients with macular telangiectasia type 2: a randomized clinical trial. *Ophthalmology* 2019; 126:540-549.

Complications and Costs of Gene- and Cell-Based Therapy

David J Wilson MD

I. Gene Therapy Trials

Since 2012, the US FDA has approved > 1100 gene therapy trials.

A. Achromatopsia: CNGA3
B. Achromatopsia: CNGB3
C. Choroideremia
D. Leber congenital amaurosis (LCA) RPE65
E. LCA: CEP290
F. Stargardt: ABCA4
G. Ushers: MYO7A
H. ProQR USH2A
I. X-linked retinitis pigmentosa (XLRP): RPGR
J. X-linked retinoschisis (XLRS): RS1

II. Complications of Gene and Cell Therapies

A. Presurgery
   1. Manufacturing
   2. Pharmacy
B. Injection
   1. Position
   2. Fluid
   3. Material
   4. Injection rate
   5. Catheter size
C. Immune response
   1. Immune privilege
   2. Immunosuppressives
D. Wound healing
   1. Mechanical issues
   2. Cell reaction

III. Luxturna: Adverse Reactions (Clinical Trial $n = 41$)

A. Subretinal deposits*: 7%
B. Eye Inflammation*: 5%
C. Foveal thinning: 2%
D. Foveal dehiscence: 2%
E. 33% chance of detecting a complication that has 1/100 frequency

* Patients were treated with systemic steroids before and after subretinal injections.

IV. Injection

A. Intravitreal
B. Sub-RPE (retinal pigment epithelium)
C. Foveal detachment
D. Surgical consideration re: cannula
   1. Cell recovery and viability is highly dependent on cannula gauge.
   2. Smaller cannulas will deliver cell.

V. Viral Vector

A. Impurities
B. Empty capsids and virus aggregates
C. Host cell proteins
D. Nucleic acids
E. Buffer, tonicity agent, cryoprotector , surfactant

VI. Immune Response

A. Privilege
   1. Tolerance
   2. Rodents vs. primates
   3. Partial vs. total
B. Route of administration
   1. Subretinal
   2. Intravitreal: most inflammatory
   3. Suprachoroidal
   4. Viral vectors
   5. Cells

VII. Cost of Gene Therapy

A. RPE65: 1 per 100,000
B. Choroideremia: 1 per 50,000
C. X-linked RP: 1 per 25,000
D. Stargardt disease: 1 per 10,000

VIII. Conclusions

A. Complications of gene- and cell-based therapy
B. Surgical
C. Immunologic
D. Wound healing
E. Cost
F. Alternative funding mechanisms will be necessary to fund gene- and cell-based therapies at their projected price.

Video Surgical Complications—What Would You Do?

Surgical Complications of Internal Limiting Membrane Peeling

Kazuaki Kadonosono MD

Internal limiting membrane (ILM) peeling is an essential procedure for macular surgery. Some dyes, such as indocyanine green and brilliant blue G, allow us to remove the ILM more effectively, resulting in better configuration of the macular region and improvement in vision. However, at approximately 10 microns, the ILM is such a thin membrane that ILM peeling is a difficult surgical procedure. As a result, several surgical complications are associated with ILM peeling.

Intraoperative complications include direct surgical damage to the retina with forceps during the pinch and peeling processes,[1] causing small retinal tears and/or bleeding; and phototoxicity caused by endoillumination. Such intraoperative complications might cause postoperative visual field defects[2] or visual impairment. In order to avoid these complications, we have to consider the best site at which to initiate removal of the ILM, which forceps and lens should be used (see Figure 1), and the optimal approach to take.

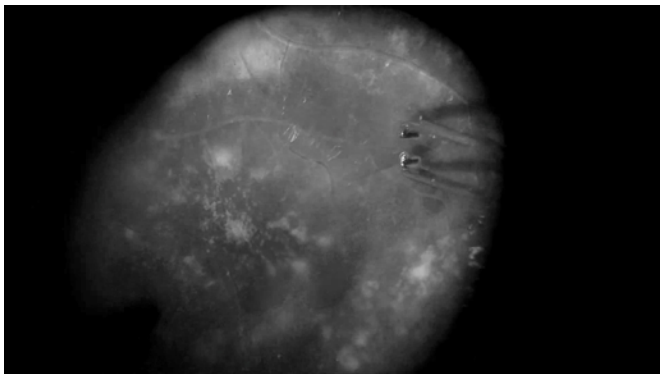

Figure 1. This is a picture of an eye with diabetic macular edema with a new kind of forceps used to effectively remove ILM.

References

1. Karacorlu M, Karacorlu S, Ozdemir H. Iatrogenic punctate chorioretinopathy after internal limiting membrane peeling. *Am J Ophthalmol*. 2003; 135(2):178-182.
2. Tadayoni R, Svorenova I, Erginay A, Gaudric A, Massin P. Decreased retinal sensitivity after internal limiting membrane peeling for macular hole surgery. *Br J Ophthalmol*. 2012; 96(12):1513-1516.

Intraocular Scissors

Khalid K Sabti MD

Dexamethasone Intravitreal Implant Injection

Andre Maia MD

Scleral Buckling

Geoffrey G Emerson MD PhD

This 56-year-old with macula-off retinal detachment underwent pars plana vitrectomy with scleral buckling, which was complicated by a scleral perforation during the buckle, resulting in subretinal hemorrhage beneath the retina. The subretinal hemorrhage was managed by removing hemorrhage through a posterior retinotomy. The suture penetration was managed by leaving it in place and lasering the retina in the vicinity of the perforation at the posterior edge of the buckle.

Trauma and Contact Lens

"Always be prepared "

Carl C Claes MD

A 40-year-old wood worker suffered from a nail perforation injury to the right eye, inflicted by a nail-gun he was manipulating himself on the workfloor. Immediate primary wound repair was performed by the anterior segment surgeon in the hospital nearby.

Three days later, the patient presented in the retina surgery department of Antwerp University Hospital with an inferior horizontal corneal wound, limbus to limbus with interrupted 10/0 nylon sutures, a complete aniridia, a crystal-clear lens, and a dense vitreous hemorrhage.

Ultrasound examination revealed absence of an intraocular foreign body and retinal detachment with suspicion of a posterior perforation site.

Patient was transferred to the OR.

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Novo Nordisk: C
Retinal Solutions: C

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Allergan: C
Bausch + Lomb: C
Clearside: C
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Santen, Inc.: C

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Genetech: C
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Metro Biotech International: O
Mylan: C
Novartis, Alcon Pharmaceuticals: C
Ophthotech: O
QBio: C
Ribomic: C

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Allergan: C
Eyepoint: C
Kala Pharmaceuticals: C
Novartis, Alcon Pharmaceuticals: C
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Carl Zeiss, Inc.: L
Genentech: C,L
Novartis Pharma AG: L
Ocular Therapeutix: C
ThromboGenics: C

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Limelight Bio: O,S
NightStar: C
Odyllia: C
ProQR: C
Roche Diagnostics: C
Sparing Vision: C
Spark Therapeutics, Inc.: S

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DORC International, bv/Dutch Ophthalmic, USA: C,L
Phoenix: C
Visunex: C
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Allergan: L,C
Hemera: O

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Adverum Biotechnologies: C
Aerie Pharmaceuticals: C
Aerpio: C
Alcon Laboratories, Inc.: C
Alkahest: C
Allegro: C,O
Allergan: C
Allgenesis: C
Appelis: C
AsclepiX Therapeutics: C
Bausch + Lomb: C
Bayer Healthcare Pharmaceuticals: C
Biogen Inc.: C
BioMotiv: C
BioTime, Inc.: C
Boehringer-Ingelheim Pharmaceuticals: C
Cell Cure: C
Chengdu Kanghong Biotec: C
CoDa Therapeutics: C
Daiichi Sankyo Co. LTD: C
DigiSight: O
Everads Therapy, LTD: C
EyePoint Pharmaceuticals: C
Foresight Biotherapeutics: C
Galimedix Therapeutics: C
Genentech: C
GenSight Biologics: C
Glaukos: C
GrayBug Vision: C
Iconic Therapeutics: C
Interface Biologics, Inc.: C
Ionis: C
Kala Pharmaceuticals: C
LumiThera, Inc.: C
Neurotech: C
NGM Biopharma: C
Notal Vision, Inc.: C
Novartis Pharmaceuticals Corp.: C
Ocugen, Inc.: C
Ocular Therapeutics: C
Ohr: C
Ophthotech: C
Opthea: C
Optos, Inc.: C
Optovue: C
Ora, Inc.: C
Orbit Biomedical: C
Oxurion: C
RecensMedical Inc.: C
Regeneron Pharmaceuticals, Inc.: C
Regenxbio: C
Regulus Therapeutics: C
River Vision: C
Samumed, LLC: C
Santen, Inc.: C
SciFluor: C
Semathera: C
Shire: C
Stealth BioTherapeutics: C
Sun Pharmaceutical Industries: C
Taiwan Liposomal Company: C

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Roche: S
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Eye Point: S
Genentech: S
Mylan: S
Notal Vision, Inc.: S
Novartis, Alcon Pharmaceuticals: S

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Allegro: C,S
Allergan: C,S
Apellis: S,C
Astellas: S
Avalanche/Adverum: S
Boehringer Ingelheim: S,C
Carl Zeiss, Inc.: C
Clearside: C,S
Genentech: C,S
Heidelberg Engineering: C
Iconic: S
Janssen: C
Johnson & Johnson: C
Kanghong Pharma: C
National Eye Institute: S
Notal Vision, Inc.: C
Novartis, Alcon Pharmaceuticals: C,S
Ohr: C,S
Ophthotech: C,S
Opthea: S
Optos, Inc.: C,P
Optovue, Inc.: C
Pfizer, Inc.: C
PRN Physician Recommended Nutriceuticals: S
Regeneron Pharmaceuticals, Inc.: C,S
Regenix Bio: C,S
Samsung Bioepsis: C,S
Samsung: C,S
Santen: C,S
SciFlour Life Sciences: S
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Stealth Biotherapeutics: C
Taiwan Liposome: S
ThromboGenics, Inc.: C,S
Tyrogenix: C,S

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Allegro: C,O
Allergan: C,S
Applied Genetic Technologies: C
AsclipiX: C,S
Astellas: C
Cleaside: S
Exonate: C
Genentech: C,S
Genzyme: S
Graybug: C,O,P,S
Intrexon: C
Merck & Co., Inc.: C
Merck: C
Novartis, Alcon Pharmaceuticals: C
Oxford BioMedica: S
Regeneron: S,C
RegenX Bio: S
Roche: C,S
Rxi: C,S
Wave Life Sciences: C

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Broadspot: O
Genentech: S
interVIEW: O,P
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Phoenix Technology Group: O
Spark Therapeutics: C

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Carl Zeiss Meditec: L
Heidelberg Engineering: L
Novartis Pharma AG: L
Roche Diagnostics: L

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Genentech: C
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Allergan, Inc.: C
Bayer Healthcare Pharmaceuticals: C,L,S
Hoffman La Roche, Ltd.: C
Novartis Pharma AG: C,L

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Genentech: C
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Bayer Healthcare Pharmaceuticals: C,L,S
Carl Zeiss Meditec: S
Heidelberg Engineering: L
Novartis, Alcon Pharmaceuticals: C,L,S
Topcon Medical Systems Inc.: S

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Alcon Laboratories, Inc.: C
Allergan: C
Bayer Healthcare Pharmaceuticals: C,L
DORC International, bv/Dutch Ophthalmic, USA: C
DORC: L
Katalyst: C,P
Novartis, Alcon Pharmaceuticals: C,L
Optovue: L

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Alcon Laboratories, Inc.: C

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Castle Biosciences: C

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Acucela: C
AGTC: C
Allergan: C
Astellas: O
Genentech: C
Gyroscope: C
Heidelberg Engineering: C
Novartis Pharma AG: C
Ocular Therapeutix: C
Ophthotech: C
Regeneron Pharmaceuticals, Inc.: C
Ribomics: C

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Alcon Laboratories, Inc.: C

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Allergan: C
EyePharma: S

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Alcon: C
Bayer: C
eSight: O
LEH Pharma: C
Lumithera: O

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Aerie Pharmaceuticals, Inc.: C
Bayer Healthcare Pharmaceuticals: C
BioTime Inc.: C
Genentech: C
Kodiak Sciences: C
Novartis: C
Regeneron Pharmaceuticals, Inc.: S,C
Santen, Inc.: C

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Allergan: C
Interview Medical Systems: O
Orbit Biomedical: C
Phoenix LLC: O
Regeneron Pharmaceuticals, Inc.: C
Retinal Solutions: O
Spark Therapeutics: C

Pravin U Dugel MD
Abfero: C
Acucela: C
Aerie Pharmaceutical: C
Aerie: C
Aerpio: C,O
Alcon Laboratories, Inc.: C
Alimera Sciences, Inc.: C,O
Alimera: C,O
Allegro Ophthalmics, LLC: C,O
Allergan: C
Amgen: C
Annidis: C,O
Arctic Vision: C,O
ArcticDx, Inc.: C
Asclepix: C
Bausch + Lomb: C
Beyeonics: C
Boehringer Ingelheim Pharma GmbH: C
Boehringer Ingelheim: C
Byeonics: C
Changdu Kanghong Biotechnology: C
Clearside Biomedical: C,O
Daiichi Sankyo: C
Digisight: C,O
DOSE Medical: C
Eyepoint: C
Fox Kiser: C,O
Gemini: C
Genentech: C
Graybug Vision: C
Ionis: C
Irenix: C,O
Kodiak Sciences: C
Lux BioScience: C
Macusight: C
Merck: C
Nan Fung Group: C,O
NeoVista, Inc.: C
Novartis, Alcon Pharmaceuticals: C
Oculis SA: C
Omeros: C
Ophthotech: C,O
Opthea: C
Optos, Inc.: C
Optovue: C
ORA: C
PanOptica: C,O
Pentavision: C
Pieris: C
pSivida Corp.: C
Regeneron Pharmaceuticals, Inc.: C
Regeneron: C
Regenxbio: C
Reneuron: C
Roche Diagnostics: C
Santen, Inc.: C
SciFluor Life Sciences: C
Shire Human Genetics: C
Spark Therapeutics: C
Stealth Biotherapeutics: C
ThromboGenics, Inc.: C
Topcon Medical Systems Inc.: C
TrueVision: C

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Akebia: C
Allegro: C
Allergan: C
Aura Bio: C
Bausch + Lomb: C
Beyeonics: C
Carl Zeiss Meditec: S
EyePoint Pharma: C
Graybug: C
Helio Vision: C
Hemera Biosciencies: O
Hoffman La Roche, Ltd.: C
Kala Pharma: C
Novartis, Alcon Pharmaceuticals: C
OptoVue: S
Sesen Bio: C
Sigilon: C

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Vitreq B.V.: P

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Aerpio: S,C
Alcon Laboratories, Inc.: C,S
Allergan: C
Bioptigen: C,P
Carl Zeiss Meditec: C
Genentech: C,S
Leica: P,C
National Eye Institute: S
Novartis Pharma AG: S,C
Regeneron Pharmaceuticals, Inc.: S
Santen, Inc.: C
Thrombogenics: C,S

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None

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Alcon: C
Aldeyra Therapeutics: C,O,P
Alimera: C
Allergan: C
DORC: C
Genentech: C
Neurotech: S
Pykus Therapeutics: C,O
Regenxbio: C

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Allergan, Inc.: O
Gilead Sciences: O
Glaukos Corp.: O
Mallinckrodt Medical Affairs: O
Novartis Pharma AG: O
Pfizer, Inc.: O
Regeneron Pharmaceuticals, Inc.: O

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Alimera Sciences, Inc.: C,L
Allergan: C,L
Bayer Healthcare Pharmaceuticals: C,L,S
Novartis Pharmaceuticals Corp.: C,L,S
Roche: C

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Abbvie: L
Allergan, Inc.: C,L
Genentech: C
Santen, Inc.: C

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ArcticDx, Inc.: O
Genentech: C,S

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Allergan: C
Genentech/Roche: S
Heidelberg Engineering: C
Novartis, Alcon Pharmaceuticals: C
Optovue: C
Zeiss: C

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Aerpio: S
Allergan, Inc.: S
Apellis: S
Bausch + Lomb: C
Deciphera: C
EyeGate Pharmaceuticals, Inc.: S
Johnson & Johnson: C
Nexttech: O
Santen, Inc.: C
Topivert: C

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Novartis: C
ThromboGenics, Inc.: C

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Allergan: C,L,S
Bayer Healthcare Pharmaceuticals: C,L,S
Novartis Pharmaceuticals Corp.: C,L,S
Opthea: C
Roche Diagnostics: C

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Aura Pharmaceuticals: C
Iconic Therapeutics: C
Valeant: P

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Heidelberg Engineering: L
Jaeb Center for Health Research: S
Optos, Inc.: L

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Apellis: C
Bayer Healthcare Pharmaceuticals: C
Genentech: C
Novartis Pharma AG: C

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Aura Biosciences: C
Celgene: O
KalVista: C
Lowy Medical Research Institute: C
Novartis Pharmaceuticals Corp.: C

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Aura Biosciences: C
Castle Biosciences, Inc.: C,P
Immunocore: C

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Lippincott Williams and Wilkins: P
NIH/NEI: S
Novartis: S
Parexel: S

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Allergan: C
ArcticDx, Inc.: C,O
Bayer Healthcare Pharmaceuticals: C
Genentech: C
Hoffman La Roche, Ltd.: C
Iconic Therapeutics: C
Katalyst Surgical, LLC.: C
Novartis Pharmaceuticals Corp.: C
Ocugenix: C
Oculus, Inc.: C,O
Regeneron Pharmaceuticals, Inc.: C
Surgicube: C
Vitreq: C
Vortex Surgical: C

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Adverum: C,O
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Aerpio: C,S
Akros: C
Aldeyra: C,O
Alkahest: C
Allegro: C,O
Apellis: C,S
Array Biopharma: C
Asclepix: C
Bayer Healthcare Pharmaceuticals: C
Beaver-Visitec International, Inc.: C
BioMarin: C
Chengdu Kanghong Biotech: C,S
Clearside: S
Daiichi: C,S
Digital Surgery Systems: C
Eloxx: C
Galecto: C
Galimedix: C
Genentech: C,S
Generation Bio: C
Genzyme: S
Helio: C
Hemera: C,S
Interface: C
Irenix: C
Janssen R&D: C,S
jCyte: O,C
Kala: C
Kalvista: S
Kodiak: C
Notal Vision, Inc.: C,S
Novartis Pharma AG: C,S
Ocudyne: S
Ocular Therapeutix: C,O
Omeicos: C
Ophthotech: S
Optos: S
Optovue, Inc.: S
Orbit Biomedical: C
Regeneron Pharmaceuticals, Inc.: C,S
Regenxbio: C,S
Retrotope: C
Scifluor: C
Shire: C
Stealth Biotherapeutix: C,S
ThromboGenics, Inc.: C,S
Voyant: C
Zeiss: C

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AGTC: C,S
Alcon Laboratories, Inc.: C,S
Allergan: C,S
Apellis: S
Asclepix: C
Beaver-Visitec International, Inc.: C
BioTime: C
Chengdu Kanghong Biotechnology: C,S
Covalent Medical, LLC.: O
Genentech: C,S
Iconic: C,S
Iridex: C,S
Johnson & Johnson: C,S
National Eye Institute: S
ONL: C,O
Ophthotech: S
Optovue, Inc.: C,S
PanOptica: C,O
PRN Physician Recommended Nutriceuticals: C,O
Regeneron Pharmaceuticals, Inc.: C,S
Regenexbio: C,S
Second Sight Medical Products, Inc.: C,S
Tyrogenix: C

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Alimera Sciences, Inc.: S,L
Allegro: C
Allergan, Inc.: C,L
BioTime, Inc.: C
Clearside: C
Gemini: C,S
Genentech: C,L,S
Katalyst: C,O,P
Regeneron Pharmaceuticals, Inc.: C,L
Spark: L

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Allergan: C,S
Apellis: C
Bayer Healthcare Pharmaceuticals: C,L,S
Boehringer-Ingelheim: C
Centervue: S
Genentech: C,S
Heidelberg Engineering: C,S
Hoffman La Roche, Ltd: C,S
LIN Bioscience: C
Nightstar: S
Novartis Pharmaceuticals Corp.: C,L,S
Optos: S

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Ophthotech, Inc.: S
Santen, Inc.: S

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Clarity Vision Technologies: C
Diopsys: C,L,S
Lumoptic: O,C
NEI/NIH: C
Novo Nordisk: S
Outlook Therapeutics: C
Regenerative Patch Technologies: C
RegenXbio: C
Second Sight Medical Products: C
Second Sight: C
Volk Optical, Inc.: C,L
Washington University (St. Louis) DOLF study: C

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Alcon: C
Allergan: C
Bausch + Lomb: C
UCLA: P
Zeiss: C

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Alcon Laboratories, Inc.: C,L
Allergan: C,L
Clearside: C
Duke Eye Center: P
Eyemedix: C,O,P,S
Iridex: P
John Hopkins University: P
Lutronic Vision: C,O
MTTR: C,O
Regenerative Patch Technologies (RPT): C,O,P
Replenish: C,O,P
Santen, Inc.: C,L
Second Sight Medical Products, Inc.: O,P
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Bayer Healthcare Pharmaceuticals: C,S
Novartis: C,S

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Boehringer Ingelheim: C
Genentech: C
Novartis Pharma AG: C
Quark: C
ThromboGenics, Inc.: C

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EyePoint: C
EyeVensys: C
Heidelberg Engineering: C
Neurotech: C
Novartis Pharma AG: C

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Sanofi: C

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Apellis: S
Pfizer, Inc.: C
Syneos Health: C

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Aerpio: C
Alcon Laboratories, Inc.: C,L
Allegro: C
Allergan: C
Bayer Healthcare Pharmaceuticals: C,L
Biogen, Inc.: C
Boerenger: C
Eyevensys: C
Formycon: C
Galecto: C
Galimedix: C
iRenix: C
jCyte: C
Kala: C
Kanghong: C
Kodiak: C
Novartis Pharmaceuticals Corp.: C,L
Ocugenix: C
Omeros: C
Ophthotech: C,L
Opthea: C
Oxurion: C
Regeneron Pharmaceuticals, Inc.: C,L
RegenexBio: C
Retinal Sciences: C,O
Santen: C
SciFluor Lide Sciences: C
Shire: C
Stealth: C

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Pan Optica: C

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California Institute for Regenerative Medicine: S
Carl Zeiss Meditec: L,S,C
National Eye Institute: S
Opternative, Inc.: C
Regenerative Patch Technologies: S

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Biophytis: C
Castle Biosciences: C
Novartis, Alcon Pharmaceuticals: C

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Cellcure: C
Clearside: C
Eyepoint: C
Genentech: C
Kodiak: C
Notal Vision, Inc.: S
Notal Vision: C
Novartis: L
Optos, Inc.: S

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Adverum: C,O
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Alimera Sciences, Inc.: C
Allergan: C
BIomarin: C
Genentech: C
Novartis Pharma AG: C
Optos, Inc.: C
Regeneron Pharmaceuticals, Inc.: C
RegenxBio: C
Spark: C

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Allegro: C,S
Allergan: C,S
Apellis: C,S
Cell Care: C
Dose: C
Eyedaptic: C,O
Galimedix: C
Genentech, Inc.: C,S
Glaukos Corp.: C
Interface Biologics: C
Ionis: S
J-Cyte: C,S
Novartis Pharma AG: C,S
Ophthotech: C
Regeneron Pharmaceuticals, Inc.: C,S
ReVana Therapeutics: C
ThromboGenics, Inc.: S

Linda A Lam MD MBA
Ocutrx: C

Yannek I Leiderman MD PhD
Alcon Laboratories, Inc: C,L,S
Allergan, Inc: L,O
DORC International, bv/Dutch Ophthalmic, USA: C
Genentech: L,C
Regeneron Pharmaceuticals, Inc: C,L
RegenXBio: C

Jennifer Irene Lim MD
Alcon Laboratories, Inc.: C
Chengdu Kanghong: S
Clearside: S
CRC Press/ Taylor and Francis: P
Genentech: C,L,S
JAMA Ophthalmology Editorial Board: C
Janssen: S
Kodiak: C
Novartis: L
Ophthea: C
pSivida: C
Quark: C
Regeneron Pharmaceuticals, Inc.: S
Santen, Inc.: C
Second Sight Medical Products, Inc.: S

Phoebe Lin MD PhD
None

Anat Loewenstein MD
Allergan: C,S;
Bayer Healthcare Pharmaceuticals: C,S;
Beyeonics Surgical, Ltd.: C;
Forsightlabs: C;
KHB: C;
Multicentre Trial: S;
Notal Vision, Inc.: C;
Novartis Pharmaceuticals Corporation: C,S;
Pres-by: C;
Roche: C;
Sensor: S;
Syneos Health: C;
WebMD: C;
Xbran: C

Andrew J Lotery MBCHB
Allergan: S
Gyroscope Therapuetics: C,O

Brandon J Lujan MD
BioTime: C
Genentech: C,S
Southern California Desert Retina Consultants: C
Translations Imaging Innovations, Inc.: C,O
University of California, Berkeley: P

Albert M Maguire MD
Foundation Fighting Blindness: S
Nightstar: S
Novartis Pharma AG: C
Regenxbio, Inc.: C,S
Spark Therapeutics: C,S

Tamer H Mahmoud MD
Hoffman La Roche, Ltd.: S
National Eye Institute: S
Novartis Pharma AG: S
ThromboGenics: S
Vortex: P

Andre Maia MD
None

Daniel F Martin MD
None

Colin A McCannel MD
Allergan: S
DORC International, bv/Dutch Ophthalmic, USA: C,L
Genentech: S

Tara A McCannel MD
None

H Richard McDonald MD
Abbvie: S
Alcon Laboratories, Inc.: S
Carl Zeiss Meditec: S
Kodiak Sciences Inc.: C
Regeneron Pharmaceuticals, Inc.: S
Santen, Inc.: S

Michel Michaelides MD
Acucela: C
MeiraGTx: C,O

William F Mieler MD
None

Joan W Miller MD
Bausch + Lomb: C
Kalvista Pharmaceuticals: C
Lowy Medical Research Institute, Ltd.: S
ONL Therapeutics, LLC: C,O,P
Sonovion: C
Valeant Pharmaceuticals: P

Andrew A Moshfeghi MD, MBA
Alimera Sciences, Inc.: C
Allegro, Inc.: C
Allergan: C,L
Bausch + Lomb: C
Clearside: C
EyePoint: C
Genentech: C,S
Novartis Pharma AG: C
OptiSTENT: C,O
Pr3vent: C,O
Regeneron Pharmaceuticals, Inc.: C,S
Spark: C
Visunex Medical Systems: C,O

Darius M Moshfeghi MD
1800Contacts: C
Akebia: C
Congruence Medical Solutions: C
dSentz, Inc.: C,O
Grand Legend Technology, LTD: C,O
Iconic Therapeutics, Inc.: C
Irenix: C
Novartis: C
Pr3vent: O
Promisight, Inc.: C,O
pSivida: C
Pykus: C,O
Regeneron Pharmaceuticals, Inc.: C
SLACK: C
Versl, Inc.: O
Vindico: L
Visunex Medical Systems, Co. Ltd: C,O

Prithvi Mruthyunjaya MD
Aura: C
Castle Biosciences Inc.: C
Optos, Inc.: C
Santen, Inc.: C
Spark: C

Timothy G Murray MD MBA
Alcon: C
FDA: C

Quan Dong Nguyen MD
AbbVie: C
Bayer Healthcare Pharmaceuticals: C
Genentech: C
Regeneron Pharmaceuticals, Inc.: C
Santen, Inc.: C

Kyoko Ohno-Matsui MD
Bayer Healthcare Pharmaceuticals: C
Santen, Inc.: C

Timothy W Olsen MD
iMacular Regeneration LLC: O
National Eye Institute: S

Kirk H Packo MD
Alcon Laboratories, Inc.: C
Allergan: S
Covalent Medical: O
US Retina: O

David W Parke II MD
OMIC-Ophthalmic Mutual Insurance Company: C

Purnima S Patel MD
None

Dante Pieramici MD
None

John S Pollack MD
Allegro: C
Covalent Medical: O
DORC International, bv/Dutch Ophthalmic, USA: C
Genentech: C,S
Notal Vision, Inc.: C,O
Novartis Pharma AG: C
Regenxbio: C
Vestrum Health: O

Jonathan L Prenner MD
Alcon Laboratories, Inc.: C
Panoptica: C,O
Regeneron Pharmaceuticals, Inc.: C

Hugo Quiroz-Mercado MD
Allegro Ophthalmics: O

Narsing A Rao MD
None

Carl D Regillo MD FACS
Aerpio: S
Alcon Laboratories, Inc.: C,S
Allergan: C,S
Genentech: C,S
GlaxoSmithKline: S
Kodiak: C,S
Notal Vision, Inc.: C,S
Novartis Pharmaceuticals Corp.: C,S
Regeneron Pharmaceuticals, Inc.: S
Shire: C

Kourous Rezaei MD
Alcon Laboratories, Inc.: C
BMC: C
Ophthotech: E,O

William L Rich III MD FACS
None

Stanislao Rizzo MD
None

Richard B Rosen MD
Allergan: S
Astellas: C
Boehringer Ingelheim: C
CellView: C
Diopsys, Inc.: C
Genentech: S
Guardion Health: C,O
Nano Retina: C
Ocata: C
OD-OS: C
Opticology: O
Optovue: C,P
Regeneron Pharmaceuticals, Inc.: C
Teva: C

Philip J Rosenfeld MD PhD
Apellis: C,O
Boehringer-Ingelheim: C
Carl Zeiss Meditec: C,S
Chengdu Kanghong Biotech: C
Digisight: O
Genentech: C,S
Healios K.K.: C
Hemera Biosciences: C
Isarna Pharmaceuticals: C
Lin Bioscience: C
NGM Biopharmaceuticals: C
Ocudyne: C,O
Ocunexus: C
Unity Biotechnology: C

Khalid K Sabti MD
Alcon: C

Srinivas R Sadda MD
4DMT: C
Allergan: C,S
Amgen: C
Bayer: C
Carl Zeiss Meditec: C,S
Centervue: C
Genentech: C
Heidelberg Engineering: C
Nidek: L
NightstarRx: C
Novartis Pharma AG: C
Optos, Inc.: C
ThromboGenics, Inc.: C
Topcon Medical Systems Inc.: L

Reginald J Sanders MD
Allergan, Inc.: C

David Sarraf MD
Amgen: C
Bayer Healthcare Pharmaceuticals: L
Genentech: C,S
Heidelberg Engineering: S
Novartis Pharmaceuticals Corp.: L
Optovue: C,S
Regeneron Pharmaceuticals, Inc.: S
Topcon Medical Systems Inc.: S

Andrew P Schachat MD
American Academy of Ophthalmology: C
Cleveland Clinic Foundation: E
Easton Capital: O
Elsevier: P
State of Ohio: E

Amy C Schefler MD
Allergan: C
Aura Biosciences: S
Castle Biosciences: S
Genentech: C,S
Regeneron Pharmaceuticals, Inc.: S

Ursula M Schmidt-Erfurth MD
Boehringer Ingelheim: C
Genentech: C
Novartis Pharma AG: C
Roche Diagnostics: C

Steven D Schwartz MD
Astellas: S
Nidek, Inc.: S
Nikon: S
Verana Health: O

Gaurav K Shah MD
Allergan, Inc.: C, S
DORC International b.v./Dutch Ophthlamics, USA: S
OMIC-Ophthalmic Mutual Insurance Company: C
Regeneron Pharmaceuticals, Inc.: C, L

Carol L Shields MD
Aura Biosciences, Inc.: C
Immunocore, Inc.: C

Jerry A Shields MD
None

Michael A Singer MD
Aerpio: C,S
Aestelis: S
Alimera Sciences, Inc.: S
Allergan: C,L,S
Ampio: C,L,S
Clearside: C,S
Genentech: C,L,S
Guidepoint: C
Kodiak: C
Mallinckrodt Pharmaceuticals: L
Novartis Pharma AG: C,S
Optos, Inc.: S
pSivida: C
Regeneron Pharmaceuticals, Inc.: L,S
Santen, Inc.: C
Spark Therapeutics, Inc.: C

Lawrence J Singerman MD
Aerpio: S
Alcon Laboratories, Inc.: S
Alkeus: S
Allergan, Inc.: S
Apellis: S
Chengdu: S
DigiSight: S
Genentech: S
National Eye Institute: S
Novartis, Alcon Pharmaceuticals: S
Ophthotech: S
PanOptica: S
Roche: S
Samsung: S

Rishi P Singh MD
Alcon Laboratories, Inc.: C
Apellis: S
Genentech: C
Novartis, Alcon Pharmaceuticals: C,S
Optos, Inc.: C
Regeneron Pharmaceuticals, Inc.: C

William E Smiddy MD
None

Elliott H Sohn MD
DORC International: C
Oxford BioMedica UK Ltd.: S
Sanofi Fovea: S

Richard F Spaide MD
Bayer Healthcare Pharmaceuticals: C
DORC International, bv/Dutch Ophthalmic, USA: P
Topcon Medical Systems Inc.: C,P

Sunil K Srivastava MD
Allergan: C,S
Bausch + Lomb: C,S
Carl Zeiss Inc.: C
Clearside: C
Gilead Sciences: C
Optos, Inc.: C
pSivida: C
Regeneron Pharmaceuticals, Inc.: C
Santen, Inc.: C,S

Giovanni Staurenghi MD
Apellis: C
Bayer Healthcare Pharmaceuticals: C
Boheringer: C
Carl Zeiss Meditec: C,L,S
Centervue: C,L,S
Genentech: C
Graybug: C
Heidelberg Engineering: C,L,S
Hoffman La Roche, Ltd.: C,L,S
Nidek, Inc.: S
Novartis Pharmaceuticals Corp.: C,L,S
Ocular Instruments Inc.: P
Optos, Inc.: C
Optovue, Inc.: S
Quantel Medical: C,L,S

Paul Sternberg Jr MD
Diabetic Retinopathy Clinical Research Network: C
International Retinal Research Foundation: C,S
Nektar Therapeutics: C

Jennifer K Sun MD
Adaptive Sensory Technology: S
Boehringer Ingelheim: S
Boston Micromachines: S
JAMA Ophthalmology: E
Kalvista: S
Merck & Co., Inc.: C
Novartis Pharmaceuticals Corp.: C
Novo Nordisk: S,C
Optovue: S
Roche: C,S

Ramin Tadayoni MD PhD
Alcon Laboratories, Inc.: C
Allergan: C
Bausch + Lomb: C
Bayer Healthcare Pharmaceuticals: C
Carl Zeiss Meditec: C
Chibret International: C
Genentech: C
Hoffman La Roche, Ltd.: C
MORIA: C
Novartis, Alcon Pharmaceuticals: C
Oculis: C
ThromboGenics, Inc.: C

John T Thompson MD
Genentech: S,C
Opthea: S

Cynthia A Toth MD
Alcon Laboratories, Inc.: P
EMMES: C
Heidelberg Engineering: S
Hemosonics, LLC: P
National Eye Institute: S

Michael T Trese MD
Digisight: C,O
Interview medical systems: O,P
Phoenix Clinical Technologies: C,O
Regeneron Pharmaceuticals, Inc.: C
Retinal Solutions: O,P

Stephen H Tsang MD PhD
5R01EY026682: S
Edward N. & Della L. Thome Memorial Foundation: S
Foundation Fighting Blindness TA-NMT-0116-0692-COLU: S
NYSTEM IIRP Contract C32590GG: S
R01EY018213: S
R01EY024698: S
R24EY027285: S

Lejla Vajzovic MD
Alcon Laboratories, Inc.: C,S
Alimera Sciences, Inc.: C
Bausch + Lomb: C
DORC International, bv/Dutch Ophthalmic, USA: C,L
Genentech: C
Heidelberg Engineering: S
Johnson & Johnson: C
Roche Diagnostics: S
Second Sight Medical Products, Inc.: C,S

Demetrios Vavvas MD
None

Albert T Vitale MD
AbbVie: C
Aciont: C

Robin A Vora MD
None

Nadia Khalida Waheed MD
Bayer Healthcare Pharmaceuticals: S
Carl Zeiss Meditec: S,C
Genentech: C
Heidelberg Engineering: C
Johnson & Johnson: C,S
Nidek, Inc.: S
Ocudyne: O
Optovue: C,L
Regeneron Pharmaceuticals, Inc.: C,S
Topcon Medical Systems Inc.: C

John A Wells III MD
Adverum: S
Genentech: C,S
Iconic Pharmaceuticals: C
Jaeb Center for Health Research: C,S
National Eye Institute: S
Ohr Pharmaceuticals: S
Opthea: S
Optos, Inc.: S
Regeneron: S
ThromboGenics: S

David F Williams MD
Covalent: O
Vestrum Health: O

George A Williams MD
None

David J Wilson MD
NIH: S

Sebastian Wolf MD PhD
Allergan: S
Bayer Healthcare Pharmaceuticals: C,S
Carl Zeiss Meditec: C,S
Chengdu Kanghong Biotechnology: C
Heidelberg Engineering: C,S
Novartis Pharmaceuticals Corp.: C,S
RetinAI: C
Roche: C,S

Tien Yin Wong MBBS
Allergan Singapore Pte Ltd: C,L
Allergan, Inc.: C,L
Bayer Healthcare Company Limited: C,L,S
Bayer Healthcare Pharmaceuticals Inc.: C,L,S
EyRIS Pte Ltd: O
Genentech: C,L,S
Novartis Pharma AG: C,L,S
Oxurion NV: C
Plano Pte Ltd: O
Roche Diagnostics: C,L,S

Charles C Wykoff MD PhD
Adverum Biotechnologies: S,C
Aerpio: C,S
Alimera Sciences, Inc.: C
Allegro Ophthalmics: C
Allergan: C,S
Apellis Pharmaceuticals: C,S
Bayer Healthcare Pharmaceuticals: C
Chengdu Kanghong: S
Clearside Biomedical, Inc.: C,S
Dutch Ophthalmic Research Center International: C
EyePoint Pharmaceuticals (formerly pSivida): C
Fosun: C
Genentech: C,S
Kodiak Sciences: C,S
NEI: S
Neurotech: S
Notal Vision, Inc.: C
Novartis Pharmaceuticals Corp.: C,S
ONL Therapeutic: C
Ophthotech: C,S
Opthea: S
PolyPhotonix: C
RecensMedical: C,S
Regeneron Pharmaceuticals, Inc.: C,L,S
Regenxbio: C,S
Roche: C,S
Samsung: S
Santen, Inc.: C,S
Takeda: C

Steven Yeh MD
Clearside: C
Santen, Inc.: C

Yoshihiro Yonekawa MD
Alcon Laboratories, Inc.: C
Regeneron Pharmaceuticals, Inc.: C

Young Hee Yoon MD
Alcon Laboratories, Inc.: C,L
Allergan: C,L,S
Bayer Healthcare Pharmaceuticals: C,L,S
Boehringer Ingelheim: C

Seung Young Yu MD PhD
Bayer Healthcare Pharmaceuticals: S
Carl Zeiss Meditec: C

David N Zacks MD PhD
ONL Therapeutics: C,O,P

Marco A Zarbin MD PhD FACS
Aerie Pharmaceuticals, Inc.: S
Boerhinger Ingelheim Pharma: C
Calhoun Vision, Inc.: C
Cell Cure: C
Chengdu Kanghong Biotechnology: C
Coherus Biosciences: C
Daiichi Sankyo: C
EyEngineering: C
Frequency Therapeutics: O, C
Genentech: C
Helios, KK: C
Hoffman La Roche, Ltd.: C
Iridex: L, C
Isarna Therapeutics: C
Makindus: C
Novartis, Alcon Pharmaceuticals: C, L
Ophthotech Corp.: C
Percept: C, O
Rutgers University: P

Presenter Index

* Indicates that the presenter has financial interest. No asterisk indicates that the presenter has no financial interest.